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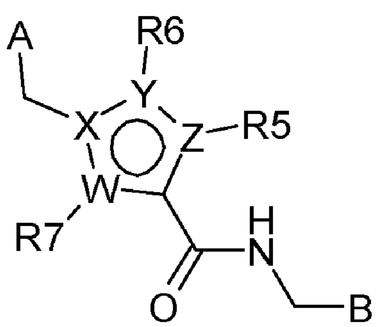

(I)

(57) Abstract: The present invention provides compounds of formula (I): compositions comprising such compounds; the use of such compounds in therapy (for example in the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated); and methods of treating patients with such compounds; wherein R5, R6, R7, A, B,W, X, Y and Z are as defined herein.

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HETEROCYCLIC DERIVATES

This invention relates to heterocyclic derivatives that are inhibitors of plasma kallikrein and to pharmaceutical compositions containing and the uses of, such derivatives.

Background to the Invention

The heterocyclic derivatives of the present invention are inhibitors of plasma kallikrein and have a number of therapeutic applications, particularly in the treatment of retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Plasma kallikrein is a trypsin-like serine protease that can liberate kinins from kininogens (see K. D. Bhoola *et al.*, "Kallikrein-Kinin Cascade", *Encyclopedia of Respiratory Medicine*, p483-493; J. W. Bryant *et al.*, "Human plasma kallikrein-kinin system: physiological and biochemical parameters" *Cardiovascular and haematological agents in medicinal chemistry*, 7, p234-250, 2009; K. D. Bhoola *et al.*, *Pharmacological Rev.*, 1992, **44**, 1; and D. J. Campbell, "Towards understanding the kallikrein-kinin system: insights from the measurement of kinin peptides", *Brazilian Journal of Medical and Biological Research* 2000, **33**, 665-677). It is an essential member of the intrinsic blood coagulation cascade although its role in this cascade does not involve the release of bradykinin or enzymatic cleavage. Plasma prekallikrein is encoded by a single gene and synthesized in the liver. It is secreted by hepatocytes as an inactive plasma prekallikrein that circulates in plasma as a heterodimer complex bound to high molecular weight kininogen which is activated to give the active plasma kallikrein. Kinins are potent mediators of inflammation that act through G protein-coupled receptors and antagonists of kinins (such as bradykinin antagonists) have previously been investigated as potential therapeutic agents for the treatment of a number of disorders (F. Marceau and D. Regoli, Nature Rev., Drug Discovery, 2004, **3**, 845-852).

Plasma kallikrein is thought to play a role in a number of inflammatory disorders. The major inhibitor of plasma kallikrein is the serpin C1 esterase inhibitor. Patients who present with a genetic deficiency in C1 esterase inhibitor suffer from hereditary angioedema (HAE) which results in intermittent swelling of face, hands, throat, gastro-intestinal tract and genitals. Blisters formed during acute episodes contain high levels of plasma kallikrein which cleaves high molecular weight kininogen liberating bradykinin leading to increased vascular permeability. Treatment with a large protein plasma kallikrein inhibitor has been shown to effectively treat HAE by preventing the release of bradykinin which causes increased vascular permeability (A. Lehmann "Ecallantide (DX-88), a plasma kallikrein inhibitor for the treatment of hereditary angioedema and the prevention of blood loss in on-pump cardiothoracic surgery" *Expert Opin. Biol. The*r. 8, p1187-99).

The plasma kallikrein-kinin system is abnormally abundant in patients with advanced diabetic macular edema. It has been recently published that plasma kallikrein contributes to retinal vascular dysfunctions in diabetic rats (A. Clermont *et al.* "Plasma kallikrein mediates retinal vascular dysfunction and induces retinal thickening in diabetic rats" *Diabetes*, 2011, 60, p1590-98). Furthermore, administration of the plasma kallikrein inhibitor ASP-440 ameliorated both retinal vascular permeability and retinal blood flow abnormalities in diabetic rats. Therefore a plasma kallikrein inhibitor should have utility as a treatment to reduce retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Other complications of diabetes such as cerebral haemorrhage, nephropathy, cardiomyopathy and neuropathy, all of which have associations with plasma kallikrein may also be considered as targets for a plasma kallikrein inhibitor.

Synthetic and small molecule plasma kallikrein inhibitors have been described previously, for example by Garrett et al. ("Peptide aldehyde…." *J. Peptide Res.* 52, p62-71 (1998)), T. Griesbacher *et al.* ("Involvement of tissue kallikrein but not plasma kallikrein in the development of symptoms mediated by endogenous kinins in acute pancreatitis in rats" *British Journal of Pharmacology* 137, p692-700 (2002)), Evans ("Selective dipeptide inhibitors of kallikrein" WO03/076458), Szelke *et al.* ("Kininogenase inhibitors" WO92/04371), D. M. Evans *et al.* (*Immunolpharmacology*, 32, p115-116 (1996)), Szelke *et al.* ("Kininogen inhibitors" WO95/07921), Antonsson *et al.* ("New peptides derivatives" WO94/29335), J. Corte et al. ("Six membered heterocycles useful as serine protease inhibitors" WO2005/123680), J. Stürzbecher *et al.* (*Brazilian J. Med. Biol. Res* 27, p1929-34 (1994)), Kettner *et al.* (US 5,187,157), N. Teno *et al.* (*Chem. Pharm. Bull.* 41, p1079-1090 (1993)), W. B. Young *et al.* ("Small molecule inhibitors of plasma kallikrein" *Bioorg. Med. Chem. Letts.* 16, p2034-2036 (2006)), Okada *et al.* ("Development of potent and selective plasmin and plasma kallikrein inhibitors and studies on the structure-activity relationship" *Chem. Pharm. Bull.* 48, p1964-72 (2000)), Steinmetzer *et al.* ("Trypsin-like serine protease inhibitors and their preparation and use" WO08/049595), Zhang *et al.* ("Discovery of highly potent small molecule kallikrein inhibitors" *Medicinal Chemistry 2*, p545-553 (2006)), Sinha *et al.* ("Inhibitors of plasma kallikrein" WO08/016883), Shigenaga et al. ("Plasma Kallikrein Inhibitors" WO2011/118672), and Kolte et al. ("Biochemical characterization of a novel high-affinity and specific kallikrein inhibitor", British Journal of Pharmacology (2011), 162(7), 1639-1649). Also, Steinmetzer *et al.* ("Serine protease inhibitors" WO2012/004678) describes cyclized peptide analogs which are inhibitors of human plasmin and plasma kallikrein.

To date, no small molecule synthetic plasma kallikrein inhibitor has been approved for medical use. The molecules described in the known art suffer from limitations such as poor selectivity over related enzymes such as KLK1, thrombin and other serine proteases, and poor oral availability. The large protein plasma kallikrein inhibitors present risks of anaphylactic reactions, as has been reported for Ecallantide. Thus there remains a need for compounds that selectively inhibit plasma kallikrein, that do not induce anaphylaxis and that are orally available. Furthermore, the vast majority of molecules in the known art feature a highly polar and ionisable guanidine or amidine functionality. It is well known that such functionalities may be limiting to gut permeability and therefore to oral availability. For example, it has been reported by *Tamie J. Chilcote and Sukanto Sinha* ("ASP-634: An Oral Drug Candidate for Diabetic MacularEdema", ARVO 2012 May 6th – May 9th, 2012, Fort Lauderdale, Florida, Presentation 2240) that ASP-440, a benzamidine, suffers from poor oral availability. It is further reported that absorption may be improved by creating a prodrug such as ASP-634. However, it is well known that prodrugs can suffer from several drawbacks, for example, poor chemical stability and potential toxicity from the inert carrier or from unexpected metabolites. In another report, indole amides are claimed as compounds that might overcome problems associated with drugs possessing poor or inadequate ADME-tox and physicochemical properties although no inhibition against plasma kallikrein is presented or claimed (Griffioen et al, "Indole amide derivatives and related compounds for use in the treatment of neurodegenerative diseases", WO2010, 142801).

BioCryst Pharmaceuticals Inc. have reported the discovery of the orally available plasma kallikrein inhibitor BCX4161 ("BCX4161, An Oral Kallikrein Inhibitor: Safety and Pharmacokinetic Results Of a Phase 1 Study In Healthy Volunteers", Journal of Allergy and Clinical Immunology, Volume 133, Issue 2, Supplement, February 2014, page AB39 and "A Simple, Sensitive and Selective Fluorogenic Assay to Monitor Plasma Kallikrein Inhibitory Activity of BCX4161 in Activated Plasma", Journal of Allergy and Clinical Immunology, Volume 133, Issue 2, Supplement February 2014, page AB40). However, human doses are relatively large, currently being tested in proof of concept studies at doses of 400 mg three times daily.

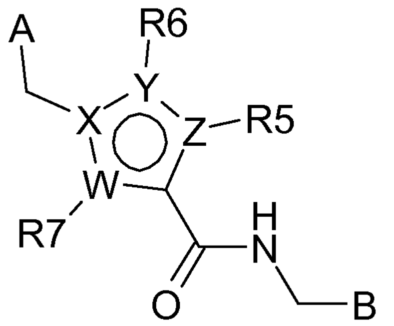
There are only few reports of plasma kallikrein inhibitors that do not feature guanidine or amidine functionalities. One example is Brandl *et al.* ("N-((6-amino-pyridin-3-yl)methyl)-heteroaryl-carboxamides as inhibitors of plasma kallikrein" WO2012/017020), which describes compounds that feature an amino-pyridine functionality. Oral efficacy in a rat model is demonstrated at relatively high doses of 30 mg/kg and 100 mg/kg but the pharmacokinetic profile is not reported. Thus it is not yet known whether such compounds will provide sufficient oral availability or efficacy for progression to the clinic. Other examples are Brandl *et al.* ("Aminopyridine derivatives as plasma kallikrein inhibitors" WO2013/111107) and Flohr *et al*. ("5-membered heteroarylcarboxamide derivatives as plasma kallikrein inhibitors" WO2013/111108). However, neither of these documents report any *in vivo* data and therefore it is not yet known whether such compounds will provide sufficient oral availability or efficacy for progression to the clinic.

Therefore there remains a need to develop new plasma kallikrein inhibitors that will have utility to treat a wide range of disorders, in particular to reduce retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema. Preferred compounds will possess a good pharmacokinetic profile and in particular will be suitable as drugs for oral delivery.

<u>Summary of the Invention</u>

The present invention relates to a series of heterocyclic derivatives that are inhibitors of plasma kallikrein. These compounds demonstrate good selectivity for plasma kallikrein and are potentially useful in the treatment of impaired visual acuity, diabetic retinopathy, macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery. The invention further relates to pharmaceutical compositions of the inhibitors, to the use of the compositions as therapeutic agents, and to methods of treatment using these compositions.

In a first aspect, the present invention provides compounds of formula I



Formula (I)

wherein

B is a fused 6,5- or 6,6-heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein when B is a fused 6,5-heteroaromatic bicyclic ring, it is linked to –CONH-(CH_2)- *via* its 6-membered ring component;

W, X, Y and Z are independently selected from C, N, O and S, such that the ring containing W, X, Y and Z is a five membered aromatic heterocycle;

wherein,

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9, CF_3, and R16; wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9, CF_3 and R16;

A is selected from aryl and heteroaryl;

R8 and R9 are independently selected from H and alkyl;

R16 is a carbon-containing 3-, 4-, 5- or 6-membered monocyclic ring system which may be aromatic, saturated or unsaturated non-aromatic and which may optionally contain 1, 2, 3 or 4 heteroatoms selected from N, O and S, wherein the ring system R16 is in turn optionally substituted with substituents selected from alkyl and oxo;

alkyl is a linear saturated hydrocarbon having up to 10 carbon atoms (C_1-C_{10}) or a branched saturated hydrocarbon of between 3 and 10 carbon atoms (C_3-C_{10}); alkyl may optionally be substituted with 1 or 2 substituents independently selected from (C_1-C_6)alkoxy, OH, CN, CF_3, COOR10, CONR10R11, fluoro and NR10R11;

alkoxy is a linear O-linked hydrocarbon of between 1 and 6 carbon atoms (C_1-C_6) or a branched O-linked hydrocarbon of between 3 and 6 carbon atoms (C_3-C_6); alkoxy may optionally be substituted with 1 or 2 substituents independently selected from OH, CN, CF_3, COOR10, CONR10R11, fluoro and NR10R11;

aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, methylenedioxy, ethylenedioxy, OH, halo, CN, morpholinyl, piperidinyl, heteroaryl, -$(CH_2)_{0-3}$-O-heteroaryl, $aryl^b$, -O-$aryl^b$, -$(CH_2)_{1-3}$-$aryl^b$, -$(CH_2)_{1-3}$-heteroaryl, -COOR10, -CONR10R11, -$(CH_2)_{1-3}$-NR14R15, CF_3 and -NR10R11;

$aryl^b$ is phenyl, biphenyl or naphthyl, which may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, -COOR10, -CONR10R11, CF_3 and NR10R11;

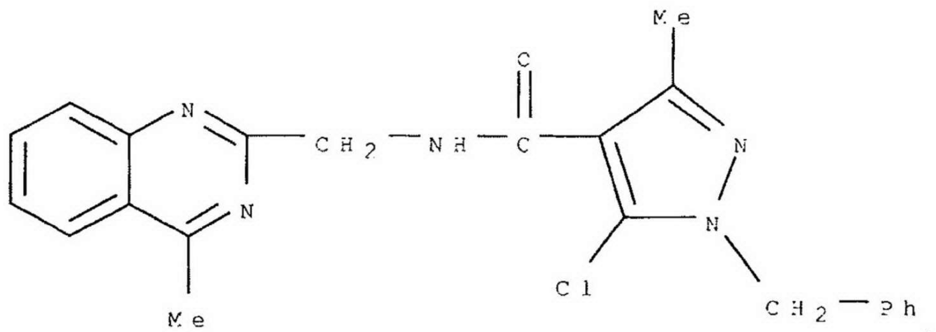
heteroaryl is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2 or 3 ring members independently selected from N, NR8, S and O; heteroaryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, OCF_3, halo, CN, aryl, morpholinyl, piperidinyl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b, -COOR10, -CONR10R11, CF_3 and -NR10R11;

heteroaryl^b is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2 or 3 ring members independently selected from N, NR8, S and O; wherein heteroaryl^b may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, aryl, -$(CH_2)_{1-3}$-aryl, -COOR10, -CONR10R11, CF_3 and NR10R11;

R10 and R11 are independently selected from H and alkyl or R10 and R11 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds and which may be optionally mono- or di-substituted with substituents selected from oxo, alkyl, alkoxy, OH, F and CF_3;

R14 and R15 are independently selected from alkyl, aryl^b and heteroaryl^b; or R14 and R15 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds, and optionally may be oxo substituted;

and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof;
wherein the compound of formula (I) is not:

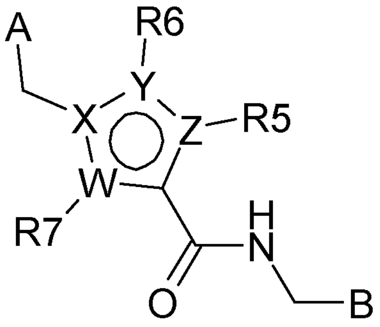


In another aspect the present invention provides a prodrug of a compound of formula (I) as herein defined, or a pharmaceutically acceptable salt thereof.

In yet another aspect the present invention provides an N-oxide of a compound of formula (I) as herein defined, or a prodrug or pharmaceutically acceptable salt thereof.

It will be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms.

In a second aspect, the invention comprises a subset of the compounds of formula I,



Formula (I)

wherein:

A, W, X, Y and Z are as defined in the first aspect above;

B is a fused 6,5- or 6,6-heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein when B is a fused 6,5-heteroaromatic bicyclic ring, it is linked to -CONH–CH_2- *via* its 6-membered ring component;

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, OH, aryl, heteroaryl and CF_3; with the proviso that at least one of R5, R6 and R7 must be present and when so present be independently selected from alkyl, halo, aryl, heteroaryl and CF_3;

heteroaryl is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2 or 3 ring members independently selected from N, NR8, S and O; heteroaryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, aryl, morpholinyl, piperidinyl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b, -COOR10, -CONR10R11, CF_3 and -NR10R11;

alkyl, alkoxy, aryl, heteroaryl^b, R8, R9, R10 and R11 are as defined in the first aspect above;

and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

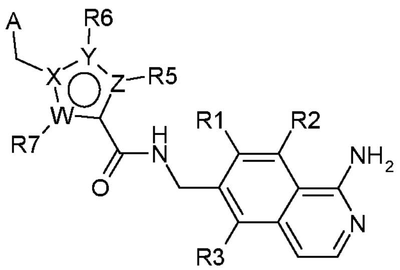
In another aspect, the invention comprises a compound according to the first aspect above, wherein B is a fused 6,6-heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the second aspect above, wherein B is a fused 6,6-heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein alkyl, alkoxy, R8 and R9 are as defined in in the first aspect above.

In another aspect, the invention comprises a compound according to the first aspect above, wherein B is selected from optionally mono-, di or tri-substituted isoquinolinyl wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the second aspect above, wherein B is selected from optionally mono-, di or tri-substituted isoquinolinyl wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

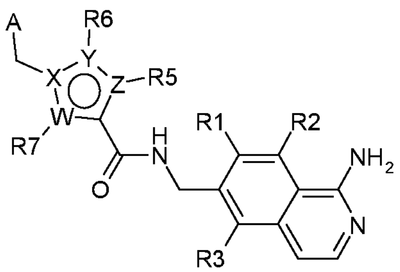
In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (II),



Formula (II)

wherein R1, R2 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl; and wherein A,W, X, Y, Z, R5, R6, R7, alkyl, alkoxy, R8 and R9 are as defined in the first or second aspect above; and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (II),



Formula (II)

wherein

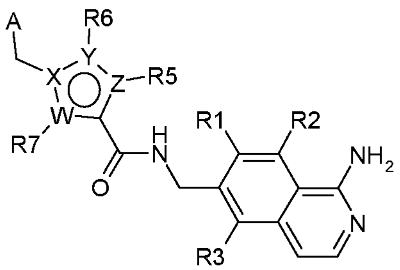
W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered heterocycle selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole;

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9 and CF_3; wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, OH, aryl, heteroaryl, -NR8R9 CN, COOR8, CONR8R9, -NR8COR9, R16 and CF_3;

R1, R2 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl;

and wherein A, R8, R9, alkyl, alkoxy, aryl and heteroaryl are as defined in the first aspect above; and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (II),



Formula (II)

wherein

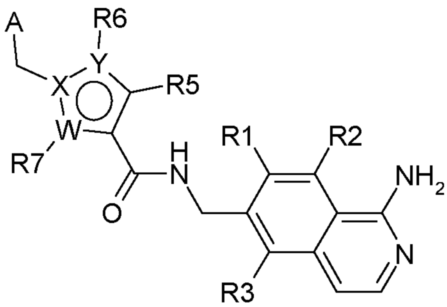
W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered heterocycle selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole;

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, aryl, heteroaryl and CF_3; wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, aryl, heteroaryl, and CF_3;

R1, R2 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl;

and wherein A, R8, R9, alkyl, alkoxy, aryl and heteroaryl are as defined in the first aspect above; and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (IIa),

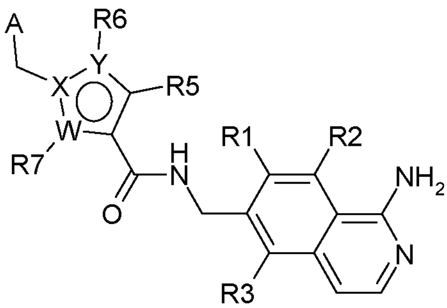


Formula (IIa)

wherein R1, R2 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl; and wherein A, W, X, Y, R5, R6, R7, alkyl, alkoxy, R8 and R9 are as defined in the first or second aspect above;

and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (IIa),



Formula (IIa)

wherein R1, R2 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl;

W, X and Y are independently selected from C, N, O and S, such that the ring containing W, X and Y is a five-membered membered aromatic heterocycle;

and wherein A, R5, R6, R7, alkyl, alkoxy, R8 and R9 are as defined in the first or second aspect above;

and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

In another aspect, the invention comprises a compound according to the first aspect above, wherein B is a fused 6,5- heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the second aspect above, wherein B is a fused 6,5- heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein B is linked to -CONH–CH_2- *via* its 6-membered ring component; and wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the first or second aspect above, wherein B is a fused 6,5- heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, F, Cl and -CN; and wherein alkyl is as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the first aspect above, wherein B is selected from optionally substituted indole, optionally substituted indazole and optionally substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the second aspect above, wherein B is selected from optionally substituted indole, optionally substituted indazole and optionally substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein said indole, indazole or 1H-pyrrolo[2,3-b]pyridine ring is linked to -CONH–CH_2- *via* its 6-membered ring component; and wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

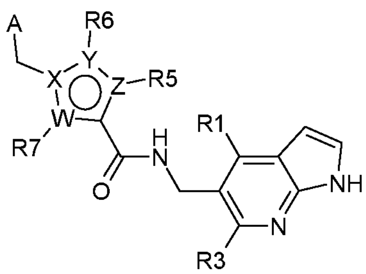
In another aspect, the invention comprises a compound according to the first or second aspect above, wherein B is selected from optionally substituted indole, optionally substituted indazole and optionally substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, F, Cl and -CN; and wherein alkyl is as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the first aspect above, wherein B is selected from optionally mono-, di or tri-substituted 1H-pyrrolo[2,3-b]pyridine, wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the second aspect above, wherein B is selected from optionally mono-, di or tri-substituted 1H-pyrrolo[2,3-b]pyridine, wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein said 1H-pyrrolo[2,3-b]pyridine ring is linked to -CONH–CH_2- *via* its 6-membered ring component; and wherein alkyl, alkoxy, R8 and R9 are as defined in the first aspect above.

In another aspect, the invention comprises a compound according to the first or second aspect above, wherein B is selected from optionally mono-, di or tri-substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, F, Cl and -CN; and wherein alkyl is as defined in the first aspect above.

In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (III),

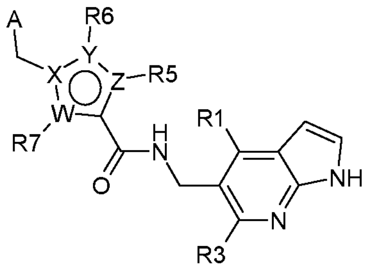


Formula (III)

wherein R1 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl; and wherein A, W, X, Y, Z, R5, R6, R7, alkyl, alkoxy, R8 and R9 are as defined in the first aspect above;

and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (III),



Formula (III)

wherein

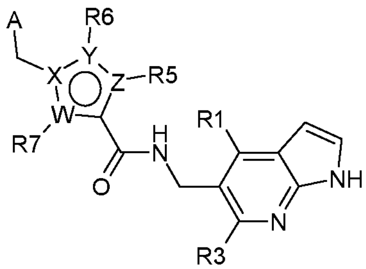
W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered heterocycle selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole;

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, aryl, heteroaryl and CF_3; wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, aryl, heteroaryl, and CF_3;

R1 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl;

and wherein A, R8, R9, alkyl, alkoxy, aryl and heteroaryl are as defined in the first aspect above; and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

In another aspect, the invention comprises a subset of the compounds of formula (I), as defined by formula (III),



Formula (III)

wherein

W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered heterocycle selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole;

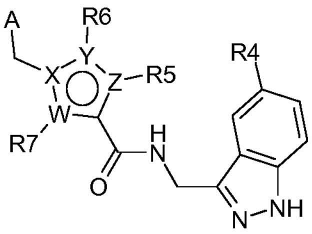
R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, aryl, heteroaryl and CF_3; wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, aryl, heteroaryl, and CF_3;

R1 and R3 are independently selected from H and alkyl;

and wherein A, alkyl, aryl, heteroaryl are as defined in the first aspect above;

and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

Also described herein are compounds defined by formula (IV),

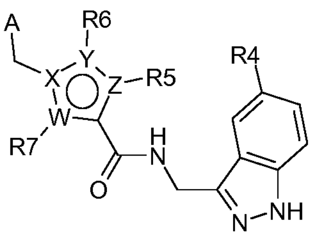


Formula (IV)

wherein R4 is independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl; and wherein A, W, X, Y, Z, R5, R6, R7, alkyl, alkoxy, R8 and R9 are as defined in the first aspect above;

and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

Also described herein is a subset of the compounds defined by formula (IV),



Formula (IV)

wherein

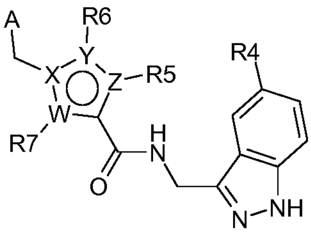
W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered heterocycle selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole;

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, aryl, heteroaryl, -NR8R9, -CN, cyclopropyl and CF_3 and at least one of R5, R6 and R7 is not absent and is independently selected from alkyl, halo, aryl, heteroaryl, -NR8R9, -CN, cyclopropyl and CF_3;

R4 is selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl;

and wherein A, R8, R9, alkyl, alkoxy are as defined in the first aspect above;
and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

Also described herein is a subset of the compounds defined by formula (IV),



Formula (IV)

wherein

W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered heterocycle selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole;

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, aryl, heteroaryl and CF_3 and at least one of R5, R6 and R7 is not absent and is independently selected from alkyl, halo, aryl, heteroaryl, and CF_3;

R4 is selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl;

and wherein A, R8, R9, alkyl, alkoxy are as defined in the first aspect above;
and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

The present invention also comprises the following limitations, which may be applied to any of the aspects of the invention described above:

B is a fused 6,5 or 6,6-heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and

NR8R9; wherein R8 and R9 are independently selected from H and alkyl; wherein when B is a fused 6,5-heteroaromatic bicyclic ring, it is linked to $-(CH_2)_n-$ *via* its 6-membered ring component.

- B is a fused 6,5 or 6,6-heteroaromatic bicyclic ring, containing one, two or three N atoms, and no other heteroatoms, which is optionally mono- substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- B is a fused 6,6-heteroaromatic bicyclic ring containing one N atom, and no other heteroatoms, which is optionally mono- substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- B is a fused 6,6-heteroaromatic bicyclic ring, containing one N atom and, optionally, one or two additional heteroatoms independently selected from N and O, which is optionally mono- substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- B is a fused 6,6-heteroaromatic bicyclic ring, containing one N atom, and no other heteroatoms, which is optionally mono- substituted with a substituent selected from alkyl, alkoxy, OH, and NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- B is a fused 6,6-heteroaromatic bicyclic ring, containing one N atom, and no other heteroatoms, which is optionally mono- substituted with NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- B is a fused 6,5- heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, F, Cl and –CN.
- B is a fused 6,5- heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, F, Cl and –CN; wherein B is linked to $-CONH-CH_2-$ *via* its 6-membered ring component.
- B is selected from optionally substituted indole, optionally substituted indazole and optionally substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, F, Cl and –CN.
- B is selected from optionally substituted indole, optionally substituted indazole and optionally substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, F, Cl and –CN; and wherein said indole, indazole or 1H-pyrrolo[2,3-b]pyridine ring is linked to $-CONH-CH_2-$ *via* its 6-membered ring component.

- B is optionally mono-, di or tri-substituted isoquinolinyl, wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- B is optionally mono-substituted isoquinolinyl; wherein said optional substituent is selected from alkyl, alkoxy, OH, and NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- B is optionally substituted 1H-pyrrolo[2,3-b]pyridine wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9 and wherein R8 and R9 are independently selected from H and alkyl.
- B is selected from optionally mono-, di or tri-substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, F, Cl and –CN; and wherein said 1H-pyrrolo[2,3-b]pyridine ring is linked to -CONH–CH_2- *via* its 6-membered ring component.
- Preferably, B is optionally mono-substituted isoquinolinyl, wherein said optional substituent is NR8R9; wherein R8 and R9 are independently selected from H and alkyl.
- Preferably, B is optionally di- or tri-substituted isoquinolinyl, wherein one of said optional substituent is NR8R9 and the other said optional substituents are alkyl; wherein R8 and R9 are independently selected from H and alkyl.
- More preferably, B is optionally di- or tri-substituted isoquinolinyl, wherein one of said optional substituent is NR8R9 and the other said optional substituents are alkyl; wherein R8 and R9 are H.
- More preferably, B is optionally mono-substituted isoquinolinyl, wherein said optional substituent is NR8R9; and wherein R8 and R9 are H.
- More preferably, B is optionally di- or tri-substituted isoquinolinyl, wherein one of said optional substituent is NR8R9 and the other one or two said optional substituents are alkyl; wherein R8 and R9 are H.

- R1, R2, R3 and R4 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl.
- Preferably, R1, R2, R3 and R4 are independently selected from H, alkyl, Cl and F.
- Preferably, R1, R2, R3 and R4 are independently selected from H, alkyl and Cl.
- More preferably, R1, R2 and R3 are independently selected from H and alkyl.
- More preferably, R1, R2 and R3 are independently selected from H and methyl.
- More preferably R4 is selected from H and Cl.

- W, X, Y and Z are independently selected from C, N, O and S, such that the ring containing W, X, Y and Z is a five-membered aromatic heterocycle.

- W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered aromatic heterocycle.
- W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole.
- Preferably, X is N.
- W is C, X and Y are N and Z is C or N.
- X and Y are N and W and Z are C.
- X, Y and Z are N and W is C.
- X and Z are N and W and Y are C.
- W is N and X, Y and Z are C.
- X is N and W, Y and Z are C.

- R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9, CF_3, and -R16, wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9, R16 and CF_3.
- R5, R6 and R7 are independently absent, or are independently selected from H, alkyl, halo, OH, aryl, heteroaryl and CF_3, wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, OH, aryl, heteroaryl and CF_3.
- R5 is absent or is selected from H, alkyl, -NR8R9, -CN, R16, CF_3 and aryl.
- R5 is absent or is selected from H, alkyl, -NR8R9, -CN, cyclopropyl, CF_3 and aryl.
- R5 is absent or is selected from H, methyl, $-NH_2$, -CN, cyclopropyl, CF_3 and aryl.
- R5 is absent or is selected from H, methyl, $-NH_2$, cyclopropyl, CF_3 and aryl.
- R5 is absent or is selected from H, alkyl, CF_3 and aryl.
- R5 is absent or is selected from H, methyl, CF_3 and phenyl.
- R6 and R7 are independently absent, or are independently selected from H, alkyl, aryl and CF_3.
- R6 and R7 are independently absent, or are independently selected from H, methyl, ethyl, n-propyl, phenyl and CF_3.
- Preferably, R5 is H and R6 and R7 are methyl.

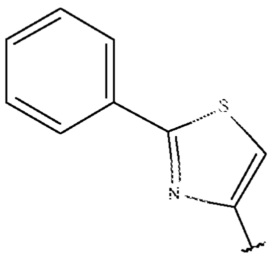
- R14 and R15 are independently selected from alkyl, aryl[b] and heteroaryl[b]; or R14 and R15 together with the nitrogen atom to which they are attached form a carbon containing 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds, and optionally may be oxo substituted.
- R14 and R15 are independently selected from alkyl and heteroaryl[b]; or R14 and R15 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered carbon containing heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds, and optionally may be oxo substituted.
- R14 and R15 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered carbon containing heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds, and optionally may be oxo substituted.

- R16 is a carbon-containing 3-, 4-, 5- or 6-membered monocyclic ring system which may be aromatic, saturated or unsaturated non-aromatic and which may optionally contain 1, 2, 3 or 4 heteroatoms selected from N, O and S, wherein the ring system R16 is in turn optionally substituted with substituents selected from alkyl and oxo.
- R16 is a carbon-containing 3-, 4-, 5- or 6-membered monocyclic ring system which may be aromatic, saturated or unsaturated non-aromatic and which may optionally contain 1 or 2 heteroatoms selected from N, O and S, wherein the ring system R16 is in turn optionally substituted with substituents selected from methyl, ethyl and oxo.
- R16 is selected from oxazole, thiophene, cyclopropyl, cyclobutyl, pyrrolidinyl and morpholinyl, each optionally substituted with substituents selected from methyl and oxo.

- X and Y are N, W and Z are C, and R5 and R7 are H.
- X, Y and Z are N, W is C, and R7 is H.
- W is N, X, Y and Z are C, R7 is ethyl, R6 is methyl and R5 is H.
- X is N, W, Y and Z are C, R5 is H and R6 and R7 are methyl.
- X and Y are N, W and Z are C, and R5 is selected from alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9, R16 and CF_3, and R7 is H.
- X and Y are N, W and Z are C, and R5 is selected from alkyl, -NR8R9, -CN, cyclopropyl, CF_3 and aryl, and R7 is H.
- X and Y are N, W and Z are C, and R5 is selected from methyl, $-NH_2$, -CN, cyclopropyl, CF_3 and R7 is H.
- X and Y are N, W and Z are C, and R5 is R16 and R16 is as previously defined in the first aspect above.

- X and Y are N, W and Z are C, and R5 selected from alkyl, halo, OH, aryl, heteroaryl and CF_3, and R7 is H.

- A is selected from aryl and heteroaryl, each optionally substituted as specified in the first aspect above.
- A is heteroaryl optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, aryl, morpholinyl, piperidinyl, -COOR10, -CONR10R11, CF_3 and -NR10R11; wherein R10 and R11 are selected from H and alkyl or R10 and R11 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds and which may be optionally mono- or di-substituted with substituents selected from oxo, alkyl, alkoxy, OH, F and CF_3.
- A is heteroaryl optionally substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, aryl, morpholinyl and piperidinyl.
- Preferably, A is heteroaryl substituted by phenyl.
- Preferably, A is heteroaryl substituted by NR10R11; wherein R10 and R11 are selected from H and alkyl or R10 and R11 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds and which may be optionally mono- or di-substituted with substituents selected from oxo, alkyl, alkoxy, OH, F and CF_3.
- Preferably, A is thiazolyl substituted by phenyl.
- Preferably, A is phenyl substituted by heteroaryl, $-(CH_2)_{1-3}$-heteroaryl and $-(CH_2)_{1-3}$-NR14R15.
- Preferably, A is selected from:



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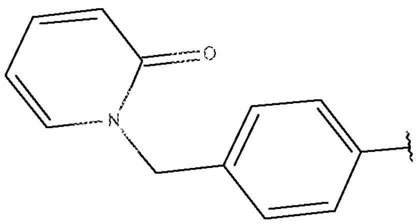

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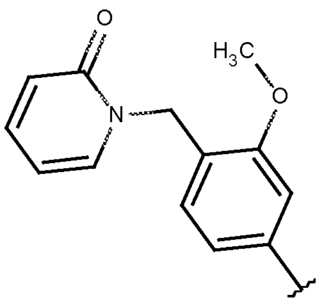

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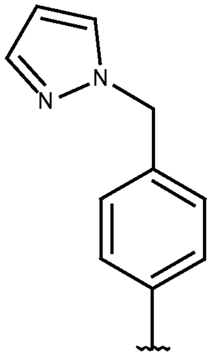
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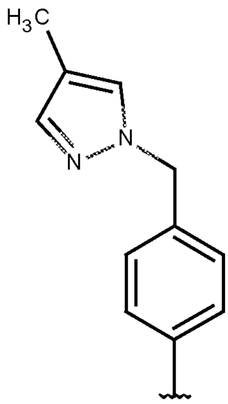
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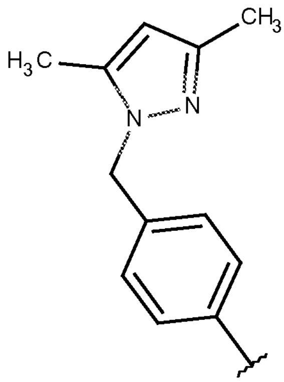
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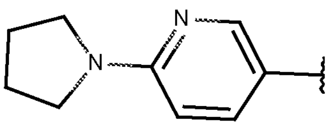
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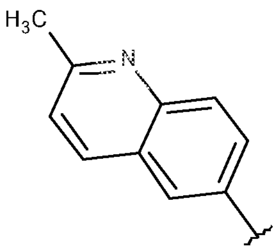
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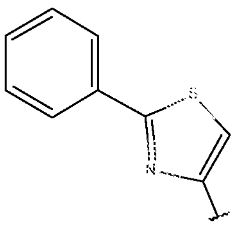
- Preferably, A is selected from: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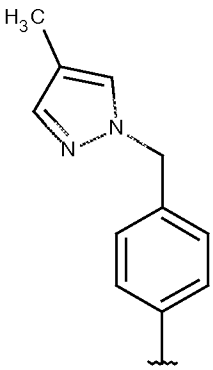
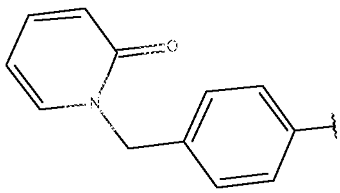

, and

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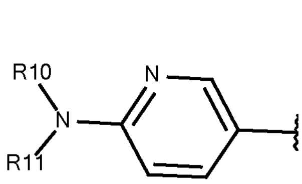
- Preferably, A is selected from: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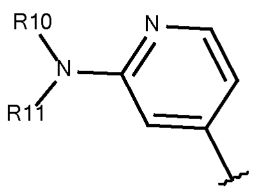
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and R10 and R11 are as defined in the first aspect above.

The present invention also encompasses, but is not limited to, the compounds listed in the aspects below.

In an aspect, the invention comprises a compound selected from:

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(Pyridin-2-yloxy)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Isopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclobutyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Hydroxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

4-Methyl-2-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-thiazole-5-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-(3,5-Dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

5-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methylpyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-phenyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Amino-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Difluoromethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-thiophen-3-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

5-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Pyrrolidin-1-yl-pyridin-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Ethoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-pyridin-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-(3,3-Difluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-3-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((S)-3-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((S)-3-Fluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-3-Fluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((S)-2-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-2-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Pyrrolidin-1-yl-pyrazin-2-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[2-((S)-3-Methyl-pyrrolidin-1-yl)-pyridin-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-(3-Hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-3-Hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Propoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Fluoro-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Ethoxy-5-fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(4-Pyrazol-1-ylmethyl-benzyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Cyano-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Carbamoyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Pyrazol-1-ylmethyl-thiazol-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[2-(4-Methyl-pyrazol-1-ylmethyl)-thiazol-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-{6-[(2-methoxy-ethyl)-methyl-amino]-pyridin-3-ylmethyl}-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(4-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(4-[1,2,3]triazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(6-phenoxy-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Chloro-6-ethoxy-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(6-diethylamino-5-fluoro-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Chloro-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Amino-1-(6-ethoxy-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Amino-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

and pharmaceutically acceptable salts and solvates thereof.

In an aspect, the invention comprises a compound selected from:

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(Pyridin-2-yloxy)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methylpyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

and pharmaceutically acceptable salts and solvates thereof.

In an aspect, the invention comprises a compound selected from:

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-7-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-aminoisoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-2-carboxylic acid (1-aminoisoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Phenyl-thiazol-4-ylmethyl)-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Phenyl-thiazol-4-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1-aminoisoquinolin-6-ylmethyl)-amide;

and pharmaceutically acceptable salts and solvates thereof.

In an aspect, the invention comprises a compound selected from:

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indol-5-ylmethyl)-amide;

3-Amino-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-indazol-4-ylmethyl)-amide;

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indazol-4-ylmethyl)-amide;

and pharmaceutically acceptable salts and solvates thereof.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Therapeutic Applications

As previously mentioned, the compounds of the present invention are potent and selective inhibitors of plasma kallikrein. They are therefore useful in the treatment of disease conditions for which over-activity of plasma kallikrein is a causative factor.

Accordingly, the present invention provides a compound of formula (I) for use in medicine.

The present invention also provides for the use of a compound of formula (I) in the manufacture of a medicament for the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated.

The present invention also provides a compound of formula (I) for use in the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated.

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The present invention also provides a method of treatment of a disease or condition in which plasma kallikrein activity is implicated comprising administration to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

In one aspect, the disease or condition in which plasma kallikrein activity is implicated is selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.

In a preferred aspect, the disease or condition in which plasma kallikrein activity is implicated is retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Combination Therapy

The compounds of the present invention may be administered in combination with other therapeutic agents. Suitable combination therapies include a compound of formula (I) combined with one or more agents selected from agents that inhibit platelet-derived growth factor (PDGF), endothelial growth factor (VEGF), integrin alpha5beta1, steroids, other agents that inhibit plasma kallikrein and other inhibitors of inflammation. Specific examples of therapeutic agents that may be combined with the compounds of the present invention include those disclosed in EP2281885A and by S. Patel in *Retina*, 2009 Jun;29(6 Suppl):S45-8.

When combination therapy is employed, the compounds of the present invention and said combination agents may exist in the same or different pharmaceutical compositions, and may be administered separately, sequentially or simultaneously.

In another aspect, the compounds of the present invention may be administered in combination with laser treatment of the retina. The combination of laser therapy with intravitreal injection of an inhibitor of VEGF for the treatment of diabetic macular edema is known (Elman M, Aiello L, Beck R, et al. “Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema” .Ophthalmology. 27 April 2010).

