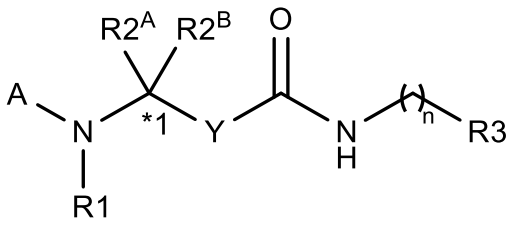
CLAIMS

1. A compound of formula (I):



Formula (I)

wherein

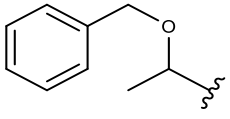
*1 denotes a chiral centre

n = 0, 1 or 2;

A is selected from H, -(C=O)R4, -SO_2R6, and -(CH_2)-R13;

Y is either a bond, or -[CHR5]-;

R1 is H or alkyl^b;

$R2^A$ is selected from H, alkyl, -$(CH_2)_{0-3}$aryl, -$(CH_2)_{0-3}$heteroaryl, -$(CH_2)_{0-3}$cycloalkyl, -$(CH_2)_{0-3}$-[benzothiophene], -$(CH_2)_{0-3}$-[indole], and 

; or,

when Y is a bond, R1 and $R2^A$, together with nitrogen atom to which R1 is attached and the carbon atom to which $R2^A$ is attached, may be linked by alkylene to form a 4-, 5-, or 6-membered saturated heterocycle, optionally wherein the 4-, 5-, or 6- membered saturated heterocycle may be substituted with aryl, or wherein two adjacent carbon atoms on the 4-, 5-, or 6- membered saturated heterocycle may be linked to form a 6-membered aromatic ring, or wherein two adjacent carbon atoms on the 4-, 5-, or 6- membered saturated heterocycle may be linked to form a 3-, 4-, or 5- membered saturated hydrocarbon ring which may be optionally mono- or di- substituted by alkyl^b;

when Y is -[CHR5]-, R5 is H; or,

when Y is -[CHR5]-, together with the carbon atoms to which each of R5 and $R2^A$ are attached, R5 and $R2^A$ may be linked by alkylene to form a 4-, 5-, 6- membered saturated ring; or,

when Y is -[CHR5]-, together with the nitrogen atom to which R1 is attached, the carbon atom to which R5 is attached, and the carbon atom to which $R2^A$ and $R2^B$ are both attached,

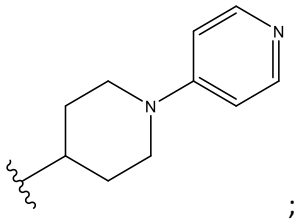
R5 and R1 may be linked by alkylene to form a saturated 4-, 5-, or 6-membered heterocycle, optionally wherein one atom on the saturated 4-, 5-, or 6- membered heterocycle may be linked by alkylene to join with $R2^A$;

$R2^B$ is H or $alkyl^b$; or,
$R2^A$ and $R2^B$, together with the carbon to which $R2^A$ and $R2^B$ are both attached, may be linked by alkylene or heteroalkylene to form a 3-, 4-, 5-, or 6- membered saturated ring, optionally wherein the 3-, 4-, 5-, or 6- membered saturated ring contains one or two ring members that are selected from N and O;

R3 is:

(i) a fused 6,5- or 6,6- bicyclic ring, containing one heteroatom selected from S and N, wherein at least one of the rings is aromatic and, optionally the bicyclic ring contains one additional heteroatom independently selected from N, O and S;
optionally wherein the fused 6,5- or 6,6- bicyclic ring may be substituted with 1, 2, or 3 substituents selected from $alkyl^b$, alkoxy, OH, NH_2, halo, CN, and CF_3;
wherein the fused 6,5- bicyclic ring may be attached via the 6- or 5- membered ring; or

