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(54) Benævnelse: **SUBSTITUTEREDE PYRROLIDINER SOM FAKTOR XIA-HÆMMERE TIL BEHANDLING AF TROMBOEMBOLISKE SYGDOMME**

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MODESTO DE CANDIA ET AL: "Novel factor Xa inhibitors: a patent review", EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 19, no. 11, 1 November 2009 (2009-11-01), pages

Fortsættes ...

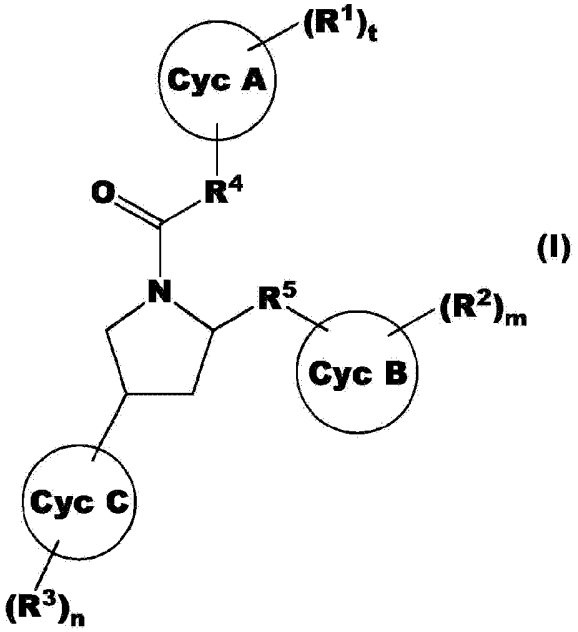
1535-1580, XP002634218, ISSN: 1354-3776, DOI: 10.1517/13543770903270532

DESCRIPTION

TECHNICAL FIELD

[0001] The present invention relates to a pyrrolidine derivative which is useful as an inhibitor of factor XIa.

[0002] Disclosed herein is a compound of formula (I):



(I)

(wherein all symbols have the same meanings as described hereinafter) or a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof, , use of such compounds in treatment and/or prevention of a thromboembolic disease and processes for the preparation of said compounds.

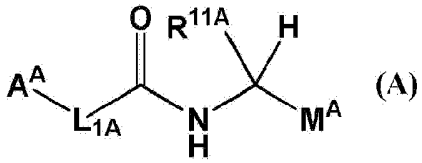
BACKGROUND OF THE INVENTION

[0003] Thromboembolism is an important cause of morbidity and mortality. It occurs when a blood clot breaks free and is carried by the blood stream to obstruct a blood vessel at another site. Thromboembolic disease includes venous thromboembolism, for example deep vein thrombosis or pulmonary embolism, arterial thrombosis, stroke and myocardial infarction.

[0004] Thromboembolic diseases may be treated using anticoagulants. One approach has been to target the inhibition of factor XIa (FXIa). Factor XIa is a plasma serine protease involved in the regulation of blood coagulation. Factor XIa is an activated form of factor XI, which is activated by factor XIIa, thrombin, and it is also autocatalytic. FXIa is a component of the "contact pathway" and activates factor IX by selectively cleaving arg-ala and arg-val peptide bonds. Factor IXa, in turn, activates factor X. The safety of this target is supported by

the observations that FXI deficiency in humans (hemophilia C) results in a mild bleeding disorder. In addition to this, the efficacy and side effects of this target have been shown using experimental thrombosis and bleeding models in mice lacking FXI, and in baboons and rabbits treated with anti-FXI neutralizing antibodies. These results suggest that FXIa inhibitors will show a potent anti-thrombotic effect without bleeding. Therefore, factor XIa is an attractive target for anti-thrombotic therapy without the side effect of bleeding.

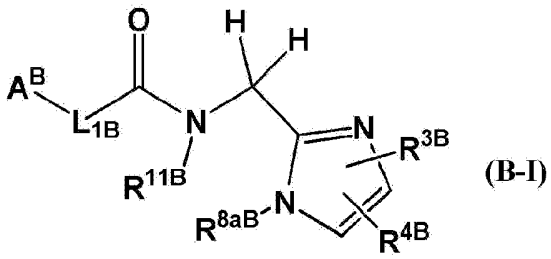
[0005] It has been described in Patent literature 1 that compound of formula (A):



(A)

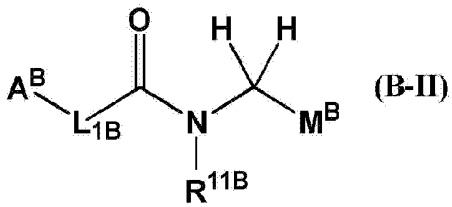
wherein A^A represents a 5- to 12- membered heterocycle, etc.; L_{1A} represents - CH=CH-, etc.; R^{11A} represents benzyl, etc.; M^A represents imidazolyl, etc; are useful as selective inhibitors of factor XIa or dual inhibitors of FXIa and plasma kallikrein.

[0006] Furthermore, it has been described in Patent literature 2 that a compound of formula (B-I):



(B-I)

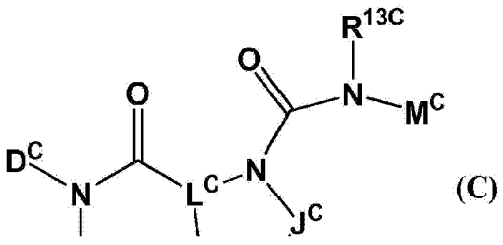
wherein A^B represents a 5- to 12- membered heterocycle, etc.; L_{1B} represents - CH=CH-, etc.; R^{11B} represents benzyl, etc.; R^{3B} represents phenyl, etc.; R^{4B} represents chlorine, etc.; R^{8aB} represents hydrogen, etc; or formula (B-II):



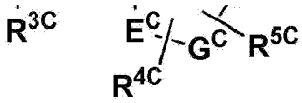
(B-II)

wherein M^B represents pyridyl, etc.; and the other symbols have the same meanings as described above; inhibit factor XIa and/or plasma kallikrein.

[0007] Furthermore, it has been described in Patent literature 3 that a compound of formula (C):

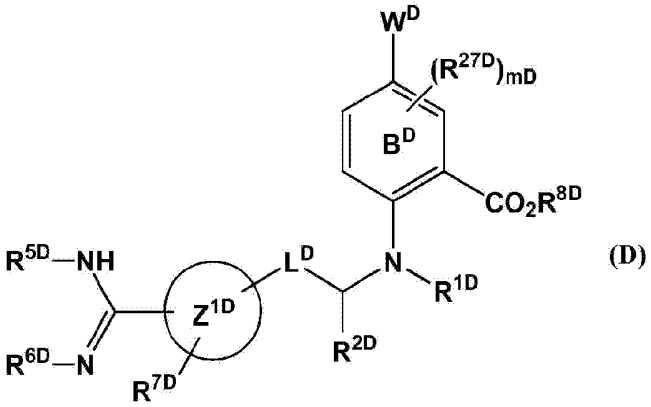


(C)



wherein D^C represents C10 cycloalkyl or 10-membered heterocycloalkyl, etc.; - L^C-E^C-G^C-J^C- represents -C-C-C-C, etc.; R^{3C} represents hydrogen, etc.; R^{4C} represents mono- or bicyclic heteroaryl, etc.; R^{5C} represents hydrogen, etc.; R^{13C} represents hydrogen, etc.; M^C represents phenyl, etc.; are useful as inhibitors of factor Xa.

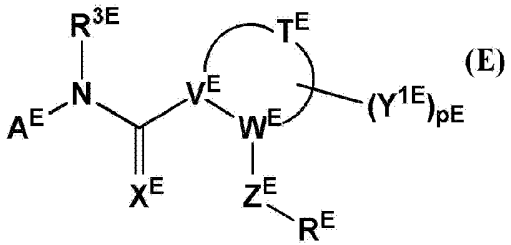
[0008] Furthermore, it has been described in Patent literature 4 that a compound of formula (D):



(D)

wherein ring B^D represents phenyl, etc.; W^D represents -NH_2, etc.; Z^{1D} represents 5 to 7-membered monocyclic, etc.; L^D represents -NH-CO-, etc.; R^{1D} and R^{2D} independently represents (i) hydrogen or (ii) are taken together to form a five-to-seven membered fully saturated heterocycle, etc.; R^{5D} and R^{6D} independently represents hydrogen, etc.; R^{7D} represents -COOH, etc.; R^{8D} represents hydrogen, etc.; $(R^{27D})_{mD}$ represents -COOH, etc.; are useful as inhibitors of factor VIIa, factor IXa, factor FXIa, tryptase, and urokinase.

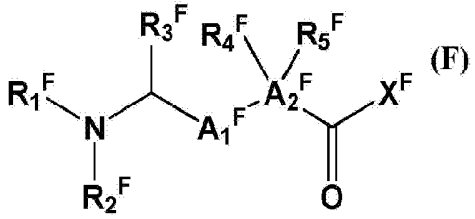
[0009] Furthermore, it has been described in Patent literature 5 that a compound of formula (E):



(E)

wherein A^E represents aryl substituted by carboxyl, etc.; R^{3E} represents hydrogen, etc.; X^E represents oxygen, etc.; V^E represents nitrogen, etc.; W^E represents carbon, etc.; Z^E represents -CO-, etc.; R^E represents aryl substituted by -C(=NH)NH_2, etc.; T^E represents C_{2-6} alkylene, etc.; $(Y^{1E})_{pE}$ represents heterocyclo substituted by - SO_2-Me, etc.; are useful as anti-viral agent, however, it is not reported that the compound represented by formula (E) has factor XIa inhibitory activity.

[0010] Furthermore, it has been described in Patent literature 6 that a compound of formula (F):



wherein ring X^F represents N-containing ring, etc.; $A_1{}^F$ represents a bond, etc.; $A_2{}^F$ represents Aryl, etc.; $R_1{}^F$, $R_2{}^F$, $R_3{}^F$, $R_4{}^F$ and $R_5{}^F$ independently represents hydrogen, etc.; are useful as inhibitors of Apoptosis Proteins.

[Patent literature 1] WO2007070826

[Patent literature 2] WO2008076805

[Patent literature 3] WO2007131982

[Patent literature 4] WO2002037937

[Patent literature 5] WO2008064218

[Patent literature 6] WO2009152824

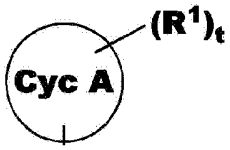
DISCLOSURE OF THE INVENTION

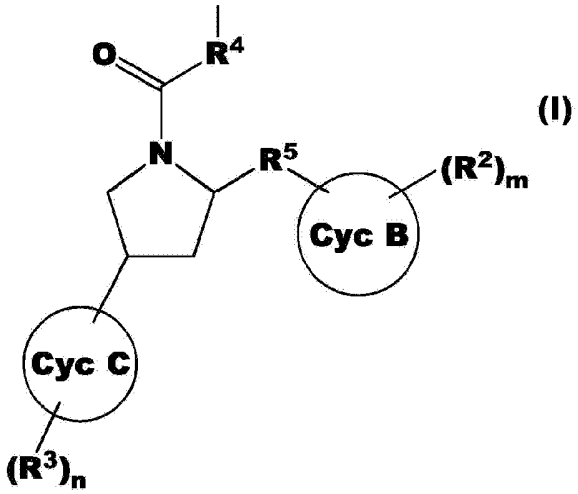
[0011] It is desirable to find new compounds which may be more effective in treating thromboembolic diseases. Advantageous compounds desirably have good inhibitory and selectivity for factor XIa.

[0012] The present inventors have made extensive studies to find a compound that can become a therapeutic agent for thromboembolic diseases. As a result, we have found that the object is achieved by a compound represented by formula (I), a salt thereof, an N-oxide thereof or a solvate thereof(hereinafter, which may be abbreviated to compound of the present invention) having good inhibitory and selectivity for factor XIa and then we have completed the present invention.

[0013] Namely, the following compounds are disclosed:

1. (1) A compound represented by formula (I):





(I)

wherein Cyc A represents C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C6-C10 aryl or 5- to 10-membered heteroaryl;

Cyc B represents C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C6-C10 aryl or 5- to 10-membered heteroaryl;

Cyc C represents C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C6-C10 aryl or 5- to 10-membered heteroaryl;

each R^1 may be the same or different and represents (1) C6-C10 aryl, (2) 5- to 10-membered heteroaryl, (3) C6-C10 aryl or 5- to 10-membered heteroaryl substituted with 1 to 5 groups selected from halogen, C1-4 alkyl, C1-4 alkoxy, -C1-4 alkylene-C1-4 alkoxy, CN, -COOH, -COO-C1-4 alkyl, -CO-NH_2, -OCONH_2, -OCONH-C1-4 alkyl, -CONH-C1-4 alkyl, -NHCOO-C1-4 alkyl and -NHCO-C1-4 alkyl, (4) -C(=NH)NH_2, (5) -NH-C(=NH)NH_2, (6) C1-4 alkyl, (7) C2-4 alkenyl, (8) C2-4 alkynyl, (9) -C1-4 alkylene-NH_2, (10) C1-4 alkoxy, (11) CN, (12) -CO-C1-4 alkyl, (13) halogen or (14) - R^{10}-C(=NR^{11})$NR^{12}R^{13}$;

wherein R^{10} represents (1) a bond or (2) NH;

R^{11}, R^{12} and R^{13} each independently represents (1) hydrogen, (2) OH, (3) C1-4 alkyl, (4) C2-4 alkenyl, (5) C2-4 alkynyl, (6) C1-4 alkoxy, (7) -C1-4 alkylene-C1-4 alkoxy, (8) -CO-C1-4 alkyl, (9) -COO-C1-4 alkyl, (10) -OCO-C1-4 alkyl, (11) -CO-R^{14}, (12) -COO-R^{15} or (13) -OCO-R^{16}, with the proviso that R^{11}, R^{12} and R^{13} do not all simultaneously represent hydrogen;

wherein R^{14}, R^{15} and R^{16} each independently represents C1-4 alkyl, C2-4 alkenyl or C2-4 alkynyl, which are substituted with 1 to 5 groups selected from C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, halogen, trifluoromethyl, OH, -COO-C1-4 alkyl, COOH, oxo, C1-4 alkoxy, C6-C10 aryl, 5- to 10-membered heteroaryl and $NR^{17}R^{18}$;

wherein R^{17} and R^{18} each independently represents (1) hydrogen, (2) C1-4 alkyl, (3) C2-4 alkenyl or (4) C2-4 alkynyl;

t represents an integer of 0 to 6;

each R^2 may be the same or different and represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -COO-C1-4 alkylene-C1-4 alkoxy, (4) $-NH_2$, (5) -NH-C1-4 alkyl, (6) - NH-C1-4 alkylene-C1-4 alkoxy, (7) -NHCO-C1-4 alkyl, (8) -NHCO-C1-4 alkylene-C1-4 alkoxy, (9) - NHCOO-C1-4 alkyl, (10) -NHCOO-C1-4 alkylene-C1-4 alkoxy, (11) - $CONH_2$, (12) - CONH-C1-4 alkyl, (13) -CONH-C2-4 alkylene-C1-4 alkoxy, (14) halogen, (15) $-SO_2$-C1-4 alkyl, (16) oxo, (17) C1-4 alkoxy, (18) -CO-C1-4 alkyl, (19) - CO-C1-4 alkylene-C1-4 alkoxy or (20) -COO- C1-4 alkyl substituted with 1 to 5 groups selected from C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, halogen, trifluoromethyl, OH, - COO-C1-4 alkyl, COOH, oxo, C1-4 alkoxy, C6-C10 aryl, 5- to 10-membered heteroaryl and $NR^{19}R^{20}$;

wherein R^{19} and R^{20} each independently represents (1) hydrogen, (2) C1-4 alkyl, (3) C2-4 alkenyl or (4) C2-4 alkynyl;

m represents an integer of 0 to 6;

each R^3 may be the same or different and represents (1) -COO-C1-4 alkyl, (2) oxo, (3) - CO-C1-4 alkyl, (4) $-CO-NH_2$, (5) $-SO_2-NH_2$ or (6) $-SO_2-R^6-R^7$;

n represents an integer of 0 to 6;

R^6 represents (1) a bond or (2) NH;

R^7 represents (1) C1-4 alkyl, (2) Cyc D or (3) C1-4 alkyl or Cyc D substituted with 1 to 5 R^8;

wherein Cyc D represents C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C6-C10 aryl or 5- to 10-membered heteroaryl;

each R^8 may be the same or different and represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -COO-C1-4 alkylene-C1-4 alkoxy, (4) $-NH_2$, (5) -NH-C1-4 alkyl, (6) - NHCO-C1-4 alkyl, (7) $-CONH_2$, (8) -CONH-C1-4 alkyl (9) OH or (10) halogen;

R^4 represents (1) a bond, (2) C1-4 alkylene, (3) C2-4 alkenylene or (4) C2-4 alkynylene;

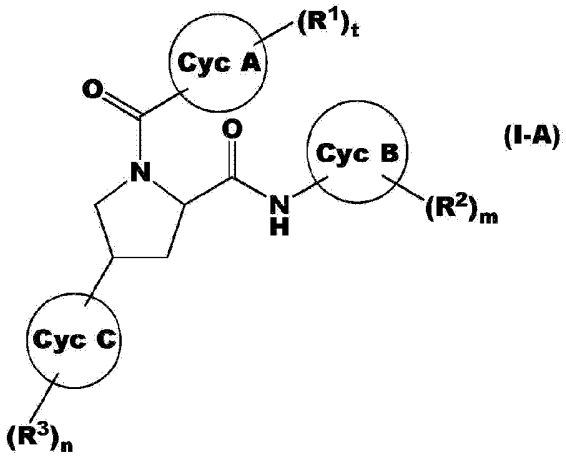
R^5 represents (1) -CONH-, (2) Cyc E or (3) Cyc E substituted with 1 to 5 R^9;

wherein Cyc E represents C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C6-C10 aryl or 5- to 10-membered heteroaryl and

each R^9 may be the same or different and represents C1-4 alkyl or halogen;

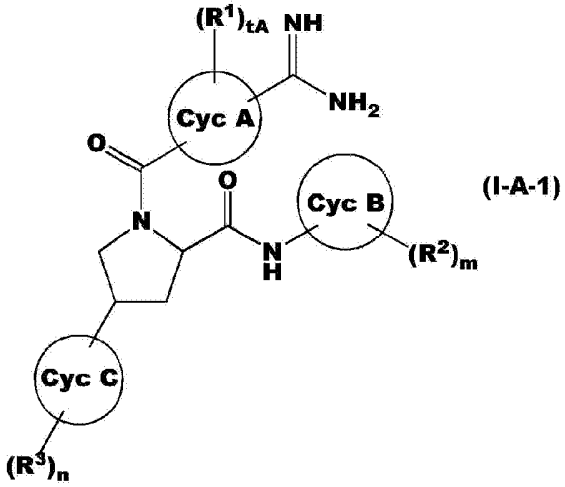
a salt thereof, an N-oxide thereof or a solvate thereof.

2. (2) The compound according to (1), wherein the compound represented by formula (I) represents a compound represented by formula (I-A):



wherein all symbols have the same meanings as described above.

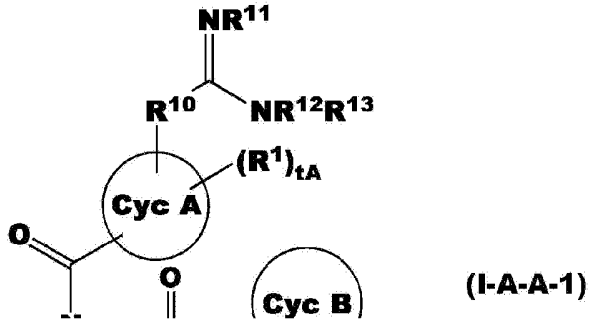
3. (3) The compound according to (2), wherein the compound represented by formula (I-A) represents a compound represented by formula (I-A-1):

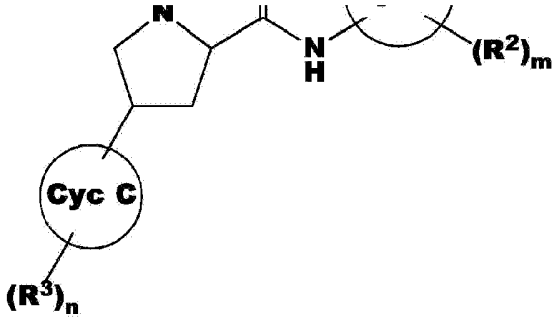


wherein tA represents an integer of 0 to 5; and

the other symbols have the same meanings as described above.

