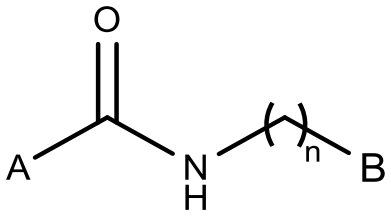
CLAIMS

1. A compound of formula (I) or (Ia),

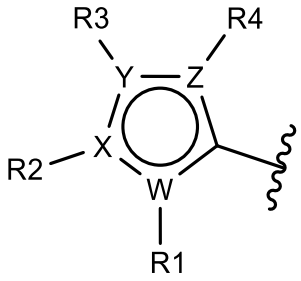


Formula (I)

wherein:

n is 0, 1, or 2;

A is (i) a 5- membered heteroaryl of formula (II),



Formula (II)

wherein W is S;

Z is C or N;

X and Y are C;

R1 is absent;

R4 is absent or H;

R2 are R3 are independently selected from H, halo, alkyl, $-SO_2NR13R14$, $-(CH_2)_{0-3}$heterocyclyl, $-(CH_2)_{0-3}NR12(CH_2)_{0-3}$(heterocyclyl), and $-(CH_2)_{0-3}$aryl; and

wherein one of R2 or R3 is not H; or

wherein W is S;

X, Y and Z are C;

R1 is absent;

R3 is halo or alkyl;

R4 is H, halo, or alkyl; and

R2 is selected from -$(CH_2)_{0-3}$NR13R14, -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(aryl), -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$O -$(CH_2)_{0-3}$(aryl), -$(CH_2)_{0-3}$-O-$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$-O-$(CH_2)_{0-3}$(heteroaryl), -$(CH_2)_{0-3}$-O-$(CH_2)_{1-4}$NR13R14, and -$(CH_2)_{0-3}$heterocyclyl; or

wherein X, Y and Z are independently N, C or S;

wherein at least one of X, Y and Z is N or S;

W is C;

R3 and R4 are independently absent or independently selected from H, alkyl and halo;

R2 is selected from H, halo, alkyl, and cycloalkyl ; and

R1 is selected from -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$NR12CO$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$-O-$(CH_2)_{0-3}$(heterocyclyl), and -$(CH_2)_{0-3}$heterocyclyl; or

wherein Y and Z are N ;

W and X are C;

R1 and R2 are selected from H, halo, alkyl, cycloalkyl, and -$(CH_2)_{0-3}$aryl;

R3 and R4 are independently absent or independently selected from -$(CH_2)_{0-3}$heterocyclyl, and -$(CH_2)_{0-3}$aryl; and

wherein at least one of R3 or R4 is selected from -$(CH_2)_{0-3}$heterocyclyl, and -$(CH_2)_{0-3}$aryl; or

wherein Y or Z are independently C, N or S;

wherein at least one of Y and Z is N or S;

W and X are C;

R1 is H;

R2 is selected from H, alkyl, aryl, and halo;

R4 is absent, or selected from H and alkyl; and

R3 is $(CH_2)_{0-3}$(heterocyclyl); or

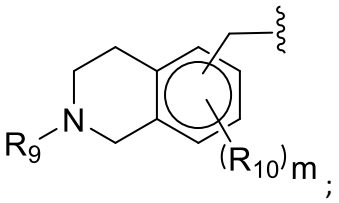
wherein Y and X are independently C or N;

wherein at least one of Y or X is N;

W and Z are C;

R1 and R4 are independently selected from H, alkyl, and halo; and

one of R2 and R3 is absent and the other of R2 and R3 is

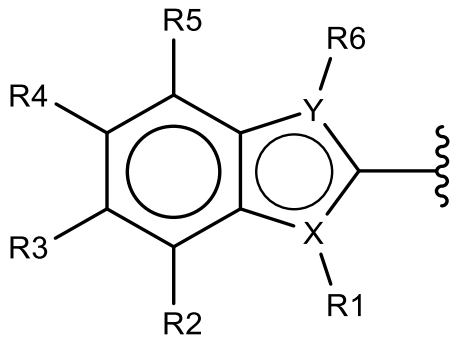


m is 0, 1, 2, or 3;