Definitions

The term "alkyl" includes saturated hydrocarbon residues including:

- linear groups up to 10 carbon atoms (C_1-C_{10}), or of up to 6 carbon atoms (C_1-C_6), or of up to 4 carbon atoms (C_1-C_4). Examples of such alkyl groups include, but are not limited, to C_1 - methyl, C_2 - ethyl, C_3 - propyl and C_4- n-butyl.
- branched groups of between 3 and 10 carbon atoms (C_3-C_{10}), or of up to 7 carbon atoms (C_3-C_7), or of up to 4 carbon atoms (C_3-C_4). Examples of such alkyl groups include, but are not limited to, C_3 - iso-propyl, C_4 - sec-butyl, C_4 - iso-butyl, C_4 - tert-butyl and C_5 - neo-pentyl.

each optionally substituted as stated above.

Cycloalkyl is a monocyclic saturated hydrocarbon of between 3 and 7 carbon atoms; wherein cycloalkyl may be optionally substituted with a substituent selected from alkyl, alkoxy and NR10R11; wherein R10 and R11 are independently selected from H and alkyl or R10 and R11 together with the nitrogen to which they are attached form a 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds and which may be optionally mono- or di-substituted with substituents selected from oxo, alkyl, alkoxy, OH, F and CF_3. Cycloalkyl groups may contain from 3 to 7 carbon atoms, or from 3 to 6 carbon atoms, or from 3 to 5 carbon atoms, or from 3 to 4 carbon atoms. Examples of suitable monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "alkoxy" includes O-linked hydrocarbon residues including:

- linear groups of between 1 and 6 carbon atoms (C_1-C_6), or of between 1 and 4 carbon atoms (C_1-C_4). Examples of such alkoxy groups include, but are not limited to, C_1 - methoxy, C_2 - ethoxy, C_3 - n-propoxy and C_4 - n-butoxy.
- branched groups of between 3 and 6 carbon atoms (C_3-C_6) or of between 3 and 4 carbon atoms (C_3-C_4). Examples of such alkoxy groups include, but are not limited to, C_3 - iso-propoxy, and C_4 - sec-butoxy and tert-butoxy.

each optionally substituted as stated above.

Unless otherwise stated, halo is selected from Cl, F, Br and I.

Aryl is as defined above. Typically, aryl will be optionally substituted with 1, 2 or 3 substituents. Optional substituents are selected from those stated above. Examples of suitable aryl groups include phenyl and naphthyl (each optionally substituted as stated above). Preferably aryl is selected from phenyl, substituted phenyl (substituted as stated above) and naphthyl.

Heteroaryl is as defined above. Examples of suitable heteroaryl groups include thienyl, furanyl, pyrrolyl, pyrazolyl, imidazoyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzimidazolyl, benzotriazolyl, quinolinyl and isoquinolinyl (optionally substituted as stated above). Preferably heteroaryl is selected from pyridyl, benzothiazole, indole, N-methylindole, thiazole, substituted thiazole, thiophenyl, furyl, pyrazine, pyrazole and substituted pyrazole; wherein substituents are as stated above.

The term "N-linked", such as in "N-linked heterocycloalkyl", means that the heterocycloalkyl group is joined to the remainder of the molecule *via* a ring nitrogen atom.

The term "O-linked", such as in "O-linked hydrocarbon residue", means that the hydrocarbon residue is joined to the remainder of the molecule *via* an oxygen atom.

In groups such as –COOR* and -$(CH_2)_{1-3}$-aryl, "-" denotes the point of attachment of the substituent group to the remainder of the molecule.

"Pharmaceutically acceptable salt" means a physiologically or toxicologically tolerable salt and includes, when appropriate, pharmaceutically acceptable base addition salts and pharmaceutically acceptable acid addition salts. For example (i) where a compound of the invention contains one or more acidic groups, for example carboxy groups, pharmaceutically acceptable base addition salts that can be formed include sodium, potassium, calcium, magnesium and ammonium salts, or salts with organic amines, such as, diethylamine, *N*-methyl-glucamine, diethanolamine or amino acids (e.g. lysine) and the like; (ii) where a compound of the invention contains a basic group, such as an amino group, pharmaceutically acceptable acid addition salts that can be formed include hydrochlorides, hydrobromides, sulfates, phosphates, acetates, citrates, lactates, tartrates, mesylates, succinates, oxalates, phosphates, esylates, tosylates, benzenesulfonates, naphthalenedisulphonates, maleates, adipates, fumarates, hippurates, camphorates, xinafoates, p-acetamidobenzoates, dihydroxybenzoates, hydroxynaphthoates, succinates, ascorbates, oleates, bisulfates and the like.

Hemisalts of acids and bases can also be formed, for example, hemisulfate and hemicalcium salts.

For a review of suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

“Prodrug” refers to a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of the invention. Suitable groups for forming prodrugs are described in ‘The Practice of Medicinal Chemistry, 2nd Ed. pp561-585 (2003) and in F. J. Leinweber, *Drug Metab. Res.,* 1987, **18**, 379.

The compounds of the invention can exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when the solvent is water.

Where compounds of the invention exist in one or more geometrical, optical, enantiomeric, diastereomeric and tautomeric forms, including but not limited to *cis*- and *trans*-forms, *E*- and *Z*-forms, *R*-, *S*- and *meso*-forms, keto-, and enol-forms. Unless otherwise stated a reference to a particular compound includes all such isomeric forms, including racemic and other mixtures thereof. Where appropriate such isomers can be separated from their mixtures by the application or adaptation of known methods (e.g. chromatographic techniques and recrystallisation techniques). Where appropriate such isomers can be prepared by the application or adaptation of known methods (e.g. asymmetric synthesis).

In the context of the present invention, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

General Methods

The compounds of formula (I) should be assessed for their biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, *etc.*, in order to select the most appropriate dosage form and route of administration for treatment of the proposed indication. They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention which may impart either a functional (i.e., drug release rate controlling) and/or a non-functional (i.e., processing aid or diluent) characteristic to the formulations. 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.

Compounds of the invention intended for pharmaceutical use may be administered as a solid or liquid, such as a tablet, capsule or solution. 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).

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier, diluent or excipient.

For the treatment of conditions such as retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema, the compounds of the invention may be administered in a form suitable for injection into the ocular region of a patient, in particular, in a form suitable for intra-vitreal injection. It is envisaged that formulations suitable for such use will take the form of sterile solutions of a compound of the invention in a suitable aqueous vehicle. The compositions may be administered to the patient under the supervision of the attending physician.

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

Parenteral formulations are typically aqueous or oily solutions. Where the solution is aqueous, excipients such as sugars (including but not restricted to glucose, manitol, sorbitol, etc.), salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

Parenteral formulations may include implants derived from degradable polymers such as polyesters (i.e., polylactic acid, polylactide, polylactide-co-glycolide, polycapro-lactone, polyhydroxybutyrate), polyorthoesters and polyanhydrides. These formulations may be administered via surgical incision into the subcutaneous tissue, muscular tissue or directly into specific organs.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of co-solvents and/or solubility-enhancing agents such as surfactants, micelle structures and cyclodextrins.

In one embodiment, the compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid plugs, solid microparticulates, semi-solid and liquid (including multiple phases or dispersed systems) such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, emulsions or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Formulations suitable for oral administration may also be designed to deliver the compounds of the invention in an immediate release manner or in a rate-sustaining manner, wherein the release profile can be delayed, pulsed, controlled, sustained, or delayed and sustained or modified in such a manner which optimises the therapeutic efficacy of the said compounds. Means to deliver compounds in a rate-sustaining manner are known in the art and include slow release polymers that can be formulated with the said compounds to control their release.

Examples of rate-sustaining polymers include degradable and non-degradable polymers that can be used to release the said compounds by diffusion or a combination of diffusion and polymer erosion. Examples of rate-sustaining polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, xanthum gum, polymethacrylates, polyethylene oxide and polyethylene glycol.

Liquid (including multiple phases and dispersed systems) formulations include emulsions, solutions, syrups and elixirs. Such formulations may be presented as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) 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.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, Expert Opinion in Therapeutic Patents, 2001, **11 (6)**, 981-986.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.01 mg and 1000 mg, or between 0.1 mg and 250 mg, or between 1 mg and 50 mg depending, of course, on the mode of administration.

The total 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 60kg 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.

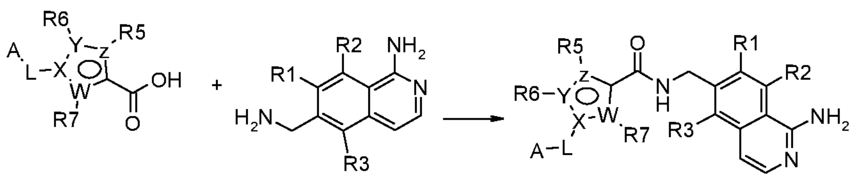
Synthetic Methods

The compounds of the present invention can be prepared according to the procedures of the following schemes and examples, using appropriate materials, and are further exemplified by the specific examples provided herein below. Moreover, by utilising the procedures described herein, one of ordinary skill in the art can readily prepare additional compounds that fall within the scope of the present invention claimed herein. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

The compounds of the invention may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above.

It may be necessary to protect reactive functional groups (e.g. hydroxy, amino, thio or carboxy) in intermediates used in the preparation of compounds of the invention to avoid their unwanted participation in a reaction leading to the formation of the compounds. Conventional protecting groups, for example those described by T. W. Greene and P. G. M. Wuts in "Protective groups in organic chemistry" John Wiley and Sons, 4th Edition, 2006, may be used. For example, a common amino protecting group suitable for use herein is tert-butoxy carbonyl (Boc), which is readily removed by treatment with an acid such as trifluoroacetic acid or hydrogen chloride in an organic solvent such as dichloromethane. Alternatively the amino protecting group may be a benzyloxycarbonyl (Z) group which can be removed by hydrogenation with a palladium catalyst under a hydrogen atmosphere or 9-fluorenylmethyloxycarbonyl (Fmoc) group which can be removed by solutions of secondary organic amines such as diethylamine or piperidine in an organic solvents. Carboxyl groups are typically protected as esters such as methyl, ethyl, benzyl or tert-butyl which can all be removed by hydrolysis in the presence of bases such as lithium or sodium hydroxide. Benzyl protecting groups can also be removed by hydrogenation with a palladium catalyst under a hydrogen atmosphere whilst tert-butyl groups can also be removed by trifluoroacetic acid. Alternatively a trichloroethyl ester protecting group is removed with zinc in acetic acid. A common hydroxy protecting group suitable for use herein is a methyl ether, deprotection conditions comprise refluxing in 48% aqueous HBr for 1-24 hours, or by stirring with borane tribromide in dichloromethane for 1-24 hours. Alternatively where a hydroxy group is protected as a benzyl ether, deprotection conditions comprise hydrogenation with a palladium catalyst under a hydrogen atmosphere.

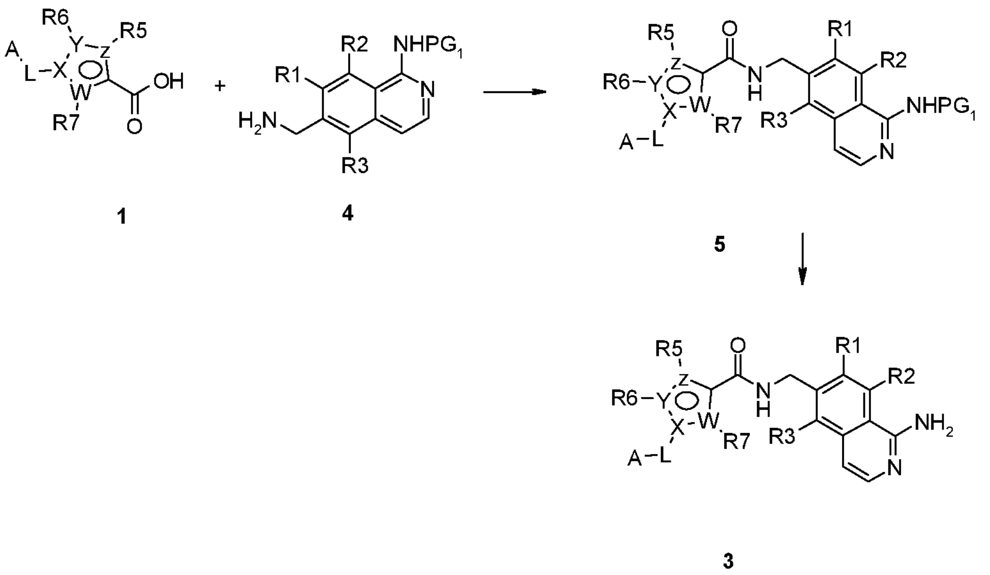
The compounds according to general formula **I** can be prepared using conventional synthetic methods for example, but not limited to, the route outlined in Scheme 1. The amine **2** is coupled to an acid **1** to give the compound **3** This coupling is typically carried out using standard coupling condition such as hydroxybenzotriazole and carbodiimide such as water soluble carbodiimide in the presence of an organic base. Other standard coupling methods include the reaction of acids with amines in the presence of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate or benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphoium hexaffluorophosphate or bromo-trispyrolidino-phosphoium hexafluorophosphate in the presence of organic bases such as triethylamine, diisopropylethylamine or N-methylmorpholine. Alternatively the amide formation can take place via an acid chloride in the presence of an organic base. Such acid chlorides can be formed by methods well known in the literature, for example reaction of the acid with oxalyl chloride or thionyl chloride.



1 **2** **3**

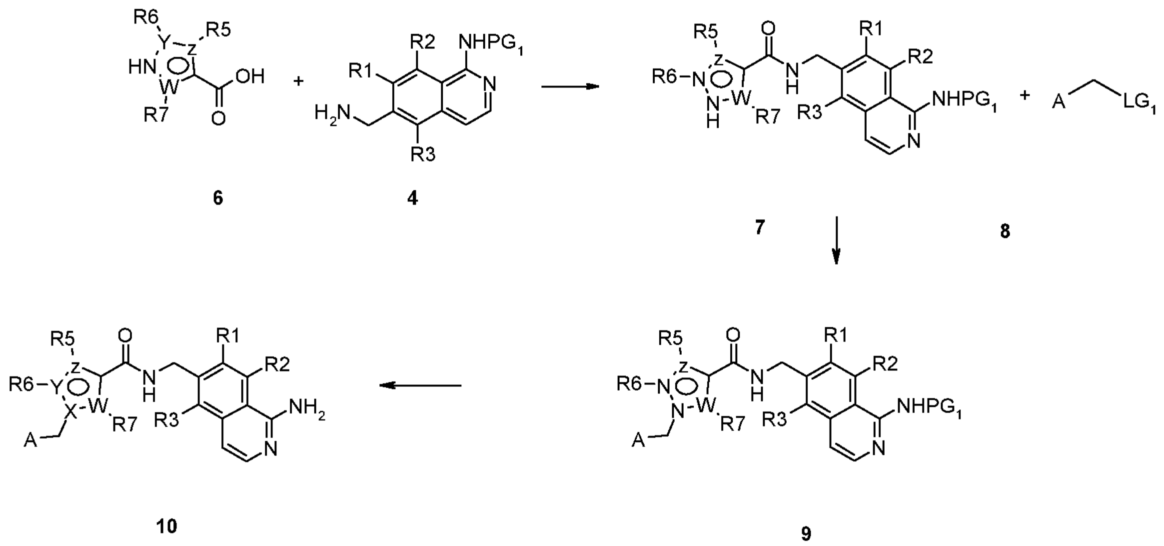
Scheme 1

Alternatively compounds according to general formula **I** can be prepared using the route exemplified in Scheme 2. The acid **1** can be coupled to an amine **4** using suitable coupling methods as previously described to give compound **5** in which the second amino group is amino-protected with a standard protecting group such as tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) or 9-fluorenylmethyloxycarbonyl (Fmoc). In a typical second step the protecting group is removed to give compound **3** using standard methods as previously described.



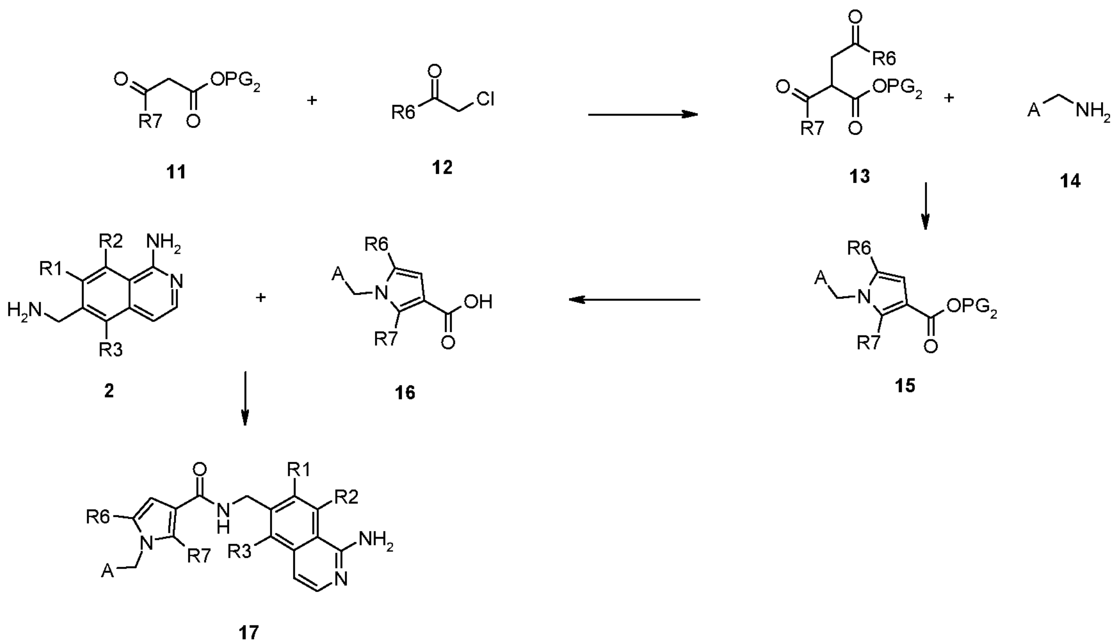
Scheme 2

Alternatively compounds according to general formula **I** can be prepared using the route outlined in Scheme 3. The acid **6** can be coupled to an amine **4** using suitable coupling methods as previously described to give compound **7** in which the second amino group is amino-protected with a standard protecting group such as tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) or 9-fluorenylmethyloxycarbonyl (Fmoc). In a typical second step the nitrogen of the heterocyclic ring is alkylated with compound **8** to give compound **9.** The alkylation can be carried out in the presence of a base such as potassium carbonate, cesium carbonate, sodium carbonate or sodium hydride in which case the leaving group is a halide or sulphonate. Alternatively the alkylation may be carried out using an alcohol under Mitsunobu conditions in the presence of triphenylphosphine. In a third step the protecting group is removed to give compound **10** using standard methods as previously described.



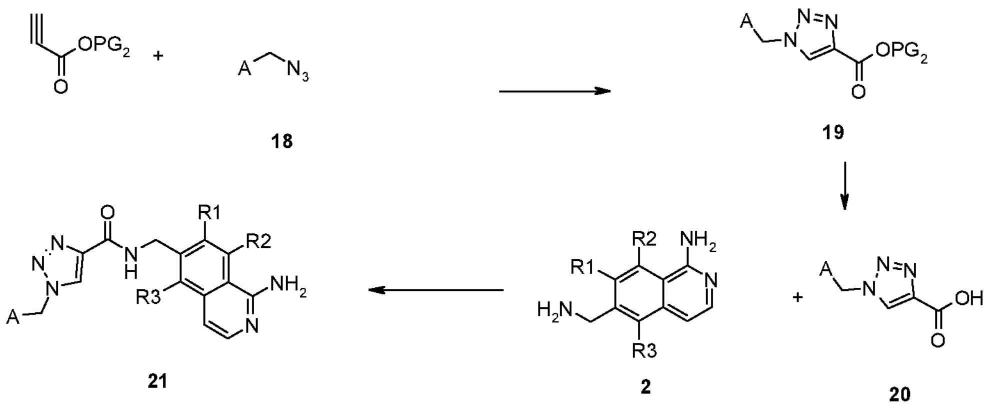
Scheme 3

Alternatively compounds according to general formula **I** can be prepared using the route outlined in Scheme 4. The pyrrole **15** can be formed in two steps the first of which involves reaction of the sodium salt of an alkyl ketoacetate **11** with a chloroketone **12** in the presence of a base such as potassium carbonate to give compound **13** which in a typical second step is reacted with the amine **14** in the presence of an acid such as but not limited to sulphonic acid derivatives e.g. p-toluenesulphonic acid to yield compound **15** which in a typical third step is subsequently hydrolysed to the corresponding acid **16** using standard methods as described previously. In a typical fourth step the acid **16** can be coupled to an amine **2** using suitable coupling methods as previously described to give compound **17.** The second amino group may be amino-protected with a standard protecting group such as tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) or 9-fluorenylmethyloxycarbonyl (Fmoc), if such protection is used the final step will involve removal of the protecting group using standard methods as previously described.



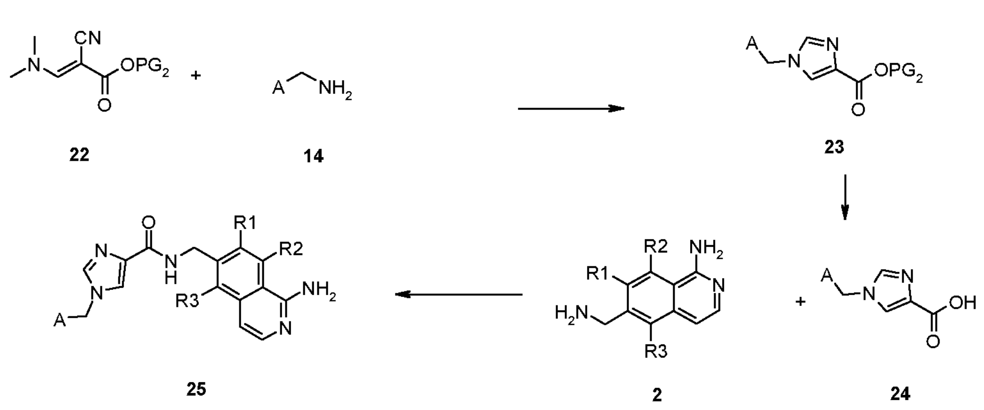
Scheme 4

Alternatively compounds according to general formula **I** can be prepared using the route outlined in Scheme 5. The triazole **19** can be formed by reaction of an alkyl propiolate with the azide **18** under azide alkyne Huisgen cycloaddition conditions employing a catalyst such as copper salts with abscorbic acid derivatives. In a typical second step the ester is hydrolysed to the corresponding acid **20** using standard methods as described previously. In a typical third step the acid **20** can be coupled to an amine **2** using suitable coupling methods as previously described to give compound **21.** The second amino group may be amino-protected with a standard protecting group such as tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) or 9-fluorenylmethyloxycarbonyl (Fmoc), if such protection is used the final step will involve removal of the protecting group using standard methods as previously described.



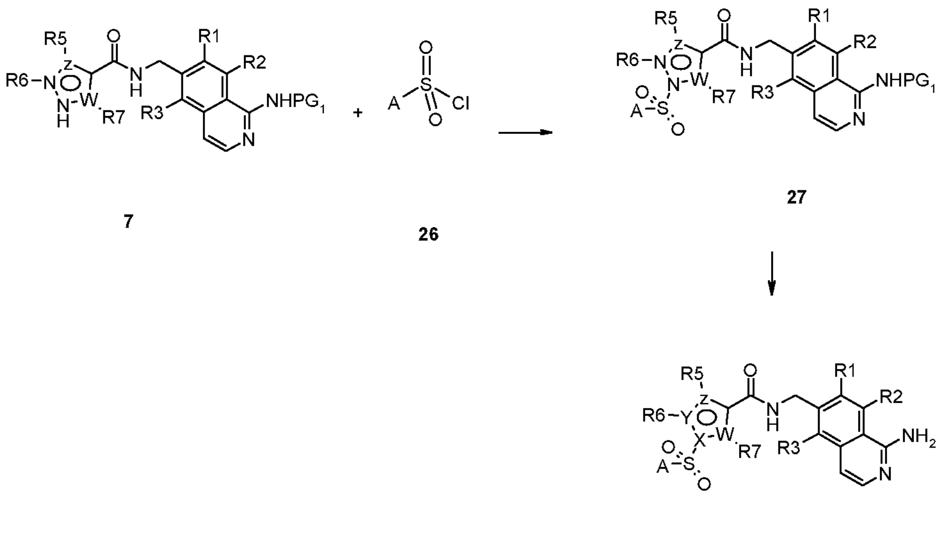
Scheme 5

Alternatively compounds according to general formula **I** can be prepared using the route outlined in Scheme 6. The imidazole **23** can be formed by reaction of the acrylate derivative **22** with the amine **14** in the presence of organic bases such as diisopropylethylamine or triethylamine. In a typical second step the ester is hydrolysed to the corresponding acid **24** using standard methods as described previously. In a typical third step the acid **24** can be coupled to an amine **2** using suitable coupling methods as previously described to give compound **25.** The second amino group may be amino-protected with a standard protecting group such as tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) or 9-fluorenylmethyloxycarbonyl (Fmoc), if such protection is used the final step will involve removal of the protecting group using standard methods as previously described.



Scheme 6

Alternatively compounds according to general formula **I** can be prepared using the route outlined in Scheme 7. In a typical first step the nitrogen of the heterocyclic ring is derivatised by reaction of compound **7** with the sulphonyl chloride **26** in the presence of organic bases such as diisopropylethylamine or triethylamine to give compound **27.** In a typical final step the protecting group is removed to give compound **28** using standard methods as previously described.



Scheme 7

Examples

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

DCM	Dichloromethane
DMF	N,N-Dimethylformamide
EtOAc	Ethyl Acetate
HATU	2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V)
hrs	Hours
HOBt	Hydroxybenzotriazole
LCMS	Liquid chromatography mass spectrometry
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Min	Minutes
MS	Mass spectrum
NMR	Nuclear magnetic resonance spectrum – NMR spectra were recorded at a frequency of 400MHz unless otherwise indicated
Pet. Ether	Petroleum ether fraction boiling at 60-80°C

Ph	Phenyl
rt	room temperature
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid

All reactions were carried out under an atmosphere of nitrogen unless specified otherwise.

^{1}H NMR spectra were recorded on a Bruker (400MHz) spectrometer with reference to deuterium solvent and at rt.
Molecular ions were obtained using LCMS which was carried out using a Chromolith Speedrod RP-18e column, 50 x 4.6 mm, with a linear gradient 10% to 90% 0.1% HCO_2H/MeCN into 0.1% HCO_2H/H_2O over 13 min, flow rate 1.5 mL/min, or using Agilent, X-Select, acidic, 5-95% MeCN/water over 4 min. Data was collected using a Thermofinnigan Surveyor MSQ mass spectrometer with electospray ionisation in conjunction with a Thermofinnigan Surveyor LC system.

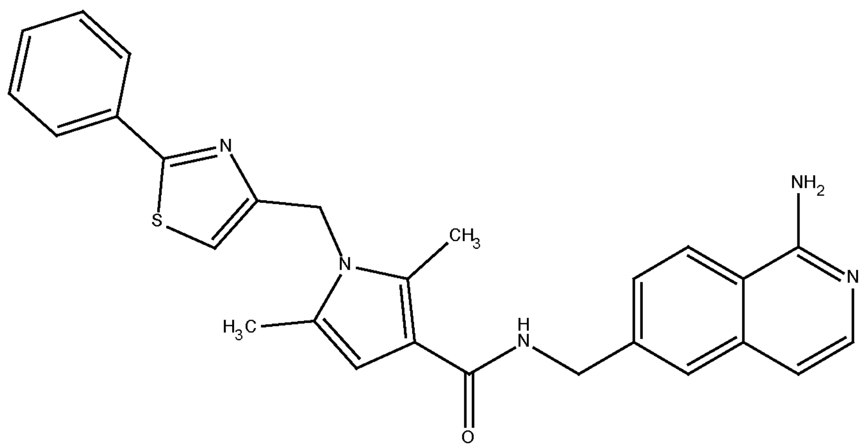
Chemical names were generated using the Autonom software provided as part of the ISIS draw package from MDL Information Systems.

Where products were purified by flash chromatography, ‘silica’ refers to silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Merck silica gel 60), and an applied pressure of nitrogen up to 10 p.s.i accelerated column elution. Reverse phase preparative HPLC purifications were carried out using a Waters 2525 binary gradient pumping system at flow rates of typically 20 mL/min using a Waters 2996 photodiode array detector.

All solvents and commercial reagents were used as received.

EXAMPLE 1

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 2-Acetyl-4-oxo-pentanoic acid ethyl ester

Ethylacetoacetate sodium salt (17.10g, 112mmol) was suspended in acetone (500mL). Potassium carbonate (15.54g, 112mmol) and potassium iodide (3.73g, 22.48mmol) were added and the resulting solution was refluxed. Chloroacetone (11.41g, 124mmol) was added dropwise over a period of 5 min. Once the addition was complete the mixture was heated under reflux for a further 2 hrs. The reaction mixture was allowed to cool to rt and the solid material was filtered off and washed with acetone. The resultant filtrate was evaporated and purified by flash chromatography (silica), eluent 75% Pet. Ether, 25% EtOAc, fractions combined and evaporated *in vacuo* to give a yellow oil identified as 2-acetyl-4-oxo-pentanoic acid ethyl ester (10.1g, 54.2mmol, 48% yield).

B. 1-[2-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester

2-Acetyl-4-oxo-pentanoic acid ethyl ester (1.8g, 9.66mmol) was dissolved in toluene (35mL), 2-phenyl-thiazoyl-4-methylamine (2.02g, 10.62mmol) and p-toluenesulphonic acid (183mg, 0.97mmol) were added. The reaction mixture was heated at reflux for 4 hrs after which time it was diluted with ethyl acetate and washed with $NaHCO_3$ (1x30mL), water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 85% Pet. Ether, 15% EtOAc, fractions combined and evaporated *in vacuo* to give a colourless oil identified as 1-[2-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester (1.26g, 3.69mmol, 38% yield).

$[M+H]^+$ = 341.

C. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid

1-[2-Phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester (1.07g, 3.14mmol) was dissolved in ethanol (50mL). Sodium hydroxide (629mg, 15.72mmol) in water (5mL) was added. The reaction mixture was heated at 90°C for 3 days after which time the solvent was removed *in vacuo*. The residue was diluted with water and acidified to pH1 with 1M HCl and extracted with ethyl acetate (3x 50mL). The combined extracts were washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give an off white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (980mg, 3.14mmol, 100% yield).

$[M+H]^+$ = 313.

D. 2-((*E*)-2-Dimethylamino-vinyl)-terephthalonitrile ester

Methylterephthalonitrile (1.42g, 9.99mmol) and Bredereck's reagent (3.48g, 19.98mmol) were dissolved in DMF (15mL). The reaction mixture was heated at 75°C under nitrogen for 72hrs after which time the solvent was removed *in vacuo*. Trituration with Pet. Ether gave a bright yellow solid identified as 2-((E)-2-dimethylamino-vinyl)-terephthalonitrile ester (1.88g, 0.95mmol, 95% yield).

^{1}H NMR (CD_3OD) δ: 3.20 (6H, s), 5.34 (1H, d, J = 13.4Hz), 7.21 (1H, dd, J = 8.0Hz, 1.4Hz), 7.9 (1H, d, 13.4Hz), 7.61 (1H, d, J = 8.0Hz), 7.94 (1H, d, J =1.2Hz)

E. 1-Amino-2-(2,4-dimethoxy-benzyl)-1,2-dihydro-isoquinoline-6-carbonitrile

2-((*E*)-2-Dimethylamino-vinyl)-terephthalonitrile ester (1.85g, 9.38mmol) was dissolved in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (5mL) and 2,4-dimethoxybenzylamine (2.35g, 14.07mmol) was added. The reaction mixture was heated at 75°C under nitrogen. After 3hrs the reaction mixture was cooled and diethyl ether/ Pet. Ether (15:85) was added. The yellow solid was filtered off, dried *in vacuo,* and identified as 1-amino-2-(2,4-dimethoxy-benzyl)-1,2-dihydro-isoquinoline-6-carbonitrile (2.65g, 8.38mmol, 89% yield)

$[M+H]^+$ = 320

^{1}H NMR (CD_3OD) δ: 3.85 (3H, s), 3.92 (3H, s), 5.02 (2H, s), 6.39 (1H, d, J = 7.4Hz), 6.57 (1H, dd, J = 8.4Hz, 2.4Hz), 6.66 (1H, d, J = 2.4Hz), 7.18 (1H, d, J = 8.4Hz), 7.24(1H, d, J = 7.4Hz), 7.72 (1H, dd, J = 8.5Hz, 1.4Hz), 7.93 (1H,s), 8.45 (1H, d, J = 8.5 Hz)

F. 1-Amino-isoquinoline-6-carbonitrile

1-Amino-2-(2,4-dimethoxy-benzyl)-1,2-dihydro-isoquinoline-6-carbonitrile (1.6g, 5.0mmol) was dissolved in anisole (17mL) and trifluoroacetic acid (20mL). The reaction mixture was heated at 105°C under nitrogen for 12hrs after which time the reaction mixture was cooled, diethyl ether/Pet. Ether (3:7) was added, the resultant solid was filtered off, dried *in vacuo* and identified as 1-amino-isoquinoline-6-carbonitrile (770mg, 4.54mmol, 91%).

$[M+H]^+$ = 170.

^{1}H NMR (CD_3OD) δ: 7.23 - 7.25 (1H, d, J = 6.9Hz), 7.65 (1H, d, J = 6.8Hz), 8.11 (1H, dd, J = 8.7Hz, 1.6Hz), 8.33 (1H, s), 8.45 (1H, d, J = 8.7Hz).

G. (1-Amino-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester

1-Amino-isoquinoline-6-carbonitrile (200mg, 1.18mmol) was dissolved in methanol (20mL). This solution was cooled to 0°C. Nickel (II) chloride hexahydrate (28mg, 0.12mmol) and di-tertbutyl dicarbonate (516g, 2.36mmol) were added followed by sodium borohydride (313g, 8.22mmol) portionwise. The reaction mixture was stirred at 0°C to room temp for 3 days. The MeOH was removed by evaporation. The residue was dissolved in $CHCl_3$ (70mL), washed with sat $NaHCO_3$ (1x30mL), water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil identified as (1-amino-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester (110mg, 0.4mmol, 34% yield).

$[M+H]^+$ = 274.

H. 6-Aminomethyl-isoquinolin-1-ylamine hydrochloride

(1-Amino-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester (110mg, 0.40mmol) was dissolved in 4M HCl in dioxane (40mL). After 18 hrs at rt the solvent was removed *in vacuo* to give a pale brown solid identified as 6-aminomethyl-isoquinolin-1-ylamine hydrochloride (67mg, 0.39mmol, 96% yield).

[M+H]+ = 174.

I. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

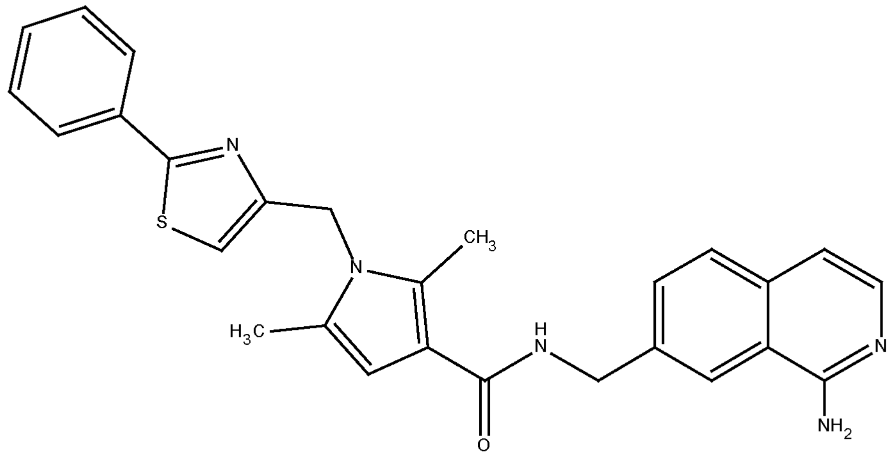
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (87mg, 0.28mmol) was dissolved in CH_2Cl_2(15mL). This solution was cooled to 0°C. 6-Aminomethyl-isoquinolin-1-ylamine hydrochloride (48mg, 0.28mmol) was added followed by HOBt (45mg, 0.31mmol) and triethylamine (147mg, 1.4mmol). Water soluble carbodiimide (75mg, 0.39mmol) was then added. After 18 hrs at 0°C to rt, reaction mixture was diluted with chloroform (200mL) and washed with $NaHCO_3$ (1x50mL), water (1x50mL), brine (1x50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent dichloromethane:MeOH:NH_3 (100:10:1), fractions combined and evaporated *in vacuo* to give a white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (68mg, 0.14mmol, 52% yield).

$[M+H]^+$ = 468.

^{1}H NMR: (d6-DMSO), δ: 2.28 (3H, s), 2.56 (3H, s), 4.52 (2H, d, J= 5.9Hz), 5.18 (2H, s), 6.33 (1H, s), 7.05 (1H, d, J= 6.4Hz), 7.31 (1H, s), 7.48 - 7.52 (3H, m), 7.55 (1H, d, J= 9.9Hz), 7.65 (1H, s), 7.68 (1H, d, J= 6.5Hz), 7.81 - 8.00 (2H, s, br.), 7.89 - 7.91 (2H, m), 8.25 (1H, t, J= 5.9Hz), 8.32 (1H, d, J= 8.6Hz).

<u>EXAMPLE 2</u>

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-7-ylmethyl)-amide



A. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-7-ylmethyl)-amide

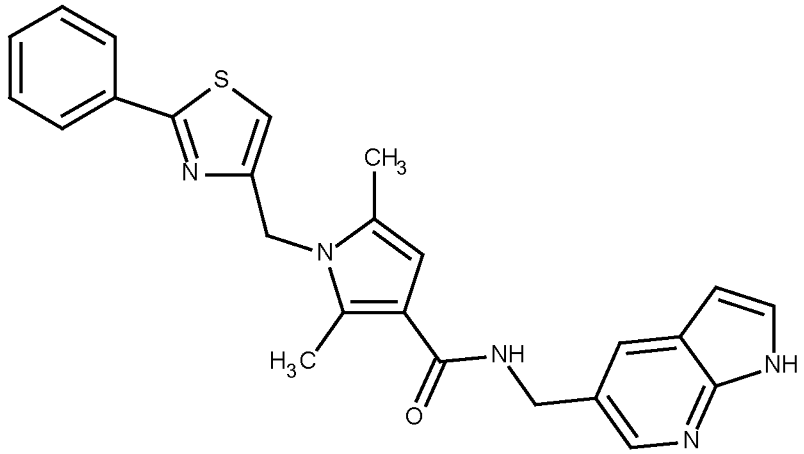
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (93mg, 0.30mmol) was dissolved in CH_2Cl_2 (15mL). This solution was cooled to 0°C. 7-Aminomethyl-isoquinolin-1-ylamine hydrochloride (C. A. A. Van Boeckel *et al.*,WO 98/47876) (56mg, 0.33mmol) was added followed by HOBt (48mg, 0.32mmol) and triethylamine (211mg, 2.1mmol). Water soluble carbodiimide (80mg, 0.42mmol) was then added. After 18 hrs at 0°C to rt reaction mixture was diluted with chloroform (200mL) and washed with $NaHCO_3$ (1x50mL), water (1x50mL), brine (1x50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent dichloromethane:MeOH:NH_3 (100:10:1), fractions combined and evaporated *in vacuo* to give a white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-7-ylmethyl)-amide (30mg, 0.06mmol, 21% yield).

$[M+H]^+$ = 468.

^{1}H NMR: (d6-DMSO), δ: 2.26 (3H, s), 2.57 (3H, s), 4.49 (2H, d, J = 5.9Hz), 5.17 (2H, s), 6.32 (1H, s), 6.85 (2H, s, br), 6.88 (1H, d, J = 5.9Hz), 7.28 (1H, s), 7.46 - 7.52 (3H, m), 7.58 (1H, dd, J = 8.1, 0.9Hz), 7.65 (1H, d, J = 8.4Hz), 7.73 (1H, d, J = 5.9Hz), 7.89 - 7.92 (2H, m), 8.10 (1H, s, br), 8.17 (1H, t, J = 5.9Hz).

EXAMPLE 3

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide



A. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

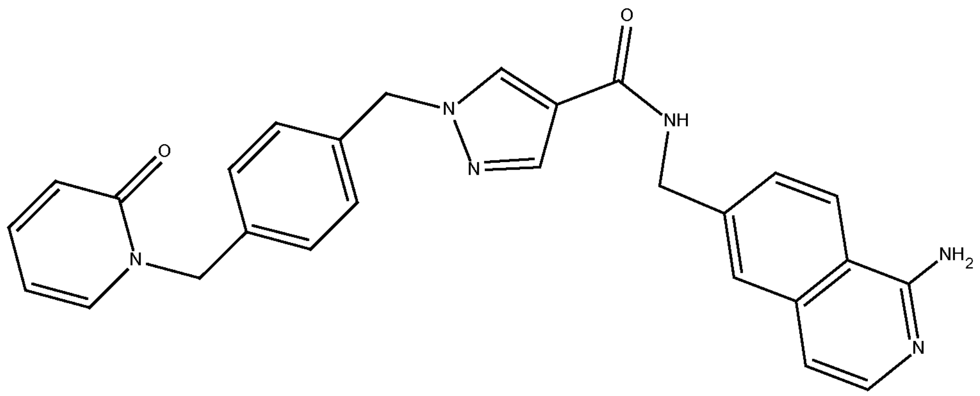
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (120mg, 0.38mmol) was dissolved in CH_2Cl_2(20mL) and DMF(2mL). This solution was cooled to 0°C. 5-Aminomethyl-7-azaindole hydrochloride (57mg, 0.38mmol), HOBt (62mg, 0.41mmol) and triethylamine (192mg, 1.92mmol). and water soluble carbodiimide (104mg, 0.54mmol) were then added. After 18 hrs at 0°C to rt reaction mixture was diluted with chloroform (100mL) and washed with $NaHCO_3$ (1x30mL), water (1x50mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 4% MeOH, 96% dichloromethane, fractions combined and evaporated *in vacuo* to give a white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide (62mg, 0.14mmol, 37% yield).