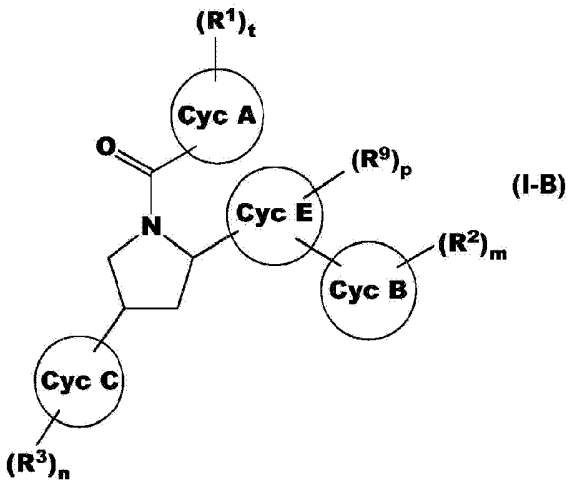
4. (4) The compound according to (2), wherein the compound represented by formula (I-A) represents a compound represented by formula (I-A-A-1):





wherein all symbols have the same meanings as described above.

5. (5) The compound according to (1), wherein the compound represented by formula (I) represents a compound represented by formula (I-B):

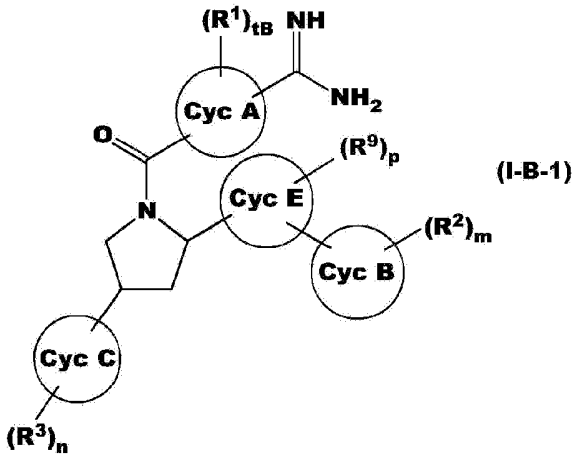


(I-B)

wherein p represents an integer of 0 to 5; and

the other symbols have the same meanings as described above.

6. (6) The compound according to (5), wherein the compound represented by formula (I-B) represents a compound represented by formula (I-B-1):

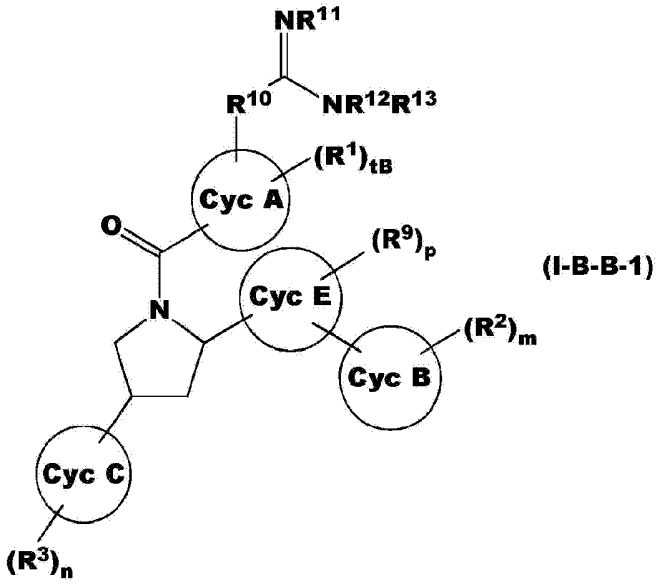


(I-B-1)

wherein tB represents an integer of 0 to 5; and

the other symbols have the same meanings as described above.

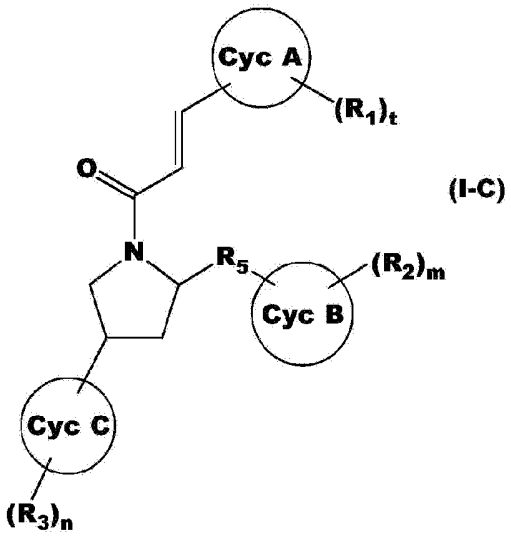
7. (7) The compound according to (5), wherein the compound represented by formula (I-B) represents a compound represented by formula (I-B-B-1):



(I-B-B-1)

wherein all symbols have the same meanings as described above.

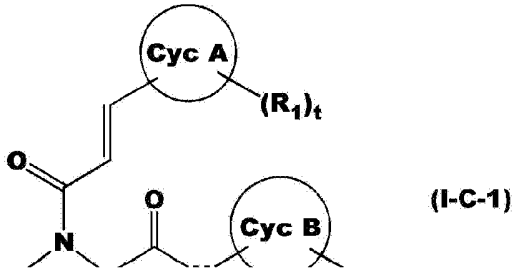
8. (8) The compound according to any one of (5) to (7), wherein Cyc E represents imidazolyl.
9. (9) The compound according to (1), wherein the compound represented by formula (I) represents a compound represented by formula (I-C):



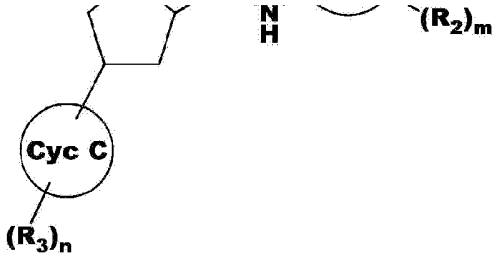
(I-C)

wherein all symbols have the same meanings as described above.

10. (10) The compound according to (9), wherein the compound represented by formula (I-C) represents a compound represented by formula (I-C-1):

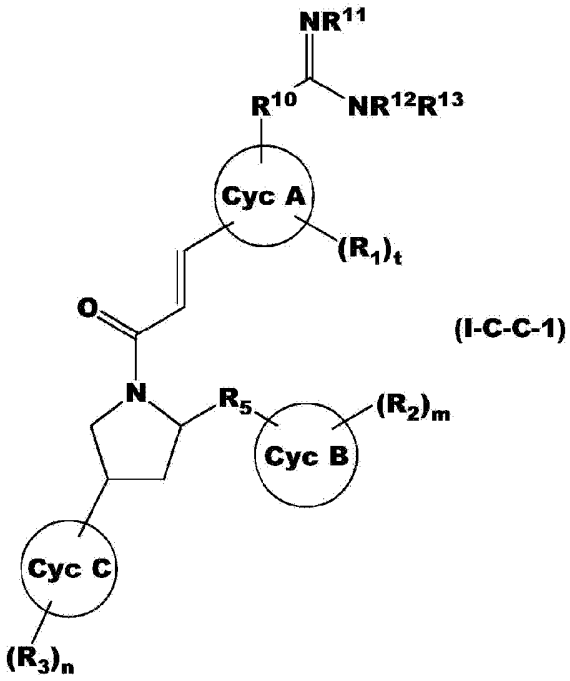


(I-C-1)



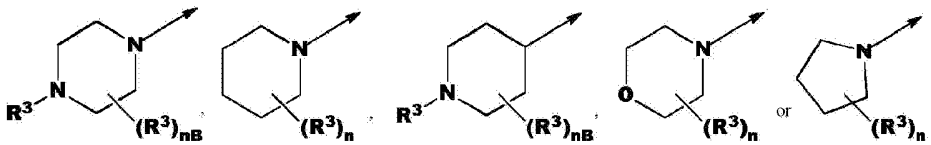
wherein all symbols have the same meanings as described above.

11. (11) The compound according to (9), wherein the compound represented by formula (I-C) represents a compound represented by formula (I-C-C-1):



wherein all symbols have the same meanings as described above.

12. (12) The compound according to any one of (1) to (11), wherein Cyc A represents C3-C6 cycloalkyl, C6-C10 aryl or 5- to 6-membered heterocycloalkyl.
13. (13) The compound according to any one of (1) to (12), wherein Cyc A represents cyclohexyl, phenyl, piperidinyl or piperazinyl.
14. (14) The compound according to any one of (1) to (13), wherein Cyc B represents C6-C10 aryl or 5- to 6-membered heteroaryl.
15. (15) The compound according to any one of (1) to (14), wherein Cyc B represents phenyl or pyridyl.
16. (16) The compound according to any one of (1) to (15), wherein Cyc C represents pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl.
17. (17) The compound according to any one of (1) to (16), wherein -Cyc C -$(R^3)_n$ represents

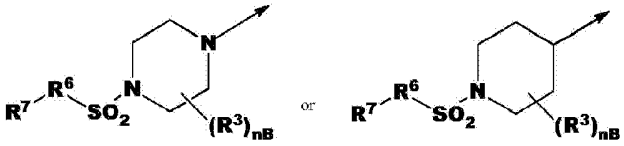


wherein nB represents an integer of 0 to 5;

the arrow represents a binding position; and

the other symbols have the same meanings as described above.

18. (18) The compound according to (17), wherein -Cyc C -$(R^3)_n$ represents



wherein the arrow represents a binding position; and

the other symbols have the same meanings as described above.

19. (19) The present invention is a compound which is 4-[({(2S,4S)-1-(4-carbamimidoylbenzoyl)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl} carbonyl)amino]benzoic acid.
20. (20) A pharmaceutical composition which comprises the compound according to (19), a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof.
21. (21) The pharmaceutical composition according to (20), for use as a factor XIa inhibitor.
22. (22) The pharmaceutical composition for use according to (21), in the treatment or prevention of a thromboembolic disease.
23. (23) The compound according to (19) or a pharmaceutically acceptable salt thereof for use in treating or preventing a thromboembolic disease.
24. (24) The compound for use according to (23), wherein the thromboembolic disease is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, venous cerebrovascular thromboembolic disorders and thromboembolic disorders in the chambers of the heart or in the peripheral circulation.
25. (25) The compound for use according to (24), wherein the thromboembolic disease is selected from disseminated intravascular coagulopathy (DIC), acute respiratory distress syndrome, acute lung injury, sepsis, angina, unstable angina, an acute coronary syndrome, coronary artery disease, myocardial infarction, atrial fibrillation, ischemic sudden death, transient ischemic attack, stroke, acute stroke, lacuna infarction, atherosclerotic thrombolic cerebral infarction, atherothrombosis, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral thrombosis, cerebral arterial thrombosis, cerebral embolism, cardiogenic embolism, kidney embolism, portal vein thrombosis, pulmonary embolism, pulmonary infarction, liver embolism, mesenteric artery and/or vein embolism, occlusion of retinal vein and/or artery, systemic embolism, antiphospholipid antibody syndrome, thrombosis resulting from coronary artery bypass graft surgery and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis.

26. (26) Use of a compound according (19), in the manufacture of a medicament for use in treating or preventing a thromboembolic disease.
27. (27) The use according to (26), wherein the thromboembolic disease is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, venous cerebrovascular thromboembolic disorders and thromboembolic disorders in the chambers of the heart or in the peripheral circulation.
28. (28) The use according to (27), wherein the thromboembolic disease is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface that promotes thrombosis.

Definitions:

[0014] As used herein, a C1-4 alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 4 carbon atoms. Examples of C1-4 alkyl groups and moieties include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. For the avoidance of doubt, where two alkyl moieties are present in a group, the alkyl moieties may be the same or different.

[0015] In the present specification, a C1-4 alkoxy group or moiety is a linear or branched alkoxy group or moiety containing from 1 to 4 carbon atoms. Examples of C1-4 alkoxy groups and moieties include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. For the avoidance of doubt, where two alkoxy moieties are present in a group, the alkoxy moieties may be the same or different.

[0016] In the present specification, the C2-4 alkenyl includes, for example, ethenyl, propenyl, butenyl and isomers thereof.

[0017] In the present specification, the C2-4 alkynyl includes, for example, ethynyl, propynyl, butynyl and isomers thereof.

[0018] In the present specification, the C1-4 alkylene includes linear or branched alkylene such as methylene, ethylene, propylene, isopropylene, butylenes, and isobutylene.

[0019] In the present specification, the C2-4 alkenylene includes linear or branched alkenylene such as vinylene, propenylene, 1- or 2-butenylene, and butadienylene.

[0020] In the present specification, the C2-4 alkynylene includes linear or branched alkynylene such as ethynylene, 1- or 2-propynylene and 1- or 2-butynylene.

[0021] In the present specification, the halogen atom includes, for example, fluorine, chlorine, bromine and iodine, and is preferably fluorine, chlorine or bromine.

[0022] Cyc A, Cyc B, Cyc C, Cyc D and Cyc E each independently represent C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C6-C10 aryl or 5- to 10-membered heteroaryl.

[0023] "C3-C8 cycloalkyl" refers to a C3-C8 cyclic hydrocarbon. Examples of C3-C8 cycloalkyl include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclobutadiene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene rings and the like. Moreover, the term "C3-C8 cycloalkyl" also includes "C3-C6 cycloalkyl". The term "C3-C6 cycloalkyl" refers to a C3-C6 cyclic hydrocarbon. Examples of C3-C6 cycloalkyl include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclobutene, cyclopentene, cyclohexene, cyclobutadiene, cyclopentadiene, cyclohexadiene rings and the like.

[0024] "5- to 10-membered heterocycloalkyl" refers to a "5- to 10-membered mono- or bi-non-aromatic heterocyclic ring having 1 to 4 nitrogen atom(s), 1 or 2 oxygen atom(s) and/or 1 or 2 sulfur atom(s) as a hetero atom(s)". Examples of 5- to 10-membered heterocycloalkyl include pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydroxepine, tetrahydroxepine, perhydroxepine, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydroxazole, tetrahydroxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydroxadiazole, tetrahydroxadiazole (oxadiazolidine), dihydroxazine, tetrahydroxazine, dihydroxadiazine, tetrahydroxadiazine, dihydroxazepine, tetrahydroxazepine, perhydroxazepine, dihydroxadiazepine, tetrahydroxadiazepine, perhydroxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine,

perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorpholine, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, dioxolane, 1,4-dioxane, dithiolane, dithiane, dioxaindane, benzodioxane, chroman, benzodithiolane, benzodithiane, 6,7-dihydro-5H-cyclopenta[b]pyrazine, 5H-cyclopenta[b]pyrazine, 2,4-dihydro-1H-benzo[d][1,3]oxazine rings and the like. Moreover, the term "5- to 10-membered heterocycloalkyl" also includes "5- to 6-membered heterocycloalkyl". The term "5- to 6-membered heterocycloalkyl" refers to a "5- to 6-membered mono-non-aromatic heterocyclic ring having 1 to 3 nitrogen atom(s), 1 or 2 oxygen atom(s) and/or 1 or 2 sulfur atom(s) as a hetero atom(s)". Examples of 5- to 6-membered heterocycloalkyl include pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydroxazole, tetrahydroxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydroxadiazole, tetrahydroxadiazole (oxadiazolidine), dihydroxazine, tetrahydroxazine, dihydroxadiazine, tetrahydroxadiazine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiadiazine, tetrahydrothiadiazine, morpholine, thiomorpholine, oxathiane, dioxolane, 1,4-dioxane, dithiolane, dithiane rings and the like.

[0025] "C6-C10 aryl" refers to a "C6-10 mono- or bi- aromatic carbocyclic ring". Examples of C6-C10 aryl include benzene, azulene, naphthalene rings and the like. Thus the C6-C10 aryl may be, for example, a phenyl ring and the like.

[0026] "5- to 10-membered heteroaryl" refers to a "5- to 10-membered mono- or bi-aromatic heterocyclic ring having 1 to 4 nitrogen atom(s), 1 or 2 oxygen atom(s) and/or 1 or 2 sulfur atom(s) as a hetero atom(s)". Examples of 5- to 10-membered heteroaryl include pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, thiadiazole, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isoquinoline, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzimidazole, benzofurazan, benzothiadiazole, benzotriazole, isoxazolo[4,5-d]pyridazine rings and the like. Moreover, the term "5- to 10-membered heteroaryl" also includes "5- to 6-membered heteroaryl". The term "5- to 6-membered heteroaryl" refers to a "5- to 6-membered mono-aromatic heterocyclic ring having 1 to 3 nitrogen atom(s), 1 or 2 oxygen atom(s) and/or 1 or 2 sulfur atom(s) as a hetero atom(s)". Examples of 5- to 6-membered heteroaryl include pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, thiadiazole rings and the like.

[0027] Cyc D represents C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C5-C10 aryl or 5- to 10-membered heteroaryl, any of which may be optionally substituted with 1 to 5 R^8.

[0028] Cyc E represents C3-C8 cycloalkyl, 5- to 10-membered heterocycloalkyl, C5-C10 aryl or 5- to 10-membered heteroaryl, any of which may be optionally substituted with 1 to 5 R^9.

[0029] The optionally substituted "C3-C8 cycloalkyl" represented by Cyc D or Cyc E may be selected from any of the examples provided above for "C3-C8 cycloalkyl".

[0030] The optionally substituted "5- to 10-membered heterocycloalkyl" represented by Cyc D or Cyc E may be selected from any of the examples provided above for "5- to 10-membered heterocycloalkyl".

[0031] The optionally substituted "C6-C10 aryl" represented by Cyc D or Cyc E may be selected from any of the examples provided above for "C6-C10 aryl".

[0032] The optionally substituted "5- to 10-membered heteroaryl" represented by Cyc D or Cyc E may be selected from any of the examples provided above for "5- to 10-membered heteroaryl".

[0033] R^1 represents C6-C10 aryl or 5- to 10-membered heteroaryl, any of which may be optionally substituted with 1 to 5 groups selected from halogen, C1-4 alkyl, C1-4 alkoxy, -C1-4 alkylene-C1-4 alkoxy, CN, -COOH, -COO-C1-4 alkyl, -CO-NH_2, - $OCONH_2$, -OCONH-C1-4 alkyl, -CONH-C1-4 alkyl, -NHCOO-C1-4 alkyl and - NHCO-C1-4 alkyl.

[0034] The optionally substituted "C6-C10 aryl" represented by R^1 may be selected from any of the examples provided above for "C6-C10 aryl".

[0035] The optionally substituted "5- to 10-membered heteroaryl" represented by R^1 may be selected from any of the examples provided above for "5- to 10-membered heteroaryl".

[0036] Preferably, Cyc A represents cyclohexyl, phenyl, piperidinyl, piperazinyl or indolyl, more preferably phenyl, cyclohexyl piperidinyl or piperazinyl, and further more preferably phenyl, cyclohexyl or piperidinyl.

[0037] Preferably, Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl, more preferably phenyl or pyridyl.

[0038] Preferably, Cyc C represents 5- to 10-membered heterocycloalkyl, more preferably pyrrolidinyl, piperidinyl piperazinyl or morpholinyl, further more preferably piperidinyl or piperazinyl.

[0039] Preferably, Cyc D represents C3-C8 cycloalkyl or C6-C10 aryl, more preferably

cyclopropyl or phenyl, any of which may be optionally substituted as set out above.

[0040] Preferably, Cyc E represents 5- to 10-membered heteroaryl, more preferably imidazolyl which may be optionally substituted as set out above.

[0041] Preferably, each R^1 independently represents 5- to 10-membered heteroaryl which may be optionally substituted as set out above, -C(=NH)NH_2, -NH-C(=NH)NH_2, C1-4 alkyl, -C1-4 alkylene-NH_2 or halogen, more preferably tetrazolyl, -C(=NH)NH_2, - NH-C(=NH)NH_2, -CH_2NH_2, methyl, chlorine or fluorine.

[0042] Preferably, t represents an integer of 0 to 2, more preferably 1 or 2.

[0043] Preferably, tA represents an integer of 0 or 1, more preferably 0.

[0044] Preferably, tB represents an integer of 0 or 1, more preferably 0.

[0045] Preferably, each R^2 independently represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -NH_2, (4) -NHCOO-C1-4 alkyl, (5) halogen, (6) -SO_2-C1-4 alkyl or (7) C1-4 alkoxy, more preferably -COOH, -COOMe, -NH_2, -NHCOOMe, chlorine, fluorine, -SO_2-Me or methoxy.

[0046] Preferably, m represents an integer of 0, 1 or 2, more preferably 1 or 2.

[0047] Preferably, each R^3 independently represents (1) -COO-Me, (2) oxo, (3) -CO-Me, (4) -CO-NH_2, (5) -SO_2-NH_2 or (6) -SO_2-R^6-R^7, more preferably -SO_2-R^6-R^7, wherein R^6 is a bond or NH and R^7 is preferably C1-4 alkyl or Cyc D, wherein Cyc D is preferably as set out above.

[0048] Preferably, n represents an integer of 0 or 1, more preferably 1.

[0049] Preferably, nB represents an integer of 0 or 1, more preferably 0.

[0050] Preferably, R^4 represents a bond or vinylene, more preferably a bond.

[0051] Preferably, R^5 represents (1) -CONH-, (2) Cyc E or (3) Cyc E substituted by with halogen (preferably chlorine), wherein Cyc E is preferably as set out above.

[0052] Preferably, p represents an integer of 0 or 5, more preferably 0 or 1.

