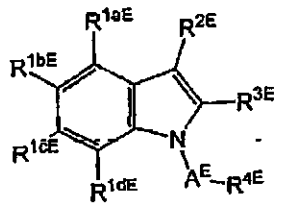
-C(O)OR^{23D} (wherein R^{23D} represents a hydrogen atom etc.) or -R^{27D} (wherein R^{27D} represents optionally substituted alkyl etc.) and R^{9D} represents optionally substituted alkyl etc. (extract of a part of definitions of groups)) (see Patent Document 7), an Xa factor inhibitor consisting of a compound represented by the general formula (E):

[0011]

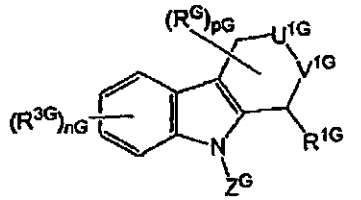


(E)

[0012]

(wherein R^{1aE}, R^{1bE}, R^{1cE} and R^{1dE} each represent independently a hydrogen atom, a halogen or a C1-4 alkyl group etc., R^{2E} and R^{3E} are taken together to form -CH$_2$-CH$_2$-N(-CO-R^{20E})-CH$_2$- (wherein R^{20E} is phenyl, phenyl-C1-4 alkyl-, pyridyl or pyridyl-C1-4 alkyl-, phenyl is substituted with R^{15aE}, and pyridyl may be substituted with R^{14E} at its nitrogen atom), A^E represents a C1-4 alkyl- etc., and R^{4E} represents phenyl having a substituent or pyridyl optionally having a substituent etc. (extract of a part of definitions of groups)) (see Patent Document 8) and a synthesis intermediate of a cholecystokinin or gastrin receptor binding agent consisting of a compound represented by the general formula (G):

[0013]



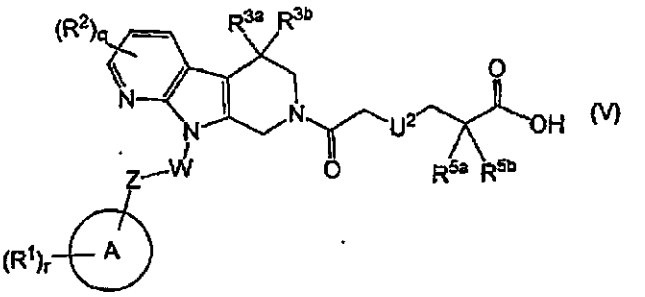
(G)

[0014]

(wherein U^{1G} represents -CH$_2$- etc., V^{1G} represents -N(COR^{4G})- etc. (wherein R^{4G} represents an aryl group optionally having a substituent or an arylalkyl group optionally having a substituent etc.), Z^G represents -C1-3 alkyl-R^{8G} etc. (wherein R^{8G} represents a phenyl group optionally having a substituent), R^{3G} represents a halogen or an alkyl group etc., R^G represents a C1-3 alkyl group, and nG and pG each represent an integer of 0 to 3 (extract of a part of definitions of groups)) (see Patent Document 9).

[0015]

Further, as the prior art concerning the present compound, there are a PDE inhibitor (see Patent Documents 10 to 15), a histamine receptor antagonist (see Patent Document 16), a 5-HT2 antagonist (see Patent Document 17), a histamine H3 antagonist (see Patent Document 18), a 5-HT6 antagonist (see Patent Document 19), a PPAT inhibitor (see Patnet Document 20), a HDAC inhibitor (see Patent Document 21), a sPLAS2 inhibitor (see Patent Document 22), a farnesyltransferase inhibitor (see Patent Document 23), an angiotensin II converting enzyme inhibitor (see Patent Document 24), an EDG-5 antagonist (see Patent Document 25), a PTPase inhibitor (see Patent Document 26), an ADAM-TS inhibitor (see Patent Document 27), an anti-cancer agent (see Patent



(V)

[0033]

(wherein U^2 represents a methylene group, an oxygen atom or -NR^6-, R^{5a} and R^{5b} each represent independently a hydrogen atom or a methyl group, and other symbols are as defined in the above mentioned [1], provided that R^{5a} nad R^{5b} may be taken together with a carbon atom to which they are bound, to form cyclopropyl).

[16] The compound according to any one of the above mentioned [1] to [15], wherein the ring A is (i) a 5-to 6-membered monocyclic heterocyclic ring containing one to four heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom or (ii) a 9- to 10-membered bicyclic heterocyclic ring containing one to four heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom.

[17] The compound according to any one of the above mentioned [1] to[15], wherein the ring A is a C5-6 monocyclic carbon ring or a C9-10 bicyclic carbon ring.

[18] The compound according to the above mentioned [16], wherein the 5- to 6-membered monocyclic heterocyclic ring containing one to four heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom is thiophene, furan, pyrazole, isoxazole, thiazole or pyridine, and the 9- to 10-membered bicyclic heterocyclic ring containing one to four heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom is benzothiophene, indole or imidazopyridine.