$[M+H]^+$ = 442

^{1}H NMR: (d6-DMSO), δ: 2.24 (3H, s), 2.55 (3H, s), 4.43 (2H, d, J= 6.0Hz), 5.15 (2H, s), 6.27 (1H, s), 6.38-6.39 (1H, m), 7.22 (1H, s), 7.41 (1H, t, J= 2.9Hz), 7.46-7.51 (3H, m), 7.83 (1H, d, J= 1.6Hz), 7.85-7.90 (2H, m), 8.09 (1H, t, J= 6.0Hz), 8.17 (1H, d, J= 1.9Hz), 11.51 (1H, s).

REFERENCE EXAMPLE 4

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one

4-(Chloromethyl)benzylalcohol (5.0g, 31.93mmol) was dissolved in acetone (150mL) 2-hydroxypyridine (3.64g, 38.3mmol) and potassium carbonate (13.24g, 95.78mmol) were added and the reaction mixture was stirred at 50°C for 3 hrs after which time the solvent was removed *in vacuo* and the residue taken up in chloroform (100mL), this solution was washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3%MeOH, 97% $CHCl_3$, fractions combined and evaporated *in vacuo* to give a white solid identified as 1-(4-hydroxymethyl-benzyl)-1H-pyridin-2-one (5.30g, 24.62mmol, 77% yield).

$[M+Na]^+$ = 238

B. 1-(4-Bromomethyl-benzyl)-1H-pyridin-2-one

1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one (2.30g, 6.97mmol) was dissolved in dichloromethane (250mL). To this solution was added phosphorous tribromide (5.78g, 21.37mmol) The reaction mixture was stirred at rt for 18 hrs and diluted with $CHCl_3$ (250mL) the filtrate was washed with saturated $NaHCO_3$ (1x30mL), water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a white solid which was identified as 1-(4-bromomethyl-benzyl)-1H-pyridin-2-one (2.90g, 10.43mmol, 98% yield).

$[M+H]^+$ = 278

C. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester

1-(4-Bromomethyl-benzyl)-1H-pyridin-2-one (2.80g, 10.07mmol) was dissolved in DMF (50mL) ethyl 1H-pyrazole-4-carboxylate (1.69g, 12.08mmol) and caesium carbonate (9.84g, 30.2mmol) were added and the reaction mixture was stirred at 50°C for 18 hrs after which time the reaction mixture was diluted with EtOAc (100mL), this solution was washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3%MeOH, 97% $CHCl_3$, fractions combined and evaporated *in vacuo* to give a white foamy solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (3.20g, 9.49mmol, 94% yield).

$[M+H]^+$ = 338

D. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (3.20g, 9.49mmol) was dissolved in THF (50mL) and water (5mL) lithium hydroxide (1.13g, 47.43mmol) was added. The reaction mixture was stirred at 50°C for 48 hrs after which time the solvent was concentrated *in vacuo* and the residue taken up in $CHCl_3$ (150mL), the aqueous layer was extracted and acidified with 1M HCl to pH2 and extracted with $CHCl_3$ (3x50mL), the combined extracts were washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*, the residue was triturated with EtOAc and Pet. Ether to give a white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3.20g, 6.14mmol, 65% yield).

$[M+H]^+$ = 310, 332 (M+Na)

E. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

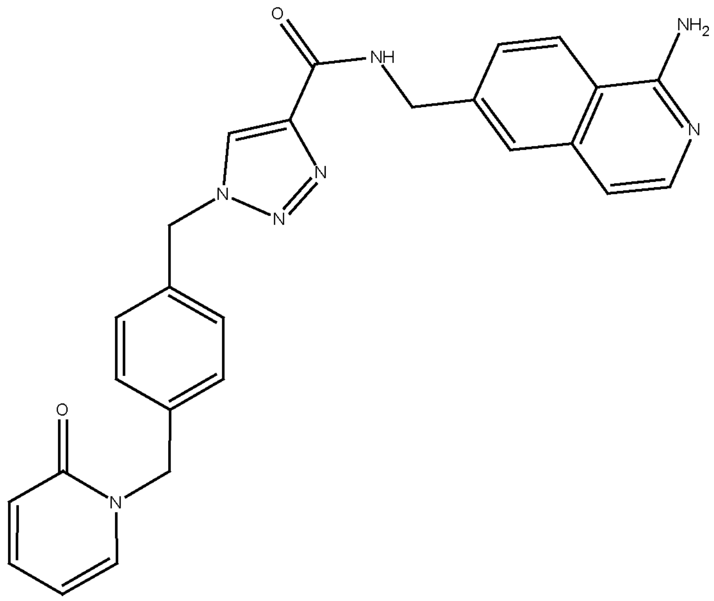
1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (80mg, 0.26mmol) was dissolved in CH_2Cl_2 (2.5mL). HATU (108mg, 0.28mmol) was added followed by 6-(aminomethyl)isoquinolin-1-amine (49mg, 0.28mmol) and N,N-diisopropylethylamine (67mg, 0.52mmol). After 18 hrs at rt the reaction mixture was diluted with chloroform (400mL) washed with NH_4Cl (1x30mL), water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* giving a yellow oil. The residue was purified by flash chromatography (silica), eluent dichloromethane:MeOH:NH_3 (100:10:1). Fractions combined and evaporated *in vacuo* to give a white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (22mg, 0.046mmol, 18% yield).

$[M+H]^+$ = 465

^{1}H NMR: (d6-DMSO), δ: 4.55 (2H, d, J = 6.0Hz), 5.08 (2H, s), 5.33 (2H, s), 6.23 (1H, td, J = 1.4, 6.7Hz), 6.40 (1H, dd, J = 1.3, 9.5Hz), 6.94 (1H, d, J = 6.1Hz), 7.10-7.32 (5H, m), 7.38-7.47 (2H, m), 7.59 (1H, s, br), 7.71-7.81 (2H, m), 7.92 (1H, s), 8.21 (1H, d, J = 8.6Hz), 8.28 (1H, s), 8.72 (1H, t, J = 5.9Hz).

REFERENCE EXAMPLE 5

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 1-(4-Azidomethyl-benzyl)-1H-pyridin-2-one

1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one (570mg, 2.65mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (806mg, 5.30mmol) were dissolved in DMF (20mL). Diphenylphosphoryl azide (1.09g, 3.97mmol) was added and the reaction mixture was stirred at rt for 3 hrs after which time the reaction mixture was diluted with EtOAc (100mL), this solution was washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3%MeOH, 97% $CHCl_3$, fractions combined and evaporated *in vacuo* to give a white foamy solid identified as 1-(4-azidomethyl-benzyl)-1H-pyridin-2-one (430mg, 1.79mmol, 68% yield).

$[M+Na]^+$ = 361

B. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid ethyl ester

1-(4-Azidomethyl-benzyl)-1H-pyridin-2-one (340mg, 1.41mmol), ethyl propiolate (139mg, 1.41mmol), (+)-sodium L-ascorbate (280mg, 1.41mmol) and copper (II) sulphate pentahydrate (71mg, 0.28mmol) were dissolved in tert-butanol (20mL) and water (5mL). The reaction mixture was stirred at rt for 18 hrs after which time the reaction mixture was diluted with chloroform (100mL), this solution was washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was triturated with ethyl acetate and Pet. Ether to give a white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid ethyl ester (430mg, 1.27mmol, 90% yield).

$[M+H]^+$ = 486

C. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid ethyl ester (110mg, 0.32mmol) was dissolved in THF (50mL) and water (5mL), lithium hydroxide (39mg, 1.62mmol) was added. The reaction mixture was stirred at 50°C for 18 hrs after which time the solvent was concentrated *in vacuo* and the residue taken up in EtOAc (50mL), the aqueous layer was separated, acidified with 1M HCl to pH2 and extracted $CHCl_3$ (3x50mL) the combined extracts were washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3% MeOH, 97% $CHCl_3$, fractions combined and evaporated *in vacuo* to give a colourless oil identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (140mg, 0.45mmol, 49% yield).

D. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

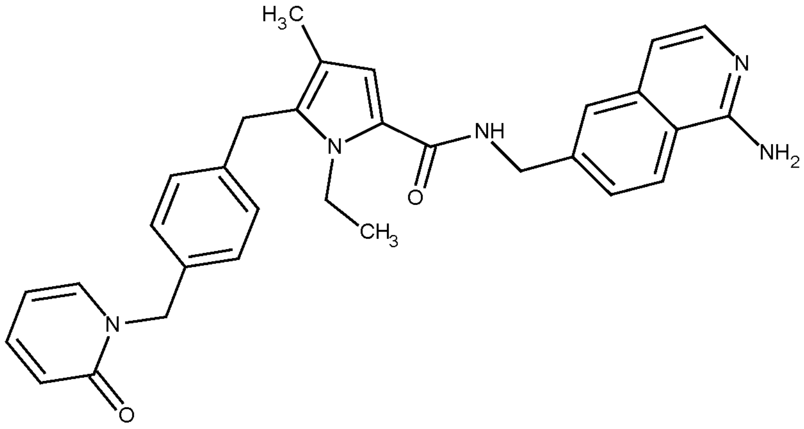
1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (100mg, 0.26mmol) was dissolved in CH_2Cl_2 (3.5mL). HATU (147mg, 0.39mmol) and 6-(aminomethyl)isoquinolin-1-amine (61.4mg, 0.35mmol) were added followed by N,N-diisopropylethylamine (67mg, 0.52mmol). After 1 hour at rt the reaction mixture was diluted with chloroform (400mL) washed with NH_4Cl (1x30mL), water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* giving a yellow oil. Trituration with methanol/diethyl ether (3:7, 10mL) gave a yellow solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (107mg, 0.22mmol, 85% yield).

$[M+H]^+$ = 466

^{1}H NMR: (d6-DMSO), δ: 4.61 (2H, d, J = 6.2 Hz), 5.08 (2H, s), 5.63 (2H, s), 6.22 (1H, td, J = 1.4, 6.7 Hz), 6.34-6.48 (1H, m), 7.12 (1H, d, J = 6.7 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.34 (2H, d, J = 8.3 Hz), 7.41 (1H, ddd, J = 2.1, 6.6, 8.9 Hz), 7.63 (1H, dd, J = 1.5, 8.7 Hz), 7.67 (1H, d, J = 6.7 Hz), 7.72 (1H, s); 7.74-7.81 (1H, m), 8.42 (3H, d, J = 8.7 Hz), 8.67 (1H, s), 9.26 (1H, t, J = 6.2 Hz).

EXAMPLE 6

1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. Ethyl 1-ethyl-4-methyl-1H-pyrrole-2-carboxylate

To a colourless solution of ethyl 4-methyl-1H-pyrrole-2-carboxylate (0.5 g, 3.26 mmol) in DMF (5 mL) at 0°C was added sodium hydride (0.137 g, 3.43 mmol) (effervescence). After stirring for 30 min, ethyl iodide (0.317 mL, 3.92 mmol) was added to the suspension. The resultant white thick suspension was stirred at RT over the week-end. The reaction mixture was diluted with water (10 mL) and EtOAc (50 mL) was added. The layers were separated and the organic phase was washed with water (4 x 10 mL) and saturated brine (20 mL). The organic was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a pale yellow oil (0.6456 g) that was dried further to afford ethyl 1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (0.5657 g, 3.06 mmol, 94 % yield).

$[M+H]^+$ = 182

B. Ethyl 5-(4-(chloromethyl)benzoyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate

The zinc(II) chloride (3.35 g, 24.61 mmol) was weighed out to a 100 mL flask and dried under vacuum at 120 °C for 2 hrs to remove any water. The flask was placed under nitrogen and a solution of 4-(chloromethyl)benzoyl chloride (4.0 g, 21.16 mmol) in anhydrous dichloroethane (25 mL) was added. The mixture was cooled in an ice-bath and a solution of ethyl 1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (2.23 g, 12.30 mmol) in anhydrous dichloroethane (8 mL) was added dropwise. After 10 min, the ice-bath was removed and the reaction allowed to stir at 40 °C for 1h 30 min. The mixture was allowed to heat for a further 30 min, then poured into ice-water (200 mL) and extracted with DCM (3 x 125 mL). The combined organics were washed with water (100 mL), 1M HCl (100 mL) and brine (100 mL), then dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by chromatography (silica) eluting with a gradient of 0 to 15% EtOAc/Iso-Hexanes, holding at 0% and 10% EtOAc to afford the desired product ethyl 5-(4-(chloromethyl)benzoyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (2.12 g, 6.16 mmol, 50.1 % yield) as a pale yellow solid and the undesired isomer ethyl 3-(4-(chloromethyl)benzoyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (1.00 g, 2.097 mmol, 17.04 % yield) as a gummy solid, contaminated with 4-chloromethylbenzoic acid.

$[M+H]^+$ =334/336

C. Ethyl 5-((4-(chloromethyl)phenyl)(hydroxy)methyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate

A solution of ethyl 5-(4-(chloromethyl)benzoyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (2.26 g, 6.77 mmol) in anhydrous THF (20 mL) and anhydrous MeOH (3 mL) was treated with sodium borohydride (0.512 g, 13.54 mmol) portionwise (an ice-bath was added after 5 min to control exotherm) and the mixture stirred at ambient temperature for 1 hour. HPLC (XSelect, 4min) indicated >95% conversion to the desired compound. A further 100 mg of sodium borohydride were added and the mixture stirred for a further 30 min. The reaction mixture was poured into saturated aqueous NH_4Cl solution (120 mL) and stirred for 5 min. The aqueous layer was extracted with DCM (3 x 50 mL) and the combined organics washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to afford ethyl 5-((4-(chloromethyl)phenyl)(hydroxy)methyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (2.30 g, 6.84mmol) as a clear oily foam.

$[M-H_2O+H]^+$ = 318/320

D. Ethyl 5-(4-(chloromethyl)benzyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate

A solution of ethyl 5-((4-(chloromethyl)phenyl)(hydroxy)methyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (2.16 g, 6.43 mmol) in anhydrous DCM (22 mL) was cooled in an ice-bath and treated with 2,2,2-trifluoroacetic acid (9.85 mL, 129 mmol) then triethylsilane (1.233 mL, 7.72 mmol). The mixture was allowed to stir at ambient temperature for 45 min. The mixture was poured carefully into saturated aqueous $NaHCO_3$ solution (250 mL, cooled in an ice-bath) and the biphasic mixture stirred for 15 min before extraction with DCM (3 x 75 mL). The combined organics were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by chromatography (silica) eluting with a gradient of 0 to 10% EtOAc/Iso-Hexanes to afford ethyl 5-(4-(chloromethyl)benzyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (1.46 g, 4.34 mmol, 64.4 % yield) as a clear gummy oil.

$[M+H]^+$ = 320/322

E. Ethyl 1-ethyl-4-methyl-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrole-2-carboxylate

Ethyl 5-(4-(chloromethyl)benzyl)-1-ethyl-4-methyl-1H-pyrrole-2-carboxylate (715 mg, 2.236 mmol) and pyridin-2(1H)-one (425 mg, 4.47 mmol) were dissolved in anhydrous MeCN (8 mL) and potassium carbonate (618 mg, 4.47 mmol) added. The mixture was stirred at 67 °C (DrySyn bath temperature) overnight. The mixture was partitioned between EtOAc (30 mL) and water (30 mL). The pH was adjusted to ~7 with 1M HCl and the organic layer collected. The aqueous was extracted with further EtOAc (2 x 30 mL) and the combined organics washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by chromatography (silica) eluting with a gradient of 10 to 90% EtOAc/Iso-Hexanes, holding at ~65% to elute product. Product containing fractions were combined to afford ethyl 1-ethyl-4-methyl-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrole-2-carboxylate (715 mg, 1.851 mmol, 83 % yield) as a pale yellow gum after drying overnight under vacuum.

$[M+H]^+$ = 379

F. 1-Ethyl-4-methyl-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrole-2-carboxylic acid

A solution of ethyl 1-ethyl-4-methyl-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrole-2-carboxylate (621 mg, 1.641 mmol) in THF (11 mL), MeOH (7 mL) and water (10 mL) was treated with lithium hydroxide (295 mg, 12.31 mmol) and the mixture heated at 65 °C with stirring overnight. The majority of the solvents were removed under vacuum. The resultant cloudy mixture was partitioned between EtOAc (20 mL) and water (20 mL) containing 1M NaOH (1 mL). The organic layer was discarded and the aqueous layer acidified to ~pH 6 with 1M HCl forming a precipitate. This was allowed to stand for 20 min before filtration, washing with water (10 mL). The solid was dried under vacuum in the presence of $CaCl_2$ for 3 hrs to afford 1-ethyl-4-methyl-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrole-2-carboxylic acid (543 mg, 1.534 mmol, 93 % yield).

$[M+H]^+$ = 351

G. 1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

A scintillation vial was charged with 1-ethyl-4-methyl-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrole-2-carboxylic acid (75 mg, 0.214 mmol), 6-(aminomethyl)isoquinolin-1-amine (40.8 mg, 0.235mmol), HATU (90mg, 0.235 mmol) and DCM (3.5 mL). N,N-diisopropylethylamine (74.6 µL, 0.428 mmol) was added and the mixture allowed to stir over a weekend.

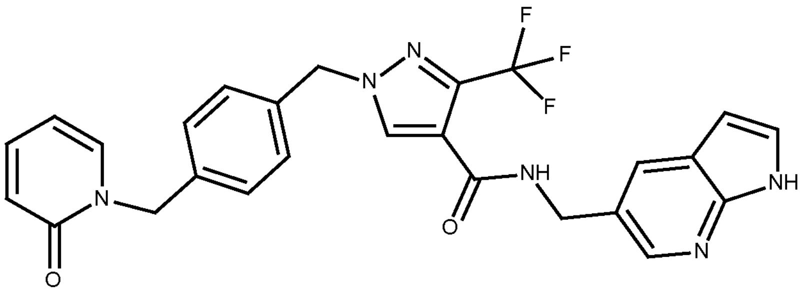
The mixture was diluted with DCM (containing trace MeOH for solubility) (3 mL) and saturated aqueous NH_4Cl (4 mL) and shaken, then left to stand until the layers separated. The mixture was passed through a phase separation cartridge (15 mL), the organic layer collected then concentrated under vacuum. The crude material was purified by chromatography (silica) eluting with a gradient of 0.5 to 6.5% MeOH (1%NH3)/DCM to afford 1-ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (97 mg, 0.188 mmol, 88% yield) as an off-white foam.

^{1}H NMR: (d6-DMSO), δ: 0.94 (3H, t, J = 7.0Hz), 2.00 (3H, s), 3.93 (2H, s), 4.15 (2H, q, J = 6.9Hz), 4.49 (2H, d, J = 6.0Hz), 5.04 (2H, s), 6.21 (1H, td, J = 6.7,1.4Hz), 6.39 (1H, d, J = 9.1Hz), 6.70-6.74 (3H, m), 6.84 (1H, d, J = 5.6Hz), 7.04 (2H, d, J = 8.2Hz), 7.20 (2H, d, J = 8.2Hz), 7.33-7.44 (2H, m), 7.51 (1H, s), 7.68-7.81 (2H, m), 8.12 (1H, d, J = 8.6Hz), 8.48 (1H, t, J = 6.1Hz).

$[M+H]^+ = 506$

EXAMPLE 7

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide



A. 1-(4-Chloromethyl-benzyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester

Polymer-supported triphenylphospine (3.0mmol/g, 3 equiv, 1.0g) was swollen in THF/dichloromethane (1:1, 100mL). Under a nitrogen atmosphere ethyl 3-trifluoromethyl-1H-pyrazole-4-carboxylate (1.0g, 4.80mmol) and 4-(chloromethyl)benzylalcohol (903mg, 5.76mmol) were added followed by a solution of diisopropyl azodicarboxylate (1.46g, 7.21mmol) in THF/dichloromethane (1:1, 10mL) over a period of 30min. The reaction mixture was stirred at rt for 18 hrs, the mixture was filtered and the resin was washed with 3 cycles of dichloromethane/methanol (15mL). The combined filtrates were evaporated *in vacuo*. Two main products were identified which were separated by flash chromatography (silica), eluent 20% EtOAc, 80% Pet. Ether, fractions combined and evaporated *in vacuo* to give white solids identified as 1-(4-chloromethyl-benzyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (450mg, 1.3mmol, 27% yield) and 1-(4-chloromethyl-benzyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (1.12g, 3.23mmol, 67% yield)

$[M+H]^+ = 347$

B. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester

1-(4-Chloromethyl-benzyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (980mg, 2.84mmol) was dissolved in acetone (50mL). 2-Hydroxypyridine (323mg, 3.39mmol) and potassium carbonate (1.17g, 8.48mmol) were added and the reaction mixture was stirred at 50°C for 3 hrs after which time the solvent was removed *in vacuo* and the residue taken up in EtOAc (100mL), this solution was washed with water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3%MeOH, 97% $CHCl_3$, fractions combined and evaporated *in vacuo* to give a colourless oil identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (1.10g, 2.71mmol, 96% yield).

$[M+H]^+$ = 406

C. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (1.10g, 2.71mmol) was dissolved in THF (50mL)and water (5 mL), and lithium hydroxide (325mg, 13.57mmol) was added. The reaction mixture was stirred at 50°C for 18 hrs after which time the solvent was concentrated *in vacuo* and the residue taken up in EtOAc (50mL), the aqueous layer was extracted and acidified with 1M HCl to pH2 and extracted $CHCl_3$ (3x50mL). The combined extracts were washed with water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (980mg, 2.60mmol, 96% yield).

$[M+H]^+$ = 379

D. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

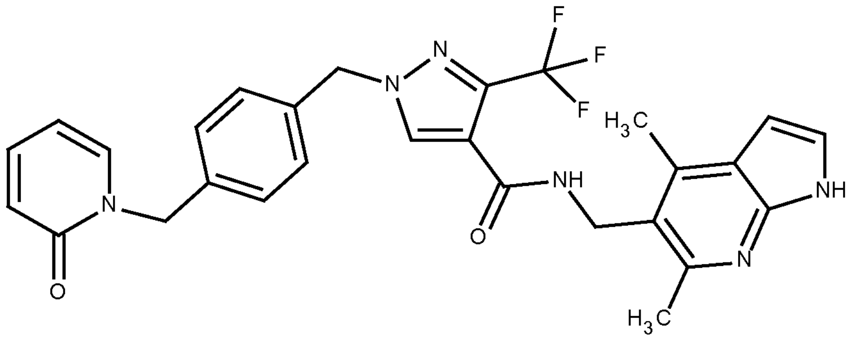
1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (80mg, 0.21mmol) was dissolved in CH_2Cl_2(50mL) and DMF (2.5mL). This solution was cooled to 0°C. 5-aminomethyl-7-azaindole hydrochloride (37mg, 0.25mmol) was added followed by HOBt (32mg, 0.23mmol) and triethylamine (64mg, 0.64mmol). Water soluble carbodiimide (49mg, 0.25mmol) was then added. After 18 hrs at 0°C to rt reaction mixture was diluted with chloroform (200mL), $NaHCO_3$ (1x30mL), water (1x30mL), brine (1x30mL),), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 8%MeOH, 92% $CHCl_3$, fractions combined and evaporated *in vacuo*. The residue was freeze dried from water/acetonitrile to give a white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide (55mg, 0.11mmol, 51% yield).

$[M+H]^+$ = 507

^{1}H NMR: (d6-DMSO), δ: 4.45 (2H, d, J = 5.7Hz), 5.07 (2H, s), 5.39 (2H, s), 6.20 (1H, q, J = 7.6Hz), 6.38-6.41 (2H, m), 7.28 (4H, s), 7.41-7.46 (2H, m), 7.76 (1H, q, J = 6.8Hz), 7.85 (1H, d, J = 1.7Hz), 8.17 (1H, d, J = 2.0Hz), 8.41 (1H, s), 8.75-8.77 (1H, m), 11.59 (1H, s).

EXAMPLE 8

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide



A. 1-tert-Butyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

A mixture of 5-amino-1-tert-butyl-1H-pyrrole-3-carbonitrile (2.6g, 15.93 mmol) and pentane-2,4-dione (1.595g, 15.93mmol,) were dissolved in ethanol (80mL) and concentrated HCl (0.2mL) was added. The reaction mixture was heated at reflux for 18 hrs. The mixture was concentrated *in vacuo* and the crude purified by flash chromatography (silica) eluting in step gradients 95:5 to 9:1 Pet. Ether/ethyl acetate to give a yellow oil identified as 1-tert-butyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (3.05g,13mmol, 84% yield).

$[M+H]^+$ = 228.4

^{1}H NMR: ($CDCl_3$), δ: 1.81 (9H, s), 2.58 (3H, s), 2.70 (3H, s), 6.84 (1H, s), 7.75 (1H, s)

B. 5-Bromo-1-tert-butyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

A solution of 1-tert-butyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (2.820g, 12.4 mmol) in dichloromethane (50mL) under an atmosphere of N_2 was cooled to at least -5°C (Ice/NaCl, 3:1). 1,3-Dibromo-5,5-dimethylhydantoin (1.774g, 6.203mmol) was then added and the reaction was stirred at -5°C or below. After stirring at -5°C further 1,3-dibromo-5,5-dimethylhydantoin (88mg, 0.31mmol) was added and stirring continued at -5°C for a further 3 hrs The reaction mixture was quenched with Na_2SO_3 (aq) before warming the reaction to rt. 1M NaOH was added and the layers separated. The aqueous phase was extracted with dichloromethane (2×10 mL), the combined organic extracts were washed with brine (2×10 mL) and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica eluting with Pet. Ether/ethyl acetate 95:5. Fractions containing product were concentrated and the residue recrystalised from ethyl acetate/Pet. Ether to give a white solid identified as 5-bromo-1-tert-butyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (3.19g, 10.42mmol, 84% yield).

$[M+H]^+$ = 305.7

^{1}H NMR: ($CDCl_3$), δ: 1.81 (9H, s), 2.78 (3H, s), 2.82 (3H, s), 7.78 (1H, s)

C. 5-Bromo-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile

5-Bromo-1-(tert-butyl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (2.1 g, 6.87 mmol) was added portionwise to a stirring suspension of aluminum trichloride (2.75 g, 20.6 mmol) in chlorobenzene (160 mL). After the addition, the mixture was heated to 100 °C overnight forming a black gummy solution. After 24 hrs, the reaction was allowed to cool then poured into water (300mL) and dichloromethane (300 mL). The mixture was treated cautiously with conc. HCl (135 mL) and the mixture stirred for 10 min then filtered, washing with water and dichloromethane. The resultant solid was dried under vacuum in the presence of $CaCl_2$ over a weekend to give a pale grey solid identified as 5-bromo-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (1.56mg, 6.16mmol, 90% yield).

D. 5-Bromo-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine

A suspension of 5-bromo-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (1.56 g, 6.16mmol) in conc. hydrochloric acid, 37% (235 mL) was heated at reflux overnight. Further conc. HCl (100mL) was added and the reaction was heated at reflux for a further 20 hrs. The mixture was cooled and poured into ice-water (1 L) and neutralised with 2N NaOH until pH 9, forming a precipitate. This was filtered, washed with water then dried under vacuum in the presence of $CaCl_2$ to give a grey solid identified as 5-bromo-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine (1.3g, 5.72mmol, 92% yield).

$[M+H]^+$ = 225.1

^{1}H NMR: ($CDCl_3$), δ: 2.66 (3H, s), 2.82 (3H, s), 6.49 (1H, dd, J = 3.5, 2.1 Hz), 7.29 (1H, dd, J = 3.4, 2.7 Hz), 11.14 (1H, br.s)

E. 4,6-Dimethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

5-Bromo-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine (1.3g, 5.72mmol) was dissolved in N,N-dimethylacetamide (20mL). The solution was degassed with N_2 before the addition of zinc powder (45mg, 0.693mmol), zinc acetate (127mg, 0.693mmol), 1,1'-bis(diphenylphosphino)ferrocene (128mg, 0.23mmol), $Zn(CN)_2$ (339mg, 2.888mmol) and tris(dibenzylideneacetone)dipalladium(0) (106mg, 0.116mmol). The reaction was heated at 120°C for 48hrs. After cooling to rt the reaction was diluted with ethyl acetate and washed with 2M NH_4OH and brine. Organic layer was dried over MgSO4 and filtered. After concentration *in vacuo* crude product was purified by flash column chromatography on silica eluting with 9:1, 8:2, 7:3, 1:1. (Pet. Ether/Ethyl acetate). Fractions were collected and concentrated *in vacuo*. The yellow solid was triturated in diethyl ether to give an off white solid identified as 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (660mg, 3.83mmol, 67% yield).

$[M+H]^+$ = 172.1

^{1}H NMR: ($CDCl_3$), δ: 2.76 (3H, s), 2.86 (3H, s), 6.59 (1H, dd, J = 3.5, 2.0 Hz), 7.36 (1H, dd, J = 3.5, 2.4 Hz), 10.86 (1H, br.s)

F. (4,6-Dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-carbamic acid tert-butyl ester

4,6-Dimethyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (610mg, 3.56mmol) was dissolved in methanol (75mL). This solution was cooled to 0°C. Nickel (II) chloride hexahydrate (85mg, 0.36mmol) and di-tertbutyl dicarbonate (1.56g, 7.13mmol) were added followed by sodium borohydride (943mg, 24.94mmol) portionwise. The reaction mixture was stirred at 0°C to room temp for 18 hrs. The MeOH was removed by evaporation. The residue was dissolved in $CHCl_3$ (70mL), washed with sat $NaHCO_3$(1x30mL), water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. Purified by flash chromatography, (silica), eluant 40%Pet. Ether, 60% EtOAc to give white solid identified as identified as (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-carbamic acid tert-butyl ester (710mg, 2.56mmol, 72% yield).

$[M+H]^+$ = 276.1

^{1}H NMR: ($CDCl_3$), 1.49 (9H, s), 2.61 (3H, s), 2.71 (3H, s), 4.46 (1H, br.s), 4.51 (2H, d, J = 4.4 Hz), 6.50 (1H, dd, J = 3.5, 2.0 Hz), 7.25 (1H, dd, J = 3.4, 2.5 Hz), 9.64 (1H, br.s);

G. C-(4,6-Dimethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine hydrochloride

4,6-Dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-carbamic acid tert-butyl ester (710mg, 2.56mmol) was dissolved in 4M HCl in dioxane (10mL). After 2 hrs at rt the solvent was removed *in vacuo* to give a yellow solid identified as C-(4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine hydrochloride (360mg, 2.00mmol, 80% yield).

$[M+H]^+$ = 176.4

^{1}H NMR: (d6-DMSO), 2.53 (3H, s), 2.60 (3H, s), 3.94 (2H, s), 4.76 (2H, br.s), 6.43 (1H, d, J = 2.3 Hz), 7.28 (1H, dd, J = 3.2, 1.9 Hz), 11.32 (1H, br.s)

H. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (80mg, 0.21mmol) was dissolved in CH_2Cl_2(50mL) and DMF(2.5mL). This solution was cooled to 0°C. C-(4,6-Dimethyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine hydrochloride (44mg, 0.25mmol) was added followed by HOBt (32mg, 0.23mmol) and triethylamine (64mg, 0.64mmol). Water soluble carbodiimide

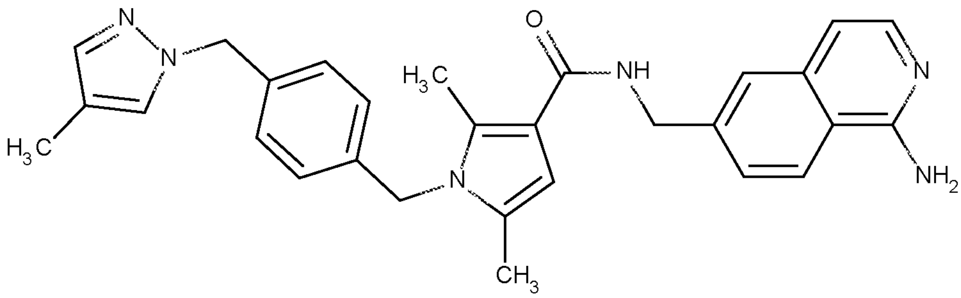
(49mg, 0.25mmol) was then added. After 18 hrs at 0°C to rt reaction mixture was diluted with chloroform (200mL) and washed with $NaHCO_3$ (1x30mL), water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 8%MeOH, 92% $CHCl_3$, fractions combined and evaporated *in vacuo*. The residue was freeze dried from water/acetontrile to give a white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide (55mg, 0.11mmol, 51% yield).

$[M+H]^+$ = 535

^1H NMR: (d6-DMSO), δ: 4.69 (2H, d, J = 5.8Hz), 5.07 (2H, s), 5.40 (2H, s), 6.21-6.24 (1H, m), 6.39 (1H, d, J = 9.0Hz), 7.00 (1H, d, J = 6.9Hz), 7.26-7.30 (5H, m), 7.39-7.44 (2H, m), 7.77 (1H, q, J = 6.6Hz), 8.14 (1H, s), 8.43 (1H, s), 8.89 (1H, t, J = 5.8Hz), 13.11 (1H, s).

EXAMPLE 9

2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. [4-(4-Methyl-pyrazol-1-ylmethyl)-phenyl]-methanol

4-(Chloromethyl)benzylalcohol (5.47g, 34.9mmol) was dissolved in acetone (50mL) 4-methylpyrazole (2.86g, 34.9mmol) and potassium carbonate (5.07g, 36.7mmol) were added and the reaction mixture was stirred at rt for 18 hrs and at 60°C for 30 hrs after which time the solvent was removed *in vacuo* and the residue taken up in EtOAc (100mL), this solution was washed with water (1x30mL), brine (1x30mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent gradient of 10 to 80% EtOAc in iso-Hexane, fractions combined and evaporated *in vacuo* to give a white solid identified as [4-(4-methyl-pyrazol-1-ylmethyl)-phenyl]-methanol (3.94g, 18.90mmol, 54% yield).

$[M+H]^+$ = 203

B. 1-(4-Chloromethyl-benzyl)-4-methyl-1H-pyrazole

[4-(4-Methyl-pyrazol-1-ylmethyl)-phenyl]-methanol (2.03g, 10.04mmol) and triethylamine (1.13g, 11.54mmol) was dissolved in dichloromethane (40mL). To this solution was added methanesulphonyl chloride (1.26g, 11.04mmol) dropwise. The reaction mixture was stirred at rt for 18 hrs and diluted with $CHCl_3$ (250mL) the filtrate was washed with saturated NH_4Cl (1x30mL), water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent gradient of 0 to 60% EtOAc in iso-Hexane, fractions combined and evaporated *in vacuo* to give a white solid identified as 1-(4-chloromethyl-benzyl)-4-methyl-1H-pyrazole (1.49g, 6.62mmol, 60% yield).
$[M+H]^+$ = 221, 223

C: 2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid methyl ester
A solution of methyl 2,5-dimethyl-1H-pyrrole-3-carboxylate (0.382 g, 2.492 mmol) in anhydrous DMF (8 mL) was cooled in an ice-bath, then treated sequentially portionwise with sodium hydride (0.071 g, 2.95 mmol), then 1-(4-(chloromethyl)benzyl)-4-methyl-1H-pyrazole (0.50 g, 2.266 mmol) and the mixture allowed to stir at ~ 5 °C for 1 hour. The ice-bath was removed and the mixture stirred for a further 45 min. Further sodium hydride (~0.5 eq) was added and the mixture allowed to stir overnight. The reaction was quenched with water (40 mL) and attempted to extract into DCM(3 x 40 mL), but presence of DMF caused emulsion. Combined DCM layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Brine (40 mL) was added to the initial aqueous layer and this extracted with EtOAc (3 x 40 mL). The combined EtOAc layers were washed with water (3 x 20 mL), brine (30 mL), dried ($MgSO_4$), and concentrated with the DCM extract residue (4 mbar @ 55 ºC) to remove residual DMF. The compound was purified by chromatography (silica) eluting with a gradient of 0 to 70% EtOAc/Iso-Hexanes to afford 2,5-dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid methyl ester (602 mg, 1.748 mmol, 77 % yield) as a pale yellow oil which crystallized slowly on standing.

$[M+H]^+$ = 338

D: 2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid
A solution of methyl 2,5-dimethyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrrole-3-carboxylate (459 mg, 1.360 mmol) in tetrahydrofuran (8 mL), methanol (5 mL) and water (7 mL) were treated with lithium hydroxide (163 mg, 6.80 mmol) and the mixture heated at 65 ºC with stirring for 48 hrs until completion. The majority of the solvents were removed under vacuum. The resultant cloudy mixture was partitioned between EtOAc (50 mL) and water (50 mL) containing 1M NaOH (2 mL). The organic layer was discarded and the aqueous layer acidified to ~pH3 with 1M HCl (turned cloudy). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics dried ($MgSO_4$), filtered

and concentrated under vacuum to afford 2,5-dimethyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrrole-3-carboxylic acid (448 mg, 1.358 mmol, 90 % yield) as a pale yellow solid.

$[M+H]^+$ = 324

E: 2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

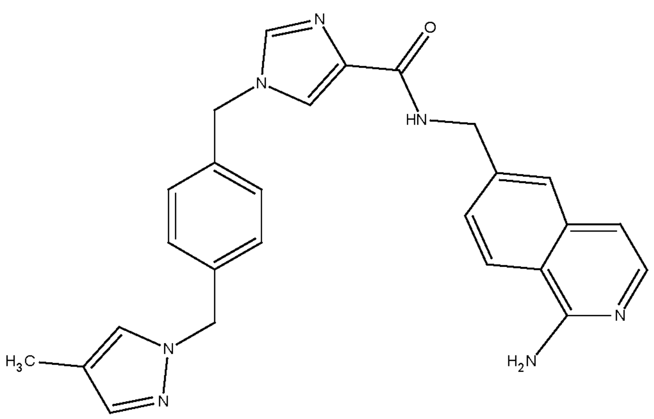
A scintillation vial was charged with 2,5-dimethyl-1-(4-((4-methyl-1H-pyrazol-1l) methyl)benzyl)-1H-pyrrole-3-carboxylic acid (93 mg, 0.289 mmol), 6-(aminomethyl)isoquinolin-1-amine (80 mg, 0.462 mmol), HATU (121 mg, 0.318 mmol) and 25% DMF/DCM (3.5 mL). Next, N,N-diisopropylethylamine (101 µl, 0.577 mmol) was added and the mixture allowed to stir overnight. The reaction mixture was diluted with MeOH (10 mL) to form a solution. This was passed through a strong cation exchange chromatography column (3 g), washing with MeOH, eluting with 1% NH_3/MeOH. The crude material was purified by chromatography (silica) eluting with a gradient of 0 to 8% MeOH/DCM(1% NH_3) to afford 2,5-dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (66 mg, 0.134 mmol, 46.3 % yield) as a pale yellow powder.

$[M+H]^+$ = 479

^{1}H NMR: (d6-DMSO), δ: 1.99 (3H, d, J = 0.7Hz), 2.07 (3H, s), 2.37 (3H, s), 4.50 (2H, d, J = 6.0Hz), 5.07 (2H, s), 5.20 (2H, s), 6.37 (1H, d, J = 1.1Hz), 6.70 (2H, s), 6.83-6.92 (3H, m), 7.16 (2H, d, J = 8.2Hz), 7.22 (1H, s), 7.39 (1H, dd, J = 1.7, 8.6Hz), 7.52 (2H, s, br), 7.76 (1H, d, J = 5.8Hz), 8.13 (1H, d, J = 8.6Hz), 8.21 (1H, t, J = 6.1Hz).

__REFERENCE EXAMPLE 10__

__1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide__



A. 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid ethyl ester

1-(4-Chloromethyl-benzyl)-4-methyl-1H-pyrazole (986mg, 4.47mmol) was dissolved in DMF (28mL) ethyl 1H-imidazole-4-carboxylate (626mg, 4.47mmol) and potassium carbonate (1.42g, 10.28mmol) were added and the reaction mixture was stirred at rt for 3 days after which time the reaction mixture was diluted with EtOAc (100mL), this solution was washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent gradient of 50 to 100% EtOAc in iso-Hexane, 2 products eluted the first at ~90% EtOAc/Iso-Hexane with the second eluting at 100% EtOAc. Fractions combined and evaporated *in vacuo*.

The first product eluted was isolated as a white solid identified as 3-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3H-imidazole-4-carboxylic acid ethyl ester (675mg, 2.06mmol, 46% yield).

$[M+H]^+$ = 325

The second product eluted was isolated as a clear gum identified as 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid ethyl ester (540mg, 1.652mmol, 37% yield).

