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BENZYLAMINDERIVATE

DÉRIVÉS DE BENZYLAMINE

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Description

[0001] This invention relates to benzylamine derivatives and to pharmaceutical compositions containing and the uses of, such derivatives.

Background to the Invention

[0002] The benzylamine 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.

[0003] 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).

[0004] 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. Ther. 8, p1187-99).

[0005] 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.

[0006] 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.

[0007] 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), Sinha et al. ("Prodrugs of inhibitors of plasma kallikrein" WO2012/142308), 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.

[0008] 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.

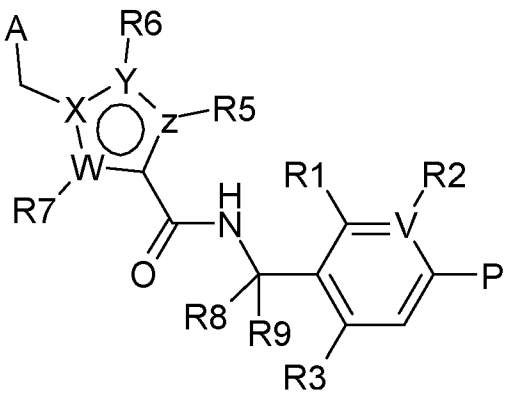
[0009] There are only few reports of plasma kallikrein inhibitors that do not feature guanidine or amidine functionalities. For example, BioCryst Pharmaceuticals Inc. have reported the discovery of BCX4161 which is a benzylamine derivative (http://files.shareholder.com/downloads/BCRX/ 0x0x403076/97a18d6e-1621-4fc6-8f5f-d0828bddab4f/Dr._Yarlagadda_S._Babu_Ph.D._Drug_ Discovery.pdf). Data relating to its oral exposure in the rat are reported in their Second Quarter 2012 Financial Results & Corporate Update. Oral efficacy in a rat model is reported but at the relatively high dose of 100 mg/kg. Another 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.

[0010] 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.

Summary of the Invention

[0011] The present invention relates to a series of benzylamine 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 compositions for use as therapeutic agents, and to these compositions for use in methods of treatment.

[0012] In an aspect, the present invention provides compounds of formula I



Formula (I)

wherein,

V is selected from C and N such that the aromatic ring containing V is phenyl or pyridine;

R2 is absent when V is N; or, when present, R2 is selected from H, alkyl, alkoxy, CN, halo and CF_3;

R1 and R3 are independently selected from H, alkyl, alkoxy, CN, halo and CF_3;

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, aryl, heteroaryl and CF_3;

P is $-C(R10)(R11)NH_2$;

R8 and R9 are independently selected from H and alkyl, or may together form a cycloalkyl ring;

R10 and R11 are independently selected from H and alkyl, or may together form a cycloalkyl ring or a cyclic ether;

A is selected from N-linked morpholine, aryl, heteroaryl,

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_1C_6)alkoxy, OH, CN, CF_3,-COOR12, -CONR12R13, $H(CH_2)_{1-3}CON(R12)(CH_2)_{1-3}$-, fluoro and -NR12R13;

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 NR12R13;

a cyclic ether is a monocyclic saturated hydrocarbon of between 4 and 7 carbon atoms, wherein one of the ring carbons is replaced by an oxygen atom;

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 aryl, OH, CN, CF_3, -COOR12, - CONR12R13, fluoro and NR12R13;

aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, -morpholinyl, -piperidinyl, heteroaryl, $aryl^b$, -O-$aryl^b$, $-(CH_2)_{1-3}$-$aryl^b$, $-(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, $-(CH_2)_{1-3}$-NR14R15, CF_3 and NR12R13;

$aryl^b$ 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,-COOR12, -CONR12R13, CF_3 and NR12R13

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, NR12, S and O; heteroaryl 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, $heteroaryl^b$, -COOR12, - CONR12R13, CF_3 and NR12R13;

$heteroaryl^b$ 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, NR12, 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, -COOR12, - CONR12R13, CF_3 and NR12R13;

R12 and R13 are independently selected from H and alkyl; or R12 and R13 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

R14 and R15 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 optionally may be oxo substituted;

wherein,

when R5, R6 and R7 are absent or H, then:

either
R10 and R11 together form a cycloalkyl ring or a cyclic ether; or
A is aryl and aryl is phenyl, biphenyl or naphthyl substituted with 1, 2 or 3 substituents independently selected from OH, heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, and -$(CH_2)_3$-NR14R15; wherein,

aryl^b is phenyl, biphenyl or naphthyl, wherein aryl^b is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, -COOR12, -CONR12R13, CF_3 and NR12R13; and 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, NR12, S and O, wherein heteroaryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, halo, CN, aryl, morpholinyl, piperidinyl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b, -COOR12, -CONR12R13, CF_3 and -NR12R13;

or
A is heteroaryl and 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, NR12, S and O, wherein heteroaryl is substituted with 1, 2 or 3 substituents independently selected from aryl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b, -COOR12, and-CONR12R13;wherein,

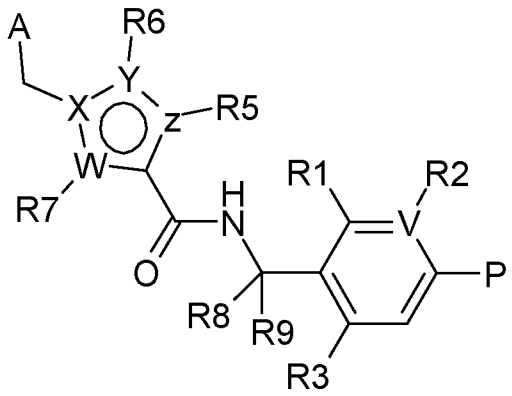
aryl is phenyl, biphenyl or naphthyl, wherein aryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, heteroaryl, aryl^b, -O-aryl^b, -$(CH2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, -COR12R13, -$(CH_2)_{1-3}$-NR14R15, CF_3 and -NR12R13; and 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, NR12, S and O, wherein heteroaryl^b is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, halo, CN, morpholinyl, piperidinyl, aryl, -$(CH_2)_{1-3}$-aryl, -COOR12, -CONR12R13, CF_3 and NR12R13;

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

[0013] Also described is a prodrug of a compound of formula (I) as herein defined, or a pharmaceutically acceptable salt thereof.

[0014] Also described is 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 an aspect the invention comprises a subset of the compounds of formula (I):



(I)

wherein A, W, X, Y, Z, V, P, R1, R2, R3, R5, R6, R7, R8 and R9 are as defined above, with the proviso that at least one of R5, R6 and R7 must be present and be independently selected from alkyl, halo, aryl, heteroaryl and CF_3; and tautomers, isomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

[0015] In an aspect, the invention comprises a subset of the compounds of formula (I) wherein:

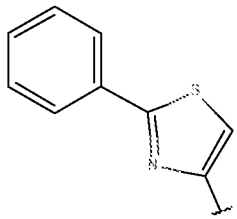
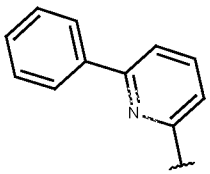
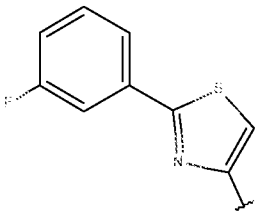
R1 is H, F, Cl, CF_3, OCH_3 or CH_3;
R2 is H or F if V is C; or R2 is absent if V is N; and
R3 is H or CH_3;
and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

[0016] In another aspect, the invention comprises a subset of the compounds of formula (I) wherein:

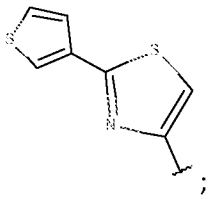
W is C;
X is N;
Y is C;
Z is C;
R5 is H;
R6 and R7 are CH_3;
R8 and R9 are H; and
R10 and R11 are both H or together form a cyclopropane ring;
and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

[0017] In another aspect, the invention comprises a subset of the compounds of formula (I) wherein:

W is C;
X is N;
Y is C;
Z is C;
R5 is H;
R6 and R7 are CH_3;
R8 and R9 are both H;
R10 and R11 are both H or together form a cyclopropane ring; and A is selected from:

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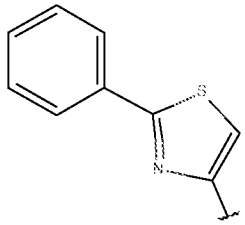
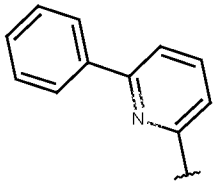
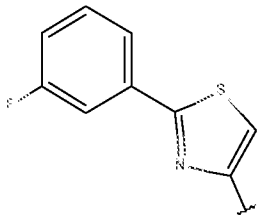
and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

[0018] In another aspect, the invention comprises a subset of the compounds of formula (I) wherein:

R1 is H, F, Cl, CF_3, OCH_3 or CH_3;
R2 is H or F if V is C; or R2 is absent if V is N; and

R3 is H or CH_3;
W is C;
X is N;
Y is C;
Z is C;
R5 is H;
R6 and R7 are CH_3;
R8 and R9 are both H;
R10 and R11 are both H or together form a cyclopropane ring; and
A is selected from:

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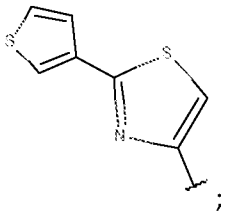
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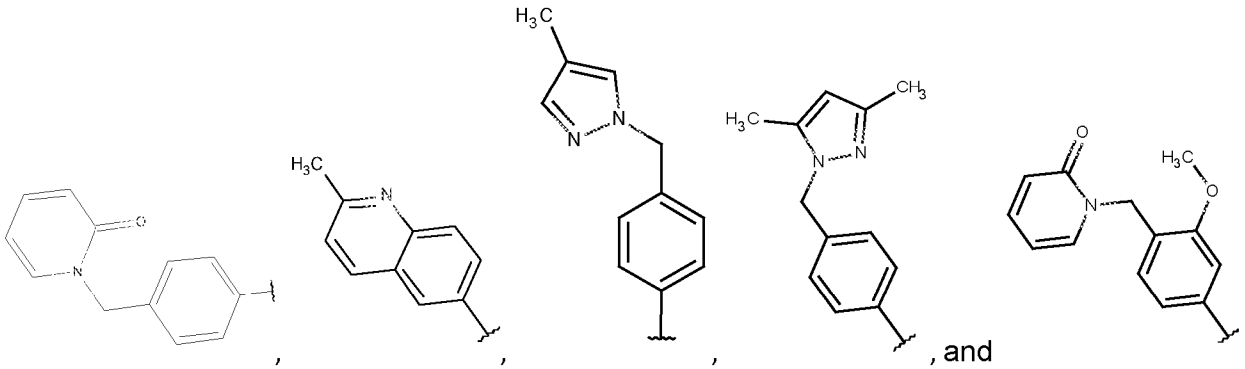
and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

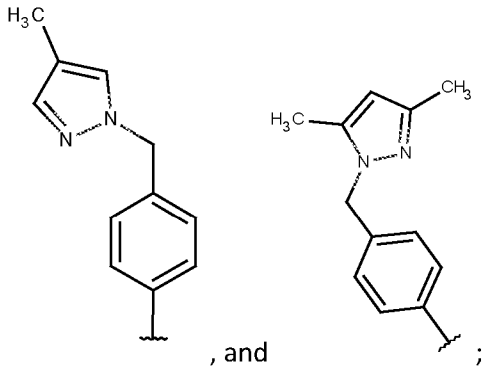
[0019] In another aspect, the invention comprises a subset of the compounds of formula (I) wherein:

V is C;
R1 is H or CH_3;
R2 is H or F;
R3 is H or CH_3;
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;
R5, R6 and R7 are independently absent, or are independently selected from H and alkyl;
R8 and R9 are both H;
R10 and R11 together form a cyclopropane ring; and
A is selected from:



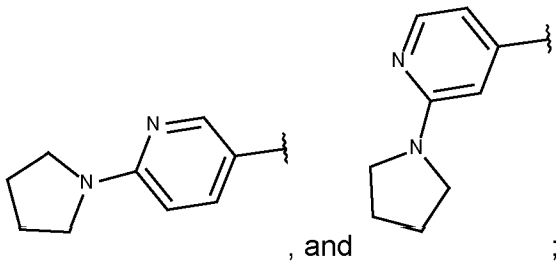
[0020] In another aspect, the invention comprises a subset of the compounds of formula (I) wherein:

V is C;
R1 is H or CH_3;
R2 is H;
R3 is H or CH_3;
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;
R5, R6 and R7 are independently absent, or are independently selected from H, alkyl, halo, aryl, heteroaryl and CF_3;
R8 and R9 are both H;
R10 and R11 are both H or together form a cyclopropane ring; and
A is selected from:

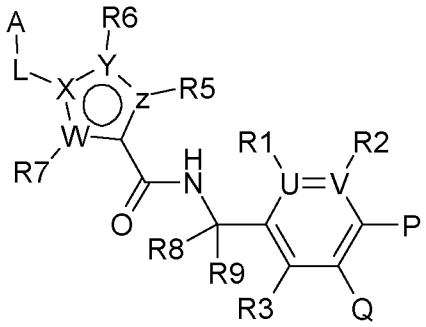


and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof), pharmaceutically acceptable salts and solvates thereof.

[0021] In another aspect, the invention comprises a subset of the compounds of formula (I) wherein A is selected from:



[0022] In an aspect, the invention comprises compounds of formula (II):



Formula (II)

wherein,

U and V are independently selected from C and N such that the aromatic ring containing U and V is phenyl, pyridine or pyrazine;

R1 is absent when U is N;

R2 is absent when V is N;

or, when present, R1 and R2 are independently selected from H, alkyl, alkoxy, CN, halo and CF_3;

R3 is selected from H, alkyl, alkoxy, CN, halo and CF_3;

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

R5, R6 and R7 are independently absent, or are independently selected from H, alkyl, halo, aryl, heteroaryl and CF_3;

or, optionally, when Y and/or Z is C, R5 and R6 may together form an aromatic ring, optionally containing 1 or 2 atoms selected from N, O or S, fused to the five-membered heterocyclic aromatic ring containing W, X, Y and Z; wherein the resulting aromatic fused bicycle may be optionally mono-, di- or tri-substituted with a substituent selected from alkyl, alkoxy, OH, halo, CN, -COOR12, -CONR12R13, CF_3 and NR12R13;

P and Q are, independently, H or $-C(R10)(R11)NH_2$;

R8 and R9 are independently selected from H and alkyl, or may together form a cycloalkyl ring;

R10 and R11 are independently selected from H and alkyl, or may together form a cycloalkyl ring or a cyclic ether;

L is a linker selected from a covalent bond, $-(CH_2)_{1-10}-$, $-O-(CH_2)_{2-10}-$, $-(CH_2)_{1-10}-O-(CH_2)_{1-10}-$, $-(CH_2)_{1-10}-NH-(CH_2)_{1-10}-$, $-CONH-(CH_2)_{1-10}-$, -CO-, and $-SO_2-$;

A is selected from N-linked morpholine, aryl, and heteroaryl;

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,-COOR12, -CONR12R13, $H(CH_2)_{1-3}CON(R12)(CH_2)_{1-3}-$, fluoro and -NR12R13;

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 NR12R13;

a cyclic ether is a monocyclic saturated hydrocarbon of between 4 and 7 carbon atoms, wherein one of the ring carbons is replaced by an oxygen atom;

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 aryl, OH, CN, CF_3, -COOR12, - CONR12R13, fluoro and NR12R13;

aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, -morpholinyl, -piperidinyl, heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, -COR14R15, - $(CH_2)_{1-3}$-NR14R15, CF_3 and NR12R13;

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,-COOR12, -CONR12R13, CF_3 and NR12R13

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, NR12, S and O; heteroaryl 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, heteroaryl^b, -COOR12, - CONR12R13, CF_3 and NR12R13;

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, NR12, 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, -COOR12, -CONR12R13, CF_3 and NR12R13;

R12 and R13 are independently selected from H and alkyl;

R14 and R15 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 optionally may be oxo substituted;
wherein,
when R5, R6 and R7 are absent or H, then:

either
R10 and R11 together form a cycloalkyl ring or a cyclic ether;
or
A is aryl and aryl is phenyl, biphenyl or naphthyl substituted with 1, 2 or 3 substituents independently selected from OH, heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, and -$(CH_2)_3$-NR14R15; wherein,

aryl^b is phenyl, biphenyl or naphthyl, wherein aryl^b is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, -COOR12, -CONR12R13, CF_3 and NR12R13; and 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, NR12, S and O, wherein heteroaryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, halo, CN, aryl, morpholinyl, piperidinyl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b, -COOR12, -CONR12R13, CF_3 and -NR12R13;

or
A is heteroaryl and 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, NR12, S and O, wherein heteroaryl is substituted with 1, 2 or 3 substituents independently selected from aryl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b, -COOR12, and-CONR12R13;wherein,

aryl is phenyl, biphenyl or naphthyl, wherein aryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, -COR12R13, -$(CH_2)_{1-3}$-NR14R15, CF_3 and -NR12R13; and

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, NR12, S and O, wherein heteroaryl^b is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, halo, CN, morpholinyl, piperidinyl, aryl, -$(CH_2)_{1-3}$-aryl, -COOR12, -CONR12R13, CF_3 and NR12R13;

and tautomers, stereoisomers (including enantiomers, diastereoisomers and racemic and scalemic mixtures thereof),

pharmaceutically acceptable salts and solvates thereof.

[0023] The present invention also comprises the following aspects and combinations thereof:

[0024] V is selected from C and N such that the aromatic ring containing V is phenyl or pyridine.

In an embodiment, V is N such that the aromatic ring containing V is pyridine.

In an embodiment, V is C such that the aromatic ring containing V is phenyl.

In a preferred embodiment U is C.

R2 is absent when V is N.

R1 and, when present, R2 are independently selected from H, alkyl, alkoxy, CN, halo and CF_3.

In an embodiment, R1 and, when present, R2 are independently selected from H, alkyl, alkoxy, halo and CF_3.

In an embodiment, R1 and, when present, R2 are independently selected from H, methyl, methoxy, Cl, F and CF_3.

In an embodiment, R1 is selected from H, methyl, methoxy, Cl, F and CF_3.

In an embodiment, R1 is selected from alkyl, alkoxy, CN, halo and CF_3.

In a preferred embodiment, R1 is selected from H and methyl.

In a more preferred embodiment, R1 is H.

In an embodiment, when present, R2 is selected from H, methyl, methoxy, and F.

In a preferred embodiment, when present, R2 is H.

[0025] R3 is selected from H, alkyl, alkoxy, CN, halo and CF_3;

In an embodiment, R3 is selected from H and alkyl.

In a preferred embodiment, R3 is selected from H and methyl.

In a more preferred embodiment, R3 is H.

[0026] In an embodiment, when R2 is present, R1 is selected from H, methyl, methoxy, Cl, F and CF_3; R2 is H; and R3 is selected from H and methyl.

In an embodiment, R2 is present and R1, R2 and R3 are H.

In an embodiment, R1 and R3 are methyl.

In an embodiment, when R2 is present, R1 and R3 are methyl; and R2 is H.

In a preferred embodiment, R1 is methyl.

[0027] 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.

In an embodiment, 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.

In an embodiment, 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.

In a preferred embodiment, X is N.

In an embodiment, W is C, X and Y are N and Z is C or N.

In an embodiment, X and Y are N and W and Z are C.

In an embodiment, X, Y and Z are N and W is C.

In a more preferred embodiment, X is N and W, Y and Z are C.

[0028] R5, R6 and R7 are independently absent, or are independently selected from H, alkyl, halo, aryl, heteroaryl and CF_3.

In an embodiment, R5 is absent or is selected from H, alkyl, CF_3 and aryl.

In an embodiment, R5 is absent or is selected from H, methyl CF_3 and phenyl.

In a preferred embodiment R5 is H.

In an embodiment, R6 and R7 are independently absent, or are independently selected from H, alkyl, aryl and CF_3.

In an embodiment, R6 and R7 are independently absent, or are independently selected from H, methyl, ethyl, n-propyl, phenyl and CF_3.

In a preferred embodiment, R6 and R7 are methyl.

[0029] In an embodiment, X and Y are N, W and Z are C, and R5 and R7 are H.

In an embodiment, X, Y and Z are N, W is C, and R7 is H.

In a preferred embodiment, X is N, W, Y and Z are C, R5 is H and R6 and R7 are methyl.

[0030] R14 and R15 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 optionally may be oxo substituted.

[0031] In a preferred embodiment, P is $-C(R10)(R11)NH_2$ and Q is H.

[0032] R8 and R9 are independently selected from H and alkyl, or may together form a cycloalkyl ring. In an embodiment, R8 and R9 are independently selected from H and alkyl, or may together form a cyclopropyl ring.

In an embodiment, R8 and R9 are independently selected from H and methyl, or may together form a cyclopropyl ring.

In a preferred embodiment, R8 and R9 are H.

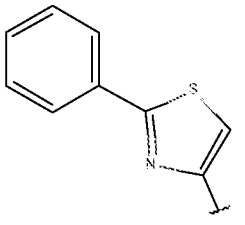
[0033] R10 and R11 are independently selected from H and alkyl, or may together form a cycloalkyl ring or a cyclic ether.

In an embodiment, R10 and R11 are independently selected from H and alkyl, or may together form a cyclopropyl ring.

In an embodiment, R10 and R11 are independently selected from H and methyl, or may together form a cyclopropyl ring.
In a preferred embodiment, R10 and R11 are H.

[0034] In a preferred embodiment, L is methylene.

[0035] A is selected from N-linked morpholine, aryl, and heteroaryl.
In an embodiment, A is selected from aryl, and heteroaryl.
In an embodiment, A is selected from: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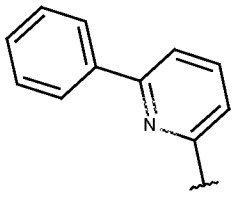
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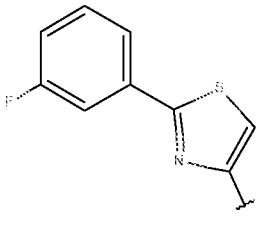
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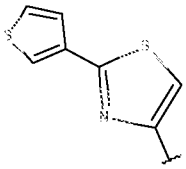
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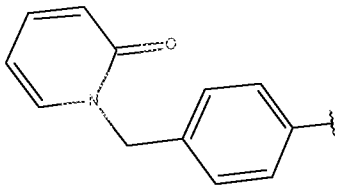
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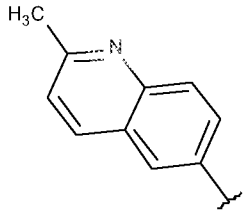
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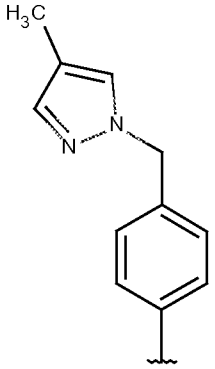
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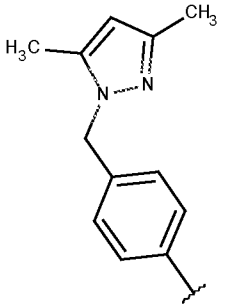
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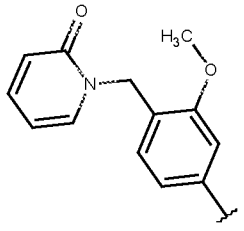
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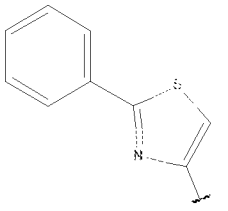
[0036] In an embodiment A is selected from: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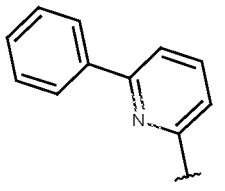
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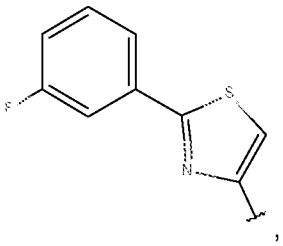
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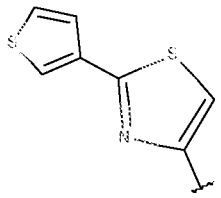
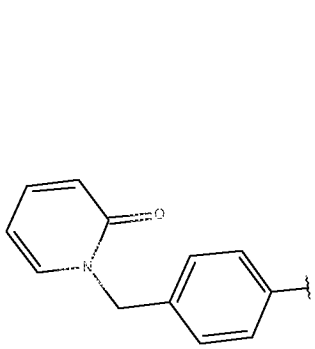


[0037] In an embodiment, A is selected from: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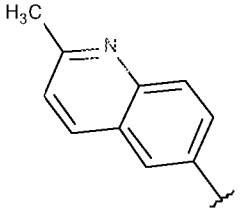
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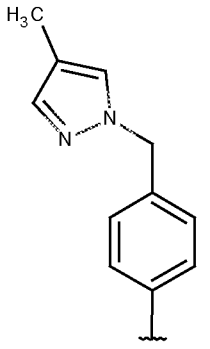
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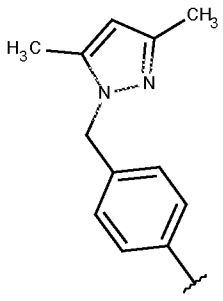
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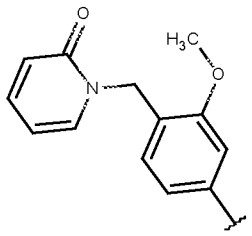
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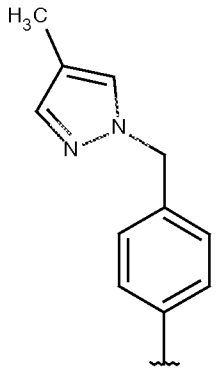
[0038] In an aspect, R5, R6 and R7 are absent or H; and A is selected from: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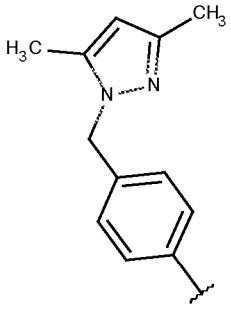
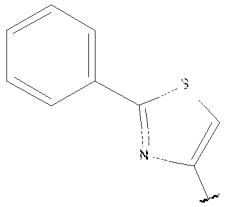


[0039] In a preferred aspect, A is:



[0040] In an aspect, the invention comprises a compound selected from:

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide;
2,5-Dimethyl-1-(6-phenyl-pyridin-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
1-[2-(3-Fluoro-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-(2-thiophen-3-yl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (6-aminomethyl-pyridin-3-ylmethyl)-amide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-3-fluoro-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-fluoro-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-chloro-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-trifluoromethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methoxy-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide;
1-[4-(3,5-Dimethyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrrole-2-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrrole-2-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrrole-2-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrrole-2-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid 4-aminomethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;

1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide;
5-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-3-fluoro-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-3-fluoro-2-methyl-benzylamide;
3-Methyl-1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
5-Methyl-1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-(2-Methyl-quinolin-6-ylmethyl)-3-trifluoromethyl-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-(2-Pyrrolidin-1-yl-pyridin-4-ylmethyl)-3-trifluoromethyl-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;

and pharmaceutically acceptable salts and solvates thereof.

Therapeutic Applications

[0041] 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.

[0042] 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.

[0043] 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.

[0044] Also disclosed is 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).

[0045] In one aspect, the disease or condition in which plasma kallikrein activity is implicated is selected from diseases or conditions in which plasma kallikrein activity is implicated include impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammaotory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.

[0046] 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

[0047] 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.

[0048] 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.

[0049] 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

[0050] 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.

[0051] 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.

[0052] Unless otherwise stated, halo is selected from Cl, F, Br and I.

[0053] Cycloalkyl is as defined above. Cycloalkyl may be substituted with a substituent selected from those stated above. 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.

[0054] 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.

[0055] 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, substituted pyrazole, quinolone and substituted quinolone; wherein substituents are as stated above.

[0056] The term "N-linked", such as in "N-linked morpholine", means that the morpholinyl group is joined to the remainder of the molecule *via* a ring nitrogen atom.

[0057] 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.

[0058] In groups such as -COOR12, "-" denotes the point of attachment of the substituent group to the remainder of the molecule.

[0059] "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.

[0060] Hemisalts of acids and bases can also be formed, for example, hemisulfate and hemicalcium salts.

[0061] For a review of suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[0062] "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.

[0063] 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.

[0064] 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).

[0065] In the context of the present invention, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

General Methods

[0066] 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.

[0067] 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).

[0068] Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier, diluent or excipient.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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 cosolvents and/or solubility-enhancing agents such as surfactants, micelle structures and cyclodextrins.

[0075] 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.

[0076] Formulations suitable for oral administration include solid plugs, solid microparticulates, semisolid 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

[0082] 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.

[0083] 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

[0084] 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.

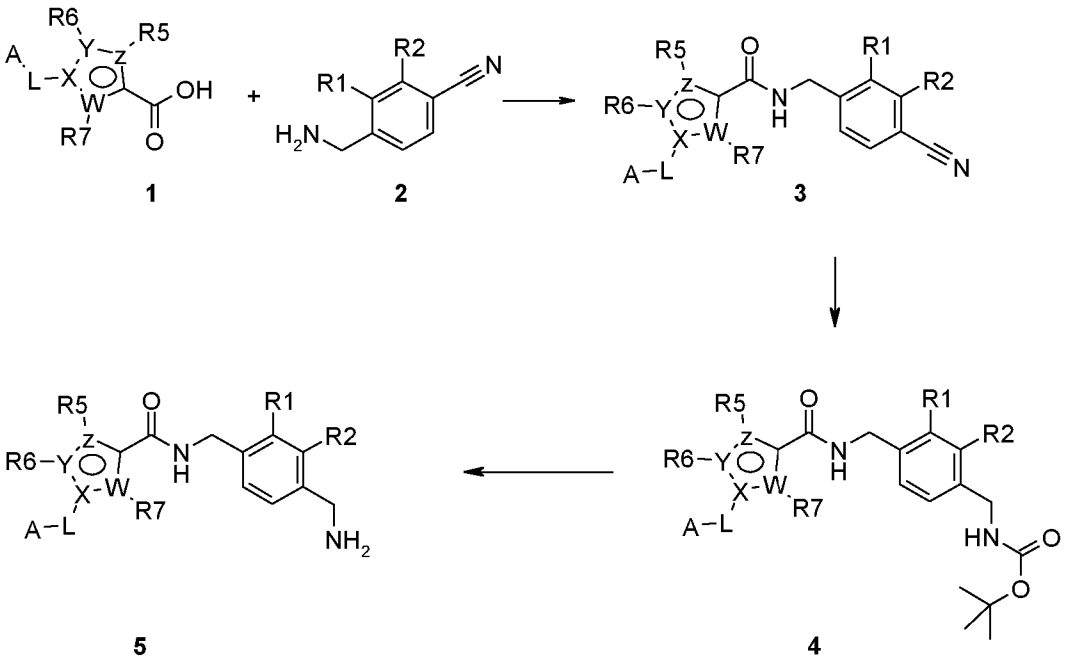
[0085] The compounds of the invention may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above.

[0086] 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.

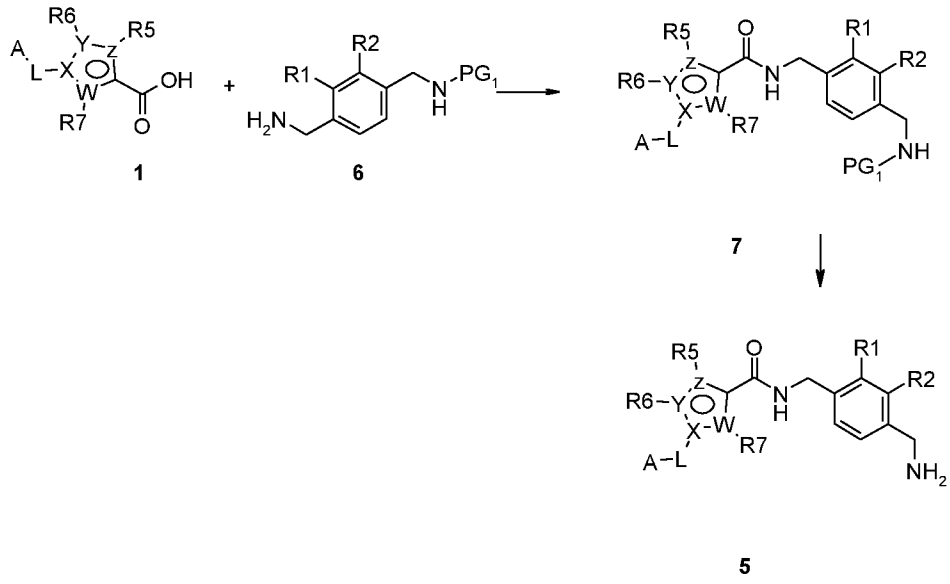
[0087] The compounds according to general formula I can be prepared using conventional synthetic methods for example, but not limited to, the route outlined in Scheme 1. In a typical first step the amine 2 is coupled to an acid 1 using standard coupling condition such as hydroxybenzotriazole and carbodiimide 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-(1 H-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, N,N-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.