[19] The compound according to the above mentioned [17], wherein the monocyclic carbon ring is cyclopentane, cyclohexane, cyclohexene or benzene, and the C9-10 bicyclic carbocyle is naphthalene.

[20] The compound according to the above mentioned [14], wherein the compound represented by the general formula (IV-3) is

(1) cis-4-(2-{9-[(2,5-dimethyl-1,3-thiazol-4-yl)methyl]-1,3,4,9-tetrahydro-2H-beta-carbolin-2-yl}-2-oxoethyl)cyclohexanecarboxylic acid, or

(2) rel-[(2R,6S)-4-(2-{9-[(5-chloro-2-thienyl)methyl]-1,3,4,9-tetrahydro-2H-beta-carbolin-2-yl}-2-oxoethyl)-2,6-dimethyl-1-piperazinyl]acetic acid.

[21] The compound according to the above mentioned [18], wherein the compound represented by the general formula (IV-2) is 4-(2-{9-[(5-chloro-3-thienyl)methyl]-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-2-oxoethyl)-2-methylbenzoic acid.

[22] The compound according to the above mentioned [19], wherein the compound represented by the general formula (IV-2) is:

(1) cis-4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}cyclohexanecarboxylic acid,

(2) trans-4-{2-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-

b]pyridin-7-yl]-2-oxoethyl}cyclohexanecarboxylic acid,
(50) cis-4-{2-[9-(3,5-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}cyclohexanecarboxylic acid,
(51) cis-4-{2-[9-(3-chloro-5-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}cyclohexanecarboxylic acid,
(57) 4-{2-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-2-ethoxybenzoic acid,
(58) 2-ethoxy-4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid,
(59) (3-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}phenyl)acetic acid,
(60) (3-{2-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}phenyl)acetic acid,
(61) 4-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}benzoic acid,
(62) 4-{3-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}benzoic acid,
(63) 3-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}benzoic acid,
(64) 3-{3-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}benzoic acid,
(65) 2-chloro-4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid,
(66) 3-fluoro-4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid,
(67) 3-chloro-4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid,
(68) 2-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}benzoic acid,
(69) 2-{3-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}benzoic acid,
(70) 2-chloro-4-{2-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid,
(71) 2-fluoro-4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid,
(72) 4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-3-methylbenzoic acid,
(73) 4-{2-[9-(2-cyclohexylethyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid,
(74) 4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-

(18) (1-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-2-pyrrolidinyl)acetic acid hydrochloride,
(19) (2S)-1-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}-2-pyrrolidinecarboxylic acid,
(20) 1-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}-4-piperidinecarboxylic acid,
(21) 1-{2-[9-(4-chloro-2-fluorobenzyl)-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinecarboxylic acid,
(23) (2R)-1-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}-2-pyrrolidinecarboxylic acid,
(24) (1-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}-4-piperidinyl)acetic acid,
(25) (1-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}-2-pyrrolidinyl)acetic acid,
(26) 1-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}-3-pyrrolidinecarboxylic acid,
(27) 1-{3-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3-oxopropyl}-2-piperidinecarboxylic acid,
(28) (1-{2-[9-(4-chloro-2-fluorobenzyl)-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinyl)acetic acid,
(30) (4-{2-[9-(4-chloro-2-fluorobenzyl)-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-1-piperidinyl)acetic acid,
(32) (4-{[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]carbonyl}-1-piperidinyl)acetic acid,
(33) (4-{2-[9-(3-chloro-2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-1-piperazinyl)acetic acid,
(35) (4-{2-[9-(3,5-dichlorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-1-piperazinyl)acetic acid,
(38) 1-{2-[9-(3-chloro-2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinecarboxylic acid,
(40) 1-{2-[9-(3,5-dichlorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinecarboxylic acid,
(43) 1-{2-[9-(3-chloro-2,4-difluorobenzyl)-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinecarboxylic acid,
(44) 1-{2-[9-(3,5-dichlorobenzyl)-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinecarboxylic acid,
(46) (1-{2-[9-(3-chloro-2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinyl)acetic acid,
(48) (1-{2-[9-(3,5-dichlorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-4-piperidinyl)acetic aci,

On the other hand, the deprotection reaction under the acidic condition is performed, for example, at a temperature of 0 to 100°C in an organic solvent (dichloromethane, chloroform, 1,4-dioxane, ethyl acetate or anisole alone, or a mixed solvent consisting of a plurality of solvents among them at an arbitrary ratio) in 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 (hydrogen bromide/acetic acid etc.).