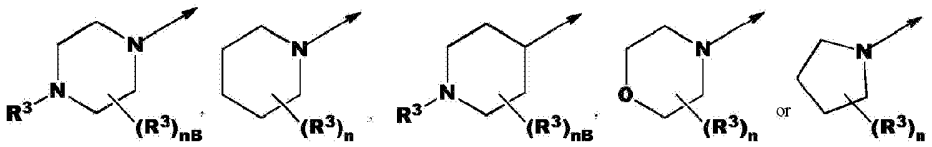
[0053] In a preferred embodiment, Cyc A represents cyclohexyl, phenyl, piperidinyl, piperazinyl or indolyl, more preferably phenyl, cyclohexyl or piperidinyl, t is 1 and R^1 represents -C(=NH)NH_2, -NH-C(=NH)NH_2 or-C1-4 alkylene-NH_2, or t is 2 and one R^1 represents tetrazolyl which may be optionally substituted as set out above and the other R^1 represents halogen.

[0054] In a preferred embodiment, Cyc A represents cyclohexyl, phenyl, piperidinyl, piperazinyl or indolyl, more preferably phenyl, cyclohexyl or piperidinyl, R^4 represent a bond and t is 1 and R^1 represents -C(=NH)NH_2, -NH-C(=NH)NH_2 or -C1-4 alkylene-NH_2, or R^4 represent vinylene and t is 2 and one R^1 represents tetrazolyl which may be optionally substituted as set out above and the other R^1 represents halogen.

[0055] In a preferred embodiment, Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl, more preferably phenyl or pyridyl, m is 1 and R^2 represents (1) -COOH, (2) - COO-C1-4 alkyl, (3) -NH_2, (4) -NHCOO-C1-4 alkyl, (5) halogen, (6) -SO_2-C1-4 alkyl or (7) C1-4 alkoxy, more preferably -COOH, -COOMe, -NH_2, -NHCOOMe, chlorine, fluorine, -SO_2-Me or methoxy.

[0056] In a preferred embodiment, Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl, more preferably phenyl or pyridyl, R^5 represents -CONH- and m is 1 and R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -NH_2, (4) -NHCOO-C1-4 alkyl, (5) halogen, (6) -SO_2-C1-4 alkyl or (7) C1-4 alkoxy, more preferably -COOH, -COOMe, - NH_2, -NHCOOMe, chlorine, fluorine, -SO_2-Me or methoxy, or R^5 represents Cyc E or Cyc E substited with halogen and m is 1 and R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -NHCOO-C1-4 alkyl, (4) halogen, (5) -SO_2-C1-4 alkyl or (6) C1-4 alkoxy, more preferably -COOH, -COOMe, -NHCOOMe, chlorine, fluorine, -SO_2-Me or methoxy.

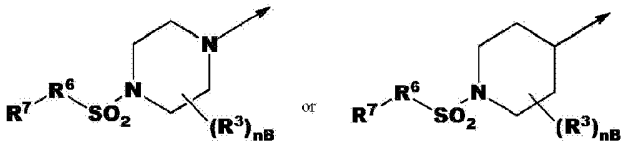
[0057] In a preferred embodiment, -Cyc C -$(R^3)_n$ represents



wherein the arrow represents a binding position; and

the other symbols have the same meanings as described above, preferably wherein n is 0, or nB is 0 and R^3 represents -SO_2-NH2, -SO_2-R^7 or -SO_2-NH-R^7.

[0058] In a preferred embodiment, -Cyc C -$(R^3)_n$ represents

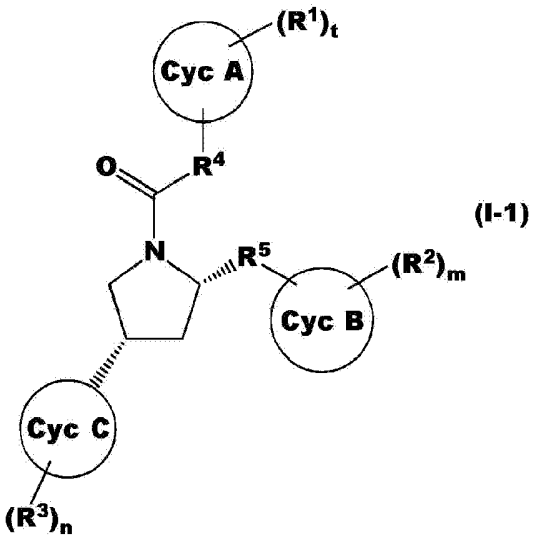


wherein the arrow represents a binding position and

the other symbols have the same meanings as described above, preferably wherein nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2-R^7$ or $-SO_2-NH-R^7$, more preferably nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2$-C1-4 alkyl or $-SO_2$-cyclopropyl.

[0059] The above preferred embodiments of Cyc A, Cyc B and Cyc C $-(R^3)_n$ may be included in preferred compound of the disclosure in any combination.

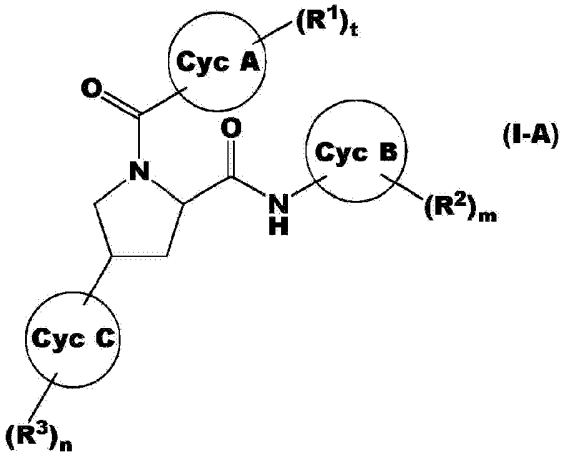
[0060] In one embodiment, preferred compounds of the present disclosure are pyrrolidine derivatives represented by formula (1-1):



(I-1)

wherein the other symbols have the same meanings as described above. Preferably Cyc A, Cyc B, Cyc C, R^1, t, R^2, m, R^3 and n in the formula (I-1) are the preferred options as described above.

[0061] In one embodiment, preferred compounds of the present disclosure are pyrrolidine derivatives represented by formula (I-A):



(I-A)

wherein the other symbols have the same meanings as described above. Preferably Cyc A,

Cyc B, Cyc C, R^1, t, R^2, m, R^3 and n in the formula (I-A) are the preferred options as described above.

[0062] Preferred compounds of formula (I-A) are those in which:

Cyc A represents C3-C8 cycloalkyl or C6-C10 aryl;

Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl;

Cyc C represents 5- to 10-membered heterocycloalkyl;

each R^1 independently represents 5- to 10-membered heteroaryl which may be optionally substituted as set out above, -C(=NH)NH_2, -NH-C(=NH)NH_2, C1-4 alkyl, - C1-4 alkylene-NH_2 or halogen;

t represents an integer of 0, 1 or 2;

R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -NH_2, (4) -NHCOO-C1-4 alkyl, (5) halogen, (6) -SO_2-C1-4 alkyl or (7) C1-4 alkoxy;

m represents an integer of 0, 1 or 2;

each R^3 independently represents (1) -COO-Me, (2) oxo, (3) -CO-Me, (4) -CO-NH_2, (5) -SO_2-NH_2 or (6) -SO_2-R^6-R^7, wherein R^6 is a bond or NH and R^7 is preferably C1-4 alkyl or Cyc D, wherein Cyc D is preferably as set out above;

n represents an integer of 0 or 1.

[0063] Preferred compounds of formula (I-A) include those in which:

Cyc A represents cyclohexyl, phenyl, piperidinyl or piperazinyl;

Cyc B represents phenyl or pyridyl;

Cyc C represents pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl;

each R^1 independently represents tetrazolyl, -C(=NH)NH_2, -NH-C(=NH)NH_2, - CH_2NH_2, methyl, chlorine or fluorine;

t represents an integer of 1 or 2;

R^2 represents -COOH, -COOMe, -NH_2, -NHCOOMe, chlorine, fluorine, -SO_2-Me or methoxy;

m represents an integer of 1 or 2;

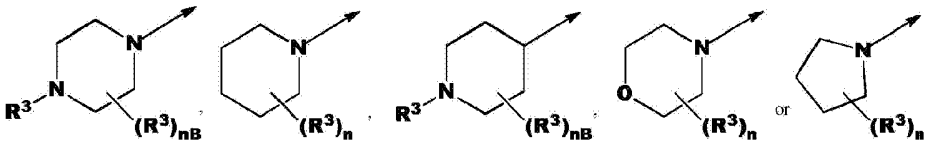
each R^3 independently represents $-SO_2-R^6-R^7$, wherein R^6 is a bond or NH and R^7 is preferably C1-4 alkyl, cyclopropyl or phenyl;

n represents an integer of 1.

[0064] Further preferred compounds of formula (I-A) include those in which Cyc A represents cyclohexyl, phenyl, piperidinyl, piperazinyl or indolyl, more preferably phenyl, cyclohexyl or piperidinyl and t is 1 and R^1 represents $C(=NH)NH_2$, $-NH-C(=NH)NH_2$ or $-CH_2NH_2$.

[0065] Further preferred compounds of formula (I-A) include those in which Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl, more preferably phenyl or pyridyl, and m is 1 and R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -NHCOO-C1-4 alkyl, (4) halogen, (5) $-SO_2$-C1-4 alkyl or (6) C1-4 alkoxy, more preferably - COOH, -COOMe, -NHCOOMe, chlorine, fluorine, $-SO_2$-Me.

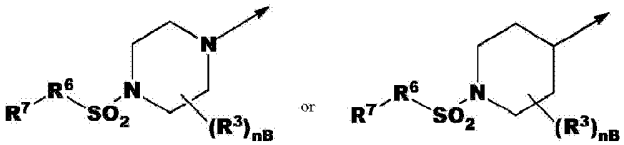
[0066] Further preferred compounds of formula (I-A) include those in which -Cyc C - $(R^3)_n$ represents



wherein the arrow represents a binding position; and

the other symbols have the same meanings as described above, preferably wherein n is 0, or nB is 0 and R^3 represents $-SO_2-NH_2$, $-SO_2-R^7$ or $-SO_2-NH-R^7$.

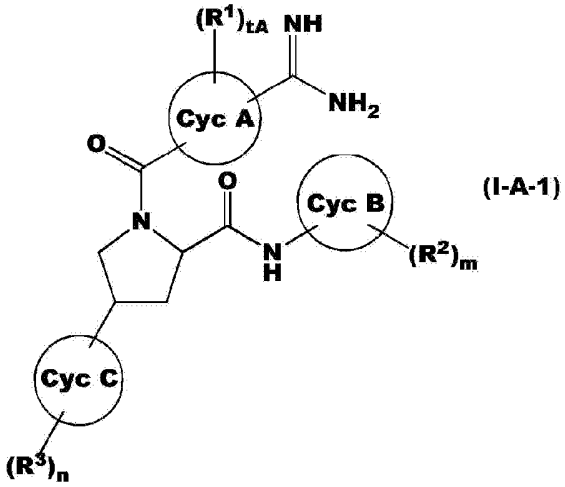
[0067] Further preferred compounds of formula (I-A) include those in which -Cyc C - $(R^3)_n$ represents



wherein the arrow represents a binding position; and

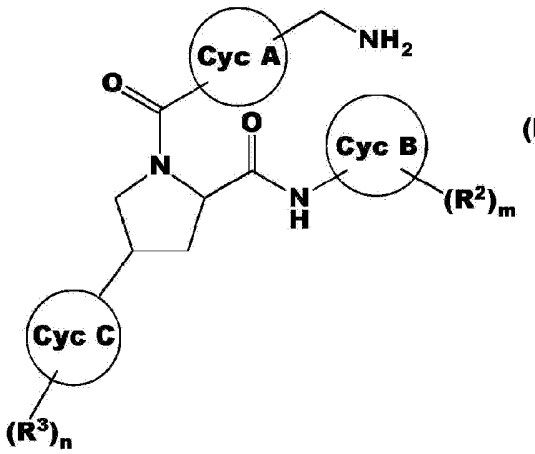
the other symbols have the same meanings as described above, preferably wherein nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2-R^7$ or $-SO_2-NH-R^7$, more preferably nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2$-C1-4 alkyl or $-SO_2$-cyclopropyl.

[0068] Further preferred compounds of formula (I-A) include a compound of (I-A-1):



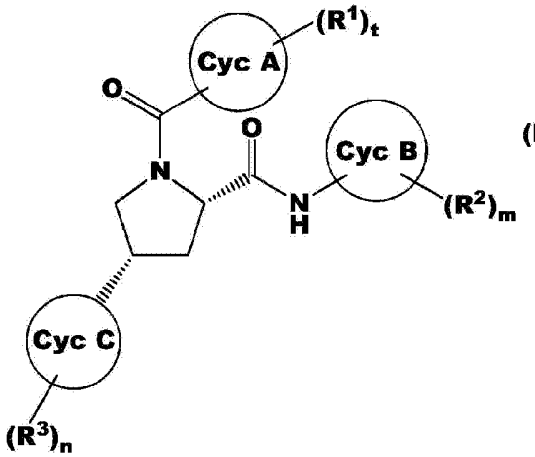
(I-A-1)

wherein tA represents an integer of 0 or 1, more preferably 0, and the other symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-2):



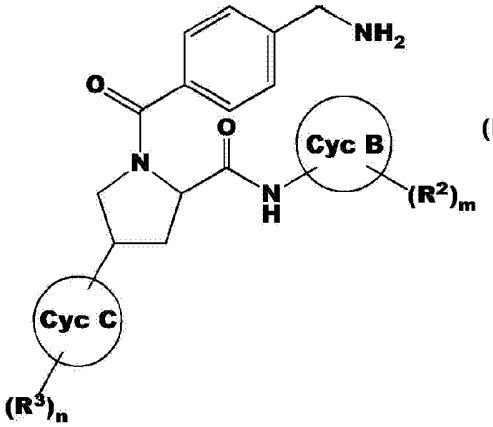
(I-A-2)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-3):



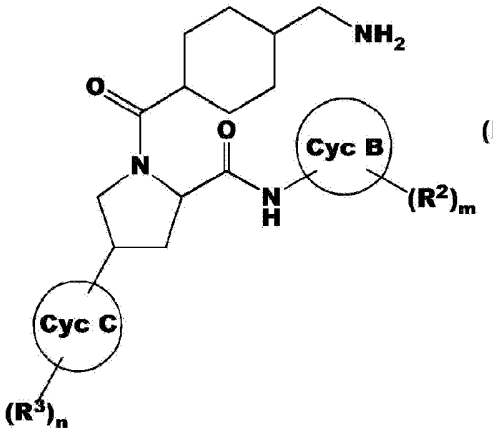
(I-A-3)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-4):



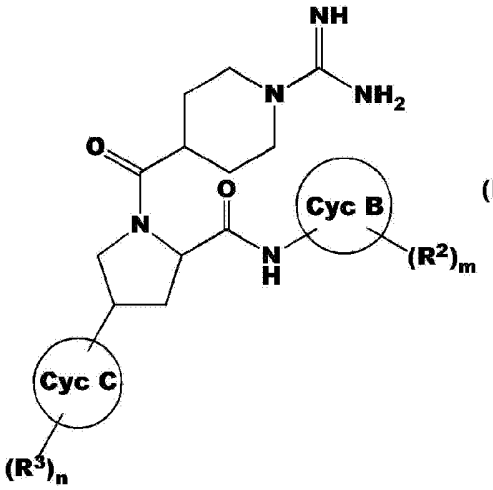
(I-A-4)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-5):



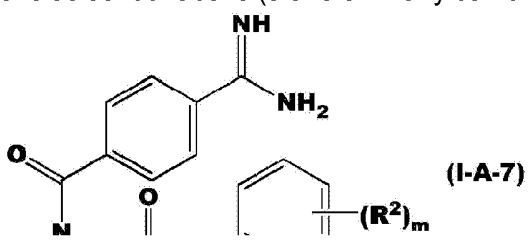
(I-A-5)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-6):

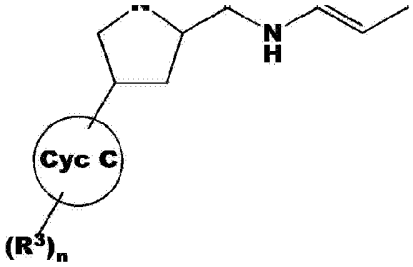


(I-A-6)

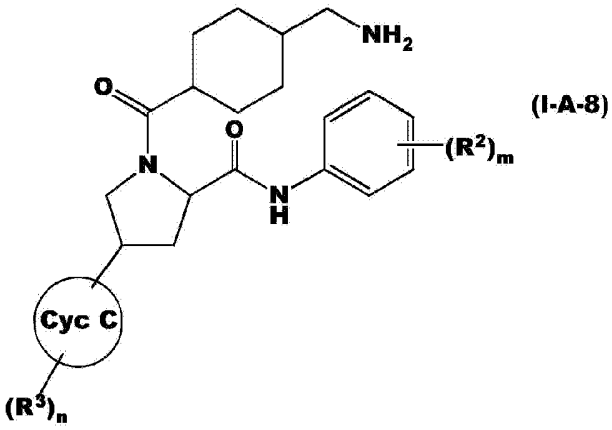
wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-7):



(I-A-7)

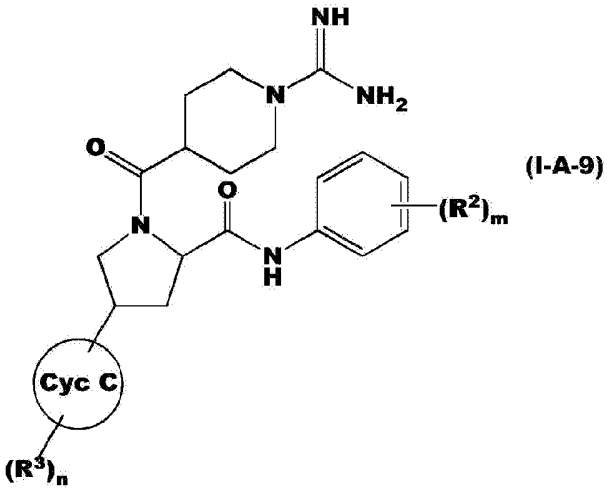


wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-8):



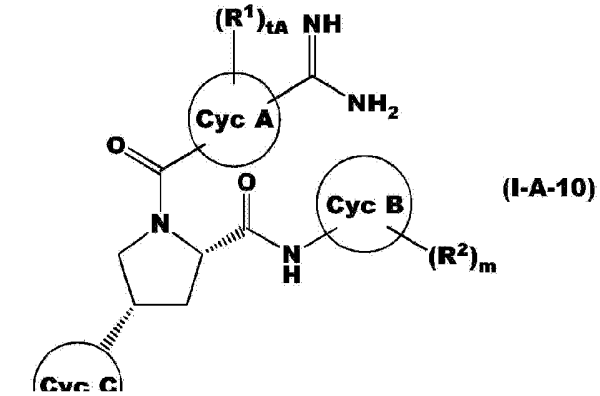
(I-A-8)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-9):



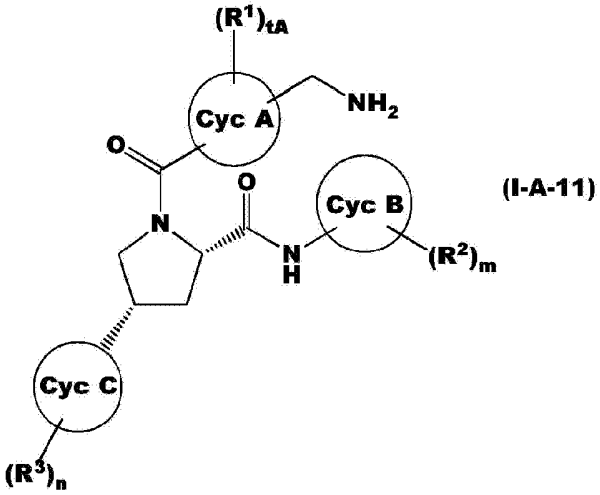
(I-A-9)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-10):



(I-A-10)

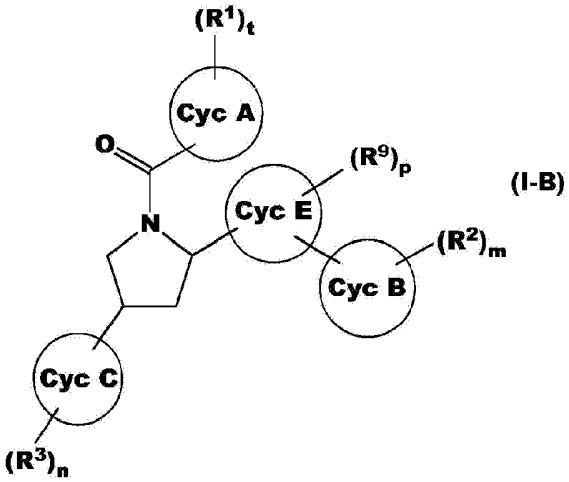
wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-A-11):



(I-A-11)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), and the like.