[0088] The route exemplified in Scheme 1 then proceeds in the third step involving reduction of a nitrile. Reduction of compound **3** to compound **5** may be achieved in a single step by reduction with a suitable borohydride in the presence of a suitable transition metal such as cobalt or nickel chloride in a suitable solvent such as methanol at room temperature, alternatively this may be achieved in a single step by direct reduction of the nitrile by hydrogenation in a suitable solvent such as methanol in the presence of a suitable catalyst such as palladium on charcoal in the presence of an acid such as hydrochloric acid to yield the amine **5.** In the exemplified scheme the *tert*-butoxycarbonyl (Boc) protected amine **4** may be isolated (using, for example, the method as described in S. Caddick et al., *Tetrahedron Lett.*, 2000, **41,** 3513) and subsequently deprotected by standard means described previously to give the amine **5.**



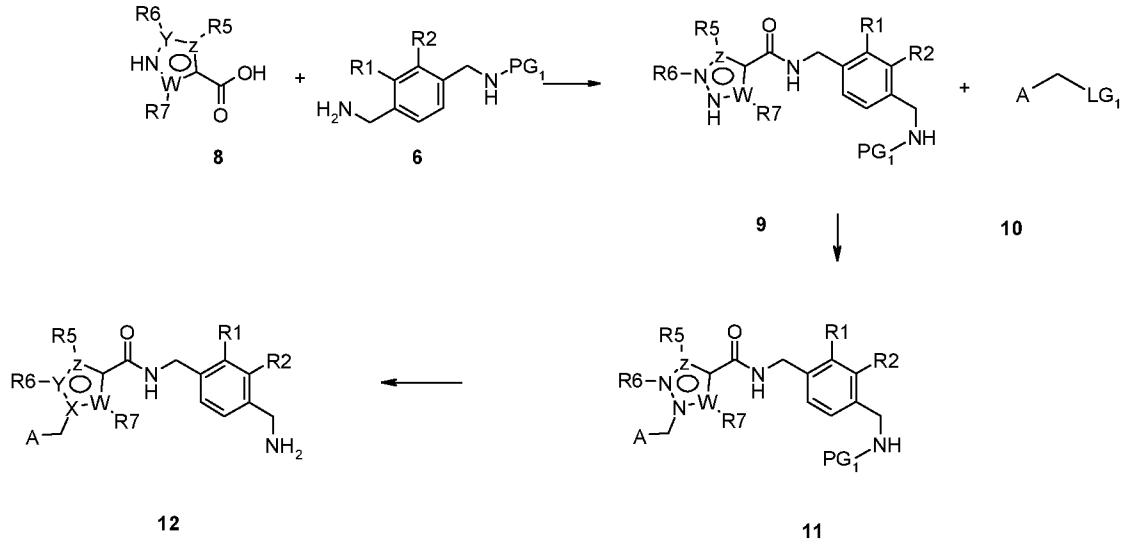
Scheme 1

[0089] 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 **6** 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 protecting group is removed to give compound **5** using standard methods as previously described.



Scheme 2

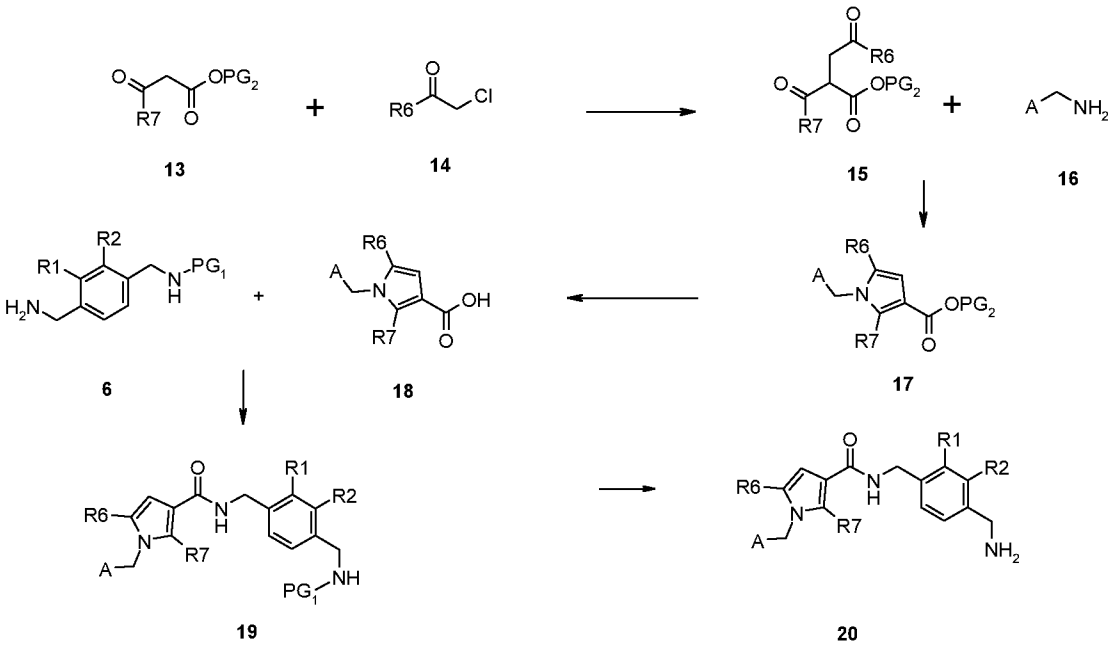
[0090] Alternatively compounds according to general formula I can be prepared using the route outlined in Scheme 3. The acid **8** can be coupled to an amine **6** using suitable coupling methods as previously described to give compound **9** in which the second amino group is amino-protected with a 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 **10** to give compound **11.** 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 **12** using standard methods as previously described.



Scheme 3

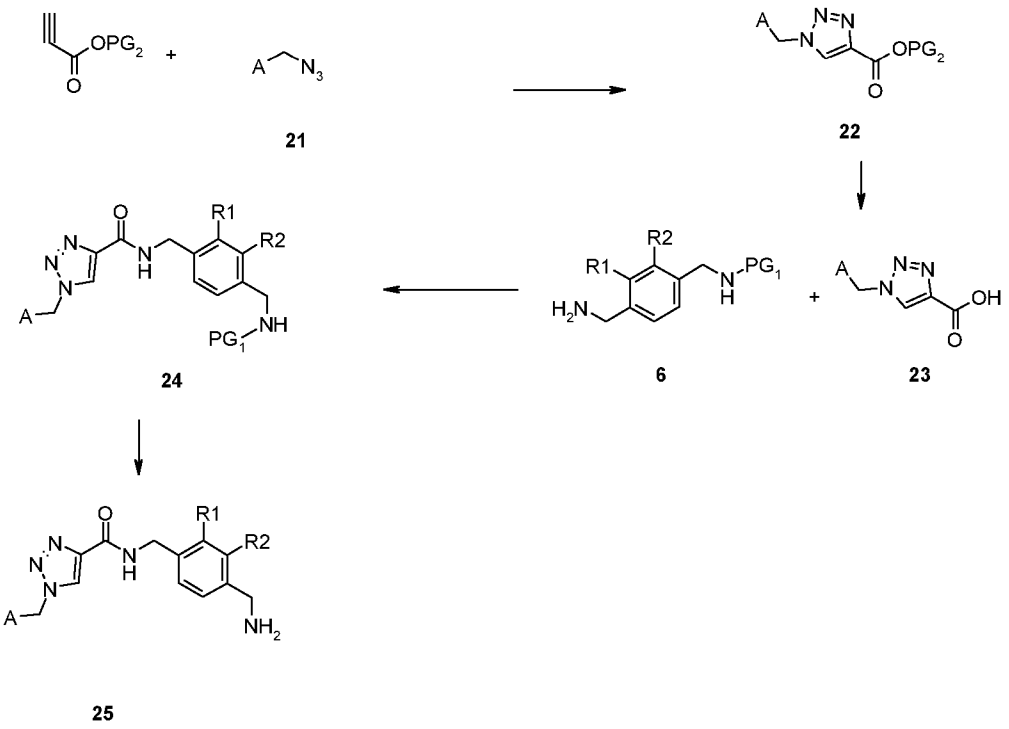
[0091] Alternatively compounds according to general formula I can be prepared using the route outlined in Scheme 4. The pyrrole **17** can be formed in two steps the first of which involves reaction of the sodium salt of an alkyl ketoacetate **13** with a chloroketone **14** in the presence of a base such as potassium carbonate to give compound **15** which in a typical second step is reacted with the amine **16** in the presence of an acid such as but not limited to sulphonic acid derivatives e.g. p-toluenesulphonic acid to yield compound **17** which in a typical third step is subsequently hydrolysed to the corresponding acid **18** using standard methods as described previously. In a typical fourth step the acid **18** can be coupled to an amine **6** using suitable coupling methods as previously described to give compound **19** 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 final step the protecting group is removed to give compound **20** using standard methods as previously described.



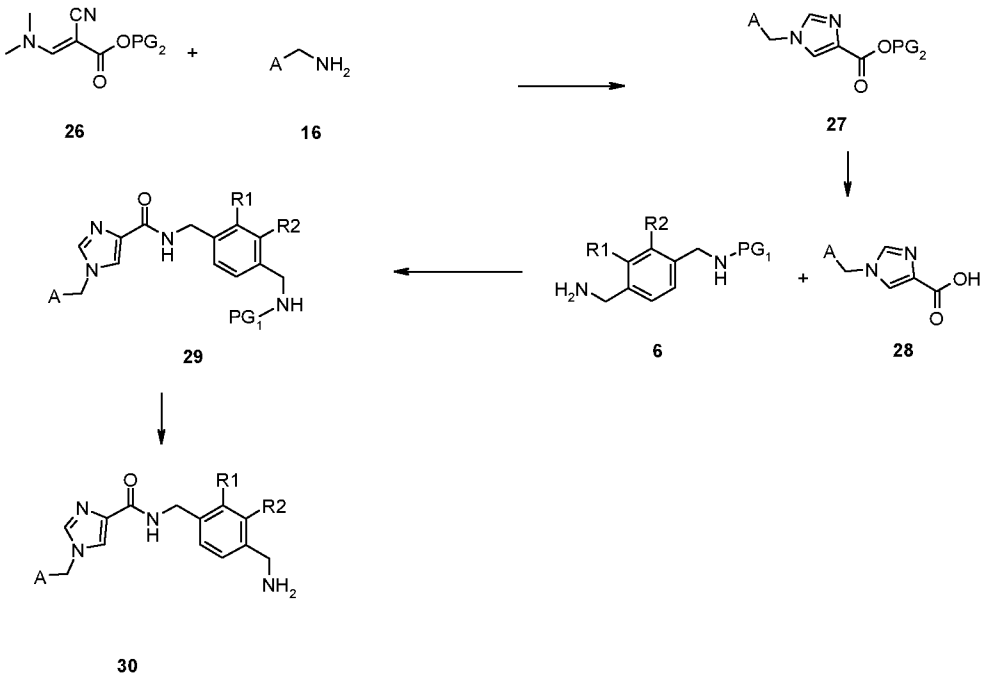
Scheme 4

[0092] Alternatively compounds according to general formula I can be prepared using the route outlined in Scheme 5. The triazole **22** can be formed by reaction of an alkyl propiolate with the azide **21** 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 **23** using standard methods as described previously. In a typical third step the acid **23** can be coupled to an amine 6 using suitable coupling methods as previously described to give compound **24** 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 final step the protecting group is removed to give compound **25** using standard methods as previously described.



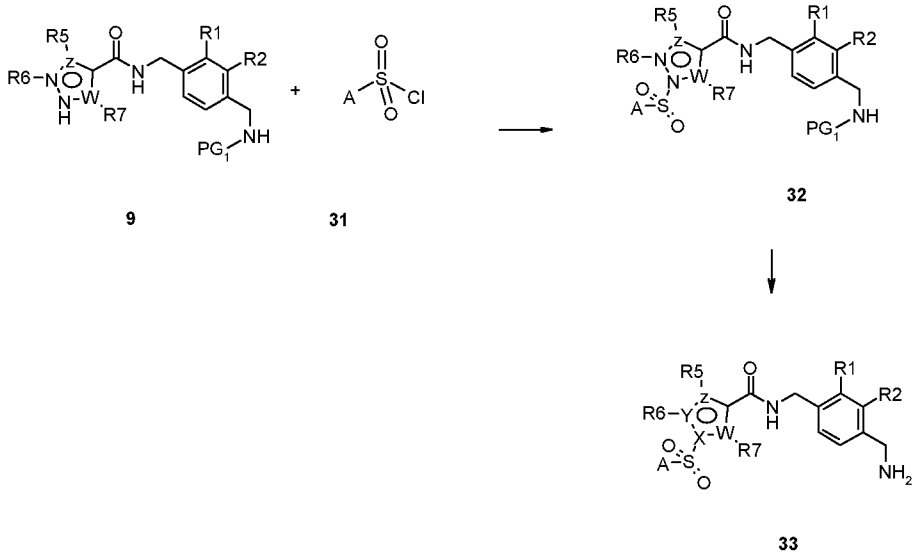
Scheme 5

[0093] Alternatively compounds according to general formula I can be prepared using the route outlined in Scheme 6. The imidazole **26** can be formed by reaction of the acrylate derivative **26** with the amine **16** in the presence of organic bases such as N,N-diisopropylethylamine or triethylamine. In a typical second step the ester is hydrolysed to the corresponding acid **28** using standard methods as described previously. In a typical third step the acid **28** can be coupled to an amine **6** using suitable coupling methods as previously described to give compound **29** 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 final step the protecting group is removed to give compound **30** using standard methods as previously described.



Scheme 6

[0094] 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 **9** with the sulphonyl chloride **31** in the presence of organic bases such as N,N-diisopropylethylamine or triethylamine to give compound **32.** In a typical final step the protecting group is removed to give compound **33** using standard methods as previously described.



Scheme 7

EXAMPLES

[0095] The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

DMF	N,N-Dimethylformamide
EtOAc	Ethyl Acetate
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
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid

[0096] All reactions were carried out under an atmosphere of nitrogen unless specified otherwise.

[0097] ^{1}H NMR spectra were recorded on a Bruker Avance III (400MHz) spectrometer with reference to deuterium solvent and at room temperature.

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 11 min, flow rate 1.5 mL/min. Data was collected using a Thermofinnigan Surveyor MSQ mass spectrometer with electospray ionisation in conjunction with a Thermofinnigan Surveyor LC system.

[0098] Chemical names were generated using the Autonom software provided as part of the ISIS Draw package from MDL Information Systems.

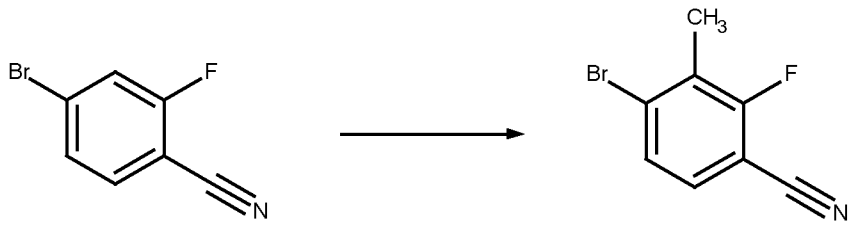
[0099] Where products were purified by flash chromatography, 'silica' refers to silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Merck silica gel 60), and an applied pressure of nitrogen up to 10 p.s.i accelerated column elution. Reverse phase preparative HPLC purifications were carried out using a Waters 2525 binary gradient pumping system at flow rates of typically 20ml/min using a Waters 2996 photodiode array detector.

[0100] All solvents and commercial reagents were used as received.

COMPOUND A

4-Bromo-2-fluoro-3-methyl-benzonitrile

[0101]



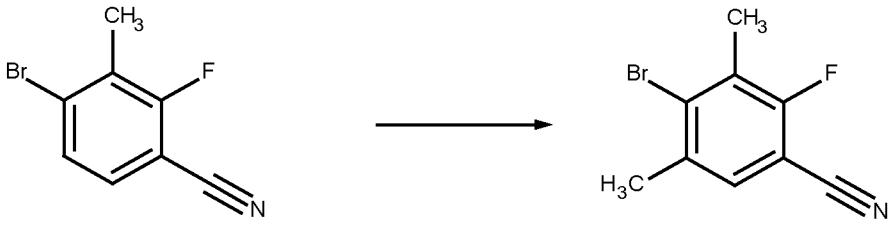
[0102] To a solution of diisopropylamine (4.2mL, 30mmol) in dry THF (5ml) was added a solution of nBuLi in THF (2.5M, 11mL, 27.5mmol) dropwise at -78 °C. Once addition was complete, the reaction was allowed to warm to 0 °C and stirred in an ice-salt bath for 40 mins. The resulting solution was added dropwise to a solution of 4-bromo-2-fluorobenzonitrile (5g, 25mmol) in dry THF (50ml) at -78 °C and the mixture stirred for 2.5 hrs. The reaction mixture was

then cooled to -78 °C and methyl iodide added in one portion and the mixture slowly allowed to warm to room temperature. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc (3x 40ml). The combined organics were washed with water (40ml) and brine (40ml). The organics were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography eluting with 9:1 pet ether: ethyl acetate to afford 4-bromo-2-fluoro-3-methyl-benzonitrile as an off white solid (2.40g, 45% yield).

COMPOUND B

4-Bromo-2-fluoro-3,5-dimethyl-benzonitrile

[0103]

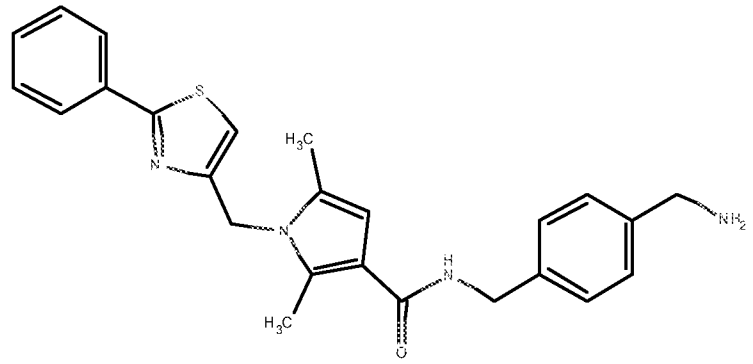


[0104] Following a similar procedure to that described for the preparation of Compound A, 4-bromo-2-fluoro-3-methyl-benzonitrile was converted to 4-bromo-2-fluoro-3,5-dimethyl-benzonitrile which was isolated as a lime green oil.

EXAMPLE 1

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

[0105]



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

[0106] Ethylacetoacetate sodium salt (17.10g, 112mmol) was suspended in acetone (500mls) Potassium carbonate (15.54g, 112mmol) and potassium iodide (3.73g, 22.48mmol) were added and the resulting solution was refluxed. Chloroacetone (11.41 g, 124mmol) was added dropwise over a period of 5 mins). Once the addition was complete the mixture was heated under reflux for a further 2 hours. The reaction mixture was allowed to cool to room temperature and the solid material was filtered off and washed with acetone. The resultant filtrate was evaporated and purified by flash chromatography (silica), eluant 75% Pet. Ether (60-80°C), 25% EtOAc, fractions combined and evaporated in vacuo to give a yellow oil identified as 2-acetyl-4-oxo-pentanoic acid ethyl ester (10.1 g, 54.2mmol, 48%).

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

[0107] 2-Acetyl-4-oxo-pentanoic acid ethyl ester (1.8g, 9.66mmol) was dissolved in toluene (35mls), 2-phenyl-thiazoyl-4-methylamine (2.02g, 10.62mmol) and p-toluenesulphonic acid (183mg, 0.966mmol) were added. The reaction mixture

was heated at reflux for 4 hours after which time it was diluted with ethyl acetate and washed with $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 85% Pet. Ether (60-80°C), 15% EtOAc, fractions combined and evaporated in vacuo to give a colourless oil identified as 1-[2-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1 H-pyrrole-3-carboxylic acid ethyl ester (1.26g, 3.69mmol, 38%).
[M+H]+ = 341.27

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

[0108] 1-[2-Phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester (1.07g, 3.14mmol) was dissolved in ethanol (50mls). Sodium hydroxide (629mg, 15.72mmol) in water (5mls) 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 pH 1 with 1 M HCl and extracted with ethyl acetate (3x 50mls). The combined extracts were washed with water (1x30mls), brine (1x30mls), 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)-1 H-pyrrole-3-carboxylic acid (980mg, 3.14mmol, 100%).
[M+H]+ = 313.23

D. [4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester

[0109] 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (1.60g, 5.12mmol) was dissolved in CH_2Cl_2 (100mls) and DMF(5mls). This solution was cooled to 0°C. 1-(N-Boc-aminomethyl)-4-(aminomethyl) benzene (1.21g, 5.12mmol) was added followed by HOBt (830mg, 6.14mmol) and triethylamine (2.59g, 25.6mmol). Water soluble carbodiimide (1.37g, 4.33mmol) was then added. After 18 hrs at 0°C to room temperature reaction mixture was diluted with chloroform (200mls) and washed with $NaHCO_3$ (1x50mls), water (1x50mls), brine (1x50mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 50%Pet. Ether (60-80°C), 50% EtOAc, fractions combined and evaporated in vacuo to give a white solid identified as [4-({[2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester (2.30g, 4.33mmol, 85%).
$[M+H]^+$ = 531.29.

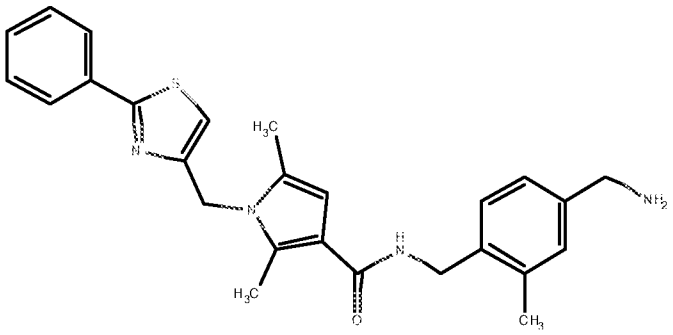
E. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide

[0110] [4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester (2.30g, 4.33mmol) was dissolved in methanol (40mls) to which 4M HCl in dioxan (10mls) was added. After three hours at room temperature the solvent was removed in vacuo and the residue was azeotroped from toluene. The free base was liberated with a mixture of dichloromethane, MeOH and NH_3 then evaporated. The residue was purified by flash chromatography (silica), eluant dichlromethane:MeOH:NH_3 (100:10:1). The residue was triturated with EtOAc/Pet Ether 60-80°C to give an off white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide (1.2g, 2.79mmol, 64%).
[M+H]+ = 431.20
^{1}H NMR: (d6-DMSO), δ: 2.26(3H,s), 2.56(3H,s), 3.33(2H,br s), 3.68(2H,s), 4.33(2H,d,J= 6.1Hz), 5.17(2H,s), 6.29(1 H,s), 7.19-7.26(5H,m), 7.48(3H,m), 7.90-7.92(2H,m), 8.05(1 H,t,J= 6.1 Hz).

EXAMPLE 2

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide

[0111]



A. (4-Cyano-2-methyl-benzyl)-carbamic acid benzyl ester

[0112] 4-Aminomethyl-3-methylbenzonitrile (1.0g, 5.48mmol) was dissolved in dichloromethane (50mls) and the solution was cooled to 0°C. N,N-Diisopropylethylamine (1.56g, 12.05mmol) was added followed by benzyl chloroformate 1.12g, 6.57mmol) was added. After 3 days at 0°C to room temperature the reaction mixture was diluted with chloroform, this solution was washed with sat $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo to give a brown oil identified as (4-cyano-2-methyl-benzyl)-carbamic acid benzyl ester (1.50g, 5.35mmol, 98%).
$[M+H]^+$ = 281.25

B. [4-(tert-Butoxycarbonylamino-methyl)-2-methyl-benzyl]-carbamic acid benzyl ester

[0113] (4-Cyano-2-methyl-benzyl)-carbamic acid benzyl ester (1.5g, 5.35mmol) was dissolved in methanol (75mls). This solution was cooled to 0°C. Nickel (II) chloride hexahydrate (127mg, 0.54mmol) and di-tertbutyl dicarbonate (2.34g, 10.70mmol) were added followed by sodium borohydride (1.42g, 37.56mmol) 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 $CHCl_3$ (70mls), washed with sat $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil. Purified by flash chromatography, (silica), eluant 40%Pet. Ether (60-80°C), 60% EtOAc to give white solid identified as [4-(tert-butoxycarbonylamino-methyl)-2-methyl-benzyl]-carbamic acid benzyl ester (1.11g, 2.38mmol, 54%).
$[M+H]^+$ = 285.32.

C. (4-Aminomethyl-3-methyl-benzyl)-carbamic acid tert-butyl ester

[0114] [4-(tert-Butoxycarbonylamino-methyl)-2-methyl-benzyl]-carbamic acid benzyl ester (130mg, 0.34mmol) was dissolved in methanol (40mls). This solution was hydrogenated over 10% Pd/C (40mg) at atmospheric pressure and room temperature for one hour after which time the catalyst was filtered off and washed with methanol (30mls), the combined filtrates were evaporated in vacuo to give a white solid identified as (4-aminomethyl-3-methyl-benzyl)-carbamic acid tert-butyl ester (80mg, 0.32mmol, 95%).

D. [4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-3-methyl-benzyl]-carbamic acid tert-butyl ester

[0115] 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (100mg, 0.32mmol) was dissolved in CH_2Cl_2(20mls). This solution was cooled to 0°C. (4-Aminomethyl-3-methyl-benzyl)-carbamic acid tert-butyl ester (80mg, 0.32mmol) was added followed by HOBt (52mg, 0.38mmol) and triethylamine (162mg, 1.60mmol). Water soluble carbodiimide (86mg, 0.45mmol) was then added. After 18 hrs at 0°C to room temperature reaction mixture was diluted with chloroform (200mls) and washed with $NaHCO_3$ (1x50mls), water (1x50mls), brine (1x50mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 50% Pet. Ether (60-80°C), 50% EtOAc, fractions combined and evaporated in vacuo to give a white solid identified as [4-({[2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-3-methyl-benzyl]-carbamic acid tert-butyl ester (105mg, 0.19mmol, 60%).
$[M+H]^+$ = 567.14.

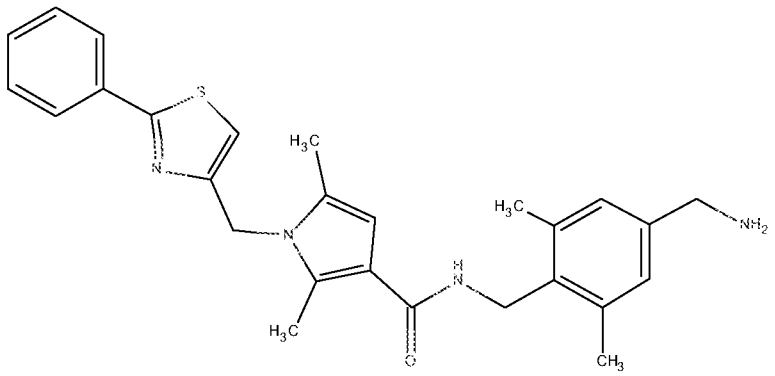
E. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide

[0116] [4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-3-methyl-benzyl]-carbamic acid tert-butyl ester (105mg, 0.93mmol) was dissolved in methanol (20mls) to which 4M HCl in dioxan (5mls) was added. After three hours at room temperature the solvent was removed in vacuo and the residue was azeotroped from toluene. The free base was liberated with a mixture of dichloromethane, MeOH and NH_3 then evaporated. The residue was purified by flash chromatography (silica), eluant dichlromethane:MeOH:NH_3 (100:10:1). The residue freeze dried from acetonitrile and water to give an off white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide (58mg, 0.13mmol, 68%).
$[M+H]+ = 445.17$
^1H NMR: (d6-DMSO), δ: 2.26(3H,s), 2.27(3H,s), 2.55(3H,s), 3.32(2H,br s), 3.65(2H,s), 4.30(2H,s), 5.16(2H,s), 6.31(1H,s), 7.08-7.13(3H,m), 7.27(1H,s), 7.48-7.54(3H,m), 7.87-7.92(3H,m).

EXAMPLE 3

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide

[0117]



A. (4-Bromo-2,6-dimethyl-benzyl)-carbamic acid tert-butyl ester

[0118] 4-Bromo-2,6-dimethylbenzonitrile (2.5g, 11.9mmol) was dissolved in methanol (150mls). This solution was cooled to 0°C. Nickel (II) chloride hexahydrate (238mg, 1.19mmol) and di-tertbutyl dicarbonate (5.19g, 23.80mmol) were added followed by sodium borohydride (3.15g, 83.30mmol) 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 $CHCl_3$ (70mls), washed with sat $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo to give a colourless oil identified as (4-bromo-2,6-dimethyl-benzyl)-carbamic acid tert-butyl ester (3.0g, 9.55mmol, 80%).

B. (4-Cyano-2,6-dimethyl-benzyl)-carbamic acid tert-butyl ester

[0119] To a degassed solution of (4-bromo-2,6-dimethyl-benzyl)-carbamic acid tert-butyl ester (3.0g, 9.55mmol) in N,N-dimethylacetamide (30mls) was added zinc powder (75mg, 1.15mmol), zinc acetate (210mg, 1.15mmol), 1,1'-bis(diphenylphosphino) ferrocine (635mg, 1.15mmol), zinc cyanide (560mg, 4.77mmol), and tris(dibenzylideneacetone) dipalladium(0) (524mg, 0.57mmol). The reaction was heated at 120°C for 4 hrs. After which the reaction mixture was cooled to room temperature and extra 1,1'-bis(diphenylphosphino) ferrocine (423mg, 0.77mmol) and tris(dibenzylideneacetone) dipalladium(0) (350mg, 0.38mmol) were added and the reaction was heated at 120°C for a further 28 hrs. The reaction mixture was cooled to RT filtered through celite and washed with ethyl acetate (250 mls). The filtrate washed with sat $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography, (silica), eluant 80%Pet. Ether (60-80°C), 20% EtOAc to give an off white solid identified as (4-cyano-2,6-dimethyl-benzyl)-carbamic acid tert-butyl ester (630mg, 2.42mmol, 25%).
$[M+H]^+ = 261.06$.

C. 4-Aminomethyl-3,5-dimethyl-benzonitrile Hydrochloride

[0120] (4-Cyano-2,6-dimethyl-benzyl)-carbamic acid tert-butyl ester (630mg, 2.42mmol) was dissolved in 4M HCl in dioxan (10mls). After one hour at room temperature the solvent was removed in vacuo to give a pale brown solid identified as 4-aminomethyl-3,5-dimethyl-benzonitrile hydrochloride (470mg, 2.39mmol, 99%).

D. (4-Cyano-2,6-dimethyl-benzyl)-carbamic acid benzyl ester

[0121] 4-Aminomethyl-3,5-dimethyl-benzonitrile hydrochloride (470mg, 2.39mmol) was dissolved in dichloromethane (50mls) and the solution was cooled to 0°C. N,N-Diisopropylethylamine (679mg, 5.26mmol) was added followed by benzyl chloroformate (489mg, 2.87mmol) was added. After one hour at 0°C to room temperature the reaction mixture was diluted with chloroform, this solution was washed with sat $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo to give a brown oil identified as (4-cyano-2,6-dimethyl-benzyl)-carbamic acid benzyl ester (700mg, 2.38mmol, 99%).
$[M+H]^+$ = 295.04

E. [4-(tert-Butoxycarbonylamino-methyl)-2,6-dimethyl-benzyl]-carbamic acid benzyl ester

[0122] (4-Cyano-2,6-dimethyl-benzyl)-carbamic acid benzyl ester (700mg, 2.38mmol) was dissolved in methanol (75mls). This solution was cooled to 0°C. Nickel (II) chloride hexahydrate (57mg, 0.24mmol) and di-tertbutyl dicarbonate (1.04g, 4.76mmol) were added followed by sodium borohydride (630mg, 16.65mmol) 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 $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography, (silica), eluant 65%Pet. Ether (60-80°C), 35% EtOAc to give an off white solid identified as [4-(tert-butoxycarbonylamino-methyl)-2,6-dimethyl-benzyl]-carbamic acid benzyl ester (600mg, 1.51mmol, 63%).
$[M+H]^+$ = 421.05 (M+Na).

F. (4-Aminomethyl-3,5-dimethyl-benzyl)-carbamic acid tert-butyl ester

[0123] [4-(tert-Butoxycarbonylamino-methyl)-2,6-dimethyl-benzyl]-carbamic acid benzyl ester (600mg, 1.51mmol) was dissolved in methanol (60mls). This solution was hydrogenated over 10% Pd/C (100mg) at atmospheric pressure and room temperature for one hour after which time the catalyst was filtered off and washed with methanol (30mls), the combined filtrates were evaporated in vacuo to give a white solid identified as (4-aminomethyl-3,5-dimethyl-benzyl)-carbamic acid tert-butyl ester (350mg, 1.32mmol, 88%).
$[M+H]^+$ = 287.07 (M+Na).

G. [4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-3,5-dimethyl-benzyl]-carbamic acid tert-butyl ester

[0124] 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (118mg, 0.38mmol) was dissolved in CH_2Cl_2(20mls). This solution was cooled to 0°C. (4-(4-Aminomethyl-3,5-dimethyl-benzyl)-carbamic acid tert-butyl ester (100mg, 0.38mmol) was added followed by HOBt (61mg, 0.45mmol) and triethylamine (191mg, 1.89mmol). Water soluble carbodiimide (102mg, 0.53mmol) was then added. After 18 hrs at 0°C to room temperature reaction mixture was diluted with chloroform (200mls) and washed with $NaHCO_3$ (1x50mls), water (1x50mls), brine (1x50mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 50% Pet. Ether (60-80°C), 50% EtOAc, fractions combined and evaporated in vacuo to give a white solid identified as [4-({[2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-3,5-dimethyl-benzyl]-carbamic acid tert-butyl ester (110mg, 0.20mmol, 52%).
$[M+H]^+$ = 567.14.

H. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide

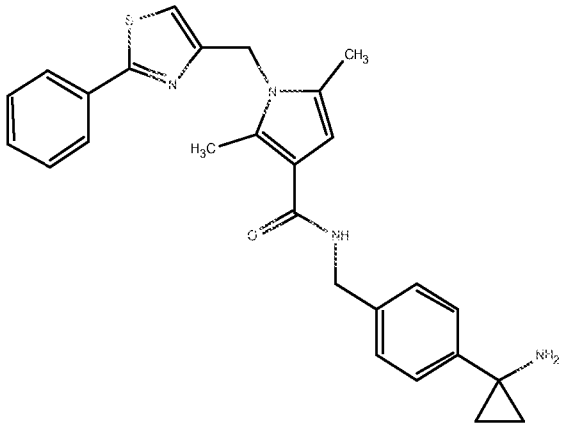
[0125] [4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-3,5-dimethyl-benzyl]-carbamic acid tert-butyl ester (110mg, 0.20mmol) was dissolved in methanol (20mls) to which 4M HCl in dioxan (5mls) was added. After three hours at room temperature the solvent was removed in vacuo and the residue was azeotroped from toluene. The free base was liberated with a mixture of dichloromethane, MeOH and NH_3 then evaporated.