$[M+H]^+$ = 325

B. 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid ethyl ester (471mg, 1.45mmol) was dissolved in THF(7mL) ethanol (4.5mL) and water (6.3mL) lithium hydroxide (174mg, 7.26mmol) was added. The reaction mixture was stirred at 65°C for 2 hrs after which time the solvent was concentrated *in vacuo* and the residue taken up in $CHCl_3$ (150mL), the aqueous layer was extracted and acidified with 1M HCl to pH2 and extracted $CHCl_3$ (3x50mL) the combined extracts were washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent dichloromethane:MeOH:NH_3 (100:10:1). Fractions combined and evaporated *in vacuo* to give a white solid identified as 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (245mg, 0.82mmol, 51% yield).

$[M+H]^+$ = 295

C. 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

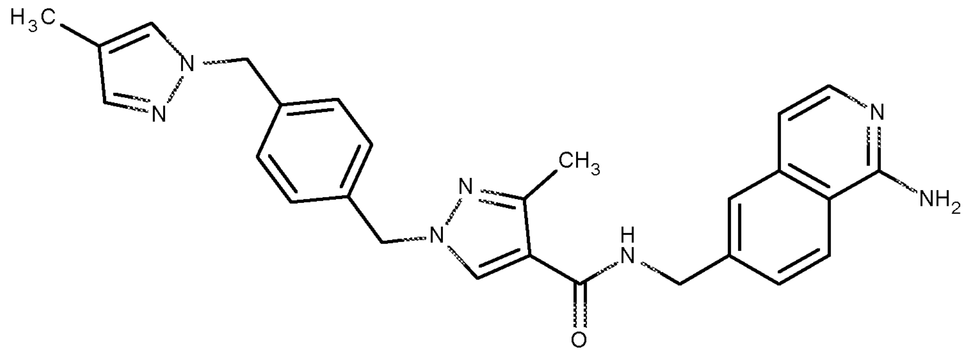
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (50mg, 0.169mmol) was dissolved in DMF/CH_2Cl_2(1:3, 3mL). HATU (71mg, 0.186mmol) was added followed by 6-(aminomethyl)isoquinolin-1-amine (80mg, 0.464mmol) and N,N-diisopropylethylamine (44mg, 0.337mmol). After 18 hrs at rt reaction mixture was diluted with chloroform (400mL) washed with NH_4Cl (1x30mL), water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* giving a yellow oil. The residue was purified by flash chromatography (silica), eluent dichloromethane:MeOH:NH_3 (100:10:1). fractions combined and evaporated *in vacuo* to give a white solid identified as 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (47mg, 0.102mmol, 60% yield).

$[M+H]^+$ = 452

^{1}H NMR: (d6-DMSO), δ: 1.99 (3H, s), 4.52 (2H, d, J = 6.3Hz), 5.20 (1H, s), 5.22 (1H, s), 6.70 (2H, s), 6.83 (1H, d, J = 5.8Hz), 7.16-7.25 (3H, m), 7.26-7.32 (2H, m), 7.38 (1H, dd, J = 1.7, 8.6Hz), 7.46-7.56 (2H, m), 7.69-7.78 (2H, m), 7.85 (1H, d, J = 1.3Hz), 8.11 (1H, d, J = 8.6Hz), 8.58 (1H, t, J = 6.3Hz).

EXAMPLE 11

3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. N'-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-hydrazinecarboxylic acid tert-butyl ester

A solution of 1-(4-(chloromethyl)benzyl)-4-methyl-1H-pyrazole (3.5 g, 15.86 mmol) and tert-butyl carbazate (8.38 g, 63.4 mmol) in absolute EtOH (21 mL) was treated with N,N-diisopropylethylamine (2.76 mL, 15.86 mmol) and the mixture stirred at 60 ºC for 24 hrs . LCMS indicated desired product and reaction of product with a second equivalent of starting chloride $[445]^+$ in a 3 : 1 ratio. Solvents were removed under vacuum and the residue partitioned between EtOAc (150 mL) and saturated aqueous NH_4Cl (turned cloudy, some water added). The organic layer was separated and washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography (silica) eluting with a gradient of 0 to 50% EtOAc/Iso-Hexanes. Note chromaphore is weak; product streaked over many fractions. Every 5th fraction was examined by HPLC and the cleanest set of fractions combined to afford >7g of material. ^{1}H NMR (DMSO-d_6, 1119-13-1) showed ~85% purity aside from the presence of excess tert butyl carbazate. The product was purified by Kugelrohr distillation (3 runs until no more material evident in collection bulb) at 2.9 mBar / 110-115 ºC (indicated). ^{1}H NMR (DMSO-d_6) showed removal of the tert-butyl carbazate. The mixture was further purified by chromatography (silica) eluting with a gradient of 0 to 60% THF/DCM. The compound eluted more quickly than expected (in ~15% THF). Some clean product fractions were obtained at the tail of the peak to afford 1.77g of the desired compound at >95% purity by ^{1}H NMR. Mixed fractions were also obtained and were consistent with the desired compound at 78% purity by ^{1}H NMR.

$[M+H]^+$ = 317

B. [4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-hydrazine

To a stirred solution of 4-tert-butyl 2-(4-((4-methyl-1H-pyrazol-1- l)methyl)benzyl) hydrazinecarboxylate (369 mg, 1.166 mmol) in dioxane (5 mL) was added HCl 4M in dioxane (1 mL, 32.9 mmol) dropwise, a thick precipitate formed and stirring continued for 2 hrs. Reaction mixture was diluted with diethyl ether (20 mL). The thick precipitate did not break up on sonication. Attempts to filter the material were difficult. Drying for ~30 min on filter paper did not give dry solid. Material was slightly hygroscopic. The bulk was transferred into a flask and used directly in the next step without further purification

$[M+H]^+$ = 217

C. 3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester

To a stirred suspension of 5-acetyl-uracil (150mg, 0.971 mmol) and [4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-hydrazine dihydrochloride (337 mg, 1.165 mmol) in EtOH (10 mL) was added conc HCl (0.5 mL) and the reaction heated at reflux (80 °C) for 24 hrs. A fine white suspension was observed. Analysis by LCMS showed the main peak $[M+H]^+$ = 353 corresponding to the imine intermediate. After a further 3 hrs no further reaction had occurred. The reaction mixture was charged with H_2SO_4 (conc.) (0.5 mL) and heated to 120°C for 50 min in a microwave. The reaction mixture was evaporated to dryness and the residue taken up into EtOAc (100 mL). The organics were washed with NaOH (2M, 50 mL), brine (50 mL), dried over magnesium sulfate, filtered and evaporated to dryness. The crude product was purified by chromatography (12 g column, 0-50% EtOAc in isohexanes) to afford 3-methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (144 mg, 0.417 mmol, 42.9 % yield) as a colourless oil. Analysis by HPLC, (PFP column, 40% Methanol, acidic, 225 nm detection) showed clean 3-regioisomer.

$[M+H]^+$ = 339

D. 3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid

To a stirred solution of 3-methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (144 mg, 0.426 mmol) in THF (3 mL) and MeOH (2 mL) was added NaOH 2M (638 µl, 1.277 mmol) and left at RT overnight. Analysis showed clean conversion to the desired acid. Reaction mixture was acidified to pH5 using 1M HCl. The product was extracted into EtOAc (20 mL) and the organics washed with brine (2 x 20 mL), dried over magnesium sulfate, filtered and solvent removed to give a white solid identified as 3-methyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (83 mg, 0.254 mmol, 59.7 % yield).

$[M+H]^+$ =311

E. 3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

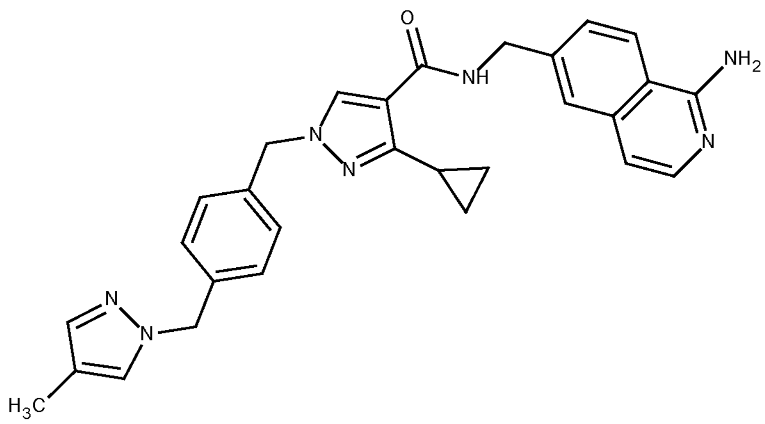
To a stirred solution of 3-methyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (75 mg, 0.242 mmol) and 6-(aminomethyl)isoquinolin-1-amine, 2HCl (59.5 mg, 0.242 mmol) in DMF (3 mL) was added N,N-diisopropylethylamine (169 µl, 0.967 mmol) and HATU (96 mg, 0.254 mmol). The reaction was stirred at rt for 2 hrs. Analysis showed complete conversion to desired product. The reaction mixture was diluted with EtOAc (30 mL) and washed with NaOH (2M, 20 mL), brine (50 mL), dried over magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude solid was pre-absorbed onto silica before purification by chromatography (12 g column, 0-10% MeOH (1%NH_3) in DCM, pausing at 5% to afford 3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride (65.2 mg, 0.140 mmol, 58.0 % yield) as a white powder. The free base was taken up into MeOH (1 mL) and HCl 4M in dioxane (35.0 µl, 0.140 mmol, 1eq.) was added. A solid precipitated and the MeOH was removed under a flow of air. The dioxane was removed under vacuum. The residue was triturated from diethyl ether (5 mL) to afford 3-methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride (62 mg, 0.117 mmol, 48.6 % yield) as white solid.

$[M+H]^+$ = 466

NMR (d6-DMSO) δ: 1.99 (3H, J= 0.7 Hz), 2.31 (3H, s), 4.57 (2H, d, J = 5.9 Hz), 5.23 (4H, d, J= 7.4 Hz), 7.16–7.28 (6H, m), 7.54 (1H, t, J= 0.9 Hz), 7.64–7.73 (2H, m), 7.79 (1H, d, J= 1.6 Hz), 8.24 (1H, s), 8.54 (1H, d, J= 8.7 Hz), 8.61 (1H, t, J= 6.0 Hz), 9.05 (2H, br s), 13.14 (1H, s)

EXAMPLE 12

3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 1-(4-Bromomethyl-benzyl)-4-methyl-1H-pyrazole

[4-(4-Methyl-pyrazol-1-ylmethyl)-phenyl]-methanol (2.05g, 10.1mmol) was dissolved in dichloromethane (50mL). To this solution was added triphenylphosphine (3.05 g, 11.6 mmol). The resultant solution was cooled in an ice bath before carbon tetrabromide (3.69 g, 11.1 mmol) was added portionwise. The reaction mixture was stirred at rt for 18 hrs and diluted with $CHCl_3$ (100mL). The filtrate was washed with saturated $NaHCO_3$ (1x30mL), water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 95% Pet. Ether, 5% EtOAc, fractions combined and evaporated *in vacuo* to give a white solid which was identified as 1-(4-bromomethyl-benzyl)-4-methyl-1H-pyrazole (1.64g, 6.19mmol, 61% yield).

$[M+H]^+$ = 265

B. 3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester

Ethyl 3-cyclopropyl-1H-pyrazole-4-carboxylate (100mg, 0.56mmol) was dissolved in DMF (20mL). 1-(4-Bromomethyl-benzyl)-4-methyl-1H-pyrazole (155mg, 0.58mmol) and potassium carbonate (153mg, 1.1mmol) were added and the reaction mixture was stirred at rt for 2 days after which time the reaction mixture was diluted with EtOAc (100mL), this solution was washed with water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 98% dichloromethane, 2% methanol, fractions combined and evaporated *in vacuo* to give a white solid identified as 3-cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (190mg, 0.52mmol, 94% yield).

$[M+H]^+$ = 365

C. 3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid

3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (190mg, 0.52mmol) was dissolved ethanol (10mL) and sodium hydroxide (208mg, 5.2mmol) was added.

The reaction mixture was stirred at reflux for 18 hrs after which time the solvent was concentrated *in vacuo* and the residue taken up in $CHCl_3$ (150mL), the aqueous layer was extracted and acidified with 1M HCl to pH2 and extracted $CHCl_3$ (3x50mL). The combined extracts were washed with water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent dichloromethane:MeOH:NH_3 (100:10:1) fractions combined and evaporated *in vacuo* to give a white solid identified as 3-cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (150mg, 0.45mmol, 86% yield).

$[M+H]^+$ = 337

D. 3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

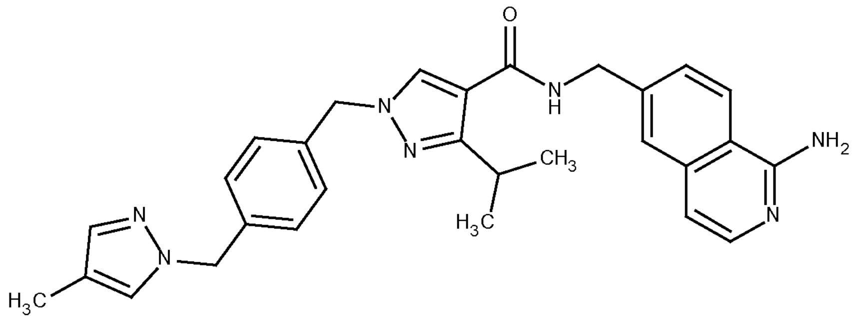
3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (65mg, 0.19mmol) was dissolved in CH_2Cl_2 (50mL) and DMF(2.5mL). This solution was cooled to 0°C. 6-Aminomethyl-isoquinolin-1-ylamine (34mg, 0.19mmol) was added followed by HOBt (31mg, 0.23mmol) and triethylamine (98mg, 0.97mmol). Water soluble carbodiimide (52mg, 0.27mmol) was then added. After 18 hrs at 0°C to rt reaction mixture was diluted with chloroform (100mL) and IPA (10mLmL), washed with $NaHCO_3$ (1x30mL), water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* giving a yellow oil. The residue was purified by flash chromatography (silica), eluent dichloromethane:MeOH:NH_3 (100:10:1), fractions combined and evaporated *in vacuo* to give a white solid identified as 3-cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (46mg, 0.09mmol, 48% yield).

$[M+H]^+$ = 496

^{1}H NMR: (d6-DMSO), δ: 0.73-0.76 (2H, m), 0.79-0.84 (2H, m), 1.98 (3H, s), 2.55-2.67 (1H, m), 4.50 (2H, d, J= 5.9Hz), 5.19 (2H, s), 5.21 (2H, s), 6.71 (2H, s), 6.85 (1H, d, J= 5.8Hz), 7.18 (4H,s), 7.23 (1H, s), 7.36-7.39 (1H, m), 7.52 (2H, s), 7.76 (1H, d, J= 5.8Hz), 8.12 (2H, d, J= 8.4Hz), 8.46 (1H, t, J= 5.9Hz).

EXAMPLE 13

3-Isopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. Ethyl 3-isopropyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate

To a stirred solution of ethyl 3-isopropyl-1H-pyrazole-4-carboxylate (446 mg, 2.447 mmol) and 1-(4-(chloromethyl)benzyl)-4-methyl-1H-pyrazole (540 mg, 2.447 mmol) in DMF (8 mL) was added K_2CO_3 (676 mg, 4.89 mmol) and stirred at rt overnight. The reaction was diluted with brine (10 mL) and EtOAc (10 mL) and the layers separated. The aqueous was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude was purified by chromatography (24 g column, EtOAc in iso-Hexanes 0-50% yield) to afford ethyl 3-isopropyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (702 mg, 1.762 mmol, 72.0 % yield) as a thick pale yellow oil.

$[M+H]^+$ = 367

B. 3-Isopropyl -1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid

To a stirred mixture of ethyl 3-isopropyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (690 mg, 1.883 mmol) and lithium hydroxide (135 mg, 5.65 mmol) in THF (8 mL) and water (4 mL) at rt was added lithium hydroxide (135 mg, 5.65 mmol). MeOH (1 mL) added to increase solubility. The reaction was stirred and heated at 50 °C for 5 hrs. The reaction was allowed to cool to rt, acidified to pH ~3 with 1M HCl and extracted with EtOAc (3 x 5mL). Organic dried (Mg_2SO_4), filtered and evaporated under reduced pressure to give) as a pale yellow solid. This sample crude was purified by chromatography (12 g column, (2:1 EtOAc-MeCN) in DCM 0-50% yield) to afford 3-isopropyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (256 mg, 0.749mmol, 40% yield). No undesired 5-regioisomer was observed.

$[M+H]^+$ = 339

C. 3-Isopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

To a stirred solution of 3-isopropyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (129 mg, 0.381 mmol), 6-(aminomethyl)isoquinolin-1-amine dihydrochloride (100 mg, 0.406 mmol) and HATU (174 mg, 0.457 mmol) in DMF (2 mL) was added N,N-diisopropylethylamine

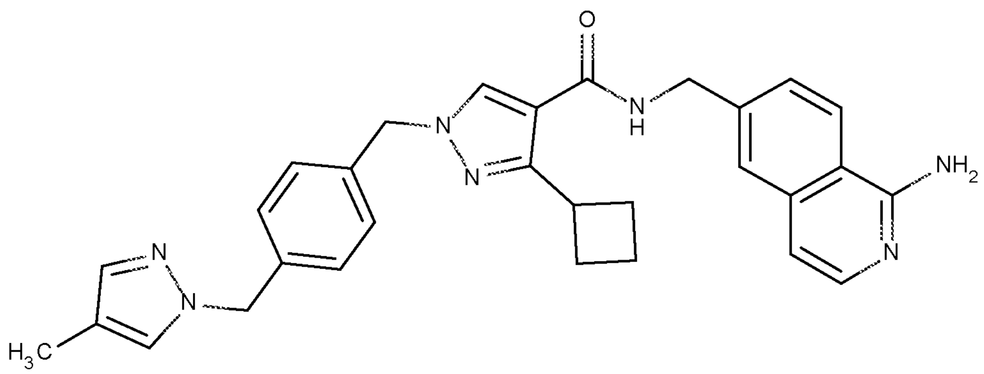
(266 µL, 1.525 mmol). The resulting mixture was stirred at rt overnight. The reaction was diluted with EtOAc (15 mL) and washed with 2M NaOH (2 x 20 mL). Organic dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude was purified by chromatography (4 g column, MeOH in DCM 0-5% and 1% Et_3N) to afford the desired compound as a free base. ^{1}H NMR in DMSO-d6 was consistent with the free amine structure. The product was dissolved in DCM (1 mL), 4M HCl in dioxane (124 µL, 0.496 mmol) added and the resulting flocculent mixture stirred at rt for 15 min. The solvent was then evaporated under reduced pressure to give N-((1-aminoisoquinolin-6-yl)methyl)-3-isopropyl-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide, HCl (170 mg, 0.319 mmol, 84 % yield) as a white solid.

$[M+H]^+$ = 494

^{1}H NMR: (d6-DMSO), δ: 1.17 (6H, d, J = 6.9 Hz); 1.99 (3H, t, J = 0.7 Hz); 3.57 (1H, hept, J = 6.2 Hz); 4.56 (2H, d, J = 5.8 Hz); 5.25 (4H, d, J = 15.4 Hz); 7.16 - 7.27 (6H, m); 7.55 (1H, q, J = 0.8 Hz); 7.63 - 7.72 (2H, m); 7.79 (1H, d, J = 1.6 Hz); 8.19 (1H, s); 8.54 (1H, d, J = 8.6 Hz); 8.64 (1H, t, J = 5.9 Hz); 9.08 (2H, s); 13.22 (1H, s).

EXAMPLE 14

3-Cyclobutyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. (*E*)-Ethyl 2-(cyclobutanecarbonyl)-3-(dimethylamino)acrylate

To a flask charged with ethyl 3-cyclobutyl-3-oxopropanoate (0.935 g, 5.49 mmol) was added 1,1-dimethoxy-*N,N*-dimethylmethanamine (0.876 mL, 6.59 mmol) and dioxane (30 mL). Heated at 70 °C for 7 hrs. Reaction mixture was azeotroped with toluene (2 x 30 mL) to remove any residual 1,1-dimethoxy-*N,N*-dimethylmethanamine. Quantitative yield assumed and material used directly in the next step.

$[M+H]^+$ = 216

B. Ethyl 3-cyclobutyl-1H-pyrazole-4-carboxylate

To a stirred solution of 1132-12 (*E*)-ethyl 2-(cyclobutanecarbonyl)-3-(dimethylamino)acrylate (1.24 g, 5.50mmol) (crude) in EtOH (30 mL) was added hydrazine, H_2O (0.803 mL, 8.26 mmol) and heated to reflux overnight. Reaction mixture evaporated to remove excess hydrazine. Crude material was taken up into EtOAc (150 mL) and washed with $NaHCO_3$ (aq, 100 mL), then brine (100 mL), dried over magnesium sulfate and solvent removed to afford ethyl 3-cyclobutyl-1H-pyrazole-4-carboxylate (709 mg, 3.54 mmol, 64.3 % yield) as a waxy solid on standing.

$[M+H]^+$ = 195

C. 3-Cyclobutyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

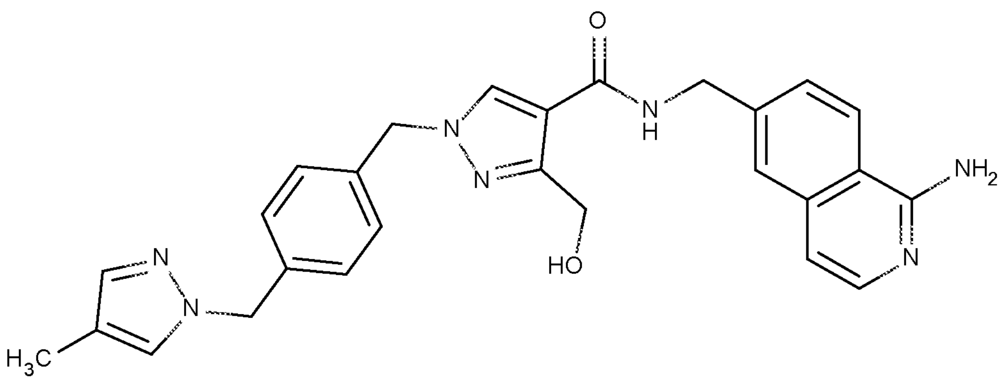
Procedure as for Example 13 methods A-C

$[M+H]^+$ = 506

^{1}H NMR: (d6-DMSO), δ: 1.70 - 1.83 (1H, m); 1.81 - 1.98 (1H, m); 1.99 (3H, d, J = 0.8 Hz); 2.12 - 2.25 (4H, m); 4.55 (2H, d, J = 5.8 Hz); 5.23 (2H, s); 5.29 (2H, s); 7.15 - 7.29 (6H, m); 7.55 (1H, t, J = 0.9 Hz); 7.63 - 7.72 (2H, m); 7.78 (1H, d, J = 1.5 Hz); 8.20 (1H, s); 8.49 - 8.61 (2H, m); 9.03 (2H, s); 13.11 (1H, s).

EXAMPLE 15

3-Hydroxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 3-Hydroxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

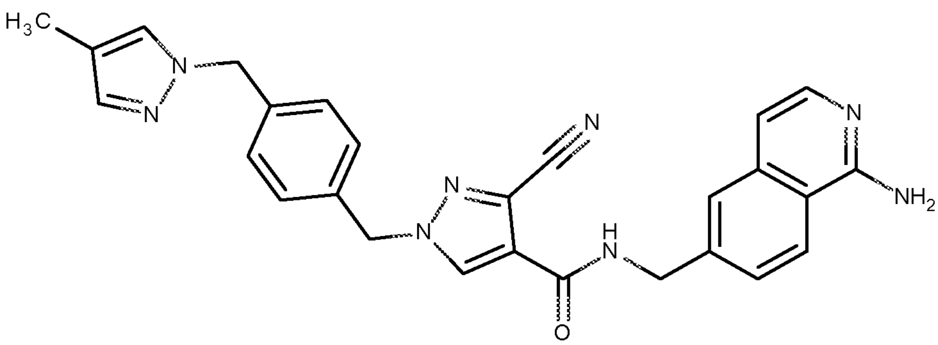
Tribromoborane (118 µl, 0.118 mmol) was added to a stirred solution of 3-methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (45 mg, 0.091 mmol) in DCM (0.3 mL). The resulting mixture was stirred at rt for 3 hrs. The solvent was evaporated under reduced pressure and the residue was absorbed on silica before purification by chromatography (4 g column, 0-10% MeOH in DCM, 1% Et_3N) to afford the free base of the desired compound as a white solid. This solid was dissolved in DCM (1 mL) and MeOH (0.5 mL). 4M

HCl in dioxane (29.5 µl, 0.118 mmol) was added and the resulting mixture was stirred at rt for 15 min. The solvents were evaporated under reduced pressure to give 3-hydroxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride (39 mg, 0.075 mmol, 82 % yield) as a white solid.
$[M+H]^+$ =482.3

^{1}H NMR: (d6-DMSO), δ: 1.99 (3H, s), 4.56 (2H, s), 4.64 (2H, d, J = 5.8 Hz), 5.22 (2H, s), 5.28 (2H, s), 7.16 - 7.31 (6H, m), 7.55 (1H, t, J = 0.9 Hz), 7.63 - 7.74 (2H, m), 7.82 (1H, d, J = 1.6 Hz), 8.34 (1H, s), 8.55 (1H, d, J = 8.7 Hz), 8.90 - 9.05 (3H, m), 13.17 (1H, s).

EXAMPLE 16

3-Cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. Ethyl 3-cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylate
Procedure as Example 13 method A

$[M+H]^+$ = 350

B. 3-Cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid
A stirred solution of ethyl 3-cyano-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (100 mg, 0.286 mmol) in THF (0.3 mL) and MeOH (0.3 mL) was treated with a solution of lithium hydroxide (10.28 mg, 0.429 mmol) in water (0.3 mL). The mixture was allowed to stir at ambient temperature for 18hrs. Solvents were removed under vacuum and the residue partitioned between EtOAc (1 mL) and water (1 mL). The organic layer was removed and the aqueous layer adjusted to pH 4 with 1M HCl, forming a precipitate. This was briefly sonicated then filtered, washing with copious water. On drying under vacuum, 3-cyano-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (70 mg, 0.196 mmol, 68.5 % yield) was recovered as a white solid.
$[M+H]^+$ = 322

C. 3-Cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

A vial was charged with 3-cyano-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (232 mg, 0.722 mmol), 6-(aminomethyl)isoquinolin-1-amine dihydrochloride (195 mg, 0.794 mmol), HATU (302 mg, 0.794 mmol), anhydrous DCM (4.5 mL) and anhydrous DMF (1.5 mL). N,N-Disopropylethylamine (503 µl, 2.89 mmol) was added and the mixture allowed to stir at ambient temperature. A precipitate formed. Solvents were removed under vacuum, slurried in methanol and filtered to give 293 mg of solid. This was purified by strong cation exchange chromatography (8 g), loading in a large quantity of MeOH/DCM (3:1, ~150 mL), washing with MeOH, eluting with 1% NH_3/MeOH to afford 243 mg of material. This was purified by chromatography (silica) eluting with a gradient of 0 to 10% MeOH (1% NH_3/DCM) to afford 3-cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride (193 mg, 56 % yield) as a white powder.

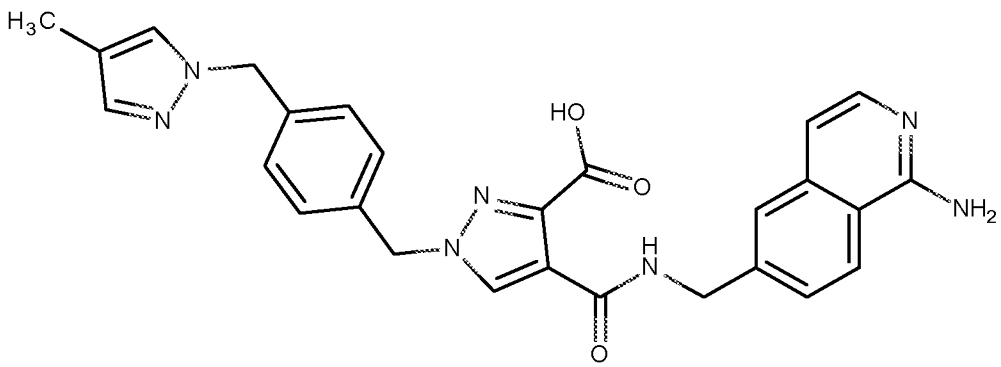
A sample of the product(60 mg) was dissolved in DCM (1 mL) and MeOH (0.5 mL) then treated with 4M HCl in dioxane (~100 µL), forming a precipitate. This was allowed to stand for 1 minute, then concentrated under vacuum to afford 63 mg of the mono-HCl salt

$[M+H]^+$ = 477

^{1}H NMR: (d6-DMSO), δ: 1.98 (3H, s), 4.60 (2H, d, J = 5.8Hz), 5.24 (2H, s), 5.47 (2H, s), 7.17-7.28 (4H, m), 7.32 (2H, d, J = 8.1Hz), 7.55 (1H, s), 7.63-7.74 (2H, m), 7.82 (1H, s), 8.56 (1H, d, J = 8.6Hz), 8.61 (1H, s), 9.12 (2H, brs), 9.23 (1H, t, J = 5.9Hz), 13.29 (1H, s).

EXAMPLE 17

4-[(1-Amino-isoquinolin-6-ylmethyl)-carbamoyl]-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-3-carboxylic acid



A. 4-[(1-Amino-isoquinolin-6-ylmethyl)-carbamoyl]-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-3-carboxylic acid hydrochloride

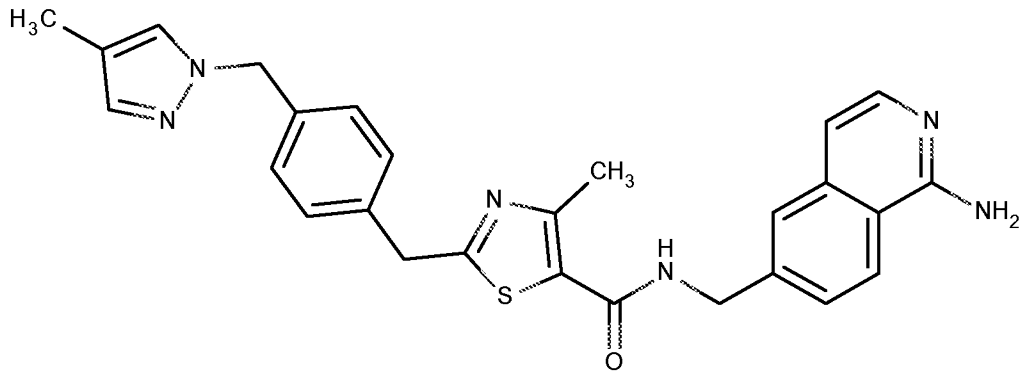
A stirred suspension of 3-cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (25 mg, 0.052 mmol) in MeOH (0.25 mL) was treated with a solution of lithium hydroxide (12.56 mg, 0.525 mmol) in water (0.25 mL). The mixture was allowed to stir at 60 °C (DrySyn bath temperature) overnight. The reaction was allowed to cool, then adjusted to pH 3 with 1M HCl. The precipitate was filtered, washing with water and dried under vacuum to afford a white powder. The mixture was taken up in DCM (0.5 mL) and MeOH (0.5 mL) and treated with 4M HCl in dioxane (29.5 µL, 0.118 mmol). The mixture was allowed to stand for 1 minute, then concentrated under vacuum to afford 4-[(1-amino-isoquinolin-6-ylmethyl)-carbamoyl]-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-3-carboxylic acid hydrochloride (20 mg, 0.036 mmol, 68.1 % yield) as a white powder.

$[M+H]^+$ = 496

^{1}H NMR: (d6-DMSO), δ: 1.98 (3H, s), 4.69 (2H, d, J = 5.8Hz), 5.23 (2H, s), 5.43 (2H, s), 7.18-7.26 (4H, m), 7.31 (2H, d, J = 8.1Hz), 7.54 (1H, s), 7.63-7.77 (2H, m), 7.85 (1H, s), 8.57 (1H, d, J = 8.6Hz), 8.64 (1H, s), 9.13 (2H, brs), 10.04 (1H, t, J = 5.8Hz), 13.31 (1H, s), 14.85 (1H, brs).

EXAMPLE 18

4-Methyl-2-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-thiazole-5-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 2-(4-Bromo-benzyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester

A solution of 2-(4-bromophenyl)ethanethioamide (1.98 g, 8.60 mmol) and ethyl 2-chloro-3-oxobutanoate (1.428 mL, 10.32 mmol) in pyridine (30 mL) and ethanol (30 mL) was stirred at 90°C for 18 hrs. Then the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was diluted with ethyl acetate (100 mL), and 2N hydrochloric acid (100 mL) was added. The organic layer was separated, washed with saturated brine (50 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude was purified by chromatography (40 g column, EtOAc in Hex 0-50% yield) to afford 2-(4-bromo-benzyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester (1.33 g, 5.00 mmol, 52.1 % yield) as a white crystalline solid.

$[M+H]^+$ = 340, 342

B. Potassium trifluoro(N-methylfomepizole)borate

Potassium hexamethyldisilazide (2.992g, 15.00 mmol) was added dropwise to a stirred mixture of 4-methyl-1H-pyrazole (1.067g, 13.00 mmol) and potassium bromomethyltrifluoroborate (2.008g, 10 mmol) in dioxane (10 mL). The resulting mixture stirred at 85 °C overnight then at rt over the weekend. The reaction mixture was quenched with water (2 mL) and dried under reduced pressure (water bath at 50 °C). The crude solid was dissolved in a solution of hot HPLC grade acetone then filtered to remove KCl. The filtrate was concentrated under reduced pressure, dissolved in acetone (14 mL) and precipitated by addition of Et_2O (30 mL) to afford the desired product (660 mg, 2.91 mmol, 29.1 % yield) as a white solid.

C. 4-Methyl-2-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-thiazole-5-carboxylic acid ethyl ester

A mixture of potassium trifluoro(N-methylfomepizole)borate (386 mg, 1.911 mmol) and 2-(4-bromo-benzyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester (591 mg, 1.737 mmol), in dioxane (4 mL) and water (1 mL) was stirred and heated at reflux for 1 hour. Sodium 2'-(dicyclohexylphosphino)-2,6-dimethoxy-[1,1'-biphenyl]-3-sulfonate (89 mg, 0.174 mmol), $[PdCl(allyl)]_2$ (31.8 mg, 0.087 mmol) and caesium carbonate (1698 mg, 5.21 mmol) in dioxane (8 mL) and water (2 mL) was degassed with argon for 15 min. Then, the mixture was heated and stirred at 100 °C overnight. The reaction mixture was diluted, absorbed on silica and purified by chromatography (12 g column, 0-50% EtOAc in isohexanes) to afford 4-methyl-2-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-thiazole-5-carboxylic acid ethyl ester (278 mg, 0.547 mmol, 31.5 % yield) as a yellow thick oil.

$[M+H]^+$ = 356

D. 4-Methyl-2-[4-(4-methyl-pyrazol-1-yl methyl)-benzyl]-thiazole-5-carboxylic acid

To a stirred mixture of 4-methyl-2-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-thiazole-5-carboxylic acid ethyl ester (278 mg, 0.782 mmol) in THF (1 mL) and water (0.5 mL) at rt was added sodium hydroxide (130 mg, 3.25 mmol). The resulting solution was stirred at rt overnight and evaporated under reduced pressure. The residue was redissolved in 2M NaOH (5 mL) and extracted with EtOAc (3 x 5 mL). Then, the aqueous was acidified to pH ~3 and extracted with EtOAc (3 x 5mL). Combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 4-methyl-2-[4-(4-methyl-pyrazol-1-yl methyl)-benzyl]-thiazole-5-carboxylic acid (232 mg, 0.602 mmol, 77 % yield) as a pale yellow solid.

$[M+H]^+$ = 328

E. 4-Methyl-2-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-thiazole-5-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

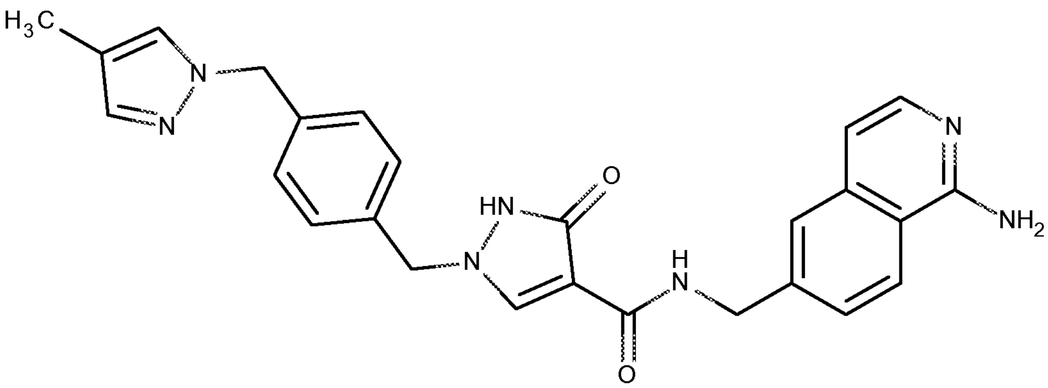
Procedure as for Example 13 method C

$[M+H]^+$ = 483

^{1}H NMR: (d6-DMSO), δ: 2.00 (3H, s); 2.55 (3H, s); 4.28 (2H, s); 4.56 (2H, d, J = 5.8 Hz); 5.23 (2H, s); 7.15 - 7.36 (6H, m); 7.56 (1H, t, J = 0.9 Hz); 7.62 - 7.71 (2H, m); 7.78 (1H, d, J = 1.6 Hz); 8.52 (1H, d, J = 8.7 Hz); 8.80 (1H, t, J = 5.9 Hz); 9.00 (2H, s); 13.04 (1H, s)

EXAMPLE 19

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. Ethyl 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

To a solution of sodium ethanolate (1418 mg, 20.83 mmol) and diethyl 2-(ethoxymethylene)malonate (842µl, 4.17 mmol) in EtOH (10mL) was added dropwise a solution of 1-(4-(hydrazinylmethyl)benzyl)-4-methyl-1H-pyrazole, 2HCl (1446 mg, 5 mmol) in EtOH (20 mL) with cooling in an ice-water bath. The resulting mixture was stirred allowed to warm to rt overnight. The reaction mixture was concentrated under vacuum, then partitioned between DCM (50 mL) and water (50 mL, adjusted to pH 5 with 1N HCl). The aqueous layer was extracted with DCM (2 x 50 mL) and the combined organics washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to a yellow oil. This was purified by chromatography (silica) eluting with a gradient of 0 to 40% MeCN/DCM to afford 210 mg of ethyl 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate.

$[M+H]^+$ = 341

B. 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid

A solution of ethyl 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (200 mg, 0.588 mmol) in a mixture of THF (2 mL) and MeOH (0.5 mL) was treated with lithium hydroxide (70.4 mg, 2.94 mmol) and water (0.75 mL). The mixture was allowed to stir at ambient temperature for 1 hour. Further water (0.5 mL) was added to clarify, and the mixture heated at 50 °C overnight. Organics were removed under vacuum and the aqueous transferred to a separating funnel with water (7 mL). The aqueous (at pH 10) was extracted with EtOAc (10 mL). The aqueous layer was collected and adjusted to pH 4 with 1M HCl, forming a precipitate. This was allowed to stand for 5 min, then sonicated to a fine powder before being collected by filtration, washing with a small quantity of water. On drying under vacuum in the presence of $CaCl_2$, 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (147 mg, 0.466 mmol, 79 % yield) was isolated as an off-white powder.

$[M+H]^+$ = 313

C. 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

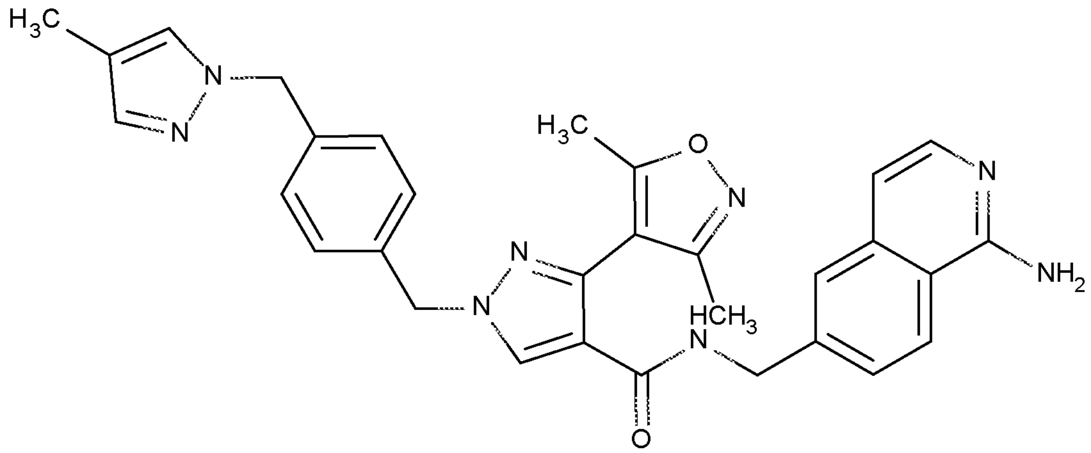
A scintillation vial was charged with 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (75 mg, 0.240 mmol), 6-(aminomethyl)isoquinolin-1-amine dihydrochloride (65.0 mg, 0.264 mmol), HATU (100 mg, 0.264 mmol) and anhydrous DCM (2 mL) and anhydrous DMF (0.3 mL). N,N-Diisopropylethylamine (167 µl, 0.961 mmol) was added and the mixture allowed to stir at ambient temperature for 2 hrs. Further HATU (30 mg), N,N-diisopropylethylamine (80 µL) and amine (20 mg) were added, along with DMF (1 mL). The mixture was heated at 40 °C for 2.5 hrs. The reaction was partitioned between EtOAc (25 mL) and 2N NaOH (15 mL). The aqueous layer was extracted with further EtOAc (2 x 25 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated. HPLC of the aqueous and isolated organics indicated that all product was in the aqueous layer. This was adjusted to pH 7 with conc. HCl (forming some relatively insoluble material) and extracted with EtOAc (containing trace MeOH, 2 x 30 mL) and DCM (containing trace MeOH, 30 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated. The residue was triturated with DCM and then MeOH to afford ~15 mg of a yellow solid. Chromatography (silica) eluting with THF afforded 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (9 mg, 0.012 mmol, 4.81 % yield, 70% purity) as a white powder.