R9 is selected from H and alkyl;

Each R10 is independently selected from alkyl and halo; or

A is (ii) a 9- membered heteroaromatic bicycle of formula (III)



Formula (III)

wherein X and Y are independently selected from C, N or S;

wherein at least one of X and Y is N or S;

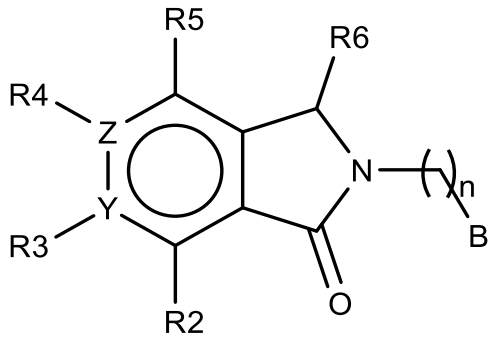
wherein R1 and R6 are independently absent or independently selected from H and -$(CH_2)_{0-3}$heterocyclyl;

wherein R2 is selected from H, halo, -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), and -$(CH_2)_{0-3}$heterocyclyl;

R3, R4, and R5 are independently selected from H, alkyl and halo; and

wherein at least one of R2, R3, R4, R5 is not absent or H;

or,



Formula (Ia)

wherein n is 0, 1, or 2;

wherein Z and Y and independently selected from C and N;

wherein R6 is selected from H and alkyl;

wherein R4 and R5 are independently absent, or independently selected from H, alkyl, and halo; and

wherein one of R2 and R5 is -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), and the other of R2 and R5 is selected from H, alkyl, and halo;

B is:

(i) a fused 6,5- or 6,6- heteroaromatic bicyclic ring, containing N and, optionally, one or two additional heteroatoms independently selected from N, O and S;

wherein the fused 6,5- or 6,6- heteroaromatic bicyclic ring may be optionally substituted with 1, 2, or 3 substituents selected from alkyl, alkoxy, OH, halo, CN, -COOR13, -CONR13R14, CF_3 and -NR13R14;

wherein the 6,5- heteroaromatic bicyclic ring may be attached *via* the 6- or 5-membered ring; or

(ii) phenyl substituted with –$(CH_2)_{1-3}NH_2$ and two groups selected from methyl, ethyl and propyl; or

(iii) pyridine substituted with NH_2 and two groups selected from methyl, ethyl and propyl;

(iv) a fused 6,5- or 6,6- bicyclic ring containing N and containing an aromatic ring fused to a non-aromatic ring and, optionally, one or two additional heteroatoms independently selected from N, O and S;

wherein the fused 6,5- or 6,6- bicyclic ring may be optionally substituted with 1, 2, or 3 substituents selected from alkyl, alkoxy, OH, halo, CN, -COOR13, -CONR13R14, CF_3 and -NR13R14;

wherein the 6,5- bicyclic ring may be attached *via* the 6- or 5- membered ring;

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, -$N(R12)_2$ and fluoro;

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, -NR13R14, -$NHCOCH_3$, -CO(heterocyclyl^b), -COOR13, -CONR13R14, CN, CF_3, halo, oxo, and heterocyclyl^b;

alkyl^b 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, -$N(R12)_2$, -$NHCOCH_3$, CF_3, halo, oxo, cyclopropane, -O(aryl^b), aryl^b, and heterocyclyl^b;

alkylene is a bivalent linear saturated hydrocarbon having 1 to 5 carbon atoms (C_1-C_5); alkylene may optionally be substituted with 1 or 2 substituents independently selected from alkyl, (C_1-C_6)alkoxy, OH, CN, CF_3, and halo;