The residue was purified by flash chromatography (silica), eluant dichloromethane:MeOH:NH_3 (100:10:1). The residue freeze dried from acetonitrile and water to give an off white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide (77mg, 0.17mmol, 85%).
$[M+H]^+$ = 459.09
^1H NMR: (d6-DMSO), δ: 2.22(3H,s), 2.34(6H,s), 2.54(3H,s), 3.74(2H,s), 4.34(2H,d,J= 5.0Hz), 5.15(2H,s), 5.44(2H,br s), 6.24(1H,s), 7.00(2H,s), 7.25(1H,s), 7.45(1H,t,J= 5.1Hz), 7.49-7.51(3H,m), 7.88-7.91(2H,m).

EXAMPLE 4

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide

[0126]



A. 4-(1-Amino-cyclopropyl)-benzonitrile

[0127] In oven dried glassware under an atmosphere of nitrogen a solution of 1,4-dicyanobenzene (2.50g, 20mmol) in anhydrous dichloromethane (80mls) was cooled to -70C. Titanium isopropoxide (6.1g, 21.46 mmol) was added followed by dropwise addition of 3M solution of ethyl magnesium bromide in diethyl ether (14.37mls, 43mmol). The reaction was stirred at -70°C for 10 min and then allowed to warm to room temperature). After 1 hour boron trifluoride etherate (5.54g, 39.02mmol) was added and the reaction stirred at room temperature for 18 hours. The reaction was quenched with NH_4Cl and then the pH adjusted to 9-10 with 1 M NaOH. The layers were separated and the aqueous extracted dichloromethane (5 x 20 mls) then with ethyl acetate (3 x 20mls). Organic layers were combined and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica), eluant dichloromethane/MeOH/NH_4OH (99:1:1, 98:2:1, 97:3:1, 95:5:1) giving a yellow oil identified as 4-(1-amino-cyclopropyl)-benzonitrile (1.61 g, 10mmol, 52%).
^1H NMR: ($CDCl_3$), δ: 1.07 - 1.10 (2H, m), 1.21 - 1.24 (2H, m), 1.86 (2H, br,s), 7.39 (2H, dt, J = 8.4, 1.9 Hz), 7.61 (2H, dt, J = 8.4, 1.9 Hz).

B. [1-(4-Cyano-phenyl)-cyclopropyl]-carbamic acid benzyl ester

[0128] 4-(1-Amino-cyclopropyl)-benzonitrile (1.61g, 10.18mmol) was dissolved in dichloromethane (250mls) and the solution was cooled to 0°C. N,N-Diisopropylethylamine (2.89g, 22.39mmol) was added followed by benzyl chloroformate 2.08g, 12.21mmol) was added. After 18 hours at 0°C to room temperature the reaction mixture was diluted with chloroform, this solution was washed with sat $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 90%Pet. Ether (60-80°C), 10% EtOAc, fractions combined and evaporated in vacuo to give a to give a yellow oil identified as [1-(4-cyano-phenyl)-cyclopropyl]-carbamic acid benzyl ester (1.33g, 4.55mmol, 45%).
$[M+H]^+$ = 293.04
^1H NMR: ($CDCl_3$), δ: 1.24 (6H, t, J = 7.2 Hz), 3.02 (4H, q, J = 7.2 Hz), 4.70 (2H, s), 7.34 - 7.37 (5H, m), 7.77 (2H, d, J = 8.4 Hz), 8.04 (2H, d, J = 8.6 Hz).

C. {1-[4-(tert-Butoxycarbonylamino-methyl)-phenyl]-cyclopropyl}-carbamic acid benzyl ester

[0129] [1-(4-Cyano-phenyl)-cyclopropyl]-carbamic acid benzyl ester (1.33g, 4.55mmol) was dissolved in methanol (100mls). This solution was cooled to 0°C. Nickel (II) chloride hexahydrate (108mg, 0.46mmol) and di-tertbutyl dicarbonate (1.99g, 9.10mmol) were added followed by sodium borohydride (1.21g, 31.85mmol) portionwise. The reaction mixture was stirred at 0°C to room temp for 18 hours. The MeOH was removed by evaporation. The residue was dissolved in $CHCl_3$ (70mls), washed with sat $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil. Purified by flash chromatography, (silica), eluant 30%Pet. Ether (60-80°C), 70% EtOAc to give white solid identified as {1-[4-(tert-butoxycarbonylamino-methyl)-phenyl]-cyclopropyl}-carbamic acid benzyl ester (1.06g, 2.67mmol, 59%).
$[M+H]^+$ = 419.2 (M+Na).

D. [1-(4-Aminomethyl-phenyl)-cyclopropyl]-carbamic acid benzyl ester Hydrochloride

[0130] {1-[4-(tert-butoxycarbonylamino-methyl)-phenyl]-cyclopropyl}-carbamic acid benzyl ester (90mg, 0.23mmol) was dissolved in 4M HCl in dioxan (10mls). After 3 hours at room temperature the solvent was removed in vacuo to give a yellow solid identified as [1-(4-aminomethyl-phenyl)-cyclopropyl]-carbamic acid benzyl ester hydrochloride (84mg, 0.23mmol, 100%).
$[M+H]^+$ = 318.97 (M+Na).

E. {11-[4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-phenyl]-cyclopropyl}-carbamic acid benzyl ester

[0131] 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (78mg, 0.25mmol) was dissolved in CH_2Cl_2(20mls). This solution was cooled to 0°C. [1-(4-Aminomethyl-phenyl)-cyclopropyl]-carbamic acid benzyl ester hydrochloride (84mg, 0.23mmol) was added followed by HOBt (37mg, 0.27mmol) and triethylamine (115mg, 1.14mmol). Water soluble carbodiimide (61 mg, 0.32mmol) was then added. After 18 hrs at 0°C to room temperature reaction mixture was diluted with chloroform (100mls) and washed with $NaHCO_3$ (1x20mls), water (1x20mls), brine (1x20mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 50%Pet. Ether (60-80°C), 50% EtOAc, fractions combined and evaporated in vacuo to give a white solid identified as {1-[4-({[2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-phenyl]-cyclopropyl}-carbamic acid benzyl ester (66mg, 0.11mmol, 49%).
$[M+H]^+$ = 613.02 (M+Na).

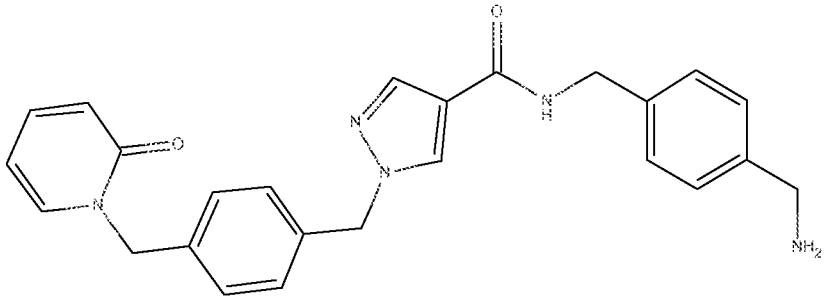
F. 2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide

[0132] {1-[4-({[2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carbonyl]-amino}-methyl)-phenyl]-cyclopropyl}-carbamic acid benzyl ester (70mg, 0.12mmol) was dissolved in methanol (40mls). This solution was hydrogenated over 10% Pd/C (10mg) at atmospheric pressure and room temperature for 5 hours after which time the catalyst was filtered off and washed with methanol (30mls), the combined filtrates were evaporated in vacuo and freeze dried from acetonitrile and water to give a white solid identified as 2,5-dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1 H-pyrrole-3-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide (21 mg, 0.046mmol, 38%).
$[M+H]^+$ = 480.16.
^1H NMR: (d6-DMSO) δ: 0.75 (2H, t, J = 7.4 Hz), 1.45-1.57 (2H, m), 2.25 (3H, s), 2.55 (3H, s), 3.63 (1H, t, J = 6.7 Hz), 4.32 (2H, d, J = 6.1 Hz), 5.16 (2H, s), 6.29 (2H, s), 7.18 (2H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.25 (1 H, s), 7.49 (2H, d, J = 1.8 Hz), 7.50 - 7.51 (1 H, m), 7.89 (1 H, d, J = 1.7 Hz), 7.91 (1 H, d, J = 2.6 Hz), 8.03 (1 H, t, J = 6.1 Hz).

REFERENCE EXAMPLE 5

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

[0133]



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

[0134] Polymer-supported triphenylphospine (3.0mmol/g, 3 equiv, 1.0g) was swollen in THF/dichloromethane (1:1, 100mls) under a nitrogen atmosphere. Ethyl 1H-pyrazole-4-carboxylate (500mg, 3.57mmol) and 4-(chloromethyl)benzyl alcohol (671 mg, 4.28mmol) were added followed by a solution of diisopropyl azodicarboxylate (1.08g, 5.35mmol) in THF/dichloromethane (1:1, 10mls) over a period of 30mins. The reaction mixture was stirred at room temperature for 18 hours, the mixture was filtered through celite and the resin was washed with 3 cycles of dichloromethane/methanol (15mls). The combined filtrates were evaporated in vacuo and triturated with ethanol to give a white solid identified as 1-(4-chloromethyl-benzyl)-1 H-pyrazole-4-carboxylic acid ethyl ester (741 mg, 2.66mmol, 75%).
$[M+H]^+$ = 279.05

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

[0135] 1-(4-Chloromethyl-benzyl)-1 H-pyrazole-4-carboxylic acid ethyl ester (300mg, 1.076mmol) was dissolved in acetone (50mls) 2-hydroxypyridine (123mg, 0.001mmol) and potassium carbonate (446mg, 0.003mmol) were added and the reaction mixture was stirred at 50°C for 3 hours after which time the solvent was removed in vacuo and the residue taken up in EtOAc (100mls), this solution was washed with water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 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]-1 H-pyrazole-4-carboxylic acid ethyl ester (310mg, 0.92, 85%).
$[M+H]^+$ = 337.78, 350.84 (M+Na).

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

[0136] 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid ethyl este (310mg, 0.92mmol) was dissolved in THF (50mls)and water (5mls) lithium hydroxide (110mg, 4.6mmol) was added. The reaction mixture was stirred at 50°C for 18 hours after which time the solvent was concentrated in vacuo and the residue taken up in EtOAc (50mls), the aqueous layer was separated, acidified with 1 M HCl to pH2 and extracted $CHCl_3$ (3x50mls) the combined extracts were washed with water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 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]-1 H-pyrazole-4-carboxylic acid (140mg, 0.453mmol, 49%).
$[M+H]^+$ = 309.93

D. {4-[({1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carbonyl}-amino)-methyl]-benzyl}-carbamic acid tert-butyl ester

[0137] 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (130mg, 0.42mmol) was dissolved in CH_2Cl_2 (50mls) and DMF (2.5mls). This solution was cooled to 0°C. tert-Butyl 4-(Aminomethyl)benzylcarbamate (119mg, 0.50mmol) was added followed by HOBt (62mg, 0.46mmol) and triethylamine (128mg, 1.27mmol). Water soluble carbodiimide (97mg, 0.50mmol) was then added. After 18 hours at 0°C to room temperature reaction mixture was diluted with chloroform (400mls) washed with 0.3M $KHSO_4$ (1x30mls), $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 6%MeOH, 94% $CHCl_3$, fractions combined and evaporated in vacuo to give a white solid identified as {4-[({1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carbonyl}-amino)-methyl]-benzyl}-carbamic acid tert-butyl ester (156mg, 0.296mmol, 70%).
$[M+H]^+$ = 550.45

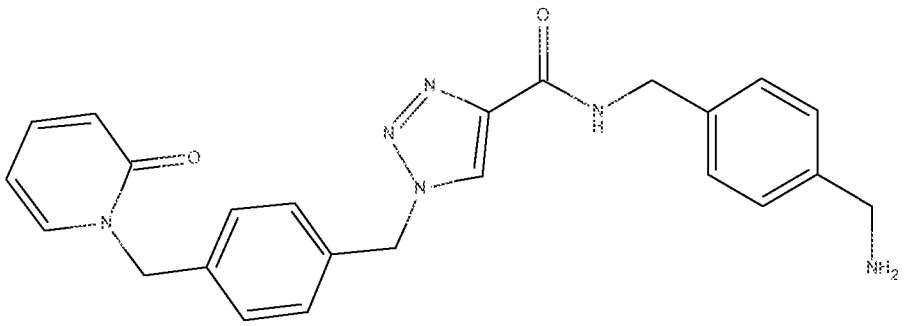
E. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide Hydrochloride

[0138] {4-[({1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carbonyl}-amino)-methyl]-benzyl}-carbamic acid tert-butyl ester (52mg, 0.10mmol) was dissolved in 4M HCl in dioxan (25mls). After one hour at room temperature the solvent was removed in vacuo. The residue was slurried with acetone and the solid was filtered off to give a white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide hydrochloride (89mg, 0.19mmol, 47%).
$[M+H]^+$ = 428.32
^1H NMR: (d6-DMSO), δ: 3.97 (2H, q, J = 5.72Hz), 4.38 (2H, dq, J = 6.06Hz), 5.08 (2H, s), 5.31 (2H, s), 6.23 (1H, q, J = 6.34Hz), 6.40 (1H, d, J = 5.72Hz), 7.22- 7.32 (6H, m), 7.41-7.44 (2H, m), 7.77 (1 H, d, J = 6.62Hz), 7.91 (1 H, s), 8.27 (1 H, s), 8.39 (3H, s, br), 8.71-8.74 (1 H, m).

REFERENCE EXAMPLE 6

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

[0139]



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

[0140] 4-(Chloromethyl)benzylalcohol (1.0g, 6.38mmol) was dissolved in acetone (50mls) 2-hydroxypyridine (729mg, 7.66mmol) and potassium carbonate (2.65g, 19.20mmol) were added and the reaction mixture was stirred at 50°C for 3 hours after which time the solvent was removed in vacuo and the residue taken up in chloroform (100mls), this solution was washed with water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 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 (1.10g, 5.11, 80%)
$[M+H]^+$ = 238.09 (M+Na)

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

[0141] 1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one (570mg, 2.65mmol) and DBU (806mg, 5.30mmol) were dissolved in DMF (20mls). Diphenylphosphoryl azide (1.09g, 3.97mmol) was added and the reaction mixture was stirred at room temperature for 3 hours after which time the reaction mixture was diluted with EtOAc (100mls), this solution was washed with water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 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%).
$[M+H]^+$ = 360.90 (M+Na).

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

[0142] 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 (71 mg, 0.28mmol) were dissolved in tert-butanol (20mls) and water (5mls). The reaction mixture was stirred at room temperature for 18 hours after which time the reaction mixture was diluted with chloroform (100mls), this solution was washed with water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was triturated with ethyl acetate and pet ether 60-80 to give a

white solid identified as 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-[1,2,3]triazole-4-carboxylic acid ethyl ester (110mg, 0.33mmol, 23%).
$[M+H]^+$ = 486.18

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

[0143] 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(50mls) and water (5mls), lithium hydroxide (39mg, 1.62mmol) was added. The reaction mixture was stirred at 50°C for 18 hours after which time the solvent was concentrated in vacuo and the residue taken up in EtOAc (50mls), the aqueous layer was separated, acidified with 1 M HCl to pH2 and extracted $CHCl_3$ (3x50mls) the combined extracts were washed with water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 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]-1 H-[1,2,3]triazole-4-carboxylic acid (80mg, 0.26mmol, 79%).

E. {4-[({1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carbonyl}-amino)-methyl]-benzyl}-carbamic acid tert-butyl ester

[0144] 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylicacid (80mg, 0.26mmol) was dissolved in CH_2Cl_2(50mls) and DMF(2.5mls). This solution was cooled to 0°C. tert-Butyl 4-(aminomethyl)benzylcarbamate (73mg, 0.31mmol) was added followed by HOBt (38mg, 0.28mmol) and triethylamine (78mg, 0.77mmol). Water soluble carbodiimide (59mg, 0.31mmol) was then added. After 18 hours at 0°C to room temperature reaction mixture was diluted with chloroform (400mls) washed with 0.3M $KHSO_4$ (1x30mls), $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo giving a yellow oil. The residue was purified by flash chromatography (silica), eluant 6%MeOH, 94% $CHCl_3$, fractions combined and evaporated in vacuo to give a white solid identified as {4-[({1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carbonyl}-amino)-methyl]-benzyl}-carbamic acid tert-butyl ester (85mg, 0.166mmol, 62%).
$[M+H]^+$ = 550.45

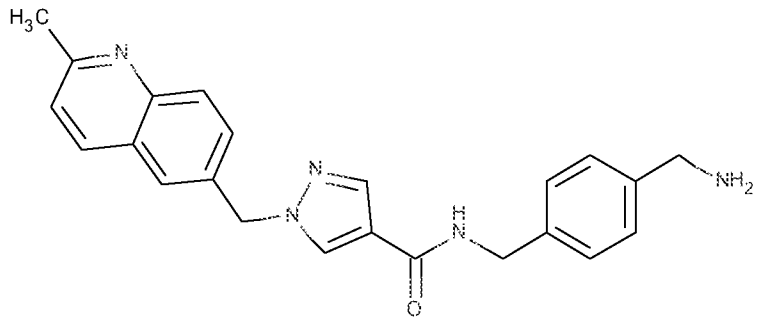
F. 1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-benzylamide Hydrochloride

[0145] {4-[({1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carbonyl}-amino)-methyl]-benzyl}-carbamic acid tert-butyl ester (85mg, 0.16mmol) was dissolved in 4M HCl in dioxan (25mls). After one hour at room temperature the solvent was removed in vacuo. The residue was slurried with acetone and the solid was filtered off to give a white solid identified 1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1 H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-benzylamide hydrochloride (76mg, 0.18mmol, 60%).
$[M+H]^+$ = 429.10
^1H NMR: (d6-DMSO), δ: 4.00 (2H, q, J = 5.72Hz), 4.43 (2H, q, J = 6.25Hz), 5.08 (2H, s), 5.31 (2H, s), 6.23 (1 H, q, J = 6.52Hz), 6.40 (1 H, d, J = 8.92Hz), 7.27- 7.48 (7H, m), 7.77 (1 H, q, J = 8.82Hz), 7.91 (1 H, s), 8.21 (3H, s, br), 8.64 (1 H, s), 9.12 (1 H, t, J = 5.83Hz).

REFERENCE EXAMPLE 7

1-(2-Methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide

[0146]



A. (4-{[(1H-Pyrazole-4-carbonyl)-amino]-methyl}-benzyl)-carbamic acid tert-butyl ester

[0147] 4-Pyrazolecarboxylic acid (400mg, 3.57mmol) was dissolved in CH_2Cl_2 (50mls) and DMF(2.5mls). This solution was cooled to 0°C. tert-Butyl 4-(aminomethyl)benzylcarbamate (1.01g, 4.28mmol) was added followed by HOBt (530mg, 3.93mmol) and triethylamine (1.08g, 10.71mmol). Water soluble carbodiimide (821 mg, 4.28mmol) was then added. After 18 hours at 0°C to room temperature reaction mixture was diluted with chloroform (400mls) washed with 0.3M $KHSO_4$ (1x30mls), $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo giving a yellow oil. The residue was purified by flash chromatography (silica), eluant 7%MeOH, 93% $CHCl_3$, fractions combined and evaporated in vacuo to give a white solid identified as (4-{[(1H-pyrazole-4-carbonyl)-amino]-methyl}-benzyl)-carbamic acid tert-butyl ester (1.10g, 3.33mmol, 93%).
$[M+H]^+$ = 352.95 (M+Na)

B. (2-Methyl-quinolin-6-yl)-methanol

[0148] 2-Methyl-quinoline-6-carboxylic acid (1.0g, 5.34mmol) was dissolved in THF (100mls), this solution was cooled to -20°C, to this solution was added triethylamine (1.62g, 16.03mmol) and isobutyl chloroformate (875mg, 6.41mmol). The reaction mixture was stirred at -20°C for 20mins and then poured into a solution of sodium borohydride (1.0g, 26.71mmol) in water (10mls) at 0°C. The reaction mixture was stirred at 0°C to room temperature for 18 hours and diluted with EtOAc (200mls) 0.3M $KHSO_4$ (1x50mls), water (1x50mls), brine (1x50mls), dried (Na_2SO_4) and evaporated in vacuo to give a white solid. The solid were triturated with EtOAc/Pet Ether 60-80°Cto give a white solid identified as (2-methyl-quinolin-6-yl)-methanol (890mg, 5.14mmol, 96%).
$[M+H]^+$ = 174.24

C. 6-Bromomethyl-2-methyl-quinoline

[0149] (2-Methyl-quinolin-6-yl)-methanol (150mg, 0.87mmol) was dissolved in dichloromethane (50mls). To this solution was added phosphorous tribromide (215mg, 2.13mmol) The reaction mixture was stirred at room temperature for 18 hours and diluted with $CHCl_3$ (100mls) the filtrate was washed with sat. $NaHCO_3$ (1x30mls), water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo to give a white solid which was identified as 6-bromomethyl-2-methyl-quinoline (180mg, 0.76mmol, 88%).
$[M+H]^+$ = 235.96

D. [4-({[1-(2-Methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester

[0150] 6-Bromomethyl-2-methyl-quinoline (180mg, 0.76mmol) was dissolved in DMF (10mls). (4-{(1H-Pyrazole-4-carbonyl)-amino]-methyl}-benzyl)-carbamic acid tert-butyl ester (302mg, 0.915mmol) and cesium carbonate (745mg, 2.29mmol) were added and the reaction mixture was stirred at 50°C for 18 hours after which time the reaction mixture was diluted with EtOAc (1 00mls), this solution was washed with water (1x30mls), brine (1x30mls), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluant 3%MeOH, 97% $CHCl_3$, fractions combined and evaporated in vacuo to give a white foamy solid identified as [4-({[1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester (145mg, 0.30mmol, 39%).
$[M+H]^+$ = 486.18

E. 1-(2-Methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide Hydrochloride

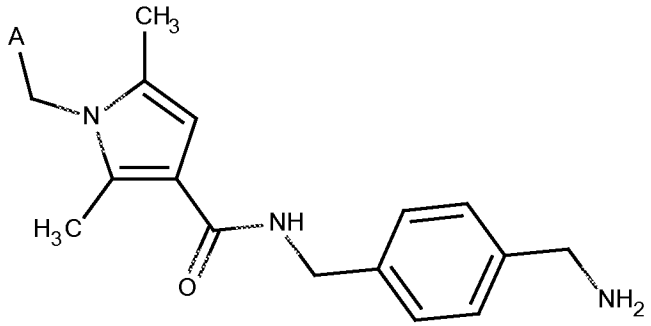
[0151] [4-({[1-(2-Methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester (145mg, 0.30mmol) was dissolved in 4M HCl in dioxan (25mls). After one hour at room temperature the solvent was removed in vacuo. The residue was slurried with acetone and the solid was filtered off to give a white solid identified as 1-(2-methyl-quinolin-6-ylmethyl)-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide hydrochloride (76mg, 0.18mmol, 60%).

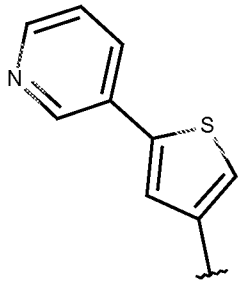
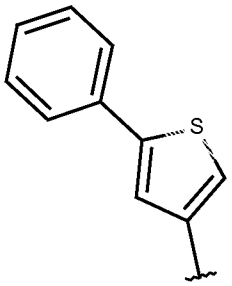
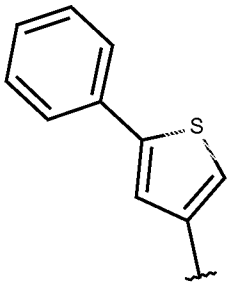
$[M+H]^+ = 385.94$

^1H NMR: (d6-DMSO), δ: 2.97 (3H, s), 3.98 (2H, q, J = 5.53Hz), 4.40 (2H, d, J = 6.00Hz), 5.66 (2H, s), 7.32 (2H, d, J = 8.02Hz), 7.42 (2H, d, J = 8.30Hz), 7.94-7.99 (1H, m), 8.00 (1H, s), 8.10 (1 H, s), 8.37-8.43 (5H, m), 8.82 (1 H, t, J = 6.09Hz), 9.00 (1 H, d, J = 8.60Hz).

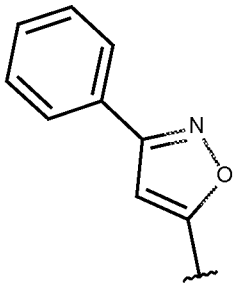
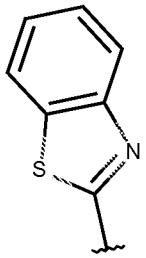
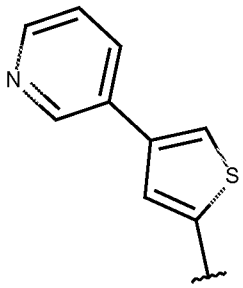
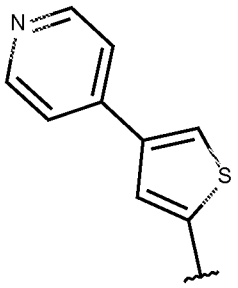
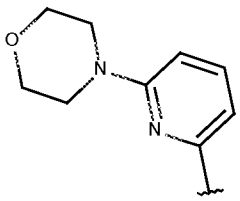
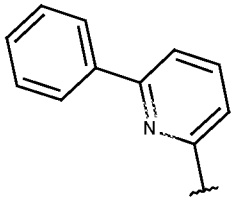
[0152] The compounds in the following tables were synthesised as described for Examples 1 to 4 and reference examples 5-7.

Table 1



Example No	A	Free Base MW	$[M+H]^+$
8		430.6	431.29
9		429.6	430.1
10		429.6	430.16

(continued)

Example No	A	Free Base MW	$[M+H]^+$
11		414.5	437.2 (M+Na)
12		404.5	405.19
13		430.6	431.17
14		430.6	431.36
15		433.5	434.24
16		424.5	425.35

(continued)

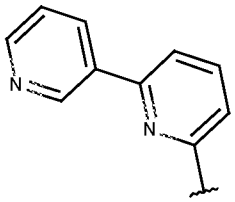
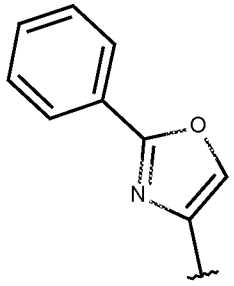
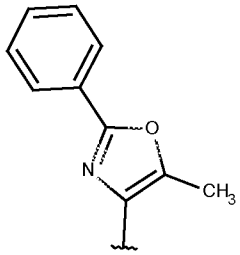
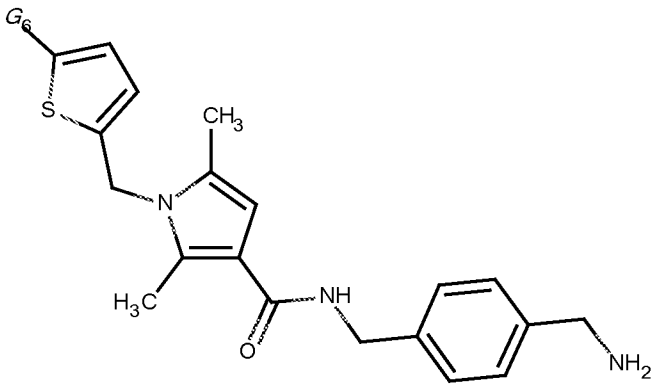
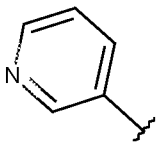
Example No	A	Free Base MW	$[M+H]^+$
17		425.5	426.23
18		414.5	415.24
19		428.5	429.42

Table 2



Example No	G6	Free Base MW	$[M+H]^+$
20	H	353.5	353.87
21		430.6	431.16

(continued)

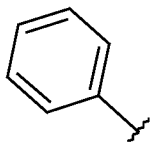
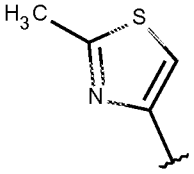
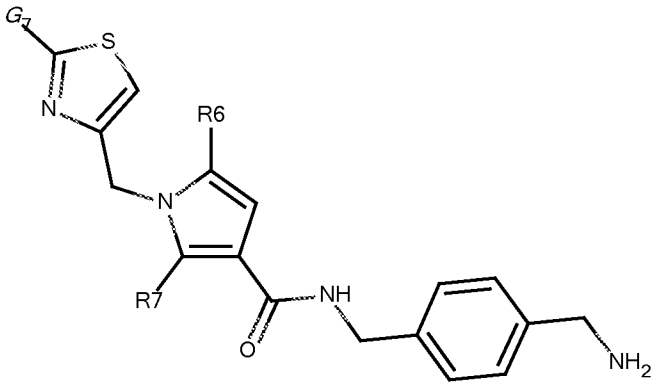
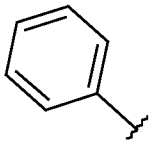
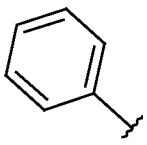
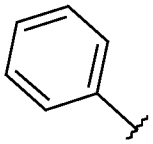
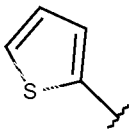
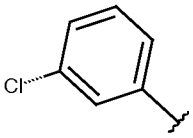
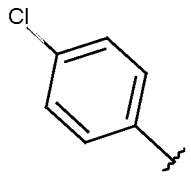
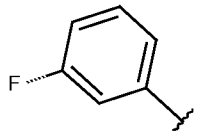
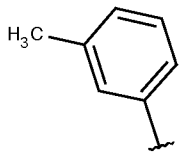
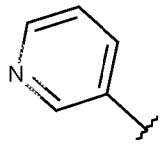
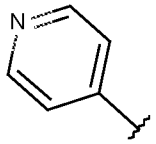
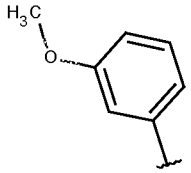
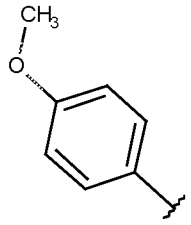
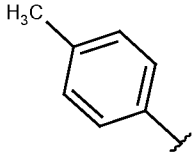
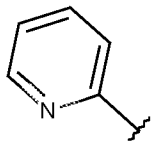
Example No	G6	Free Base MW	$[M+H]^+$
22		429.6	430.15
23		450.6	451.16

Table 3



Example No	G7	R6	R7	Free Base MW	$[M+H]^+$
24			CH_3	492.6	493.19
25		CH_3	H	416.5	416.83
26		CH_3	CH_3	436.6	437.14
27		CH_3	CH_3	465.0	465.13

(continued)

Example No	G7	R6	R7	Free Base MW	$[M+H]^+$
28		CH_3	CH_3	465.0	465.14
29		CH_3	CH_3	448.6	449.16
30		CH_3	CH_3	444.6	445.32
31		CH_3	CH_3	431.6	454.18 (M+Na)
32		CH_3	CH_3	431.6	432.38
33		CH_3	CH_3	460.6	461.36
34		CH_3	CH_3	460.6	461.37
35		CH_3	CH_3	444.6	445.37
36		CH_3	CH_3	431.6	432.39

(continued)

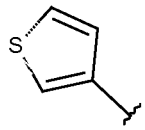
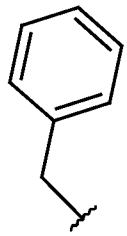
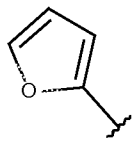
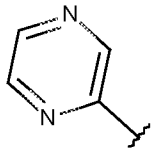
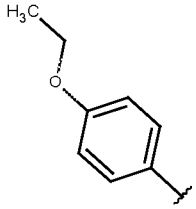
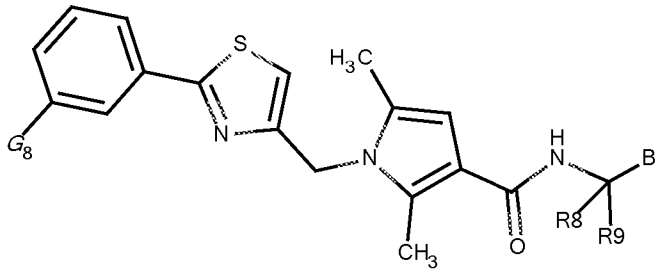
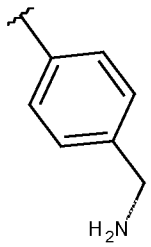
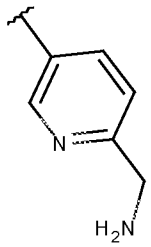
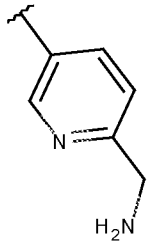
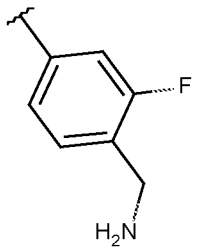
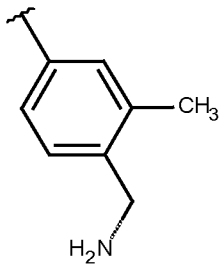
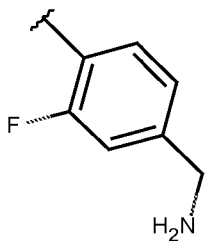
Example No	G7	R6	R7	Free Base MW	$[M+H]^+$
37		CH_3	CH_3	436.6	437.32
38		CH_3	CH_3	444.6	445.36
39		CH_3	CH_3	420.5	421.19
40		CH_3	CH_3	432.5	433.21
41		CH_3	CH_3	474.6	475.26