$[M+H]^+$ = 468

NMR (d6-DMSO) δ: 1.98 (3H, s), 4.55 (2H, d, J= 6.0Hz), 5.09 (2H, s), 5.21 (2H, s), 6.82 (2H, br.s), 6.87 (1H, d, J= 6.2Hz), 7.16-7.26 (5H, m), 7.38 (1H, dd, J= 8.6, 1.8Hz), 7.52 (2H, m), 7.74 (1H, d, J= 5.8Hz), 7.93 (1H, t, J= 6.1Hz), 8.04 (1H, s), 8.14 (1H, d, J= 8.6Hz), 11.10 (1H, br.s).

EXAMPLE 20

3-(3,5-Dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A: Ethyl 3-bromo-1H-pyrazole-4-carboxylate

To a solution of tert-butyl nitrite (3.04 mL, 25.6 mmol) in anhydrous MeCN (80 mL) was added copper(II) bromide (5.71 g, 25.6 mmol). The mixture was stirred at ambient temperature for 1 hour under N_2, then ethyl 3-amino-1H-pyrazole-4-carboxylate (3.39 g, 21.85 mmol) added in portions over 15 min. The mixture was stirred at ambient temperature for 30 min, then heated at 70 °C for 2 hrs. The reaction was allowed to cool and the acetonitrile removed under vacuum. The residue was dissolved in EtOAc (250 mL) and washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated to a dark green solid (5.64 g, 18.02mmol, 82% yield, 70% purity). The product was used directly in the next step without purification.

$[M+H]^+$ = 219/221

B: 3-Bromo-1-[4-(4-methyl-pyrazol-1-yl methyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester

To a stirred suspension of ethyl 3-bromo-1H-pyrazole-4-carboxylate (500 mg, 2.283 mmol) and 1-(4-(chloromethyl)benzyl)-4-methyl-1H-pyrazole (504 mg, 2.283 mmol) in DMF (2.5 mL) was added potassium carbonate (631 mg, 4.57 mmol) and the mixture stirred at ambient temperature for 1.5 hrs. Heating was increased to 50 °C for 24hrs then the reaction was diluted with EtOAc (50 mL) and water (30 mL) containing brine (30 mL). The aqueous layer was extracted with further EtOAc (2 x 40 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated. The crude material was purified by chromatography (silica) eluting with a gradient of 0 to 45% EtOAc/Iso-Hexanes holding at 40% to elute the two regioisomers.

5-Bromo-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester (54 mg, 0.100 mmol, 4.40 % yield) was isolated as a clear gum which crystallized on standing, 2D nOesy showed no interaction between the benzylic protons and the pyrazole core ring proton (at 8.03 ppm).

[M+H]+ = 403/405

The desired isomer 3-bromo-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester (217 mg, 0.527 mmol, 23 % yield) was isolated as a clear gum which crystallized on standing. 2D nOesy showed an interaction between one of the pairs of benzylic protons and the pyrazole core ring proton (at 8.52 ppm) confirming the desired isomer.

$[M+H]^+$ = 403/405

C: 3-(3,5-Dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester

A mixture of 3-bromo-1-[4-(4-methyl-pyrazol-1-yl methyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (85 mg, 0.211 mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (58.8 mg, 0.263 mmol), potassium carbonate (65.5 mg, 0.474 mmol) and tetrakis(triphenylphosphine) palladium(0) (24.36 mg, 0.021 mmol) were combined in a microwave vial and dioxane (0.6 mL) and water (0.2 mL) were added. The mixture was degassed with N_2 for 5 min, then heated at 100 °C for 5.5 hrs, then at ambient temperature overnight. The reaction mixture was partitioned between EtOAc (40 mL) and water (30 mL). The aqueous layer was extracted with further EtOAc (2 x 15 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography (silica) eluting with a gradient of 0 to 60 % EtOAc/Iso-Hexanes to afford 3-(3,5-dimethylisoxazol-4-yl)-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester (37 mg, 0.086 mmol, 41.0 % yield) as a white powder.

$[M+H]^+$ = 420

D: 3-(3,5-Dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid

A stirred solution of 3-(3,5-dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (32.3 mg, 0.077 mmol) in THF (0.25 mL) and MeOH (0.25 mL) was treated with a solution of lithium hydroxide (4.61 mg, 0.193 mmol) in water (0.25 mL). A precipitate quickly formed. Further MeOH (0.5 mL) was added and the mixture was allowed to stir at ambient temperature for 3 hrs. LCMS indicated only ~15% hydrolysis. Further THF was added until solution formed (total volume ~2.5 mL). Further LiOH (5 mg) was added and the mixture heated at 50 °C for 3 hrs, then at ambient temperature overnight. Solvents were removed under vacuum and the residue partitioned between EtOAc (5 mL) and water (4 mL). The aqueous layer was adjusted to ~pH 4 with 1M HCl, forming a precipitate. This was filtered, washing with water, then dried under vacuum to afford 3-(3,5-dimethylisoxazol-4-yl)-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (21 mg, 0.053 mmol, 69.0 % yield) as a white solid.

$[M+H]^+$ = 392

E: 3-(3,5-Dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

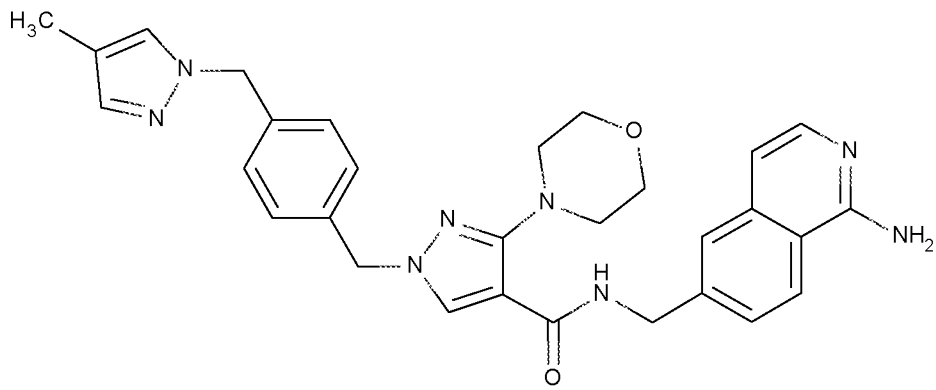
A scintillation vial was charged with 3-(3,5-dimethylisoxazol-4-yl)-1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (18.7 mg, 0.048 mmol), 6-(aminomethyl)isoquinolin-1-amine dihydrochloride (18.81 mg, 0.076 mmol), HATU (19.98 mg, 0.053 mmol), anhydrous DCM (0.5 mL) and anhydrous DMF (0.15 mL). N,N-Disopropylethylamine (33.3 µl, 0.191 mmol) was added and the mixture allowed to stir at ambient temperature overnight. Solvents were removed under vacuum. The residue was redissolved in MeOH (2 mL) and purified by strong cation exchange chromatography (1.5 g), washing with MeOH, eluting with 1% NH_3/MeOH. The resultant material was purified by chromatography (silica) eluting with a gradient of 0 to 10% MeOH (0.3% NH_3)/DCM to afford the free base as a white powder. The free base was dissolved in DCM (0.75 mL), then treated with 4M HCl in dioxane (26.3 µl, 0.105 mmol). This was allowed to stand for 10 min before being concentrated. On drying, 3-(3,5-dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (19 mg, 0.030 mmol, 63.4 % yield) was isolated as a pale yellow powder.

$[M+H]^+$ = 547

NMR (d6-DMSO): 1.98 (3H, s), 2.04 (3H, s), 2.21 (3H, s), 4.53 (2H, d, J= 5.9Hz), 5.23 (2H, s), 5.38 (2H, s), 7.15-7.26 (4H, m), 7.30 (2H, d, J= 8.2Hz), 7.54 (1H, s), 7.63-7.71 (2H, m), 7.76 (1H, s), 8.44 (1H, s), 8.53 (1H, d, J= 8.6Hz), 8.80 (1H, t, J= 6.0Hz), 9.09 (2H, brs), 13.26 (1H, brs).

EXAMPLE 21

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A: 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid ethyl ester

A microwave vial was charged with 3-bromo-1-[4-(4-methyl-pyrazol-1-yl methyl)-benzyl]-1H-pyrazole-4-carboxylic acid ethyl ester (300 mg, 0.744 mmol), RuPhos Precatalyst, chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (34.7 mg, 0.045 mmol), dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine - RuPhos (20.83 mg, 0.045 mmol), morpholine (386 µl, 4.46 mmol), caesium carbonate (630 mg, 1.934 mmol) and anhydrous THF (5 mL). The mixture was briefly degassed with N_2, and stirred at ambient temperature for 10 min, before heating to 85 °C (DrySyn bath temperature) overnight. LCMS indicated a ~1:1:1 mixture of starting material:debromination:product. Further RuPhos Precatalyst, chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (34.7 mg, 0.045 mmol), dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine - RuPhos (20.83 mg, 0.045 mmol) and morpholine (150 µL) were added and the mixture stirred at 85 °C (DrySyn bath temperature) overnight. Solvents were removed under vacuum and the residue partitioned between EtOAc (10 mL) and water (10 mL). The aqueous was extracted with EtOAc (10 mL) and the combined organics washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by chromatography (silica) eluting with a gradient of 0 to 80% EtOAc/Iso-Hexanes to afford 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid ethyl ester (128 mg, 0.309 mmol, 41.6 % yield) as a clear gum.

$[M+H]^+$ = 410

B: 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid

A stirred solution of ethyl 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid ethyl ester (125 mg, 0.305 mmol) in THF (1 mL) and MeOH (1 mL) was treated with a solution of lithium hydroxide (18.28 mg, 0.763 mmol) in water (1 mL) and the mixture heated at 40 °C over a weekend. Any remaining organic solvents were removed under vacuum and the residue partitioned between EtOAc (10 mL) and water (7 mL). The aqueous layer was adjusted to ~pH 4 with 1M HCl. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated to afford 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3-morpholino-1H-pyrazole-4-carboxylic acid (109 mg, 0.271 mmol, 89 % yield) as a gummy yellow solid.

$[M+H]^+$ = 382

C: 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

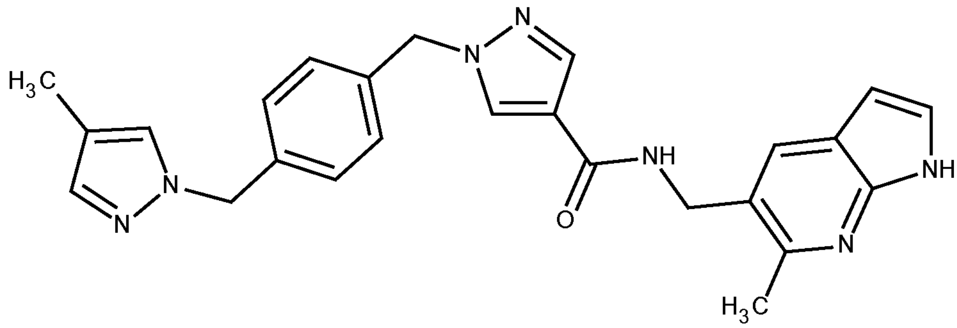
A scintillation vial was charged with 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3-morpholino-1H-pyrazole-4-carboxylic acid (106 mg, 0.278 mmol), 6-(aminomethyl)isoquinolin-1-amine dihydrochloride (82 mg, 0.333 mmol), HATU (116 mg, 0.306 mmol), anhydrous DCM (1 mL) and anhydrous DMF (0.3 mL). *N,N*-Disopropylethylamine (194 µl, 1.112 mmol) was added and the mixture allowed to stir at ambient temperature overnight. Solvents were removed under vacuum. The residue was redissolved in MeOH (2 mL) and purified by strong cation exchange chromatography (2.5 g), washing with MeOH, eluting with 1% NH_3/MeOH. The resultant material was purified by chromatography (silica) eluting with a gradient of 0 to 10% MeOH (0.3% NH_3)/DCM to afford the free base as a white foam. The free base was dissolved in DCM (0.75 mL) and MeOH (0.15 mL), then treated with 4M HCl in dioxane (153 µl, 0.611 mmol). This was allowed to stand for 10 min before being concentrated. On drying, 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (125 mg, 0.212 mmol, 76 % yield) was isolated as a mono HCl salt, as a pale yellow powder.

$[M+H]^+$ = 537

NMR (d6-DMSO): 1.98 (3H, s), 3.03-3.10 (4H, m), 3.58-3.64 (4H, m), 4.58 (2H, d, J= 5.8Hz), 5.18 (2H, s), 5.23 (2H, s), 7.16-7.28 (6H, m), 7.55 (1H, s), 7.65-7.72 (2H, m), 7.79 (1H, s), 8.20 (1H, s), 8.48-8.60 (2H, m), 9.16 (2H, br.s), 13.39 (1H, br.s).

<u>REFERENCE EXAMPLE 22</u>

<u>1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide</u>



A. 6-Amino-5-iodo-2-methylnicotinonitrile

6-Amino-2-methylnicotinonitrile (3.0 g, 22.53 mmol) and 1-iodopyrrolidine-2,5-dione (8.62 g, 38.3 mmol) were dissolved in dry DMF (35 mL). The brown solution was heated to 80 °C for 24 hrs after which time the reaction mixture was diluted with water (50 mL). Extracted with EtOAc (4 x 75 mL). Combined organic layers were washed with water (5 x 30 mL), brine (50 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RediSep (80 g column, 0-30% EtOAc in iso-hexanes) to give a brown coloured solid identified as 6-amino-5-iodo-2-methylnicotinonitrile (3.0 g, 9.84 mmol, 43.7 % yield)

$[M+H]^+$ = 260

B. 6-Amino-2-methyl-5-((trimethylsilyl)ethynyl)nicotinonitrile

To a dried flask under N_2 was added 6-amino-5-iodo-2-methylnicotinonitrile (4 g, 13.13 mmol), triethylamine (2.74 mL, 19.69 mmol), dry THF (30 mL) and dry DCM (10 mL) to give an orange solution. Degassed with N_2 for 5 min before bis(triphenylphosphine)palladium(II) chloride (0.276 g, 0.394 mmol) and copper(I) iodide (0.125 g, 0.656 mmol) were added to give a black coloured suspension. Next, ethynyltrimethylsilane (2.040 mL, 14.44 mmol) was added drop-wise over 5 min resulting in a red/brown coloured solution which was stirred at rt for 1 hour. The reaction mixture was partitioned with EtOAc (100 mL) and water (100 mL).The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with water (2 x 50 mL) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RediSep (80 g column, 0-25% EtOAc in iso-hexanes) to give a pale orange solid identified as 6-amino-2-methyl-5-((trimethylsilyl)ethynyl)nicotinonitrile (2.2 g, 9.40 mmol, 72 % yield)

$[M+H]^+$ = 230

C. N-Acetyl-N-(5-cyano-6-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide

To a flask under N_2 was added 6-amino-2-methyl-5-((trimethylsilyl)ethynyl)nicotinonitrile (2.2 g, 9.59 mmol) and pyridine (15 mL, 9.59 mmol). The mixture was cooled in an ice bath before acetyl chloride (1.569 mL, 22.06 mmol) was added drop-wise to give a light tan coloured suspension. Stirred for 10 min, allowed to warm to rt then heated at 40 °C for 1 hour. Dry THF (10 mL) was added and the reaction was stirred for a further 2 hrs. Dry DCM (10 mL) added and stirred at rt for 3 days. Heated to 60 °C for 2 hrs. Stirred at rt for a further 18 hrs. The volatiles were removed *in vacuo* and the residue was azeotroped with toluene (30 mL). LCMS showed mainly starting material and some evidence of mono and di acylation. Resuspended in DCM (20 mL) and treated with pyridine (1.940 mL, 23.98 mmol) then acetyl chloride (1.569 mL, 22.06 mmol). The resulting suspension was stirred at rt for 18 hrs. LCMS showed conversion to mono and bis acylation with evidence of starting material present in m/z trace. The reaction was heated to 40 °C for 1 hour. LCMS showed conversion to bis-acylated material (~60% purity). Diluted with EtOAc (200 mL) and washed with 1N HCl (60 mL). Aqueous layer extracted with EtOAc (50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo* to a brown coloured residue (4.0 g). The crude product was purified by chromatography on RediSep (40 g column, 0-20% EtOAc in iso-hexanes). Material isolated (4.0 g) as a brown oil. Analysis by LCMS confirmed N-acetyl-N-(5-cyano-6-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (60% purity by UV) along with 3 impurities (10-15% each). Material used in subsequent reaction without further purification/analysis.

D. 6-Methyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

To a flask under N_2 was added N-acetyl-N-(5-cyano-6-methyl-3-((trimethylsilyl)ethynyl)pyridin-2-yl)acetamide (4.3 g, 6.86 mmol), dry THF (20.0 mL) followed by tetrabutylammonium fluoride (1.0 M in THF) (10.29 mL, 10.29 mmol). The dark brown reaction mixture was heated to 70 °C before being diluted with EtOAc (100 mL), washed with water (50 mL) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on RediSep (40 g column, 0-35% EtOAc in iso-hexanes) and two major peaks eluted. To a flask under N_2 was added N-(5-cyano-3-ethynyl-6-methylpyridin-2-yl)acetamide (1.03 g, 3.21 mmol), dry THF (2.0 mL) to give a pale yellow solution. Next, tetrabutylammonium fluoride (1.0 M in THF) (15 mL, 15.00 mmol) was added and heated to 72 °C for 1 h to give a dark orange solution. HPLC showed complete consumption of starting material. Allowed to cool to rt. Diluted with EtOAc (150 mL) and washed with water (100 mL). Aqueous layer extracted with EtOAc (2 x 50 mL) before the combined organic layers were washed with water (2 x 50 mL), brine (50 mL) and dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an orange solid slurried in Et_2O:MeOH (9:1, 15 mL), collected by filtration and washed with Et_2O (15 mL). Dried by suction for 10 min then in vacuum oven for 1 h to give a tan solid identified as 6-methyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (0.69 g, 4.26 mmol, 74.7 % yield).

$[M+H]^+$ = 158

E. *tert*-Butyl ((6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)carbamate

To a flask under N_2 was added: 6-methyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (0.64 g, 4.07 mmol), di-tert-butyl dicarbonate (1.777 g, 8.14 mmol), nickel(II) chloride (0.053 g, 0.407 mmol) and MeOH (50 mL) to give a pale tan coloured suspension. Cooled in an ice bath before sodium borohydride (1.078 g, 28.5 mmol) was added portion-wise over 1 hrs. Allowed to warm to rt in ice bath for 18 hrs. Volatiles were removed *in vacuo* and the brown residue was partitioned between DCM (100 mL) and saturated $NaHCO_3$ (50 mL). Aqueous layer extracted with DCM (2 x 30 mL) before the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purified by column chromatography (RediSep 40 g, dry loaded, 0-100% EtOAc in iso-hexanes). Dried in vacuum oven (40 °C) overnight. Giving a white solid identified as *tert*-butyl ((6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)carbamate (0.74 g, 2.78 mmol, 68.2 % yield).

$[M+H]^+$ = 262

F. 6-Methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine

tert-Butyl ((6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)carbamate (0.74 g, 2.83 mmol) was suspended in DCM (7.0 mL). TFA (5 mL, 64.9 mmol) was added and the resulting clear yellow solution was stirred at rt for 1 hrs. Material isolated by capture and release using strong cation exchange chromatography, washing with MeOH (50 mL) and eluting with 1% NH_3 in MeOH (100 mL). Concentrated *in vacuo* and dried in vacuum oven (40 °C for 2 h) to give an off-white solid identified as 6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine (0.47 g, 2.62 mmol, 93 % yield).

$[M+H]^+$ = 162

G. Ethyl 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate

A solution of (4-((4-methyl-1H-pyrazol-1-yl)methyl)phenyl)methanol (500 mg, 2.472 mmol), ethyl 1H-pyrazole-4-carboxylate (364 mg, 2.60 mmol) and triphenylphosphine (713 mg, 2.72 mmol) in anhydrous THF (8 mL) was treated dropwise with (*E*)-diisopropyl diazene-1,2-dicarboxylate (560 µL, 2.84 mmol). After 4 hrs at rt the reaction mixture was concentrated onto silica and purified by flash chromatography (silica) eluting with a gradient of 10 to 100% EtOAc/Iso-Hexanes (product eluted at ~70% EtOAc). Fractions were evaporated to give a white solid identified as ethyl 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (610 mg, 1.862 mmol, 75 % yield).

$[M+H]^+$ = 325

H. 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid

A solution of ethyl 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (610 mg, 1.881 mmol) in tetrahydrofuran (20 mL) and water (10 mL) was treated with lithium hydroxide (225 mg, 9.40 mmol) and the mixture heated at 50 °C with stirring overnight. Solvents were removed under vacuum and the residue suspended between EtOAc (50 mL) and water (50 mL). The aqueous phase was adjusted to pH 1 with 1M HCl and the organic layer collected. The aqueous was extracted with EtOAc (2 x 50 mL) and the combined organics washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give a white solid identified as 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (518 mg, 1.713 mmol, 91 % yield).

$[M+H]^+$ = 297.

I. 1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

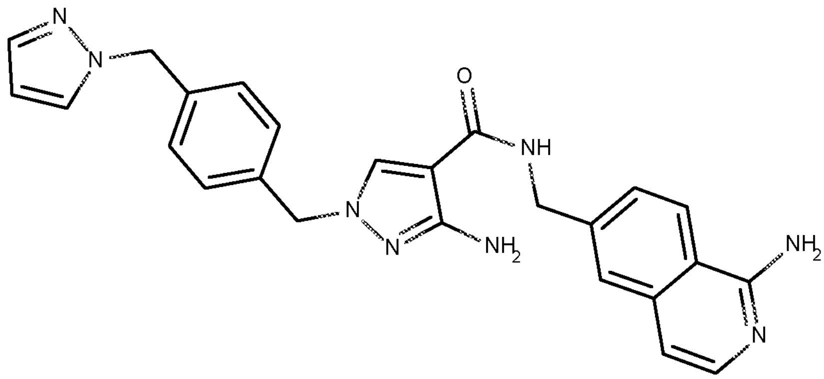
A scintillation vial was charged with 1-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1H-pyrazole-4-carboxylic acid (0.092 g, 0.310 mmol) and suspended in dry DCM (3mL) to which was added (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine (0.050 g, 0.310 mmol), HATU (0.130 g, 0.341 mmol) and then *N,N*-disopropylethylamine (0.108 mL, 0.620 mmol), the suspension was left to stir at rt. The reaction mixture was evaporated and the resulting residue quenched with saturated solution of ammonium chloride (5mL) and left to stir at rt overnight. The solid was filtered under reduced pressure and placed in the vacuum oven at 40°C for 2 days. The solid was triturated with ethyl acetate (5mL) doped with methanol (0.1mL), sonicated and then filtered under reduced pressure to give a pale brown solid which was placed in the vacuum oven at 40°C to give a white solid identified as 1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide (62mg, 0.14mmol, 37% yield).

$[M+H]^+$ = 440

^{1}H NMR: (d6-DMSO), δ: 1.98 (3H, t, J = 0.7Hz), 2.51 (3H, s), 4.45 (2H, d, J = 5.5Hz), 5.20 (2H, s), 5.30 (2H, s), 6.34 (1H, dd, J = 1.9, 3.4Hz), 7.15-7.19 (2H, m), 7.20-7.25 (3H, m), 7.32 (1H, dd, J = 2.4, 3.4Hz), 7.51 (1H, t, J = 0.9Hz), 7.74 (1H, s), 7.90 (1H, d, J = 0.7Hz), 8.25 (1H, d, J = 0.7Hz), 8.41 (1H, t, J = 5.5Hz), 11.37 (1H, s).

EXAMPLE 23

5-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 1-(4-Hydroxymethyl-benzyl)-1H-pyrazole

4-(Chloromethyl)benzyl alcohol (650mg, 4.15mmol) and pyrazole (311mg, 4.57mmol) were taken up in MeCN (30mL). K_2CO_3 (860.5mg, 6.23mmol) was added and the reaction was heated to 50°C for 48hrs. Volatiles were removed *in vacuo*. Ethyl acetate (60mL) and water (20mL) added. Organic layer filtered and evaporated under vacuum. Purified by flash chromatography (silica) eluting with 40% EtOAc in Pet. Ether to afford a colourless oil identified as 1-(4-hydroxymethyl-benzyl)-1H-pyrazole (480mg, 61% yield).

B. 1-(4-Bromomethyl-benzyl)-1H-pyrazole

1-(4-Hydroxymethyl-benzyl)-1H-pyrazole (480mg, 2.55mmol) and triphenylphosphine (769mg, 2.93mmol) were taken up in DCM (15mL). The resultant solution was cooled in an ice bath before carbon tetrabromide (930mg, 2.81mmol) was added portionwise. The mixture was stirred at RT for 18 hrs. The mixture was diluted with DCM, washed with water (2 x 50 mL) and brine (30 mL) and concentrated under vacuum. The crude material was purified via flash chromatography (silica) (20-40 % EtOAC/ Pet. Ether). The compound containing fractions were concentrated *in vacuo* to afford to an off white solid identified as 1-(4-bromomethyl-benzyl)-1H-pyrazole (410mg, 64% yield).

C. 3-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester and 5-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester.

To 5-amino-1H-pyrazole-4-carboxylic acid ethyl ester (200mg, 1.29mmol) in acetonitrile (7mL) was added potassium carbonate (356mg, 2.58mmol) and 1-(4-bromomethyl-benzyl)-1H-pyrazole (324mg, 1.29mmol) and the reaction stirred at rt for 18hrs. The reaction mixture was concentrated and the residue purified by column chromatography (silica) eluting with 6:6:7 Acetonitrile : Ethyl acetate : Pet. Ether to afford 3-amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester (129mg, 31% yield) and 5-amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester (119mg, 28% yield).

D. 3-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid

To 3-amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid ethyl ester (119mg, 0.37mmol) in ethanol (20mL) was added sodium hydroxide (102mg, 2.56mmol) and the reaction heated at reflux for 48hrs. The reaction mixture was cooled and concentrated *in vacuo*. The crude residue was dissolved in water (2 mL) and the pH adjusted to pH ~ 5 with 2M HCl (until reaction mixture turned opaque). EtOAc was added and solid went into organic layer but did not dissolve. Aqueous layer was removed and the organic layer filtered to afford an off white solid that was washed with diethyl ether to afford 3-amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid which was used in next step without further purification.

E. 3-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide TFA salt

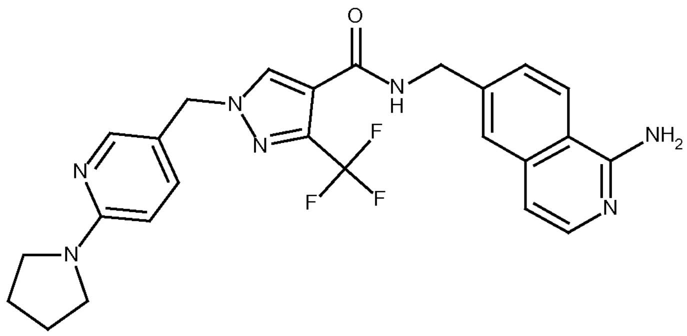
To 3-amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (49.1mg, 0.17mmol) in dichloromethane (15mL) and DMF (2mL) at 0°C was added HOBt (26.8mg, 0.20mmol) and water soluble carbodiimide (44.3mg, 0.23mmol). After stirring for 15 min triethylamine (115µL, 0.83mmol) and 6-aminomethyl-isoquinolin-1-ylamine (28.6mg, 0.17mmol) was added and the reaction allowed to warm to rt and stirred for 18 hrs. The reaction mixture was partitioned between EtOAc (30mL) and water (10mL). The organic layer was washed with brine (30mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification by prep HPLC afforded 3-amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide TFA salt as an off white solid.

$[M+H]^+$ = 453

^{1}H NMR: (d6-DMSO), δ: 2.98 (1H, br s), 4.02 (2H, br s), 4.55 (2H, d, J= 5.8Hz), 5.07 (2H, s), 5.31 (2H, s), 6.26 (1H, t, J= 2.0), 7.19-7.25 (5H, m), 7.44 (1H, d, 1.8Hz), 7.64 (1H, d, J= 7.0Hz), 7.68 (1H, dd, J= 8.7, 1.3 Hz), 7.79 (2H, dd, J= 9.0, 2.0Hz), 8.02 (1H, s), 8.49 (1H, d, J= 8.6Hz), 8.51 (1H, t, J= 5.7Hz), 8.93 (2H, br s), 12.84 (1H, br s).

<u>EXAMPLE 24</u>

<u>1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide</u>



A. 5-Bromomethyl-2-fluoro-pyridine

2-Fuoro-5-methylpyridine (5.0g, 45mmol) was dissolved in 1,2-dichloroethane (120mL). To this solution was added N-bromosuccinimide (9.61g, 54mmol) and azobisisobutyronitrile (AIBN) (739mg, 4.5mmol). The reaction was stirred at reflux. After 18 hrs the reaction mixture was diluted with chloroform (100mL) and washed with water (1x50mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 95% Pet. Ether, 5% EtOAc, fractions combined and evaporated *in vacuo* to give a yellow oil identified as 5-bromomethyl-2-fluoro-pyridine (6.89g, 36.25mmol, 81% yield).

$[M+H]^+$ = 192

B. 1-(6-Fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester

Ethyl 3-trifluoromethyl-1H-pyrazole-4-carboxylate (1.57g, 7.53mmol) was dissolved in DMF (20mL), 5-bromomethyl-2-fluoro-pyridine (1.3g, 6.84mmol) and caesium carbonate (6.69g, 20.53mmol) were added and the reaction mixture was stirred at 50°C. After 18 hrs the reaction mixture was diluted with EtOAc (100mL), this solution was washed with water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 85% Pet. Ether, 15% EtOAc, fractions combined and evaporated *in vacuo* to give a white solid identified as 1-(6-fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester.

(1.26g, 3.97mmol, 58% yield).

C. 1-(6-Fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid

1-(6-Fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (1.26g, 3.97mmol) was dissolved in THF (50mL)and water (5mL) and lithium hydroxide (476mg, 19.86mmol) was added. The reaction mixture was stirred at 50°C. After 18 hrs the solvent was concentrated *in vacuo* and the residue taken up in EtOAc (50mL), the aqueous layer was separated and acidified with 1M HCl to pH2 and extracted with $CHCl_3$ (3x50mL). The combined extracts were washed with water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 1-(6-fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (980mg, 3.39mmol, 85% yield).

$[M+H]^+$ = 290

D. 1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid

1-(6-Fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (300mg, 1.04mmol) was dissolved in dioxane (25mL) and pyrrolidine (2mL) and the reaction mixture was stirred at 80°C. After 18 hrs the reaction mixture was diluted with EtOAc (100mLmL), this solution was washed with water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 1% AcOH, 9%MeOH, 90% $CHCl_3$, fractions combined and evaporated *in vacuo* to give a white foamy solid identified as 1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid. (267mg, 0.785mmol, 76% yield).

$[M+H]^+$ = 341

E. 1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

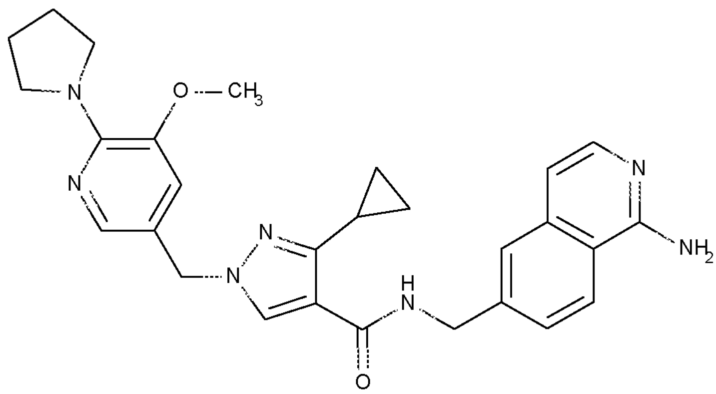
1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (180mg, 0.53mmol) was dissolved in CH_2Cl_2 (50mL) and DMF (2.5mL). This solution was cooled to 0°C. 6-Aminomethyl-isoquinolin-1-ylamine.HCl (122mg, 0.58mmol) was added followed by HOBt (77mg, 0.58mmol) and triethylamine (161mg, 1.58mmol). Water soluble carbodiimide (122mg, 0.63mmol) was then added. After 18 hrs at 0°C to rt reaction mixture was diluted with chloroform (100mL) and isopropanol (10mL) and washed with $NaHCO_3$ (1x30mL), water (1x30mL) and brine (1x30mL), dried (Na_2SO_4) and evaporated *in vacuo* giving a yellow oil. The residue was purified by flash chromatography (silica), eluent 15%MeOH, 85% $CHCl_3$, fractions combined and evaporated *in vacuo* to give a white solid. The residue was treated with HCl in methanol (4mL), the solvent was evaporated *in vacuo* and the residue freeze dried from water/acetonitrile to give a white solid identified as 1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (135mg, 0.254mmol, 48% yield).

$[M+H]^+$ = 496

^{1}H NMR: (d6-DMSO), δ: 2.01 (4H, t, J= 6.0Hz), 3.47 (4H, t, J= 6.3Hz), 4.59 (2H, d, J= 5.8Hz), 5.45 (2H, s), 7.10 (1H, d, , J= 9.0Hz), 7.20 (1H, d, J= 7.1Hz), 7.70 (2H, dd, J= 1.2 and 8.3Hz), 7.81 (1H, s), 7.94 (1H, d, J= 8.8Hz), 8.15 (1H, s), 8.58 (1H, d, J= 8.7Hz), 8.64 (1H, s), 9.17-9.20 (2H, m), 13.30 (1H, s).

EXAMPLE 25

3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A: (6-Chloro-5-methoxy-pyridin-3-yl)-methanol

To a stirred solution of 6-chloro-5-methoxy-nicotinic acid methyl ester (0.5g, 2.48mmol) in anhydrous THF (20mL) cooled to 0 °C under nitrogen, $LiAlH_4$ (104mg, 2.728mmol) was added. The reaction was allowed to warm to rt for 2 hrs. The reaction was cooled to 0 °C and quenched with water (5mL). Potassium sodium tartrate (Rochelle's salt) was added to help break up the suspension. The mixture was filtered through Celite, washing well with water (20mL) and ethyl acetate (100mL). The filtrate was collected and the layers separated. The aqueous extracted with ethyl acetate (3 x 20mL). The combined organic layers were washed with brine (50mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude was purified by flash chromatography (silica) eluting in step gradients up to 40% Pet. Ether, 60% ethyl acetate. Pure fractions were concentrated affording the title compound (6-chloro-5-methoxy-pyridin-3-yl)-methanol as a white solid (360mg, 2.074mmol, 84% yield).

$[M+H]^+$ = 174

B. 5-Bromomethyl-2-chloro-3-methoxy-pyridine

Under an atmosphere of N_2, (6-chloro-5-methoxy-pyridin-3-yl)-methanol (360 mg, 2.074 mmol) and triphenylphosphine (626 mg, 2.385 mmol) were dissolved in dry DCM (5 mL). The resultant solution was cooled in an ice bath before carbon tetrabromide (756 mg, 2.281 mmol) was added portionwise. The mixture was stirred at ambient temperature for 18 hrs. The mixture was diluted with dichloromethane (30 mL), washed with water (2 x 50 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated under vacuum. The crude material was purified by flash chromatography (silica) eluting in step gradients up to 85% Pet. Ether, 15% ethyl acetate. The compound containing fractions were concentrated *in vacuo* to afford a colourless oil identified as 5-bromomethyl-2-chloro-3-methoxy-pyridine (220mg, 0.93 mmol, 45% yield).

$[M+H]^+$ = 238

^{1}H NMR (400 MHz, CDCl3) δ: 3.97 (3H, s), 4.47 (2H, s), 7.25 (1H, d, J= 2.0Hz), 8.01 (1H, d, J= 2.0Hz)

C. 1-(6-Chloro-5-methoxy-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid ethyl ester

3-Cyclopropyl-1H-pyrazole-4-carboxylic acid ethyl ester (60mg, 0.333mmol) was taken up in DMF (2mL) and treated with potassium carbonate (91mg, 0.660mmol). 5-Bromomethyl-2-chloro-3-methoxy-pyridine (78mg, 0.330mmol) was added and the reaction stirred at rt over the weekend. Ethyl acetate (60mL) and water (20mL) were added and the layers separated. The organic layer was washed with water (3 x 15mL), brine (10mL), filtered and evaporated. The crude product was purified by flash chromatography (silica) eluting in step gradients up to 60% Pet. Ether, 40% ethyl acetate. 1-(6-Chloro-5-methoxy-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid ethyl ester was isolated as a colourless oil which solidified on standing to a white solid, (78mg, 0.232mmol, 70% yield).

$[M+H]^+$ = 336

D. 3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid ethyl ester

A suspension of 1-(6-chloro-5-methoxy-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid ethyl ester (78 mg, 0.232 mmol) in pyrrolidine (763 µLS, 9.282 mmol) and 1,4-dioxane (300 µL) was heated at 90 °C overnight. The reaction was then cooled and taken up in ethyl acetate (20mL), $NaHCO_3$ (10mL) was added and the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica) eluting in step gradients up to 60% Pet. Ether, 40% ethyl acetate. 3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid ethyl ester was isolated as a colourless oil (85mg, 0.229mmol, 98% yield).

$[M+H]^+$ = 371

E. 3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid

To 3-cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid ethyl ester (85mg, 0.229mmol) in ethanol (20mL) was added sodium hydroxide (92mg, 2.295mmol). The reaction mixture was heated at reflux overnight. Then the reaction was cooled and concentrated under reduced pressure. The crude residue was dissolved in water (2 mL) and the pH adjusted to pH ~ 4.7 with 2M HCl. The aqueous layer was washed with chloroform (3 x 10mL). The combined organics were concentrated to afford the desired product 3-cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid as a white solid (60mg, 0.175mmol, 76% yield).

$[M+H]^+$ = 343

F. 3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

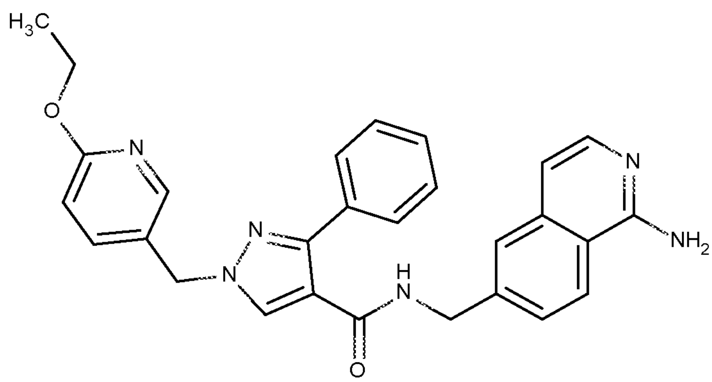
To 3-cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (60mg, 0.175 mmol) in dichloromethane (5mL) at 0°C was added HOBt (28mg, 0.210mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (47mg, 0.245mmol). After 10-15 min triethylamine (122 µl, 0.876mmol) and 6-(aminomethyl)isoquinolin-1-amine (30mg, 0.175mmol) was added. DMF (3mL) was added to aid solubility and the reaction allowed to warm to rt and stirred for 3 days. The reaction mixture was diluted with chloroform (50mL) and saturated aqueous $NaHCO_3$ (15mL) added. The layers were separated and the organic layer washed with water (5 x 20mL), followed by brine (15mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (silica) eluting in step gradients up to 3.5% methanol, 95.5% dichloromethane, 1% NH_4OH. The product was treated with HCl/dioxane for 30 min, concentrated *in vacuo* and freeze dried in acetonitrile/water. 3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide was isolated as the di hydrochloride salt as an off white solid (50mg, 0.088mmol, 99% yield).