aryl is phenyl, biphenyl or naphthyl; aryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, OH, -SO_2CH_3, halo, CN, -$(CH_2)_{0-3}$-O-heteroaryl^b, aryl^b, -O-aryl^b, -$(CH_2)_{0-3}$-heterocyclyl^b, -$(CH_2)_{1-3}$-aryl^b, -$(CH_2)_{0-3}$-heteroaryl^b, -COOR13, -CONR13R14, -$(CH_2)_{0-3}$-NR13R14, OCF_3 and CF_3; or two adjacent carbon ring atoms on the aryl may be optionally linked by a heteroalkylene to form a non-aromatic ring containing 5, 6, or 7 ring members; or optionally wherein two adjacent ring atoms on aryl are linked to form a 5- or 6- membered aromatic ring containing 1 or 2 heteroatoms that are selected from N, NR8, S, and O;

aryl^b is phenyl, biphenyl or naphthyl, which may be optionally substituted with 1, 2 or 3 substituents independently selected from methyl, ethyl, propyl, isopropyl, alkoxy, OH, -SO_2CH_3, $N(R12)_2$, halo, CN,

and CF_3; or two adjacent carbon ring atoms on the aryl may be optionally linked by a heteroalkylene to form a non-aromatic ring containing 5, 6, or 7 ring members;

cycloalkyl is a monocyclic saturated hydrocarbon ring of between 3 and 6 carbon atoms (C_3-C_6); cycloalkyl may optionally be substituted with 1 or 2 substituents independently selected from alkyl^b, (C_1-C_6)alkoxy, OH, CN, CF_3, and halo;

halo is F, Cl, Br, or I;

heteroalkylene is a bivalent linear saturated hydrocarbon having 2 to 5 carbon atoms (C_2-C_5), wherein 1 or 2 of the 2 to 5 carbon atoms are replaced with NR8, S, or O; heteroalkylene may optionally be substituted with 1 or 2 substituents independently selected from alkyl (C_1-C_6)alkoxy, OH, CN, CF_3, and halo;

heteroaryl is a 5- or 6- membered carbon-containing aromatic ring containing 1, 2, 3, or 4 ring members that are selected from N, NR8, S, and O; heteroaryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, aryl^b, OH, OCF_3, halo, heterocyclyl^b, CN, and CF_3;

heteroaryl^b is a 5- or 6- membered carbon-containing aromatic ring containing one, two or three ring members that are selected from N, NR8, S, and O; heteroaryl^b may be optionally substituted with 1, 2 or 3 substituents independently selected from methyl, ethyl, propyl, isopropyl, alkoxy, OH, OCF_3, halo, CN, and CF_3;

heterocyclyl is a 4-, 5-, 6-, or 7- membered carbon-containing non-aromatic ring containing one or two ring members that are selected from N, NR8, S, SO, SO_2 and O; heterocyclyl may be optionally substituted with 1, 2, 3, or 4 substituents independently selected from alkyl^b, alkoxy, OH, OCF_3, halo, oxo, CN, -NR13R14, -O(aryl^b), -O(heteroaryl^b) and CF_3; or optionally wherein two ring atoms on heterocyclyl are linked with an alkylene to form a non-aromatic ring containing 5, 6, or 7 ring members; or optionally wherein two adjacent ring atoms on heterocyclyl are linked to form a 5- or 6- membered aromatic ring containing 1 or 2 heteroatoms that are selected from N, NR8, S, and O; or optionally wherein a carbon ring atom on heterocyclyl is substituted with a heteroalkylene such that the carbon ring atom on heterocyclyl together with the heteroalkylene forms a heterocyclyl^b that is spiro to ring heterocyclyl;

heterocyclyl^b is a 4-, 5-, 6-, or 7- membered carbon-containing non-aromatic ring containing one or two ring members that are selected from N, NR12, S, SO, SO_2 and O; heterocyclyl^b may be optionally substituted with 1, 2, 3, or 4 substituents independently selected from methyl, ethyl, propyl, isopropyl, alkoxy, OH, OCF_3, halo, oxo, CN, and CF_3;

