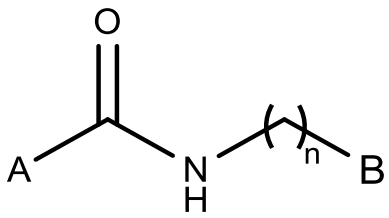
CLAIMS

1. A compound of formula (I),

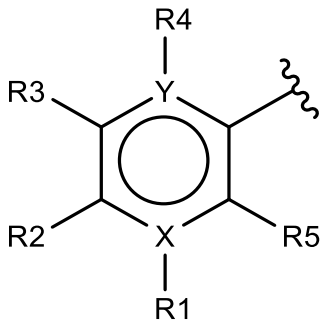


Formula (I)

wherein:

n is 0, 1, or 2;

A is a 6- membered heteroaryl of formula (II),



Formula (II)

wherein X and Y are independently selected from C and N, wherein at least one of X or Y is N;

wherein R5 is selected from -NR12$(CH_2)_{0-3}$(heterocyclyl), -NR12$(CH_2)_{0-3}$(heteroaryl), -NR12$(CH_2)_{0-3}$(aryl), -NR13R14, -O$(CH_2)_{0-3}$(aryl), -O$(CH_2)_{0-3}$(heterocyclyl), -O-$(CH_2)_{1-4}$NR13R14, and -NR12$(CH_2)_{0-3}$O(aryl);

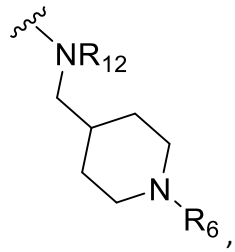
wherein R2 and R3 are independently selected from H, halo, alkoxy, alkyl, cycloalkyl, aryl, and heteroaryl;

wherein R1 and R4 are independently absent, or independently selected from H, halo, alkoxy, alkyl, cycloalkyl, aryl, and heteroaryl; or

wherein X and Y are independently selected from C and N, wherein at least one of X or Y is N;

wherein R1, R4, and R5 are independently absent or independently selected from H, halo and alkyl;

wherein one of R2 or R3 is



, and the other of R2 or R3 is selected from H, halo or alkyl;

wherein R6 is H, alkyl, or heteroaryl[b]; or

wherein X and Y are independently selected from C and N, wherein at least one of X or Y is N;

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

wherein R3 is halo;

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

wherein R5 is H, alkyl and halo; or

wherein X and Y are C;

wherein R4 is H, halo, alkyl;

wherein R5 is H or alkyl;

wherein R3 is H or halo;

wherein one of R1 and R2 is -(CH_2)(heterocyclyl) or –N(R12)CO$(CH_2)_{0-3}$(heterocyclyl), and the other of R1 and R2 is selected from H and alkyl;

wherein X is C or N, and Y is C;

R1 is absent, H or alkyl;

R4 is H or alkyl;

R5 is H or alkyl;

wherein either: (a) R2 and R3 together with the carbon atoms to which they are bonded form phenyl or a 5- or 6-membered nitrogen-containing heteroaryl, wherein phenyl may be optionally substituted as for aryl[b], and wherein the 5- or 6-membered

nitrogen-containing heteroaryl may be optionally substituted as for heteroaryl^b, or (b) R2 and R3 are independently selected from H and halo, wherein at least one of R2 or R3 is halo, or (c) R2 and R3 are independently selected from H, aryl^b and heteroaryl^b, wherein at least one of R2 or R3 is aryl^b, or heteroaryl^b;

B is one of:

(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, CF3 and -NR13R14;
wherein the 6,5- heteroaromatic bicyclic ring may be attached via the 6- or 5- membered ring;

(ii) phenyl, which may be optionally substituted with 1, 2 or 3 substituents independently selected from, alkyl, heteroaryl, alkoxy, heterocyclyl, OH, halo, CN, CF_3, and a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring containing 1, 2 or 3 heteroatoms independently selected from N and NR12, 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, alkoxy, OH, halo, and CF_3; or

(iii) phenyl, wherein two adjacent carbon atoms on the phenyl are either linked together by –N=C-N(R8)-C(=O)- to form a quinazolinone or linked together by $–CH_2$-N(R8)-C(=O)- to form an isoindolinone; or