$[M+H]^+$ = 498

1H NMR (d6-DMSO): 0.75-0.79 (2H, m), 0.81-0.87 (2H, m), 1.11-1.95 (4H, m), 2.57-2.63 (1H, m), 3.77 (4H, br.s), 3.86 (3H, s), 4.58 (2H, d, J= 5.8Hz), 5.19 (2H, s), 7.21 (1H, d, J= 7.0Hz), 7.41 (1H, d, J= 1.3Hz), 7.54 (1H, d, J= 1.0Hz), 7.67-7.69 (1H, m), 7.69-7.72 (1H, m), 7.80 (1H, s), 8.31 (1H, s), 8.59 (1H, d, J= 8.6Hz), 8.79 (1H, t, J= 5.8Hz), 9.17 (2H, br.s), 13.39 (1H, s)

EXAMPLE 26

1-(6-Ethoxy-pyridin-3-ylmethyl)-3-phenyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A: 5-Chloromethyl-2-fluoro-pyridine

A 500mL flask was charged with 2-fluoro-5-methylpyridine (23.42 g, 211 mmol), 1-chloropyrrolidine-2,5-dione (42.2 g, 316 mmol), benzoic peroxyanhydride (1.361 g, 4.22 mmol), acetic acid (1mL, 17.47 mmol) and acetonitrile (132 mL, 2527 mmol). The reaction mixture was heated to reflux giving a pale yellow solution which was left to reflux for 5 hrs. The reaction mixture was cooled and quenched with water (20 mL), followed by ethyl acetate (30 mL) and brine (30 mL). The two phases were separated and the aqueous re-extracted with ethyl acetate (30 mL). The combined organics were washed with brine (30 mL), dried over magnesium sulphate, filtered and evaporated to give a viscous orange suspension. The product was triturated with DCM (100 mL) and the resulting solid removed by filtration. The filtrate was evaporated under reduced pressure to give a clear orange oil. The crude product was divided into two 19g batches and purified on a 330g silica column, liquid loaded in DCM and gradient eluted with ethyl acetate-Iso-hexane (5:95). Product containing fractions were combined and evaporated *in vacuo* to give a clear almost colourless oil identified as 5-(chloromethyl)-2-fluoropyridine (14.6 g, 99 mmol, 46.9 % yield).

$[M+H]^+$ = 146

B. 1-(6-Fluoro-pyridin-3-ylmethyl)-3-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester

To a stirred solution of 5-(chloromethyl)-2-fluoropyridine (750 mg, 5.15 mmol) and ethyl 3-phenyl-1H-pyrazole-4-carboxylate (1114 mg, 5.15 mmol) in DMF (15 mL) was added K_2CO_3 (1424 mg, 10.30 mmol) and stirred at RT over the weekend. The reaction mixture was diluted with EtOAc (150 mL) and washed with water (100 mL) and brine (2 x 100 mL), dried over magneisum sulfate, filtered and crude material evaporated directly onto silica. The crude product was purified by chromatography (40 g column, 0-60% (3:1 EtOAc:MeCN) in isohexanes). 1-(6-Fluoro-pyridin-3-ylmethyl)-3-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester (1.69 g, 4.16 mmol, 81 % yield) was isolated as a waxy solid on standing, as a mixture of regioisomers. The material was used directly in the next step

$[M+H]^+$ = 326

C: 1-(6-Ethoxy-pyridin-3-ylmethyl)-3-phenyl-1H-pyrazole-4-carboxylic acid

To a stirred microwave vial containing ethanol (3 mL) was added sodium ethoxide (586 mg, 8.61 mmol) and 1-(6-fluoro-pyridin-3-ylmethyl)-3-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester (700 mg, 2.152 mmol). The reaction vessel was sealed and heated to 90 °C overnight. The reaction mixture was allowed to cool to rt and diluted with EtOAc (100 mL), NH_4Cl (sat, 10 mL) and water (100 mL). The organics were washed with brine (100mL) and solvent was removed. The crude material was taken up into THF (10 mL) and MeOH (3 mL) then 2M NaOH (2152 µl, 4.30 mmol) was added and left at RT for 2 hrs. The reaction mixture was acidified to ~ pH 5 with 1M HCl and the product extracted into EtOAc (2 x 30 mL). The organics were washed with brine (30 mL), dried over magnesium sulfate, filtered and solvent removed. The crude product was purified by chromatography (40 g column, 0-70% (3:1 EtOAc:MeCN, 1% acetic acid) in isohexanes) to afford 1-((6-ethoxypyridin-3-yl)methyl)-3-phenyl-1H-pyrazole-4-carboxylic acid (65 mg, 0.191 mmol, 9 % yield) as a white solid.

$[M+H]^+$ =324

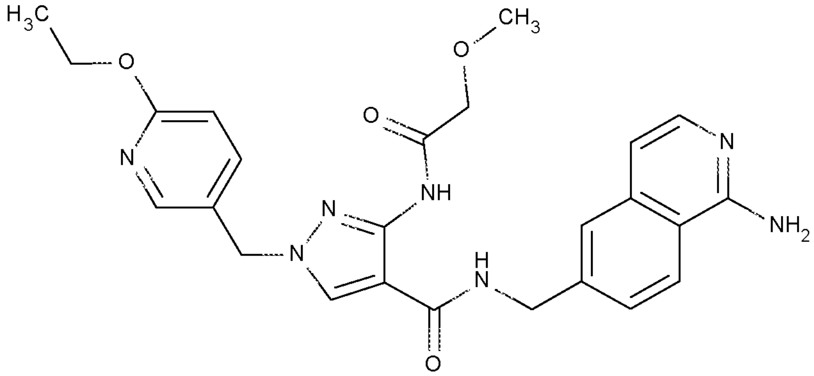
D: 1-(6-Ethoxy-pyridin-3-ylmethyl)-3-phenyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

To a stirred solution of 1-((6-ethoxypyridin-3-yl)methyl)-3-phenyl-1H-pyrazole-4-carboxylic acid (65 mg, 0.201 mmol) and 6-(aminomethyl)isoquinolin-1-amine.2HCl (49.5 mg, 0.201 mmol) in DMF (2 mL) was added N,N-diisopropylethylamine (140 µl, 0.804 mmol) and HATU (84 mg, 0.221 mmol) and left at RT for 2 hrs. The reaction mixture was diluted with EtOAc (30 mL) and washed with NaOH (2 M, 20 mL) and then brine (2 x 40 mL). The organics were preabsorbed directly onto silica and purified by chromatography (12 g column, 0-7% MeOH (1% NH3) in DCM) to afford the free base of the title compound (54.2 mg, 0.100 mmol, 49.7 % yield) as a white powder. The solid was azeotroped from toluene (3 x 5 mL) under high vacuum to remove any residual N,N-diisopropylethylamine before salt formation. The material was suspended in DCM (3 mL) and HCl 4M in dioxane (27.1 µl, 0.109 mmol, 1eq) was added. The solvent was removed under vacuum. The residue was suspended in water (3 mL) and then freeze dried overnight to give 1-(6-ethoxy-pyridin-3-ylmethyl)-3-phenyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide as a HCl salt, as a white solid (54.2 mg, 0.100 mmol, 49.7 % yield).

$[M+H]^+$ = 479.3

EXAMPLE 27

1-(6-Ethoxy-pyridin-3-ylmethyl)-3-(2-methoxy-acetylamino)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



A. 3-Amino-1-(6-fluoro-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid ethyl ester 1132-35

To a stirred solution of 3-amino-1H-pyrazole-4-carboxylic acid ethyl ester (1.785 g, 11.51 mmol) in ethanol (10 mL) was added sodium ethoxide (1.566 g, 23.01 mmol). After 5 min a solution of 5-(chloromethyl)-2-fluoropyridine (1.675 g, 11.51 mmol) in EtOH (3 mL) was added and the reaction heated to 80 °C. After 90 min the reaction mixture was reduced in volume under vacuum and then diluted with EtOAc (200 mL) and water (100 mL). The organics were isolated and washed with brine (100 mL), dried over magnesium sulfate, filtered and solvent removed. The crude product was purified by chromatography (80 g column, slowly 0-40% (3:1 EtOAc:MeCN) in isohexanes). The undesired regioisomer 5-amino-1-(6-fluoro-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid ethyl ester was isolated from the first set of fractions (768 mg, 2.76 mmol, 24 % yield) as an oil that solidified to a waxy solid on standing. The desired isomer 3-amino-1-(6-fluoro-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid ethyl ester (712 mg, 2.61 mmol, 22.7% yield) was isolated as a waxy solid from the second set of fractions.

[M+H]+ =265

B. 3-Amino-1-(6-ethoxy-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid

To a microwave vial containing EtOH (5 mL) was added NaH (260 mg, 6.51 mmol) and allowed to stir for 10 min. To this was added a suspension of ethyl 3-amino-1-((6-fluoropyridin-3-yl)methyl)-1H-pyrazole-4-carboxylate (430 mg, 1.627 mmol) in EtOH (4 mL). The mixture was sealed and heated to 90 °C overnight. NaOH (2M, 2 mL) was added and heated to 50 °C for 1 hour. The reaction mixture was evaporated to dryness and the residue dissolved in water (10 mL) and the pH adjusted to pH5 then extracted with EtOAc (10 x 20 mL). The combined organics were then evaporated. The crude material was purified by chromatography (12 g column, 0-70% (3:1 EtOAc:MeCN, 1% acetic acid in isohexanes) to afford 3-amino-1-((6-ethoxypyridin-3-yl)methyl)-1H-pyrazole-4-carboxylic acid (195 mg, 0.736 mmol, 45.2 % yield) as a white powder after azeotroping with toluene (2 x 20 mL).

$[M+H]^+$ = 263

C. 1-((6-Ethoxypyridin-3-yl)methyl)-3-(2-methoxyacetamido)-1H-pyrazole-4-carboxylic acid

To a stirred solution of 3-amino-1-((6-ethoxypyridin-3-yl)methyl)-1H-pyrazole-4-carboxylic acid (142 mg, 0.541 mmol) in DCM (3 mL) was added N,N-diisopropylethylamine (142 µL, 0.812 mmol) and 2-methoxyacetyl chloride (54.5 µL, 0.596 mmol) and stirred at rt for 1 hour. The reaction mixture was evaporated to remove DCM. The crude residue was sonicated in water (10 mL). Hydrochloric acid (2M, 1 mL) was added and the product extracted into EtOAc (30 mL). The organic layer was dried over magnesium sulfate and solvent evaporated under reduced pressure to afford 1-((6-ethoxypyridin-3-yl)methyl)-3-(2-methoxyacetamido)-1H-pyrazole-4-carboxylic acid as a yellow solid (160 mg, 0.469 mmol, 87 % yield).

[M+H]+ = 335

D. 1-(6-Ethoxy-pyridin-3-ylmethyl)-3-(2-methoxy-acetylamino)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride

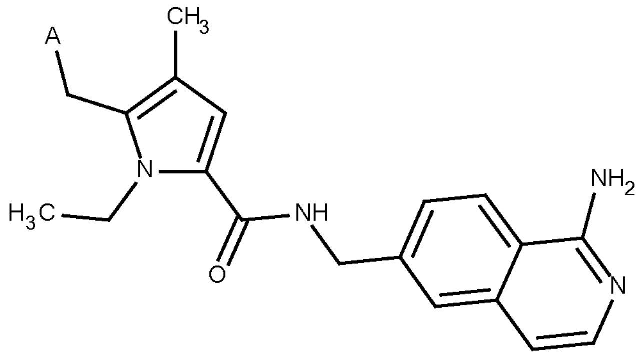
To a stirred solution of 1-((6-ethoxypyridin-3-yl)methyl)-3-(2-methoxyacetamido)-1H-pyrazole-4-carboxylic acid (81.0 mg, 0.242 mmol), 6-(aminomethyl)isoquinolin-1-amine dihydrochloride (65.6 mg, 0.267 mmol) and HATU (111 mg, 0.291 mmol) in DMF (2 mL) was added triethylamine (135 µL, 0.969 mmol). The resulting mixture was stirred at rt overnight. The reaction mixture was then diluted with EtOAc (15 mL) and washed with 2M NaOH (2 x 20 mL). The organic was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude was purified by chromatography (4 g column, MeOH in DCM 0-5% and 1% Et_3N) to afford the desired product as a free base. The product was dissolved in DCM (1 mL), 4M HCl in dioxane (79 µl, 0.315 mmol) added and the resulting mixture stirred at rt for 15 min. The solvent was then evaporated under reduced pressure to give 1-(6-ethoxy-pyridin-3-ylmethyl)-3-(2-methoxy-acetylamino)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide hydrochloride (47.5 mg, 0.089 mmol, 36.5 % yield) as a white solid.

[M+H] = 490

NMR (d6-DMSO) 1.31 (3H, t, J= 7.0Hz), 3.36 (3H, s), 3.96 (2H, s), 4.30 (2H, q, J= 7.0Hz), 4.60 (2H, d, J= 5.9Hz), 5.27 (2H, s), 6.83 (1H, dd, J= 0.7, 8.5Hz), 7.17 (1H, d, J= 6.8Hz), 7.60-7.72 (3H, m), 7.73-7.78 (1H, m), 8.17-8.27 (2H, m), 8.40-8.50 (3H, m), 8.83 (1H, t, J= 6.0Hz), 10.51 (1H, s), 12.74 (1H, s).

The compounds in the following tables were synthesised as described for Examples 1-3 and 6-27 and Reference Examples 4 and 5. Compounds 31-33, 45-50, 52, 105-109, 115-118 and 127-129 are reference examples.

Table 1



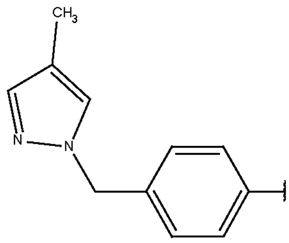
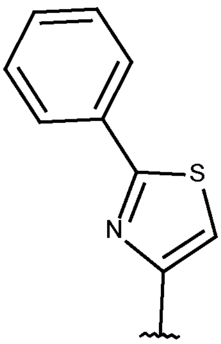
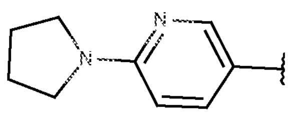
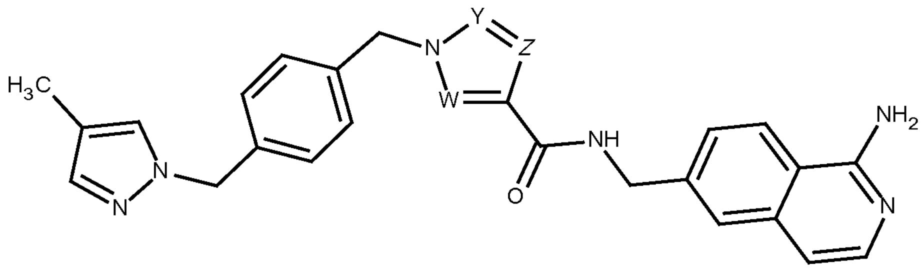
Example Number	A	Free Base MW	[M+H]$^+$
28		492.6	493
29		481.6	482
30		468.6	469

Table 2



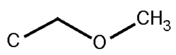
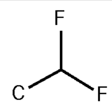
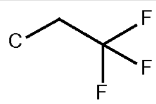
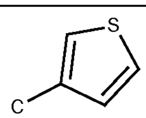
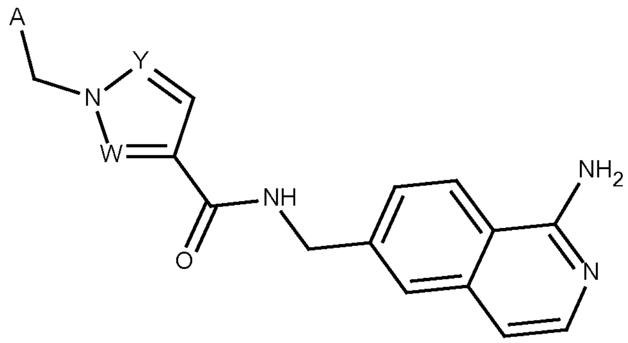
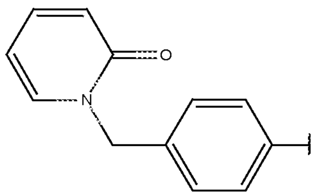
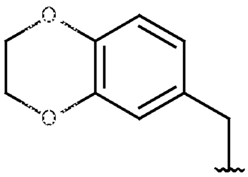
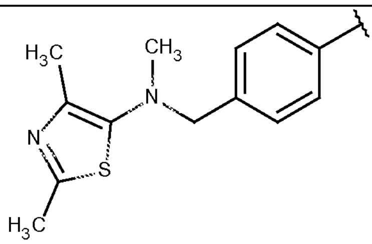
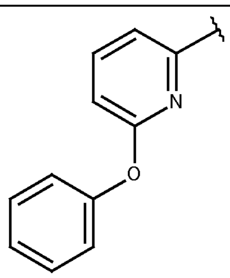
Example Number	W	Z	Y	Free Base MW	[M+H]⁺
31	CH	CH	N	451.5	452
32	CH	N	CH	451.5	452
33	CH	N	N	452.5	453
34	C-CH_3	C-CH_3	N	479.6	480
35	CH	C-Ph	N	527.6	528
36	CH	C-CF_3	N	519.5	520
37	CH	C-NH_2	N	466.5	467
38	CH		N	495.6	496
39	CH		N	501.5	502
40	CH		N	533.6	268 [M+2H]/2
41	CH	C-CON$(CH_3)_2$	N	522.6	523
42	CH		N	533.7	534
43	CH	C-Cl	N	486.0	486

Table 3



Example Number	A	W	Y	Free Base MW	[M+H]+
44		C-CH_3	C-CH_3	491.6	492
45		CH	N	429.5	430
46		CH	N	511.6	513
47		CH	N	450.5	451

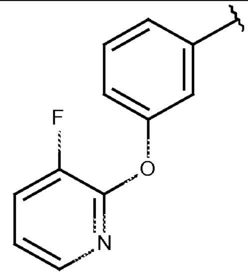
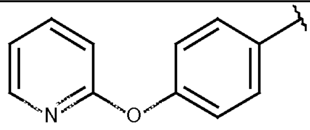
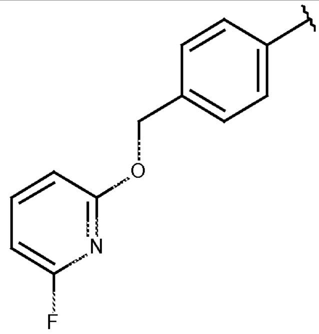
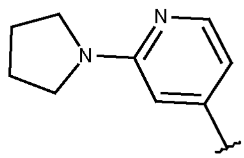
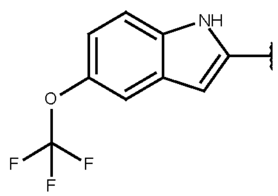
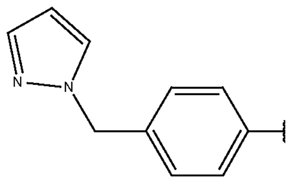
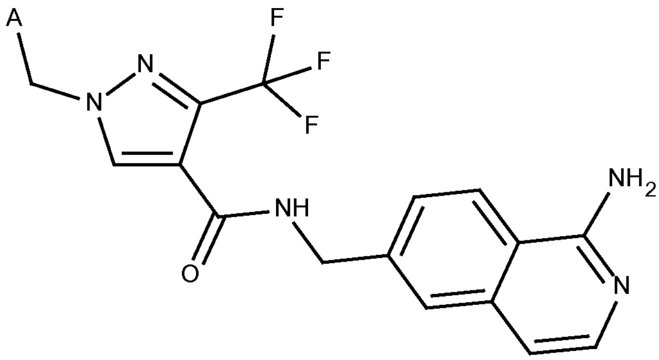
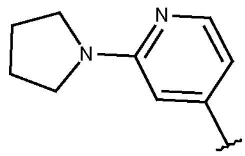
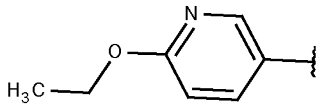
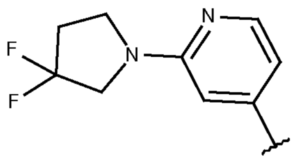
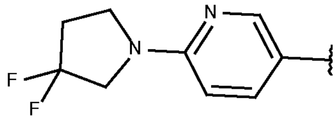
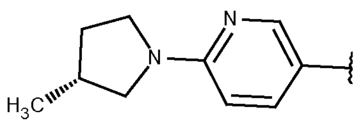
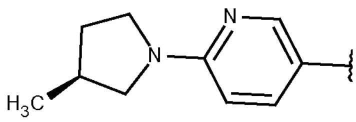
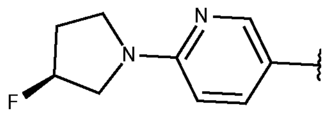
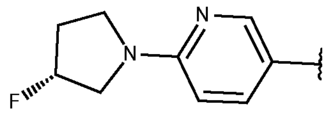
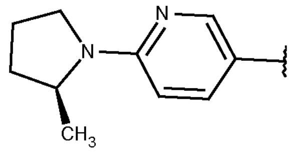
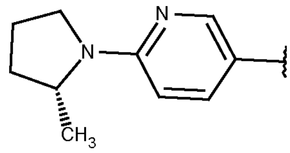
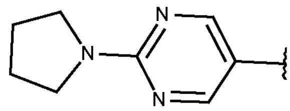
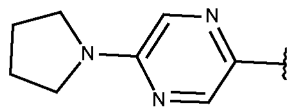
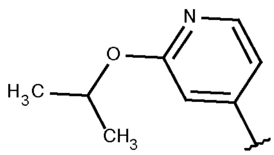
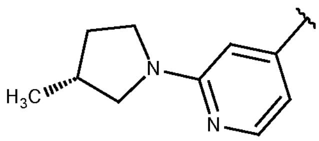
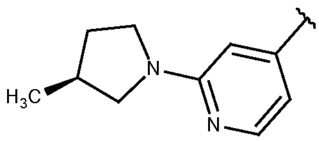
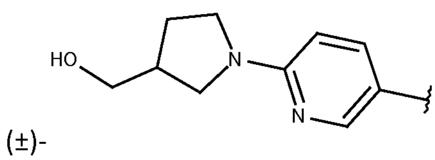
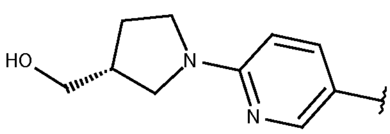
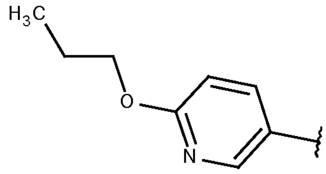
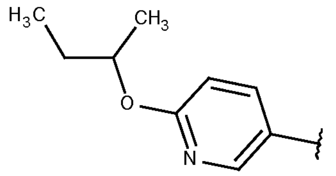
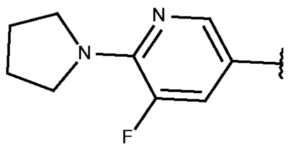
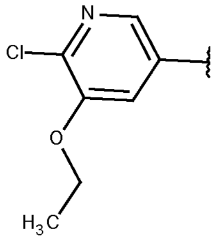
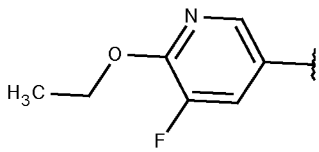
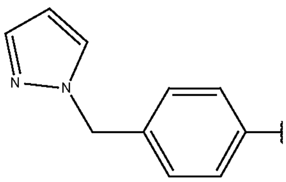
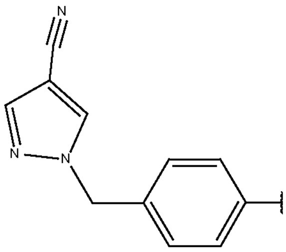
48		CH	N	468.5	469
49		CH	N	450.6	451
50		CH	N	482.5	483
51		C-CF_3	N	495.5	496
52		CH	N	480.4	481
53		C-NH_2	N	452.5	453

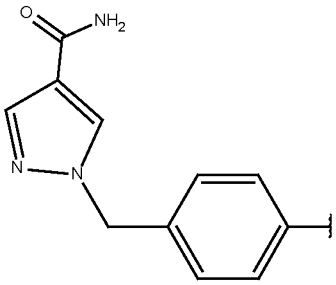
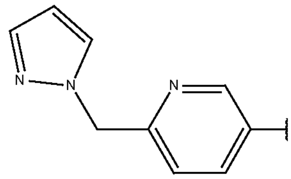
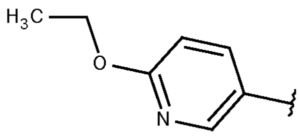
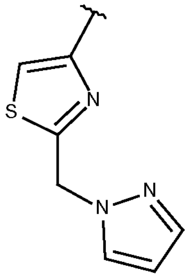
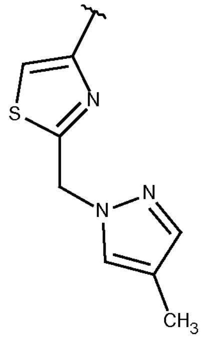
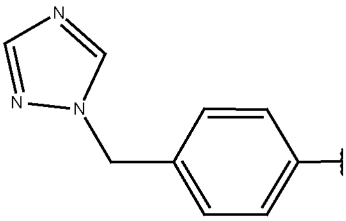
Table 4



Example Number	A	Free Base MW	[M+H]+
54		495.5	496
55		470.5	471
56		531.5	532
57		531.5	532
58		509.5	510
59		509.5	510
60		513.5	514

61		513.5	514
62		509.5	510
63		509.5	510
64		496.5	497
65		496.5	497
66		484.5	485
67		509.5	510
68		509.5	510
69		525.5	526
70		525.5	526

71		484.5	485
72		498.5	499
73		513.5	514
74		504.9	505
75		488.4	489
76		505.5	506
77		530.5	531

78		548.5	549
79		506.5	507
80		470.5	471
81		512.5	513
82		526.5	527
83		506.5	507

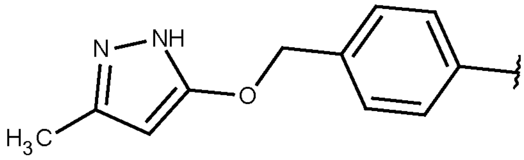
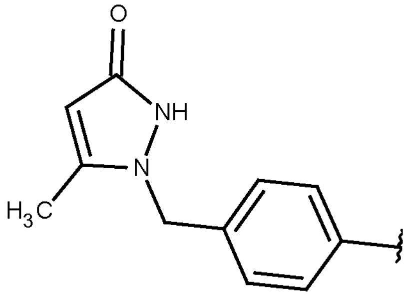
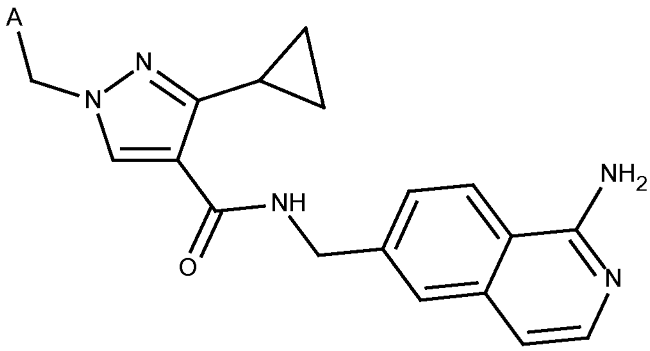
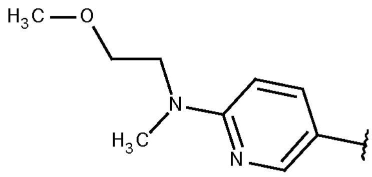
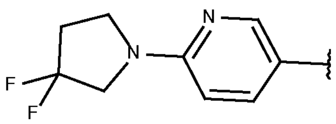
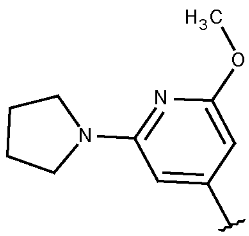
84		535.5	536
85		535.5	536

Table 5



Example Number	A	Free Base MW	$[M+H]^+$
86		485.6	486
87		503.6	504
88		497.6	498

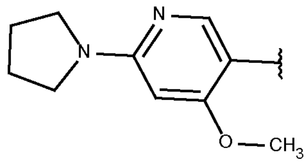
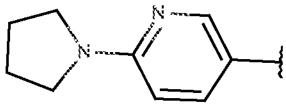
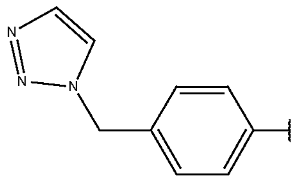
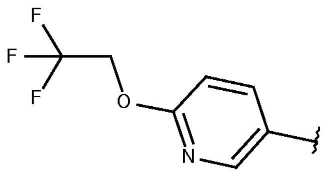
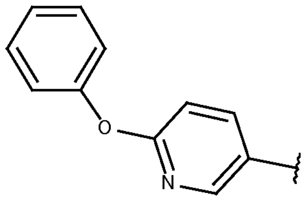
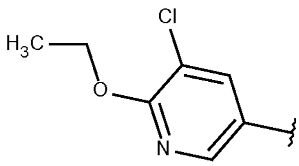
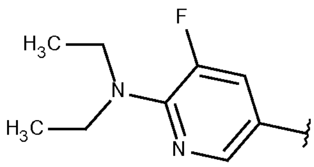
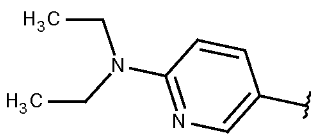
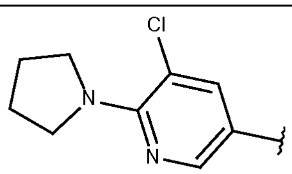
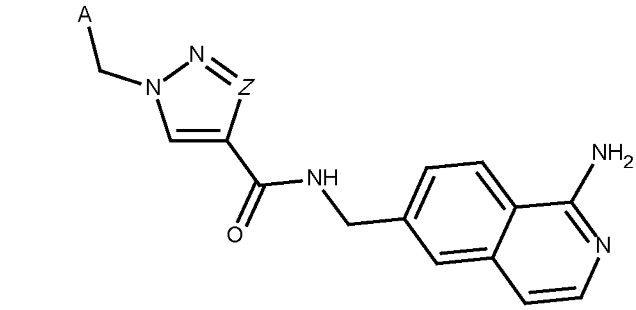
89		497.6	498
90		467.6	468
91		478.6	479
92		496.5	497
93		490.6	491
94		477	477
95		487.6	488
96		469.6	470
97		502.0	502

Table 6



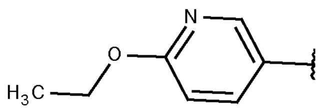
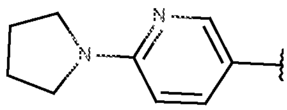
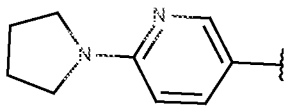
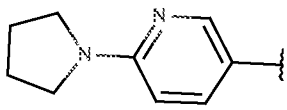
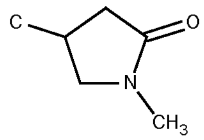
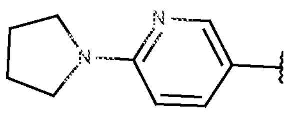
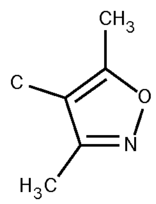
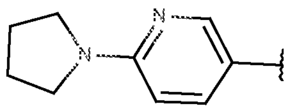
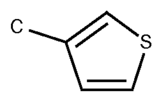
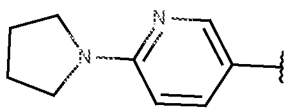
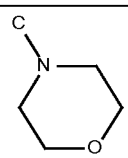
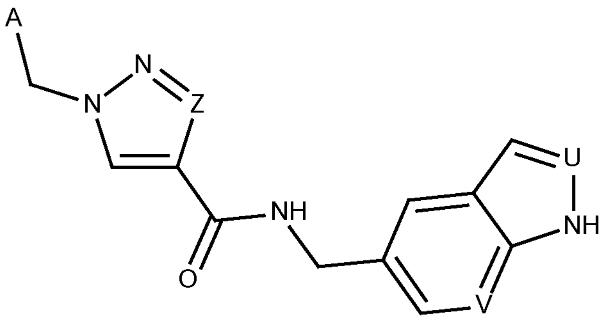
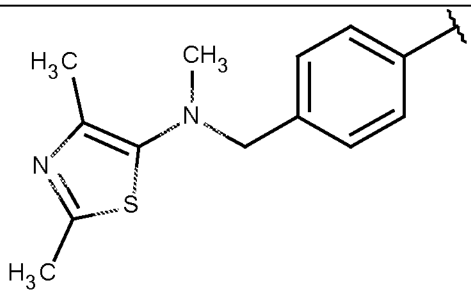
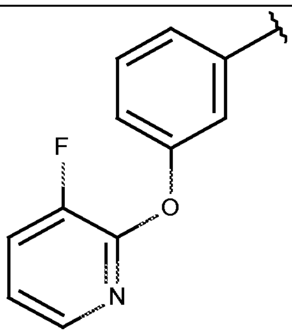
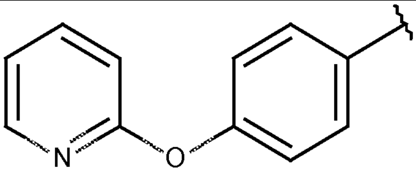
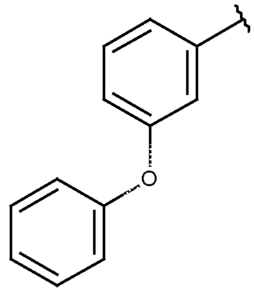
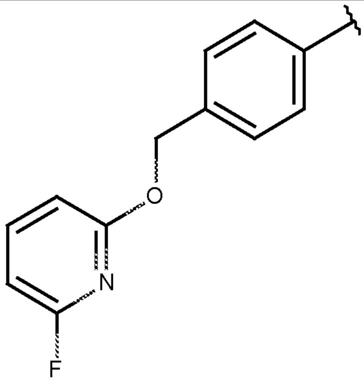
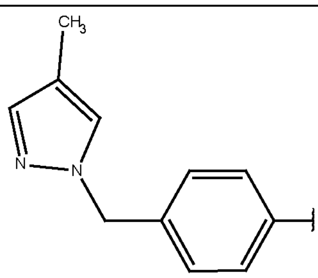
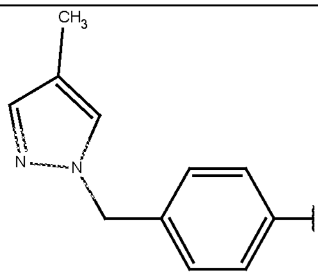
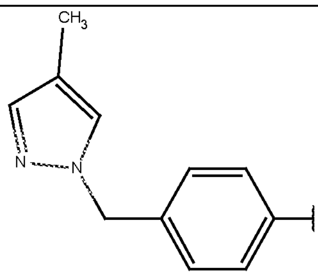
Example Number	A	Z	Free Base MW	[M+H]+
98		C-NH_2	417.5	418
99		C-NH_2	442.5	443
100		C-$N(CH_3)_2$	470.6	471
101			524.6	525
102			522.6	523
103			509.6	256 [M+2H]/2
104			512.6	513

Table 7



Example Number	A	V	U	Z	Free Base MW	[M+H]$^+$
105		N	CH	CH	485.6	486
106		N	CH	CH	442.5	443
107		N	CH	CH	424.5	425

Example Number	A	V	U	Z	Free Base MW	[M+H]$^+$
108		N	CH	CH	423.5	424
109		N	CH	CH	456.5	457
110		CH	C-CH_3	C-CF_3	506.5	507
111		CH	N	C-CF_3	493.5	494
112		CH	CH	C-CF_3	492.5	493.1

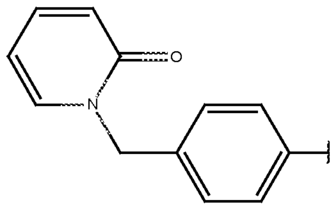
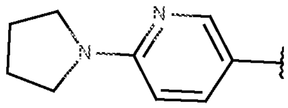
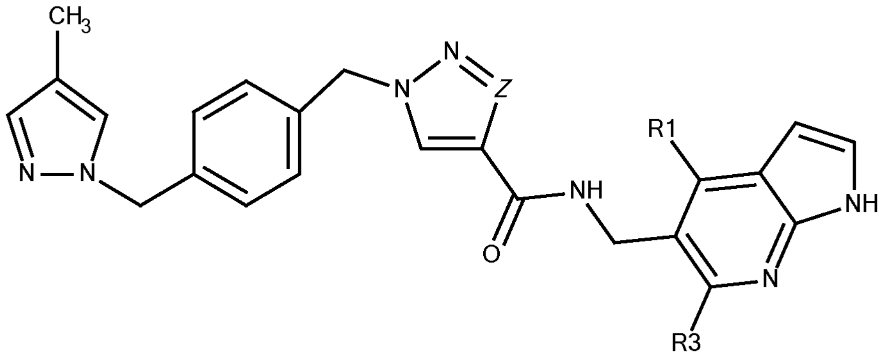
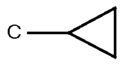
Example Number	A	V	U	Z	Free Base MW	$[M+H]^+$
113		CH	N	C-NH_2	453.5	454
114		N	CH	C-CF_3	469.5	470

Table 8



Example Number	R1	R3	Z	Free Base MW	$[M+H]^+$
115	H	H	N	426.5	427
116	H	CH_3	N	440.5	441
117	H	H	CH	425.5	426
118	CH_3	CH_3	CH	453.5	454
119	CH_3	CH_3	C-CF_3	521.5	522
120	H	H		465.6	466
121	H	H	C-CF_3	493.5	494

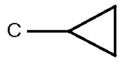
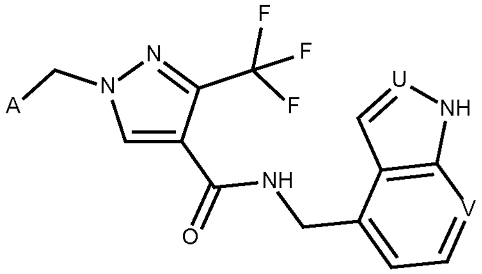
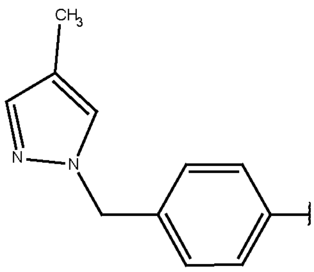
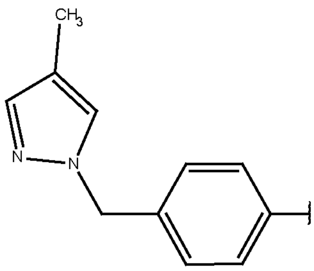
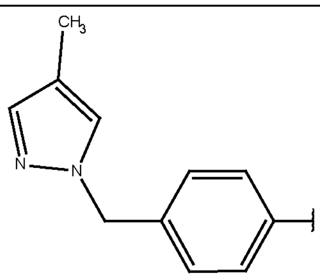
Example Number	R1	R3	Z	Free Base MW	[M+H]+
122	CH_3	CH_3		493.6	494

Table 9



Example Number	A	U	V	Free Base MW	[M+H]+
123		CH	CH	492.5	493
124		N	CH	493.5	494
125		CH	N	493.5	494

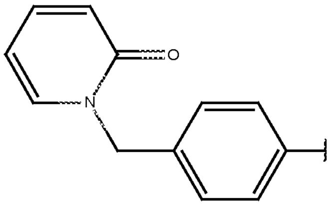
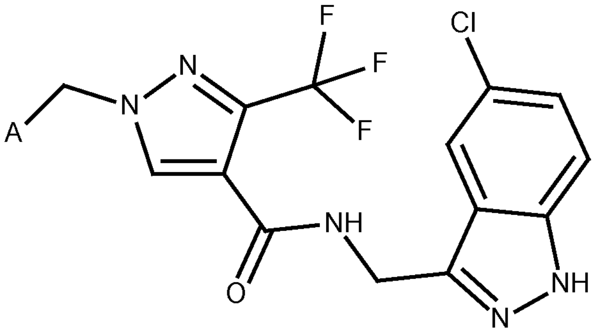
Example Number	A	U	V	Free Base MW	[M+H]+
126		N	CH	506.5	507

Table 10



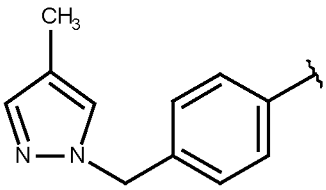
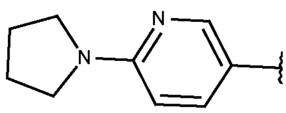
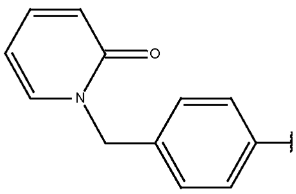
Example Number	A	Free Base MW	[M+H]+
127		527.9	528
128		503.9	504
129		540.9	541

Table 11

Example Number	Name
28	1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
29	1-Ethyl-4-methyl-5-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
30	1-Ethyl-4-methyl-5-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
31	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
32	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
33	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
34	3,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
35	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-phenyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
36	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
37	3-Amino-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
38	3-Methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
39	3-Difluoromethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
40	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-(2,2,2-trifluoro-ethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
41	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-3,4-dicarboxylic acid 4-[(1-amino-isoquinolin-6-ylmethyl)-amide] 3-dimethylamide
42	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-thiophen-3-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

Example Number	Name
43	3-Chloro-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
44	2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
45	1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
46	1-(4-{[(2,4-Dimethyl-thiazol-5-yl)-methyl-amino]-methyl}-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
47	1-(6-Phenoxy-pyridin-2-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
48	1-[3-(3-Fluoro-pyridin-2-yloxy)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
49	1-[4-(Pyridin-2-yloxy)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
50	1-[4-(6-Fluoro-pyridin-2-yloxymethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
51	1-(2-Pyrrolidin-1-yl-pyridin-4-ylmethyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
52	1-(5-Trifluoromethoxy-1H-indol-2-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
53	5-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
54	1-(2-Pyrrolidin-1-yl-pyridin-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
55	1-(6-Ethoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
56	1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-pyridin-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
57	1-[6-(3,3-Difluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
58	1-[6-((R)-3-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

Example Number	Name
59	1-[6-((S)-3-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
60	1-[6-((S)-3-Fluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
61	1-[6-((R)-3-Fluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
62	1-[6-((S)-2-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
63	1-[6-((R)-2-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
64	1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
65	1-(5-Pyrrolidin-1-yl-pyrazin-2-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
66	1-(2-Isopropoxy-pyridin-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
67	1-[2-((R)-3-Methyl-pyrrolidin-1-yl)-pyridin-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
68	1-[2-((S)-3-Methyl-pyrrolidin-1-yl)-pyridin-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
69	1-[6-(3-Hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
70	1-[6-((R)-3-Hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
71	1-(6-Propoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
72	1-(6-sec-Butoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
73	1-(5-Fluoro-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
74	1-(6-Chloro-5-ethoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

Example Number	Name
75	1-(6-Ethoxy-5-fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
76	1-(4-Pyrazol-1-ylmethyl-benzyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
77	1-[4-(4-Cyano-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
78	1-[4-(4-Carbamoyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
79	1-(6-Pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
80	1-(2-Ethoxy-pyridin-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
81	1-(2-Pyrazol-1-ylmethyl-thiazol-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
82	1-[2-(4-Methyl-pyrazol-1-ylmethyl)-thiazol-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
83	1-(4-[1,2,4]Triazol-1-ylmethyl-benzyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
84	1-[4-(5-Methyl-2H-pyrazol-3-yloxymethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
85	1-[4-(3-Methyl-5-oxo-4,5-dihydro-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
86	3-Cyclopropyl-1-{6-[(2-methoxy-ethyl)-methyl-amino]-pyridin-3-ylmethyl}-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
87	3-Cyclopropyl-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
88	3-Cyclopropyl-1-(2-methoxy-6-pyrrolidin-1-yl-pyridin-4-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
89	3-Cyclopropyl-1-(4-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
90	3-Cyclopropyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

Example Number	Name
91	3-Cyclopropyl-1-(4-[1,2,3]triazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
92	3-Cyclopropyl-1-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
93	3-Cyclopropyl-1-(6-phenoxy-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
94	1-(5-Chloro-6-ethoxy-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
95	3-Cyclopropyl-1-(6-diethylamino-5-fluoro-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
96	3-Cyclopropyl-1-(6-diethylamino-pyr idin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6- ylmethyl)-amide
97	1-(5-Chloro-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
98	3-Amino-1-(6-ethoxy-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
99	3-Amino-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
100	3-Dimethylamino-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
101	3-(1-Methyl-5-oxo-pyrrolidin-3-yl)-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
102	3-(3,5-Dimethyl-isoxazol-4-yl)-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
103	1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-thiophen-3-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
104	3-Morpholin-4-yl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
105	1-(4-{[(2,4-Dimethyl-thiazol-5-yl)-methyl-amino]-methyl}-benzyl)-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
106	1-[3-(3-Fluoro-pyridin-2-yloxy)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

Example Number	Name
107	1-[4-(Pyridin-2-yloxy)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
108	1-(3-Phenoxy-benzyl)-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
109	1-[4-(6-Fluoro-pyridin-2-yloxymethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
110	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (2-methyl-1H-indol-5-ylmethyl)-amide
111	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indazol-5-ylmethyl)-amide
112	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indol-5-ylmethyl)-amide
113	3-Amino-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-indazol-4-ylmethyl)-amide
114	1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
115	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
116	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
117	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
118	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
119	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
120	3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
121	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
122	3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

Example Number	Name
123	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indol-4-ylmethyl)-amide
124	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indazol-4-ylmethyl)-amide
125	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)-amide
126	1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indazol-4-ylmethyl)-amide
127	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (5-chloro-1H-indazol-3-ylmethyl)-amide
128	1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (5-chloro-1H-indazol-3-ylmethyl)-amide
129	1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (5-chloro-1H-indazol-3-ylmethyl)-amide

<u>**Table 12**</u>

NMR data of examples (solvent d6 DMSO)

Example Number	Chemical Shift (ppm)
28	0.94 (3H, t, J = 7.0Hz), 1.98 (3H, s), 2.00 (3H, s), 3.93 (2H, s), 4.15 (2H, q, J = 6.9Hz), 4.49 (2H, d, J = 6.0Hz), 5.17 (2H, s), 6.70 (2H, s, br), 6.73 (1H, s), 6.84 (1H, d, J = 5.7Hz), 7.03 (2H, d, J = 8.2Hz), 7.12 (2H, d, J = 8.2Hz), 7.22 (1H, s), 7.37 (1H, dd, J = 8.6, 1.6Hz), 7.45-7.55 (2H, m), 7.75 (1H, d, J = 5.8Hz), 8.12 (1H, d, J = 8.6Hz), 8.48 (1H, t, J = 6.1Hz)
29	1.10 (3H, t, J = 6.9Hz), 2.08 (3H, s), 4.11 (2H, s), 4.41 (2H, q, J = 6.9Hz), 4.56 (2H, d, J = 6.0Hz), 6.74 (1H, s), 7.19 (1H, d, J = 6.9Hz), 7.26 (1H, s), 7.46-7.50 (3H, m), 7.59-7.70 (2H, m), 7.76 (1H, d, J = 1.7Hz); 7.86-7.94 (2H, m), 8.48 (1H, d, J = 8.7Hz), 8.57 (1H, t, J = 6.1Hz), 8.79 (2H, s), 12.93 (1H, s).