Table 4



(continued)

Example No	B	R8	R9	G8	Free Base MW	$[M+H]^+$
42		(*R*)-CH_3	H	H	444.6	445.15
43		H	H	H	431.6	432.22
44		H	H	F	449.5	450.18
45		H	H	H	448.6	449.14
46		H	H	H	444.6	445.18
47		H	H	H	448.6	449.07

(continued)

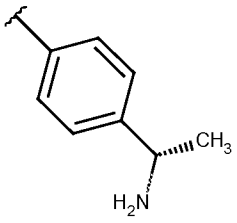
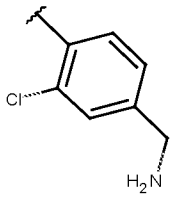
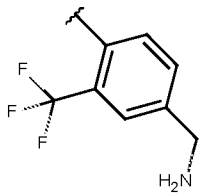
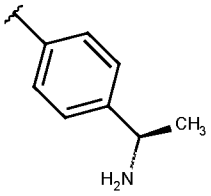
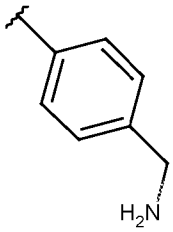
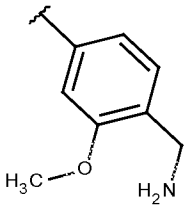
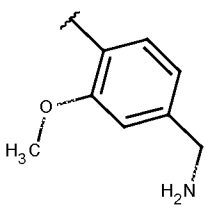
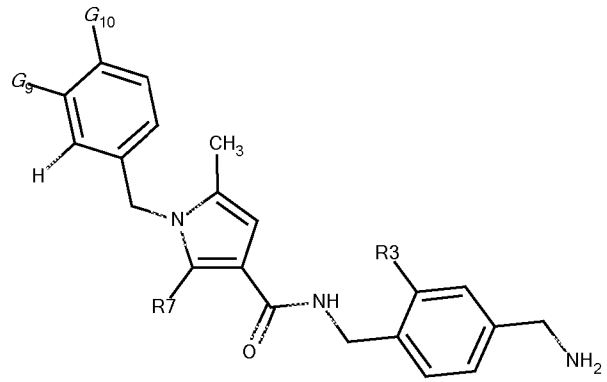
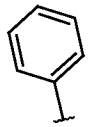
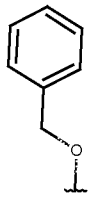
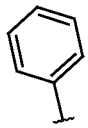
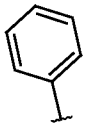
Example No	B	R8	R9	G8	Free Base MW	$[M+H]^+$
48		H	H	H	444.593	467.15 (M+Na)
49		H	H	H	465.01	465.00
50		H	H	H	498.564	499.04
51		H	H	H	444.593	467.03 (M+Na)
52		-CH_2-CH_2- (so as to form spiro-cyclopropyl)		H	456.604	
53		H	H	H	460.592	483.21 (M+Na)
54		H	H	H	460.592	483.29 (M+Na)

Table 5



Example No	G9	G10	R3	R7	Free Base MW	$[M+H]^+$
55	H	H	H	H	347.5	348.24
56	H	H	Cl	H	381.9	382.15
57	H	H	H		409.5	410.24
58	CH_3CH_2O	H	H	CH_3	391.5	392.21
59	H	CH_3CH_2O	H	CH_3	391.5	392.21
60	H		H	CH_3	453.6	454.2
61	H	CH_3O	H	CH_3	377.5	378.71
62	H_2NCO	H	H	CH_3	390.5	391.15
63	H	H_2NCO	H	CH_3	390.5	391.13
64	NC	H	H	CH_3	372.5	373.14
65	H	NC	H	CH_3	372.5	373.13
66	H_2NCH_2	H	H	CH_3	376.5	377.18
67	H	H_2NCH_2	H	CH_3	376.5	377.19
68	H	$H_3CCONHCH_2$	H	CH_3	418.5	419.16
69		H	H	CH_3	423.5	424.28
70	H		H	CH_3	423.5	424.33

(continued)

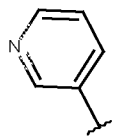
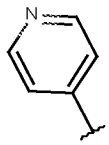
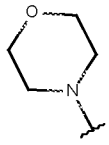
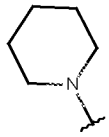
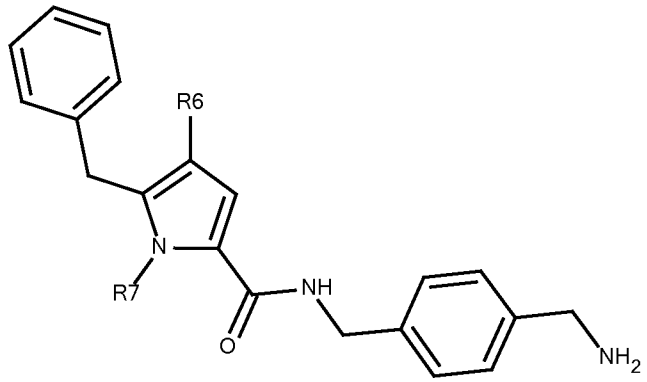
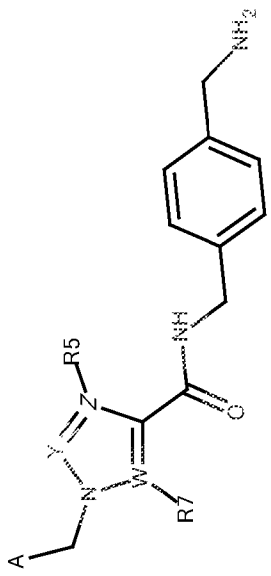
Example No	G9	G10	R3	R7	Free Base MW	$[M+H]^+$
71		H	H	CH_3	424.5	425.41
72		H	H	CH_3	424.5	425.36
73		H	H	CH_3	432.6	433.24
74		H	H	CH_3	430.6	431.28

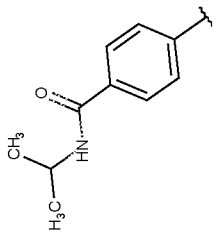
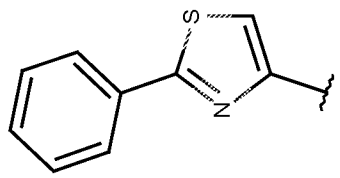
Table 6



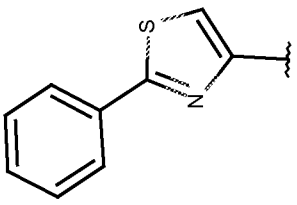
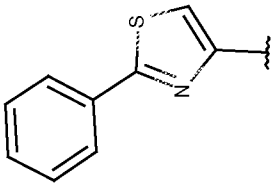
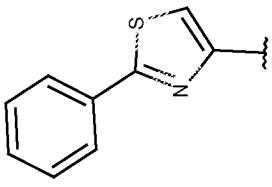
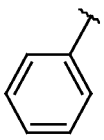
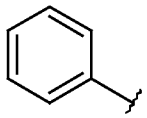
Example No	R7	R6	Free Base MW	$[M+H]^+$
75	CH_3	CH_3	347.5	348.2
76	H	CH_3	333.4	334.17
77	$CH_3CH_2CH_2$	CH_3	361.5	362.19
78	CH_3CH_2	CH_3	375.5	376.21

Table 7

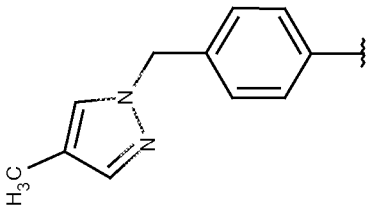
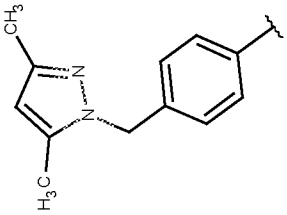
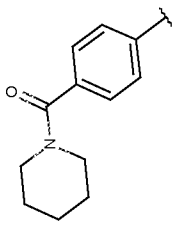


Example No	A	R7	R5	W	Z	Y	Free Base MW	$[M+H]^+$
79		H	H	C	C	N	405.5	
80		CH_3	H	C	C	N	417.5	418.16

(continued)

Example No	A	R7	R5	W	Z	Y	Free Base MW	$[M+H]^+$
81		H	CH_3	C	C	N	417.5	418.14
82		CF_3	H	C	C	N	471.5	494.06 (M+Na)
83		H	CF_3	C	C	N	471.5	494.04 (M+Na)
84		H		C	C	N	396.5	397.21

(continued)

Example No	A	R7	R5	W	Z	Y	Free Base MW	[M+H]+
85		H	H	C	C	N	414.5	437.32 (M+Na)
86		H	H	C	C	N	428.5	429.31
87		H	H	C	C	N	431.53	432.24

(continued)

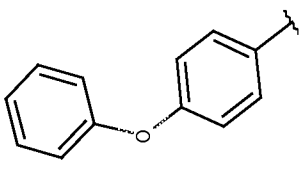
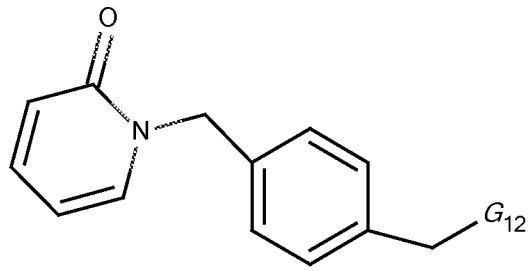
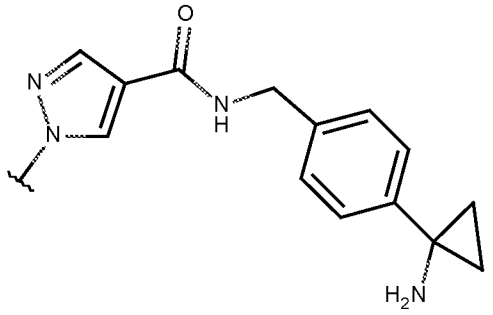
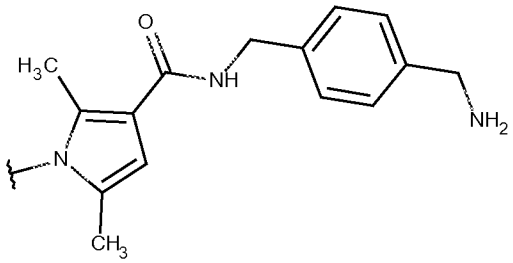
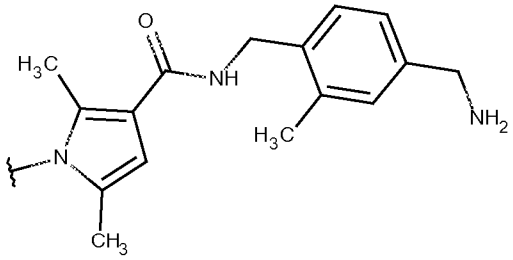
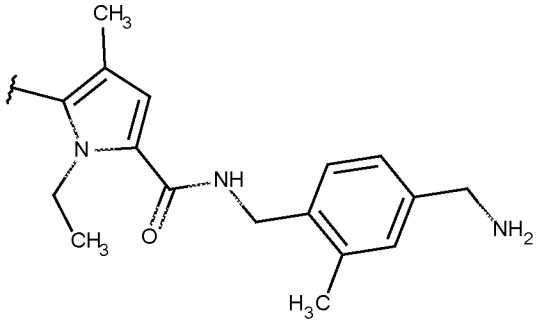
Example No	A	R7	R5	W	Z	Y	Free Base MW	$[M+H]^+$
88		absent	absent	N	N	CH	413.48	455.06 (M+MeCN)

Table 8



Example No	G12	Free Base MW	$[M+H]^+$
89		453.5	454.3
90		454.6	455.3
91		468.6	469.3
92		482.6	483.2

(continued)

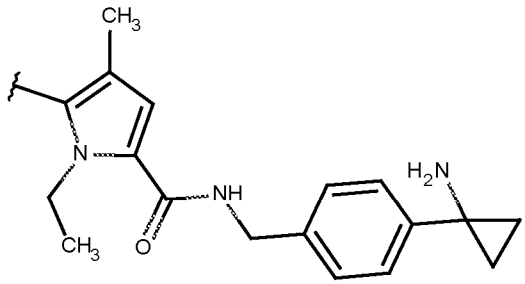
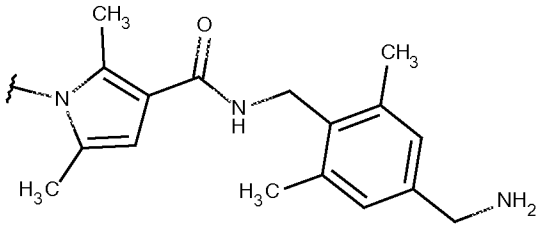
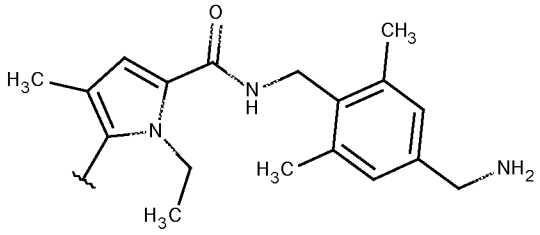
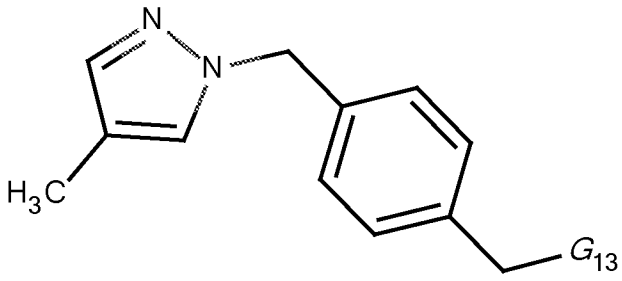
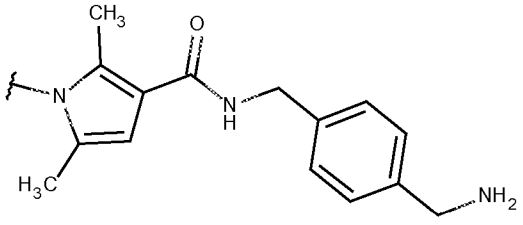
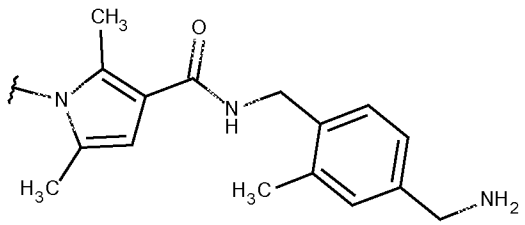
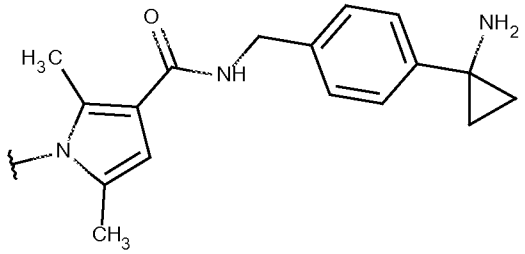
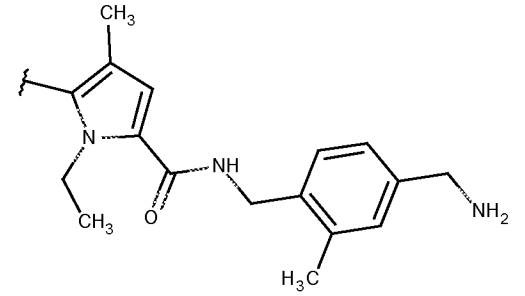
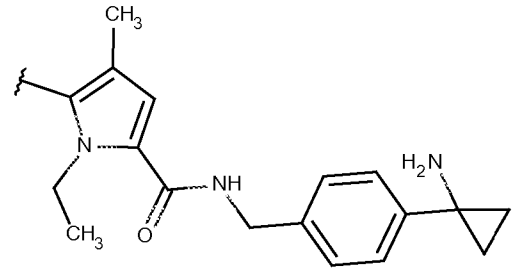
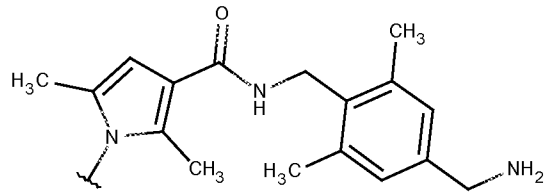
Example No	G12	Free Base MW	$[M+H]^+$
93		494.6	495.2
94		482.6	483.3
95		496.6	497.4

Table 9

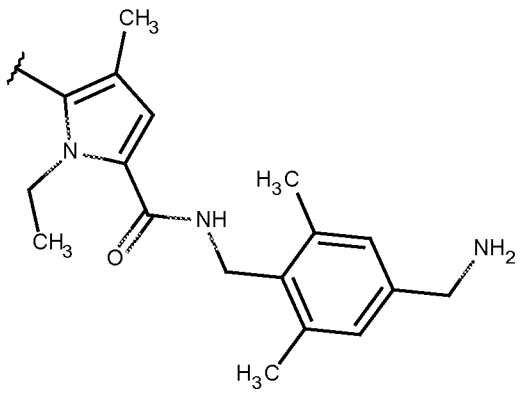
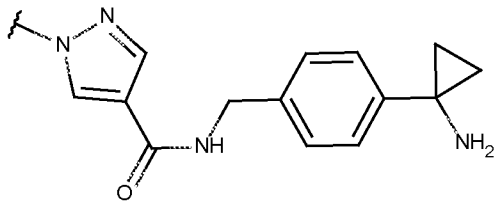
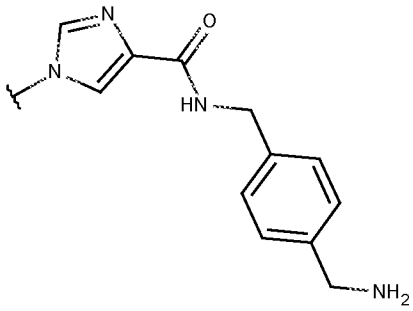
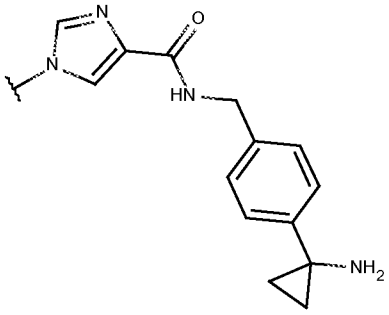
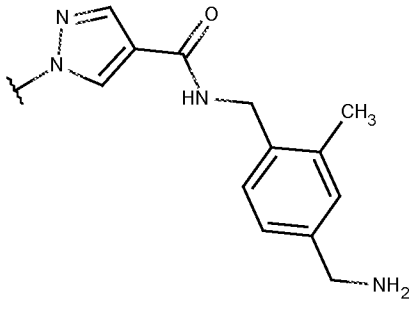


Example No	G13	Free Base MW	$[M+H]^+$
96		441.6	442.3

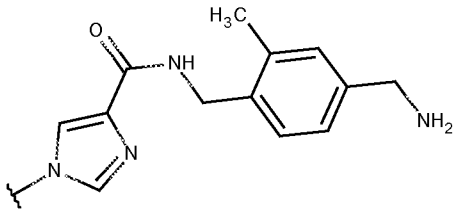
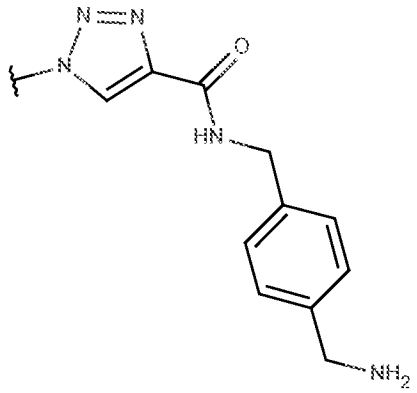
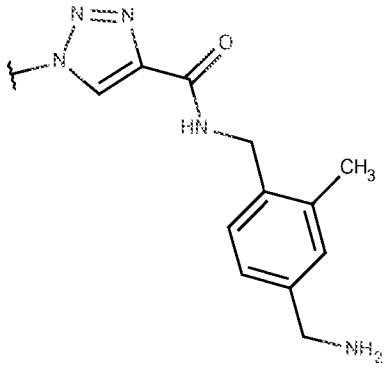
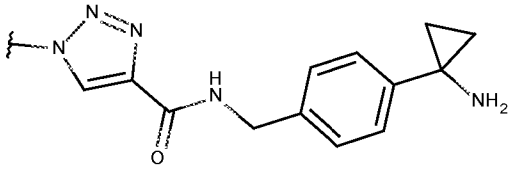
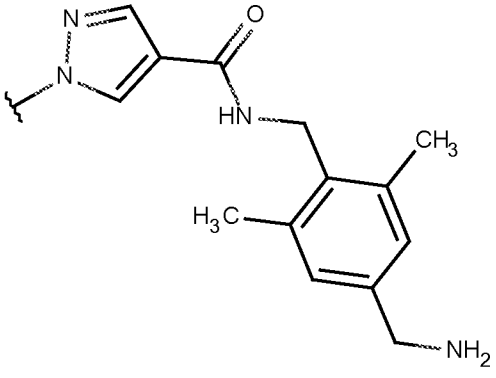
(continued)

Example No	G13	Free Base MW	$[M+H]^+$
97		455.6	456.3
98		467.6	468.3
99		469.6	470.2
100		481.6	482.3
101		469.6	470.3

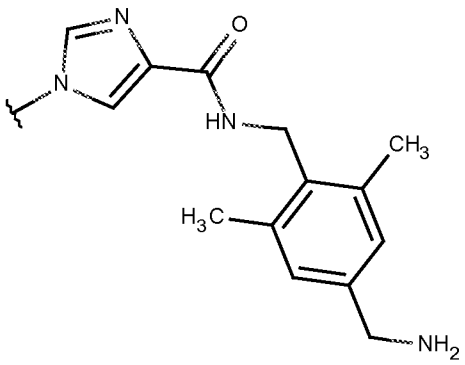
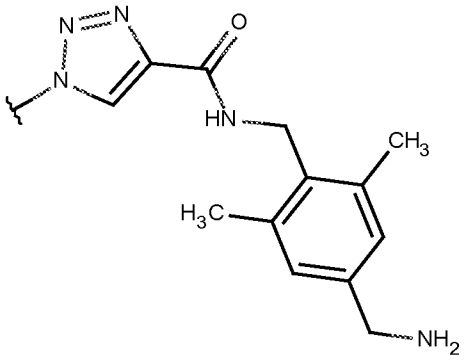
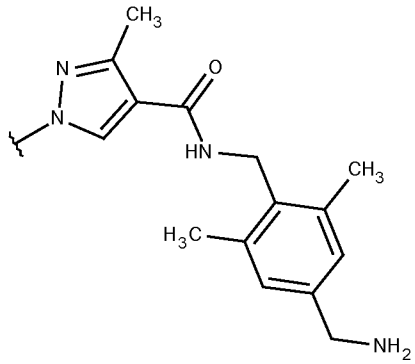
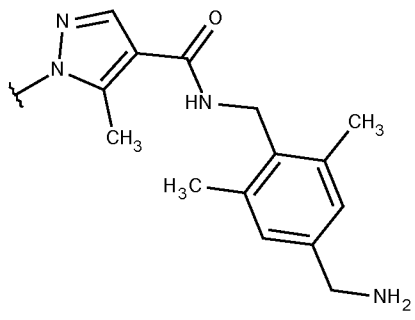
(continued)

Example No	G13	Free Base MW	$[M+H]^+$
102		483.7	484.3
103		440.54	441.2
104		414.50	415.3
105		440.54	441.3
106		428.53	429.3

(continued)

Example No	G13	Free Base MW	$[M+H]^+$
107		428.53	429.3
108		415.49	416.3
109		429.52	430.3
110		441.53	442.2
111		442.56	443.3

(continued)

Example No	G13	Free Base MW	$[M+H]^+$
112		442.56	443.3
113		443.54	444.3
114		456.58	457.05
115		456.58	457.05

(continued)

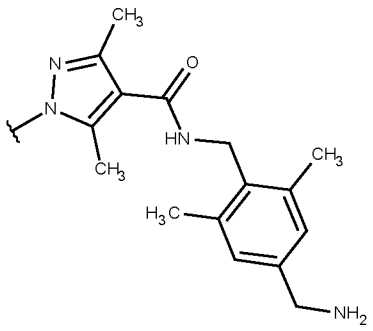
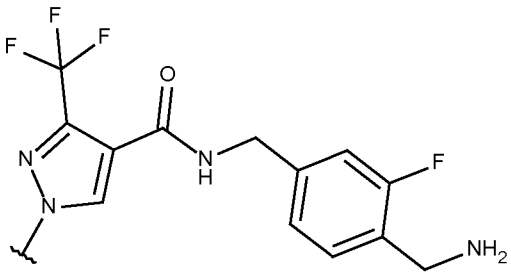
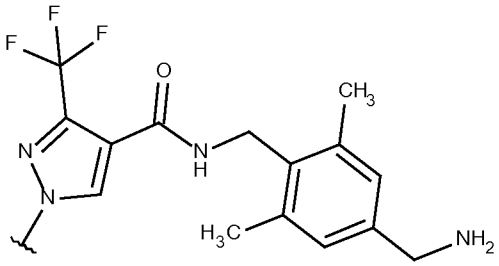
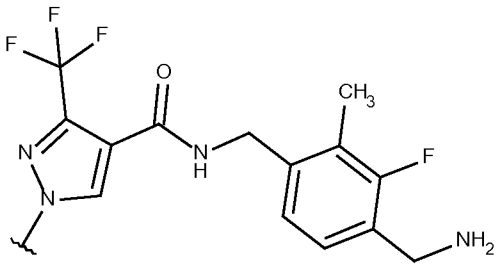
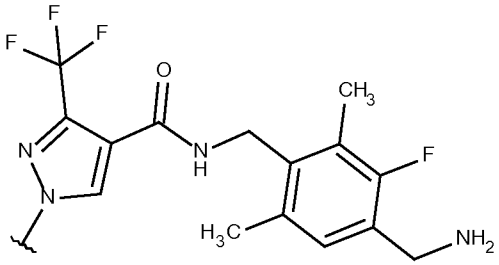
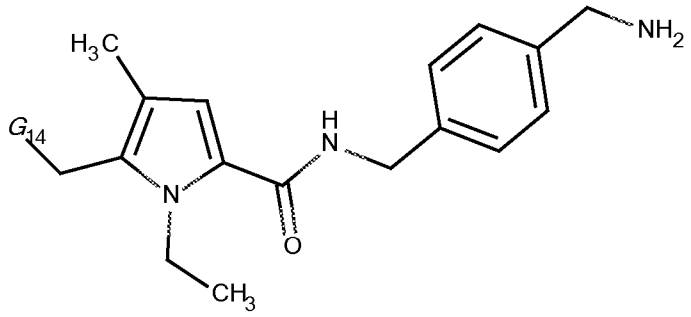
Example No	G13	Free Base MW	$[M+H]^+$
116		470.61	471.07
117		500.49	500.96
118		510.55	511.00
119		514.52	514.98
120		528.54	528.90

Table 10



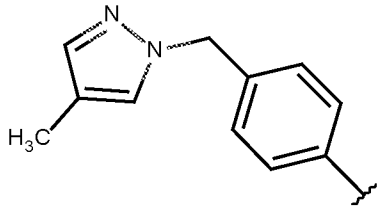
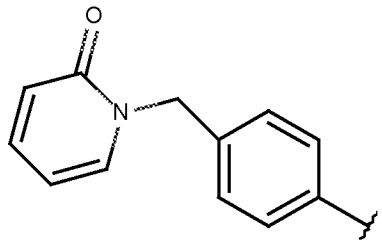
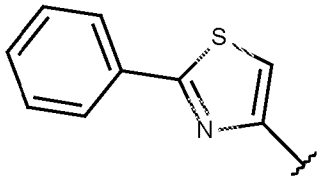
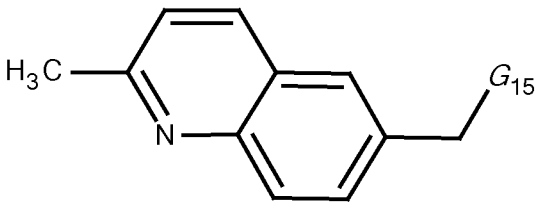
Example No	G14	Free Base MW	$[M+H]^+$
121		455.6	456.2
122		468.6	469.2
123		444.6	445

Table 11



(continued)

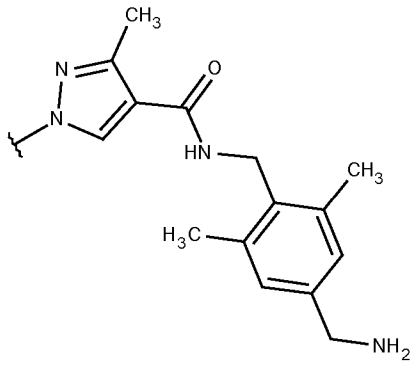
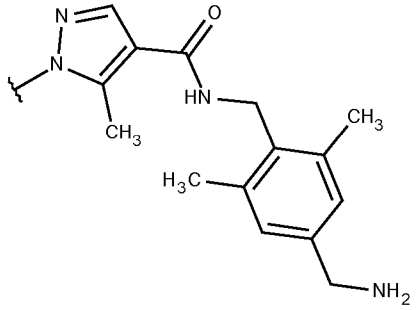
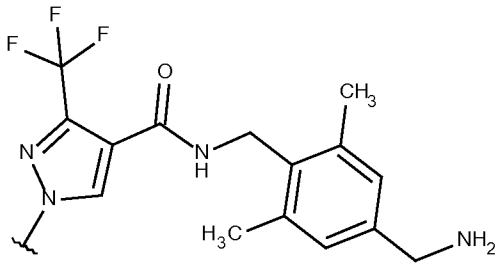
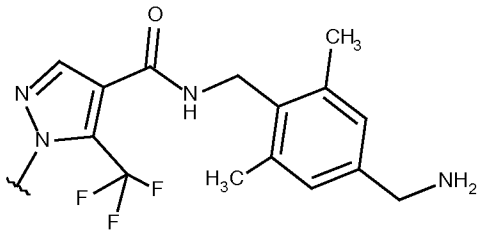
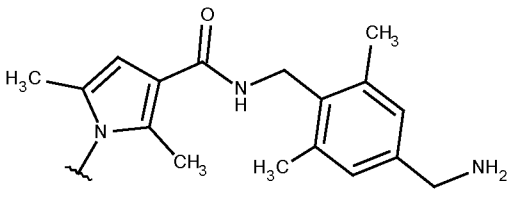
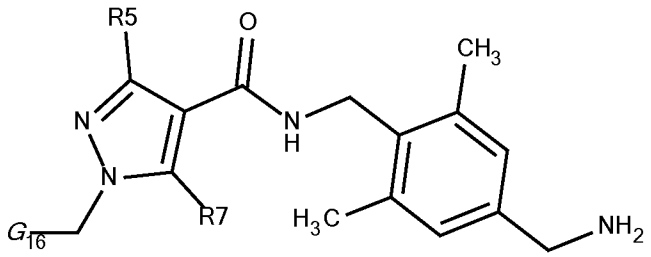
Example No	G15	Free Base MW	$[M+H]^+$
124		427.55	428.00
125		427.55	428.01
126		481.53	481.88
127		481.53	481.89
128		440.58	441.07

Table 12



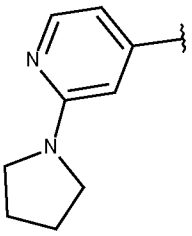
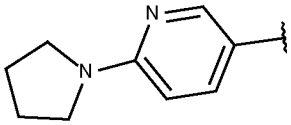
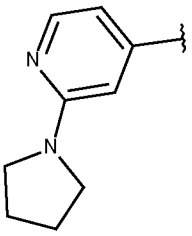
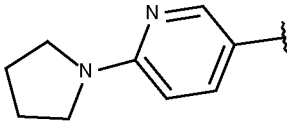
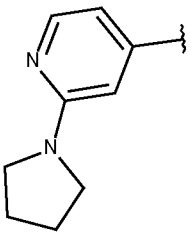
Example No	G16	R5	R7	Free Base MW	[M+H]+
129		CF_3	H	486.54	487.03
130		CF_3	H	486.54	
131		H	CH_3	432.57	432.99
132		CH_3	H	432.57	
133		CH_3	H	432.57	432.99

Table 13

Example No	Name
8	2,5-Dimethyl-1-(5-pyridin-3-yl-thiophen-3-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
9	2,5-Dimethyl-1-(4-phenyl-thiophen-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide

(continued)

Example No	Name
10	2,5-Dimethyl-1-(5-phenyl-thiophen-3-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
11	2,5-Dimethyl-1-(3-phenyl-isoxazol-5-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
12	1-Benzothiazol-2-ylmethyl-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
13	2,5-Dimethyl-1-(4-pyridin-3-yl-thiophen-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
14	2,5-Dimethyl-1-(4-pyridin-4-yl-thiophen-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
15	2,5-Dimethyl-1-(6-morpholin-4-yl-pyridin-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
16	2,5-Dimethyl-1-(6-phenyl-pyridin-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
17	1-[2,3']Bipyridinyl-6-ylmethyl-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
18	2,5-Methyl-1-(2-phenyl-oxazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
19	2,5-Dimethyl-1-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
20	2,5-Dimethyl-1-thiophen-2-ylmethyl-1H-pyrrole-3-carboxylic acid 4-amidomethyl-benzylamide
21	2,5-Dimethyl-1-(5-pyridin-4-yl-thiophen-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
22	2,5-Dimethyl-1-(5-phenyl-thiophen-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
23	2,5-Dimethyl-1-[5-(2-methyl-thiazol-4-yl)-thiophen-2-ylmethyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
24	5-Methyl-2-phenyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
25	2-Methyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
26	2,5-Dimethyl-1-[2-(2-thienyl)-thiazol-4-ylmethyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
27	2,5-Dimethyl-1-[2-(3-chlorophenyl)-thiazol-4-ylmethyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
28	2,5-Dimethyl-1-[2-(4-chlorophenyl)-thiazol-4-ylmethyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
29	1-[2-(3-Fluoro-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
30	2,5-Dimethyl-1-(2-m-tolyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
31	2,5-Dimethyl-1-(2-pyridin-3-yl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide

(continued)

Example No	Name
32	2,5-Dimethyl-1-(2-pyridin-4-yl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
33	2,5-Dimethyl-1-(3-methoxyphenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
34	2,5-Dimethyl-1-(4-methoxyphenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
35	2,5-Dimethyl-1-(2-p-tolyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
36	2,5-Dimethyl-1-(2-pyridin-2-yl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
37	2,5-Dimethyl-1-(2-thiophen-3-yl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
38	1-(2-Benzyl-thiazol-4-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
39	2,5-Dimethyl-1-(2-furan-3-yl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
40	2,5-Dimethyl-1-(2-pyrazin-2-yl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
41	1-[2-(4-Ethoxy-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
42	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid [(R)-1-(4-aminomethyl-phenyl)-ethyl]-amide
43	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (6-aminomethyl-pyridin-3-ylmethyl)-amide
44	1-[2-(3-Fluoro-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid (6-aminomethyl-pyridin-3-ylmethyl)-amide
45	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-3-fluoro-benzylamide
46	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-3-methyl-benzylamide
47	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-fluoro-benzylamide
48	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-((R)-1-amino-ethyl)-benzylamide
49	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-chloro-benzylamide
50	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-trifluoromethyl-benzylamide
51	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid-4-((S)-1-amino-ethyl)-benzylamide
52	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid [1-(4-aminomethyl-phenyl)-cyclopropyl]-amide
53	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-3-methoxy-benzylamide

(continued)

Example No	Name
54	2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methoxy-benzylamide
55	1-Benzyl-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
56	1-Benzyl-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-chloro-benzylamide
57	1-Benzyl-5-methyl-2-phenyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
58	1-(3-Ethoxy-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
59	1-(4-Ethoxy-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
60	1-(4-Benzyloxy-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
61	1-(4-Methoxy-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
62	1-(3-Carbamoyl-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
63	1-(4-Carbamoyl-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
64	1-(3-Cyano-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
65	1-(4-Cyano-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
66	1-(3-Aminomethyl-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
67	1-(4-Aminomethyl-benzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
68	1-[4-(Acetylamino-methyl)-benzyl]-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
69	1-Biphenyl-3-ylmethyl-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
70	1-Biphenyl-4-ylmethyl-2,5-dimethyl-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
71	2,5-Dimethyl-1-(3-pyridin-3-yl-benzyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
72	2,5-Dimethyl-1-(3-pyridin-4-yl-benzyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
73	2,5-Dimethyl-1-(3-morpholin-4-yl-benzyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
74	2,5-Dimethyl-1-(3-piperidin-1-yl-benzyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
75	5-Benzyl-1,4-dimethyl-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide
76	5-Benzyl-4-methyl-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide
77	5-Benzyl-1-ethyl-4-methyl-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide
78	5-Benzyl-4-methyl-1-propyl-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide
79	1-(4-Isopropylcarbamoyl-benzyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
80	5-Methyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
81	3-Methyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
82	1-(2-Phenyl-thiazol-4-ylmethyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
83	1-(2-Phenyl-thiazol-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
84	1-Benzyl-3-phenyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide

(continued)

Example No	Name
85	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
86	1-[4-(3,5-Dimethyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
87	1-[4-(Piperidine-1-carbonyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide
88	1-(4-Phenoxy-benzyl)-1H-[1,2,4]triazole-3-carboxylic acid 4-aminomethyl-benzylamide
89	1-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide
90	2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
91	2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide
92	1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2-methyl-benzylamide
93	1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide
94	2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
95	1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
96	2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide
97	2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide
98	2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide
99	1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2-methyl-benzylamide
100	1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide
101	2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
102	1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
103	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide
104	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid 4-aminomethyl-benzylamide
105	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide
106	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide
107	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide

(continued)

Example No	Name
108	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-benzylamide
109	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide
110	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide
111	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
112	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-imidazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
113	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
114	3-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
115	5-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
116	3,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
117	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-3-fluoro-benzylamide
118	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
119	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-3-fluoro-2-methyl-benzylamide
120	1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-3-fluoro-2,6-dimethyl-benzylamide
121	1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide
122	1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide
123	1-Ethyl-4-methyl-5-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide
124	3-Methyl-1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
125	5-Methyl-1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
126	1-(2-Methyl-quinolin-6-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
127	1-(2-Methyl-quinolin-6-ylmethyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
128	2,5-Dimethyl-1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
129	1-(2-Pyrrolidin-1-yl-pyridin-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide

(continued)

Example No	Name
130	1-(6-Pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
131	5-Methyl-1-(2-pyrrolidin-1-yl-pyridin-4-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
132	3-Methyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide
133	3-Methyl-1-(2-pyrrolidin-1-yl-pyridin-4-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide

Table 14

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
8	d6-DMSO	2.16(3H,s), 2.46(3H,s), 3.20-3.38 (2H, s, br), 3.66(2H,s), 4.32(2H,d,J= 6.0Hz), 5.03(2H,s), 6.30(1H,s), 7.00(1 H,d,J= 0.8Hz), 7.15-7.25(4H,m), 7.38(1H,d,J= 1.3Hz), 7.40-7.43(1H,m), 7.98-8.01 (1H,m), 8.04(1H,t,J= 6.1 Hz), 8.49(1H,dd,J= 4.8,1.5Hz), 8.84(1H,d,J= 2.4Hz).
9	CD_3OD	2.24 (3H, s), 2.54 (3H, s), 3.77 (2H, s), 4.48 (2H, s), 5.27 (2H, s), 6.23 (1H, d, J= 0.7 Hz), 7.13 (1H, d, J= 1.2 Hz), 7.24-7.37 (7H, m), 7.48 (1H, d, J= 1.5 Hz), 7.57 (2H, d, J= 1.2 Hz).
10	CD_3OD	2.19 (3H, s), 2.48 (3H, s), 3.80 (2H, s), 4.48 (2H, s), 5.07 (2H, s), 6.24 (1H, d, J= 0.7 Hz), 6.70 (1H, d, J= 0.9 Hz), 7.11 (1H, d, J= 1.2 Hz), 7.25-7.37 (7H, m), 7.56 (2H, d, J= 7.5 Hz).
11	CD_3OD	2.28 (3H, s), 2.55 (3H, s), 4.08 (2H, s), 4.50 (2H, d, J= 4.9 Hz), 5.29 (2H, s), 6.24 (1H, d, J= 0.6 Hz), 6.57 (1H, s), 7.39 (2H, d, J= 8.7 Hz), 7.42 (2H, d, J= 8.9 Hz), 7.44-7.50 (3H, m), 7.77-7.80 (2H, m).
12	CD_3OD	2.23 (3H, s), 2.52 (3H, s), 3.78 (2H, s), 4.48 (2H, s), 5.50 (2H, s), 6.29 (1H, d, J= 0.7 Hz), 7.29 (2H, d, J= 8.4 Hz), 7.32 (2H, d, J= 8.5 Hz), 7.41 (1H, ddd, J= 8.0, 8.0, 1.0 Hz), 7.51 (1H, ddd, J= 8.2, 8.2, 1.0 Hz), 7.92 (1H, d, J= 8.0 Hz), 7.96 (1H, d, J= 8.2 Hz).
13	d6-DMSO	2.48-2.50 (6H, m) 3.89 (2H, s) 4.34 (2H, d, J = 8.0 Hz) 5.26 (2H, d, J = 8.0 Hz) 6.29 (1H, s) 7.17-7.43 (8H, m) 7.91 (1H, d, J = 4.0 Hz) 8.48 (1H, dd, J = 8.0, 4.0 Hz) 8.90 (1H, s)
14	CD_3OD	2.16 (3H, s) 2.43 (3H, s) 3.72 (2H, s) 4.36 (2H, s) 5.21 (2H, s) 6.19 (1H, s) 7.16-7.33 (5H, m) 7.48-7.59 (2H, m) 7.76-7.79 (1H, m) 8.39-8.44 (2H, m)
15	d6-DMSO	2.12 (3H, s), 2.40 (3H, s), 2.62-2.85 (2H, s, br), 3.21-3.37 (2H, br), 3.41 (4H, t, J=5.0Hz), 3.65-3.69 (4H, m), 4.32 (2H, d, J=6.0Hz), 4.93 (2H, s), 5.99 (1H, d, J=7.3Hz), 6.29 (1H, d, J=0.6Hz), 6.70 (1H, d, J=8.5Hz), 7.20 (2H, d, J=8.0Hz), 7.25 (2H, d, J=8.0Hz), 7.48 (1H, dd, J=7.5, 8.5Hz), 8.02 (1H, t, J=6.0Hz)
16	d6-DMSO	2.17 (3H, s), 2.46 (3H, s), 3.28-3.48 (2H, s, br), 3.73 (2H, s), 4.33 (2H, d, J=6.0Hz), 5.21 (2H, d), 6.34 (1H, d, J=0.5Hz), 6.67-6.72 (1H, m), 7.23 (2H, d, J=8.1Hz), 7.27 (2H, d, J=9.2Hz), 7.41-7.52 (3H, m), 7.82-7.89 (2H, m), 8.06-8.08 (2H, m), 8.14 (1H, t, J=6.0Hz)
17	d6-DMSO	2.17 (3H, s), 2.46 (3H, s), 3.28-3.45 (2H,s, br), 3.68 (2H, s), 4.33 (2H, d, J=6.1 Hz), 5.24 (2H, s), 6.34 (1H, d, J=0.6Hz), 6.79 (1H, d, J=7.5Hz), 7.21 (2H, d, J=8.1 Hz), 7.25 (2H, d, J=8.1Hz), 7.51-7.54 (1H, m), 7.89 (1H, t, J=7.7Hz), 7.97 (1H, d, J=7.5Hz), 8.11 (1H, t, J=6.1Hz), 8.39 (1H, dt, J=1.9, 7.9Hz), 8.64 (1H, dd, J=1.6, 5.0Hz), 9.23-9.26 (1H, m)
18	CD_3OD	2.26 (3H, s), 2.56 (3H, s), 3.73 (2H, s), 4.41 (2H, s), 4.91 (2H, s), 6.20 (1H, s), 7.24-7.30 (4H, m), 7.42-7.45 (3H, m), 7.51 (1H, s), 7.93-7.97 (2H, m).

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
19	d6-DMSO	2.25 (3H, s), 2.26 (3H, s), 2.55 (3H, s), 3.97 (2H, dt, J = 11.4, 5.6 Hz), 4.33 (2H, d, J = 5.9 Hz), 4.94 (2H, s), 6.26 (1H, s), 7.30 (2H, d, J = 8.1 Hz), 7.39 (2H, d, J = 8.1 Hz), 7.48-7.51 (3H, m), 7.86-7.89 (2H, m), 8.11 (1H, t, J = 6.0 Hz), 8.20-8.45 (2H, s, br)
20	CD_3OD	7.52-7.42 (4H, m), 7.36 (1H, dd, J= 5.0, 1.0Hz), 7.00 (1H, dd, J= 5.0, 3.0Hz), 6.85 (1H, dd, J= 3.0, 1.0Hz), 6.27 (1H, s), 5.31 (2H, d, J= 0.6 Hz), 4.57 (2H, s), 4.14 (2H, s), 2.55 (3H, s), 2.28 (3H, s).
21	CD_3OD	2.22 (3H, s), 2.52 (3H, s), 3.76 (2H, s), 4.46 (2H, s), 5.23 (2H, s), 6.24 (1H, d, J= 0.7 Hz), 6.80 (1H, d, J= 3.7 Hz), 7.24-7.31 (5H, m), 7.36-7.40 (1H, m), 7.92 (1H, dd, J= 8.0, 1.6 Hz), 8.38 (1H, dd, J= 5.0, 1.5 Hz), 8.68 (1H, dd, J= 1.6, 0.7 Hz).
22	CD_3OD	2.23 (3H, s), 2.52 (3H, s), 3.78 (2H, s), 4.47 (2H, s), 5.20 (2H, s), 6.22 (1H, s), 6.73 (1H, d, J= 3.6 Hz), 7.18 (1H, d, J= 3.8 Hz), 7.21-7.36 (7H, m), 7.57 (2H, d, J= 7.3 Hz).
23	CD_3OD	2.23 (3H, s), 2.52 (3H, s), 2.66 (3H, s), 3.94 (2H, s), 4.48 (2H, s), 5.22 (2H, s), 6.23 (1H, d, J= 0.8 Hz), 6.75 (1H, d, J= 3.8 Hz), 7.27 (1H, d, J= 3.6 Hz), 7.33 (2H, d, J= 8.6 Hz), 7.36 (2H, d, J= 8.6 Hz), 7.40 (1H, s).
24	CD_3OD	2.28 (3H, s), 3.80 (2H, s), 4.32 (2H, s), 5.03 (2H, d, J = 0.7 Hz), 6.41 (1H, d, J = 0.7 Hz), 6.69 (1H, s), 7.08 (2H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.1 Hz), 7.32-7.36 (5H, m), 7.41-7.43 (3H, m), 7.84-7.86 (2H, m).
25	d6-DMSO	2.53(3H,s), 3.28(2H,br s), 3.66(2H,s), 4.33(2H,d,J= 6.1Hz), 5.21(2H,s), 6.53(1H,d,J= 3.1Hz), 6.79(1H,d,J= 3.1 Hz), 7.15-7.24(4H,m), 7.30(1 H,s), 7.47-7.51 (3H,m), 7.88-7.93(2H,m), 8.13(1 H,t,J= 6.1Hz).
26	CD_3OD	2.25 (3H, s), 2.52 (3H, s), 4.06 (2H, s), 4.50 (2H, s), 5.16 (2H, d, J= 0.7 Hz), 6.24 (1H, s), 6.73 (1H, s), 7.11 (1H, d, J= 5.0, 3.6 Hz), 7.38 (2H, d, J= 8.6 Hz), 7.41 (2H, d, J= 8.6 Hz), 7.55 (1H, dd, J= 5.0, 1.0 Hz), 7.41 (1H, dd, J= 3.5, 1.0 Hz).
27	CD_3OD	2.27 (3H, s), 2.54 (3H, s), 4.05 (2H, s), 4.50 (2H, s), 5.22 (2H, d, J= 0.7 Hz), 6.24 (1H, d, J= 0.7 Hz), 6.84 (1H, s), 7.38 (2H, d, J= 8.5 Hz), 7.41 (2H, d, J= 8.5 Hz), 7.45-7.47 (2H, m), 7.82-7.85 (1H, m), 7.95 (1H, dd, J= 2.2, 1.4 Hz).
28	CD_3OD	2.25 (3H, s), 2.54 (3H, s), 3.79 (2H, s), 4.47 (2H, s), 5.20 (2H, s), 6.23 (1H, d, J= 0.7 Hz), 6.88 (1H, s), 7.28 (2H, d, J= 8.4 Hz), 7.41 (2H, d, J= 8.4 Hz), 7.47 (2H, d, J= 8.6 Hz), 7.91 (2H, d, J= 8.6 Hz).
29	d6-DMSO	2.24(3H,s), 2.53(3H,s), 3.10-3.43 (2H, s, br), 3.66(2H,s), 4.31(2H,d,J= 6.0Hz), 5.16(2H,s), 6.28(1H,s), 7.15-7.24(4H,m), 7.30(1H,s), 7.33-7.35(1H,m), 7.52-7.57(1H,m), 7.66-7.69(1 H,m), 7.73-7.75(1H,m), 8.02(1 H,t,J= 6.1Hz).
30	d6-DMSO	2.24(3H,s), 2.37(3H,s), 2.54(3H,s), 2.80-3.38 (2H, br s), 3.66(2H,s), 4.32(2H,d,J= 6.0Hz), 5.15(2H,s), 6.29(1H,s), 7.15-7.24(5H,m), 7.29(1H,d,J= 7.6Hz), 7.37(1H,t,J= 7.6Hz), 7.69(2H,d,J= 9.2Hz), 8.03(1H,t,J= 6.1Hz).
31	d6-DMSO	2.26 (3H, s), 2.54 (3H, s), 2.80 (2H, s), 4.33 (2H, d, J = 6.0 Hz), 5.19 (2H, s), 5.20-5.55 (2H, s, br), 6.29 (1H, s), 7.24 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.36 (1H, s), 7.54 (1H, ddd, J = 8.0, 4.9, 0.6 Hz), 8.08 (1H, t, J = 6.1 Hz), 8.26 (1H, dt, J = 8.2, 1.8 Hz), 8.67 (1H, dd, J = 4.8, 1.6 Hz), 9.09 (1H, d, J = 1.8 Hz).
32	CD_3OD	2.25 (3H, s), 2.55 (3H, s), 3.77 (2H, s), 4.47 (2H, s), 5.21 (2H, s), 6.24 (1H, s), 7.09 (1H, s), 7.26-7.32 (4H, m), 7.87 (2H, dd, J = 4.8, 1.4 Hz), 8.60 (2H, dd, J = 4.7, 1.5 Hz).
33	CD_3OD	2.25 (3H, s), 2.54 (3H, s), 3.20-3.45 (2H, br s), 3.66 (2H, s), 3.82 (3H, s), 4.32 (2H, d, J = 6.1 Hz), 5.16 (2H, s), 6.29 (1H, s), 7.05-7.08 (1H, m), 7.18-7.25 (5H, m), 7.38-7.48 (3H, m), 8.04 (1H, t, J = 6.1 Hz).

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
34	d6-DMSO	2.25 (3H, s), 2.54 (3H, s), 3.20-3.40 (2H, br s), 3.71 (2H, s), 3.81 (3H, s), 4.32 (2H, d, J = 6.0 Hz), 5.13 (2H, s), 6.28 (1H, s), 7.05 (2H, dt, J = 8.9, 2.9 Hz), 7.14 (1H, s), 7.20 (2H, d, J = 8.2 Hz), 7.25 (2H, d, J = 8.1 Hz), 7.84 (2H, dt, J = 8.9, 2.9 Hz), 8.04 (1H, t, J = 6.1 Hz).
35	d6-DMSO	2.08(2H,br s), 2.24(3H,s), 2.34(3H,s), 2.54(3H,s), 3.65(2H,s), 4.31(2H,d,J= 6.1Hz), 5.14(2H,s), 6.28(1 H,s), 7.17-7.24(5H,m), 7.30(2H,d,J= 8.1 Hz), 7.78(2H,d,J= 8.1 Hz), 8.02(1 H,t,J= 6.0Hz).
36	CD_3OD	2.24 (3H, s), 2.55 (3H, s), 3.78 (2H, s), 4.47 (2H, s), 5.18 (2H, s), 6.23 (1H, d, J = 0.7 Hz), 6.95 (1H, s), 7.27 (2H, d, J = 8.2 Hz), 7.31 (2H, d, J = 8.2 Hz), 7.37-7.40 (1H, m), 7.86 (1 H, dt, J = 7.8, 6.1 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.51-8.53 (1H, m).
37	CD_3OD	2.26 (3H, s), 2.56 (3H, s), 3.88 (2H, s), 4.52 (2H, s), 5.21 (2H, s), 6.28 (1H, s), 6.73 (1H, s), 7.34 (2H, d, J = 8.3 Hz), 7.37 (2H, d, J = 8.3 Hz), 7.54-7.59 (2H, m), 7.99 (1H, dd, J = 2.8, 1.4 Hz).
38	d6-DMSO	2.18 (3H, s), 2.48 (3H, s), 3.22-3.36 (2H, br s), 3.68 (2H, s), 4.28 (2H, s), 4.31 (2H, d, J=6.1 Hz), 5.10 (2H, s), 6.25 (1H, d, J=0.6Hz), 6.98 (1H, s), 7.18-7.28 (5H, m), 7.31-7.35 (4H, m), 8.02 (1H, t, J=6.1 Hz)
39	d6-DMSO	2.22 (3H, s), 2.51 (3H, s), 3.78 (2H, s), 4.33 (2H, d, J = 6.0 Hz), 4.72-5.10 (2H, br s), 5.12 (2H, s), 6.29 (1 H, s), 6.89 (1H, dd, J = 1.1, 0.9 Hz), 7.05 (1H, s), 7.24 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.82 (1H, dd, J = 1.8, 1.6 Hz), 8.07 (1H, t, J = 6.1 Hz), 8.36 (1H, dd, J = 1.2, 1.0 Hz).
40	d6-DMSO	2.26 (3H, s), 2.54 (3H, s), 3.96 (2H, s), 4.35 (2H, d, J = 6.1 Hz), 5.22 (2H, s), 6.32 (1H, s), 7.30 (2H, d, J = 8.1 Hz), 7.41 (2H, d, J = 8.1 Hz), 7.46 (1H, s), 7.46-7.70 (2H, br s), 8.17 (1H, t, J = 6.1 Hz), 8.71 (1H, d, J = 1.8 Hz), 8.74 (1H, dd, J = 14.3, 1.5 Hz), 9.24(1H, d, J = 1.4 Hz).
41	d6-DMSO	1.34 (3H, t, J=7.0Hz), 2.25 (3H, s), 2.54 (3H, s), 3.26-3.46 (2H, br), 3.69 (2H, s), 4.08 (2H, q, J=7.0Hz), 4.32 (2H, d, J=6.0Hz), 5.12 (2H, s), 6.28 (1H, s), 7.02 (2H, d, J=8.8Hz), 7.15 (1H, s), 7.20 (2H, d, J=7.9Hz), 7.24 (2H, d, J=7.9Hz), 7.82 (2H, d, J=8.8Hz), 8.03 (1H, t, J=6.0Hz)
42	d6-DMSO	1.38 (3H, d, J = 7.0 Hz), 2.26 (3H, s), 2.33 (3H, t, J = 2.0 Hz), 2.67 (1H, t, J = 1.7 Hz), 3.28 (2H, d, J = 10.5 Hz), 3.37 (1H, s), 3.65 (2H, s), 5.15 (2H, s), 6.39 (1 H, s), 7.22 - 7.28 (5H, m), 7.49 (2H, d, J = 1.8 Hz), 7.50 (1H, d, J = 2.6 Hz), 7.88 (1H, d, J = 1.7 Hz), 7.90 (1H, d, J = 3.0 Hz)
43	d6-DMSO	2.25(3H,s), 2.53(3H,s), 3.32(2H, s, br), 3.82(2H,s), 4.33(2H,d,J= 6.0Hz), 5.15(2H,s), 6.26(1H,s), 7.25(1H,s), 7.35(1H,d,J= 8.0Hz), 7.47-7.52(3H,m), 7.63(1H,dd,J= 8.0,2.1Hz), 7.88-7.92(2H,m), 8.12 (1H,t,J= 6.1Hz), 8.41(1H,s).
44	d6-DMSO	2.10(2H,br s), 2.24(3H,s), 2.53(3H,s), 3.74(2H,s), 4.37(2H,d,J= 6.4Hz), 5.16(2H,s), 6.26(1H,s), 7.30(1H,s), 7.34(2H,d,J= 7.7Hz), 7.52-7.57(1H,m), 7.62(1H,dd,J= 8.0,2.2Hz), 7.65-7.75(2H,m), 8.10(1H,t,J= 6.0Hz), 8.38(1H,d,J= 1.8Hz).
45	CD_3OD	2.23(3H, s), 2.54(3H, s), 3.81(2H, s), 4.46(2H, s), 5.17(2H, s), 6.25(1H, d, J=0.8 Hz), 6.79(1H, s), 7.06(1H, dd, J= 11.1, 1.2 Hz), 7.12(1H, dd, J= 7.9, 1.3 Hz), 7.32(1H, t, J=7.8 Hz), 7.42-7.45(3H, m), 7.89-7.91(2H, m).
46	d6-DMSO	2.27(3H,s), 2.31(3H,s), 2.55(3H,s), 3.99(2H,q,J= 5.7Hz), 4.31(2H,d,J= 6.0Hz), 5.16(2H,s), 6.28(1H,s), 7.14-7.15(2H,m), 7.26-7.29(2H,m), 7.49-7.53(3H,m), 7.89-7.91(2H,m), 8.03(2H, s, s, br), 8.09(1H,t,J= 6.0Hz).
47	d6-DMSO	2.27(3H,s), 2.54(3H,s) 3.33(2H,S), 3.89(2H,s), 4.37(2H,d,J= 5.9Hz), 5.17(2H,s), 6.31(1H,s), 7.17(1H,d,J= 7.9Hz), 7.23-7.32(3H,m), 7.49-7.52(3H,s), 7.88-7.91(2H,m), 8.09(1H,t,J= 5.6Hz).

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
48	d6-DMSO	1.46 (3H, d, J = 6.8 Hz), 2.27 (3H, s, br), 2.32-2.33 (2H, m), 2.66-2.68 (1H, m), 4.35 (3H, d, J = 6.1 Hz), 5.16 (2H, s), 6.28 (1H, s), 7.29 (1H, s), 7.32 (2H, d, J = 8.1 Hz), 7.37 (2H, d, J = 8.1 Hz), 7.50 (3H, dd, J = 5.2 Hz, 1.9 Hz), 7.89 - 7.91 (2H,. m), 8.12 (3H, s, s, br)
49	d6-DMSO	2.28(3H,s), 2.55(3H,s), 2.77(2H,br s), 3.69(2H,s), 4.38(2H,d,J= 6.0Hz), 5.18(2H,s), 6.34(1H,d,J= 0.6Hz), 7.21(2H,s), 7.30(1H,s), 7.41(1H,s), 7.49-7.55(3H,m),7.90-7.92(2H,m), 8.07(1H,t,J= 6.0Hz).
50	d6-DMSO	2.29(3H,s), 2.56(3H,s), 3.07(2H,br s), 3.78(2H,s), 4.51(2H,d,J= 5.6Hz), 5.18(2H,s), 6.35(1H,s), 7.32(1H,s), 7.39(1H,d,J= 8.0Hz), 7.49-7.55(4H,m), 7.69(1H,s), 7.90-7.92(2H,m), 8.13(1H,t,J= 5.8Hz).
51	d6-DMSO	1.46 (3H, d, J = 6.8 Hz), 2.27 (3H, br.s), 2.32-2.33 (1H, m), 2.59-2.60 (1H, m), 2.66-2.68 (1H, m), 4.35 (3H, d, J = 6.1 Hz), 5.17 (2H, s), 6.28 (1H, s), 7.29 (1H, s), 7.32 (2H, d, J = 8.3 Hz), 7.38 (2H, d, J = 8.3 Hz), 7.50 (3H, dd, J = 5.1 Hz, 1.9 Hz), 7.89 - 7.92 (2H,. m), 8.12 (3H, s, br)
52	d6-DMSO	0.85 (2H, t, J = 7.2 Hz), 1.66-1.81 (2H, m), 2.26 (3H, s), 3.28 (1H, d, J = 11.0 Hz), 3.65 (2H, s), 4.79 (1H, q, J = 8.8 Hz), 5.14 (2H, s), 6.40 (1H, s), 7.21 - 7.27 (5H, m), 7.48 (2H, d, J = 1.8 Hz), 7.50 (1H, d, J = 2.3 Hz), 7.66 (1H, d, J = 8.4 Hz), 7.88 (1H, d, J = 1.6 Hz), 7.90 (1H, d, J = 2.8 Hz) (3H, s, obscured by DMSO)
53	d6-DMSO	2.26 (3H, s), 2.55 (3H, s), 3.75 - 3.80 (2H, s, brs), 3.78 (3H, s), 4.33 - 4.35 (2H, d, J = 6.0Hz), 5.16 (2H, s), 6.29 (1H, s), 6.83 - 6.85 (1H, d, J = 7.6Hz), 6.95 (1H, s), 7.22 - 7.24 (1H, d, J = 7.7Hz), 7.28 (1H, s), 7.48 - 7.52 (3H, m), 7.89 - 7.91 (2H, m), 8.06 - 8.09 (1H, t, J = 6.0Hz)
54	d6-DMSO	2.27 (3H, s), 2.54 (3H, s), 3.68 (2H, s, br), 3.81 (3H, s), 4.29 - 4.30 (2H, d, J = 5.9Hz), 5.17 (2H, s), 6.32 (1H, s), 6.80 - 6.82 (1H, d, J =7.6Hz), 6.96 (1H, s), 7.04 - 7.06 (1H, d, J= 7.6Hz), 7.27 (1H, s), 7.48 - 7.52 (3H, m), 7.78 - 7.85 (1H, m), 7.89 - 7.92 (2H, m)
55	CD_3OD	2.18 (3H, s), 2.46 (3H, s), 4.14 (2H, s), 4.57 (2H, s), 5.18 (2H, s), 6.31 (1H, s), 6.96 (2H, d, J=7.5Hz), 7.29-7.31 (1H, m), 7.34-7.39 (2H, m), 7.44-7.50 (4H, m).
56	CD_3OD	2.20 (3H, s), 2.46 (3H, s), 4.15 (2H,s), 4.65 (2H,d, J=5.5Hz), 5.19 (2H, s), 6.35 (1H, d, J=0.6Hz), 6.97 (2H, d, J=7.2 Hz), 7.28-7.42 (4H, m), 7.51 (1H, d, J=8.0 Hz), 7.58 (1H, d, J=1.6Hz).
57	CD_3OD	2.20 (3H, s), 3.76 (2H, s), 4.22 (2H, s), 4.84 (2H, s), 6.30 (1H, d, J= 0.7Hz), 6.70 (2H, d, J= 7.1 Hz), 7.00 (2H, d, J= 8.0Hz), 7.04-7.26 (10H, m).
58	d6-DMSO	1.29 (3H, t, J=7.0 Hz), 2.07 (3H, s), 2.36 (3H, s), 3.46-3.89 (2H, br s), 3.74 (2H, s), 3.95 (2H, q, J=7.0 Hz), 4.34 (2H, d, J=6.0 Hz), 5.04 (2H, s), 6.33 (1H, s), 6.37 (1H, s), 6.44 (1H, d, J=7.6 Hz), 6.80 (1H, dd, J=8.1, 2.3 Hz), 7.17-7.29 (5H, m), 8.12 (1H, t, J=6.1 Hz).
59	d6-DMSO	1.29 (3H, t, J=7.0 Hz), 2.07 (3H, s), 2.37 (3H, s), 3.74 (2H, s), 3.74-4.10 (2H, br s), 3.96 (2H, q, J=7.0 Hz), 4.33 (2H, d, J=6.0 Hz), 4.99 (2H, s), 6.31 (1H, s), 6.81 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.7 Hz), 7.23 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.2 Hz), 8.10 (1H, t, J=6.1 Hz).
60	d6-DMSO	2.08 (3H, s), 3.37 (2H, s), 3.98 (2H, q, J=5.6Hz), 4.35 (2H, d, J=6.1 Hz), 5.00 (2H, s), 5.06 (2H, s), 6.32 (1H, s), 6.83 (2H, d, J=8.6Hz), 6.96 (2H, d, J=8.6Hz), 7.28-7.35 (4H, m), 7.37-7.45 (6H, m), 8.14 (1H, t, J=6.1Hz), 8.27-8.38 (2H, s, br)
61	d6-DMSO	2.08 (3H, s), 2.37 (3H, s), 3.71 (3H, s), 3.99 (2H, q, J=5.7Hz), 4.35 (2H, d, J=6.1Hz), 5.00 (2H, s), 6.31 (1H, s), 6.83 (2H, d, J=8.8Hz), 6.89 (2H, d, J=8.8Hz), 7.31 (2H, d, J=8.1 Hz), 7.40 (2H, d, J=8.1Hz), 8.14 (1H, t, J=6.1Hz), 8.23-8.35 (2H, s, br)