R13 and R14 are independently selected from H, $-SO_2CH_3$, alkyl^b, heteroaryl^b, and cycloalkyl; or R13 and R14 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, NR8, S, SO, SO_2, 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 independently selected from oxo, alkyl^b, alkoxy, OH, halo, $-SO_2CH_3$, and CF_3; or R13 and R14 together with the nitrogen atom to which they are attached form a carbon-containing 5- or 6- membered heterocylic ring, which is fused to an aryl^b or a heteroaryl^b;

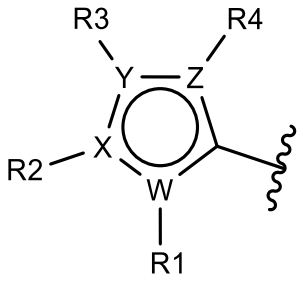
R8 is independently selected from H, $-SO_2CH_3$, alkyl^b, $-(CH_2)_{0-3}$aryl^b, $-(CH_2)_{0-3}$heteroaryl^b, $-(CH_2)_{0-3}$cycloalkyl, and $-(CH_2)_{0-3}$heterocyclyl^b; or R8 is a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring containing 1, 2 or 3 heteroatoms independently selected from N, N12, S, SO, SO_2, 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 independently selected from oxo, alkyl^b, alkoxy, OH, halo, $-SO_2CH_3$, and CF_3;

R12 is independently selected from H, $-SO_2CH_3$, $-COCH_3$, methyl, ethyl, propyl, isopropyl, and cycloalkyl;

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 and scalemic mixture thereof), a deuterated isotope, and a pharmaceutically acceptable salt and/or solvate thereof,

wherein A is a 5- membered heteroaryl of formula (II),



Formula (II)

(a) wherein W is S;

Z is C or N;

X and Y are C;

R1 is absent;

R4 is absent or H;

R2 are R3 are independently selected from H, halo, alkyl, $-SO_2NR13R14$, $-(CH_2)_{0-3}$heterocyclyl, $-(CH_2)_{0-3}NR12(CH_2)_{0-3}$(heterocyclyl), and $-(CH_2)_{0-3}$aryl; and

wherein one of R2 or R3 is not H, optionally,

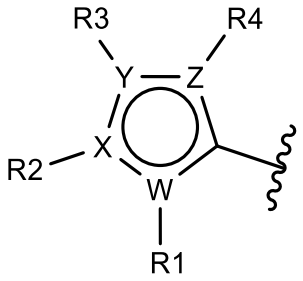
wherein at least one of R2 and R3 is either (i) halo, or (ii) selected from $-(CH_2)_{0-3}$heterocyclyl, $-(CH_2)_{0-3}NR12(CH_2)_{0-3}$(heterocyclyl), and $-(CH_2)_{0-3}$aryl, and/or

(b) wherein R2 is alkyl and R3 is halo, or

(c) wherein R2 is H and R3 is $-(CH_2)_{0-3}$heterocyclyl.

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

wherein A is a 5- membered heteroaryl of formula (II),



Formula (II)

wherein W is S;

X, Y and Z are C;

R1 is absent;

R3 is halo or alkyl;

R4 is H, halo, or alkyl; and

R2 is selected from -$(CH_2)_{0-3}$NR13R14, -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(aryl), -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$O -$(CH_2)_{0-3}$(aryl), -$(CH_2)_{0-3}$-O-$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$-O-$(CH_2)_{0-3}$(heteroaryl), -$(CH_2)_{0-3}$-O-$(CH_2)_{1-4}$NR13R14, and -$(CH_2)_{0-3}$heterocyclyl, optionally,

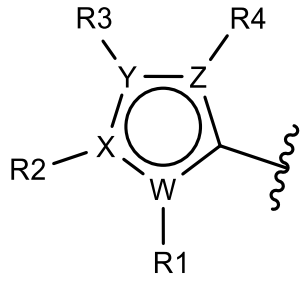
wherein R4 is H and R2 is -$(CH_2)_{0-3}$NR13R14, further optionally

(i) wherein R3 is halo, or

(ii) wherein R3 is alkyl.