[0069] In another embodiment, preferred compounds of the present disclosure are pyridinone derivatives represented by formula (I-B):



(I-B)

wherein the other symbols have the same meanings as described above. Preferably, Cyc A, Cyc B, Cyc C, Cyc E, R^1, t, R^2, m, R^3, n, R^9 and p in the formula (I-B) are the preferred options as described above.

[0070] Preferred compounds of formula (I-B) are those in which:

Cyc A represents C3-C8 cycloalkyl or C6-C10 aryl;

Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl;

Cyc C represents 5- to 10-membered heterocycloalkyl;

Cyc E represents 5- to 10-membered heteroaryl;

each R^1 independently represents 5- to 10-membered heteroaryl which may be optionally substituted as set out above, -C(=NH)NH_2, -NH-C(=NH)NH_2, C1-4 alkyl, - C1-4 alkylene-NH_2 or halogen;

t represents an integer of 0, 1 or 2;

each R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -NH_2, (4) -NHCOO-C1-4 alkyl, (5) halogen, (6) -SO_2-C1-4 alkyl or (7) C1-4 alkoxy;

m represents an integer of 0, 1 or 2;

each R^3 independently represents (1) -COO-Me, (2) oxo, (3) -CO-Me, (4) -CO-NH_2, (5) -SO_2-NH_2 or (6) -SO_2-R^6-R^7, wherein R^6 is a bond or NH and R^7 is preferably C1-4 alkyl or Cyc D, wherein Cyc D is preferably as set out above;

n represents an integer of 0 or 1;

each R^9 represents halogen;

p represents an integer of 0 or 1.

[0071] Preferred compounds of formula (I-B) include those in which:

Cyc A represents cyclohexyl, phenyl, piperidinyl or piperazinyl;

Cyc B represents phenyl or pyridyl;

Cyc C represents pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl;

Cyc E represents imidazolyl;

each R^1 independently represents tetrazolyl, -C(=NH)NH_2, -NH-C(=NH)NH_2,-CH_2NH_2, methyl, chlorine or fluorine;

t represents an integer of 1 or 2;

R^2 represents -COOH, -COOMe, -NH_2, -NHCOOMe, chlorine, fluorine, -SO_2-Me or methoxy;

m represents an integer of 1 or 2;

each R^3 independently represents -SO_2-R^6-R^7, wherein R^6 is a bond or NH and R^7 is preferably C1-4 alkyl, cyclopropyl or phenyl;

n represents an integer of 1;

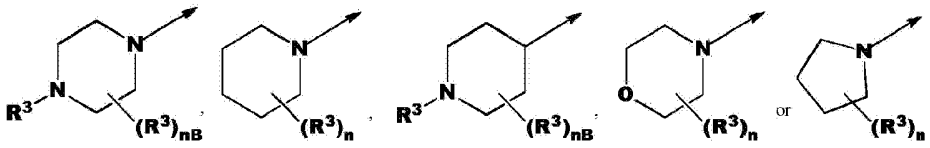
each R^9 represents chlorine;

p represents an integer of 0 or 1.

[0072] Further preferred compounds of formula (I-B) include those in which Cyc A represents cyclohexyl, phenyl, piperidinyl, piperazinyl or indolyl, more preferably phenyl, cyclohexyl or piperidinyl and t is 1 and R^1 represents $-C(=NH)NH_2$, $-NH-C(=NH)NH_2$, or $-CH_2NH_2$.

[0073] Further preferred compounds of formula (I-B) include those in which Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl, more preferably phenyl or pyridyl, and m is 1 and R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) $-NH_2$, (4)-NHCOO-C1-4 alkyl, (5) halogen, (6) $-SO_2$-C1-4 alkyl or (7) C1-4 alkoxy, more preferably -COOH, -COOMe, $-NH_2$, -NHCOOMe, chlorine, fluorine, $-SO_2$-Me.

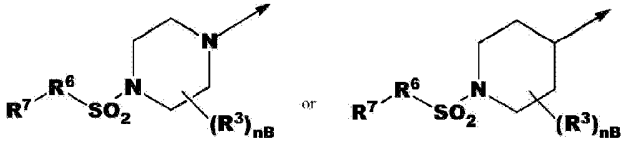
[0074] Further preferred compounds of formula (I-B) include those in which -Cyc C-$(R^3)_n$ represents



wherein the arrow represents a binding position; and

the other symbols have the same meanings as described above, preferably wherein n is 0, or nB is 0 and R^3 represents $-SO_2-NH_2$, $-SO_2-R^7$ or $-SO_2-NH-R^7$.

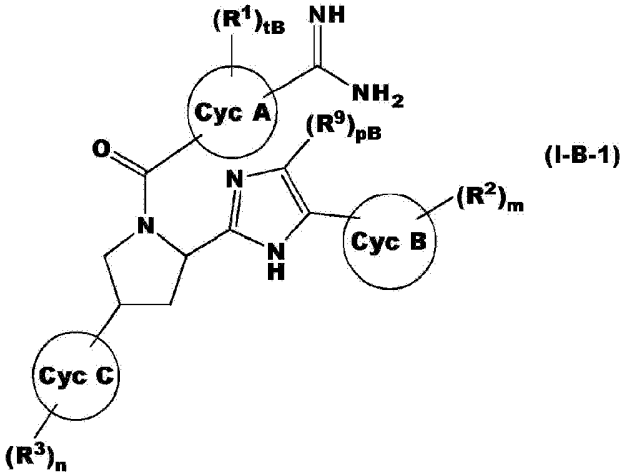
[0075] Further preferred compounds of formula (I-B) include those in which -Cyc C-$(R^3)_n$ represents



wherein the arrow represents a binding position; and

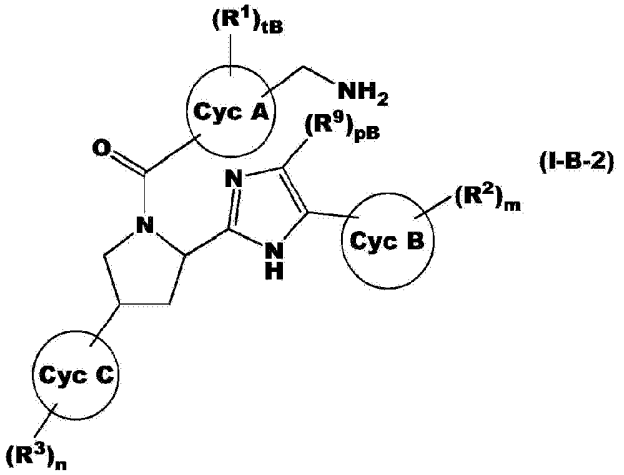
the other symbols have the same meanings as described above, preferably wherein nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2-R^7$ or $-SO_2-NH-R^7$, more preferably nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2$-C1-4 alkyl or $-SO_2$-cyclopropyl

[0076] Further preferred compounds of formula (I-B) include a compound of (I-B-1):



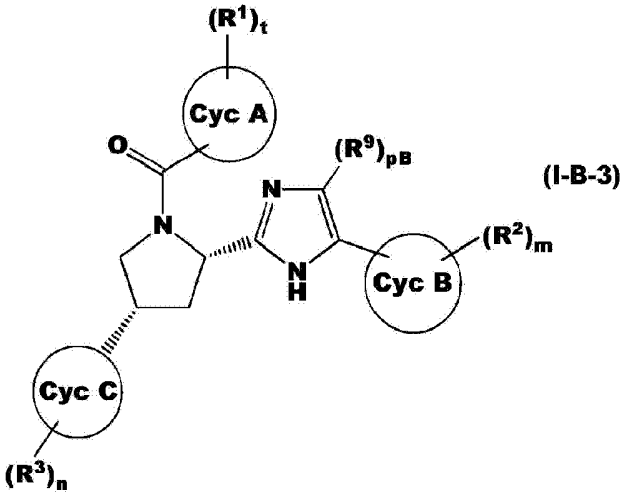
(I-B-1)

wherein tB represents an integer of 0 or 1, more preferably 0, pB represents an integer of 0 or 1, more preferably 0, and the other symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-2):



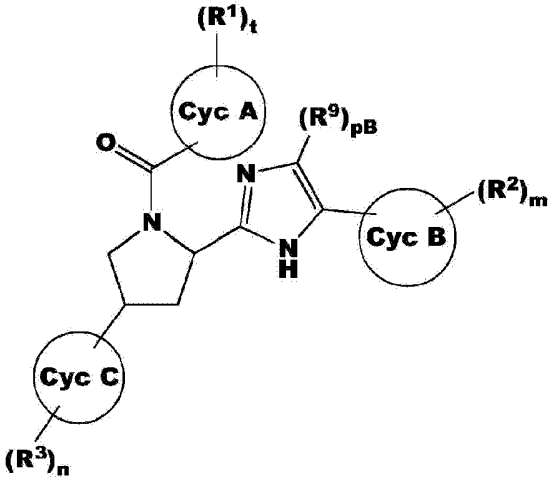
(I-B-2)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-3):



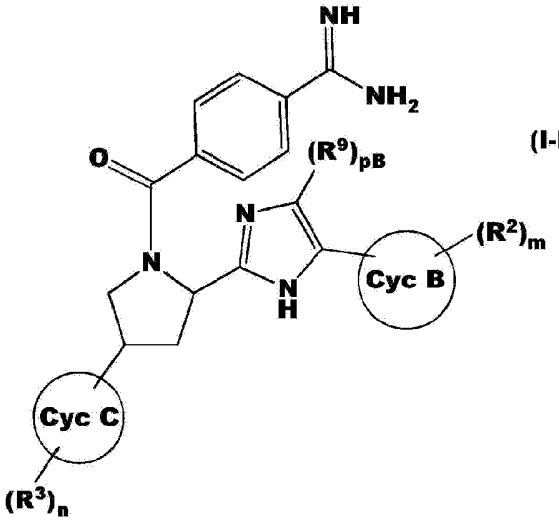
(I-B-3)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-4):



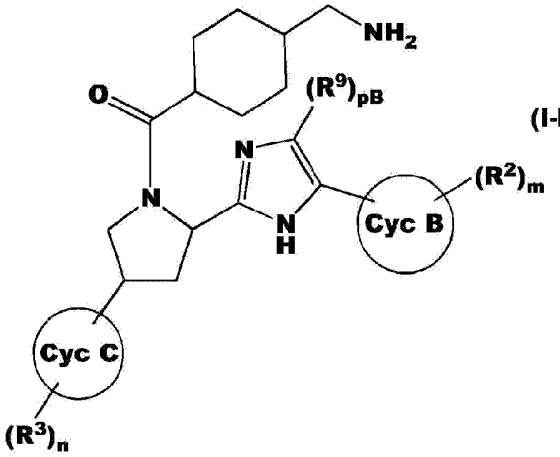
(I-B-4)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-5):



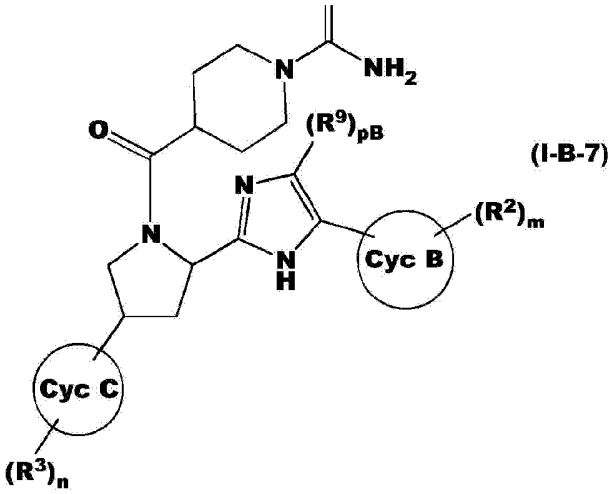
(I-B-5)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-6):



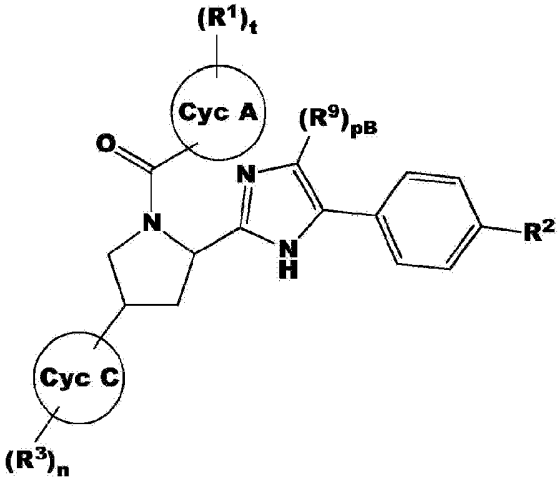
(I-B-6)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-7):



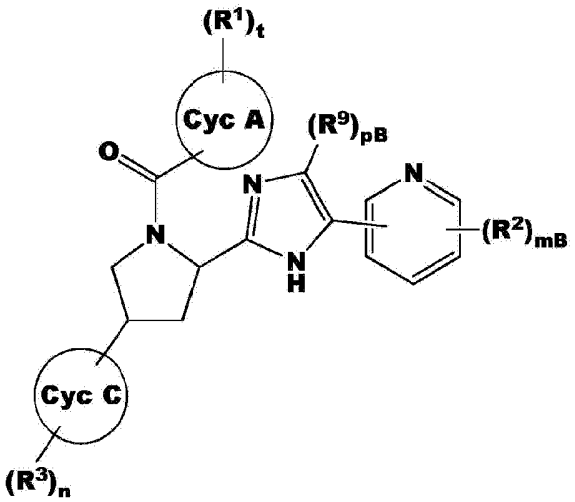
(I-B-7)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-8):



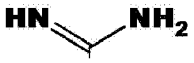
(I-B-8)

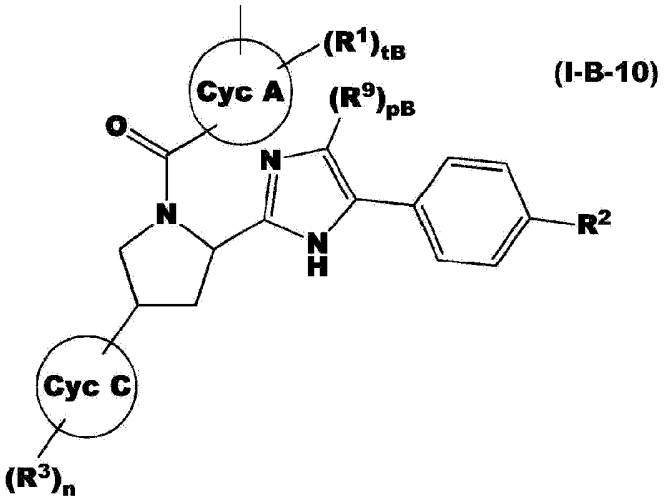
wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-9):



(I-B-9)

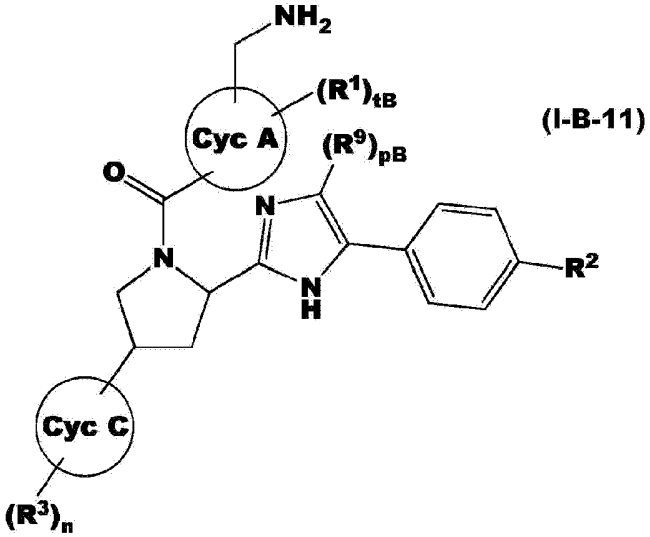
wherein mB represents an integer of 0 to 4, more preferably 0 or 1, and the other symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-10):





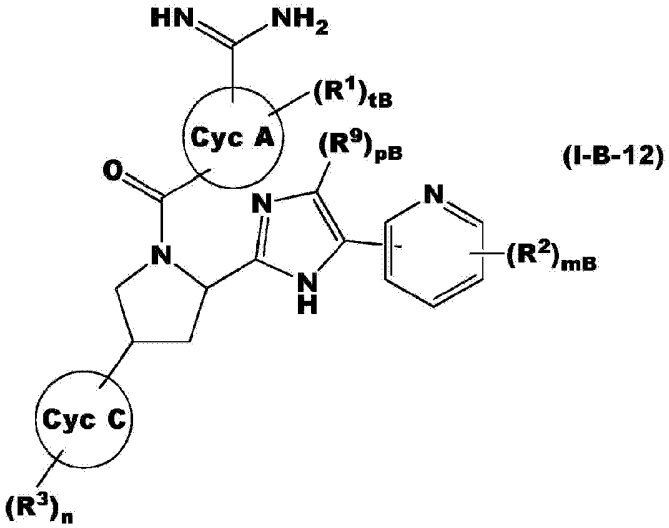
(I-B-10)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-11):



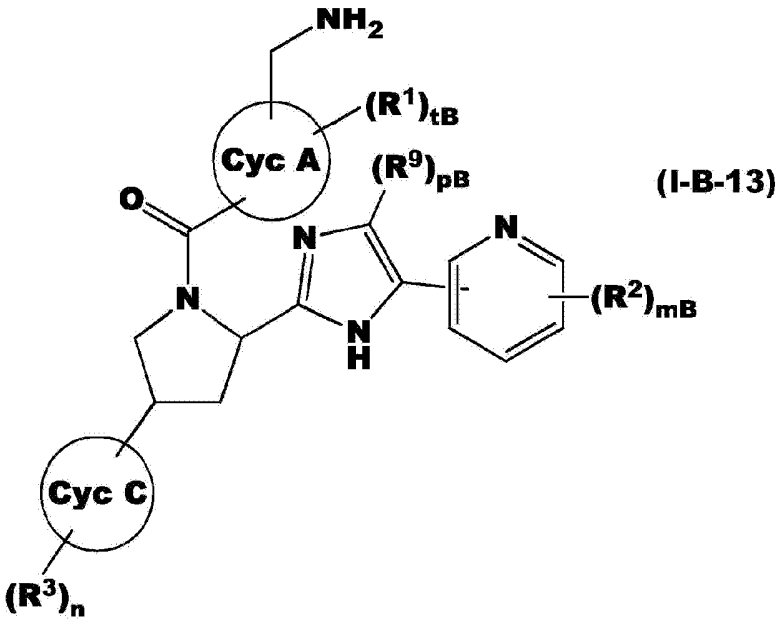
(I-B-11)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-12):



(I-B-12)

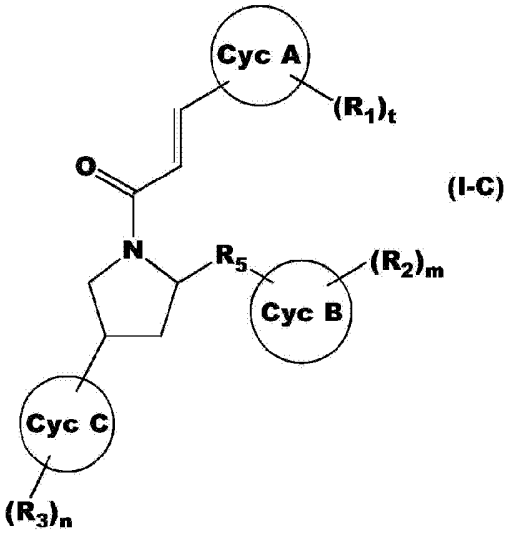
wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-B-13):



(I-B-13)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), and the like.

[0077] In another embodiment, preferred compounds of the present disclosure are pyridinone derivatives represented by formula (I-C):



(I-C)

wherein the other symbols have the same meanings as described above. Preferably, Cyc A, Cyc B, Cyc C, R^1, t, R^2, m, R^3, n and R^5 in the formula (I-C) are the preferred options as described above.

[0078] Preferred compounds of formula (I-C) are those in which:

Cyc A represents C3-C8 cycloalkyl or C6-C10 aryl;

Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl;

Cyc C represents 5- to 10-membered heterocycloalkyl;

each R^1 independently represents 5- to 10-membered heteroaryl which may be optionally substituted as set out above, -C(=NH)NH_2, -NH-C(=NH)NH_2, C1-4 alkyl, - C1-4 alkylene-NH_2 or halogen;

t represents an integer of 0, 1 or 2;

each R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) -NH_2, (4) -NHCOO-C1-4 alkyl, (5) halogen, (6) -SO_2-C1-4 alkyl or (7) C1-4 alkoxy;

m represents an integer of 0, 1 or 2;

each R^3 independently represents (1) -COO-Me, (2) oxo, (3) -CO-Me, (4) -CO-NH_2, (5) -SO_2-NH_2 or (6) -SO_2-R^6-R^7, wherein R^6 is a bond or NH and R^7 is preferably C1-4 alkyl or Cyc D, wherein Cyc D is preferably as set out above;

n represents an integer of 0 or 1;

R^5 represents (1) -CONH-, (2) Cyc E or (3) Cyc E substituted by with halogen.