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
62	d6-DMSO	2.08 (3H, s), 2.37 (3H, s), 3.98 (2H, d, J=5.8Hz), 4.36 (2H, d, J=6.0Hz), 5.13 (2H, s), 6.33 (1H, s), 7.32 (2H, d, J=8.2Hz), 7.35-7.42 (5H, m), 7.51 (1H, s), 7.74 (1H, d, J=7.8Hz), 7.97 (1H, s), 8.19 (1H, t, J=6.0Hz), 8.20-8.29 (2H, s, br)
63	d6-DMSO	2.07 (3H, s), 2.36 (3H, s), 3.99 (2H, q, J=5.8Hz), 4.24 (2H, d, J=6.0Hz), 5.14 (2H, s), 6.35 (1H, s), 6.94 (2H, d, J=8.3Hz), 7.32 (3H, d, J=8.1Hz), 7.40 (2H, d, J=8.1 Hz), 7.81 (2H, d, J=8.3Hz), 7.92 (1H, s), 8.17 (1H, t, J=6.0Hz), 8.19-8.27 (2H, s, br)
64	d6-DMSO	2.07 (3H, s), 2.36 (3H, s), 3.99 (2H, q, J=5.6Hz), 4.36 (2H, d, J=6.0Hz), 5.17 (2H, s), 6.36 (1H, s), 7.19 (1H, d, J=7.3Hz), 7.31 (1H, s), 7.32 (2H, d, J=8.0Hz), 7.39 (2H, d, J=8.0Hz), 7.56 (1H, t, J=7.8Hz), 7.74 (1H, d, J=7.7Hz), 8.15-8.28 (3H, m)
65	d6-DMSO	2.05 (3H, s), 2.34 (3H, s), 3.99 (2H, q, J=5.7Hz), 4.336 (2H, d, J=6.0Hz), 5.21 (2H, s), 6.36 (1H, s), 7.04 (2H, d, J=8.2Hz), 7.32 (2H, d, J=8.0Hz), 7.40 (2H, d, J=8.0Hz), 7.81 (2H, d, J=8.2Hz), 8.18 (1H, t, J=6.0Hz), 8.25-8.34 (2H, s, br)
66	d6-DMSO	2.10 (3H, s), 2.39 (3H, s), 3.98 (4H, d, J=5.2Hz), 4.36 (2H, d, J=6.1Hz), 5.09 (2H, s), 6.34 (1H, s), 6.83-6.87 (1H, m), 7.13 (1H, s), 7.31 (2H, d, J=8.1Hz), 7.36 (2H, d, J=3.4Hz), 7.40 (2H, d, J=8.1Hz), 8.17 (1H, t, J=6.1Hz), 8.24-8.38 (4H, s, br)
67	d6-DMSO	2.07 (3H, s), 2.36 (3H, s), 3.70 (4H, s), 4.36 (2H, d, J=6.1Hz), 5.11 (2H, s), 6.35 (1H, s), 6.92 (2H, d, J=8.1Hz), 7.31 (2H, d, J=8.1Hz), 7.40 (2H, d, J=8.1Hz), 7.43 (2H, d, J=8.1Hz), 8.17 (1H, t, J=6.1Hz), 8.23-8.36 (4H, s, br)
68	d6-DMSO	1.84 (3H, s), 2.07 (3H, s), 2.36 (3H, s), 3.98 (2H, dt, J= 5.8, 5.7 Hz), 4.19 (2H, d, J= 5.9 Hz), 4.36 (2H, d, J= 6.0 Hz), 5.06 (2H, s), 6.32 (1H, s), 6.84 (2H, d, J= 8.1Hz), 7.19 (2H, d, J= 8.1Hz), 7.32 (2H, d, J= 8.1Hz), 7.40 (2H, d, J= 8.2 Hz), 8.15 (1H, t, J= 6.1 Hz), 8.25 (2H, s, br), 8.31 (1H, d, J= 6.0 Hz).
69	d6-DMSO	2.10(3H, s), 2.40(3H, s), 2.72(2H, s, br), 3.69(2H, s), 4.33(2H, d, J= 6.1Hz), 5.16(2H, s), 6.34(1H, s), 6.80(1H, d, J= 7.7Hz), 7.20-7.26(5H, m), 7.34-7.47(4H, m), 7.52-7.63(3H, m), 8.08(1H, t, J= 6.1Hz).
70	d6-DMSO	2.10(3H,s), 2.20(2H,s, br), 2.40(3H,s), 3.67(2H,s), 4.33(2H,d,J= 6.0Hz), 5.13(2H,s), 6.34(1H,s), 6.97(2H,d,J= 8.2Hz), 7.20-7.26(4H,m), 7.32-7.39(1H,m), 7.41-7.47(2H,m), 7.52-7.63(4H,m), 8.08(1H,t,J= 6.1Hz).
71	d6-DMSO	2.11 (3H, s), 2.41 (3H,s), 3.20-3.40 (2H, s, br), 3.69 (2H,s), 4.33 (2H,d, J=6.1Hz), 5.18 (2H,s), 6.34 (1H,s), 6.82 (1H, d, J=7.5Hz), 7.21 (2H, d, J=8.1Hz), 7.25 (2H, d, J=8.1Hz), 7.34 (1H, s), 7.45 (1H, t, J=7.5Hz), 7.47-7.50 (1H, m), 7.61 (1H, d, J=7.9Hz), 7.99-8.01 (1H, m), 8.09 (1H, t, J=6.1 Hz), 8.57 (1H, dd, J=1.5, 5.0Hz), 8.81-8.83 (1H, m)
72	d6-DMSO	2.11 (3H, s), 2.41 (3H,s), 3.20-3.40 (2H, br s), 3.68 (2H,s), 4.33 (2H,d, J=6.1 Hz), 5.19 (2H,s), 6.36 (1 H,s), 6.86 (1H, d, J=7.5Hz), 7.23 (2H, d, J=8.1 Hz), 7.25 (2H, d, J=8.1Hz), 7.43 (1H, s), 7.45 (1H, t, J=7.5Hz), 7.62 (2H, dd, J=1.5, 4.5Hz), 7.68 (1H, d, J=7.5Hz), 8.09 (1H, t, J=6.1Hz), 8.63 (2H, dd, J=1.5, 4.5Hz)
73	d6-DMSO	2.08 (3H, s), 2.37 (3H, s), 3.04 (4H, t, J=4.9Hz), 3.23-3.37 (2H, s, br), 3.68 (2H, s), 3.71 (4H, t, J=4.9Hz), 4.33 (2H, d, J=6.1Hz), 5.01 (2H, s), 6.19 (1H, 7.6Hz), 6.31 (1H, s), 6.61 (1H, s), 6.81 (1H, dd, J=2.1, 9.2Hz), 7.12-7.15 (1H, m), 7.20 (2H, d, J=8.2Hz), 7.25 (2H, d, J=8.2Hz), 8.05 (1H, t, J=6.1 Hz)
74	d6-DMSO	1.48-1.54 (2H, m), 1.55-1.59 (4H, m), 2.08 (3H, s), 2.37 (3H, s), 3.05-3.09 (4H, m) 3.25-3.36 (2H, s, br), 3.72 (2H, s), 4.33 (2H, d, J=6.0Hz), 5.00 (2H, s)m 6.16 (1H, d, J=7.5Hz), 6.31 (1H, s), 6.55 (1H, s), 6.78 (1H, dd, J=2.0, 8.2Hz), 7.10 (1H, t, J=7.8Hz), 7.22 (2H, d, J=8.2Hz), 7.26 (2H, d, J=8.2Hz), 8.06 (1 H, t, J=6.0Hz)
75	CD_3OD	2.05 (3H, s), 3.61 (3H, s), 3.91 (2H, s), 3.97 (2H, s), 4.46 (2H, s), 6.65 (1H, s), 7.03 (2H, d, J= 7.2 Hz), 7.15 (1H, d, J= 7.3 Hz), 7.22 (2H, d, J= 7.6 Hz), 7.34 (4H, s).

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
76	d6-DMSO	1.92 (3H, s), 3.19-3.42 (2H, s, br), 3.67 (2H, s), 3.85 (2H, s), 4.36 (2H, d, J= 6.1 Hz), 6.57 (1H, d, J= 2.3 Hz), 7.12-7.30 (9H, m), 8.25 (1H, t, J= 6.0 Hz), 11.10 (1H, s, br).
77	d6-DMSO	0.91 (3H, t, J=7.0Hz), 2.01 (3H, s), 3.69 (2H, s), 3.96 (2H, s), 4.15 (2H, q, J=7.0Hz), 4.33 (2H, d, J=6.1Hz), 6.69 (1H, s), 7.07 (2H, d, J=7.2Hz), 7.14-7.22 (4H, m), 7.25-7.31 (5H, m), 8.36 (1H, t, J=6.1 Hz)
78	d6-DMSO	0.67 (3H, t, J=7.6Hz), 1.24-1.34 (2H, m), 2.01 (3H, s), 3.70 (2H, s), 3.95 (2H, s), 4.09 (2H, t, J=7.6Hz), 4.32 (2H, d, J=6.1Hz), 6.68 (1H, s), 7.07 (2H, d, J=7.2Hz), 7.16-7.22 (4H, m), 7.25-7.31 (5H, m), 8.35 (1H, t, J=6.1Hz)
79	d6-DMSO	1.15 (6H, d, J = 7.6 Hz), 3.68-3.74 (1H, m), 4.00 (2H, s), 4.03-4.13 (1H, m), 4.41 (2H, d, J = 6.0 Hz), 5.40 (2H, s), 7.31-7.41 (6H, m), 7.82 (2H, d, J = 8.2 Hz), 7.93 (1H, s), 8.15 (2H, br.s +*HCl salt*), 8.28 (1H, s), 8.69 (1H, t, J = 6.0 Hz)
80	CD_3OD	2.68 (3H, s), 3.89 (2H, s), 4.50 (2H, s), 5.46 (2H, s), 7.21 (1H, s), 7.33 (2H, d, J = 8.8 Hz), 7.36 (2H, d, J = 8.7 Hz), 7.39-7.46 (3H, m), 7.89-7.92 (3H, m).
81	CD_3OD	2.40 (3H, s), 3.97 (2H, s), 4.48(2H, s), 5.40 (2H, s), 7.36 (4H, s), 7.41-7.46 (4H, m), 7.89-7.93 (2H, m), 8.16 (1H, s).
82	d6-DMSO	3.98 (2H, q, J = 5.7 Hz), 4.39 (2H, d, J = 6.0 Hz), 5.61 (2H, s), 7.33 (2H, d, J = 8.1 Hz), 7.41 (2H, d, J = 8.0 Hz), 7.49-7.53 (3H, m), 7.76 (1H, s), 7.91-7.94 (2H, m), 8.15-8.40 (2H, s, br), 8.55 (2H, s), 8.94 (1H, t, J = 5.8 Hz)
83	d6-DMSO	3.98 (2H, q, J = 5.64 Hz), 4.39 (2H, d, J = 5.96), 5.61 (2H, s), 7.32 (2H, d, J = 8.16), 7.42 (2H, d, J = 8.16 Hz), 7.50 (3H, m), 7.76 (1H, s), 7.93 (2H, d.d, J = 2.44, 7.16 Hz), 8.33 (2H, s, br), 8.56 (1H, s), 8.96 (1H, t)
84	CD_3OD	4.05 (2H, s) 4.44 (2H, s) 5.25 (2H, s) 6.96-7.03 (2H, m) 7.22-7.36 (4H, m) 7.39-7.57 (7H, m) 7.66-7.68 (1H, m) 8.09 (1H, s)
85	d6-DMSO	1.98 (3H, s), 3.98 (2H, q, J = 5.68 Hz), 4.38 (2H, d J = 5.92 Hz), 5.21 (2H, s), 5.31 (2H, s), 7.15 (2H, d, J = 5.68 Hz), 7.20 (2H, d, J = 8.16 Hz), 7.22 (2H, d, J = 7.60 Hz), 7.31 (2H, d, J = 8.08), 7.39 (2H, d, J = 8.04 Hz), 7.51 (1H, s), 7.53 (1H, s), 7.89 (1H, s), 8.25 (1H, s), 8.68 (1H, t, J = 6.08 Hz)
86	d6-DMSO	2.08 (3H, s), 2.14 (3H, s), 3.98 (2H, q, J = 5.82Hz), 4.39 (2H, d, J = 6.79Hz), 5.16 (2H, s), 5.31 (2H, s), 7.07 (2H, d, J = 8.01 Hz), 7.22 (2H, d, J = 8.01Hz), 7.32 (2H, d, J = 8.33Hz), 7.38 (2H, d, J = 8.33Hz), 7.89 (1H, s), 8.08 (3H, s, br), 8.24 (1H, s), 8.67(1H, t, J = 5.90Hz).
87	d6-DMSO	3.23 (2H, s, br), 3.55 (2H, s, br), 3.88 (6H, s, br), 3.98 (2H, q, J = 5.8 Hz), 4.40 (2H, d, J = 6.0 Hz), 5.39 (2H, s), 7.27- 7.36 (6H, m), 7.40 (2H, d, 8.1 Hz), 7.94 (1H, s), 8.25 (2H, s, br), 8.31 (1H, s), 8.71 (1H, s)
88	d6-DMSO	3.99 (2H, q, J = 5.19Hz), 4.41 (2H, d, J = 6.136Hz), 5.45 (2H, s), 7.00- 7.03 (4H, m), 7.14-7.18 (1H, m), 7.33- 7.39 (7H, m), 8.07 (3H, s, br), 8.81 (1H, s), 9.07-9.10 (1H, m).
89	d6-DMSO	0.88 - 0.95 (2H, m), 0.97 - 1.04 (2H, m), 2.50-2.70 (2H, br s), 4.33 (2H, d, J = 6.0 Hz), 5.07 (2H, s), 5.31 (2H, s), 6.21 (1H, td, J = 1.4, 6.7 Hz), 6.40 (1H, d, J = 9.2 Hz), 7.16 - 7.31 (8H, m), 7.40 (1H, ddd, J = 2.1, 6.6, 8.8 Hz), 7.75 (1H, dd, J = 1.5, 6.8 Hz), 7.87 (1H, s), 8.23 (1H, s), 8.55 (1H, t, J=6.0 Hz).
90	d6-DMSO	2.06 (3H, s), 2.35 (3H, s), 3.86 (2H, s), 4.35 (2H, d, J = 6.1 Hz), 5.06 (4H, s), 6.23 (1H, dt, J = 1.4, 6.7 Hz), 6.32 (1H, s), 6.40 (1H, d, J = 6.8 Hz), 6.86 - 6.88 (2H, m), 7.23 - 7.25 (2H, m), 7.27 - 7.29 (2H, m), 7.32 - 7.34 (2H, m), 7.42 (1H, ddd, J = 2.1, 6.6, 9.2 Hz), 7.75 (1H, ddd, J = 0.4, 2.0, 6.8 Hz), 8.11 (1H, t, J = 6.0 Hz).

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
91	d6-DMSO	2.07 (3H, s), 2.28 (3H, s), 2.38 (3H, s), 3.67 (2H, s), 4.31 (2H, d, J = 5.8 Hz), 5.07 (4H, s), 6.24 (1H, td, J = 1.4, 6.7 Hz), 6.32 - 6.37 (1H, m), 6.42 (1H, dd, J = 0.7, 9.1 Hz), 6.87 (2H, d, J = 8.2 Hz), 7.09 (2H, m), 7.17 (1H, d, J = 7.7 Hz), 7.25 (2H, d, J = 8.2 Hz), 7.42 (1H, ddd, J = 2.1, 6.6, 8.8 Hz), 7.72 - 7.79 (1H, m), 7.93 (1H, t, J = 5.9 Hz).
92	d6-DMSO	0.94 (3H, t, J = 7.0Hz), 1.98 (3H, s), 2.28 (3H, s), 3.67 (2H, s), 3.92 (2H, s), 4.14 (2H, q, J = 7.0Hz), 4.31 (2H, d, J = 5.8Hz), 5.03 (2H, s), 6.21 (1H, td, J = 6.7, 1.4Hz), 6.39 (1H, d, J = 9.1 Hz), 6.70 (1H, s), 7.03 (2H, d, J = 8.1Hz), 7.06-7.16 (3H, m), 7.20 (2H, d, J = 8.2Hz), 7.40 (1H, ddd, J = 8.9, 6.6, 2.1Hz), 7.73 (1H, dd, J = 6.8, 1.6Hz), 8.23 (1H, t, J = 5.9Hz).
93	d6-DMSO	0.80-0.88 (2H, m), 0.88-0.98 (5H, m), 1.98 (3H, s), 3.92 (2H, s), 4.13 (2H, q, J = 6.9Hz), 4.31 (2H, d, J = 6.1Hz), 5.03 (2H, s), 6.21 (1H, td, J = 6.7, 1.4Hz), 6.39 (1H, d, J = 9.1Hz), 6.67 (1H, s), 7.02 (2H, d, J = 8.1Hz), 7.11-7.28 (6H, m), 7.40 (1H, ddd, J = 8.9, 6.6, 2.1Hz), 7.73 (1H, dd, J = 6.8, 1.6Hz), 8.32 (1H, t, J = 6.1Hz).
94	d6-DMSO	1.87 (1H, s), 1.96 (1H, t, J = 1.2 Hz), 2.01 (3H, s), 2.32 - 2.35 (8H, m), 3.69 (1H, s), 4.28 (1H, s), 4.34 (2H, d, J = 4.8 Hz), 5.03 - 5.04 (4H, m), 6.22 (1H, dt, J = 1.4, 6.7 Hz), 6.28 - 6.29 (1H, m), 6.38 - 6.40 (1H, m), 6.83 - 6.85 (2H, m), 6.92 - 6.93 (1H, m), 6.98 (1H, s), 7.21 - 7.23 (2H, m), 7.40 (1H, ddd, J = 2.1, 6.6, 9.2 Hz), 7.75 (1H, ddd, J = 0.4, 2.0, 6.8 Hz) ppm. NH2 not observed
95	d6-DMSO	0.95 (3H, t, J = 6.8 Hz), 1.87 (2H, s), 1.94 (3H, s), 1.96 (2H, t, J = 1.24 Hz), 2.31 (6H, s), 3.91 (2H, s), 4.15 (2H, q, J = 6.8 Hz), 4.35 (2H, d, J = 4.9 Hz), 5.04 (2H, s), 6.21 (1H, dt, J = 1.4, 6.7 Hz), 6.38 - 6.41 (1H, m), 6.21 - 6.22 (1H, m), 6.89 - 6.96 (2H, m, 7.01 - 7.03 (2H, m), 7.19 - 7.21 (2H, m), 7.41 (1H, ddd, J = 2.1, 6.6, 9.1 Hz), 7.73 - 7.78 (2H, m)
96	d6-DMSO	1.98 (3H, s), 2.07 (3H, s), 2.35 (3H, s), 2.69 - 3.03 (2H, br s), 3.69 (2H, s), 4.34 (2H, d, J = 6.1 Hz), 5.06 (2H, s), 5.19 (2H, s), 6.26 - 6.36 (1H, m), 6.85 (2H, d, J = 8.2 Hz), 7.15 (2H, d, J = 8.2 Hz), 7.18 - 7.31 (5H, m), 7.46 - 7.55 (1H, m), 8.07 (1H, t, J = 6.2 Hz).
97	d6-DMSO	2.04 (3H, s), 2.11 (3H, s), 2.34 (3H, s), 2.41 (3H, s), 3.23 (2H, br s), 3.70 (2H, s), 4.36 (2H, d, J= 5.8Hz), 5.11 (2H, s), 5.25 (2H, s), 6.40 (1H, s), 6.91 (2H, d, J= 8.0Hz), 7.08-7.15 (2H, m), 7.19-7.22 (3H,m), 7.29 (1H, s), 7.58 (1H, s), 7.98 (1H, t, J= 5.5Hz).
98	d6-DMSO	0.82 - 0.90 (2H, m), 0.90 - 0.96 (2H, m), 1.97 (3H, s), 2.05 (3H, s), 2.35 (3H, s), 2.55 (2H, br s), 4.31 (2H, d, J = 6.1 Hz), 5.05 (2H, s), 5.19 (2H, s), 6.31 (1H, s), 6.84 (2H, d, J = 8.2 Hz), 7.11 - 7.21 (4H, m), 7.21 - 7.27 (3H, m), 7.52 (1H, s), 8.05 (1 H, t, J = 6.1 Hz).
99	d6-DMSO	0.94 (3H, t, J = 7.0Hz), 1.82 (2H, s, br), 1.98 (6H, m), 2.27 (3H, s), 3.64 (2H, s), 3.92 (2H, s), 4.14 (2H, q, J = 6.9Hz), 4.30 (2H, d, J = 5.9Hz), 5.17 (2H, s), 6.70 (1H, s), 7.02 (2H, d, J = 8.2Hz), 7.04-7.17 (5H, m), 7.22 (1H, s), 7.49 (1H, s), 8.21 (1H, t, J = 5.9Hz).
100	d6-DMSO	0.82-0.88 (2H, m), 0.88-0.98 (5H, m), 1.98 (6H, s), 3.92 (2H, s), 4.13 (2H, q, J = 6.9Hz), 4.31 (2H, d, J = 6.1Hz), 5.17 (2H, s), 6.67 (1H, s), 7.01 (2H, d, J = 8.2Hz), 7.11 (2H, d, J = 8.2Hz), 7.16 (2H, d, J = 8.4Hz), 7.19-7.26 (3H, m), 7.49 (1H, s), 8.32 (1H, t, J = 6.1Hz).
101	d6-DMSO	1.98 (3H, s), 2.01 (3H, s), 2.02-2.14 (2H, s, br), 2.32 (6H, s), 2.34 (3H, s), 3.61 (2H, s), 4.33 (2H, d, J = 5.0Hz), 5.03 (2H, s), 5.18 (2H, s), 6.29 (1H, s), 6.83 (2H, d, J =8.2Hz), 6.95 (2H, s), 7.14 (2H, d, J = 8.2Hz), 7.22 (1H, s), 7.42 (1H, t, J = 5.0Hz), 7.51 (1H, s).
102	d6-DMSO	0.94 (3H, t, J = 7.0Hz), 1.94 (3H, s), 1.98 (3H, s), 2.32 (6H, s), 3.66 (2H, s), 3.90 (2H, s), 4.14 (2H, q, J = 6.9Hz), 4.35 (2H, d, J = 5.0Hz), 5.17 (2H, s), 6.61 (1H, s), 6.97-7.01 (m, 4H), 7.10 (2H, d, J = 8.2Hz), 7.22 (1H, s), 7.49 (1H, s), 7.78 (1H, t, J = 5.0Hz).
103		0.79 - 0.95 (4H, m), 1.98 (3H, s), 2.36 (2H, br s), 4.34 (2H, d, J = 5.9 Hz), 5.20 (2H, s), 5.30 (2H, s), 7.12 - 7.27 (9H, m), 7.51 (1H, s), 7.87 (1H, s), 8.22 (1 H, s), 8.53 (1H, t, J = 6.0 Hz).

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
104		1.98 (3H, s), 3.20-3.40 (2H, br s), 3.70 (2H, s), 4.35 (2H, d, J = 6.4 Hz), 5.19 (2H, s), 5.21 (2H, s), 7.12 - 7.32 (9H, m), 7.52 (1H, d, J = 0.7 Hz), 7.67 (1H, d, J = 1.3 Hz), 7.81 (1H, d, J = 1.3 Hz), 8.38 (1H, t, J = 6.4 Hz).
105		0.81 - 0.89 (2H, m), 0.89 - 0.96 (2H, m), 1.98 (3H, s), 2.66 (2H, br s), 4.32 (2H, d, J = 6.4 Hz), 5.17 (2H, s), 5.21 (2H, s), 7.13 - 7.24 (7H, m), 7.27 (2H, d, J = 8.1 Hz), 7.51 (1H, s), 7.67 (1H, d, J = 1.3 Hz), 7.82 (1H, d, J = 1.2 Hz), 8.35 (1H, t, J = 6.4 Hz).
106		1.98 (3H, s), 2.27 (3H, s), 3.32 (2H, br s), 3.65 (2H, s), 4.34 (2H, d, J = 5.6 Hz), 5.21 (2H, s), 5.30 (2H, s), 7.05 - 7.25 (8H, m), 7.52 (1H, s), 7.89 (1H, s), 8.24 (1H, s), 8.38 (1H, t, J = 5.7 Hz).
107		1.98 (3H, s), 2.27 (3H, s), 2.19 - 2.41 (2H, br s), 3.64 (2H, s), 4.34 (2H, d, J = 6.2 Hz), 5.19 (2H, s), 5.21 (2H, s), 7.05 (1H, d, J = 7.9 Hz), 7.08 - 7.14 (2H, m), 7.18 (2H, d, J = 8.1 Hz), 7.23 (1H, s), 7.28 (2H, d, J = 8.1 Hz), 7.52 (1H, s), 7.69 (1H, d, J = 1.2 Hz), 7.82 (1H, d, J = 1.2 Hz), 8.17 (1H, t, J = 6.2 Hz).
108		1.98 (3H, s), 2.89 (2H, br s), 3.70 (2H, s), 4.39 (2H, d, J = 6.3 Hz), 5.22 (2H, s), 5.61 (2H, s), 7.11 - 7.36 (9H, m), 7.52 (1H, s), 8.61 (1H, s), 9.02 (1H, t, J = 6.2 Hz).
109		1.91 (2H, br s), 1.98 (3H, s), 2.28 (3H, s), 3.63 (2H, s), 4.38 (2H, d, J = 6.1 Hz), 5.22 (2H, s), 5.61 (2H, s), 7.01 - 7.16 (3H, m), 7.17 - 7.26 (3H, m), 7.31 (2H, d, J = 8.2 Hz), 7.52 (1H, s), 8.62 (1H, s), 8.85 (1H, t, J = 6.1 Hz).
110		0.87 - 1.11 (4H, m), 1.99 (3H, s), 4.39 (2H, d, J = 6.3 Hz), 4.80 (2H, s), 5.22 (2H, s), 5.62 (2H, s), 7.12 - 7.38 (9H, m), 7.53 (1H, s), 8.62 (1H, s), 9.03 (1H, t, J = 6.3 Hz).
111	d6-DMSO	1.97 (3H, s), 2.14-2.30 (2H, s, br), 2.29 (6H, s), 3.62 (2H, s), 4.36 (2H, d, J = 4.8Hz), 5.20 (2H, s), 5.27 (2H, s), 6.97 (2H, s), 7.16 (2H, d, J = 8.3Hz), 7.20 (2H, d, J = 8.3Hz), 7.22 (1H, s), 7.51 (1H, s), 7.86 (1H, s), 7.95 (1H, t, J = 4.7Hz), 8.23 (1H, s).
112	d6-DMSO	1.82-2.00 (2H, s, br), 1.98 (3H, s), 2.31 (6H, s), 3.60 (s, 2H), 4.39 (2H, d, J = 5.5Hz), 5.17 (2H, s), 5.20 (2H, s), 6.95 (2H, s), 7.17 (2H, d, J = 8.3Hz), 7.22 (s, 1H), 7.25 (2H, d, J = 8.2Hz), 7.45 (1H, t, J = 5.4Hz), 7.51 (1H, m), 7.69 (1H, d, J = 1.3Hz), 7.77 (1H, d, J = 1.3Hz).
113	d6-DMSO	1.91-2.04 (2H, s, br), 1.98 (3H, s), 2.32 (6H, s), 3.60 (2H, s), 4.43 (2H, d, J = 5.3Hz), 5.21 (2H, s), 5.59 (2H, s), 6.95 (2H, s), 7.18 (2H, d, J = 8.2Hz), 7.22 (1H, s), 7.28 (2H, d, J = 8.2Hz), 7.52 (1H, s), 8.29 (1H, t, J = 5.2Hz), 8.59 (1H, s).
114	d6-DMSO	1.98 (3H, s), 2.28 (3H, s), 2.36 (6H, s), 3.93 (2H, d, J= 5.5Hz), 4.37 (2H, d, J= 5.0Hz), 5.18 (2H, s), 5.20 (2H, s), 7.09 (2H, s) 7.14-7.20 (4H, m) 7.23 (1H, s), 7.52 (1H, s), 7.86 (1H, t, J = 4.9Hz), 8.08 (3H, br s), 8.14 (1H, s).
115	d6-DMSO	1.98 (3H, s), 2.38 (6H, s), 2.43 (3H, s), 3.94 (2H, d, J= 5.8Hz), 4.40 (2H, d, J= 5.0Hz), 5.20 (2H, s), 5.27 (2H, s), 7.06-7.09 (4H, m), 7.15-7.18 (2H, m) 7.23 (1H,s), 7.52 (1H, s), 7.89 (1H, s), 7.99 (1H, t, J= 4.9Hz), 8.08 (2H, br s), 8.14 (1H, s).
116	d6-DMSO	1.98 (3H, s), 2.38 (6H, s), 2.43 (3H, s), 3.94 (2H, d, J= 5.8Hz), 4.40 (2H, d, J= 5.0Hz), 5.20 (2H, s), 5.27 (2H, s), 7.06-7.09 (4H, m), 7.15-7.18 (2H, m) 7.23 (1H, s), 7.52 (1H, s), 7.89 (1H, s), 7.99 (1H, t, J= 4.9Hz), 8.08 (2H, br s), 8.14 (1H, s).
117	d6-DMSO	1.99 (3H, s), 2.09 (2H, br s), 3.71 (2H, s), 4.36 (2H, d, J= 5.9Hz), 5.23 (2H, s), 5.41 (2H, s), 7.02 (1H, d, J= 11.2Hz), 7.08 (1H, d, J= 7.9Hz), 7.21 (2H, d, J= 8.1Hz), 7.24 (1H, s), 7.29 (2H, d, J= 8.1 Hz), 7.42 (1H, t, J= 7.9Hz), 7.54 (1H, s), 8.44 (1H, s), 8.80 (1H, t, J= 5.9Hz).
118	d6-DMSO	1.98 (3H, s), 2.30 (6H, s), 3.61 (2H, s), 4.36 (2H, d, J = 4.7 Hz), 5.21 (2H, s), 5.36 (2H, s), 6.98 (2H, s), 7.17-2.26 (5H, m), 7.53 (1H, s), 8.20 (1H, t, J = 4.6 Hz), 8.38 (1H, s)

(continued)

NMR data of examples		
Example No	**Solvent**	**Chemical Shift (ppm)**
119	d6-DMSO	1.70- 2.20 (2H, br s), 1.99 (3H, s), 2.18 (3H, d, J= 1.6Hz), 3.71 (2H, s), 4.36 (2H, d, J= 5.2 Hz), 5.23 (2H, s), 5.40 (2H, s), 7.05 (1H, d, J= 8.0Hz), 7.21-7.29 (6H, m), 7.54 (1H, s), 8.44 (1H, s), 8.65 (1H, t, J= 5.2Hz).
121	d6-DMSO	0.94 (3H, t, J = 7.0Hz), 1.98 (8H, m), 3.67 (2H, s), 3.92 (2H, s), 4.14 (2H, q, J = 6.9Hz), 4.33 (2H, d, J = 6.1Hz), 5.17 (2H, s), 6.68 (1H, s), 7.01 (2H, d, J = 8.2Hz), 7.11 (2H, d, J = 8.2Hz), 7.15-7.29 (5H, m), 7.49 (1H, s), 8.34 (1H, t, J = 6.1Hz).
122	d6-DMSO	0.94 (3H, t, J = 7.0Hz), 1.98 (3H, s), 3.71 (2H, s), 3.92 (2H, s), 4.13 (2H, q, J = 6.9Hz), 4.33 (2H, d, J = 6.1Hz), 5.03 (2H, s), 6.21 (1H, td, J = 6.7, 1.4Hz), 6.39 (1H, d, J = 9.1Hz), 6.68 (1H, s), 7.02 (2H, d, J =8.1Hz), 7.17-7.23 (4H, m), 7.26 (2H, d, J = 8.2Hz), 7.40 (1H, ddd, J = 8.8, 6.6, 2.1 Hz), 7.70-7.76 (1H, m), 8.35 (1H, t, J = 6.2Hz).
123	d6-DMSO	1.11 (3H, t, J = 6.9Hz), 2.05 (3H, s), 3.67 (2H, s), 4.10 (2H, s), 4.34 (2H, d, J = 6.1 Hz), 4.40 (2H, q, J = 6.9Hz), 6.66 (1H, s), 7.15-7.28 (5H, m), 7.44-7.53 (3H, m), 7.86-7.93 (2H, m), 8.34 (1H, t, J = 6.2Hz).
124	d6-DMSO	2.31 (3H, s), 2.36 (6H, s), 2.80 (3H, s), 3.92 (2H, d, J= 5.72Hz), 4.39 (2H, d, J= 5.0Hz), 5.46 (2H, s), 7.09 (2H, s), 7.68-7.75 (2H, m), 7.91-7.92 (1H, m), 7.98-8.07 (1H, m), 8.27 (1H, s), 8.37 (3H, s), 8.62 (1H, d, J = 7.56Hz).
126	d6-DMSO	2.36 (6H, s), 2.87 (3H, s), 3.91 (2H, d, J= 5.6Hz), 4.41 (2H, d, J= 4.8Hz), 5.68 (2H, s), 7.13 (2H, s), 7.81 (1H, s), 7.86 (1H, d, J = 8.1Hz), 8.17-8.34 (4H, m), 8.39 (1H, s), 8.53 (1H, s), 8.78 (1H, br, s).
127	d6-DMSO	2.37 (6H, s), 2.89 (3H, s), 3.92 (2H, d, J= 5.36Hz), 4.43 (2H, d, J= 4.9Hz), 5.80 (2H, s), 7.14 (2H, s), 7.76-7.82 (1H, m), 7.92 (1H, s), 7.99 (1H, s), 8.27 (1H, d, J= 8.1Hz), 8.37 (3H, s), 8.64 (1H, s), 8.81 (1H, br, s).
128	d6-DMSO	2.07 (3H, s), 2.35 (6H, s), 2.41 (3H, s), 2.63 (3H, s), 3.65 (2H, s), 4.35 (2H, d, J = 4.7 Hz), 5.25 (2H, s), 6.35 (1H, s), 6.97 (2H, s), 7.30 - 7.34 (2H, m), 7.38 (1H, d, J = 8.1 Hz), 7.51 (1H, br s), 7.89 (1H, d, J = 8.1 Hz), 8.15 (1H, d, J = 8.1 Hz).
129	d6-DMSO	2.01 (4H, s), 2.37 (6H, s), 3.65-3.72 (4H, m), 3.91 (2H, d, J= 5.6Hz), 4.41 (2H, d, J= 4.9Hz), 5.55 (2H, s), 6.55 (1H, d, J= 6.4Hz), 7.03 (1H, s), 7.16 (2H, s), 7.92 (1H, d, J = 6.5Hz), 8.42 (2H, s), 8.49 (1H, s), 8.58 (1H, s).

Biological Methods

[0153] 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

[0154] 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.

[0155] Data acquired from these assays are shown in Table 15 below. Generally, but not exclusively, preferred compounds demonstrate an IC_{50} of less than 200 nM.

Table 15

Example No	IC50 (human PKal) nM
1	63
2	15
3	6
4	121
8	348
9	543
10	571
11	2419
12	5119
13	2383
14	2295
15	5694
16	186
17	492
18	435
19	768
20	4947
21	4522
22	3269
23	1596
24	431
25	1327
26	437
27	848
28	1326
29	140
30	773
31	251
32	732
33	919
34	3599
35	2100
36	203
37	170
38	2311
39	1092
40	1661
41	4704

(continued)

Example No	IC50 (human PKal) nM
42	953
43	196
44	355
45	135
46	1164
47	74
48	624
49	89
50	56
51	341
52	475
53	677
54	30
55	3267
56	3856
57	7178
58	4915
59	2742
60	3115
61	2990
62	6034
63	7338
64	6253
65	4558
66	5383
67	3503
68	2093
69	689
70	4593
71	702
72	3021
73	7580
74	1584
75	4499
76	8767
77	3722
78	4133
79	5546

(continued)

Example No	IC50 (human PKal) nM
80	2340
81	695
82	488
83	452
84	8379
85	11
86	7
87	5480
88	6989
89	226
90	114
91	29
92	40
93	2845
94	11
95	16
96	63
97	28
98	701
99	38
100	2321
101	4
102	11
103	694
104	30
105	941
106	2
107	3
108	33
109	5
110	2584
111	1
112	2
113	2
114	0.6
115	8
116	11699
117	51

(continued)

Example No	IC50 (human PKal) nM
118	1
119	9
121	155
122	151
123	2149
124	2
125	3
126	3
127	731
128	934
129	24

[0156] 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

[0157] 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.