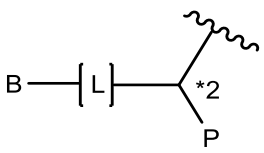
(ii) phenyl, pyridyl, or thiophenyl, which may be optionally substituted with 1, 2 or 3 substituents independently selected from $alkyl^b$, alkoxy, OH, NH_2 halo, CN, CF_3, $-C(=NH)NH_2$, and $heteroaryl^b$;
wherein when n=1, and R3 is phenyl substituted with at least one $-(CH_2NH_2)$, $R2^A$ is alkyl and $R2^B$ is H; or

(iii) 

;

R4 is one of:

(i) a group of formula (II),

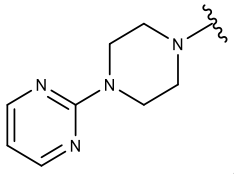


Formula (II)

wherein -[L]- is a bond, -[$(CH_2)_{1-4}$]-, -[(CH_2)-O-(CH_2)]-, or -[O-(CH_2)]-; and P is alkoxy, OH or NR11R12;

wherein *2 denotes a chiral centre, and

wherein when -[L]- is a bond, B is a C_{1-4} linear or branched chain hydrocarbon, and

wherein when -[L]- is -[$(CH_2)_{1-4}$]-, -[(CH_2)-O-(CH_2)]-, or -[O-(CH_2)]-, B is OH, aryl, heteroaryl, heterocyclyl, cycloalkyl or  ; or,

(ii) -$(CH_2)_m$-[fused 6,5- or 6,6- heteroaromatic bicyclic ring], wherein at least one ring atom is a heteroatom selected from O, N or S, and optionally, 1, 2 or 3 additional ring atoms may be selected from N or NH; wherein the fused 6,5- or 6,6- heteroaromatic bicyclic ring may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl[b]; wherein the 6,5- heteroaromatic bicyclic ring may be attached to -$(CH_2)_m$- *via* the 6- or 5- membered ring; or,

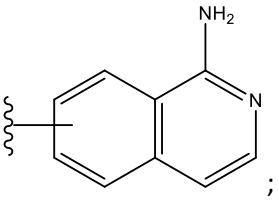
(iii) methyl, -$C(CH_3)_2$(OH), -$C(CH_3)_2$(NHMe), -$(CH_2)_m$-(aryl), -$(CH_2)_m$-(cycloalkyl), -$(CH_2)_m$-(heteroaryl), -$(CH_2)_m$-(heterocyclyl), -(CH_2)-(alkyl), -$(CH(halo)_2)$, -$(CH_2)_m$-(NR8R9), -$(CH_2)_m$-(NR10R7), -$(CH_2)_m$-O-$(CH_2)_k$-(aryl), -$(CH_2)_m$-(SO_2)-$(CH_2)_k$-(aryl), -$(CH_2)_m$-(alkoxy), -$(CH_2)_m$-O-$(CH_2)_k$-(heteroaryl), or -$(CH_2)_m$-[pyridone, which may be optionally substituted by alkyl[b], or CF_3];

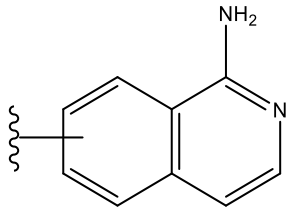
wherein k = 0, 1, 2, or 3;

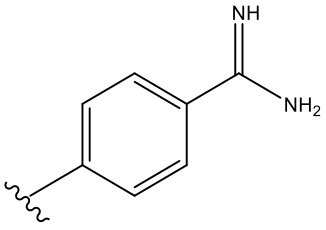
wherein m = 0, 1, 2 or 3;

wherein:

when Y is -[CHR5]- and R5 is H, $R2^A$ is CH_2-aryl or H; and

when Y is -[CHR5]-, R3 is  ;

when A is H, R3 is  ; and

when R3 is  , $R2^A$ is not H;

wherein:

R6 is alkyl or -$(CH_2)_{0-3}$-(aryl);

R7 is independently selected from H, -SO_2CH_3, methyl, ethyl, propyl, isopropyl, and cycloalkyl;

