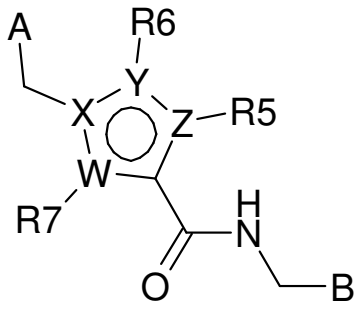
CLAIMS

1. A compound of formula (I),



Formula (I)

wherein

B is phenyl substituted with 1 to 4 substituents selected from alkyl^b, alkoxy, OH, halo, CN, heteroaryl, COO(alkyl), NHCOR8, CONR8R9, OCF_3, and CF_3;
or B is selected from benzothiophenyl, benzofuranyl, benzomorpholinyl and a 5 or 6 membered heterocyclic ring containing one or two heteroatoms selected from N, O and S; wherein said 5 or 6 membered heterocyclic ring may be aromatic or non-aromatic; and wherein said benzothiophenyl, said benzofuranyl, said benzomorpholinyl or said 5 or 6 membered heterocyclic ring is substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, OH, oxo, halo, CN, heteroaryl, COO(alkyl), NHCOR8, CONR8R9, OCF_3 and CF_3;

W is C and 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;

R5 and R6 are independently absent or independently selected from H, alkyl, cycloalkyl, -NR8R9, CN, -NR8COR9 and CF_3; wherein at least one of R5 and R6 is present and is not H;
R7 is H;

A is selected from aryl and heteroaryl; wherein aryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, methylenedioxy, ethylenedioxy, OH, halo, CN, heteroaryl, -$(CH_2)_{0-3}$-O-heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR10, -CONR10R11, -$(CH_2)_{0-3}$-NR10R11, OCF_3 and CF_3; and heteroaryl is substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, OCF_3, halo, CN, aryl, -$(CH_2)_{1-3}$-aryl, -$(CH_2)_{0-3}$-NR10R11, heteroaryl^b, -COOR10, -CONR10R11 and CF_3;

R8 and R9 are independently selected from H and alkyl;

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

alkyl^b is a linear saturated hydrocarbon having up to 6 carbon atoms or a branched saturated hydrocarbon of between 3 and 6 carbon atoms (C_{3-6}); alkyl^b may optionally be substituted with 1 or 2 substituents independently selected from (C_1-C_6)alkoxy, OH, CN, CF_3, COOR10, CONR10R11 and fluoro;

cycloalkyl is a monocyclic saturated hydrocarbon of between 3 and 6 carbon atoms;

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

aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, methylenedioxy, ethylenedioxy, OH, halo, CN, heteroaryl, -$(CH_2)_{0-3}$-O-heteroaryl, aryl^b, -O-aryl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{1-3}$-heteroaryl, -COOR10, -CONR10R11, -$(CH_2)_{0-3}$-NR10R11, OCF_3 and CF_3;

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, -COOR10, -CONR10R11, CF_3 and NR10R11;

heteroaryl is a 5, 6, 9 or 10 membered mono- or bi-cyclic aromatic ring, containing, where possible, 1, 2, 3 or 4 ring members independently selected from N, NR8, S and O; heteroaryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, OCF_3, halo, CN, aryl, -$(CH_2)_{1-3}$-aryl, -$(CH_2)_{0-3}$-NR10R11, heteroaryl^b, -COOR10, -CONR10R11 and CF_3;

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

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

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 B is selected from phenyl substituted with 1 to 4 substituents selected from alkyl^b, alkoxy, OH, halo, CN, heteroaryl, COO(alkyl), NHCOR8, CONR8R9, OCF_3, and CF_3; or B is selected from benzothiophenyl, benzofuranyl, and a 5 or 6 membered heterocyclic ring containing one or two heteroatoms selected from N, O and S; wherein said 5 or 6 membered heterocyclic ring may be aromatic or non-aromatic; and wherein said benzothiophenyl, said benzofuranyl or said 5 or 6 membered heterocyclic ring is substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, OH, oxo, halo, CN, heteroaryl, COO(alkyl), NHCOR8, CONR8R9, OCF_3 and CF_3; wherein alkyl^b, alkoxy, R8 and R9 are as defined in claim 1.

3. A compound according to claim 1 or claim 2, wherein B is selected from phenyl, thiophenyl, benzothiophenyl and pyridyl, each substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, halo, CN, COO(alkyl), CONR8R9, OCF_3 and CF_3; wherein alkyl^b, alkoxy, R8 and R9 are as defined in claim 1.