[0079] Preferred compounds of formula (I-C) include those in which:

Cyc A represents cyclohexyl, phenyl, piperidinyl or piperazinyl;

Cyc B represents phenyl or pyridyl;

Cyc C represents pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl;

each R^1 independently represents tetrazolyl, -C(=NH)NH_2, -NH-C(=NH)NH_2, - CH_2NH_2, methyl, chlorine or fluorine;

t represents an integer of 1 or 2;

R^2 represents -COOH, -COOMe, -NH_2, -NHCOOMe, chlorine, fluorine, -SO_2-Me or methoxy;

m represents an integer of 1 or 2;

each R^3 independently represents -SO_2-R^6-R^7, wherein R^6 is a bond or NH and R^7 is preferably C1-4 alkyl, cyclopropyl or phenyl;

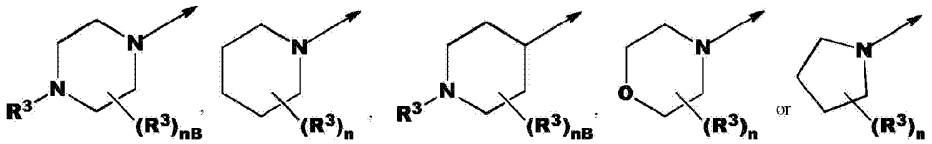
n represents an integer of 1;

R^5 represents (1) -CONH-, (2) imidazolyl or (3) imidazolyl substituted by with chlorine.

[0080] Further preferred compounds of formula (I-C) include those in which Cyc A represents cyclohexyl, phenyl, piperidinyl, piperazinyl or indolyl, more preferably phenyl, t is 2 and one R^1 represents tetrazolyl which may be optionally substituted as set out above and the other R^1 represents halogen.

[0081] Further preferred compounds of formula (I-C) include those in which Cyc B represents C6-C10 aryl or 5- to 10-membered heteroaryl, more preferably phenyl, and m is 1 and R^2 represents (1) -COOH, (2) -COO-C1-4 alkyl, (3) $-NH_2$, (4) -NHCOO-C1-4 alkyl, (5) halogen, (6) $-SO_2$-C1-4 alkyl or (7) C1-4 alkoxy, more preferably -COOH,-COOMe, -NHCOOMe, chlorine, fluorine, $-SO_2$-Me or methoxy.

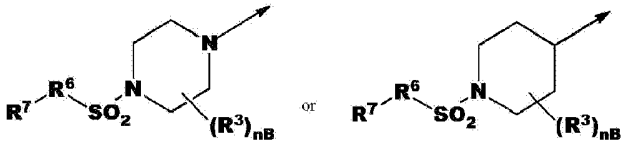
[0082] Further preferred compounds of formula (I-C) include those in which -Cyc C-$(R^3)_n$ represents



wherein the arrow represents a binding position and

the other symbols have the same meanings as described above, preferably wherein n is 0 or nB is 0 and R^3 represents $-SO_2-NH_2$, $-SO_2-R^7$ or $-SO_2-NH-R^7$.

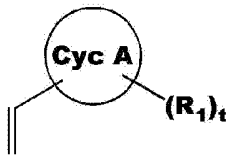
[0083] Further preferred compounds of formula (I-C) include those in which -Cyc C-$(R^3)_n$ represents

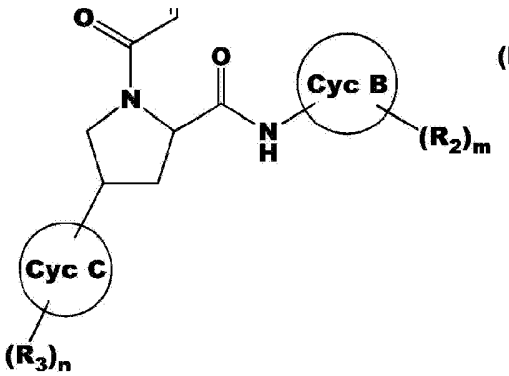


wherein the arrow represents a binding position; and

the other symbols have the same meanings as described above, preferably wherein nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2-R^7$ or $-SO_2-NH-R^7$, more preferably nB is 0 and $-SO_2-R^6-R^7$ represents $-SO_2$-C1-4 alkyl or $-SO_2$-cyclopropyl.

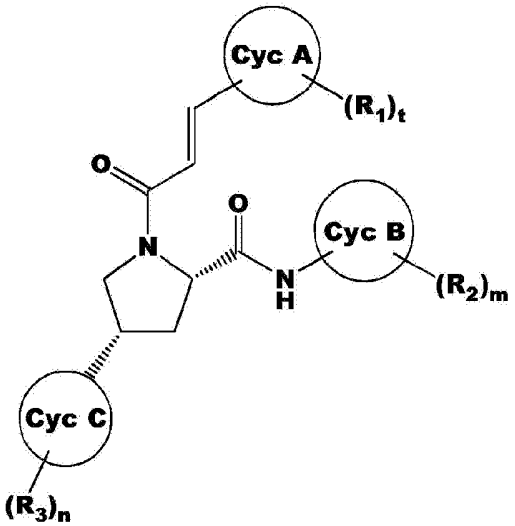
[0084] Further preferred compounds of formula (I-C) include a compound of (I-C-1):





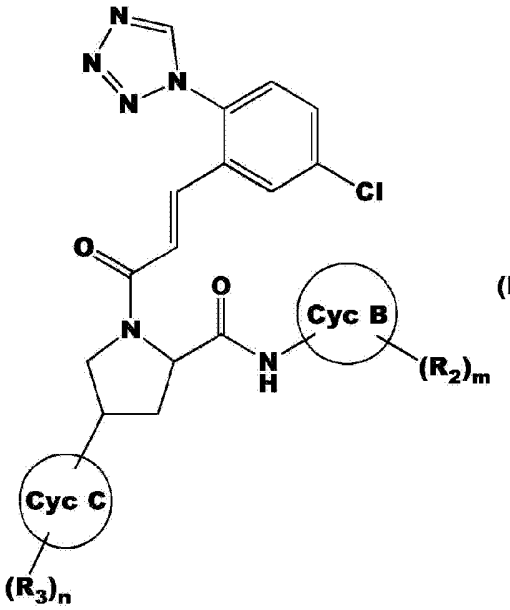
(I-C-1)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-C-2):



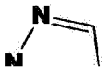
(I-C-2)

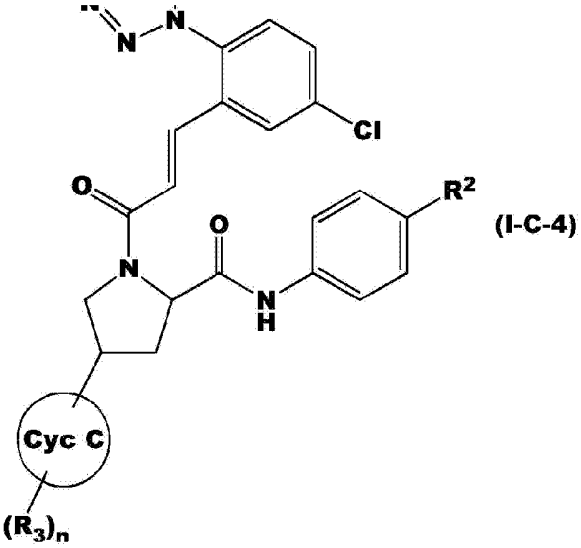
wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-C-3):



(I-C-3)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), a compound of (I-C-4):





(I-C-4)

wherein all symbols have the same meanings as described above and the same preferred definitions as set out above (alone or in any combination), and the like.

[0085] As used herein, general references to "compounds of formula (I)" include compounds of formula (I-A), (I-B) and (I-C).

[0086] The present invention relates to a compound of formula (I-A) which is:

4-[({(2S,4S)-1-(4-carbamimidoylbenzoyl)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl} carbonyl)amino]benzoic acid,

pharmaceutically acceptable salts thereof, N-oxides thereof and solvates thereof.

[0087] The compound of the present invention containing one or more chiral centres may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers. For the avoidance of doubt, the compound of the invention may be used in any tautomeric form.

[0088] Unless otherwise specifically mentioned, all isomers are included in the present invention. For example, alkyl, alkenyl, alkynyl, alkoxy and alkylthio may be straight chain or branched. Moreover, all isomers due to double bond, ring and fused ring (E-, Z-, cis- and trans-forms), isomers due to the presence of asymmetric carbon(s) etc. (R-, S-, α- and β-configuration, enantiomer and diastereomer), optically active substances having optical rotation (D-, L-, d- and 1-forms), polar compounds by chromatographic separation (more polar compounds and less polar compounds), equilibrium compounds, rotational isomers, a mixture thereof in any proportion and a racemic mixture are included in the present invention.

[0089] According to the present disclosure, symbol

represents α-configuration, symbol

represents β-configuration and symbol

represents α-configuration, β-configuration or a mixture of them. There is no particular limitation for the ratio of α-configuration and β-configuration in the mixture.

SALTS:

[0090] The salt of the compound of formula (I) includes all pharmaceutically acceptable salts. With regard to the pharmaceutically acceptable salts, those which are low-toxicity and soluble in water are preferred. Examples of appropriate salts of the compound of formula (I) are salt with alkaline metal (such as potassium, sodium and lithium), salt with alkaline earth metal (such as calcium and magnesium), ammonium salt (such as ammonium salt, tetramethylammonium salt and tetrabutylammonium salt), salt with organic amine (such as triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl) methylamine, lysine, arginine and N-methyl-D-glucamine) and acid addition salt (such as inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate and nitrate) and organic acid salt (e.g. formate, acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, benzoate, citrate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isothionate, glucuronate and gluconate), etc.). The salt of the compound of the present invention also includes solvates and also solvates with the above-mentioned alkaline (earth) metal salt, ammonium salt, organic amine salt and acid addition salt. The solvate is preferably low-toxic and water-soluble. Examples of an appropriate solvate are solvates with water and with alcoholic solvent (such as ethanol). The compounds of the present invention are converted to pharmaceutically acceptable salts by known methods.

[0091] Moreover, the salt includes a quaternary ammonium salt. The quaternary ammonium salt of the compound represented by formula (I) is the compound where nitrogen of the compounds represented by formula (I) is quarternalized by R^0 (R^0 is C1-8 alkyl or C 1-8 alkyl substituted by phenyl).

[0092] The salt also includes an N-oxide. The compound of the present invention can be converted into an N-oxide by known methods. The N-oxide is the compound where nitrogen of the compound represented by formula (I) is oxidized.

[0093] Further, the compound of formula (I) may also be labeled by a radio isotope (such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{35}S, ^{18}F, $^{36}C1$, ^{123}I, ^{125}I, etc.).

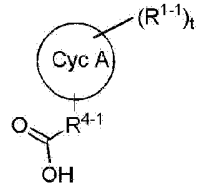
PROCESSES FOR THE PREPARATION OF THE COMPOUND OF THE PRESENT INVENTION:

[0094] The compounds of the present disclosure can, for example, be prepared according to the following reaction schemes.

[0095] The compound of the present disclosure represented by the formula (I) may be prepared by known methods, for example, a method combining the following methods, the method according to these methods, the methods described in the examples and/or methods described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc, 1999), etc., which are appropriately modified in each following method for the preparation. Salts of the starting materials may be used.

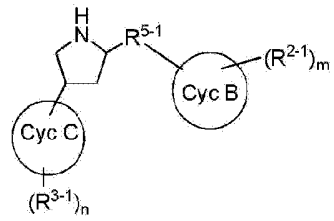
[0096] It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this disclosure. Protection reactions may be carried out by the methods, for example, described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999.

[0097] The compound of formula (I) can be prepared from a compound represented by formula (II):



(II)

wherein R^{1-1} and R^{4-1} have the same meanings as R^1 and R^4 respectively. When additional carboxyl or amino groups are present they are protected, if the protection is necessary, during the amidation process with a compound represented by the formula (III):



(III)

wherein R^{2-1}, R^{3-1} and R^{5-1} have the same meanings as R^2, R^3 and R^5 respectively. When additional carboxyl, hydroxy or amino groups are present they are protected if protection is necessary.

[0098] The amidation reaction is well known. For example, the reaction of the compound represented by formula (II) with the compound represented by formula (III) wherein all symbols have the same meaning described above is exemplified by:

1. (1) A reaction procedure with use of an acid halide,

2. (2) A reaction procedure with use of a mixed acid anhydride, and
3. (3) A reaction procedure with use of a condensing agent.

Referring specifically to these reaction procedures,

1. (1) The reaction procedure employing an acid halide is conducted in practice, for example, by reacting a carboxylic acid with an acid halogenating agent (e.g. oxalyl chloride, thionyl chloride, etc.) in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether, tetrahydrofuran, dimethoxyethane, etc.) at a temperature from about -20 °C to the refluxing temperature, followed by reaction of the resultant acid halide with an amine in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, ethyl acetate, etc.) or solvent-free in the presence of a base (e.g. pyridine, triethylamine, dimethylaniline, 4-dimethylaminopyridine, diisopropylethylamine, etc.) at a temperature of approximately 0 to 40 °C. Alternatively, the procedure can be carried out by reacting the resultant acid halide with an amine in an organic solvent (e.g. 1,4-dioxane, tetrahydrofuran, dichloromethane, etc.) in the presence or absence of a phase-transfer catalyst (e.g. tetrabutylammonium chloride, triethylbenzylammonium chloride, tri-n-octylmethylammonium chloride, trimethyldecylammonium chloride, tetramethylammonium chloride, trimethyldecylammonium chloride, tetramethylammonium chloride, etc.) at a temperature of about 0 to 40 °C, whilst using an aqueous alkali solution (e.g. an aqueous sodium bicarbonate or sodium hydroxide solution, etc.).
2. (2) The reaction procedure employing a mixed acid anhydride is conducted in practice, for example, by reacting a carboxylic acid with an acid halide (e.g. pivaloyl chloride, tosyl chloride, mesyl chloride, etc.) or an acid derivative (e.g. ethyl chloroformate, isobutyl chloroformate, etc.) in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether, tetrahydrofuran, etc.) or solvent free in the presence of base (e.g. pyridine, triethylamine, dimethylaniline, 4-dimethylaminopyridine, diisopropylethylamine, etc.) at a temperature of about 0 to 40 °C , followed by reaction of the resultant mixed acid anhydride with an amine in an organic solvent (e.g. chloroform, dichloroethane, diethyl ether, tetrahydrofuran, etc.) at a temperature of about 0 to 40 °C.
3. (3) The reaction procedure with use of a condensing agent is carried out, for example, by reacting a carboxylic acid with an amine in an organic solvent (e.g. chloroform, dichloromethane, N,N-dimethylformamide, diethyl ether, tetrahydrofuran, etc.) or solvent-free in the presence or absence of a base (e.g. pyridine, triethylamine, diisopropylethylamine, dimethylaniline, 4-dimethylaminopyridine, etc.), with use of a condensing agent (e.g. 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC), 1,1'-carbonyldiimidazole (CDI), 2-chloro-1-methylpyridinium iodide, 1,1'-propylphosphonic acid anhydride (1-propanephosphonic acid cyclic anhydride, PPA), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), etc.) and with or without use of 1-hydroxybenztriazole (HOBt), at a temperature of about 0 to 40 °C.

[0099] In the course of the synthesis of the compound of the present disclosure represented by the formula (I), the deprotection reaction can be carried out at an appropriate synthetic stage when protective groups of carboxyl, hydroxy or amino groups are present.

[0100] The deprotection reactions for protective groups of carboxyl, hydroxy or amino groups are well-known and include, for example,

1. (1) a deprotection reaction by alkali hydrolysis,
2. (2) a deprotection under acidic conditions,
3. (3) a deprotection reaction by hydrogenolysis,
4. (4) a deprotection reaction of a silyl group,
5. (5) a deprotection reaction using a metal,
6. (6) a deprotection reaction using a metal complex, etc.

To explain these methods in detail:

1. (1) The deprotection reaction by alkali hydrolysis is carried out, for example, in an organic solvent (methanol, tetrahydrofuran, 1,4-dioxane, etc.) using a hydroxide of alkali metals (sodium hydroxide, potassium hydroxide, lithium hydroxide, etc.), hydroxide of alkaline earth metals (barium hydroxide, calcium hydroxide, etc.), carbonate (sodium carbonate, potassium carbonate, etc.) or a solution thereof or a mixture thereof at a temperature of 0 to 40 °C.
2. (2) The deprotection reaction under acidic conditions is carried out, for example, in an organic solvent (dichloromethane, chloroform, 1,4-dioxane, ethyl acetate, anisole, etc.), using an organic acid (acetic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, etc.) or an inorganic acid (hydrochloric acid, sulfuric acid, etc.) or a mixture thereof (hydrobromic acid/acetic acid, etc.) in the presence or absence of 2,2,2-trifluoroethanol at a temperature of 0 to 100 °C.
3. (3) The deprotection reaction by hydrogenolysis is, for example, carried out in a solvent (e.g. ethers such as tetrahydrofuran, 1,4-dioxane, dimethoxyethane, diethyl ether, etc.; alcohols such as methanol, ethanol, etc.; benzenes such as benzene, toluene, etc.; ketones such as acetone, methyl ethyl ketone, etc.; nitriles such as acetonitrile etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide etc.; water, ethyl acetate, acetic acid or a mixture of two or more thereof, etc.) in the presence of a catalyst (palladium-carbon, palladium black, palladium hydroxide, platinum oxide, Raney nickel, etc.) under an atmosphere of hydrogen at normal or increased pressure, or in the presence of ammonium formate at a temperature of 0 to 200 °C.
4. (4) The deprotection reaction of a silyl group is, for example, carried out in a water-miscible organic solvent (tetrahydrofuran, acetonitrile, etc.) using tetrabutylammonium fluoride at a temperature of 0 to 40 °C.
5. (5) The deprotection reaction using a metal is carried out, for example, in an acidic solvent (acetic acid, a buffer of pH 4.2 to 7.2 or a mixture of the solution thereof and an organic solvent such as tetrahydrofuran etc.) in the presence of zinc powder at a temperature of 0 to 40 °C optionally under sonication.
6. (6) The deprotection reaction using a metal complex is carried out, for example, in an

organic solvent (dichloromethane, N,N-dimethylformamide, tetrahydrofuran, ethyl acetate, acetonitrile, 1,4-dioxane, ethanol, etc.), water or a mixture thereof, in the presence of a trapping reagent (tributyltin hydride, triethylsilane, dimedone, morpholine, diethylamine, pyrrolidine, 1,3-dimethylbarbituric acid, etc.), an organic acid (acetic acid, formic acid, 2-ethylhexanecarboxylic acid, etc.) and/or a salt of an organic acid (sodium 2-ethylhexanoate, potassium 2-ethylhexanoate, etc.) in the presence or absence of a phosphine reagent (triphenylphosphine etc.) using a metal complex (tetrakis(triphenylphosphine)palladium (0), palladium(II) bis(triphenylphosphine) dichloride, palladium(II) acetate, rhodium(I) tris(triphenylphosphine) chloride, etc.) at a temperature of 0 to 40 °C.

[0101] In addition to the above, deprotection reactions may be carried out by the methods, for example, described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999.

[0102] A protective group for carboxyl includes, for example, methyl, ethyl, allyl, tert-butyl, trichloroethyl, benzyl (Bn), phenacyl, p-methoxybenzyl, trityl, 2-chlorotrityl or a solid carrier containing these structures, etc.

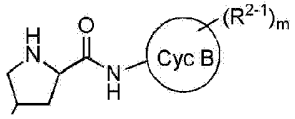
[0103] A protective group for hydroxy includes, for example, methyl (Me), trityl (Tr), methoxymethyl (MOM), 1-ethoxyethyl (EE), methoxyethoxymethyl (MEM), 2-tetrahydropyranyl (THP), trimethylsilyl (TMS), triethylsilyl (TES), tertbutyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), acetyl (Ac), pivaloyl (Pv), benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), allyloxycarbonyl (Alloc) or 2,2,2-trichloroethoxycarbonyl (Troc), etc.

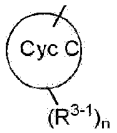
[0104] A protective group for amino includes, for example, benzyloxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl (Alloc), 1-methyl-1-(4-biphenyl)ethoxycarbonyl (Bpoc), trifluoroacetyl, 9-fluorenylmethoxycarbonyl (FMoc), benzyl (Bn), p-methoxybenzyl, benzyloxymethyl (BOM), 2-(trimethylsilyl)ethoxymethyl (SEM), etc.

[0105] Protective groups for carboxyl, hydroxy or amino group are not limited to those described above, but include groups which are easily and selectively deprotected. For example, those groups described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999.

[0106] As is easily understood by those skilled in the art, the target compound of the present disclosure may be prepared easily by selecting these deprotection reactions.