R8 and R9 are independently selected from H, -SO_2CH_3, $alkyl^b$, $heteroaryl^b$, and cycloalkyl; or R8 and R9 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocyclic ring, optionally containing an additional heteroatom selected from N, NR10, 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 independently selected from oxo, $alkyl^b$, alkoxy, OH, halo, -SO_2CH_3, and CF_3; or R8 and R9 together with the nitrogen atom to which they are attached form a carbon-containing 5- or 6- membered heterocyclic ring, which is fused to an $aryl^b$ or a $heteroaryl^b$;

R10 is independently selected from H, -SO_2R6, $alkyl^b$, -$(CH_2)_{0-3}aryl^b$, -$(CH_2)_{0-3}heteroaryl^b$, cycloalkyl, -(C=O)-(aryl), and -$(CH_2)_{0-3}heterocyclyl^b$; or R10 is a carbon-containing 4-, 5-, 6- or 7-membered heterocyclic ring, optionally containing an additional heteroatom selected from N, NR7, 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;

R11 and R12 are independently selected from H, alkyl^b, - SO_2R6, cycloalkyl, -(C=O)O-(alkyl^b), -(C=O)-phenyl, -CH_2-phenyl, and CH_2-COOH; or R11 and R12 together with the nitrogen atom to which they are attached form a carbon-containing 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing an additional heteroatom selected from N, O, and NR10, wherein the heterocyclic ring may be optionally mono- or di-substituted with substituents independently selected from alkyl^b, OH, halo and CF_3;

R13 is selected from heteroaryl, cycloalkyl, heterocyclyl and aryl^b;

wherein:

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, -$N(R7)_2$ and fluoro;

alkyl is a linear saturated hydrocarbon having up to 6 carbon atoms (C_1-C_6) or a branched saturated hydrocarbon of between 3 and 6 carbon atoms (C_3-C_6); alkyl may optionally be substituted with 1 or 2 substituents independently selected from (C_1-C_6)alkoxy, OH, -NR8R9, -$NHCOCH_3$, -CO(heterocyclyl^b), -COOR8, -CONR8R9, CN, CF_3, halo, oxo and heterocyclyl^b;

alkyl^b is a linear saturated hydrocarbon having up to 6 carbon atoms (C_1-C_6) or a branched saturated hydrocarbon of between 3 and 6 carbon atoms (C_3-C_6); alkyl may optionally be substituted with 1 or 2 substituents independently selected from (C_1-C_6)alkoxy, OH, -$N(R7)_2$, -$NHCOCH_3$, CF_3, halo, oxo and cyclopropane;

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, -SO_2NR8R9, 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, -COOR8, -CONR8R9, -$(CH_2)_{0-3}$-NR8R9, 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 which may be optionally substituted with OH; 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, NR10, 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(R7)$_2$, 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 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 methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, OH, CN, CF_3 and halo; optionally wherein two adjacent ring atoms on cycloalkyl are linked to form a 5- or 6-membered saturated hydrocarbon ring;

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 NR10, 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 one, two or three ring members that are selected from N, NR10, S, and O; heteroaryl may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl, alkoxy, heteroaryl^b, phenyl, cycloalkyl, 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, NR10, 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, $COOCH_3$, $COOCH_2CH_3$, $COO\text{-}(CH_2)_2\text{-}CH_3$, COO-(iPr), halo, CN, and CF_3;

heterocyclyl is a 4-, 5-, 6-, or 7- membered carbon-containing non-aromatic ring containing one, two, three, or four ring members that are selected from N, NR10, S, SO, SO_2 and O; heterocyclyl may be optionally substituted with 1, 2, 3, or 4 substituents independently selected from alkyl, alkoxy, $aryl^b$, OH, OCF_3, halo, oxo, CN, NR8R9, -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 ring atoms on heterocyclyl are linked with an heteroalkylene 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 which may optionally contain 1 or 2 heteroatoms that are selected from N, NR10, S, and O;