4. A compound according to any one of claims 1 to 3, wherein B is selected from phenyl and pyridyl, each substituted with 1 to 3 substituents selected from alkyl^b, alkoxy, CF_3 and halo; wherein alkyl^b and alkoxy are as defined in claim 1.

5. A compound according to any one of claims 1 to 4, wherein W is C and 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.

6. A compound according to any one of claims 1 to 5, wherein W is C, X is N and Y and Z are selected from C and N.

7. A compound according to any one of claims 1 to 6, wherein R5 and R6 are independently absent or independently selected from H, CH_2OCH_3, cycloalkyl, -NR8R9, -NR8COR9, CN and CF_3; wherein cycloalkyl, R8 and R9 are as defined in claim 1; and wherein at least one of R5 and R6 is present and is not H.

8. A compound according to any one of claims 1 to 7, wherein A is phenyl substituted with $-(CH_2)_{1-3}$-heteroaryl or $-(CH_2)_{1-3}$-NR10R11 and, optionally, 1 or 2 additional substituents independently selected from alkyl, halo and CF_3; wherein alkyl, heteroaryl, R10 and R11 are as defined in claim 1.

9. A compound according to any one of claims 1 to 7, wherein A is pyridyl substituted with heteroaryl[b] or -NR10R11 and, optionally, 1 or 2 additional substituents independently selected from alkyl, halo and CF_3; wherein alkyl, heteroaryl[b], R10 and R11 are as defined in claim 1.

10. A compound according to claim 1, selected from:
below:

3-Amino-1-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid 2-fluoro-3-methoxy-benzylamide;

N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(2-fluoro-5-methoxyphenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(4-chloro-2,6-difluorophenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-{[3-chloro-2-fluoro-6-(trifluoromethyl)phenyl]methyl}-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(2-fluoro-4-methylphenyl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(5-chloro-1-benzothiophen-3-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

3-cyclopropyl-N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2-fluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2-fluoro-3,6-dimethoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-(dimethylamino)-N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2-fluoro-5-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2-fluoro-4-methylphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2,6-difluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[2-(difluoromethyl)phenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[2-(difluoromethyl)-3-methoxyphenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-amino-N-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-acetamido-N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(3-chloro-2,6-difluorophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(5-chloro-2-cyanophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(6-cyano-2-fluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[5-methoxy-2-(trifluoromethyl)phenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[2-(difluoromethyl)-6-fluorophenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[2-(difluoromethyl)-5-methoxyphenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[2-(difluoromethyl)-6-fluoro-3-methoxyphenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2-carbamoyl-6-fluorophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2-carbamoyl-5-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[3-(difluoromethoxy)-2-fluorophenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-{[2-(difluoromethoxy)-6-fluorophenyl]methyl}-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2,5-difluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2-fluoro-6-methylphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(6-chloro-2-fluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-amino-N-[(2-fluoro-3-hydroxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(3-ethyl-2-fluorophenyl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-(methoxymethyl)-N-[(3-methoxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2,6-difluoro-3-methoxyphenyl)methyl]-3-(methoxymethyl)-1-({4-[(4-methyl-2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(2,6-difluoro-3-methoxyphenyl)methyl]-1-({4-[(5-fluoro-2-oxopyridin-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(2-fluoro-3-methoxyphenyl)methyl]-2-methyl-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(2-fluoro-3-methoxyphenyl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)-2-(trifluoromethyl)imidazole-4-carboxamide;

3-amino-N-[(7-chloro-4-methyl-2,3-dihydro-1,4-benzoxazin-2-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-amino-N-[(7-chloro-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide

and pharmaceutically acceptable salts and solvates thereof.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 and a pharmaceutically acceptable carrier, diluent or excipient.

12. A compound as claimed in any one of claims 1 to 10 for use in medicine.

13. The use of a compound as claimed in any one of claims 1 to 10 in the manufacture of a medicament for the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated, and wherein the disease or condition in which plasma kallikrein activity is implicated is selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery, or retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

14. A compound as claimed in any one of claims 1 to 10 for use in a method of treatment of a disease or condition in which plasma kallikrein activity is implicated.

15. The use of claim 13 or a compound for use as claimed in claim 14 wherein, the disease or condition in which plasma kallikrein activity is implicated is selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.

16. The use of claim 13 or a compound for use as claimed in claim 14, wherein the disease or condition in which plasma kallikrein activity is implicated is retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

17. The use of claim 13 or a compound for use as claimed in claim 14, wherein the disease or condition in which plasma kallikrein activity is implicated is diabetic macular edema.

18. The use of claim 13 or a compound for use as claimed in claim 14, wherein the disease or condition in which plasma kallikrein activity is implicated is hereditary angioedema.