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

wherein A is a 5- membered heteroaryl of formula (II),



Formula (II)

wherein X, Y and Z are independently N, C or S;

wherein at least one of X, Y and Z is N or S;

W is C;

R3 and R4 are independently absent or independently selected from H, alkyl and halo;

R2 is selected from H, halo, alkyl, and cycloalkyl; and

R1 is selected from -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$NR12CO$(CH_2)_{0-3}$(heterocyclyl), -$(CH_2)_{0-3}$-O-$(CH_2)_{0-3}$(heterocyclyl), and -$(CH_2)_{0-3}$heterocyclyl, optionally,

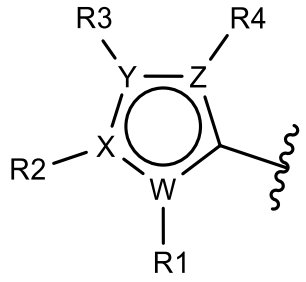
wherein R1 is -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), further optionally

(i) wherein Z is S, and Y and X and C, or

(ii) wherein Z is S, Y is C, and X is N.

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

wherein A is a 5- membered heteroaryl of formula (II),



Formula (II)

wherein Y and Z are N ;

W and X are C;

R1 and R2 are selected from H, halo, alkyl, cycloalkyl, and -$(CH_2)_{0-3}$aryl;

R3 and R4 are independently absent or independently selected from -$(CH_2)_{0-3}$heterocyclyl, and -$(CH_2)_{0-3}$aryl; and

wherein at least one of R3 or R4 is selected from -$(CH_2)_{0-3}$heterocyclyl, and -$(CH_2)_{0-3}$aryl, optionally,

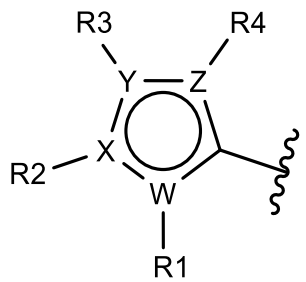
wherein R4 is -$(CH_2)_{0-3}$heterocyclyl, further optionally

(i) wherein R2 is halo, or

(ii) wherein R2 is H.

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

wherein A is a 5- membered heteroaryl of formula (II),



Formula (II)

wherein Y or Z are independently C, N or S;

wherein at least one of Y and Z is N or S;

W and X are C;

R1 is H;

R2 is selected from H, alkyl, aryl, and halo;

R4 is absent, or selected from H and alkyl; and

R3 is -$(CH_2)_{0-3}$(heterocyclyl), optionally,

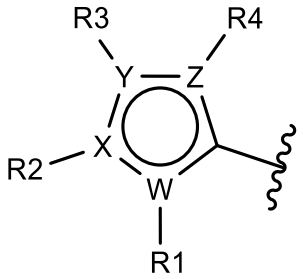
(a) wherein Z is N, and/or

(b) wherein Y is N, and/or

(c) wherein R3 is -$(CH_2)_{0-3}$(heterocyclyl).

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

wherein A is a 5- membered heteroaryl of formula (II),



Formula (II)

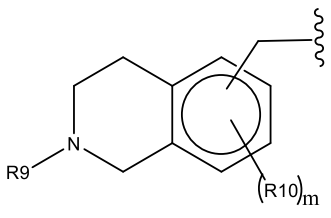
wherein Y and X are independently C or N;

wherein at least one of Y or X is N;

W and Z are C;

R1 and R4 are independently selected from H, alkyl, and halo; and

one of R2 and R3 is absent and the other of R2 and R3 is

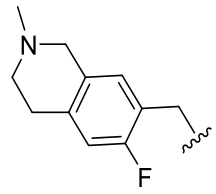


;

m is 0, 1, 2, or 3;