1. 1) The compound of formula (III) wherein R^{5-1} represents a carboxyamide which is attached to Cyc B at nitrogen atom, that is, a compound represented by formula (III-1):

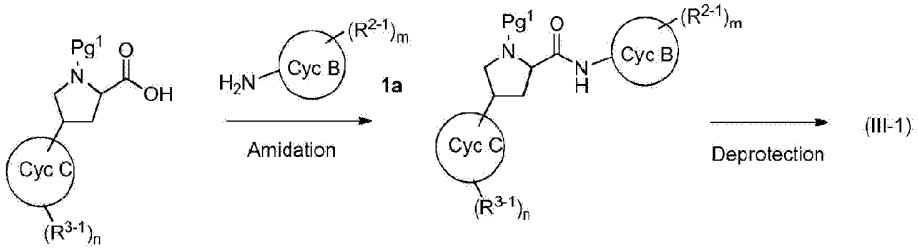




(III-1)

wherein all symbols have the same meaning described above, can be prepared as outlined in Reaction Scheme 1:

Reaction Scheme 1



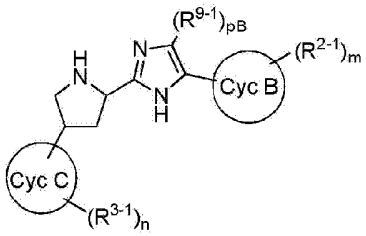
(IV)

1b

wherein Pg^1 represents a protective group for amino described above and the other symbols have the same meaning described above.

In Reaction Scheme 1, the compound represented by formula (IV) and the amine compound represented by formula 1a can be condensed to produce the compound represented by formula 1b by an amidation reaction as described above. The compound represented by formula 1b can be converted to the amine compound represented by the formula (III-1) by a deprotection reaction as described above.

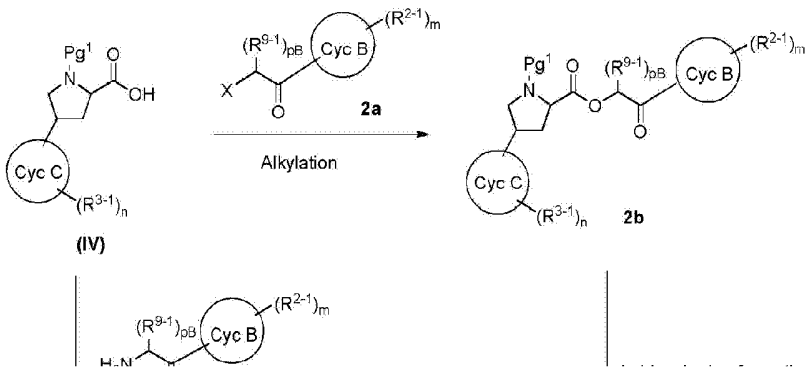
2. 2) The compound of formula (III) wherein R^{5-1} represents an imidazole which is attached to Cyc B at the 4-position, that is, a compound represented by formula (III-2):



(III-2)

wherein R^{9-1} have the same meanings as R^9, and the other symbols have the same meaning described above, can be prepared as outlined in Reaction Scheme 2:

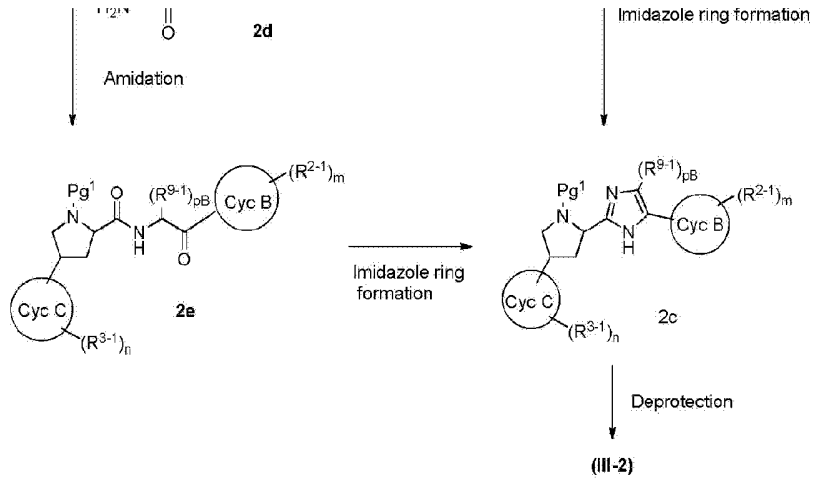
Reaction Scheme 2



(IV)

2a

2b



wherein X represents fluorine, chlorine, bromine or iodine, and the other symbols have the same meaning described above.

In Reaction Scheme 2, the reaction from the compound represented by formula (IV) to the compound represented by formula 2b is an alkylation reaction.

The alkylation reaction is well known. For example, the alkylation reaction of the compound represented by formula (IV) with the compound represented by formula 2a can be conducted in a solvent such as N,N-dimethylformamide, tetrahydrofuran, dichloromethane, acetone or acetonitrile in the presence of a base such as sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, N,N-diisopropylethylamine or triethylamine at -20 °C to reflux temperature to form a compound represented by formula 2b wherein all symbols have the same meaning described above.

The reaction from the compound represented by formula 2b to the compound represented by formula 2c is an imidazole formation reaction.

The imidazole formation reaction is well known. For example, the compound represented by formula 2b can be converted to compounds of formula 2c by heating and/or microwave irradiation in the presence of ammonium acetate or ammonium trifluoroacetate in a suitable solvent such as xylene, toluene or acetic acid.

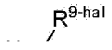
Alternatively, the compound represented by formula 2c can be prepared from the compound represented by formula 2e. The reaction from the compound represented by formula (IV) to the compound represented by formula 2e is an amidation reaction.

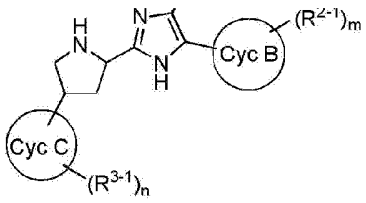
The amidation reaction of the compound represented by formula (IV) with the compound represented by formula 2d can be conducted by the method as described above.

The reaction from the compound represented by formula 2e to the compound represented by formula 2c is an imidazole formation reaction. The imidazole formation reaction can be carried out by the same method as described above.

The compound represented by formula 2c can be converted to the amine compound represented by the formula (III-2) by a deprotection reaction as described above.

3. 3) The compound of formula (III) wherein R^5 represents an imidazole ring which is attached to Cyc B at the 4-position and possesses $R^{9\text{-hal}}$, that is, a compound represented by formula (III-3):

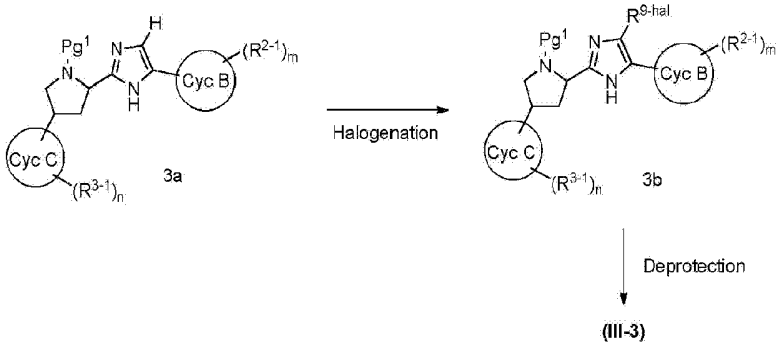




(III-3)

wherein $R^{9\text{-hal}}$ represents fluorine, chlorine, bromine or iodine, and the other symbols have the same meaning described above, can be prepared as outlined in Reaction Scheme 3.

Reaction Scheme 3



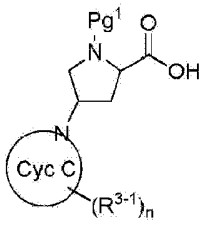
wherein all symbols have the same meanings as described above.

In Reaction Scheme 3, the reaction from the compound represented by formula 3a to the compound represented by formula 3b is a halogenation reaction.

The halogenation reaction is well known. For example, the reaction of the compound represented by formula 3 a with brominating or chlorinating agent, such as N-bromosuccinimide, N-chlorosuccinimide or 1,3-dichloro-5,5-dimethylhydantoin in a suitable solvent such as acetonitrile, chloroform or tetrahydrofuran from -20 °C to the refluxing temperature provides the compound represented by formula 3b.

The compound represented by formula 3b can be converted to the amine compound represented by the formula (III-3) by a deprotection reaction as described above.

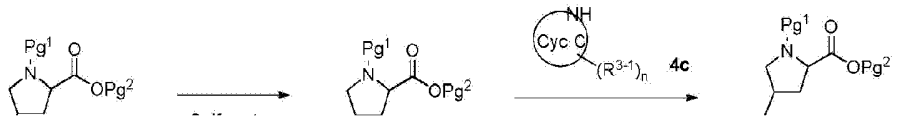
4. 4) The compound of formula (IV) wherein Cyc C is attached to pyrrolidine ring via nitrogen atom, that is, a compound represented by formula (IV-1):

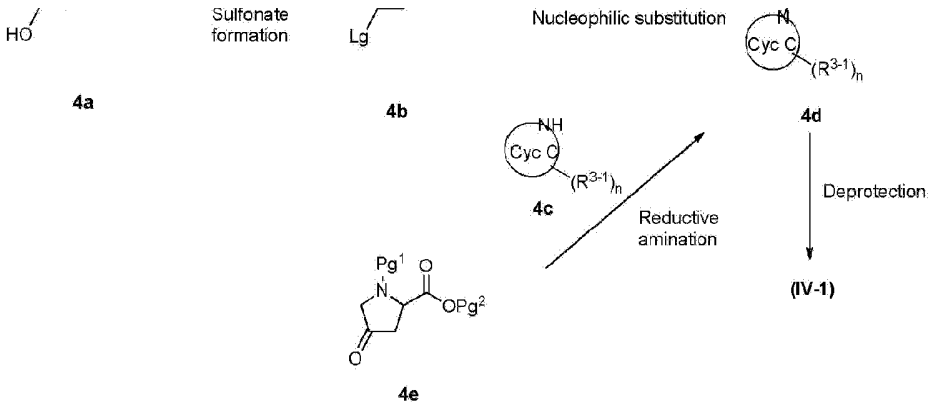


(IV-1)

wherein all symbols have the same meanings as described above, can be prepared as outlined in Reaction Scheme 4:

Reaction Scheme 4





wherein Pg^2 represents a protective group for carboxyl described above and Lg represents triflate, tosylate or mesylate and the other symbols have the same meaning described above.

In Reaction Scheme 4, the reaction from the compound represented by formula 4a to the compound represented by formula 4b is a sulfonate formation reaction.

The sulfonate formation reaction is well known. For example, the treatment of the compound represented by formula 4a with a sulfonating reagent such as trifluoromethanesulfonic anhydride, p-toluenesulfonyl chloride or methanesulfonyl chloride in a solvent such as tetrahydrofuran or dichloromethane in the presence of a base such as N,N-diisopropylethylamine or triethylamine at -20 °C to reflux temperature provides a compound represented by formula 4b.

The reaction from the compound represented by formula 4b to the compound represented by formula 4d is a nucleophilic substitution reaction.

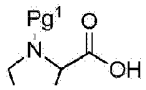
The nucleophilic substitution reaction is well known. For example, the nucleophilic substitution reaction of compound 4b with compounds of formula 4c can be conducted in a solvent such as *tert*-butanol or N,N-dimethylformamide in the presence of a base such as N,N-diisopropylethylamine or triethylamine at 20 °C to reflux temperature to provide the compound represented by formula 4d.

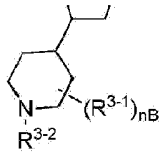
Alternatively, the compound represented by formula 4d can be prepared from the compound represented by formula 4e. The reaction from the compound represented by formula 4e to the compound represented by formula 4d is a reductive amination reaction.

The reductive amination reaction of the compound represented by formula 4e with the compound represented by formula 4c can be conducted in a solvent such as methanol, tetrahydrofuran, dichloromethane, 1,2-dichloroethane or acetic acid in the presence of a reductant such as sodium cyanoborohydride or sodium triacetoxyborohydride at -20 °C to reflux temperature to provide the compound represented by formula 4d.

The compound represented by formula 4d can be converted to the amine compound represented by the formula (IV-1) by a deprotection reaction as described above.

5. 5) The compound of formula (IV) wherein Cyc C is appropriately substituted piperidine which is attached to pyrrolidine ring at 4-position of piperidine ring, that is, a compound represented by formula (IV-2):

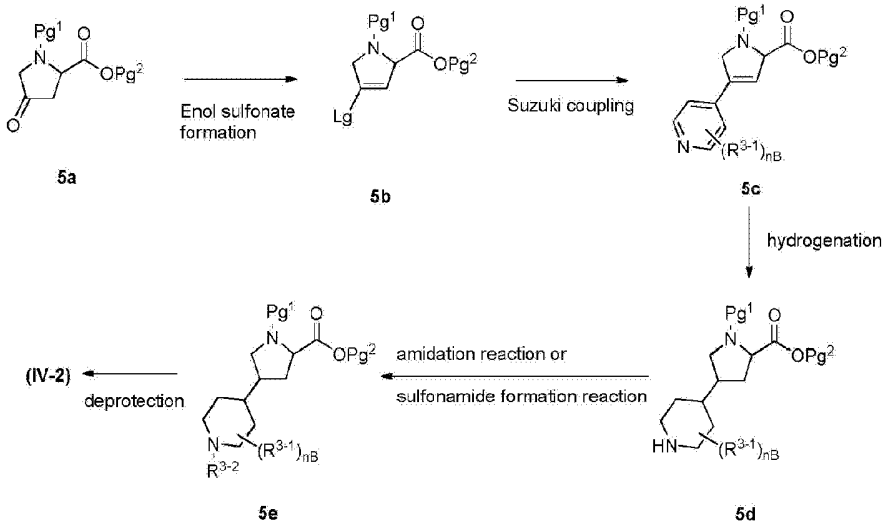




(IV-2)

wherein R^{3-1} and R^{3-2} has the same meanings as R^3, with the proviso that a carboxyl, hydroxyl or amino group in R^{3-1} and R^{3-2} may be protected if necessary, can be prepared as outlined in Reaction Scheme 5:

Reaction Scheme 5



wherein all symbols have the same meaning described above.

[0107] In Reaction Scheme 5, the reaction from the compound represented by formula 5a to the compound represented by formula 5b is an enol sulfonate formation reaction.

[0108] The enol sulfonate formation reaction is well known. For example, the treatment of the compound represented by formula 5a with a sulfonating reagent such as trifluoromethanesulfonic anhydride, N-phenyltrifluoromethanesulfonimide, 2-[N,N-bis(trifluoromethanesulfonyl)amino]pyridine, *p*-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride, *p*-toluenesulfonyl chloride and methanesulfonyl chloride in a solvent such as tetrahydrofuran or dichloromethane in the presence of a base such as lithium diisopropylamide or sodium bis(trimethylsilyl)amide at -78 °C to 0 °C provides a compound represented by formula 5b.

[0109] Suzuki coupling reaction between a compound represented by formula 5b with an appropriately functionalized 4-pyridineboronic acid or ester in the presence of a base such as anhydrous cesium carbonate, cesium fluoride, sodium carbonate or potassium phosphate in a solvent such as 1,4-dioxane, N,N-dimethylformamide or dimethylsulfoxide using a catalyst such

as tetrakis(triphenylphosphine)palladium(0), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride, palladium(II) acetate or bis(dibenzylidenacetone)palladium(0), with or without a phosphine ligand such as triphenylphosphine, tri-*tert*-butylphosphine or 1,1'-bis(diphenylphosphino)ferrocene at a temperature from about 70 °C to the refluxing temperature provides the compounds represented by formula 5c.

[0110] In cases where suitably substituted boronic acids or esters are not commercially available, the 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane intermediate can be prepared from the corresponding aryl halide or aryl triflate by a palladium mediated coupling with a diboron species such as bis(pinacolato)diboron using the method of Ishiyama, T. et al. (J. Org. Chem., 1995, 60(23), 7508). Alternatively, the corresponding boronic acid can be prepared by metal-halogen exchange of the aryl/heteroaryl halide, quenching with a trialkoxyborate reagent and aqueous workup to provide the boronic acids (Miyaura, N.; Suzuki, A. Chem. Review, 1995, 95, 2457).

[0111] The hydrogenation reaction of 5c can be conducted in a solvent such as methanol, ethanol or acetic acid in the presence of a catalyst such as palladium-carbon, palladium black, palladium hydroxide, platinum-carbon or platinum oxide under an atmospheric or increased pressure of hydrogen to give a compound represented by formula 5d.

[0112] The compound represented by formula 5d can be converted to the N-substituted compounds represented by formula 5e by an amidation reaction or sulfonamide formation reaction.

[0113] The compound of formula 5e wherein R^{3-2} represents acyl group can be prepared by an introduction of R^{3-2} group using an amidation reaction as described above.

[0114] The compound of formula 5e wherein R^{3-2} represents sulfonyl group can be prepared by an introduction of R^{3-2} group using a sulfonamide formation reaction.

[0115] The sulfonamide formation reaction is well known. For example, the treatment of the compound represented by formula 5d with appropriately substituted sulfonating reagent such as an alkylsulfonic anhydride, alkylsulfonyl chloride or aryl sulfonyl chloride in a solvent such as tetrahydrofuran or dichloromethane in the presence of a base such as N,N-diisopropylethylamine or triethylamine at -20 °C to reflux temperature to provide the compound represented by formula 5e.

[0116] The compound represented by formula 5e can be converted to the amine compound represented by the formula (IV-2) by a deprotection reaction as described above.

[0117] The compounds of the present disclosure can be prepared by the reactions or modified variants of the reactions described above.

[0118] Other starting compounds or compounds used as reagents are known compounds which can be prepared easily by a combination of known methods, for example, the methods described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Willey & Sons Inc, 1999) or Elmer J. Rauckman et al., J. Org. Chem., 1976, 41(3), 564 etc.

[0119] In each reaction of the specification the reactions with heating, as will be apparent to those skilled in the art, may be carried out using a water bath, an oil bath, a sand bath, a heating block or by microwave.

[0120] In each reaction of the specification, a solid phase reagent may be used which is supported by a polymer (for example polystyrene, polyacrylamide, polypropylene or polyethyleneglycol etc.).

[0121] In each reaction of the specification, the products obtained may be purified by conventional techniques. For example, the purification may be carried out by distillation at atmospheric or reduced pressure, by high performance liquid chromatography with silica gel or magnesium silicate, by thin layer chromatography, by ion-exchange resin, by scavenger resin, by column chromatography, by washing, trituration or recrystallization. The purification may be carried out after each reaction stage or after several reaction stages.

[0122] In a reaction of the specification where polystyrene resin is used, the obtained products may be purified by conventional techniques. For example, the purification may be carried out by multiple washing with a solvent (for example, N,N-dimethylformamide, dichloromethane, methanol, tetrahydrofuran, toluene, acetic acid/toluene, etc.).

TOXICITY:

[0123] The compound represented by formula (I), the salt thereof, the N-oxide thereof, the solvate thereof or the prodrug thereof show low toxicity (e.g. acute toxicity, chronic toxicity, genotoxicity, developmental toxicity, cardiac toxicity, drug interaction, carcinogenicity) and lack side effects such as bleeding. It may therefore be considered safe for pharmaceutical use.

APPLICATION TO PHARMACEUTICALS:

[0124] The compounds of the present disclosure are therapeutically useful. The present disclosure therefore provides a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof, for use in the treatment of the human or animal body by therapy.

[0125] Also provided is a pharmaceutical composition comprising a compound of formula (I),

as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof, and a pharmaceutically acceptable carrier or diluent.

[0126] Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer.

[0127] The compound of the present invention may normally be administered systemically or locally, usually by oral, parenteral or continuous administration.

[0128] A therapeutically effective amount of a compound of the invention is administered to a patient. The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person are generally from 1 mg to 1000 mg, by oral administration, up to several times per day, and from 1 mg to 100 mg, by parenteral administration (preferably intravenous administration), up to several times per day, or continuous administration from 1 to 24 hours per day from vein.

[0129] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0130] The compounds or pharmaceutical compositions of the present invention may be administered, for example, in the form of a solid for oral administration, liquid forms for oral administration, injections, liniments or suppositories for parenteral administration. Solid forms for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

[0131] In such solid forms, one or more of the active compound(s) may be admixed with vehicles (such as lactose, mannitol, glucose, microcrystalline cellulose or starch), binders (such as hydroxypropyl cellulose, polyvinylpyrrolidone or magnesium metasilicate aluminate), disintegrants (such as cellulose calcium glycolate), lubricants (such as magnesium stearate), stabilizing agents, solution adjuvants (such as glutamic acid or aspartic acid, disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures, dyestuffs, sweeteners, wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations and prepared according to methods well known in normal pharmaceutical practice, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes. The solid forms may, if desired, be coated with coating agents (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate) or be coated with two or more films. Furthermore, coating may include containment within capsules of absorbable materials such as gelatin.