Example Number	Chemical Shift (ppm)
30	0.97 (3H, t, J = 6.9Hz), 1.86-1.95 (4H, m), 2.02 (3H, s), 3.29-3.34 (4H, m), 3.79 (2H, s), 4.19 (2H, q, J = 6.9Hz), 4.49 (2H, d, J = 6.0Hz), 6.35 (1H, d, J = 8.6Hz), 6.67-6.78 (3H, m), 6.84 (1H, d, J = 6.0Hz), 7.14 (1H, dd, J = 8.6, 2.5Hz), 7.37 (1H, dd, J = 8.6, 1.7Hz), 7.51 (1H, s), 7.74 (1H, d, J = 5.8Hz), 7.82-7.87 (1H, m), 8.12 (1H, d, J = 8.6Hz), 8.47 (1H, t, J = 6.1Hz).
31	1.98 (3H, s), 4.53 (2H, d, J = 5.9Hz), 5.21 (2H, s), 5.32 (2H, s), 6.85 (2H, s, br), 6.87 (1H, s), 6.88-7.18 (2H, m), 7.22-7.25 (3H, m), 7.39 (1H, dd, J = 8.6, 1.5Hz), 7.51-7.54 (2H, m), 7.74 (1H, d, J = 5.9Hz), 7.92 (1H, s), 8.15 (1H, d, J = 8.6Hz), 8.26 (1H, s), 8.70 (1H, t, J = 5.9Hz).
33	1.98 (3H, s), 4.56 (2H, d, J = 6.2Hz), 5.22 (2H, s), 5.62 (2H, s), 6.79 (2H, s), 6.86 (1H, d, J = 5.8Hz), 7.19-7.23 (3H, m), 7.32 (2H, d, J = 8.2Hz), 7.41 (1H, dd, J = 8.6,1.6Hz), 7.52-7.54 (2H, m), 7.74 (1H, d, J = 5.8Hz), 8.13 (1H, d, J = 8.6Hz), 8.65 (1H, s), 9.18 (1H, t, J = 6.2Hz).
35	1.98 (3H, s), 4.56 (2H, d, J = 5.9 Hz), 5.23 (2H, s), 5.37 (2H, s), 7.15 (1H, d, J = 6.8 Hz), 7.19 – 7.24 (3H, m), 7.28 – 7.37 (5H, m), 7.54 (1H, s), 7.65 (1H, d, J = 8.6 Hz), 7.70 (3H, dd, J = 3.1 , 7.2 Hz), 7.76 (1H, s), 8.33 (1H, s), 8.47 (1H, d, J = 8.6 Hz), 8.62 (2H, s), 8.78 (1H, t, J = 6.0 Hz), 13.07 (1H, br s).
36	1.99 (3H, s), 4.51 (2H, d, J = 5.8 Hz), 5.23 (2H, s), 5.42 (2H, s), 6.73 (2H, br.s), 6.85 (1H, d, J = 5.8 Hz), 7.20 (1H, s), 7.22 (2H, d, J = 7.2 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.37 (1H, dd, J = 8.6, 1.1 Hz), 7.54 (2H, br.s), 7.77 (1H, d, J = 5.8 Hz), 8.14 (1H, d, J = 8.6 Hz), 8.47 (1H, s), 8.88 (1H, t, J = 5.9 Hz)
37	1.99 (3H, s), 4.55 (2H, d, J= 5.8 Hz), 5.07 (2H, s), 5.22 (2H, s), 5.41 (2H, s), 7.15-7.29 (6H, m), 7.54 (1H, t, J= 0.9 Hz), 7.59-7.71 (2H, m), 7.75 (1H, s), 8.03 (1H, s), 8.46 (1H, d, J= 8.6 Hz), 8.53 (1H, t, J= 6.0 Hz), 8.64 (2H, s), 12.95 (1H, s).

Example Number	Chemical Shift (ppm)
38	1.99 (3H, t, J = 0.7 Hz); 3.22 (3H, s); 4.59 (4H, d, J = 15.7 Hz); 5.23 (2H, s); 5.31 (2H, s); 7.16 - 7.29 (6H, m); 7.55 (1H, t, J = 0.9 Hz); 7.69 (2H, td, J = 3.0 & 8.7 Hz); 7.81 (1H, d, J = 1.6 Hz); 8.31 (1H, s); 8.56 (1H, d, J = 8.6 Hz); 8.64 (1H, t, J = 5.9 Hz); 9.12 (2H, s); 13.29 (1H, s).
39	1.99 (3H, s); 4.59 (2H, d, J = 5.8 Hz); 5.24 (2H, s); 5.41 (2H, s); 7.15 - 7.34 (7H, m); 7.55 (1H, t, J = 0.9 Hz); 7.69 (2H, td, J = 2.4 & 8.6 Hz); 7.81 (1H, d, J = 1.7 Hz); 8.46 (1H, t, J = 1.2 Hz); 8.55 (1H, d, J = 8.6 Hz); 9.03-9.21 (3H, m); 13.25 (1H, s).
40	1.99 (3H, s), 3.95 (2H, q, J= 11.3 Hz), 4.58 (2H, d, J= 5.8 Hz), 5.23 (2H, s), 5.35 (2H, s), 7.13-7.32 (6H, m), 7.54 (1H, s), 7.63-7.72 (2H, m), 7.78 (1H, s), 8.35 (1H, s), 8.52 (1H, d, J= 8.7 Hz), 8.86 (1H, s), 9.00 (2H, s), 13.05 (1H, br s).
41	1.98 (3H, s), 2.92 (3H, s), 2.96 (3H, s), 4.52 (2H, d, J= 5.8Hz), 5.22 (2H, s), 5.35 (2H, s), 6.74 (2H, s), 6.84 (1H, d, J= 5.7Hz), 7.19 (2H, d, J= 8.2Hz), 7.20-7.30 (3H, m), 7.36 (1H, dd, J= 8.6, 1.7Hz), 7.49-7.55 (2H, m), 7.76 (1H, d, J= 5.8Hz), 8.13 (1H, d, J= 8.6Hz), 8.35 (1H, s), 9.08 (1H, t, J = 5.9Hz).
42	1.97 (3H, s), 4.59 (2H, d, J= 5.8Hz), 5.22 (2H, s), 5.35 (2H, s), 7.16-7.23 (3H, m), 7.24 (1H, s), 7.30 (2H, d, J= 8.1Hz), 7.47 (1H, dd, J= 5.0, 3.0Hz), 7.50-7.57 (2H, m), 7.63-7.74 (2H, m), 7.81 (1H, s), 8.13 (1H, dd, J= 3.0, 1.2Hz), 8.36 (1H, s), 8.56 (1H, d, J= 8.6Hz), 8.85 (1H, t, J= 5.9Hz), 9.12 (2H, brs), 13.31 (1H, brs)
43	1.98 (3H, s), 4.51 (2H, d, J= 5.9Hz), 5.22 (2H, s), 5.29 (2H, s), 6.80 (2H, s), 6.87 (1H, d, J= 6.0Hz), 7.19 (2H, d, J= 8.2Hz), 7.23 (1H, s), 7.27 (2H, d, J= 8.2Hz), 7.39 (1H, dd, J 8.6, 1.8Hz), 7.50-7.57 (2H, m), 7.76 (1H, d, J= 5.8Hz), 8.14 (1H, d, J= 8.6Hz), 8.36 (1H, s), 8.58 (1H, t, J= 6.0Hz)

Example Number	Chemical Shift (ppm)
44	2.07 (3H, s), 2.37 (3H, s), 4.50 (2H, d, J = 6.0Hz), 5.06 (2H, s), 5.07 (2H, s), 6.23 (1H, dt, J = 1.4, 6.7Hz), 6.36 (1H, s), 6.39 (1H, d, J = 9.2Hz), 6.69 (2H, s, br), 6.79-6.94 (3H, m), 7.20-7.30 (2H, m), 7.35-7.46 (2H, m), 7.52 (1H, d, J = 1.6Hz), 7.73-7.77 (2H, m), 8.12 (1H, d, J = 8.6Hz), 8.21 (1H, t, J = 6.1Hz).
45	2.98 (2H, t, J = 7.2Hz), 4.18 (4H, s), 4.30 (2H, t, J = 7.2Hz), 4.52 (2H, t, J = 5.9Hz), 6.59 (1H, dd, J = 8.2, 2.1Hz), 6.67 (1H, d, J = 2.0Hz), 6.69- 6.77 (3H, m), 6.84 (1H, d, J = 5.8Hz), 7.36 (1H, dd, J = 8.6, 1.6Hz), 7.51 (1H, s), 7.76 (1H, d, J = 5.8Hz), 7.92 (1H, s), 8.08-8.16 (2H, m), 8.68 (1H, t, J = 6.0Hz).
46	2.10 (3H, s), 2.47 (3H, s), 2.55 (3H, s), 3.87 (2H, s), 4.53 (2H, d, J = 5.9 Hz), 5.33 (2H, s), 6.83 (2H, br. s), 6.88 (1H, d, J = 5.8Hz), 7.20 (2H, d, J = 8.2Hz), 7.26 (2H, d, J = 8.2Hz), 7.39 (1H, dd, J = 1.3, 8.6Hz), 7.54 (1H, br. s), 7.74 (1H, d, J = 5.8Hz), 7.93 (1H, d, J = 0.6Hz), 8.14 (1H, d, J = 8.6Hz), 8.27 (1H, d, 0.6Hz), 8.70 (1H, t, J = 6.0Hz)
47	4.55 (2H, d, J = 5.9Hz), 5.33 (2H, s), 6.74 (2H, s), 6.81-6.92 (3H, m), 7.05-7.19 (3H, m), 7.33-7.42 (3H, m), 7.55 (1H, d, J = 1.7Hz), 7.76 (1H, d, J = 5.8Hz), 7.83 (1H, dd, J = 7.4, 8.2Hz), 7.95 (1H, d, J = 0.7Hz), 8.15 (1H, d, J = 8.6Hz), 8.24 (1H, d, J = 0.8Hz), 8.71 (1H, t, J = 6.0Hz).
48	4.54 (2H, d, J = 5.9Hz), 5.37 (2H, s), 6.73 (2H, s), 6.86 (1H, d, J = 5.8Hz), 7.14-7.23 (3H, m), 7.31-7.41 (3H, m), 7.53 (1H, d, J = 1.7Hz), 7.75 (1H, d, J = 5.8Hz), 7.86 (1H, ddd, J = 1.5, 8.0, 10.7Hz), 7.92 (1H, dd, J = 1.5, 4.9Hz), 7.96 (1H, d, J = 0.7Hz), 8.13 (1H, d, J = 8.6Hz), 8.34 (1H, d, J = 0.8Hz), 8.73 (1H, t, J = 6.0Hz).
49	4.61 (2H, d, J = 5.9Hz), 5.37 (2H, s), 7.03 (1H, dt, J = 0.9, 8.3Hz), 7.09-7.15 (3H, m), 7.22 (1H, d, J = 7.0Hz), 7.30-7.37 (2H, m), 7.63-7.72 (2H, m), 7.80 (1H, d, J = 1.6Hz), 7.85 (1H, dd, J = 2.0, 7.2, 8.3Hz), 7.97 (1H, d, J = 0.7Hz), 8.12 (1H, ddd, J = 0.8, 2.0, 5.0Hz), 8.35 (1H, d, J = 0.8Hz), 8.51 (1H, d, J = 8.6Hz), 8.87 (1H, t, J = 6.0Hz), 8.95 (1H, s), 13.04 (1H, s).

Example Number	Chemical Shift (ppm)
50	4.53 (2H, d, J = 5.9Hz), 5.28 (2H, s), 5.36 (2H, s), 6.71-6.73 (3H, m), 6.80 (1H, dd, J = 1.5, 8.0Hz), 6.85 (1H, d, J = 5.8Hz), 7.29 (2H, d, J = 8.2Hz), 7.37 (1H, dd, J = 1.6, 8.6Hz), 7.44 (2H d, J = 8.2Hz), 7.52 (1H, br. s), 7.75 (1H, d, J = 5.8Hz), 7.89 (1H, td, J = 8.0, 8.6Hz), 7.93 (1H, d, J = 0.5Hz), 8.13 (1H, d, J = 8.6 Hz), 8.29 (1H, d, J = 0.5 Hz), 8.70 (1H, t, J = 6.0 Hz).
51	1.91-1.94 (4H, s), 3.31-3.33 (4H, m), 4.61 (2H, d, J= 5.88Hz), 5.51(2H, s), 6.13 (1H, d, J= 5.24Hz), 6.17 (1H, s), 7.15 (1H, d, J= 6.72Hz), 7.65 (1H, d, J= 8.49Hz), 7.70 (1H, d, J= 6.72Hz), 7.78 (1H, s), 7.99 (1H, d, J= 5.16Hz), 8.16 (1H, s), 8.47 (1H, d, J= 8.60Hz), 8.57 (2H, br, s), 9.22(1H, t, J= 5.76Hz).
52	4.53 (2H, d, J = 5.9Hz), 5.52 (2H, s), 6.50 (1H, d, J = 1.3Hz),6.70 (2H, s), 6.84 (1H, d, J = 5.7Hz), 7.05 (1H, dd, J = 8.8, 1.5Hz), 7.36 (1H, dd, J = 8.6, 1.7Hz), 7.43 (1H, d, J = 8.8Hz), 7.51 (2H, s), 7.75 (1H, d, J = 5.8Hz), 7.96 (1H, d, J = 0.6Hz), 8.12 (1H, d, J = 8.6Hz), 8.29 - 8.24 (1H, m), 8.72 (1H, t, J = 6.0Hz), 11.51 (1H, s)
53	3.40 (0.5H, br s), 4.57 (2H, d, J= 6.0Hz), 5.07 (2H, s), 5.29 (2H, s), 6.25 (1H, t, J= 2.0Hz), 6.32 (2H, br s), 6.52 (0.5H, br s), 7.13 (2H, d, J= 8.2Hz), 7.17 (2H, d, J= 8.0Hz), 7.24 (1H, d, J= 6.9Hz), 7.43 (1H, d, J= 1.6Hz), 7.64 (1H, d, J= 7.0Hz), 7.69 (1H, dd, J= 8.6, 1.3Hz), 7.76 (1H, s), 7.79 (2H, s), 8.45 (1H, t, J= 5.7Hz), 8.50 (1H, d, J= 8.6Hz), 8.92 (2H, br s), 12.88 (1H, br s).
54	1.91-1.95 (4H, s), 3.33-3.37 (4H, m), 4.53 (2H, d, J= 5.8Hz), 5.38(2H, s), 6.36 (2H, d, J= 1.8Hz), 6.76 (2H, s), 6.9(1H, d, J= 5.8Hz), 7.39 (1H, d, J= 8.6Hz), 7.55 (1H, s), 7.77(1H, d, J= 5.8Hz), 8.03(1H, t, J= 2.8Hz), 8.15 (1H, d, J = 8.6Hz), 8.52 (1H, s), 8.93(1H, t, J= 5.4Hz).
55	1.31(3H,t,J= 7.0Hz), 4.30(2H,q,J= 7.0Hz), 4.60(2H,d,J= 5.8Hz), 5.42(2H,s), 6.83(1H,d,J= 8.5Hz), 7.21(1H,d,J= 7.0Hz), 7.66-7.73(3H,m), 7.81(1H,s), 8.24(1H,d,J= 2.4Hz), 8.51(2H,d,J= 8.8Hz), 9.02(1H,t,J= 5.7Hz), 9.11(2H,br s), 13.33(1H,s)

Example Number	Chemical Shift (ppm)
56	2.53-2.68 (2H, m), 3.73 (2H, t, J = 7.4Hz), 3.97 (2H, t, J = 12.9Hz), 4.60 (2H, d, J = 5.9Hz), 5.53 (2H, s), 6.64 (1H, d, J = 5.7Hz), 6.87 (1H, brs), 7.19 (1H, d, J = 7.0Hz), 7.65-7.75 (2H, m), 7.82 (1H, s), 8.07 (1H, d, J = 5.6Hz), 8.58 (1H, d, J = 8.6Hz), 8.71 (1H, s), 9.15 (2H, brs), 9.25 (1H, t, J = 5.9Hz), 13.33 (1H, s).
57	2.53-2.66 (2H, m), 3.73 (2H, t, J = 7.4Hz), 3.96 (2H, t, J = 13.0Hz), 4.58 (2H, d, J = 5.9Hz), 5.41 (2H, s), 6.79-6.92 (1H, m), 7.20 (1H, d, J = 7.0Hz), 7.64-7.73 (2H, m), 7.78-7.88 (2H, m), 8.24 (1H, d, J = 2.1Hz), 8.53-8.62 (2H, m), 8.86-9.39 (3H, m), 13.27 (1H, s).
58	1.08 (3H, d, J = 6.6 Hz), 1.61 (1H, br.s), 2.12 (1H, br.s), 2.98 (3H, br.s), 3.37-3.65 (2H, m), 4.59 (2H, d, J = 5.8 Hz), 5.36 (2H, s), 7.21 (1H, d, J = 7.0 Hz), 7.66 (1H, d, J = 7.2 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.80 (1H, s), 8.13 (1H, d, J = 1.8 Hz), 8.50 (1H, br.s), 8.52 (1H, d, J = 8.6 Hz), 8.93 (1H, br.s), 9.02 (1H, br.s), 12.87 (1H, br.s)
59	1.08 (3H, d, J = 6.4 Hz), 1.63 (1H, dd, J = 11.9, 8.8 Hz), 2.15 (1H, d, J = 5.8 Hz), 3.00-3.04 (3H, m), 3.43-3.50 (2H, m), 4.59 (2H, d, J = 5.8 Hz), 5.41 (2H, s), 7.21 (1H, d, J = 7.0 Hz), 7.67 (1H, d, J = 8.5 Hz), 7.69 (1H, dd, J = 8.8, 1.4 Hz), 7.81 (1H, s), 8.14 (1H, d, J = 1.7 Hz), 8.54 (2H, d, J = 8.7 Hz), 9.01 (1H, br.s), 9.08 (1H, br.s), 13.03 (1H, br.s)
60	2.11-2.44 (2H, m), 3.55-3.65 (1H, m), 3.73-3.94 (3H, m), 4.59 (2H, d, J = 5.8Hz), 5.36-5.65 (3H, m), 7.06 (1H, brd, J= 9.1Hz), 7.19 (1H, d, J = 6.9Hz), 7.64-7.74 (2H, m), 7.80 (1H, s), 7.94 (1H, brd, J = 9.1Hz), 8.21 (1H, d, J = 1.9Hz), 8.59 (1H, d, J = 8.6Hz), 8.64 (1H, s), 8.91-9.45 (3H, m), 13.39 (1H, s).
61	2.12-2.42 (2H, m), 3.55-3.65 (1H, m), 3.70-3.93 (3H, m), 4.59 (2H, d, J = 5.9Hz), 5.36-5.64 (3H, m), 7.06 (1H, brd, J= 9.1Hz), 7.19 (1H, d, J = 7.0Hz), 7.64-7.74 (2H, m), 7.80 (1H, s), 7.92 (1H, brd, J = 9.1Hz), 8.21 (1H, d, J = 2.0Hz), 8.59 (1H, d, J = 8.6Hz), 8.64 (1H, s), 8.91-9.45 (3H, m), 13.41 (1H, s).

Example Number	Chemical Shift (ppm)
62	1.16 (3H, d, J= 6.3Hz), 1.69-1.84 (1H, m), 1.95-2.22 (3H, m), 3.38-3.47 (1H, m), 3.68-3.75 (1H, m), 4.33 (1H, br.s), 4.59 (2H, d, J= 5.9Hz), 5.44 (2H, s), 7.11 (1H, br.s), 7.19 (1H, d, J= 7.0Hz), 7.64-7.73 (2H, m), 7.81 (1H, s), 7.92 (1H, br.d, J= 9.1Hz), 8.12-8.20 (1H, m), 8.60 (1H, d, J= 8.6Hz), 8.66 (1H, s), 8.91-9.45 (3H, m), 13.40 (1H, s), 13.85 (1H, brs).
63	1.16 (3H, d, J= 6.3Hz), 1.70-1.84 (1H, m), 1.96-2.21 (3H, m), 3.37-3.47 (1H, m), 3.68-3.75 (1H, m), 4.32 (1H, brs), 4.59 (2H, d, J= 5.8Hz), 5.44 (2H, s), 7.10 (1H, brs), 7.19 (1H, d, J= 7.0Hz), 7.64-7.73 (2H, m), 7.81 (1H, s), 7.92 (1H, br.d, J= 9.2Hz), 8.13-8.20 (1H, m), 8.59 (1H, d, J= 8.7Hz), 8.66 (1H, s), 8.91-9.45 (3H, m), 13.38 (1H, s), 13.85 (1H, br.s).
64	1.90-1.93(4H,m), 3.45-3.49(4H,m), 4.59(2H,d,J= 5.8Hz), 5.30(2H,s), 7.22(1H,d,J= 7.0Hz), 7.65-7.70(2H,m), 7.80(1H,s), 8.39-8.45(3H,m), 8.50(1H,d,J= 8.6Hz), 8.96-8.99(3H,m),13.02(1H,s).
65	1.93-1.96 (4H, m), 3.41-3.44 (4H, m), 4.59 (2H, d, J= 5.8Hz), 5.39 (2H, s), 7.22 (1H, d, J= 7.0Hz), 7.65 (1H, d, J= 7.0Hz), 7.69 (1H, dd, J= 8.6,1.3Hz), 7.80 (1H, s), 7.93 (1H, d, J= 1.3Hz), 8.19 (1H, d, J= 1.2Hz), 8.47 (1H, s), 8.51 (1H, d, J= 8.6Hz), 8.97-9.00 (3H, m), 12.90 (1H, s).
66	1.21-1.32 (6H, m), 4.61 (2H, d, J= 5.8Hz), 5.23 (1H, hept, J= 6.2Hz), 5.48 (2H, s), 6.51-6.56 (1H, m), 6.81 (1H, dd, J= 1.5, 5.3Hz), 7.21 (1H, d, J= 7.0Hz), 7.64-7.74 (2H, m), 7.82 (1H, d, J= 1.7Hz), 8.14 (1H, dd, J= 0.7, 5.2Hz), 8.51-8.61 (2H, m), 8.88-9.12 (3H, m), 13.12 (1H, s).
67	1.09 (3H, d, J= 6.6Hz), 1.63 (1H, br.s), 2.14 (1H, br.s), 2.40 (3H, br.s), 3.02 (3H, br.s), 3.58 (1H, br.s), 3.66 (1H, br.s), 4.61 (2H, d, J= 5.8Hz), 5.53 (2H, br.s), 6.52 (1H, br.s), 7.21 (1H, d, J= 7.04Hz), 7.66 (1H, br.s), 7.69 (1H, dd, J= 9.7, 8.3Hz), 7.82 (1H, s), 7.97 (1H, d, J= 5.9Hz), 8.53 (1H, d, J= 8.7Hz), 8.62 (1H, s), 8.97 (1H, br.s), 9.12 (1H, br.s), 12.94 (1H, br.s)

Example Number	Chemical Shift (ppm)
68	1.09 (3H, d, J= 6.6Hz), 1.64 (1H, br.s), 2.14 (1H, br.s), 3.01 (3H, br.s), 3.58 (1H, br.s), 3.67 (1H, br.s), 4.61 (2H, d, J= 5.9Hz), 5.54 (2H, br.s), 6.54 (1H, br.s), 7.21 (1H, d, J= 7.04Hz), 7.66 (1H, br.s), 7.70 (1H, dd, J= 9.0, 7.7Hz), 7.82 (1H, s), 7.97 (1H, d, J= 5.6Hz), 8.54 (1H, d, J= 8.4Hz), 8.63 (1H, s), 8.98 (1H, br.s), 9.13 (1H, br.s), 12.95 (1H, br.s) (isoquinoline NH2 obscured by solvent)
69	1.76-1.90 (1H, m), 2.02-2.14 (1H, m), 2.44-2.52 (1H, m), 3.29-3.54 (5H, m), 3.60-3.67 (2H, m), 4.59 (2H, d, J= 6.0Hz), 5.44 (2H, s), 7.05 (1H, br.s), 7.20 (1H, d, J= 6.9Hz), 7.64-7.73 (2H, m), 7.81 (1H, s), 7.91 (1H, d, J= 9.0Hz), 8.15 (1H, d, J= 1.8Hz), 8.59 (1H, d, J= 8.7Hz), 8.64 (1H, s), 8.96-9.41 (3H, m), 13.34 (1H, br.s), 13.70 (1H, br.s).
70	1.75-1.89 (1H, m), 2.02-2.14 (1H, m), 2.44-2.52 (1H, m), 3.29-3.54 (5H, m), 3.61-3.68 (2H, m), 4.59 (2H, d, J = 6.0Hz), 5.43 (2H, s), 7.04 (1H, brs), 7.20 (1H, d, J = 7.0Hz), 7.64-7.73 (2H, m), 7.81 (1H, s), 7.91 (1H, d, J = 9.1Hz), 8.15 (1H, d, J = 1.8Hz), 8.58 (1H, d, J = 8.6Hz), 8.64 (1H, s), 8.96-9.41 (3H, m), 13.33 (1H, brs), 13.70 (1H, brs).
71	0.95 (3H, t, J= 7.4Hz), 1.67-1.76 (2H, m), 4.21 (2H, t, J= 6.7Hz), 4.60 (2H, d, J= 5.9Hz), 5.42 (2H, s), 6.85 (1H, d, J= 8.6Hz), 7.22 (1H, d, J= 7.0Hz), 7.64-7.76 (3H, m), 7.81 (1H, s), 8.24 (1H, d, J= 2.0Hz), 8.48-8.56 (2H, m), 9.03 (3H, s), 13.03 (1H, s).
72	0.89 (3H, t, J= 7.4Hz), 1.24 (3H, d, J= 6.2Hz), 1.53–1.71 (2H, m), 4.60 (2H, d, J= 5.3Hz), 5.08 (1H, q, J= 6.2Hz), 5.41 (2H, s), 6.80 (1H, d, J= 9.0Hz), 7.22 (1H, d, J= 7.0Hz), 7.64–7.73 (3H, m), 7.81 (1H, s), 8.22 (1H, d, J = 2.1Hz), 8.49–8.57 (2H, m), 8.84–9.18 (3H, m), 13.02 (1H, s).
73	1.87 (4H, q, J= 6.6Hz), 3.53 (4H, q, J= 6.3Hz), 4.59 (2H, d, J= 5.8Hz), 5.32 (2H, s), 7.21 (1H, d, J= 7.0Hz), 7.46 (1H, dd, J= 1.7, 15.8Hz), 7.65-7.70 (2H, m), 7.81 (1H, s), 8.00 (1H, s), 8.43 (1H, s), 8.50 (1H, d, J= 8.7Hz), 8.98 (2H, t, J= 5.7Hz), 12.93 (1H, s).

Example Number	Chemical Shift (ppm)
74	1.37 (3H, t, J= 6.9Hz), 4.16 (2H, q, J= 6.9Hz), 4.59 (2H, d, J= 5.8Hz), 5.52 (2H, s), 7.20 (1H, d, J= 6.9Hz), 7.65-7.70 (3H, m), 7.80 (1H, s), 8.00 (1H, d, J= 1.7Hz), 8.50 (2H, d, J= 7.5Hz), 8.91 (1H, br.s), 8.98 (1H, t, J= 5.7Hz), 12.87 (1H, s).
75	1.34 (3H, t, J= 7.0Hz), 4.00 (2H, q, J= 7.1Hz), 4.59 (2H, d, J= 5.8Hz), 5.44 (2H, s), 7.20 (1H, d, J= 7.0Hz), 7.65-7.75 (3H, m), 7.80 (1H, s), 8.07 (1H, d, J= 1.7Hz), 8.49 (2H, d, J= 10.7Hz), 8.91 (1H, br.s), 8.98 (1H, t, J= 5.8Hz), 12.92 (1H, s).
76	4.58 (2H, d, J= 5.8Hz), 5.33 (2H, s), 5.43 (2H,s), 6.26 (1H, t, J= 2.0Hz), 7.18-7.23 (3H, m), 7.31 (2H,d, J= 8.1Hz), 7.45 (1H, d, J= 1.7Hz), 7.68-7.70 (2H, m), 7.80 (1H, s), 7.82 (1H, d, J= 2.1Hz), 8.53-8.56 (2H,m), 9.04-9.07 (3H, m), 13.18 (1H, s)
77	4.58 (2H, d, J= 5.8Hz), 5.33 (2H, s), 5.43 (2H, s), 6.26 (1H, t, J= 2.0Hz), 7.18-7.23 (3H, m), 7.31 (2H, d, J= 8.1Hz), 7.45 (1H, d, J= 1.7Hz), 7.68-7.70 (2H, m), 7.80 (1H, s), 7.82 (1H, d, J= 2.1Hz), 8.53-8.56 (2H, m), 9.04-9.07 (3H, m), 13.18 (1H, s).
78	4.58 (2H, d, J= 5.8Hz), 5.33 (2H, s), 5.43 (2H, s), 6.26 (1H, t, J= 2.0Hz), 7.18-7.23 (3H, m), 7.31 (2H, d, J= 8.1Hz), 7.45 (1H, d, J= 1.7Hz), 7.68-7.70 (2H, m), 7.80 (1H, s), 7.82 (1H, d, J= 2.1Hz), 8.53-8.56 (2H, m), 9.04-9.07 (3H,m), 13.18 (1H, s).
80	1.30 (3H, t, J= 7.0Hz), 4.30 (2H, q, J= 7.0Hz), 4.61 (2H, d, J= 5.9Hz), 5.50 (2H, s), 6.59-6.65 (1H, m), 6.85 (1H, dd, J= 1.4, 5.3Hz), 7.22 (1H, d, J= 7.0Hz), 7.71 (2H, td, J= 3.4, 8.8Hz), 7.83 (1H, d, J= 1.6Hz), 8.16 (1H, dd, J= 0.7, 5.2Hz), 8.53-8.63 (2H, m), 8.80-9.20 (3H, m), 13.22 (1H, s).
86	0.72–0.80 (2H, m), 0.80–0.87 (2H, m), 2.55–2.63 (1H, m,), 3.02 (3H, s), 3.48 (2H, t, J= 5.8Hz), 3.57 (3H, s), 3.68 (2H, t, J= 5.8Hz), 4.58 (2H, d, J= 5.9Hz), 5.07 (2H, s), 6.65 (1H, d, J= 6.7Hz), 7.23 (1H, d, J= 6.9Hz), 7.46 (1H, d, J= 8.6Hz), 7.66 (1H, d, J= 7.0Hz), 7.70 (1H, d, J= 8.7Hz), 7.80 (1H, s), 8.07 (1H, d, J= 2.2Hz), 8.12 (1H, s), 8.53 (1H, d, J = 8.6Hz), 8.59 (1H, t, J = 6.0Hz), 8.99 (2H, br s), 13.06 (1H, br s).

Example Number	Chemical Shift (ppm)
87	0.74–0.79 (2H, m), 0.79–0.87 (2H, m), 2.52–2.63 (3H, m), 3.60 (2H, t, J= 7.3Hz), 3.82 (2H, t, J= 13.3Hz), 4.57 (2H, d, J= 5.9Hz), 5.10 (2H, s), 6.56 (1H, d, J= 8.5Hz), 7.18 (1H, d, J= 6.9Hz), 7.53 (1H, dd, J= 2.4, 8.6Hz), 7.59–7.70 (2H, m), 7.76 (1H, s), 8.06–8.16 (2H, m), 8.47 (1H, d, J= 8.6Hz), 8.53–8.89 (3H, m), 13.02 (1H, s).
88	0.73-0.77 (2H, m), 0.82-0.93 (2H, m), 1.91 (4H, t, J= 6.5Hz), 3.33 (4H, t, J= 6.4Hz), 3.75 (3H, s), 4.59 (2H, d, J= 5.8Hz), 5.10 (2H, s), 5.68 (1H, s), 5.82 (1H, s), 7.24 (1H, d, J= 6.8Hz), 7.65 (1H, br.s), 7.71 (1H, dd, J= 8.8, 1.4Hz), 7.81 (1H, s), 8.18 (1H, s), 8.52 (1H, d, J= 8.7Hz), 8.62 (1H, t, J= 5.5Hz), 8.96 (2H, br.s), 12.91 (1H, s)
89	0.71-0.75 (2H, m), 0.80-0.85 (2H, m), 2.02 (4H, s), 2.57-2.63 (1H, m), 3.53 (4H, br.s), 3.99 (3H, s), 4.59 (2H, d, J= 5.8Hz), 5.11 (2H, s), 6.34 (1H, s), 7.22 (1H, d, J= 7.0Hz), 7.66 (1H, d, J= 6.9Hz), 7.71 (1H, d, J= 8.7Hz), 7.82 (2H, d, J= 14.9Hz), 8.16 (1H, s), 8.54 (1H, d, J= 8.6Hz), 8.63 (1H, br.s), 9.01 (2H, br.s), 12.81 (1H, br.s), 13.05 (1H, br.s)
90	0.70-0.80 (2H, m), 0.77-0.88 (2H, m), 1.95-2.05 (4H, m), 2.58 (1H, ddd, J= 3.2, 5.2, 8.3Hz), 3.52-3.94 (4H, m), 4.58 (2H, d, J= 5.8Hz), 5.22 (2H, s), 7.08 (1H, d, J= 9.4Hz), 7.17-7.24 (1H, m), 7.64-7.74 (2H, m), 7.77-7.90 (2H, m), 7.98-8.04 (1H, m), 8.28 (1H, s), 8.59 (1H, d, J= 8.6Hz), 8.73 (1H, t, J= 5.9Hz), 9.18 (2H, s), 13.40 (1H, s), 13.82 (1H, s).
91	0.72-0.84 (4H, m), 2.55-2.62 (1H, m), 4.57 (2H,d, J= 5.7Hz), 5.22 (2H, s), 5.60 (2H,s), 7.16-7.24 (3H,m), 7.28 (2H, d, J= 8.1Hz), 7.66-7.71 (2H, m), 7.74 (1H,s), 7.80 (1H, s), 8.20 (2H, d, J= 6.6Hz), 8.56 (1H, d, J= 8.6Hz), 8.64 (1H, t, J= 5.8Hz), 9.12 (2H, br.s), 13.32 (1H,s).
92	0.73-0.76 (2H, m), 0.77-0.82 (2H, m), 2.59 (1H, tt, J= 5.1, 8.3Hz), 4.59 (2H, d, J= 5.8Hz), 4.99 (2H, q, J= 9.1Hz), 5.24 (2H, s), 7.01 (1H, dd, J= 0.7, 8.5Hz), 7.23 (1H, d, J= 7.0Hz), 7.64-7.76 (3H, m), 7.81 (1H, d, J= 1.6Hz), 8.16-8.25 (2H, m), 8.55 (1H, d, J= 8.6Hz), 8.65 (1H, t, J= 5.9Hz), 9.09 (2H, s), 13.24 (1H, s).