(iv) heteroaryl; or

(v) a fused 6,5- or 6,6- bicyclic ring containing an aromatic ring fused to a non-aromatic ring and containing N 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, heterocyclyl^b, 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, 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, which may be optionally substituted as for heteroaryl^b;

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, CH_2aryl^b, OH, OCF_3, halo, CN, and CF_3;

heterocyclyl 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, 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, two or three 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;

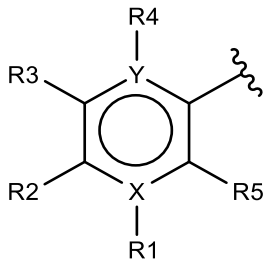
R8 is independently selected from H, -SO_2CH_3, alkyl^b, -$(CH_2)_{0-3}$aryl^b, -$(CH_2)_{0-3}$heteroaryl^b, -$(CH_2)_{0-3}$cycloalkyl, and -$(CH_2)_{0-3}$heterocyclyl^b; or R8 is a carbon-containing 4-, 5-, 6- or 7-membered heterocylic ring containing 1, 2 or 3 heteroatoms independently selected from N, NR12, 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, 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 6- membered heteroaryl of formula (II),



Formula (II)

wherein X and Y are independently selected from C and N, wherein at least one of X or Y is N;

wherein R5 is selected from -NR12$(CH_2)_{0-3}$(heterocyclyl), -NR12$(CH_2)_{0-3}$(heteroaryl), -NR12$(CH_2)_{0-3}$(aryl), -NR13R14, -O$(CH_2)_{0-3}$(aryl), -O$(CH_2)_{0-3}$(heterocyclyl), -O-$(CH_2)_{1-4}$NR13R14, and -NR12$(CH_2)_{0-3}$O(aryl);

wherein R2, R3 and R4 are independently selected from H, halo, alkoxy, alkyl, cycloalkyl, aryl, and heteroaryl.

3. A compound of formula (I) according to claim 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:

(i) X is N; and/or

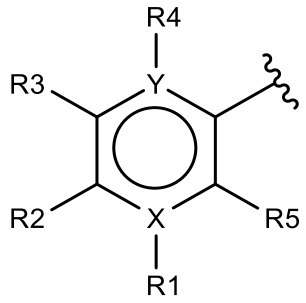
(ii) R3 is halo; and/or

(iii) R5 is -NR12(CH_2)(heterocyclyl), wherein "heterocyclyl" can be optionally substituted as defined in claim 1; and/or

(iv) R5 is -NR12(CH_2)(piperidinyl), wherein "piperidinyl" can be optionally substituted as defined for "heterocyclyl" in claim 1.

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 6- membered heteroaryl of formula (II),

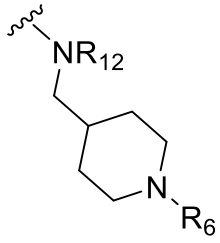


Formula (II)

wherein X and Y are independently selected from C and N, wherein at least one of X or Y is N;

wherein R1, R4, and R5 are independently absent or independently selected from H, halo and alkyl;

wherein one of R2 or R3 is



, and the other of R2 or R3 is selected from H, halo or alkyl;

wherein R6 is H, alkyl, or heteroaryl[b].

5. A compound of formula (I) according to claim 4, 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:

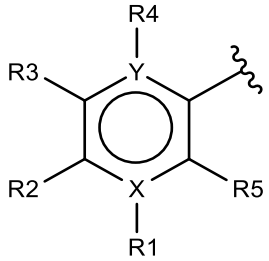
(i) X is N; and/or

(ii) Y is N; and/or

(iii) R6 is alkyl.

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 6- membered heteroaryl of formula (II),



Formula (II)

wherein X and Y are independently selected from C and N, wherein at least one of X or Y is N;

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

wherein R3 is halo;

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

wherein R5 is H, alkyl and halo.