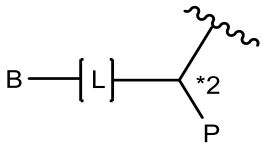
$heterocyclyl^b$ is a 4-, 5-, 6-, or 7- membered carbon-containing non-aromatic ring containing one, two or three ring members that are selected from N, NR7, S, SO, SO_2 and O; $heterocyclyl^b$ may be optionally substituted with 1, 2, 3, or 4 substituents independently selected from methyl, ethyl, propyl, isopropyl, alkoxy, OH, OCF_3, halo, oxo, CN, and CF_3;

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 n = 1.
3. A compound of formula (I) according to any preceding claim, 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 -(C=O)R4.
4. A compound of formula (I) according to any preceding claim, 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,

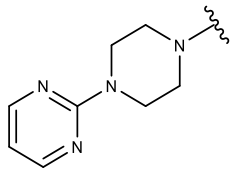
wherein R4 is a group of formula (II),



Formula (II)

wherein -[L]- is -[$(CH_2)_{1-4}$]-, -[(CH_2)-O-(CH_2)]-, or -[O-(CH_2)]-;

P is alkoxy, OH or NR11R12;

and B is OH, aryl, heteroaryl, heterocyclyl, cycloalkyl or .

5. A compound of formula (I) according to any preceding claim, 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 P is:

(i) NR11R12;

(ii) NHR12;

(iii) selected from NH_2, NH(alkyl) and NH(cyclohexyl);

(iv) NH_2;

(v) NH(iPr);

(vi) NH(cyclohexyl); or

(vii) N-linked pyrrolidinyl.

6. A compound of formula (I) according to any preceding claim, 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 -[L]- is:

(i) -[$(CH_2)_{1-4}$]-;

(ii) -[$(CH_2)_2$]-; or

(iii) -[$(CH_2)_4$]-.

7. A compound of formula (I) according to any preceding claim, 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 B is:

(i) aryl;

(ii) phenyl;

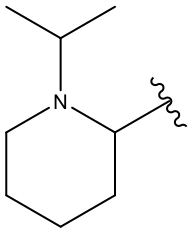
(iii) heterocyclyl; or

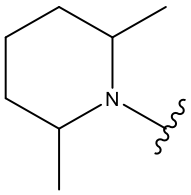
(iv) piperidinyl.

8. A compound of formula (I) according to any one of claims 1 to 3, 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 R4 is:

(i) -$(CH_2)_m$-(heterocyclyl);

(ii)  ; or

(iii) -$(CH_2)_m$-(NR8R9), optionally wherein -(NR8R9) is .

9. A compound of formula (I) according to any of claims 1 to 2, 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 -SO_2R6.

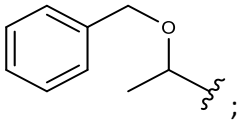
10. A compound of formula (I) according any preceding claim, or a tautomer, isomer, stereoisomer (including an enantiomer, a diastereoisomer and a racemic and scalemic mixture thereof), a deuterated isotope, and a pharmaceutically acceptable salt and/or solvate thereof,

wherein R1 is H.

11. A compound of formula (I) according to any preceding claim, 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,

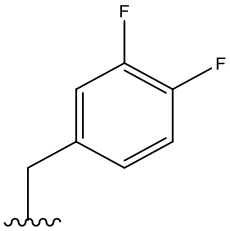
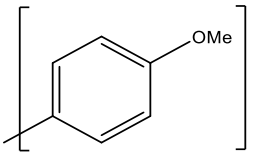
wherein $R2^A$ is:

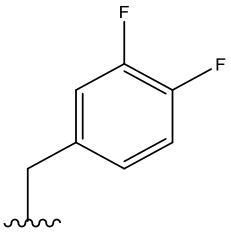
(i) selected from H, alkyl, -$(CH_2)_{0-3}$aryl, -$(CH_2)_{0-3}$heteroaryl, -$(CH_2)_{0-3}$cycloalkyl, -$(CH_2)_{0-3}$-[benzothiophene], -$(CH_2)_{0-3}$-[indole], and ;