[0158] Data acquired from this assay are shown in Table 16 below:

Table 16 (KLK1 Activity)

Example No	IC_{50} (human KLK1) nM
1	>10,000
2	>10,000
3	>10,000
4	>10,000
8	6360
9	>10,000
10	>10,000
11	>10,000
12	>10,000
13	>10,000
14	6370
15	>10,000
16	>10,000
17	>10,000
18	>10,000

(continued)

Example No	IC_{50} (human KLK1) nM
19	>10,000
20	2400
21	7500
22	>10,000
23	>10,000
24	>10,000
25	>10,000
26	>10,000
27	>10,000
28	>10,000
29	>10,000
30	>10,000
31	8080
32	>10,000
33	>10,000
34	>10,000
35	>10,000
36	>10,000
37	>10,000
38	>10,000
39	>10,000
40	>10,000
41	>10,000
42	>10,000
43	>10,000
44	>10,000
45	>10,000
46	4890
47	>10,000
48	>10,000
49	>10,000
50	>10,000
51	>10,000
52	>10,000
53	>10,000
54	>10,000
56	5480
57	>10,000

(continued)

Example No	IC_{50} (human KLK1) nM
58	>10,000
59	>10,000
60	>10,000
61	>10,000
62	>10,000
63	>10,000
64	>10,000
65	>10,000
66	4230
67	6970
68	>10,000
69	>10,000
70	>10,000
71	>10,000
72	>10,000
73	>10,000
74	>10,000
75	>10,000
76	>10,000
77	>10,000
78	>10,000
79	>10,000
80	>10,000
81	>10,000
82	>8660
83	>10,000
84	>10,000
85	>8510
86	>10,000
87	>10,000
88	>10,000
89	>10,000
90	>10,000
91	>10,000
92	10,000
93	>10,000
94	10900
95	3900

(continued)

Example No	IC_{50} (human KLK1) nM
96	>10,000
97	>10,000
98	>10,000
99	>10,000
100	>10,000
101	6310
102	4270
103	>10000
104	>10000
105	>10000
106	>10000
107	>10000
108	>10000
109	>10000
110	>10000
111	>10000
112	>10000
113	>10000
114	>10000
115	>10000
116	>10000
117	>10000
118	>10000
119	>10000
121	>10,000
122	>10,000
123	>10,000
124	301
125	657
126	566
127	>10,000
128	2660
129	>10,000

[0159] 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

[0160] 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%).

[0161] Data acquired from these assays are shown in Table 17 below:

Table 17 (Selectivity data)

Example No	IC50 (nM)			
	Thrombin	Trypsin	Plasmin	Factor XIIa
1	>40000	>40000	>40000	>10000
2	>40000	>40000	24805	>10000
83	>40000	26565	27242	>8510
84	>40000	>40000	>40000	>10000
101				>10000
119				>40000
124				>40000
125				>40000
126				>40000
127				>40000

Pharmacokinetics

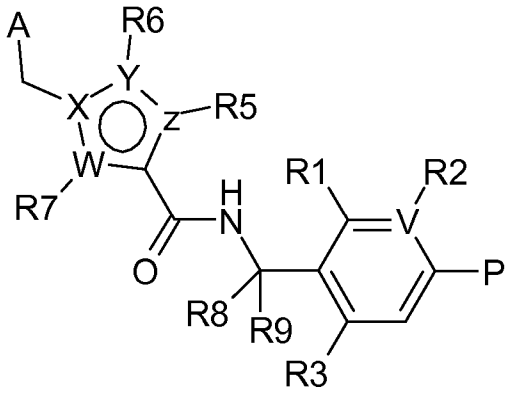
[0162] Pharmacokinetic studies of selected examples were performed to assess the pharmacokinetics following a single oral dose in male Sprague-Dawley rats. Typically, either two or three rats were given a single po dose of 5 mL/kg of a nominal 2 mg/mL (10 mg/kg) composition of test compound in either 5% cremophor:5% ethanol:90% phosphate buffered saline or 20% Labrasol:80% water. Following dosing, blood samples were collected over a period of 8 hours. Typical sample times include 5, 15 and 30 minutes then 1, 2, 4, 6 and 8 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 18 (Oral exposure data)

Example No	Dose po (mg/kg)	Cmax (ng/mL)	Tmax (mins)
1	11	81	280
2	11	59	300
37	10	171	210
43	8.9	71	240
45	10	228	155
101	9.7	67	300

Claims

1. A compound of formula (I),



Formula (I)

wherein,

V is selected from C and N such that the aromatic ring containing V is phenyl or pyridine;
R2 is absent when V is N; or, when present, R2 is selected from H, alkyl, alkoxy, CN, halo and CF_3;
R1 and R3 are independently selected from H, alkyl, alkoxy, CN, halo and CF_3;
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, aryl, heteroaryl and CF_3;
P is $-C(R10)(R11)NH_2$;
R8 and R9 are independently selected from H and alkyl, or may together form a cycloalkyl ring;
R10 and R11 are independently selected from H and alkyl, or may together form a cycloalkyl ring or a cyclic ether;
A is selected from N-linked morpholine, aryl, heteroaryl,
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, -COOR12, -CONR12R13, $H(CH_2)_{1\text{-}3}CON(R12)(CH_2)_{1\text{-}3}$-, fluoro and -NR12R13;
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 NR12R13;
a cyclic ether is a monocyclic saturated hydrocarbon of between 4 and 7 carbon atoms, wherein one of the ring carbons is replaced by an oxygen atom;
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 aryl, OH, CN, CF_3, -COOR12, -CONR12R13, fluoro and NR12R13;
aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, -morpholinyl,-piperidinyl, heteroaryl, $aryl^b$, -O-$aryl^b$, $-(CH_2)_{1\text{-}3}$-$aryl^b$, $-(CH_2)_{1\text{-}3}$-heteroaryl, -COOR12, - CONR12R13, $-(CH_2)_{1\text{-}3}$-NR14R15, CF_3 and NR12R13;
$aryl^b$ 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, -COOR12, -CONR12R13, CF_3 and NR12R13;
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, NR12, S and O; heteroaryl 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, $heteroaryl^b$, -COOR12, -CONR12R13, CF_3 and NR12R13;
$heteroaryl^b$ 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, NR12, 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,-COOR12, -CONR12R13, CF_3 and NR12R13;
R12 and R13 are independently selected from H and alkyl; or R12 and R13 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
R14 and R15 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 optionally may be oxo substituted;

wherein,
when R5, R6 and R7 are absent or H, then:
either

R10 and R11 together form a cycloalkyl ring or a cyclic ether; or
A is aryl and aryl is phenyl, biphenyl or naphthyl substituted with 1, 2 or 3 substituents independently selected from OH, heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, and -$(CH_2)_3$-NR14R15; wherein,

aryl^b is phenyl, biphenyl or naphthyl, wherein aryl^b is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, -COOR12, -CONR12R13, CF_3 and NR12R13; and
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, NR12, S and O, wherein heteroaryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, halo, CN, aryl, morpholinyl, piperidinyl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b, -COOR12, - CONR12R13, CF_3 and -NR12R13;

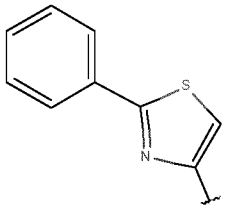
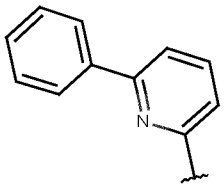
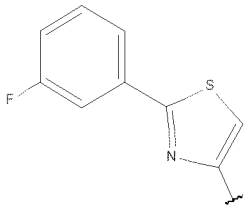
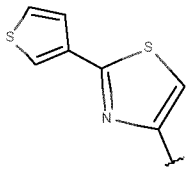
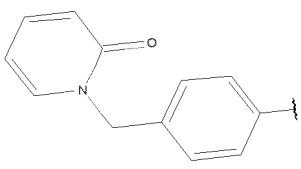
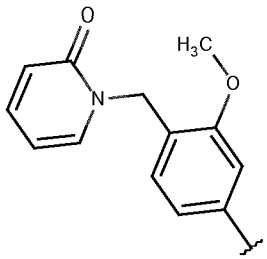
or
A is heteroaryl and heteroaryl is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2 or 3 ring members independently selected from N, NR12, S and O, wherein heteroaryl is substituted with 1, 2 or 3 substituents independently selected from aryl, -$(CH_2)_{1-3}$-aryl, heteroaryl^b,-COOR12, and -CONR12R13;wherein,

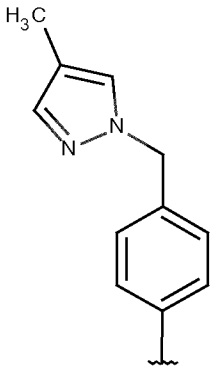
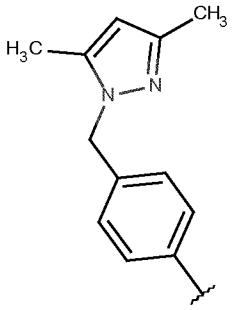
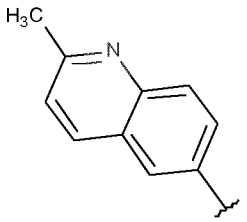
aryl is phenyl, biphenyl or naphthyl, wherein aryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, halo, CN, morpholinyl, piperidinyl, heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR12, -CONR12R13, -COR12R13, -$(CH_2)_{1-3}$-NR14R15, CF_3 and -NR12R13; and
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, NR12, S and O, wherein heteroaryl^b is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, halo, CN, morpholinyl, piperidinyl, aryl, -$(CH_2)_{1-3}$-aryl, -COOR12, -CONR12R13, CF_3 and NR12R13;

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

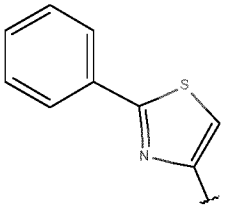
2. A compound according to claim 1 wherein at least one of R5, R6 and R7 is selected from alkyl, halo, aryl, heteroaryl and CF_3.

3. A compound according to claim 1 or claim 2 wherein A is selected from:

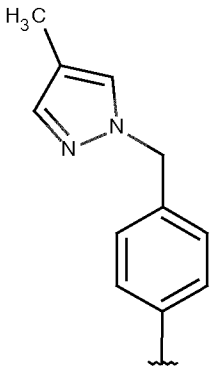
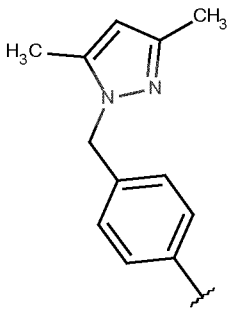









and

.

4. A compound of according to any preceding one of claims 1 to 3 wherein A is :



5. A compound according to claim 1 wherein R5, R6 and R7 are absent or H; and A is selected from:


and


6. A compound according to any one of claims 1 to 4 wherein, X is N and W, Y and Z are C.

7. A compound according to claim 6 wherein, R5 is H, and R6 and R7 are methyl.

8. A compound according to any one of claims 1 to 7 wherein R8 and R9 are H.

9. A compound according to any one of claims 1 to 5, wherein:

W is C;
X is N;
Y is C;
Z is C;
R5 is H;
R6 and R7 are CH_3;
R8 and R9 are H; and
R10 and R11 are both H or together form a cyclopropane ring.

10. A compound according to any one of claims 1 to 9 wherein V is C.

11. A compound according to any one of claims 1 to 10 wherein R1 is alkyl and/or R3 is alkyl.

12. A compound according to claim 1 selected from:

2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-(1-amino-cyclopropyl)-benzylamide;
2,5-Dimethyl-1-(6-phenyl-pyridin-2-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
1-[2-(3-Fluoro-phenyl)-thiazol-4-ylmethyl]-2,5-dimethyl-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-(2-thiophen-3-yl-thiazol-4-ylmethyl)-1 H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (6-aminomethyl-pyridin-3-ylmethyl)-amide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-3-fluoro-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-fluoro-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-chloro-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-trifluoromethyl-benzylamide;
2,5-Dimethyl-1-(2-phenyl-thiazol-4-ylmethyl)-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methoxy-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide;
1-[4-(3,5-Dimethyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-benzylamide;
2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
2,5-Dimethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-3-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-imidazole-4-carboxylic acid 4-aminomethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-imidazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-2-methyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzy-

lamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1 H-imidazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-1H-[1,2,3]triazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrrole-2-carboxylic acid 4-aminomethyl-benzylamide;
5-Methyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-3-fluoro-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-[4-(4-Methyl-pyrazol-1-ylmethyl)-benzyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-3-fluoro-2-methyl-benzylamide;
3-Methyl-1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
5-Methyl-1-(2-methyl-quinolin-6-ylmethyl)-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-(2-Methyl-quinolin-6-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;
1-(2-Pyrrolidin-1-yl-pyridin-4-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid 4-aminomethyl-2,6-dimethyl-benzylamide;

and pharmaceutically acceptable salts and solvates thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 and a pharmaceutically acceptable carrier, diluent or excipient.

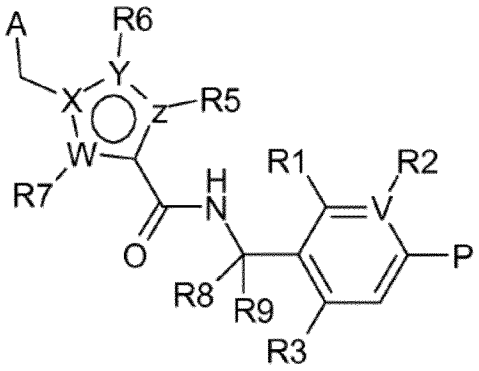
14. A compound according to any one of claims 1 to 12 for use in medicine.

15. A compound according to any one of claims 1 to 12 for use in a method of treatment of a disease or condition in which plasma kallikrein activity is implicated 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.

16. A compound for use as claimed in claim 15, wherein the disease or condition in which plasma kallikrein activity is implicated is retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Patentansprüche

1. Verbindung der Formel (I),



Formel (I)

wobei

V ausgewählt ist aus C und N, so dass der aromatische Ring, der V enthält, Phenyl oder Pyridin ist;
R2 nicht vorhanden ist, wenn V N ist; oder, wenn vorhanden, R2 ausgewählt ist aus H, Alkyl, Alkoxy, CN, Halogen und CF_3;
R1 und R3 unabhängig ausgewählt sind aus H, Alkyl, Alkoxy, CN, Halogen und CF_3;
W, X, Y und Z unabhängig ausgewählt sind aus C, N, O und S, so dass der Ring, der W, X, Y und Z enthält, ein fünfgliedriger aromatischer Heterocyclus ist;
wobei R5, R6 und R7 unabhängig nicht vorhanden sind oder unabhängig ausgewählt sind aus H, Alkyl, Halogen, Aryl, Heteroaryl und CF_3;
P-C(R10)(R11)NH_2 ist;
R8 und R9 unabhängig ausgewählt sind aus H und Alkyl oder zusammen einen Cycloalkylring bilden können;
R10 und R11 unabhängig ausgewählt sind aus H und Alkyl oder zusammen einen Cycloalkylring oder einen cyclischen Ether bilden können;
A ausgewählt ist aus N-verknüpftem Morpholin, Aryl, Heteroaryl;
Alkyl ein linearer gesättigter Kohlenwasserstoff mit bis zu 10 Kohlenstoffatomen (C_1-C_{10}) oder ein verzweigter gesättigter Kohlenwasserstoff mit zwischen 3 und 10 Kohlenstoffatomen (C_3-C_{10}) ist; wobei Alkyl gegebenenfalls mit 1 oder 2 Substituenten unabhängig ausgewählt aus (C_1-C_6)Alkoxy, OH, CN, CF_3, -COOR12, -CONR12R13, $H(CH_2)_{1-3}CON(R12)(CH_2)_{1-3}$-, Fluor und -NR12R13 substituiert sein kann;
Cycloalkyl ein monocyclischer gesättigter Kohlenwasserstoff mit zwischen 3 und 7 Kohlenstoffatomen ist; wobei Cycloalkyl gegebenenfalls mit einem Substituenten ausgewählt aus Alkyl, Alkoxy und NR12R13 substituiert sein kann;
ein cyclischer Ether ein monocyclischer gesättigter Kohlenwasserstoff mit zwischen 4 und 7 Kohlenstoffatomen ist, wobei einer der Ring-Kohlenstoffe durch ein Sauerstoffatom ersetzt ist;
Alkoxy ein linearer O-verknüpfter Kohlenwasserstoff mit zwischen 1 und 6 Kohlenstoffatomen (C_1-C_6) oder ein verzweigter O-verknüpfter Kohlenwasserstoff mit zwischen 3 und 6 Kohlenstoffatomen (C_3-C_6) ist; wobei Alkoxy gegebenenfalls mit 1 oder 2 Substituenten unabhängig ausgewählt aus Aryl, OH, CN, CF_3, -COOR12, -CONR12R13, Fluor und NR12R13 substituiert sein kann;
Aryl Phenyl, Biphenyl oder Naphthyl ist; wobei Aryl gegebenenfalls mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, OH, Halogen, CN, Morpholinyl, Piperidinyl, Heteroaryl, $Aryl^b$, -O-$Aryl^b$, $-(CH_2)_{1-3}$-$Aryl^b$, $-(CH_2)_{1-3}$-Heteroaryl, -COOR12, -CONR12R13, - $(CH_2)_{1-3}$NR14R15, CF_3 und NR12R13 substituiert sein kann;
$Aryl^b$ Phenyl, Biphenyl oder Naphthyl ist, das gegebenenfalls mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, OH, Halogen, CN, Morpholinyl, Piperidinyl, -COOR12, -CONR12R13, CF_3 und NR12R13 substituiert sein kann;
Heteroaryl ein 5-, 6-, 9- oder 10-gliedriger mono- oder bicyclischer aromatischer Ring ist, der, wenn möglich, 1, 2 oder 3 Ringelemente unabhängig ausgewählt aus N, NR12, S und O enthält; wobei Heteroaryl gegebenenfalls mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, OH, Halogen, CN, Morpholinyl, Piperidinyl, Aryl, $-(CH_2)_{1-3}$-Aryl, $Heteroaryl^b$, -COOR12, -CONR12R13, CF_3 und NR12R13 substituiert sein kann;
$Heteroaryl^b$ ein 5-, 6-, 9- oder 10-gliedriger mono- oder bicyclischer aromatischer Ring ist, der, wenn möglich, 1, 2 oder 3 Ringelemente unabhängig ausgewählt aus N, NR12, S und O enthält; wobei $Heteroaryl^b$ gegebenenfalls mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, OH, Halogen, CN, Morpholinyl, Piperidinyl, Aryl, $-(CH_2)_{1-3}$-Aryl, -COOR12, -CONR12R13, CF_3 und NR12R13 substituiert sein kann;

R12 und R13 unabhängig ausgewählt sind aus H und Alkyl; oder R12 und R13 zusammen mit dem Stickstoff, an den sie gebunden sind, einen 4-, 5-, 6- oder 7-gliedrigen heterocyclischen Ring bilden, der gesättigt oder mit 1 oder 2 Doppelbindungen ungesättigt sein kann;
R14 und R15 zusammen mit dem Stickstoff, an den sie gebunden sind, einen 4-, 5-, 6- oder 7-gliedrigen heterocyclischen Ring bilden, der gesättigt oder mit 1 oder 2 Doppelbindungen ungesättigt sein kann und gegebenenfalls Oxo-substituiert sein kann;

wobei,
wenn R5, R6 und R7 nicht vorhanden oder H sind:

entweder

R10 und R11 zusammen einen Cycloalkylring oder einen cyclischen Ether bilden;
oder
A Aryl ist und Aryl Phenyl, Biphenyl oder Naphthyl substituiert mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus OH, Heteroaryl, $Aryl^b$, -O-$Aryl^b$, $-(CH_2)_{1-3}$-$Aryl^b$, $-(CH_2)_{1-3}$-Heteroaryl, -COOR12, -CONR12R13 und $-(CH_2)_3$-NR14R15 ist; wobei

$Aryl^b$ Phenyl, Biphenyl oder Naphthyl ist, wobei $Aryl^b$ mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, OH, Halogen, CN, Morpholinyl, Piperidinyl, -COOR12, -CONR12R13, CF_3 und NR12R13 substituiert ist; und
Heteroaryl ein 5-, 6-, 9- oder 10-gliedriger mono- oder bicyclischer aromatischer Ring ist, der, wenn möglich, 1, 2 oder 3 Ringelemente unabhängig ausgewählt aus N, NR12, S und O enthält, wobei Heteroaryl mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, Halogen, CN, Aryl, Morpholinyl, Piperidinyl, $-(CH_2)_{1-3}$-Aryl, $Heteroaryl^b$, -COOR12, -CONR12R13, CF_3 und NR12R13 substituiert ist;

oder

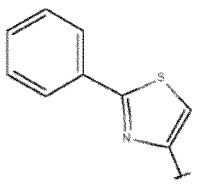
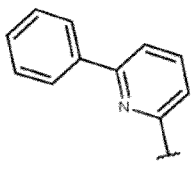
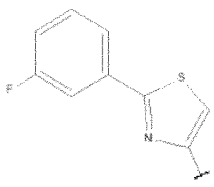
A Heteroaryl ist und Heteroaryl ein 5-, 6-, 9- oder 10-gliedriger mono- oder bicyclischer aromatischer Ring ist, der, wenn möglich, 1, 2 oder 3 Ringelemente unabhängig ausgewählt aus N, NR12, S und O enthält, wobei Heteroaryl mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Aryl, $-(CH_2)_{1-3}$-Aryl, $Heteroaryl^b$, -COOR12 und CONR12R13 substituiert ist; wobei

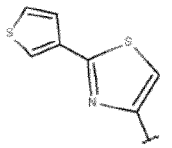
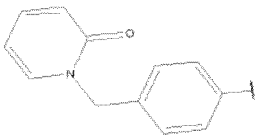
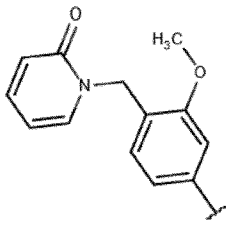
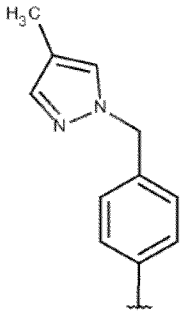
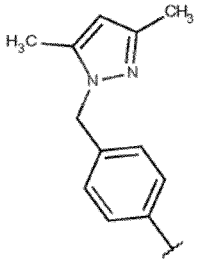
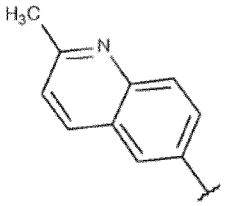
Aryl Phenyl, Biphenyl oder Naphthyl ist, wobei Aryl mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, OH, Halogen, CN, Morpholinyl, Piperidinyl, Heteroaryl, $Aryl^b$, -O-$Aryl^b$, $-(CH_2)_{1-3}$-$Aryl^b$, $-(CH_2)_{1-3}$-Heteroaryl, -COOR12, -CONR12R13, - COR12R13, $-(CH_2)_{1-3}$-NR14R15, CF_3 und -NR12R13 substituiert ist; und
$Heteroaryl^b$ ein 5-, 6-, 9- oder 10-gliedriger mono- oder bicyclischer aromatischer Ring ist, der, wenn möglich, 1, 2 oder 3 Ringelemente unabhängig ausgewählt aus N, NR12, S und O enthält, wobei $Heteroaryl^b$ mit 1, 2 oder 3 Substituenten unabhängig ausgewählt aus Alkyl, Alkoxy, Halogen, CN, Morpholinyl, Piperidinyl, Aryl, $-(CH_2)_{1-3}$-Aryl, -COOR12, -CONR12R13, CF_3 und NR12R13 substituiert ist;

und Tautomere, Stereoisomere (einschließlich Enantiomere, Diastereoisomere und racemische und scalemische Gemische davon), pharmazeutisch verträgliche Salze und Solvate davon.

2. Verbindung gemäß Anspruch 1, wobei wenigstens eines von R5, R6 und R7 ausgewählt ist aus Alkyl, Halogen, Aryl, Heteroaryl und CF_3.

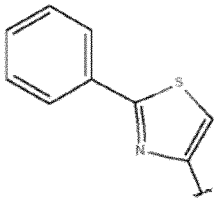
3. Verbindung gemäß Anspruch 1 oder Anspruch 2, wobei A ausgewählt ist aus:

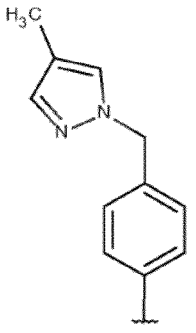
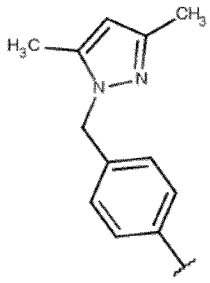
und .

4. Verbindung gemäß einem der vorstehenden Ansprüche 1 bis 3, wobei A ist:



.

5. Verbindung gemäß Anspruch 1, wobei R5, R6 und R7 nicht vorhanden oder H sind; und A ausgewählt ist aus:

und .

6. Verbindung gemäß einem der Ansprüche 1 bis 4, wobei X N ist und W, Y und Z C sind.

7. Verbindung gemäß Anspruch 6, wobei R5 H ist und R6 und R7 Methyl sind.

8. Verbindung gemäß einem der Ansprüche 1 bis 7, wobei R8 und R9 H sind.

9. Verbindung gemäß einem der Ansprüche 1 bis 5, wobei:

W C ist;
X N ist;
Y C ist;
Z C ist;
R5 H ist;

R6 und R7 CH_3 sind;
R8 und R9 H sind; und
R10 und R11 beide H sind oder zusammen einen Cyclopropanring bilden.

10. Verbindung gemäß einem der Ansprüche 1 bis 9, wobei V C ist.

11. Verbindung gemäß einem der Ansprüche 1 bis 10, wobei R1 Alkyl ist und/oder R3 Alkyl ist.

12. Verbindung gemäß Anspruch 1, ausgewählt aus:

2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethylbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethyl-2-methylbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-(1-aminocyclopropyl)benzylamid;
2,5-Dimethyl-1-(6-phenylpyridin-2-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethylbenzylamid;
1-[2-(3-Fluorphenyl)thiazol-4-ylmethyl]-2,5-dimethyl-1H-pyrrol-S-carbonsäure-4-aminomethylbenzylamid;
2,5-Dimethyl-1-(2-thiophen-3-ylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethylbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-(6-aminomethylpyridin-3-ylmethyl)amid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethyl-3-fluorbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethyl-2-fluorbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethyl-2-chlorbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethyl-2-trifluoomethylbenzylamid;
2,5-Dimethyl-1-(2-phenylthiazol-4-ylmethyl)-1H-pyrrol-3-carbonsäure-4-aminomethyl-2-methoxybenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-pyrazol-4-carbonsäure-4-aminomethylbenzylamid;
1-[4-(3,5-Dimethylpyrazol-1-ylmethyl)benzyl]-1H-pyrazol-4-carbonsäure-4-aminomethylbenzylamid;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)benzyl]-1H-pyrrol-3-carbonsäure-4-aminomethylbenzylamid;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)benzyl]-1H-pyrrol-3-carbonsäure-4-aminomethyl-2-methylbenzylamid;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)benzyl]-1H-pyrrol-2-carbonsäure-4-aminomethyl-2-methylbenzylamid;
2,5-Dimethyl-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)benzyl]-1H-pyrrol-3-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)benzyl]-1H-pyrrol-2-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
2,5-Dimethyl-1-[4-(4-methylpyrazol-1-ylmethyl)benzyl]-1H-pyrrol-3-carbonsäure-4-aminomethylbenzylamid;
2,5-Dimethyl-1-[4-(4-methylpyrazol-1-ylmethyl)benzyl]-1H-pyrrol-3-carbonsäure-4-aminomethyl-2-methylbenzylamid;
1-Ethyl-4-methyl-5-[4-(4-methylpyrazol-1-ylmethyl)benzyl]-1H-pyrrol-2-carbonsäure-4-aminomethyl-2-methylbenzylamid;
2,5-Dimethyl-1-[4-(4-methylpyrazol-1-ylmethyl)benzyl]-1H-pyrrol-3-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-Ethyl-4-methyl-5-[4-(4-methylpyrazol-1-ylmethyl)benzyl]-1H-pyrrol-2-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-imidazol-4-carbonsäure-4-aminomethylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-pyrazol-4-carbonsäure-4-aminomethyl-2-methylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-imidazol-4-carbonsäure-4-aminomethyl-2-methylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-[1,2,3]triazol-4-carbonsäure-4-aminomethylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-[1,2,3]triazol-4-carbonsäure-4-aminomethyl-2-methylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-pyrazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-imidazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-1H-[1,2,3]triazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-Ethyl-4-methyl-5-[4-(4-methylpyrazol-1-ylmethyl)benzyl]-1H-pyrrol-2-carbonsäure-4-aminomethylbenzylamid;
1-Ethyl-4-methyl-5-[4-(2-oxo-2H-pyridin-1-ylmethyl)benzyl]-1H-pyrrol-2-carbonsäure-4-aminomethylbenzyla-

mid;
5-Methyl-1-[4-(4-methylpyrazol-1-ylmethyl)benzyl]-1H-pyrazol-4-carbonsäure-4-aminomethyl-2,6-dimethyl-benzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-3-trifluormethyl-1H-pyrazol-4-carbonsäure-4-aminomethyl-3-fluor-benzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-3-trifluormethyl-1H-pyrazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-[4-(4-Methylpyrazol-1-ylmethyl)benzyl]-3-trifluormethyl-1H-pyrazol-4-carbonsäure-4-aminomethyl-3-fluor-2-methylbenzylamid;
3-Methyl-1-(2-methylchinolin-6-ylmethyl)-1H-pyrazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
5-Methyl-1-(2-methylchinolin-6-ylmethyl)-1H-pyrazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-(2-Methylchinolin-6-ylmethyl)-3-trifluormethyl-1H-pyrazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;
1-(2-Pyrrolidin-1-ylpyridin-4-ylmethyl)-3-trifluormethyl-1H-pyrazol-4-carbonsäure-4-aminomethyl-2,6-dimethylbenzylamid;

und pharmazeutisch verträgliche Salze und Solvate davon.

13. Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 12 und ein(en) pharmazeutisch verträgliches/verträglichen Träger, Verdünnungsmittel oder Hilfsstoff.

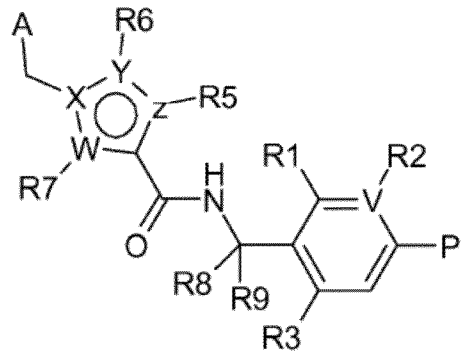
14. Verbindung gemäß einem der Ansprüche 1 bis 12 für die Verwendung in der Medizin.

15. Verbindung gemäß einem der Ansprüche 1 bis 12 für die Verwendung bei einem Verfahren zum Behandeln einer Erkrankung oder eines Zustands, bei dem/bei der Plasma-Kallikreinaktivität beteilig ist, ausgewählt aus beeinträchtigter Sehschärfe, diabetischer Retinopathie, diabetischem Makulaödem, erblichem Angioödem, Diabetes, Pankreatitis, Hirnblutung, Nephropathie, Kardiomyopathie, Neuropathie, entzündlicher Darmerkrankung, Arthritis, Entzündung, septischem Schock, Hypotonie, Krebs, adultem Atemnotsyndrom, disseminierter intravaskulärer Koagulation, kardiopulmonaler Bypass-Chirurgie und Blutung durch postoperative Chirurgie.

16. Verbindung für die Verwendung gemäß Anspruch 15, wobei die Erkrankung oder der Zustand, bei dem/bei der Plasma-Kallikreinaktivität beteilig ist, retinale Gefäßpermeabilität in Verbindung mit diabetischer Retinopathie und diabetischem Makulaödem ist.