Example Number	Chemical Shift (ppm)
93	0.74-0.78 (2H, m), 0.80–0.86 (2H, m), 2.55-2.62 (1H, m), 4.58 (2H, d, J= 5.9Hz), 5.23 (2H, s), 7.03 (1H, dd, J= 0.7, 8.5Hz), 7.09–7.14 (2H, m), 7.21 (2H, m), 7.38–7.45 (2H, m), 7.66 (1H, d, J= 7.2Hz), 7.70 (1H, dd, J= 1.7, 8.7Hz), 7.76 (1H, dd, J= 2.5, 8.5Hz), 7.80 (1H, d, J= 1.6Hz), 8.12 (1H, dd, J= 0.8, 2.5Hz), 8.20 (1H, s), 8.54 (1H, d, J= 8.6Hz), 8.62 (1H, t, J= 5.9Hz), 9.04 (2H, s, br), 13.13 (1H, s)
94	0.75-0.77 (2H, m), 0.82-0.85 (2H, m), 1.33 (3H, t, J= 7.1Hz), 2.54-2.60 (1H, m), 4.38 (2H, q, J= 7.0Hz), 4.58 (2H, d, J= 5.8Hz), 5.21 (2H, s), 7.23 (1H, d, J= 7.0Hz), 7.65 (1H, d, J= 6.9Hz), 7.69 (1H, q, J= 8.6Hz), 7.85 (1H, d, J= 2.0Hz), 8.11 (1H, d, J= 2.0Hz), 8.16 (1H, s), 8.49 (1H, d, J= 8.7Hz), 8.58 (1H, t, J= 5.92Hz), 8.90 (2H, br. s), 12.89 (1H, s).
95	0.76-0.77 (2H, m), 0.81-0.85 (2H, m), 1..11 (6H, t, J= 6.97Hz), 2.55-2.61 (1H, m), 3.46 (4H, t, J= 7.0Hz), 4.58 (2H, d, J= 5.85Hz), 5.11 (2H, s), 7.04 (1H, s), 7.17 (1H, s), 7.22(1H, t, J= 6.92Hz), 7.29 (1H, s), 7.65-7.71 (2H, m), 7.81 (1H, d, J= 4.89Hz), 7.93 (1H, d, J= 1.52Hz), 8.15 (1H, s), 8.52 (1H, d, J= 8.64Hz), 8.61 (1H, t, J= 5.92Hz), 9.02 (2H, br, s), 13.08 (1H, s).
96	0.74-0.79 (2H, m), 0.8-0.88 (2H, m), 1.11 (6H, t, J = 6.9Hz), 2.59 (1H, m), 3.55 (4H, d, J = 15.4Hz), 4.58 (2H, d, J = 5.9Hz), 5.11 (2H, s, br), 6.5-7.1 (0.5, s, br), 7.22 (1H, d, J = 7.0 Hz), 7.54 (0.5H, s, br), 7.66 (1H, d, J = 7.0Hz), 7.70 (1H, dd, J = 1.7, 8.6Hz), 7.80 (1H, d, J = 1.7Hz), 8.02 (1H, d, J = 2.3Hz), 8.17 (1H, s), 8.54 (1H, d, J = 8.6Hz), 8.63 (1H, t, J = 6.0Hz), 9.04 (2H, s, br), 13.12 (1H, s, br)
97	0.75-0.77 (2H, m), 0.82-0.84 (2H, m), 1.85-1.88 (4H, m), 2.55-2.60 (1H, m), 3.61 (4H, t, J= 6.6Hz), 4.58 (2H, d, J= 5.8Hz), 5.12 (2H, s), 7.22 (1H, d, J= 7.0Hz), 7.59-7.71 (2H, m), 7.80 (1H, s), 8.04 (1H, d, J= 1.9Hz), 8.19 (1H, s), 8.55 (1H, d, J= 8.6Hz), 8.58 (1H, t, J= 5.7Hz), 9.10 (2H, br.s), 13.53 (1H, s).

Example Number	Chemical Shift (ppm)
98	1.31 (3H, t, J = 7.0Hz), 4.29 (2H, q, J = 7.0Hz), 4.56 (2H, d, J = 5.8Hz), 5.05 (2H, s), 5.41 (2H, br.s), 6.80 (1H, d, J = 8.5Hz), 7.23 (1H, d, J = 7.0Hz), 7.60–7.71 (3H, m), 7.79 (1H, s), 8.02 (1H, s), 8.14 (1H, d, J = 2.0 Hz), 8.50–8.57 (2H, m), 9.01 (2H, s), 13.06 (1H, s).
99	1.95-2.07 (4H, m), 3.52-3.58 (4H, m), 4.56 (2H, d, J= 5.8Hz), 5.13 (2H, s), 7.11 (1H, d, J= 9.4Hz), 7.20 (1H, d, J= 7.0Hz), 7.64-7.71 (2H, m), 7.79 (1H, s), 7.89 (1H, dd, J= 9.4, 2.1Hz), 8.02 (1H, d, J= 1.8Hz), 8.23 (1H, s), 8.59 (1H, d, J= 8.6Hz), 8.82 (1H, t, J= 6.0Hz), 9.19 (2H, brs), 13.41 (1H, s), 13.86 (1H, brs).
100	1.94 (4H, m), 2.71 (6H, s), 3.38 (4H, m), 4.58 (2H, d, J= 5.9Hz), 5.04 (2H, s), 6.57 (1H, s, br), 7.21 (1H, d, J= 7.0Hz), 7.57 (1H, s, br), 7.63–7.71 (2H, m), 7.75–7.80 (1H, m), 8.00–8.08 (2H, m), 8.45 (1H, t, J= 6.0Hz), 8.51 (1H, d, J = 8.6Hz), 8.95 (2H, s, br), 13.05 (1H, s, br)
101	1.87-1.96 (4H, m), 2.50-2.66 (2H, m), 2.70 (3H, s), 3.30-3.43 (5H, m), 3.69 (1H, dd, J =9.5, 8.5Hz), 3.97-4.07 (1H, m), 4.49 (2H, d, J= 5.9Hz), 5.12 (2H, s), 6.43 (1H, d, J= 8.7Hz), 6.80 (2H, s), 6.86 (1H, d, J= 6.0Hz), 7.36 (1H, dd, J= 8.6, 1.7Hz), 7.47 (1H, dd, J= 8.7, 2.4Hz), 7.51 (1H, s), 7.75 (1H, d, J= 5.8Hz), 8.10 (1H, d, J= 2.5Hz), 8.13 (1H, d, J= 8.6Hz), 8.17 (1H, s), 8.59 (1H, t, J = 6.0Hz)
105	2.09 (3H, s), 2.46 (3H, s), 2.55 (3H, s), 3.86 (2H, s), 4.47 (2H, d, J = 5.8 Hz), 5.31 (2H, s), 6.40 (1H, dd, J = 1.9, 3.4 Hz), 7.18 (2H, d, J = 8.1 Hz), 7.25 (2H, d, J = 8.1 Hz), 7.43 (1H, dd, J = 2.7, 3.2 Hz), 7.85 (1H, d, J = 1.6 Hz), 7.88 (1H, d, J = 0.6 Hz), 8.17 (1H, d, J = 2.0 Hz), 8.24 (1H, d, J = 0.6 Hz), 8.59 (1H, t, J = 5.9 Hz), 11.6 Hz (1H, s)
106	4.48 (2H, d, J = 5.8Hz), 5.36 (2H, s), 6.41 (1H, dd, J = 1.9, 3.4Hz), 7.12-7.24 (3H, m), 7.26-7.37 (2H, m), 7.44 (1H, dd, J = 2.5, 3.4Hz), 7.78-7.99 (4H, m), 8.18 (1H, d, J = 2.0Hz), 8.30 (1H, d, J = 0.7Hz), 8.62 (1H, t, J = 5.9Hz), 11.57 (1H, s).

Example Number	Chemical Shift (ppm)
107	4.48 (2H, d, J = 5.8Hz), 5.35 (2H, s), 6.41 (1H, dd, J = 1.9, 3.4Hz), 7.02 (1H, dt, J = 0.9, 8.3Hz), 7.06-7.15 (3H, m), 7.27-7.36 (2H, m), 7.44 (1H, dd, J = 2.5, 3.4Hz), 7.81-7.88 (2H, m), 7.91 (1H, d, J = 0.7Hz), 8.12 (1H, ddd, J = 0.8, 2.0 , 4.9Hz), 8.18 (1H, d, J = 2.1Hz), 8.30 (1H, d, J = 0.8Hz), 8.62 (1H, t, J = 5.9Hz), 11.56 (1H, s).
108	4.48 (2H, d, J = 5.8Hz), 5.33 (2H, s), 6.41 (1H, dd, J =1.9, 3.4Hz); 6.90 (2H, ddq, J = 1.2, 2.5, 4.6Hz), 6.99 (3H, dq, J = 1.3, 7.9Hz), 7.08-7.19 (1H, m), 7.28-7.47 (4H, m), 7.81-7.92 (2H, m), 8.18 (1H, d, J = 2.0Hz), 8.26 (1H, d, J = 0.7 Hz), 8.61 (1H, t, J = 5.9Hz), 11.57 (1H, s).
109	4.47 (2H, d, J = 5.9Hz), 5.23 (2H, s), 5.34 (2H, s), 6.40 (1H, dd, J =1.9, 3.4Hz), 6.78 (1H, dd, J = 2.2, 7.8 Hz), 6.79 (1H, dd, J = 1.5, 8.0 Hz), 7.26 (2H, d, J = 8.1 Hz), 7.41-7.44 (3H, m), 7.84-7.85 (1H, m), 7.87-7.91 (2H, m), 8.17 (1H, d, J = 2.0 Hz), 8.25 (1H, s), 8.59 (1H, t, J = 5.9 Hz), 11.55 (1H, br. s)
110	1.98 (3H, s), 2.36 (3H, s), 4.40 (2H, d, J= 5.8Hz), 5.22 (2H, s), 5.39 (2H, s), 6.06 (1H, d, J= 0.9Hz), 6.90 (1H, dd, J= 8.2, 1.5Hz), 7.18 (3H, m), 7.23 (1H, s), 7.29-7.26 (3H, m), 7.53 (1H, s), 8.41 (1H, d, J= 0.7Hz), 8.70 (1H, t, J= 5.8Hz), 11.85 (1H, br s).
111	1.98 (3H, s), 4.46 (2H, d, J= 5.9Hz), 5.22 (2H, s), 5.40 (2H, s), 7.19 (2H, d, J= 8.2Hz), 7.23 (1H, s), 7.30-7.27 (3H, m), 7.49 (1H, d, J= 8.6Hz), 7.54 (1H, s), 7.64 (1H, s), 8.03 (1H, s), 8.43 (1H, s), 8.81 (1H, t, J= 5.8Hz), 13.03 (1H, br s).
112	1.98 (3H, s), 4.42 (2H, d, J= 5.8Hz), 5.22 (2H, s), 5.39 (2H, s), 6.37-6.38 (1H, m), 7.02 (1H, dd, J= 8.4, 1.6Hz), 7.19 (2H, d, J = 8.2Hz), 7.23 (1H, s), 7.27 (2H, d, J= 8.1Hz), 7.31-7.34 (2H, m), 7.44 (1H, s), 7.54 (1H, s), 8.42 (1H, d, J= 0.7Hz), 8.73 (1H, t, J= 5.8Hz), 11.05 (1H, br.s).

Example Number	Chemical Shift (ppm)
113	4.67 (2H, d, J= 5.8Hz), 5.03 (2H, s), 5.06 (2H,s), 5.40 (2H, s), 6.20-6.24 (1H,m), 6.39 (1H, d, J= 9.1Hz), 6.98 (1H, d, J= 6.9Hz), 7.19 (2H, d, J= 8.1Hz), 7.25-7.29 (3H, m), 7.38-7.42 (2H, m), 7.75 (1H, dd, J= 6.7, 1.9Hz), 7.99 (1H, s), 8.15 (1H, s), 8.37 (1H, t, J= 5.8Hz), 13.06 (1H, s).
114	1.90-1.93 (4H, m), 3.33-3.36 (4H, m), 4.45 (2H, d, J= 5.7Hz), 5.24 (2H, s), 6.40-6.44 (2H, m), 7.44-7.47 (2H, m), 7.84 (1H, d, J = 1.6Hz), 8.12 (1H, d, J = 1.7Hz), 8.16 (1H, d, J = 1.9Hz), 8.33 (1H, s), 8.73-8.74 (1H, m), 11.57 (1H, s).
115	1.98 (3H, s), 4.50 (2H, d, J = 6.2Hz), 5.21 (2H, s), 5.60 (2H, s), 6.39 (1H, dd, J = 1.9, 3.4Hz), 7.15-7.24 (3H, m), 7.25-7.32 (2H, m), 7.43 (1H, dd, J = 2.5, 3.4Hz), 7.51 (1H, t, J = 0.9Hz), 7.87 (1H, d, J = 2.1Hz), 8.19 (1H, d, J = 2.0Hz), 8.61 (1H, s), 9.08 (1H, t, J = 6.2Hz), 11.54 (1H, s).
116	1.98 (3H, t, J = 0.7Hz), 2.53 (3H, s), 4.50 (2H, d, J = 5.9Hz), 5.22 (2H, s), 5.61 (2H, s), 6.33 (1H, dd, J = 1.9, 3.4Hz), 7.16-7.24 (3H, m), 7.28-7.34 (3H, m), 7.49-7.56 (1H, m), 7.75 (1H, s), 8.63 (1H, s), 8.94 (1H, t, J = 6.0Hz), 11.36 (1H, s).
117	1.98 (3H, t, J = 0.7Hz), 4.47 (2H, d, J = 5.8Hz), 5.20 (2H, s), 5.30 (2H, s), 6.40 (1H, dd, J = 1.9, 3.4Hz), 7.12-7.26 (5H, m), 7.43 (1H, dd, J = 2.5, 3.4Hz), 7.51 (1H, t, J = 0.9Hz), 7.82-7.92 (2H, m), 8.17 (1H, d, J = 2.0Hz), 8.23 (1H, d, J = 0.7Hz), 8.57 (1H, t, J = 5.9Hz), 11.55 (1H, s).
118	1.97 (3H, s), 2.49 (3H, s), 2.54 (3H, s), 4.51 (2H, d, J = 4.6Hz), 5.19 (2H, s), 5.27 (2H, s), 6.43 (1H, dd, J = 3.5, 1.9Hz), 7.12-7.24 (5H, m), 7.28 (1H, dd, J = 3.5, 2.4Hz), 7.50 (1H, s), 7.86 (1H, s), 7.97 (1H, t, J = 4.6Hz), 8.22 (1H, s), 11.32 (1H, s).
119	2.03 (3H, s), 2.57 (3H, s), 2.60 (3H, s), 4.56 (2H, d, J= 4.6Hz), 5.25 (2H, s), 5.41 (2H, s), 6.49-6.50 (1H, m), 7.22 (2H, d, J= 8.1Hz), 7.27-7.30 (3H, m), 7.35 (1H, t, J= 5.9Hz), 7.57(1H, s), 8.29 (1H, t, J= 4.5Hz), 8.42 (1H, s), 11.39 (1H, s).

Example Number	Chemical Shift (ppm)
120	0.71-0.77 (2H, m), 0.79-0.84 (2H, m), 1.98 (3H,s), 2.55-2.67 (1H, m), 4.45 (2H, d, J= 5.7Hz), 5.17 (2H, s), 5.20 (2H, s), 6.40 (1H, d, J= 3.3Hz), 7.16 (4H, s), 7.22 (1H, s), 7.44 (1H, d, J= 3.3Hz), 7.51 (1H, s), 7.85 (1H, s), 8.08 (1H, s), 8.17 (1H, d, J= 1.3Hz), 8.36 (1H, t, J= 5.7Hz), 11.56 (1H, s)
121	1.98 (3H,s), 4.55 (2H, d, J= 5.7Hz), 5.21 (2H, s), 5.39 (2H, s), 6.40-6.41 (1H, m), 7.19 (2H, d, J= 8.1Hz), 7.23 (1H, s), 7.26 (2H, d, J= 8.0Hz), 7.45 (1H, t, J= 2.9Hz), 7.52 (1H, s), 7.85 (1H, d, J= 1.6Hz), 8.17 (1H, d, J= 1.9Hz), 8.40 (1H, s), 8.75 (1H, t, J= 5.6Hz), 11.57 (1H, s).
123	(1.98 (3H, s), 4.63 (2H, d, J= 5.8Hz), 5.21 (2H, s), 5.39 (2H, s), 6.51 (1H, m), 6.90 (1H, d, J= 7.0Hz), 7.03 (1H, dd, J= 8.0, 7.4Hz), 7.18 (2H, d, J= 8.2Hz), 7.23 (1H, s), 7.33-7.26 (4H, m), 7.53 (1H, s), 8.41 (1H, d, J= 0.6Hz), 8.74 (1H, t, J= 5.8Hz), 11.14 (1H, br s).
124	1.98 (3H, s), 4.69 (2H, d, J= 5.8Hz), 5.22 (2H, s), 5.40 (2H, s), 7.00 (1H, d, J= 7.0Hz), 7.18 (2H, d, J= 8.2Hz), 7.23 (1H, s), 7.30-7.26 (3H, m), 7.44 (1H, d, J= 8.3Hz), 7.54 (1H, s), 8.14 (1H, d, J= 0.6Hz), 8.43 (1H, s), 8.89 (1H, t, J= 5.9Hz), 13.11 (1H, br s).
125	2.33 (3H, s), 4.66 (2H, d, J= 5.8Hz), 5.22 (2H, s), 5.41 (2H, s), 6.54-6.55 (1H, m), 6.95 (1H, d, J= 4.8Hz), 7.20 (2H, d, J= 8.1Hz), 7.23 (1H, s), 7.29 (2H, d, J= 8.2Hz), 7.44 (1H, t, J= 3.0Hz), 7.53 (1H, s), 8.15 (1H,d, J= 4.8Hz), 8.45 (1H, s), 8.88 (1H, t, J= 5.9Hz), 11.64 (1H, s).
126	4.69 (2H, d, J= 5.8Hz), 5.07 (2H, s), 5.40 (2H, s), 6.21-6.24 (1H, m), 6.39 (1H, d, J= 8.9Hz), 7.00 (1H, d, J= 6.9Hz), 7.26-7.30 (5H, m), 7.39-7.44 (2H, m), 7.77 (1H, q, J= 6.6Hz), 8.14 (1H, s), 8.43 (1H, s), 8.89 (1H, t, J= 5.8Hz), 13.11 (1H, s).
127	1.98 (3H, s), 4.69 (2H, d, J= 5.8Hz), 5.21 (2H,s), 5.38 (2H, s), 7.17-7.26 (5H, m), 7.33 (1H, dd, J= 8.9, 2.0Hz), 7.51-7.53 (2H, m), 7.84 (1H, d, J= 1.8Hz), 8.36 (1H, s), 8.87 (1H, t, J= 5.8Hz), 13.05 (1H, s).

Example Number	Chemical Shift (ppm)
128	1.89-1.93 (4H,s), 3.35-3.42 (4H, m), 4.68 (2H, d, J= 5.88Hz), 5.24(2H, s), 6.42 (1H, s, br), 7.34(1H, dd, J= 1.96, 8.92Hz), 7.48 (2H, d, J = 6.80Hz), 7.51 (1H, d, J = 8.92Hz), 7.83 (1H, d, J = 1.80Hz), 8.11 (1H, d, J = 2.2Hz), 8.28 (1H, d, J = 4.96Hz), 13.04 (1H, s).
129	4.69 (2H, d, J = 5.84Hz), 5.06 (2H, s), 5.38 (2H, s), 6.20-6.23 (1H, m), 6.39 (1H, d, J = 9.04Hz), 7.27 (4H, s), 7.32-7.34 (1H, m),7.39-7.43 (1H, m), 7.52 (1H, d, J = 8.88Hz), 7.74-7.82 (1H, m), 7.84 (1H, d, J = 1.64Hz), 8.36 (1H, s), 8.86 (1H, d, J = 5.44Hz), 13.04 (1H, s).

Biological Methods

The ability of the compounds of formula (I) to inhibit plasma kallikrein may be determined using the following biological assays:

Determination of the IC_{50} for plasma kallikrein

Plasma kallikrein inhibitory activity *in vitro* was determined using standard published methods (see e.g. Johansen *et al.*, Int. J. Tiss. Reac. 1986, **8**, 185; Shori *et al.*, Biochem. Pharmacol., 1992, **43**, 1209; Stürzebecher *et al.*, Biol. Chem. Hoppe-Seyler, 1992, **373**, 1025). Human plasma kallikrein (Protogen) was incubated at 37°C with the fluorogenic substrate H-DPro-Phe-Arg-AFC and various concentrations of the test compound. Residual enzyme activity (initial rate of reaction) was determined by measuring the change in optical absorbance at 410nm and the IC_{50} value for the test compound was determined.

Data acquired from these assays are shown in Table 13 below:

Table 13

Example Number	IC_{50} (human PKal) nM
1	54.7
2	2110
3	2690
6	9460
7	5.38

Example Number	IC_{50} (human PKal) nM
8	3.72
9	14.3
10	2.4
11	1.89
12	2.58
13	2.14
14	4.62
15	1.17
16	0.74
17	1190
18	32.0
19	994.0
20	0.89
21	6.46
22	132
23	0.33
24	9.66
25	7.31
26	205
27	128
28	63.7
29	620
30	1470
31	2.0
32	2.4

Example Number	IC_{50} (human PKal) nM
33	2.8
34	142
35	3.68
36	2.16
37	0.67
38	1.27
39	1.68
42	4.85
44	3.9
45	3060
46	803
47	2030
48	820
49	186
50	203
51	576
52	300
53	16.8
54	46.7
55	79.2
56	71.8
57	14.9
58	13.3
59	5.84
60	9.61

Example Number	IC_{50} (human PKal) nM
61	18.1
62	13.58
63	12.3
64	10.4
65	14.9
66	281
67	108
68	59.0
69	32.3
70	66.9
71	63.6
72	118
73	22.6
74	425
75	98.3
76	0.92
77	85.4
78	91.1
79	2.29
80	206
81	26.5
82	21.2
86	56.1
87	23.2
88	112

Example Number	IC_{50} (human PKal) nM
89	17.8
90	11.6
91	13.8
92	109
93	75.1
94	53.2
95	34.0
97	18.5
98	62.4
99	4.15
105	17000
106	12000
107	2300
108	22000
109	4200
110	562
111	217
112	60.6
113	13.3
114	304
115	177
116	507
117	78
118	14
119	86.6

Example Number	IC_{50} (human PKal) nM
120	118
121	62.0
122	101
123	545
124	146
125	4010
126	22.9
127	537
128	24.9
129	2.14

Selected compounds were further screened for inhibitory activity against the related enzyme KLK1. The ability of the compounds of formula (I) to inhibit KLK1 may be determined using the following biological assay:

Determination of the IC_{50} for KLK1

KLK1 inhibitory activity *in vitro* was determined using standard published methods (see e.g. Johansen *et al.*, Int. J. Tiss. Reac. 1986, **8**, 185; Shori *et al.*, Biochem. Pharmacol., 1992, **43**, 1209; Stürzebecher *et al.*, Biol. Chem. Hoppe-Seyler, 1992, **373**, 1025). Human KLK1 (Callbiochem) was incubated at 37°C with the fluorogenic substrate H-DVal-Leu-Arg-AFC and various concentrations of the test compound. Residual enzyme activity (initial rate of reaction) was determined by measuring the change in optical absorbance at 410nm and the IC_{50} value for the test compound was determined.

Data acquired from this assay are shown in Table 14 below:

Table 14 (KLK1 Activity)

Example Number	IC50 (human KLK1) nM
1	>10000

Example Number	IC50 (human KLK1) nM
2	>10000
3	>10000
6	9460
7	>10000
8	>10000
9	>10000
10	>10000
11	8860
12	6060
13	5160
14	5970
15	6640
16	5730
17	>10000
18	>10000
19	>10000
20	>10000
21	>10000
22	>10000
23	>10000
24	>4000
25	2210
26	4730
27	3200
28	>10000

Example Number	IC50 (human KLK1) nM
29	>10000
30	5750
31	>10000
32	>10000
33	>10000
34	18170
35	>10000
36	>40000
37	3530
38	7840
39	8050
42	9050
44	7090
45	18570
46	27200
47	15750
48	4320
49	8090
50	>40000
51	11720
52	>40000
53	>10000
54	18250
55	3810
56	>10000

Example Number	IC50 (human KLK1) nM
57	>10000
58	3110
59	4000
60	9570
61	7660
62	>10000
63	5700
64	2790
65	960
66	>10000
67	8880
68	9760
69	4740
70	4910
71	>10000
72	>10000
73	1570
74	2770
75	1300
76	>1000
77	>10000
78	>10000
79	>10000
80	9280
81	8970

Example Number	IC50 (human KLK1) nM
82	4710
86	8790
87	6460
88	9630
89	960
90	4700
91	>10000
92	>10000
93	>10000
94	2000
95	9640
97	3010
98	3140
99	3460
105	>40000
106	>40000
107	38100
108	20630
109	>40000
110	>10000
111	7170
112	>10000
113	5950
114	1210
115	>10000

Example Number	IC50 (human KLK1) nM
116	>10000
117	>10000
118	>40000
119	>4000
120	>10000
121	>10000
122	>10000
123	>10000
124	7230
125	>10000
126	>10000
127	>10000
128	>10000
129	>10000

Selected compounds were further screened for inhibitory activity against the related enzymes plasmin, thrombin, trypsin, Factor Xa and Factor XIIa. The ability of the compounds of formula (I) to these enzymes may be determined using the following biological assays:

Determination of enzyme selectivity

Human serine protease enzymes plasmin, thrombin, trypsin, Factor Xa and Factor XIIa were assayed for enzymatic activity using an appropriate fluorogenic substrate. Protease activity was measured by monitoring the accumulation of liberated fluorescence from the substrate over 5 minutes. The linear rate of fluorescence increase per minute was expressed as percentage (%) activity. The Km for the cleavage of each substrate was determined by standard transformation of the Michaelis-Menten equation. The compound inhibitor assays were performed at substrate Km concentration and activities were calculated as the concentration of inhibitor giving 50% inhibition (IC_{50}) of the uninhibited enzyme activity (100%).

Data acquired from these assays are shown in Table 15 below:

Table 15 (Selectivity data)

Example Number	IC50 (nM)			
	Factor XIIa	Thrombin	Trypsin	Plasmin
1	>10000	>40000	>40000	>40000
2	>10000			
6	>10000			
11	>10000			
12	>10000			
13	>10000			
14	>10000			
18	>10000			
22	>10000			
24	>1000			
28	>10000			
30	>10000			
33	>10000			
34	>40000			
35	>10000			
36	>10000			
37	>10000			
38	>10000			
39	>10000			
44	>10000			
45	>40000			
46	>40000			

47	>40000
48	>40000
49	>40000
50	>40000
51	>40000
52	>40000
54	>4000
55	>10000
56	>10000
57	>10000
59	>1000
60	>10000
61	>10000
62	>10000
63	>10000
67	>10000
68	>10000
105	>40000
106	>40000
107	>40000
108	>40000
109	>40000
110	>10000
111	>10000
112	>10000
115	>10000

116	>10000
117	>10000
118	>40000
119	>4000
120	>10000
123	>10000
124	>10000
126	>10000

Pharmacokinetics

Pharmacokinetic studies of the compounds in Table 16 were performed to assess the pharmacokinetics following a single oral dose in male Sprague-Dawley rats. Two rats were given a single po dose of 5 mL/kg of a nominal 2 mg/mL (10 mg/kg) composition of test compound in 5% cremophor:5% ethanol:90% phosphate buffered saline. Following dosing, blood samples were collected over a period of 24 hours. Sample times were 5, 15 and 30 minutes then 1, 2, 4, 6, 8, 12 and 24 hours. Following collection, blood samples were centrifuged and the plasma fraction analysed for concentration of test compound by LCMS. Oral exposure data acquired from these studies are shown below:

Table 16 (Oral exposure data)

Example Number	Dose po (mg/kg)	Cmax (ng/mL)	Tmax (min)
11	10	134	23
12	10	155	30
24	4	97	420
36	10	642	75
117	10	98	45
126	10	56	30

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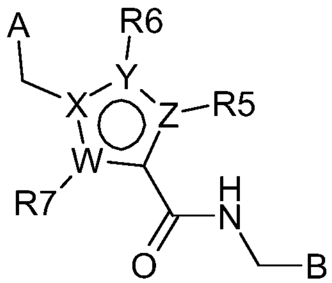
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula (I),



Formula (I)

wherein

B is a fused 6,5- or 6,6-heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein when B is a fused 6,5-heteroaromatic bicyclic ring, it is linked to –CONH-(CH_2)- *via* its 6-membered ring component;

W, X, Y and Z are independently selected from C, N, O and S, such that the ring containing W, X, Y and Z is a five membered aromatic heterocycle;

wherein,

R5, R6 and R7 are independently absent or independently selected from H, alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9, CF_3, and R16; wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, OH, aryl, heteroaryl, -NR8R9, CN, COOR8, CONR8R9, -NR8COR9, CF_3 and R16;

A is selected from aryl and heteroaryl;

R8 and R9 are independently selected from H and alkyl;

R16 is a carbon-containing 3-, 4-, 5- or 6-membered monocyclic ring system which may be aromatic, saturated or unsaturated non-aromatic and which may optionally contain 1, 2, 3 or 4 heteroatoms selected from N, O and S, wherein the ring system R16 is in turn optionally substituted with substituents selected from alkyl and oxo;

alkyl is a linear saturated hydrocarbon having up to 10 carbon atoms (C_1-C_{10}) or a branched saturated hydrocarbon of between 3 and 10 carbon atoms (C_3-C_{10}); alkyl may optionally be substituted with 1 or 2 substituents independently selected from (C_1-C_6)alkoxy, OH, CN, CF_3, COOR10, CONR10R11, fluoro and NR10R11;

alkoxy is a linear O-linked hydrocarbon of between 1 and 6 carbon atoms (C_1-C_6) or a branched O-linked hydrocarbon of between 3 and 6 carbon atoms (C_3-C_6); alkoxy may optionally be substituted with 1 or 2 substituents independently selected from OH, CN, CF_3, COOR10, CONR10R11, fluoro and NR10R11;

aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, methylenedioxy, ethylenedioxy, OH, halo, CN, morpholinyl, piperidinyl, heteroaryl, -$(CH_2)_{0\text{-}3}$-O-heteroaryl, $aryl^b$, -O-$aryl^b$, -$(CH_2)_{1\text{-}3}$-$aryl^b$, -$(CH_2)_{1\text{-}3}$-heteroaryl, -COOR10, -CONR10R11, -$(CH_2)_{1\text{-}3}$-NR14R15, CF_3 and -NR10R11;

$aryl^b$ is phenyl, biphenyl or naphthyl, which may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, -COOR10, -CONR10R11, CF_3 and NR10R11;

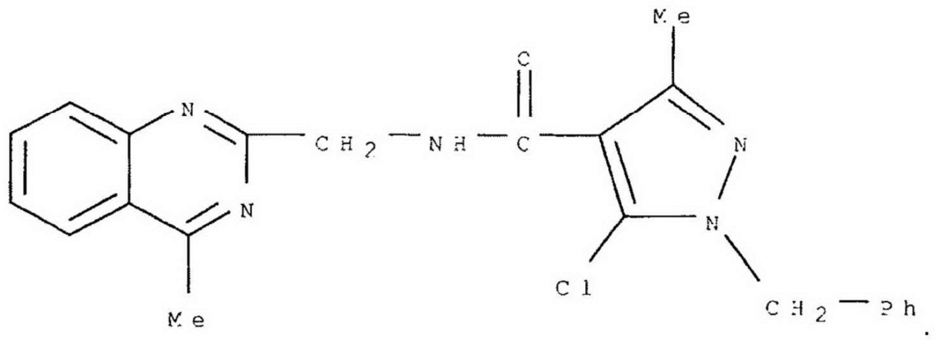
heteroaryl is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2 or 3 ring members independently selected from N, NR8, S and O; heteroaryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, OCF_3, halo, CN, aryl, morpholinyl, piperidinyl, -$(CH_2)_{1\text{-}3}$-aryl, $heteroaryl^b$, -COOR10, -CONR10R11, CF_3 and -NR10R11;

$heteroaryl^b$ is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2 or 3 ring members independently selected from N, NR8, S and O; wherein $heteroaryl^b$ may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, aryl, -$(CH_2)_{1\text{-}3}$-aryl, -COOR10, -CONR10R11, CF_3 and NR10R11;

R10 and R11 are independently selected from H and alkyl or R10 and R11 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds and which may be optionally mono- or di-substituted with substituents selected from oxo, alkyl, alkoxy, OH, F and CF_3;

R14 and R15 are independently selected from alkyl, aryl^b and heteroaryl^b; or R14 and R15 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring which may be saturated or unsaturated with 1 or 2 double bonds, and optionally may be oxo substituted;

and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof;
wherein the compound of formula (I) is not:

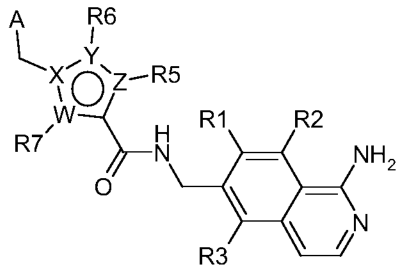


2. A compound according to claim 1, wherein B is a fused 6,6-heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein alkyl, alkoxy, R8 and R9 are as defined in claim 1.

3. A compound according to claim 2, wherein B is selected from optionally substituted quinoline, optionally substituted isoquinoline, optionally substituted quinoxaline, optionally substituted cinnoline, optionally substituted phthalazine, optionally substituted quinazoline, optionally substituted 1,2,4-benzotriazine, optionally substituted 1,2,3-benzotriazine, optionally substituted 1,7-naphthyridine, and optionally substituted 1,8-naphthyridine; wherein said optional substituents are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in claim 1.

4. A compound according to any one of claims 1 to 3, wherein B is selected from optionally mono-, di or tri-substituted isoquinolinyl wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in claim 1.

5. A compound according to claim 1, as defined by formula (II),



Formula (II)

wherein R1, R2 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl; and wherein A,W, X, Y, Z, R5, R6, R7, alkyl, alkoxy, R8 and R9 are as defined in claim 1.

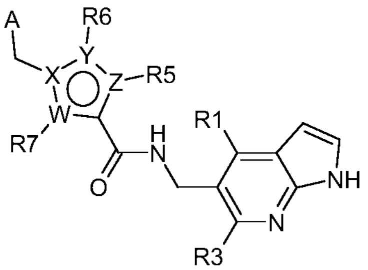
6. A compound according to claim 5, wherein R1, R2 and R3 are independently selected from H and alkyl.

7. A compound according to claim 1, wherein B is a fused 6,5- heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S, which is optionally mono-, di or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, COOR8, CONR8R9, CF_3 and NR8R9; wherein alkyl, alkoxy, R8 and R9 are as defined in claim 1.

8. A compound according to claim 7, wherein B is selected from optionally substituted indole, optionally substituted indazole and optionally substituted 1H-pyrrolo[2,3-b]pyridine; wherein said optional substituents are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in claim 1.

9. A compound according to claim 8, wherein B is selected from optionally mono-, di or tri-substituted 1H-pyrrolo[2,3-b]pyridine, wherein said optional substituent(s) are selected from alkyl, alkoxy, OH, F, Cl, CN, COOR8, CONR8R9, CF_3 and NR8R9; and wherein alkyl, alkoxy, R8 and R9 are as defined in claim 1.

10. A compound according to claim 1, as defined by formula (III),



Formula (III)

wherein R1 and R3 are independently selected from H, alkyl, COOR8, CONR8R9, OH, alkoxy, NR8R9, F and Cl; and wherein A, W, X, Y, Z, R5, R6, R7, alkyl, alkoxy, R8 and R9 are as defined in claim 1.

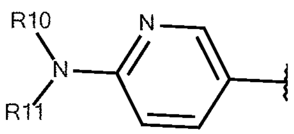
11. A compound according to claim 10, wherein R1 and R3 are independently selected from H and alkyl; and wherein alkyl is as defined in claim 1.

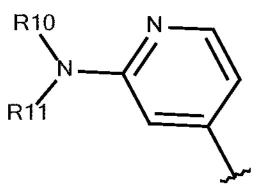
12. A compound according to any one of claims 1 to 11, wherein at least one of R5, R6 and R7 is present and is independently selected from alkyl, halo, OH, aryl, heteroaryl and CF_3; wherein alkyl, aryl and heteroaryl are as defined in claim 1.

13. A compound according to any one of claims 1 to 12 wherein W, X, Y and Z are independently selected from C and N, such that the ring containing W, X, Y and Z is a five-membered heterocycle selected from pyrrole, pyrazole, imidazole, 1, 2, 3-triazole and 1, 2, 4-triazole.

14. A compound according to any one of claims 1 to 13 wherein A is heteroaryl substituted by methyl, phenyl, morpholinyl, piperidinyl or -NR10R11 wherein phenyl is optionally substituted as defined in claim 1, and R10 and R11 are as defined in claim 1; or A is phenyl substituted by heteroaryl, -$(CH_2)_{1-3}$-heteroaryl or -$(CH_2)_{1-3}$-NR14R15, wherein heteroaryl, R14 and R15 are as defined in claim 1.

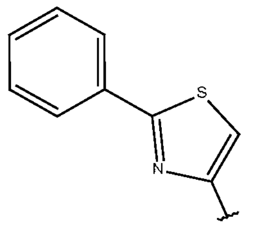
15. A compound according to claim 14 wherein A is selected from:



, and


, and R10 and R11 are as defined in claim 1.

16. A compound according to claim 14 wherein A is selected from:



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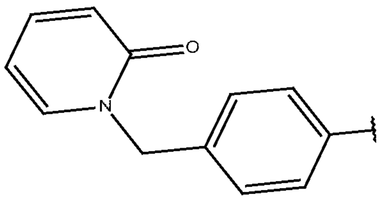

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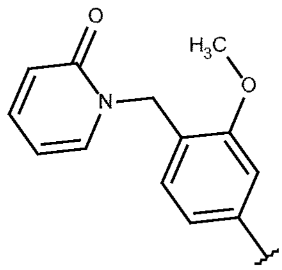

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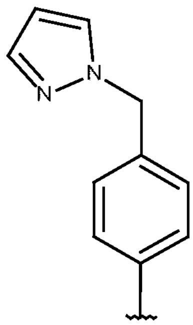

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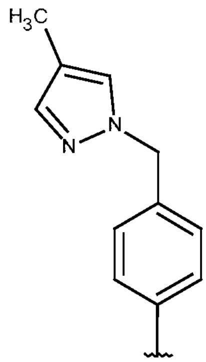

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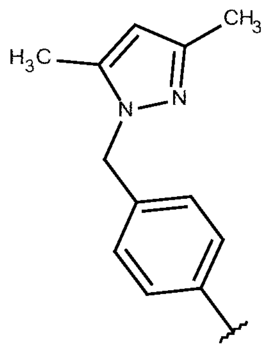

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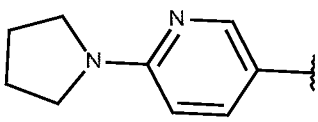

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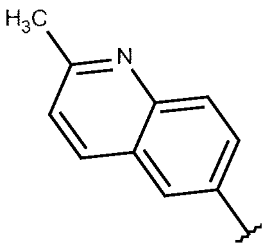

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17. A compound according to claim 1, selected from:

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Isopropyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclobutyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Hydroxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

4-Methyl-2-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-thiazole-5-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-(3,5-Dimethyl-isoxazol-4-yl)-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-morpholin-4-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

5-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(5-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-phenyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Amino-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Difluoromethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-thiophen-3-yl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

5-Amino-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Pyrrolidin-1-yl-pyridin-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Ethoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[2-(3,3-Difluoro-pyrrolidin-1-yl)-pyridin-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-(3,3-Difluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-3-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((S)-3-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((S)-3-Fluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-3-Fluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((S)-2-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-2-Methyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Pyrrolidin-1-yl-pyrazin-2-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[2-((S)-3-Methyl-pyrrolidin-1-yl)-pyridin-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-(3-Hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[6-((R)-3-Hydroxymethyl-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Propoxy-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Fluoro-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Ethoxy-5-fluoro-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(4-Pyrazol-1-ylmethyl-benzyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Cyano-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-Carbamoyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-Pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(2-Pyrazol-1-ylmethyl-thiazol-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[2-(4-Methyl-pyrazol-1-ylmethyl)-thiazol-4-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-{6-[(2-methoxy-ethyl)-methyl-amino]-pyridin-3-ylmethyl}-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(4-methoxy-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(4-[1,2,3]triazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(6-phenoxy-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Chloro-6-ethoxy-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Cyclopropyl-1-(6-diethylamino-5-fluoro-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(5-Chloro-6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-cyclopropyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Amino-1-(6-ethoxy-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Amino-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

and pharmaceutically acceptable salts and solvates thereof.

18. A compound according to claim 1, selected from:

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indol-5-ylmethyl)-amide;

3-Amino-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1H-indazol-4-ylmethyl)-amide;

1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-indazol-4-ylmethyl)-amide;

and pharmaceutically acceptable salts and solvates thereof.

19. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 18 and a pharmaceutically acceptable carrier, diluent or excipient.

20. The use of a compound as claimed in any one of claims 1 to 18 in the manufacture of a medicament for the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated.

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21. A method of treatment of a disease or condition in which plasma kallikrein activity is implicated comprising administration to a subject in need thereof a therapeutically effective amount of a compound as claimed in any one of claims 1 to 18.

22. The use of claim 20 or the method of claim 21 wherein the disease or condition in which plasma kallikrein activity is implicated is selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.

23. The use of claim 20 or the method of claim 21 wherein the disease or condition in which plasma kallikrein activity is implicated is retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

24. The use of claim 20 or the method of claim 21 wherein the disease or condition in which plasma kallikrein activity is implicated is hereditary angioedema.

25. The use of claim 20 or the method of claim 21 wherein the disease or condition in which plasma kallikrein activity is implicated is diabetic macular edema.