(ii) alkyl;

(iii) methyl;

(iv) -$(CH_2)_{0-3}$aryl;

(v) selected from , -(CH_2)-[naphthyl], -(CH_2)-[mono-, or di- chlorophenyl], -(CH_2)-[mono-, or di- fluorophenyl], -(CH_2)-phenyl, -$(CH_2)_2$-phenyl, -(CH_2)- and -(CH_2)-biphenyl; or

(vi) .

12. A compound of formula (I) according to any one of claims 1 to 9, 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 R1 and $R2^A$, together with nitrogen atom to which R1 is attached and the carbon atom to which $R2^A$ is attached, are linked by alkylene to form:

(i) a 4-, 5-, or 6- membered saturated heterocycle; or

(ii) a 4- membered saturated heterocycle.

13. A compound of formula (I) according to any preceding claim, 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 Y is a bond.

14. A compound of formula (I) according to any one of claims 1 to 9 and 13, 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 $R2^A$ and $R2^B$, together with the carbon to which $R2^A$ and $R2^B$ are both attached, are linked by alkylene or heteroalkylene to form a 3-, 4-, 5-, or 6- membered saturated ring.

15. A compound of formula (I) according to any preceding claim, 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 R3 is:

(i) a fused 6,5- or 6,6- bicyclic ring, containing one heteroatom selected from S and N, wherein at least one of the rings is aromatic and, optionally the bicyclic ring contains one additional heteroatom independently selected from N, O and S;

optionally wherein the fused 6,5- or 6,6- bicyclic ring may be substituted with 1, 2, or 3 substituents selected from $alkyl^b$, alkoxy, OH, NH_2, halo, CN, and CF_3;

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

(ii) a fused 6,5- or 6,6- bicyclic ring, containing a N atom and, optionally the bicyclic ring contains one additional heteroatom independently selected from N, and O;

(iii) a fused 6,5- or 6,6- bicyclic ring, containing one S atom, wherein at least one of the rings is aromatic;

wherein the fused 6,5- or 6,6- bicyclic ring is substituted with 1, 2, or 3 substituents selected from $alkyl^b$, alkoxy, OH, NH_2, halo, CN, and CF_3;

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

(iv) a fused 6,5- or 6,6- bicyclic ring, containing two N atoms, wherein at least one of the rings is aromatic, optionally wherein the fused 6,5- or 6,6- bicyclic ring may be substituted with 1, 2, or 3 substituents selected from $alkyl^b$, alkoxy, OH, NH_2, halo, CN, and CF_3;

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

(v) a fused 6,5- or 6,6- bicyclic ring, containing one N atom, wherein at least one of the rings is aromatic, optionally wherein the fused 6,5- or 6,6- bicyclic ring may be substituted with 1, 2, or 3 substituents selected from $alkyl^b$, alkoxy, OH, NH_2, halo, CN, and CF_3;

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

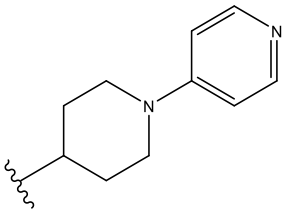
(vi) a fused 6,5- or 6,6- bicyclic ring, containing one N atom and one O atom, wherein at least one of the rings is aromatic, optionally wherein the fused 6,5- or 6,6- bicyclic ring may be substituted with 1, 2, or 3 substituents selected from alkyl[b], alkoxy, OH, NH_2, halo, CN, and CF_3;