[0132] Liquid forms for oral administration include pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs. In such forms, one or more of the active compound(s) may be dissolved, suspended or emulsified into diluent(s) commonly used in the art (such as purified water, ethanol or a mixture thereof). Besides such liquid forms may also comprise some additives, such as wetting agents, suspending agents, emulsifying agents, sweetening agents, flavoring agents, aroma, preservative or buffering agent. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

[0133] Suspensions and emulsions may contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier e.g. sterile water, olive oil, ethyl oleate, glycols (e.g. propylene glycol) and, if desired, a suitable amount of lidocaine hydrochloride.

[0134] Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

[0135] Injections for parenteral administration include sterile aqueous suspensions, emulsions and solid forms which are dissolved or suspended into solvent(s) for injection immediately before use. In injections, one or more of the active compound(s) may be dissolved, suspended or emulsified into solvent(s). The solvents may include distilled water for injection, saline, vegetable oil, propylene glycol, polyethylene glycol, alcohol such as ethanol, or a mixture thereof. Injections may comprise some additives, such as stabilizing agents, solution adjuvants (such as glutamic acid, aspartic acid or POLYSORBATE80 (registered trade mark)), suspending agents, emulsifying agents, soothing agents, buffering agents or preservatives. They may be sterilized at a final step, or may be prepared according to sterile methods. They may also be manufactured in the form of sterile solid forms such as freeze-dried products, which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before use.

[0136] Other forms for parenteral administration include liquids for external use, ointments and endermic liniments, inhalations, sprays, suppositories and vaginal suppositories which comprise one or more of the active compound(s) and may be prepared by methods known *per se*.

[0137] Sprays may comprise additional substances other than diluents used commonly, stabilizers such as sodium hydrogensulfite and buffers capable of imparting isotonicity, for example, isotonic buffers such as sodium chloride, sodium citrate or citric acid.

EFFECT OF THE INVENTION:

[0138] The compound of the present invention represented by formula (I) acts as a potent and selective inhibitor of factor XIa, and also shows superior properties as a pharmaceutical product such as stability, water solubility and the like. Thus the compound of the present invention is useful in preventing and/or treating thromboembolic diseases. One advantage of the compound of the present invention is that it can provide high inhibitory activity against FXIa and high safety without side effects such as bleeding.

[0139] The present invention therefore provides a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof, for use in treating or preventing a thromboembolic disease. Further provided is the use of a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof, in the manufacture of a medicament for use in treating or preventing a thromboembolic disease.

[0140] The thromboembolic disease may be, for example, selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, venous cerebrovascular thromboembolic disorders and thromboembolic disorders in the chambers of the heart or in the peripheral circulation.

[0141] More specifically, arterial cardiovascular thromboembolic disorders may be exemplified by coronary artery disease, ischemic cardiomyopathy, acute coronary syndrome, coronary arterial thrombosis, ischemic complications of unstable angina and non-Q-wave myocardial infarction, acute non ST-segment elevation and/or ST-segment elevation myocardial infarction managed medically or with subsequent percutaneous coronary intervention, angina pectoris such as stable effort angina pectoris, variant angina pectoris, unstable angina pectoris, myocardial infarction (e.g. first myocardial infarction or recurrent myocardial infarction), acute myocardial infarction, reocclusion and restenosis after coronary artery bypass surgery, reocclusion and restenosis after percutaneous transluminal cardiac angioplasty/ transluminal coronary artery stent placement surgery or after thrombolytic therapy for coronary artery, ischemic sudden death. Venous cardiovascular thromboembolic disorders may be exemplified by deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in major general surgery, abdominal surgery, hip replacement surgery, knee replacement surgery, hip fracture surgery, multiple fracture, multiple injury, trauma, spinal cord injury, burns, critical care unit, DVT and/or PE in medical patients with severely restricted mobility during acute illness, DVT and/or PE in patients with cancer chemotherapy, DVT and/or PE in patients with stroke, symptomatic or asymptomatic DVT with or without PE (pulmonary embolism). Arterial cerebrovascular thromboembolic disorders may be exemplified by stroke, ischemic stroke, acute stroke, stroke in patients with non-valuvelar or valuvelar atrial fibrillation, cerebral arterial thrombosis, cerebral infarction, transient ischemic attack (TIA), lacuna infraction, atherosclerotic thrombotic cerebral infarction, cerebral artery embolism, cerebral thrombosis, cerebrovascular disorder and asymptomatic cerebral infarction. Venous cerebrovascular thromboembolic disorders may be exemplified by intracranial venous thrombosis, cerebral embolism, cerevral thrombosis, sinus thrombosis, intracranial venous sinus thrombosis and cavernous sinus thrombosis.

Thromboembolic disorders in the chambers of the heart or in the peripheral circulation may be exemplified by venous thrombosis, systemic venous thromboembolism, thrombophlebitis, non-valuvelar or valuvelar atrial fibrillation, cardiogenic embolism, disseminated intravascular coagulopathy (DIC), sepsis, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), antiphospholipid antibody syndrome, kidney embolism, atherosclerosis, atherothrombosis, peripheral artery occlusive disease (PAOD), peripheral arterial disease, arterial embolism, and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface (such as catheters, stents, artificial heart valves or hemodialyzer) that promotes thrombosis.

[0142] Preferably, the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, myocardial infarction (e.g. first myocardial infarction or recurrent myocardial infarction), ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, portal vein thrombosis, pulmonary embolism, pulmonary infarction, liver embolism, mesenteric artery and/or vein embolism, occlusion of retinal vein and/or artery, systemic embolism, disseminated intravascular coagulopathy (DIC), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), antiphospholipid antibody syndrome, thrombosis resulting from coronary artery bypass graft surgery and thrombosis resulting from medical implants, devices, or procedures in which blood is exposed to an artificial surface (such as catheters, stents or artificial heart valves) that promotes thrombosis.

[0143] The compound of the present invention may also be administered in combination with one or more further therapeutic agents for use in treating a thromboembolic disorder comprising, wherein the first therapeutic agent is a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof, and the second therapeutic agent is at least one agent selected from a second factor XIa inhibitor, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, a fibrinolytic agent, a serine protease inhibitor ,an elastase inhibitor and an steroid. Preferrably, the second therapeutic agent is at least one agent selected from warfarin, unfractionated heparin, low molecular weight heparin, enoxaparin, dalteparin, bemiparin, tinzaparin, semuloparin, danaparoid, synthetic pentasaccharide, fondaparinux, hirudin, disulfatohirudin, lepirudin, bivalirudin, desirudin, argatroban, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, prasugrel, ticagrelor, cangrelor, elinogrel, cilostazol, sarpogrelate, iroprost, beraprost, limaprost, tirofiban, eptifibatide, abciximab, melagatran, ximelagatran, dabigatran, rivaroxaban, apixaban, edoxaban, darexaban, betrixaban, TAK-442, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, streptokinase, gabexate, gabexate mesilate, nafamostat, sivelestat, sivelestat sodium hydrate, alvelestat, ZD-8321/0892, ICI-200880, tiprelestat, elafin, alpha1-antitrypsin, cortisone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone and triamcinolone. Preferrably, the second therapeutic agent is at least one anti-platelet agent. Preferrably, the anti-platelet agent(s) are clopidogrel, prasugrel, ticagrelor, cangrelor, elinogrel, cilostazol,

sarpogrelate, iroprost, beraprost, limaprost and/or aspirin, or a combination thereof. The present invention also provides a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof, in combination with a second therapeutic agent selected from those listed above, for use in treating or preventing a thromboembolic disease. The present invention also provides the use of a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof, in combination with a second therapeutic agent, in the manufacture of a medicament for use in treating or preventing a thromboembolic disease.

[0144] In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, an N-oxide thereof or a solvate thereof and an additional therapeutic agent. Preferably, the further additional therapeutic agent(s) are selected from potassium channel openers, potassium channel blockers, calcium channel blockers, sodium hydrogen exchanger inhibitors, antiarrhythmic agents, antiatherosclerotic agents, anticoagulants, antiplatelets, antithrombotic agents, prothrombolytic agents, fibrinogen antagonists, diuretics, antihypertensive agents, ATPase inhibitors, mineralcorticoid receptor antagonists, phospodiesterase inhibitors, antidiabetic agents, protease inhibitors, elastase inhibitors, anti-inflammatory agents, antioxidants, angiogenesis modulators, antiosteoporosis agents, hormone replacement therapies, hormone receptor modulators, oral contraceptives, antiobesity agents, antidepressants, antianxiety agents, antipsychotic agents, antiproliferative agents, antitumor agents, antiulcer and gastroesophageal reflux disease agents, growth hormone agents and/or growth hormone secretagogues, thyroid mimetics, anti-infective agents, antiviral agents, antibacterial agents, antifungal agents, cholesterol/lipid lowering agents and lipid profile therapies, and agents that mimic ischemic preconditioning and/or myocardial stunning, or a combination thereof.

[0145] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from an antiarrhythmic agent, an anti-hypertensive agent, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, a fibrinolytic agent, a calcium channel blocker, a potassium channel blocker, a cholesterol/lipid lowering agent, a serine protease inhibitor, an elastase inhibitor, an anti-inflammatory agent, or a combination thereof.

[0146] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s) selected from warfarin, unfractionated heparin, low molecular weight heparin, enoxaparin, dalteparin, bemiparin, tinzaparin, semuloparin, danaparoid, synthetic pentasaccharide, fondaparinux, hirudin, disulfatohirudin, lepirudin, bivalirudin, desirudin, argatroban, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, dipyridamol, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, prasugrel, ticagrelor, cangrelor, elinogrel, cilostazol, sarpogrelate, iroprost, beraprost, limaprost, tirofiban, eptifibatide, abciximab, melagatran, ximelagatran, dabigatran, rivaroxaban, apixaban, edoxaban, darexaban, betrixaban, TAK-442, tissue

plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, streptokinase gabexate, gabexate mesilate, nafamostat, sivelestat, sivelestat sodium hydrate, alvelestat, ZD-8321/0892, ICI-200880, tiprelestat, elafin, alpha1-antitrypsin, cortisone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone and triamcinolone or a combination thereof.

[0147] In a preferred embodiment, the present invention provides a pharmaceutical composition wherein the additional therapeutic agent is an antihypertensive agent selected from ACE inhibitors, AT-1 receptor antagonists, beta-adrenergic receptor antagonists, ETA receptor antagonists, dual ETA/AT-1 receptor antagonists, and vasopepsidase inhibitors, an antiarrythmic agent selected from IKur inhibitors, elastase inhibitors, serine protease inhibitors, steroids, an anticoagulant selected from thrombin inhibitors, antithrombin-III activators, heparin co-factor II activators, other factor XIa inhibitors, plasma and/or tissue kallikrein inhibitors, plasminogen activator inhibitor (PAI-1) inhibitors, thrombin activatable fibrinolysis inhibitor (TAFI) inhibitors, factor VIIa inhibitors, factor VIIIa inhibitors, factor IXa inhibitors, factor Xa inhibitors and factor XIIa inhibitors, or an anti-platelet agent selected from GPII/IIIa blockers, protease activated receptor (PAR-1) antagonists, PAR-4 antagonists, phosphodiesterase-III inhibitors, other phosphodiesterase inhibitors, P2X1 antagonits, $P2Y_1$ receptor antagonists, $P2Y_{12}$ antagonists, thromboxane receptor antagonists, thromboxane A2 synthase inhibitors, cyclooxygense-1 inhibitors, phospholipase D1 inhibitors, phospholipase D2 inhibitors, phospholipase D inhibitors, glycoprotein VI (GPVI) antagonists, glycoprotein Ib (GPIb) antagonists, Growth arrest-specific gene 6 product (Gas6) antagonists and aspirin, or a combination thereof.

[0148] In a preferred embodiment, the present invention provides a pharmaceutical composition, wherein the additional therapeutic agent(s) are an anti-platelet agent or a combination thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

[0149] The present invention is illustrated by the following Examples and biological Examples, but it is not limited thereto.

[0150] The solvents in the parentheses described in chromatographic separation and TLC show the eluting or developing solvents, and the ratios of the solvents used are given as percentage mixtures in chromatographic separations or TLC. Where a compound is described as dried, either anhydrous magnesium or sodium sulphate was used. The solvents in the parentheses in NMR show the solvents used in measurement. DMSO-d_6 represents deuterated dimethylsulfoxide; $CDCl_3$ represents deuterated chloroform; CD_3OD represents deuterated methanol; D_2O represents deuterated water. The following abbreviations are used in reporting the ^1H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), br. (broad), app. (apparent), obs. (obscured).

[0151] Including compounds in the following Examples, compounds used in the present specification were commonly named using a computer program capable of naming in accordance with IUPAC rules; ACD/Name® manufactured by Advanced Chemistry Development Inc., JChem for Excel or MarvinSketch manufactured by ChemAxon Ltd., or IUPAC nomenclature. In each of the following Examples, the name of the objective compound of the Example is described subsequently to the number of the Example, and the compound is sometimes referred to as the "title compound".

Preparation Example 1: methyl (2S,4R)-4-hydroxy-2-pyrrolidinecarboxylate hydrochloride

[0152] To a solution of (2*S*,4*R*)- 4-hydroxy-2-pyrrolidinecarboxylic acid hydrochloride (1.0 g, 7.6 mmol) in methanol (25 mL) at 0 °C was added thionyl chloride (0.83 mL, 11.4 mmol). The reaction was warmed to room temperature and heated at reflux overnight. After cooling to room temperature, the reaction mixture was concentrated to dryness to give the title compound (1.2 g, 92%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.99 (br. s, 2H), 5.58 (br. s, 1H), 4.49-4.41 (m, 2H), 3.75 (s, 3H), 3.38 (dd, 1H), 3.07 (d, 1H), 2.23-2.04 (m, 2H).

Preparation Example 2: 1-benzyl 2-methyl (2S,4R)-4-hydroxy-1,2-pyrrolidinedicarboxylate

[0153] Chlorobenzylformate (1.0 mL, 7.9 mmol) was added to a mixture of the compound prepared in Example 1 (1.2 g, 6.6 mmol), $NaHCO_3$ (4.0 g) and saturated aqueous $NaHCO_3$ (5.0 mL) in THF (20 mL) at 0 °C. After stirring at room temperature for 3 h, tris(hydroxymethyl)aminomethane (1.4 g) was added and the reaction mixture was partitioned between ethyl acetate and water, the combined organic extracts were dried and concentrated and purified by flash chromatography (silica gel, 40 g, 20-80% ethyl acetate/hexanes) to give the title compound (1.3 g, 72%) as a pale yellow oil.

^{1}H NMR (300 MHz, CD_3OD, rotamers present) δ 7.35-7.29 (m, 5H), 5.18-4.97 (m, 2H), 4.47-4.39 (m, 2H), 3.71 (s, 1.5H), 3.62-3.51 (m, 3.5H), 2.30-2.25 (m, 1H), 2.09-2.00 (m, 1H).

Preparation Example 3: 1-benzyl 2-methyl (2S,4S)-4-[4-(methylsulfonyl)-1-piperazinyl]-1,2-pyrrolidinedicarboxylate

[0154] To a solution of the compound prepared in Example 2 (1.0 g, 3.6 mmol) and N,N-diisopropylethylamine (1.24 mL, 7.16 mmol) in dichloromethane (20 mL) at -20 °C was added trifluoromethylsulfonic anhydride (0.904 g, 5.36 mmol). The reaction mixture was stirred at

room temperature for 1 h then concentrated to dryness to obtain the crude triflate. The crude material was dissolved in *tert*-butanol (50 mL) and N,N-diisopropylethylamine (1.24 mL, 7.16 mmol) and 1-(methylsulfonyl)piperazine (1.76g, 10.7 mmol) were added to the reaction at room temperature. The resulting mixture was heated at 100 °C for 48 h. After cooling to room temperature, the solvent was removed and the crude reaction mixture was purified by flash chromatography (silica gel, 40 g, 20-60% ethyl acetate/hexanes) to give the title compound (2.35 g, 85%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers present) δ 7.35-7.28 (m, 5H), 5.19-5.00 (m, 2H), 4.15-4.31 (m, 1H), 3.98-3.82 (m, 1H), 3.75 (s, 1.7H), 3.55 (s, 1.3H), 3.33-3.22 (m, 5H), 2.91-2.81 (m, 1H), 2.76 (s, 3H), 2.62-2.46 (m, 5H), 1.91-1.81 (m, 1H).

Preparation Example 4: (2S,4S)-1-[(benzyloxy)carbonyl]-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinecarboxylic acid

[0155] To a solution of the compound prepared in Example 3 (0.90 g, 2.11 mmol) in tetrahydrofuran (20 mL) and water (20 mL) at 0 °C was added lithium hydroxide (0.203 g, 8.4 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction mixture was carefully acidified to pH 5 with 2 M hydrochloric acid. The aqueous solution was extracted with ethyl acetate (2 × 300 mL) and the combined organic extracts were dried and concentrated to give the title compound (0.565 g, 65%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers present) δ 7.36-7.33 (m, 5H), 5.18-5.12 (m, 2H), 4.43-4.36 (m, 1H), 3.98-3.82 (m, 2H), 3.37-3.17 (m, 4H), 3.00-2.91 (m, 1H), 2.82-2.71 (m, 6H), 2.64-2.49 (m, 2H), 2.24-2.12 (m, 1H), 1.97-1.85 (m, 1H).

Preparation Example 5: benzyl (2S,4S)-2-[(4-{[(2-methyl-2-propanyl)oxy]carbonyl}phenyl)carbamoyl]-4-[4-(methylsulfonyl)-1-piperazinyl]-1-pyrrolidinecarboxylate

[0156] To a solution of the compound prepared in Example 4 (0.20 g, 0.40 mmol) and 2-methyl-2-propanyl 4-aminobenzoate (0.154 g, 0.80 mmol) in pyridine (50 mL) was added 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (0.630 mg 3.2 mmol) at 0 °C. The reaction was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure and the resulting residue diluted with dichloromethane (20 mL). This solution was washed with brine, dried and concentrated. Purification by flash chromatography (silica gel, 40 g, 20-80% ethyl acetate/hexanes) gave the title compound (0.185 g, 65%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers present) δ 9.15 (br. s, 0.6H), 8.33 (br. s, 0.4H), 7.88 (d, 2H), 7.50 (d, 2H), 7.35-7.01 (m, 5H), 5.22-4.93 (m, 2H), 4.56-4.36 (m, 1H), 3.88-3.76 (m, 1H), 3.22-3.00 (m, 4H), 2.93-2.78 (m, 3H), 2.69-2.48 (m, 6H), 2.45-2.24 (m, 2H), 1.58 (s, 9H).

Preparation Example 6: 2-methyl-2-propanyl 4-[({(2S,4S)-4-[4-(methylsulfonyl)-1-

piperazinyl]-2-pyrrolidinyl}carbonyl)amino]benzoate

[0157] To a solution of the compound prepared in Example 5 (2.1 g, 7.4 mmol) in ethanol (100 mL) was added Pd/C (0.40 g, 20% by wt). The reaction was stirred under an atmosphere of hydrogen (50 psi) at room temperature for 6 h. The reaction mixture was filtered through diatomaceous earth and concentrated to give the title compound (1.10 g, 69%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.95 (d, 2H), 7.63 (d, 2H), 3.95 (dd, 1H), 3.28 (dd, 1H), 3.14 (t, 4H), 2.89-2.85 (m, 1H), 2.83-2.76 (m, 1H), 2.63 (s, 3H), 2.60-2.44 (m, 5H), 2.05 (br. s, 1H), 2.03-1.98 (m, 1H), 1.58 (s, 9H).

Preparation Example 7: 1-(N,N'-bis{[(2-methyl-2-propanyl)oxy]carbonyl}carbamimidoyl)-4-piperidinecarboxylic acid

[0158] To a solution of piperidine-4-carboxylic acid trifluoroacetate salt (0.20 g, 0.82 mmol) in methanol (10 mL), triethylamine (0.20 mL, 1.6 mmol) and N,N'-bis{[(2-methyl-2-propanyl)oxy]carbonyl}-1H-pyrazole-1-carboximidamide (0.30 g, 0.98 mmol) was added and the reaction mixture stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the resulting residue dissolved in ethyl acetate and washed with brine. The organic layer was dried and concentrated to dryness to obtain the title compound (200 mg, 76%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.91 (d, 2H), 3.30 (t, 2H), 2.63-2.66 (m, 1H), 1.90-1.96 (m, 2H), 1.67-1.69 (m, 2H), 1.45 (s, 18H).

