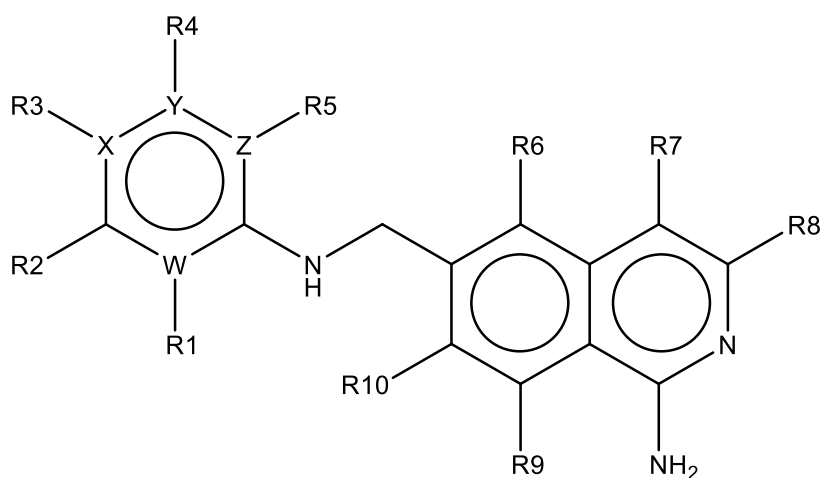


CLAIMS

1. A compound of formula (I),



Formula (I)

wherein:

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 benzene, pyridine, pyridazine, pyrimidine, pyrazine, and triazine;

R1, R4 and R5 are independently absent, or independently selected from H, alkyl, alkoxy, -CF₃, -OH, -CN, halo, -COOR₁₂, and -CONR₁₄R₁₅;

when X is C, one of R2 and R3 is -L-V-R₁₃, and the other of R2 and R3 is selected from H, alkyl, alkoxy, -CF₃, -OH, -CN, halo, -COOR₁₂, and -CONR₁₄R₁₅; or

when X is N, R2 is -L-V-R₁₃, and R3 is absent;

R6, R7, R8, R9, and R10 are independently selected from H, alkyl, alkoxy, -CF₃, -OH, -CN, halo, -COOR₁₂, and -CONR₁₄R₁₅;

L is selected from a bond, alkylene, and -C(O)-;

V is absent, or selected from O and NR₁₂;

R₁₂ is selected from H and alkyl^b;

R13 is $(\text{CH}_2)_{0-3}$ (heterocyclyl);

alkyl is a linear saturated hydrocarbon having up to 4 carbon atoms ($\text{C}_1\text{-C}_4$) or a branched saturated hydrocarbon of 3 or 4 carbon atoms ($\text{C}_3\text{-C}_4$); alkyl may optionally be substituted with 1 or 2 substituents independently selected from $(\text{C}_1\text{-C}_3)$ alkoxy, -OH, -CN, -NR14R15, -NHCOCH₃, halo, -COOR12, and -CONR14R15;

alkyl^b is a linear saturated hydrocarbon having up to 4 carbon atoms ($\text{C}_1\text{-C}_4$) or a branched saturated hydrocarbon of 3 or 4 carbon atoms ($\text{C}_3\text{-C}_4$); alkyl^b may optionally be substituted with 1 or 2 substituents independently selected from -OH, -CN, -NHCOCH₃, and halo;

alkylene is a bivalent linear saturated hydrocarbon having 1 to 4 carbon atoms ($\text{C}_1\text{-C}_4$) or a branched bivalent saturated hydrocarbon having 3 to 4 carbon atoms ($\text{C}_3\text{-C}_4$);

alkoxy is a linear O-linked hydrocarbon of between 1 and 3 carbon atoms ($\text{C}_1\text{-C}_3$) or a branched O-linked hydrocarbon of between 3 and 4 carbon atoms ($\text{C}_3\text{-C}_4$); alkoxy may optionally be substituted with 1 or 2 substituents independently selected from -OH, -CN, -CF₃, -N(R12)₂ and fluoro;

halo is F, Cl, Br, or I;

heterocyclyl is a 4-, 5-, or 6-, membered carbon-containing non-aromatic ring containing one or two ring members that are selected from N, NR16, and O; heterocyclyl may be optionally substituted with 1, 2, 3, or 4 substituents independently selected from alkyl, alkoxy, oxo, -CF₃, -OH, -CN, halo, -COOR12, and -CONR14R15;

R14 and R15 are independently selected from H, and alkyl^b;

R16 is selected from H, and alkyl;

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

2. A compound of formula (I) according to claim 1, or a tautomer, isomer, stereoisomer (including an enantiomer, a diastereoisomer and a racemic or scalemic mixture thereof), a deuterated isotope, and a pharmaceutically acceptable salt and/or solvate thereof,

(a) wherein 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 benzene, pyridine and pyridazine, and/or

(b) wherein 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 benzene, optionally,

wherein R1, R4 and R5 are H, or

(c) wherein 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 pyridine, optionally,

wherein one of R1, R4 and R5 is absent and the other two are H, or

(d) wherein 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 pyrazine, optionally,

wherein two of R1, R4 and R5 is absent and the other one is H.