7. A compound of formula (I) according to claim 6, 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) X is N; and/or

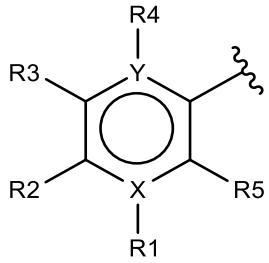
(ii) R3 is halo; and/or

(iii) R2 is $–(CH_2)_{0-3}NR13R14$; and/or

(iv) R2 is $–(CH_2)NR13R14$, wherein R13 and R14, together with the nitrogen atom to which they are attached form piperazine, which may be optionally substituted in the same manner as R13 and R14, as defined in claim 1, optionally wherein the piperazine on R2 has an NR8 group, wherein R8 is pyridinyl.

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 can be a 6- membered heteroaryl of formula (II),



Formula (II)

wherein X and Y are C;

wherein R4 is H, halo, alkyl;

wherein R5 is H or alkyl;

wherein R3 is H or halo;

wherein one of R1 and R2 is $-(CH_2)$(heterocyclyl) or $–N(R12)CO(CH_2)_{0-3}$(heterocyclyl), and the other of R1 and R2 is selected from H and alkyl.

9. A compound of formula (I) according to claim 8, 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) R3 is halo; and/or

(ii) R2 is -(CH_2)(heterocyclyl); and/or

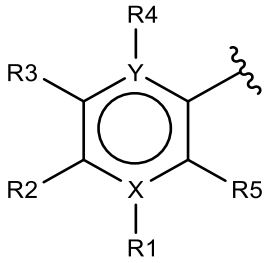
(iii) R2 is -(CH_2)(piperazinyl); and/or

(iv) R2 is -(CH_2)(heterocyclyl) and wherein the heterocyclyl on R2 has an NR8 group, and R8 is pyridinyl; and/or

(v) R2 is -(CH_2)(piperazinyl) and wherein the heterocyclyl on R2 has an NR8 group, and R8 is pyridinyl.

10. 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 can be a 6- membered heteroaryl of formula (II),



Formula (II)

wherein X is C or N, and Y is C;

R1 is absent, H or alkyl;

R4 is H or alkyl;

R5 is H or alkyl;

wherein either: (a) R2 and R3 together with the carbon atoms to which they are bonded form phenyl or a 5- or 6-membered nitrogen-containing heteroaryl, wherein phenyl may be optionally substituted as for aryl[b], and wherein the 5- or 6-membered nitrogen-containing heteroaryl may be optionally substituted as for heteroaryl[b], or (b) R2 and R3 are independently selected from H and halo, wherein at least one of R2 or R3 is

halo, or (c) R2 and R3 are independently selected from H, aryl^b and heteroaryl^b, wherein at least one of R2 or R3 is aryl^b, or heteroaryl^b.

11. A compound of formula (I) according to claim 10, 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 and R3:

(i) together with the carbon atoms to which they are bonded form phenyl or a 5- or 6-membered nitrogen-containing heteroaryl, wherein phenyl may be optionally substituted as for aryl^b, and wherein the 5- or 6-membered nitrogen-containing heteroaryl may be optionally substituted as for heteroaryl^b; or

(ii) are independently selected from H and halo, wherein at least one of R2 or R3 is halo; or

(iii) are independently selected from H, aryl^b and heteroaryl^b, wherein at least one of R2 or R3 is aryl^b, or heteroaryl^b.

12. A compound selected from any of Tables 1 to 11, and pharmaceutically acceptable salts and/or solvates thereof.

13. A pharmaceutical composition comprising: a compound, or a pharmaceutically acceptable salt and/or solvate thereof, according to any of claims 1 to 12, and at least one pharmaceutically acceptable excipient.

14. A compound, or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in any of claims 1 to 12, or the pharmaceutical composition according to claim 13, for use in medicine.

15. The use of a compound, or a pharmaceutically acceptable salt and/or solvate thereof, as claimed in any of claims 1 to 12, or the pharmaceutical composition as claimed in claim 13, in the manufacture of a medicament for the treatment or prevention of a disease or condition in which Factor XIIa activity is implicated.

16. The use of claim 15, wherein the disease or condition in which Factor XIIa activity is implicated is a bradykinin-mediated angioedema.

17. The use of claim 16, wherein the bradykinin-mediated angioedema is: (i) hereditary angioedema; or (ii) non hereditary.

18. The use of claim 15, 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.

19. The use of any of claims 15 to 18, , wherein the compound targets FXIIa.