R9 is selected from H and alkyl;

Each R10 is independently selected from alkyl and halo, optionally,

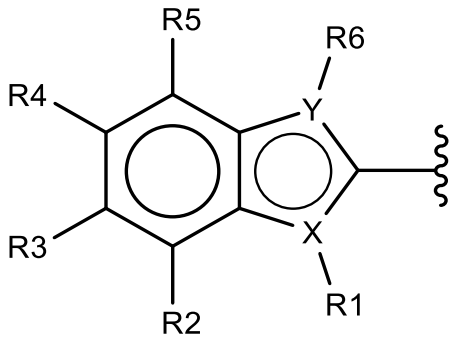


wherein one of R2 and R3 is absent and the other of R2 and R3 is , and/or

wherein R1 is alkyl, preferably $-CH_2OCH_3$.

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

wherein A is a 9- membered heteroaromatic bicycle of formula (III)



Formula (III)

wherein X and Y are independently selected from C, N or S;

wherein at least one of X and Y is N or S;

wherein R1 and R6 are independently absent or independently selected from H and $-(CH_2)_{0-3}$heterocyclyl;

wherein R2 is selected from H, halo, $-(CH_2)_{0-3}NR12(CH_2)_{0-3}$(heterocyclyl), and $-(CH_2)_{0-3}$heterocyclyl;

R3, R4, and R5 are independently selected from H, alkyl and halo; and

wherein at least one of R1, R2, R3, R4, R5 and R6 is not H, optionally,

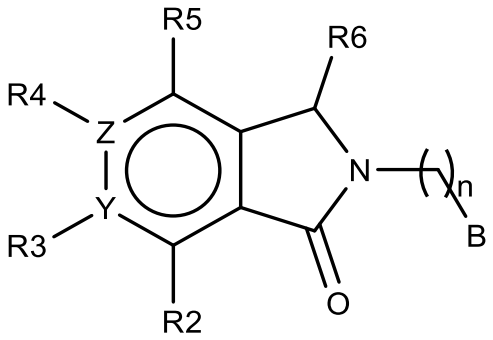
wherein R2 is chloro, further optionally

(i) wherein Y is S, or

(ii) wherein Y is N.

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

wherein A is a compound of formula (Ia),



Formula (Ia)

wherein n is 0, 1, or 2;

wherein Z and Y and independently selected from C and N;

wherein R6 is selected from H and alkyl;

wherein R4 and R5 are independently absent, or independently selected from H, alkyl, and halo; and

wherein one of R2 and R5 is -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl), and the other of R2 and R5 is selected from H, alkyl, and halo, optionally,

wherein R2 can be -$(CH_2)_{0-3}$NR12$(CH_2)_{0-3}$(heterocyclyl).

10. A compound selected from any of Tables 1 to 12, and pharmaceutically acceptable salts and/or solvates thereof.

11. A pharmaceutical composition comprising: a compound or a pharmaceutically acceptable salt and/or solvate thereof according to any of claims 1-10, and at least one pharmaceutically acceptable excipient.

12. A compound, or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in any of claims 1 to 10, or the pharmaceutical composition as claimed in claim 11, for use in medicine.

13. Use of a compound or a pharmaceutically acceptable salt and/or solvate thereof according to any of claims 1 to 10, or the pharmaceutical composition as claimed in claim 11, in the manufacture of a medicament for treatment of a disease or condition in which Factor XIIa activity is implicated.

14. The use as claimed in claim 13,

(a) wherein, the disease or condition in which Factor XIIa activity is implicated is a bradykinin-mediated angioedema, optionally,

wherein the bradykinin-mediated angioedema is hereditary angioedema, or

wherein the bradykinin-mediated angioedema is non hereditary, or

(b) 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, or

(c) wherein, the disease or condition in which Factor XIIa activity is implicated is a thrombotic disorder, optionally,

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, or

(d) 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.

15. The use as defined in claim 14, wherein the compound targets FXIIa.