Revendications

1. Composé de formule (I) :



où

V est choisi entre C et N, de sorte que le cycle aromatique contenant V soit phényle ou pyridine ;
R2 est absent si V = N ; ou si R2 est présent, R2 est choisi parmi H, alkyle, alcoxy, CN, halo et CF_3 ;
R1 et R3 sont indépendamment choisis parmi H, alkyle, alcoxy, CN, halo et CF_3 ;
W, X, Y et Z sont indépendamment choisis parmi C, N, O et S, de sorte que le cycle contenant W, X, Y et Z

soit un hétérocycle aromatique à 5 chaînons, où
R5, R6 et R7 sont indépendamment absents ou indépendamment choisis parmi H, alkyle, halo, aryle, hétéroaryle et CF_3 ;
P est $-C(R10)(R11)NH_2$;
R8 et R9 sont indépendamment choisis parmi H et alkyle, ou peuvent former ensemble un cycle cycloalkyle ;
R10 et R11 sont indépendamment choisis parmi H et alkyle, ou peuvent former ensemble un cycle cycloalkyle ou un éther cyclique ;
A est choisi parmi morpholine N-liée, aryle et hétéroaryle ;
alkyle désignant un hydrocarbure linéaire saturé comportant jusqu'à 10 atomes de carbone (C_{1-10}) ou un hydrocarbure ramifié saturé d'entre 3 et 10 atomes de carbone (C_{3-10}) ; alkyle peut être facultativement substitué par un ou deux substituants choisis indépendamment parmi C_{1-6}-alcoxy, OH, CN, CF_3, -COOR12,-CONR12R13, $H(CH_2)_{1-3}CON(R12)(CH_2)_{1-3}$-, fluoro et -NR12R13 ; cycloalkyle désigne un hydrocarbure monocyclique saturé d'entre 3 et 7 atomes de carbone ; cycloalkyle peut être facultativement substitué par un substituant choisi parmi alkyle, alcoxy et NR12R13 ;
éther cyclique désigne un hydrocarbure monocyclique saturé d'entre 4 et 7 atomes de carbone, un des carbones du cycle étant remplacé par un atome d'oxygène ;
alcoxy désigne un hydrocarbure linéaire lié par 0 d'entre 1 et 6 atomes de carbone (C_1-C_6) ou un hydrocarbure ramifié lié par 0 d'entre 3 et 6 atomes de carbone (C_{3-6}) ; alcoxy peut être facultativement substitué par un substituant choisi parmi aryle, OH, CN, CF_3, -COOR12, - CONR12R13, fluoro et NR12R13 ;
aryle est phényle, biphényle ou naphtyle ; aryle peut être facultativement substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, OH, halo, CN, morpholinyle, pipéridinyle, hétéroaryle, aryle^b, -O-aryle^b, -$(CH_2)_{1-3}$-aryle^b, -$(CH_2)_{1-3}$-hétéroaryle, -COOR12, -CONR12R13, -$(CH_2)_{1-3}$-NR14R15, CF_3 et -NR12R13 ;
aryle^b est phényle, biphényle ou naphtyle, facultativement substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, OH, halo, CN, morpholinyle, pipéridinyle, -COOR12, -CONR12R13, CF_3 et -NR12R13 ;
hétéroaryle est un cycle aromatique mono- ou bicyclique à 5, 6, 9 ou 10 chaînons contenant, si possible, un, deux ou trois membres du cycle choisis indépendamment parmi N, NR12, S et O ; hétéroaryle peut être facultativement substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, OH, halo, CN, morpholinyle, pipéridinyle, aryle, -$(CH_2)_{1-3}$-aryle, hétéroaryle^b,-COOR12, -CONR12R13, CF_3 et -NR12R13 ;
hétéroaryle^b est un cycle aromatique mono- ou bicyclique à 5, 6, 9 ou 10 chaînons contenant, si possible, un, deux ou trois membres du cycle choisis indépendamment parmi N, NR12, S et O ; hétéroaryle^b peut être facultativement substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, OH, halo, CN, morpholinyle, pipéridinyle, aryle, -$(CH_2)_{1-3}$-aryle, COOR12, -CONR12R13, CF_3 et -NR12R13 ;
R12 et R13 sont choisis indépendamment parmi H et alkyle ; ou R12 et R13 ensemble avec l'azote auquel ils sont attachés forment un hétérocycle à 4, 5, 6 ou 7 chaînons qui peut être saturé ou insaturé avec 1 ou 2 double-liaisons ;
R14 et R15 ensemble avec l'azote auquel ils sont attachés forment un hétérocycle à 4, 5, 6 ou 7 chaînons qui peut être saturé ou insaturé avec 1 ou 2 double-liaisons et peut facultativement être oxo-saturé ;
où
si R5, R6 et R7 ont absents ou H,

soit
R10 et R11 forment ensemble un cycloalkyle ou un éther cyclique ;
soit
A est un aryle, et aryle est un phényle, biphényle ou naphtyle, avec un, deux ou trois substituants indépendamment choisis parmi OH, hétéroaryle, aryle^b, -O-aryle^b, -$(CH_2)_{1-3}$-aryle^b, -$(CH_2)_{1-3}$-hétéroaryle, -COOR12, -CONR12R13 et -$(CH_2)_{1-3}$-NR14R15 ; avec
aryle^b est phényle, biphényle ou naphtyle, substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, OH, halo, CN, morpholinyle, pipéridinyle, -COOR12, -CONR12R13, CF_3 et NR12R13 ; et
hétéroaryle est un cycle aromatique mono- ou bicyclique à 5, 6, 9 ou 10 chaînons contenant, si possible, un, deux ou trois membres du cycle choisis indépendamment parmi N, NR12, S et O ; hétéroaryle peut être facultativement substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, halo, CN, aryle, morpholinyle, pipéridinyle, -$(CH_2)_{1-3}$-aryle, hétéroaryle^b, -COOR12, -CONR12R13, CF_3 et-NR12R13 ;
soit
A est un hétéroaryle, et hétéroaryle est un cycle aromatique mono- ou bicyclique à 5, 6, 9 ou 10 chaînons contenant, si possible, un, deux ou trois membres du cycle choisis indépendamment parmi N, NR12, S et O ; hétéroaryle peut être facultativement substitué par un, deux ou trois substituants choisis parmi aryle, -$(CH_2)_{1-3}$-aryle, hétéroaryle^b, -COOR12 et -CONR12R13 ; avec

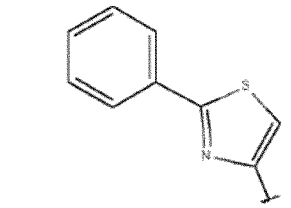
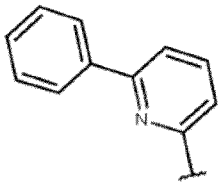
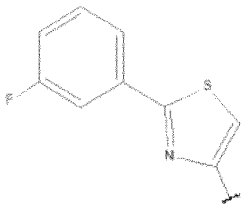
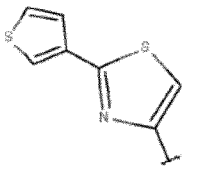
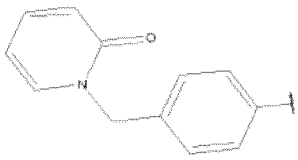
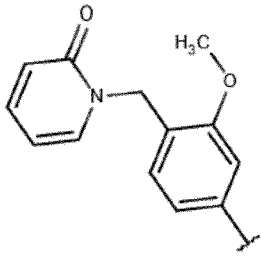
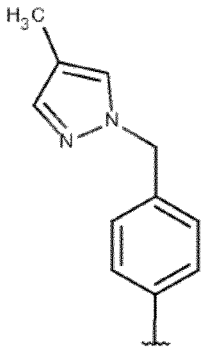
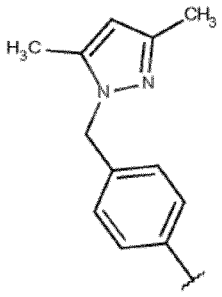
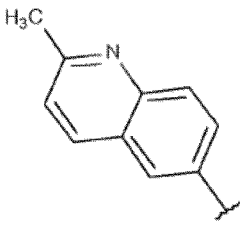
aryle est phényle, biphényle ou naphtyle ; aryle peut être facultativement substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, OH, halo, CN, morpholinyle, pipéridinyle, hétéroaryle, aryle^b, -O-aryle^b, - $(CH_2)_{1-3}$-aryle^b, - $(CH_2)_{1-3}$-hétéroaryle, -COOR12, -CONR12R13, -COR12R13,-$(CH_2)_{1-3}$-NR14R15, CF_3 et -NR12R13 ; et

hétéroaryle^b est un cycle aromatique mono- ou bicyclique à 5, 6, 9 ou 10 chaînons contenant, si possible, un, deux ou trois membres du cycle choisis indépendamment parmi N, NR12, S et O ; hétéroaryle^b peut être facultativement substitué par un, deux ou trois substituants choisis parmi alkyle, alcoxy, halo, CN, morpholinyle, pipéridinyle, aryle, -$(CH_2)_{1-3}$-aryle, -COOR12, -CONR12R13, CF_3 et -NR12R13 ;

et ses tautomères, stéréoisomères (y compris énantiomères, diastéréoisomères et mélanges racémiques et non-racémiques), sels et solvates pharmaceutiquement acceptables.

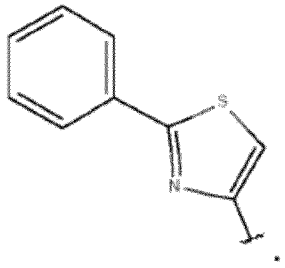
2. Composé selon la revendication 1, dans lequel au moins un parmi R5, R6 et R7 est choisi parmi alkyle, halo, hétéroaryle et CF_3.

3. Composé selon la revendication 1 ou 2, dans lequel A est choisi parmi :

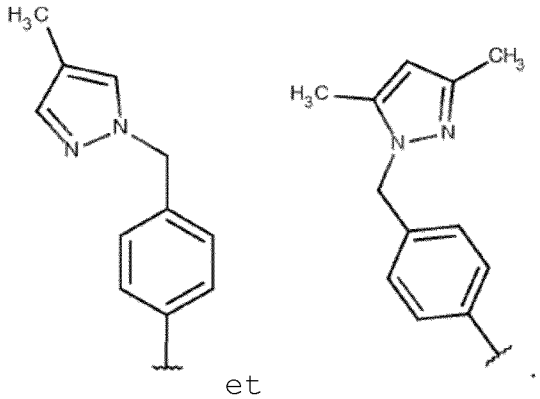










, et

4. Composé selon l'une quelconque des revendications précédentes 1 à 3, dans lequel A est :



5. Composé selon la revendication 1, dans lequel R5, R6 et R7 sont absents ou H, et A est choisi parmi :



et

6. Composé selon l'une quelconque des revendications 1 à 4, dans lequel X est N et W, Y et Z sont C.

7. Composé selon la revendication 6, dans lequel R5 = H, et R6 et R7 sont des méthyles.

8. Composé selon l'une quelconque des revendications 1 à 7, dans lequel R8 et R9 sont H.

9. Composé selon l'une quelconque des revendications 1 à 5, dans lequel W = C ;
X = N ;
Y = C ;
Z = C ;
R5 = H ;
R6 et R7 sont CH_3 ;
R8 et R9 sont H ; et
R10 et R11 sont tous les deux H ou forment ensemble un cycle cyclopropane.

10. Composé selon l'une quelconque des revendications 1 à 9, dans lequel V = C.

11. Composé selon l'une quelconque des revendications 1 à 10, dans lequel R1 est alkyle et/ou R3 est alkyle.

12. Composé selon la revendication 1 choisi parmi :

N-4-aminométhylbenzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-(1-amino-cyclopropyl)benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-benzyl 2,5-diméthyl-1-(6-phénylpyridin-2-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-benzyl 1-[2-(3-fluorophényl)thiazol-4-ylméthyl]-2,5-diméthyl-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-benzyl 2,5-diméthyl-1-(2-thiophén-3-ylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-(6-aminométhyl-pyridin-3-ylméthyl) 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-3-fluoro-benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-fluoro-benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-chloro-benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide

N-4-aminométhyl-2-trifluorométhyl-benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-méthoxy-benzyl 2,5-diméthyl-1-(2-phénylthiazol-4-ylméthyl)-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-benzyl 1-[4-(3,5-diméthylpyrazol-1-ylméthyl)benzyl]-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-benzyl 2,5-diméthyl-1-[4-(2-oxo-2H-pyridin-1-ylméthyl)benzyl]-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 2,5-diméthyl-1-[4-(2-oxo-2H-pyridin-1-ylméthyl)benzyl]-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 1-éthyl-4-méthyl-5-[4-(2-oxo-2H-pyridin-1-ylméthyl)benzyl]-1H-pyrrol-2-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 2,5-diméthyl-1-[4-(2-oxo-2H-pyridin-1-ylméthyl)benzyl]-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-éthyl-4-méthyl-5-[4-(2-oxo-2H-pyridin-1-ylméthyl)benzyl]-1H-pyrrol-2-carboxylamide
N-4-aminométhyl-benzyl 2,5-diméthyl-1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 2,5-diméthyl-1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 1-éthyl-4-méthyl-5-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrrol-2-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 2,5-diméthyl-1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrrol-3-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-éthyl-4-méthyl-5-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrrol-2-carboxylamide
N-4-aminométhyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-imidazol-4-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-imidazol-4-carboxylamide
N-4-aminométhyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-[1,2,3]triazol-4-carboxylamide
N-4-aminométhyl-2-méthyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-[1,2,3]triazol-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-imidazole-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-[1,2,3]triazol-4-carboxylamide
N-4-aminométhyl-benzyl 1-éthyl-4-méthyl-5-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrrol-2-carboxylamide
N-4-aminométhyl-benzyl 1-éthyl-4-méthyl-5-[4-(2-oxo-2H-pyridin-1-ylméthyl)benzyl]-1H-pyrrol-2-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 5-méthyl-1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-3-fluoro-benzyl 1-[4-(4-méthylpyrazol-1-ylméthyl)benzyl]-3-trifluorométhyl-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-[4-(4-méthyl-pyrazol-1-ylméthyl)benzyl]-3-trifluorométhyl-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-3-fluoro-2-méthyl-benzyl 1-[4-(4-méthyl-pyrazol-1-ylméthyl)benzyl]-3-trifluorométhyl-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 3-méthyl-1-(2-méthylquinolin-6-ylméthyl)-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 5-methyl-1-(2-méthylquinolin-6-ylméthyl)-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-(2-méthyl-quinolin-6-ylméthyl)-3-fluorométhyl-1H-pyrazol-4-carboxylamide
N-4-aminométhyl-2,6-diméthyl-benzyl 1-(2-pyrrolidin-1-ylpyridin-4-ylméthyl)-3-fluorométhyl-1H-pyrazol-4-carboxylamide

et ses sels et solvates pharmaceutiquement acceptables.

13. Composition pharmaceutique contenant un composé selon l'une quelconque des revendications 1 à 12 et un vecteur, diluant ou excipient pharmaceutiquement acceptable.

14. Composé selon l'une quelconque des revendications 1 à 12 pour utilisation en médecine.

15. Composé selon l'une quelconque des revendications 1 à 12 pour utilisation dans un procédé de traitement d'une maladie ou trouble où est impliquée l'activité de la kallicréine, choisi parmi la mauvaise acuité visuelle, la rétinopathie diabétique, l'oedème maculaire diabétique, l'angio-oedème héréditaire, le diabète, la pancréatite, l'hémorragie cérébrale, la néphropathie, la cardiomyopathie, la neuropathie, la maladie du côlon inflammatoire, l'arthrite, l'inflammation, le choc septique, l'hypotension, le cancer, le syndrome de détresse respiratoire de l'adulte, la coagulation intravasculaire disséminée, la chirurgie de pontage cardiopulmonaire et l'hémorragie post-opératoire.

16. Composé destiné à être utilisé selon la revendication 15, la maladie ou le trouble où est impliquée l'activité de la kallicréine étant la perméabilité vasculaire rétinienne associée à la rétinopathie diabétique et l'oedème maculaire diabétique.

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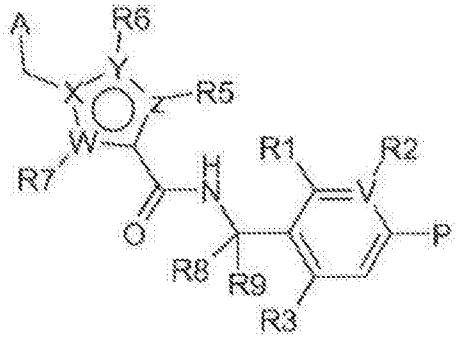
SZABADALMI IGÉNYPONTOK

1. (I) képletű vegyület



Formula (I)

ahol

V jelentése C és N közül megválasztott, így az aromás gyűrű, amelynek V tagja, jelentése fenil vagy piridin;

R2 hiányzik, ha V jelentése N; vagy, ha jelen van, R2 jelentése H, alkil, alkoxi, CN, halogén és CF_3 közül megválasztott;

R1 és R3 jelentése egymástól függetlenül H, alkil, alkoxi, CN, halogén és CF_3 közül megválasztott;

W, X, Y és Z jelentése egymástól függetlenül C, N, O és S közül megválasztott, így a gyűrű, amelynek W, X, Y és Z tagja, jelentése öt-tagú aromás heterociklus;

ahol

R5, R6 és R7 egymástól függetlenül hiányzik vagy jelentése egymástól függetlenül H, alkil, halogén, aril, heteroaril és CF_3 közül megválasztott;

P jelentése $-C(R10)(R11)NH_2$;

R8 és R9 jelentése egymástól függetlenül H és alkil közül megválasztott, vagy együtt cikloalkil gyűrű;

R10 és R11 jelentése egymástól függetlenül H és alkil közül megválasztott, vagy együtt cikloalkil gyűrű vagy ciklusos éter;

A jelentése N-atomon keresztül kapcsolódó morfolin, aril, heteroaril,

alkil jelentése lineáris telített szénhidrogén legfeljebb 10 szénatommal (C_1-C_{10}) vagy elágazó telített szénhidrogén 3 és 10 közötti szénatommal (C_3-C_{10}); amely alkil adott esetben szubsztituált 1 vagy 2 szubsztituenssel, amely egymástól függetlenül (C_1-C_6)alkoxi, OH, CN, CF_3, -COOR12, -CONR12R13, $H(CH_2)_{1-3}CON(R12)(CH_2)_{1-3}$-, fluor és -NR12R13 közül megválasztott;

cikloalkil jelentése monociklusos telített szénhidrogén 3 és 7 közötti szénatommal; ahol a cikloalkil adott esetben szubsztituált, amely szubsztituens alkil, alkoxi és NR12R13 közül megválasztott;

ciklusos éter jelentése monociklusos telített szénhidrogén 4 és 7 közötti szénatommal, ahol az egyik gyűrű szénatom helyett oxigénatom áll;

alkoxi jelentése lineáris, O-atomon keresztül kapcsolódó szénhidrogén 1 és 6 közötti szénatommal (C_1-C_6) vagy elágazó O-atomon keresztül kapcsolódó szénhidrogén 3 és 6 közötti szénatommal (C_3-C_6); amely alkoxi adott esetben szubsztituált 1 vagy 2 szubsztituenssel, amely egymástól függetlenül aril, OH, CN, CF_3, -COOR12, -CONR12R13, fluor és NR12R13 közül megválasztott;
aril jelentése fenil, bifenil vagy naftil; amely aril adott esetben szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, OH, halogén, CN, -morfolinil,-piperidinil, heteroaril, aril^b, -O-aril^b, -$(CH_2)_{1-3}$-aril^b, -$(CH_2)_{1-3}$-heteroaril, -COOR12, - CONR12R13, -$(CH_2)_{1-3}$-NR14R15, CF_3 és NR12R13 közül megválasztott;
aril^b jelentése fenil, bifenil vagy naftil, amely adott esetben szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, OH, halogén, CN, morfolinil, piperidinil, -COOR12, -CONR12R13, CF_3 és NR12R13 közül megválasztott;
heteroaril jelentése 5, 6, 9 vagy 10 tagú mono- vagy biciklusos aromás gyűrű, amely tartalmaz, ahol lehet, 1, 2 vagy 3 olyan gyűrű tagot, amely egymástól függetlenül N, NR12, S és O közül megválasztott; amely heteroaril adott esetben szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, OH, halogén, CN, morfolinil, piperidinil, aril, -$(CH_2)_{1-3}$-aril, heteroaril^b, -COOR12, -CONR12R13, CF_3 és NR12R13 közül megválasztott;
heteroaril^b jelentése 5, 6, 9 vagy 10 tagú mono- vagy biciklusos aromás gyűrű, amely tartalmaz, ahol lehet, 1, 2 vagy 3 olyan gyűrű tagot, amely egymástól függetlenül N, NR12, S és O közül megválasztott; amely heteroaril^b adott esetben szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, OH, halogén, CN, morfolinil, piperidinil, aril, -$(CH_2)_{1-3}$-aril,-COOR12, -CONR12R13, CF_3 és NR12R13 közül megválasztott;
R12 és R13 jelentése egymástól függetlenül H és alkil közül megválasztott; vagy R12 és R13 jelentése a kapcsolódó nitrogénatommal együtt 4-, 5-, 6- vagy 7-tagú heterociklusos gyűrű, amely telített vagy telítetlen 1 vagy 2 kettős kötéssel;
R14 és R15 jelentése a kapcsolódó nitrogénatommal együtt 4-, 5-, 6- vagy 7-tagú heterocicklusos gyűrű, amely telített vagy telítetlen 1 vagy 2 kettős kötéssel, és adott esetben oxo szubsztituált;
ahol
ha R5, R6 és R7 hiányzik vagy jelentése H, akkor:
vagy
R10 és R11 jelentése együtt cikloalkil gyűrű vagy ciklusos éter;
vagy
A jelentése aril és aril jelentése fenil, bifenil vagy naftil, amely szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül OH, heteroaril, aril^b, -O-aril^b, -$(CH_2)_{1-3}$-aril^b, -$(CH_2)_{1-3}$-heteroaril, -COOR12, -CONR12R13, és -$(CH_2)_3$-NR14R15 közül megválasztott; ahol
aril^b jelentése fenil, bifenil vagy naftil, ahol aril^b szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, OH, halogén, CN, morfolinil, piperidinil, -COOR12, -CONR12R13, CF_3 és NR12R13 közül megválasztott; és

heteroaril jelentése 5, 6, 9 vagy 10 tagú mono- vagy biciklusos aromás gyűrű, amely tartalmaz, ahol lehet, 1, 2 vagy 3 olyan gyűrű tagot, amely egymástól függetlenül N, NR12, S és O közül megválasztott, amely heteroaril szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, halogén, CN, aril, morfolinil, piperidinil, -$(CH_2)_{1-3}$-aril, heteroaril^b, -COOR12, - CONR12R13, CF_3 és -NR12R13 közül megválasztott;

vagy

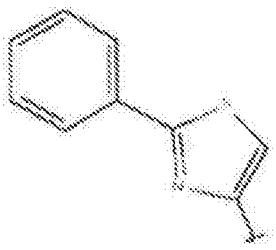
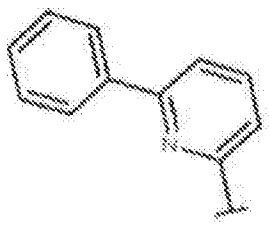
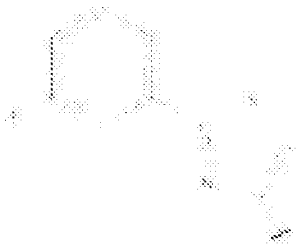
A jelentése heteroaril és heteroaril jelentése 5, 6, 9 vagy 10 tagú mono- vagy biciklusos aromás gyűrű, amely tartalmaz, ahol lehet, 1, 2 vagy 3 olyan gyűrű tagot, amely egymástól függetlenül N, NR12, S és O közül megválasztott, amely heteroaril szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül aril, -$(CH_2)_{1-3}$-aril, heteroaril^b,-COOR12, és -CONR12R13 közül megválasztott; ahol aril jelentése fenil, bifenil vagy naftil, ahol aril szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, OH, halogén, CN, morfolinil, piperidinil, heteroaril, aril^6, -O-aril^b, -$(CH_2)_{1-3}$-aril^b, -$(CH_2)_{1-3}$-heteroaril, -COOR12, -CONR12R13, -COR12R13, -$(CH_2)_{1-3}$-NR14R13, CF_3 és -NR12R13 közül megválasztott; és

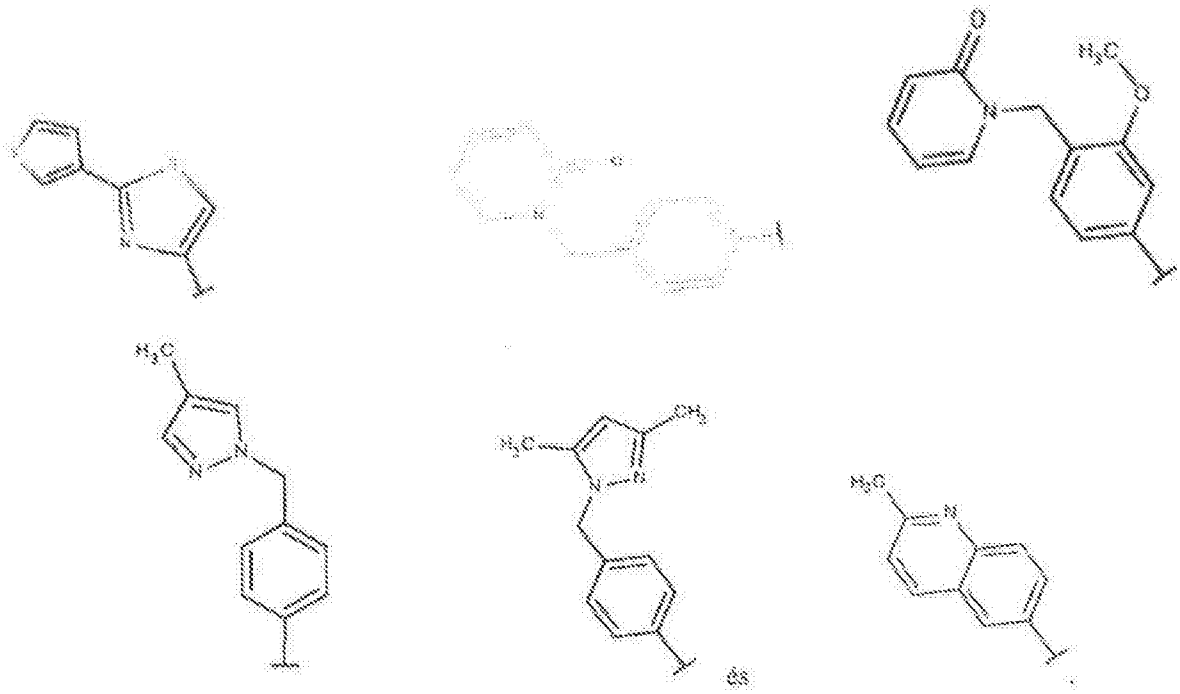
heteroaril^b jelentése 5, 6, 9 vagy 10 tagú mono- vagy biciklusos aromás gyűrű, amely tartalmaz, ahol lehet, 1, 2 vagy 3 olyan gyűrű tagot, amely egymástól függetlenül N, NR12, S és O közül megválasztott, amely heteroaril^6 szubsztituált 1, 2 vagy 3 szubsztituenssel, amely egymástól függetlenül alkil, alkoxi, halogén, CN, morfolinil, piperidinil, aril, -$(CH_2)_{1-3}$-aril, -COOR12, -CONR12R13, CF_3 és NR12R13 közül megvá̈lasztott;

és ennek tautomer formái, sztereoizomer formái (többek között enantiomer formái, diasztereoizomer formái és ezek racém és nem-racém keverékei), gyógyszerészetileg alkalmazható sói és szolvátjai.

2. Az 1. igénypont szerinti vegyület, ahol R5, R6 és R7 közül legalább az egyik jelentése alkil, halogén, aril, heteroaril és CF_3 közül megválasztott.

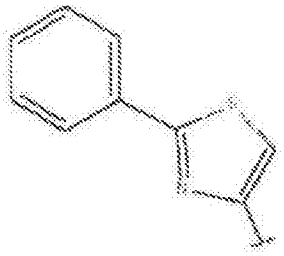
3. Az 1. igénypont vagy 2. igénypont szerinti vegyület, ahol A jelentése az alábbiak közül megválasztott:

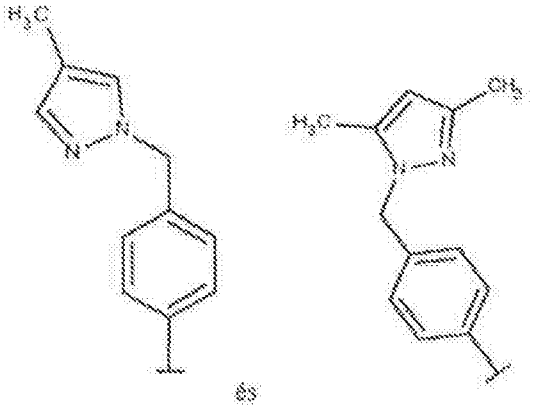


és

4. Az előző 1-3. igénypontok bármelyike szerinti vegyület, ahol A jelentése:



5. Az 1. igénypont szerinti vegyület, ahol R5, R6 és R7 hiányzik vagy jelentése H; és A jelentése az alábbiak közül megválasztott:



és

6. Az 1-4. igénypontok bármelyike szerinti vegyület, ahol X jelentése N és W, Y és Z jelentése C.

7. A 6. igénypont szerinti vegyület, ahol R5 jelentése H, és R6 és R7 jelentése metil.

8. Az 1-7. igénypontok bármelyike szerinti vegyület, ahol R8 és R9 jelentése H.

9. Az 1-5. igénypontok bármelyike szerinti vegyület, ahol:
W jelentése C;
X jelentése N;
Y jelentése C;
Z jelentése C;
R5 jelentése H;
R6 és R7 jelentése CH_3;
R8 és R9 jelentése H; és
R10 és R11 jelentése egyaránt H vagy együtt ciklopropán gyűrű.

10. Az 1-9. igénypontok bármelyike szerinti vegyület, ahol V jelentése C.

11. Az 1-10. igénypontok bármelyike szerinti vegyület, ahol R1 jelentése alkil és/vagy R3 jelentése alkil.

12. Az 1. igénypont szerinti vegyület az alábbiak közül megválasztva:
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-2-metil-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-(1-amino-ciklopropil)-benzilamid;
2,5-dimetil-1-(6-fenil-piridin-2-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-benzilamid;
1-[2-(3-fluor-fenil)-tiazol-4-ilmetil]-2,5-dimetil-1H-pirrol-3-karbonsav-4-aminometil-benzilamid;
2,5-dimetil-1-(2-tiofen-3-il-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-(6-aminometil-piridin-3-ilmetil)-amid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-3-fluor-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-2-fluor-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-2-klór-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-2-trifluormetil-benzilamid;
2,5-dimetil-1-(2-fenil-tiazol-4-ilmetil)-1H-pirrol-3-karbonsav-4-aminometil-2-metoxi-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirazol-4-karbonsaav-4-aminometil-benzilamid;
1-[4-(3,5-dimetil-pirazol-1-ilmetil)-benzil]-1H-pirazol-4-karbonsav-4-aminometil-benzilamid;
2,5-dimetil-1-[4-(2-oxo-2H-piridin-1-ilmetil)-benzil]-1H-pirrol-3-karbonsav-4-aminometil-benzilamid;
2,5-dimetil-1-[4-(2-oxo-2H-piridin-1-ilmetil)-benzil]-1H-pirrol-3-karbonsav-4-aminometil-2-metil-benzilamid;
1-etil-4-metil-5-[4-(2-oxo-2H-piridin-1-ilmetil)-benzil]-1H-pirrol-2-karbonsav-4-aminometil-2-metil-benzilamid;

2,5-dimetil-1-[4-(2-oxo-2H-piridin-1-ilmetil)-benzil]-1H-pirrol-3-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-etil-4-metil-5-[4-(2-oxo-2H-piridin-1-ilmetil)-benzil]-1H-pirrol-2-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
2,5-dimetil-1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirrol-3-karbonsav-4-aminometil-benzilamid;
2,5-dimetil-1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirrol-3-karbonsav-4-aminometil-2-metil-benzilamid;
1-etil-4-metil-5-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirrol-2-karbonsav-4-aminometil-2-metil-benzilamid;
2,5-dimetil-1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirrol-3-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-etil-4-metil-5-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirrol-2-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-imidazol-4-karbonsav-4-aminometil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirazol-4-karbonsav-4-aminometil-2-metil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-imidazol-4-karbonsav-4-aminometil-2-metil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-[1,2,3]triazol-4-karbonsav-4-aminometil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-[1,2,3]triazol-4-karbonsav-4-aminometil-2-metil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-imidazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-[1,2,3]triazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-etil-4-metil-5-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirrol-2-karbonsav-4-aminometil-benzilamid;
1-etil-4-metil-5-[4-(2-oxo-2H-piridin-1-ilmetil)-benzil]-1H-pirrol-2-karbonsav-4-aminometil-benzilamid;
5-metil-1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-1H-pirazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-3-trifluormetil-1H-pirazol-4-karbonsav-4-aminometil-3-fluor-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-3-trifluormetil-1H-pirazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-[4-(4-metil-pirazol-1-ilmetil)-benzil]-3-trifluormetil-1H-pirazol-4-karbonsav-4-aminometil-3-fluor-2-metil-benzilamid;

3-metil-1-(2-metil-kinolin-6-ilmetil)-1H-pirazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
5-metil-1-(2-metil-kinolin-6-ilmetil)-1H-pirazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-(2-metil-kinolin-6-ilmetil)-3-trifluormetil-1H-pirazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
1-(2-pirrolidin-1-il-piridin-4-ilmetil)-3-trifluormetil-1H-pirazol-4-karbonsav-4-aminometil-2,6-dimetil-benzilamid;
és ezek gyógyszerészetileg alkalmazható sói és szolvátjai.

13. Gyógyszerkészítmény, amely tartalmaz egy, az 1-12. igénypontok bármelyike szerinti vegyületet és gyógyszerészetileg alkalmazható hordozóanyagot, higítószert vagy segédanyagot.

14. Az 1-12. igénypontok bármelyike szerinti vegyület gyógyászatban történő alkalmazásra.

15. Az 1-12. igénypontok bármelyike szerinti vegyület olyan betegség vagy állapot kezelésében történő alkalmazásra, amely összefügg a plazma kallikrein aktivitással, ahol a betegség vagy állapot gyengült látáséleség, diabetikus retinopátia, diabetikus makuláris ödéma, öröklött angioödéma, diabetesz, hasnyálmirigy gyulladás, agyvérzés, nefropátia, kardiomiopátia, neuropátia, gyulladásos bélbetegség, ízületi gyulladás, gyulladás, szeptikus sokk, hipotenzió, rák, felnőtt légzési distressz szindróma, disszeminált intravaszkuláris koaguláció, kardiopulmonáris bypass műtét és műtét utáni vérzés közül megválasztott.

16. A 15. igénypont szerinti vegyület az adott alkalmazásra, ahol a betegség vagy állapot, amely összefügg a plazma kallikrein aktivitással, diabetikus retinopátiával és diabetikus makuláris ödémával összefüggő retina vaszkuláris permeabilitás.