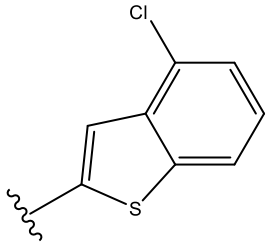
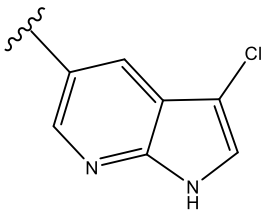
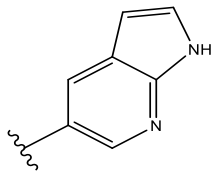
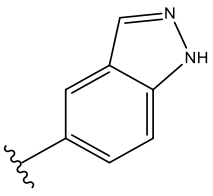
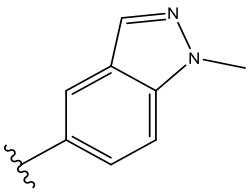
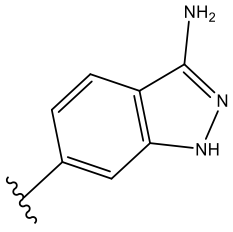
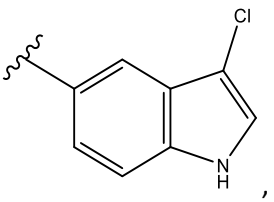
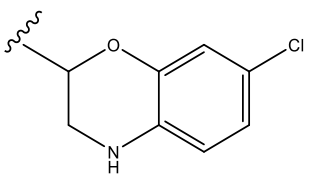
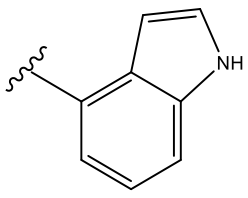
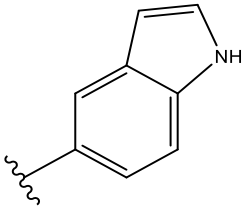
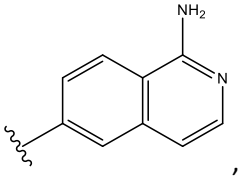
wherein the fused 6,5- bicyclic ring may be attached via the 6- or 5- membered ring;

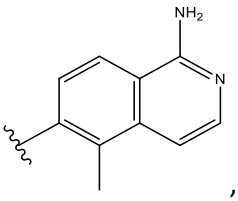
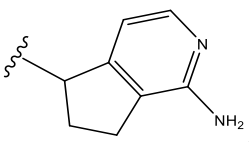
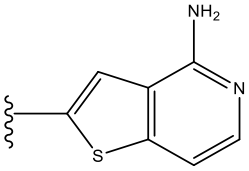
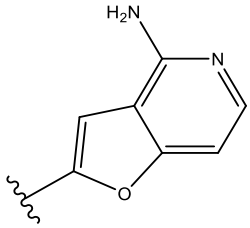
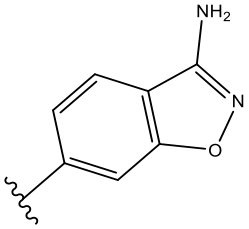
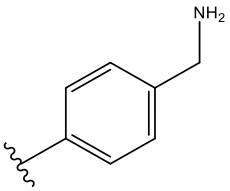
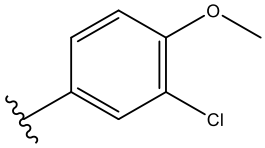
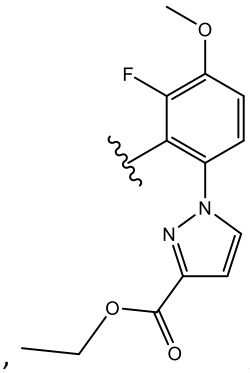
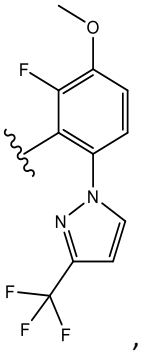
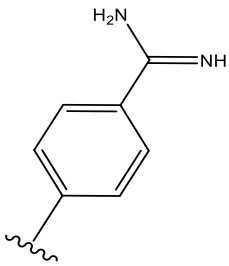
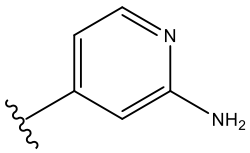
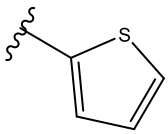
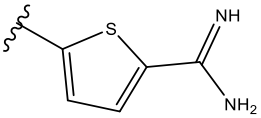
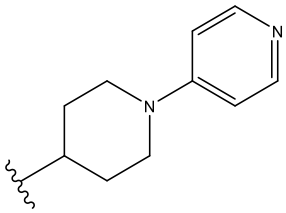
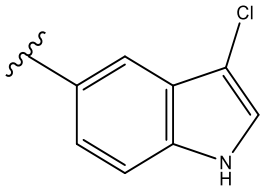
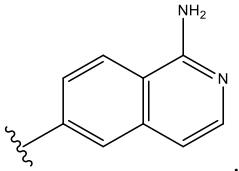
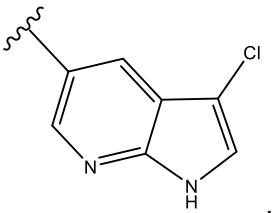
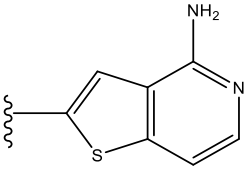
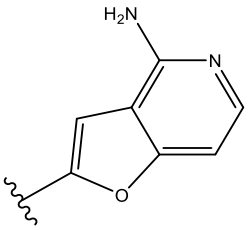
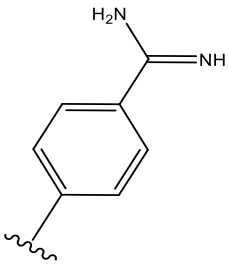
(vii) a fused 6,5- or 6,6- bicyclic ring, containing one N atom and one S atom, wherein at least one of the rings is aromatic, optionally wherein the fused 6,5- or 6,6- bicyclic ring may be substituted with 1, 2, or 3 substituents selected from alkyl[b], alkoxy, OH, NH_2, halo, CN, and CF_3;