3. A compound of formula (I) according to any of claims 1 or 2, or a tautomer, isomer, stereoisomer (including an enantiomer, a diastereoisomer and a racemic or scalemic mixture thereof), a deuterated isotope, and a pharmaceutically acceptable salt and/or solvate thereof,

(a) wherein X is C, optionally

(i) wherein R2 is selected from H, alkyl, alkoxy, -CF₃, -OH, -CN, halo, -COOR₁₂, and -CONR₁₄R₁₅ and R3 is -L-V-R₁₃, or

(ii) wherein R3 is selected from H, alkyl, alkoxy, -CF₃, -OH, -CN, halo, -COOR₁₂, and -CONR₁₄R₁₅ and R2 is -L-V-R₁₃, and/or

(b) wherein L is

(i) a bond, or

(ii) methylene, and/or

(c) wherein V is O.

4. A compound of formula (I) according to any of claims 1-3, or a tautomer, isomer, stereoisomer (including an enantiomer, a diastereoisomer and a racemic or scalemic mixture thereof), a deuterated isotope, and a pharmaceutically acceptable salt and/or solvate thereof,

(a) wherein R₁₃ is

(i) heterocyclyl, or

(ii) -CH₂-heterocyclyl, and/or

(b) wherein the heterocyclyl on R13 is piperidinyl, which may be optionally substituted as for heterocyclyl.

5 5. A compound of formula (I) according to any of claims 1-4, or a tautomer, isomer, stereoisomer (including an enantiomer, a diastereoisomer and a racemic or scalemic mixture thereof), a deuterated isotope, and a pharmaceutically acceptable salt and/or solvate thereof, wherein, when present, NR16 is NCH₃.

10 6. A compound of formula (I) according to any of claims 1-5, or a tautomer, isomer, stereoisomer (including an enantiomer, a diastereoisomer and a racemic or scalemic mixture thereof), a deuterated isotope, and a pharmaceutically acceptable salt and/or solvate thereof, wherein R6, R7, R8, R9 and R10 are all H.

15 7. A compound selected from Table 1 or Table 2, or a pharmaceutically acceptable salt, solvate, or solvate of a salt thereof.

20 8. A pharmaceutical composition comprising: a compound, or a pharmaceutically acceptable salt and/or solvate thereof, according to any of claims 1 to 7, and at least one pharmaceutically acceptable excipient.

 9. A compound, or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in any of claims 1 to 7, or the pharmaceutical composition according to claim 8, for use in medicine.

25 10. Use of a compound, or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in any of claims 1 to 7, or the pharmaceutical composition as claimed in claim 8, in the manufacture of a medicament for treatment of a disease or condition in which Factor XIIa activity is implicated.

30 11. The use as claimed in claim 10, wherein, the disease or condition in which Factor XIIa activity is implicated is a bradykinin-mediated angioedema, optionally,
(a) wherein the bradykinin-mediated angioedema is hereditary angioedema, or
(b) wherein the bradykinin-mediated angioedema is non hereditary.

12. The use as claimed in claim 10, wherein the disease or condition in which Factor XIIa activity is implicated is selected from vascular hyperpermeability; stroke including ischemic stroke and haemorrhagic accidents; retinal edema; diabetic retinopathy; DME; retinal vein occlusion; and AMD.

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13. The use as claimed in claim 10, wherein, the disease or condition in which Factor XIIa activity is implicated is a thrombotic disorder, optionally,

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wherein the thrombotic disorder is thrombosis; thromboembolism caused by increased propensity of medical devices that come into contact with blood to clot blood; prothrombotic conditions such as disseminated intravascular coagulation (DIC), Venous thromboembolism (VTE), cancer associated thrombosis, complications caused by mechanical and bioprosthetic heart valves, complications caused by catheters, complications caused by ECMO, complications caused by LVAD, complications caused by dialysis, complications caused by CPB, sickle cell disease, joint arthroplasty, thrombosis induced to tPA, Paget Schroetter syndrome and Budd-Chari syndrome; and atherosclerosis.

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14. The use as claimed in claim 10, wherein, the disease or condition in which Factor XIIa activity is implicated is selected from neuroinflammation; neuroinflammatory/neurodegenerative disorders such as MS (multiple sclerosis); other neurodegenerative diseases such as Alzheimer's disease, epilepsy and migraine; sepsis; bacterial sepsis; inflammation; vascular hyperpermeability; and anaphylaxis.

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15. The use as defined in any of claims 10-14, wherein the compound targets FXIIa.

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