Preparation Example 8: 2-methyl-2-propanyl 4-[({(2S,4S)-1-{[1-(N,N'-bis{[(2-methyl-2-propanyl)oxy]carbonyl}carbamimidoyl)-4-piperidinyl]carbonyl}-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl}carbonyl)amino]benzoate

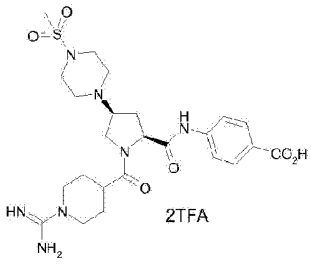
[0159] To a solution of the compound prepared in Example 6 (0.2 g, 0.7 mmol) in N,N-dimethylformamide (2 mL) was added 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.10 g, 0.26 mmol) at 0 °C. After stirring for 20 minutes, the compound prepared in Example 7 (0.12 g, 0.26 mmol) and N,N-diisopropylethylamine (0.15 mL, 0.8 mmol) were added and the reaction stirred at room temperature for 2 h. The reaction was quenched by adding ice cold water and the resulting precipitate was collected by filtration, dried and the crude product purified by flash chromatography to afford the title compound (0.11 g, 61%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers present) δ 9.35 (s, 1H), 7.92 (d, 2H), 7.52 (d, 2H), 4.75 (t, 1H), 4.28-4.10 (m, 2H), 3.88-3.84 (m, 1H), 3.37 (t, 1H), 3.34 (t, 3H), 3.10-2.93 (m, 4H), 2.75

(s, 3H), 2.73-2.57 (m, 6H), 2.30-2.22 (m, 1H), 1.83-1.75 (m, 4H), 1.57 (s, 9H), 1.47 (s, 18H).

Preparation Example 9: 4-[({(2S,4S)-1-[(1-carbamimidoyl-4-piperidinyl)carbonyl]-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl}carbonyl)amino]benzoic acid bis(trifluoroacetate)

[0160]



[0161] To a solution of the compound prepared in Example 8 (0.11 g, 0.13 mmol) in dichloromethane (15 mL) at 0 °C was added trifluoroacetic acid (0.5 mL). The reaction was warmed to room temperature and stirred for 18 h. The solvent and excess trifluoroacetic acid was removed under reduced pressure. The solid was dissolved in water and lyophilized to dryness to afford the title compound (0.030 g, 40%) as an off-white solid.

^{1}H NMR (400 MHz, CD_3OD, rotamers present) 7.97 (d, 2H), 7.69 (d, 2H), 4.55 (t, 1H), 4.26-4.01 (m, 1H), 3.93-3.87 (m, 2H), 3.72 (t, 1H), 3.55-3.51 (m, 1H), 3.41(br. s, 4H), 3.25-3.04 (m, 6H), 3.05-2.91 (m, 1H), 2.90 (s, 3H), 2.78-2.71 (m, 1H), 2.20-2.06 (m, 1H), 2.00-1.96 (m, 1H), 1.89-1.85 (m, 1H), 1.73-1.67 (m, 2H).

ESI MS *m/z* 550 $(M+H)^+$

Preparation Example 17: methyl 4-(N-{[(2-methyl-2-propanyl)oxy]carbonyl}carbamimidoyl)benzoate

[0162] To a solution of methyl 4-(N-carbamimidoyl)benzoate (2.18 g, 9.18 mmol) and triethylamine (1.02 mL, 7.32 mmol) in anhydrous methanol (100 mL) was added di-*tert*-butyl dicarbonate (3.0 g, 13.8 mmol). The mixture was heated at 40 °C under nitrogen for 5 h. The reaction mixture was cooled and then concentrated under reduced pressure. The resulting residue was diluted with ethyl acetate (100 mL) and washed with aqueous sodium bicarbonate solution. The aqueous layer was then extracted with dichloromethane (2 × 30 mL). The combined organic extracts were dried and concentrated. Purification by flash chromatography (silica gel, 80 g, 0-30% ethyl acetate/hexanes) afforded the title compound (1.98 g, 77%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, Amidine NH protons were not observed.) δ 8.09 (d, 2H), 7.91 (d, 2H), 3.94 (s, 3H), 1.55 (s, 9H).

Preparation Example 18: 4-(N-{[(2-methyl-2-propanyl)oxy]carbonyl}carbamimidoyl)benzoic acid

[0163] To a solution of the compound prepared in Example 17 (0.20 g, 0.72 mmol) in methanol (10 mL) was added 1 M aqueous sodium hydroxide (5 mL). The reaction was stirred at room temperature for 1 h. The mixture was concentrated and the resulting aqueous residue was diluted with ethyl acetate. The aqueous layer was acidified with 1 M hydrochloric acid to pH 4-5 and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried and concentrated to give the title compound (0.208 g, >99%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (app. s, 3H), 8.00 (app. s, 4H), 1.44 (s, 9H). ESI MS *m/z* 263 $(M+H)^+$

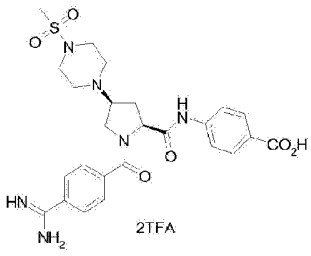
Preparation Example 19: 2-methyl-2-propanyl 4-[({(2S,4S)-1-[4-(N-{[(2-methyl-2-propanyl)oxy]carbonyl}carbamimidoyl)benzoyl]-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl}carbonyl)amino]benzoate

[0164] Following the procedure described in Example 8, the compound prepared in Example 6 was treated with the compound prepared in Example 18 to give the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers present) δ 9.47 (s, 1H), 7.93-7.89 (m, 4H), 7.61-7.56 (m, 4H), 4.97 (t, 1H), 3.69-3.64 (m, 1H), 3.41 (t, 1H), 3.28-3.19 (m, 4H), 2.87-2.80 (m, 1H), 2.77 (s, 3H), 2.65-2.60 (m, 3H), 2.48-2.34 (m, 3H), 1.57 (s, 9H), 1.54 (s, 9H).

Example 20: 4-[({(2S,4S)-1-(4-carbamimidoylbenzoyl)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl}carbonyl)amino]benzoic acid bis(trifluoroacetate)

[0165]



[0166] The compound prepared in Example 19 was treated following the procedure described in Example 9 to give the title compound as an off-white solid.

^{1}H NMR (400 MHz, D_2O, rotamers present) δ 9.47 (s, 1H), 8.01-7.61 (m, 7H), 7.17 (d, 1H),

4.84-4.76 (m, 1H), 4.09-3.81 (m, 2H), 3.62-3.44 (m, 6H), 3.43-3.25 (m, 2H), 3.04-3.00 (m, 4H), 2.36-2.29 (m, 1H).

ESI MS *m/z* 543 $(M+H)^+$

PHARMACOLOGICAL ACTIVITIES

[0167] The compound of the present invention possesses factor XIa inhibitory activity, for example, such an effect of the compound of the present invention was confirmed by the following tests.

[0168] All the procedures were conducted by conventionally used techniques on the basis of basic biological methods. Furthermore, the measuring method of the present invention was modified to improve the accuracy and/or sensitivity of measurement for evaluating the compound of the present invention. The detailed experimental method was as follows.

EXPERIMENTAL METHOD

(1) In Vitro Assay

[0169] Inhibitory activities of compound of the present invention against factor XIa, Xa, XIIa, IXa, VIIa, plasma kallikrein or thrombin were evaluated using appropriate purified proteases and synthetic substrates. The rate of hydrolysis of the chromogenic substrate by the relevant protease was continuously measured at 405 nm.

[0170] Inhibitory activity against each enzyme was calculated as % inhibition using the equation described below.

% Inhibition = [[(rate without compound)-(rate with compound)]/(rate without compound)] ×100%.

[0171] Each half maximal inhibitory concentration (IC_{50}) value was determined by plotting the concentration of compound of the invention against the % inhibition.

(1-1) Factor XIa enzyme activity

[0172] Human Factor XIa (Haematologic Technologies Inc.) activity was measured at an enzyme concentration of 0.1 U/mL in 150 mM NaCl, 5 mM KCl, 1 mg/mL PEG6000, 50 mM HEPES-NaOH (pH7.4) with 300 μM S-2366 (pyroGlu-Pro-Arg-pNA, Chromogenix).

(1-2) Plasma kallikrein enzyme activity

[0173] Human plasma kallikrein (Enzyme Research Laboratories Ltd) activity was measured at an enzyme concentration of 0.605 mU/mL in 200 mM NaCl, 5 mg/mL PEG6000, 100 mM Phosphate-NaOH (pH7.4) with 150 μM S-2302 (H-D-Pro-Phe-Arg-pNA, Chromogenix).

(1-3) Factor Xa and thrombin enzyme activity

[0174] Human Factor Xa (American Diagnostica Inc.) and human thrombin (Sigma) activities were measured at the enzyme concentrations of 0.18 U/mL and 0.12 U/mL, respectively in the same buffer containing 150 mM NaCl, 2 mg/mL PEG6000, 50 mM Tris-HCl (pH7.4), except that the reactions were started with 300 μM S-2222 (phenyl-Ile-Glu-Gly-Arg-pNA, Chromogenix) and 300 μM S-2366, respectively.

(1-4) Factor XIIa enzyme activity

[0175] Human Factor α-XIIa (Enzyme Research Laboratories Ltd) activity was measured at an enzyme concentration of 0.17 U/mL in 150 mM NaCl, 50 mM Tris-HCl (pH7.4) with 300 μM S-2302 (Pro-Phe-Arg-pNA, Chromogenix).

(1-5) Factor IXa enzyme activity

[0176] Human Factor IXa (American Diagnostica Inc.) activity was measured at an enzyme concentration of 13 U/mL in 100 mM NaCl, 5 mM $CaCl_2$, 30% ethylene glycol, 50 mM Tris-HCl (pH7.4) with 3 mM Pefachrome IXa 3960 (Leu-Ph'Gly-Arg-pNA, Pentapharm).

(1-6) Factor VIIa enzyme activity

[0177] Human Factor VIIa activity was measured using recombinant human factor VIIa (American Diagnostica Inc.) in the presence of recombinant human tissue factor which was produced according to the method described in the literature (Protein expression and purification, 3, 453-460 (1992) in a buffer containing 150 mM NaCl, 5 mM $CaCl_2$, 0.5 mg/mL PEG6000, 50 mM HEPES-NaCl (pH7.4) with 3 mM S-2288 (Ile-Pro-Arg-pNA, Chromogenix).

(1-7) APTT, PT mesurement

[0178] Activated partial thromboplastin time (APTT) and prothrombin time (PT) were measured using automatic coagulation analyzer (CA-1500, Sysmex Corporation). For the APTT or PT measurement, standard human plasma (Siemens Healthcare Diagnostics GmbH) were mixed with each compound dilutions followed by the automatic addition of APTT reagent (Siemens Healthcare Diagnostics GmbH) and 0.02 M calcium chloride or PT reagent (Siemens Healthcare Diagnostics GmbH) to start clot formation. The anticoagulant activities (APTT2 or PT2) of the compounds of the invention were expressed as the concentrations necessary to double the clotting time in vehicle (1% DMSO) group. APTT2 or PT2 was determined by plotting the concentration of compound of the invention against the fold increase of clotting time.

[0179] The compound of the present invention was tested in the factor XIa assay described above, and found to have a good factor XIa inhibitory activity as well as good selectivity against other plasma serine proteases. Table 1 described below lists factor XIa, thrombin and FXa IC_{50} values measured for the following examples.

Table 1

Example No	In vitro FXIa inhibitory activity IC_{50} (μM)	In vitro Thrombin inhibitory activity IC_{50} (μM)	In vitro FXa inhibitory activity IC_{50} (μM)
9*	0.017	>100	>100
20	0.0032	>100	>100
*Reference			

Therefore, the results indicated that the compound of the present invention possesses factor XIa inhibitory activity as well as high selectivity against other plasma serine proteases.

[0180] Additionally, the good oral bioavailability of compound of the present invention can be determined using the following experimental methods.

(2-1) Pharmacokinetic (PK) study in rat

[0181] The compound of the present invention in a solution of 20% wellsolve (celeste) was given to fasted male Crj:CD (SD) rats as a single 3 mg/kg, p.o. dose by gavage. Blood samples were drawn from jugular vein into syringes containing 3.2% sodium citrate (the volume ratio of blood to anticoagulant = 9:1) or heparinized syringes at 0.5, 1, 3, 7 hours after oral administration. Plasma was obtained by centrifugation and stored at -20°C until measurement of plasma concentration.

[0182] To measure plasma concentrations of the compound of the present invention, plasma samples were deproteinized with acetonitrile, followed by evaporation of the acetonitrile to dryness. Then the sample was reconstituted in the mobile phase and analyzed by LC/MS/MS. An analytical column (Shim-pack XR-ODSII, 2.0 mm x 75 mm, 2.2 μm) and mobile phase

(0.1% formic acid in water and 0.1% formic acid in acetonitrile, flow rate of 0.5 mL/min) were used. The system was used in multiple reaction monitoring (MRM) mode with positive ion detection.

(2-2) Pharmacokinetic (PK) study of the compound which has a functional group (e.g. an ester group, a substitued amidine group, a substituted guanidine group, etc.) in rat

[0183] The compound of the present invention in a solution of 20% wellsolve (celeste) was given to fasted male Crj:CD (SD) rats as a single 3 mg/kg, p.o. dose by gavage. Blood samples were drawn from jugular vein into syringes treated with heparin-diisopropyl fluorophosphate mixture (500:1) at 0.5, 1, 3, 7 hours after oral administration. Plasma was obtained by centrifugation and stored at -20°C until measurement of plasma concentration.

[0184] To measure plasma concentrations of the compound of the present invention, plasma samples were deproteinized with acetonitrile, followed by evaporation of the acetonitrile to dryness. Then the sample was reconstituted in the mobile phase and analyzed by LC/MS/MS. An analytical column (Shim-pack XR-ODSII, 2.0 mm x 75 mm, 2.2 µm) and mobile phase (0.1 % formic acid in water and 0.1 % formic acid in acetonitrile, flow rate of 0.5 mL/min) were used. The system was used in multiple reaction monitoring (MRM) mode with positive ion detection.

[0185] Additionally, enzymatic hydrolysis of a functional group (e.g. an ester group, a substitued amidine group, a substituted guanidine group, etc.) in the compound of the present invention can be determined using the following experimental methods.

(3-1) Analysis of enzymatic hydrolysis of a functional group (e.g. an ester group, a substitued amidine group, a substituted guanidine group, etc.) in the compounds of the present invention using hepatocytes prepared from various species (rat, dog, monkey, human)

[0186] A typical assay procedure was conducted by using cryopreserved hepatocytes prepared from various species. A mixture of hepatocytes, buffer (pH 7.4), and each test compound were incubated. The final test compound concentration was typically 100 ng/mL, with a usual cell density of 1,000,000 cells/ml for all species. The incubation was at 37°C, with time-points taken over 120 minutes. Reaction termination was achieved by addition of an aliquot of the hepatocyte / test compound mixture to acetonitrile/ethanol (7/3) to effect protein precipitation, followed by centrifugation. Then the sample was diluted with distilled water and analyzed by LC/MS/MS. An analytical column (Shim-pack XR-ODSII, 2.0 mm x 75 mm, 2.2 µm) and mobile phase (0.1% formic acid in water and 0.1% formic acid in acetonitrile, flow rate of 0.5 mL/min) were used. The system was used in multiple reactions monitoring (MRM) mode with positive ion detection.

(3-2) Analysis of enzymatic hydrolysis of a functional group (e.g. an ester group, a

substitued amidine group, a substituted guanidine group, etc.) in the compound of the present invention using blood from various species (rat, dog, monkey, human)

[0187] The compound of the present invention in a solution of acetonitrile were incubated in blood from various species. The incubation was typically performed at a concentration of 100ng/mL of test compound at 37°C, with time points taken over 60 minutes. The reaction was terminated by addition of an aliquot of blood / test compound mixture to acetonitrile/ethanol (7/3) to effect protein precipitation, followed by centrifugation. Then the sample was diluted with distilled water and analyzed by LC/MS/MS. An analytical column (Shim-pack XR-ODSII, 2.0 mm x 75 mm, 2.2 µm) and mobile phase (0.1% formic acid in water and 0.1% formic acid in acetonitrile, flow rate of 0.5 mL/min) were used. The system was used in multiple reactions monitoring (MRM) mode with positive ion detection.

Formulation example 1

[0188] The following components were admixed in conventional method and punched out to obtain 10,000 tablets each containing 10 mg of active ingredient.

- Methyl [4-(4-chloro-2-{(2S,4R)-1-{(2E)-3-[5-chloro-2-(1H-tetrazol-1-yl)phenyl]-2-propenoyl}-4-[1-(methylsulfonyl)-4-piperidinyl]-2-pyrrolidinyl}-1H-imidazol-5-yl)phenyl]carbamate 100 g
- Carboxymethylcellulose calcium (disintegrating agent) 20 g
- Magnesium stearate (lubricating agent) 10 g
- Microcrystalline cellulose 870 g

Formulation example 2

[0189] The following components were admixed in conventional method. The solution was sterilized in conventional manner, filtered through dust removal equipment, placed 5 mL portions into ampoules and sterilized by autoclave to obtain 10,000 ampoules each containing 20 mg of the active ingredient.

- Methyl [4-(4-chloro-2-{(2S,4R)-1-{(2E)-3-[5-chloro-2-(1H-tetrazol-1-yl)phenyl]-2-propenoyl}-4-[1-(methylsulfonyl)-4-piperidinyl]-2-pyrrolidinyl}-1H-imidazol-5-yl)phenyl]carbamate 200 g
- mannitol 20 g
- distilled water 50 L

INDUSTRIAL APPLICABILITY

[0190] The compound of the present invention represented by formula (I) as described above acts as a potent and selective inhibitor of factor XIa without side effects such as bleeding. In particular, the compound of the present invention acts as a Factor XIa inhibitor. Thus the compound of the present invention is useful in preventing and/or treating thromboembolic diseases, for example arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, arterial cerebrovascular thromboembolic disorders, venous cerebrovascular thromboembolic disorders and thromboembolic disorders in the chambers of the heart or in the peripheral circulation. The compound of the present invention is therefore useful as a medicament.

REFERENCES CITED IN THE DESCRIPTION

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SUBSTITUTEREDE PYRROLIDINER SOM FAKTOR XIA-HÆMMERE TIL BEHANDLING AF TROMBOEMBOLISKE SYGDOMME

PATENTKRAV

1. 4-[({(2S,4S)-1-(4-carbamimidoylbenzoyl)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl} carbonyl)amino]benzoesyre eller farmaceutisk acceptabelt salt deraf.

2. Farmaceutisk sammensætning, der omfatter 4-[({(2S,4S)-1-(4-carbamimidoylbenzoyl)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl}carbonyl)amino]benzoesyre eller et farmaceutisk acceptabelt salt deraf.

3. Farmaceutisk sammensætning ifølge krav 2, til anvendelse som en faktor XIa-hæmmer.

4. Farmaceutisk sammensætning til anvendelse ifølge krav 3 i behandlingen eller forebyggelsen af en tromboembolisk sygdom.

5. 4-[({(2S,4S)-1-(4-carbamimidoylbenzoyl)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl} carbonyl)amino]benzoesyre eller farmaceutisk acceptabelt salt deraf til anvendelse i behandling eller forebyggelse af en tromboembolisk sygdom.

6. 4-[({(2S,4S)-1-(4-carbamimidoylbenzoy1)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl} carbonyl)amino]benzoesyre eller farmaceutisk acceptabelt salt deraf til anvendelse i behandling eller forebyggelse af en tromboembolisk sygdom, hvor den tromboemboliske sygdom er udvalgt fra gruppen bestående af arterielle kardiovaskulære tromboemboliske forstyrrelser, venøse kardiovaskulære tromboemboliske forstyrrelser, arterielle cerebrovaskulære tromboemboliske forstyrrelser, venøse cerebrovaskulære tromboemboliske forstyrrelser og tromboemboliske forstyrrelser i hjertekamrene eller i det perifere kredsløb.

7. 4-[({(2S,4S)-1-(4-carbamimidoylbenzoyl)-4-[4-(methylsulfonyl)-1-piperazinyl]-2-pyrrolidinyl} carbonyl)amino]benzoesyre eller farmaceutisk acceptabelt salt deraf til anvendelse i behandling eller forebyggelse af en tromboembolisk sygdom, hvor den tromboemboliske sygdom er udvalgt fra dissemineret intravaskulær koagulopati (DIC), akut respirationsinsufficienssyndrom, akut lungelæsion, sepsis, angina, ustabil angina, et akut koronart syndom, koronar arteriesygdom, myokardieinfarkt, atrieflimren, iskæmisk pludselig død, transient iskæmisk attack, apopleksi, akut apopleksi, lakunært infarkt, atherosklerotisk trombotisk cerebralinfarkt, atherotrombose, atherosklerose, perifer okklusiv arteriesygdom, venetrombose, dyb venetrombose, thrombophlebitis, arteriel embolisme, koronar arterietrombose, cerebral trombose, cerebral arterietrombose, cerebral embolisme, kardiogen embolisme, nyreembolisme, portåretrombose, lungeembolisme, lungeinfarkt, leverembolisme, mesenterialarterie- og/eller veneembolisme, okklusion af nethindevene og/eller -arterie, systemisk embolisme, antiphospholipid-antistofsyndrom, trombose som følge af koronararterie-bypass-graft-kirurgi og trombose som følge af medicinske implantater, anordninger eller procedurer, hvor blod eksponeres for en kunstig overflade, der fremmer trombose.