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

(viii) phenyl, pyridyl, or thiophenyl, which may be optionally substituted with 1, 2 or 3 substituents independently selected from alkyl[b], alkoxy, OH, NH_2 halo, CN, CF_3, -C(=NH)NH_2, and heteroaryl[b];

(ix) ;

(x) selected from: , , , , , , , , , , ,















and ; or



(xi) selected from , , , ,



and .

16. A compound of formula (I) according to any preceding claim, 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:

(i) chiral centre *1 is in the (*S*)- configuration; and/or

(ii) chiral centre *2 is in the (*R*)- configuration.

17. A compound selected from any one of Tables 1 to 23, and pharmaceutically acceptable salts and/or solvates thereof.

18. A pharmaceutical composition comprising: a compound, or a pharmaceutically acceptable salt and/or solvate thereof, according to any of claims 1 to 17, and at least one pharmaceutically acceptable excipient.

19. A compound, or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in any of claims 1 to 17, or the pharmaceutical composition according to claim 18, for use in medicine.

20. Use of a compound, or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in any of claims 1 to 17, or the pharmaceutical composition as claimed in claim 18, in the manufacture of a medicament for treatment of a disease or condition in which Factor XIIa activity is implicated.

21. The use as claimed in claim 20, wherein, the disease or condition in which Factor XIIa activity is implicated is a bradykinin-mediated angioedema.

22. The use as claimed in claim 21, wherein the bradykinin-mediated angioedema is:

(i) hereditary angioedema; or

(ii) non hereditary.

23. The use as claimed in claim 20, wherein the disease or condition in which Factor XIIa activity is implicated is:

(i) selected from vascular hyperpermeability; stroke including ischemic stroke and haemorrhagic accidents; retinal edema; diabetic retinopathy; DME; retinal vein occlusion; and AMD;

(ii) 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

(iii) 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.

24. The use as defined in any of claims 20 or 21 to 23, wherein the compound targets FXIIa.