[0171]

The deprotection reaction by hydrogenolysis is performed, for example, at a temperature of 0 to 200°C in a solvent (ether solvent (tetrahydrofuran, 1,4-dioxane, dimethoxyethane, diethyl ether etc.), alcohol solvent (methanol, ethanol etc.), benzene solvent (benzene, toluene etc.), ketone solvent (acetone, methyl etheyl ketone etc.), nitrile solvent (acetonitrile etc.), amide solvent (N,N-dimethylformamide etc.), water, ethyl acetate, acetic acid, or a mixed solvent of two or more of them), in the presence of a catalyst (palladium-carbon, palladium black, palladium hydroxide, platinum oxide, Raney nickel etc.), under the hydrogen atmosphere under ordinary pressure or increased pressure, or in the presence of ammonium formate.

[0172]

The deprotection reaction of a silyl group is performed, for example, at a temperature of 10 to 40°C in an organic solvent which is miscible with water (tetrahydrofuran or acetonitrile alone, or a mixed solvent consisting of a plurality of solvents among them at an arbitrary ratio) using tetrabutylammonium fluoride.

[0173]

The deprotection reaction using a metal is performed, for example, at a temperature of 0 to 40°C in an acidic solvent (acetic acid, buffer having a pH of 4.2 to 7.2, or a mixed solvent of those solutions and an organic solvent such as tetrahydrofuran) in the presence of a zinc powder by applying ultrasound or applying no ultrasound.

[0174]

The deprotection reaction using a metal complex is performed, for example, at a temperature of 0 to 40°C in an organic solvent (dichloromethane, N,N-dimethylformamide, tetrahydrofuran, ethyl acetate, acetonitrile, 1,4-dioxane, ethanol etc.), water or a mixed solvent of them in the presence of a trap reagent (tributyltin hydoride, triethylsilane, dimedone, morpholine, diethylamine, pyrrolidine etc.), an organic acid (acetic acid, formic acid, 2-ethylhexanoic acid etc.) and/or an ortanic acid salt (sodium 2-ethylhexanoate, potassium 2-ethylhexanoate etc.) in the presence or absence of a phosphine reagent (triphenylphosphine etc.), using a metal complex (tetrakistriphenylphosphinepalladium (0), bis(triphenylphosphine)palladium (II) dichloride, palladium (II) acetate, tris(triphenylphosphine)rhodium (I) chloride etc.).

[0175]

Alternatively, in addition to the foregoing, the deprotection reaction can be performed, for example, by the method described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1999.

[0176]

TLC:Rf 0.43 (chloroform: methanol:water=50:10:1);

^{1}H-NMR(DMSO-d_6):δ 1.31 - 1.66 (m, 4 H) 2.09 - 2.48 (m, 4 H) 2.57 - 2.89 (m, 2 H) 3.63 - 3.89 (m, 2 H) 4.55 - 4.69 (m, 2 H) 5.42 - 5.54 (m, 2 H) 6.85 - 7.15 (m, 4 H) 7.26 - 7.40 (m, 1 H) 7.84 - 7.94 (m, 1 H) 8.16 - 8.25 (m, 1 H) 11.93 (s, 1 H).

[0297]

Example 9(1) - Example 9(83)

Corresponding alkyl halide in place of 1-(bromomethyl)-3-fluorobenzene, and the compound produced in Example 8 in place of 1,3,4,9-tetrahydro-2H-β-carboline-2-carboxylate were used, which were subjected to operation in accordance with Example 1 and, further, a corresponding carboxylic acid ester derivative in place of methyl 6-chloro-6-oxohexanoate was used, which was subjected to operation in accordance with Example 2 and, if necessary, subjected to operation in accordance with Example 3 to obtain the following compounds.

[0298]

Example 9(1): 6-[9-(cyclohexylmethyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-6-oxohexanoic acid

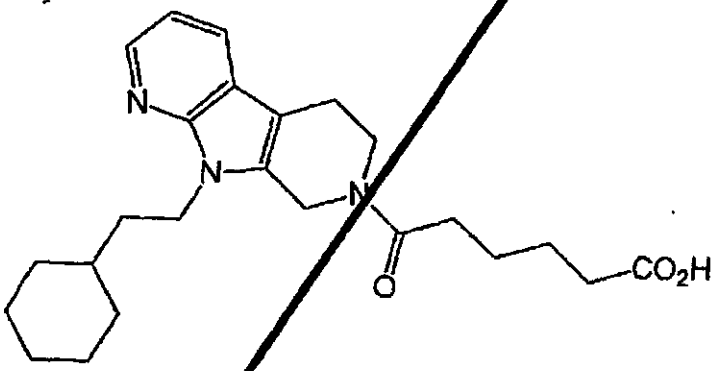
HPLC retention time (min):4.06;

MS (ESI, Pos. 20 V) : m/z=398 $(M + H)^+$.

[0299]

Example 9(2): 6-[9-(2-cyclohexylethyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-6-oxohexanoic acid

[0300]



[0301]

HPLC retention time (min):4.30;

MS (ESI, Pos. 20 V) : m/z=412 $(M + H)^+$.

[0302]

Example 9(3): 6-[9-(3-cyclohexylpropyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-6-oxohexanoic acid

HPLC retention time (min):4.39;

MS (ESI, Pos. 20 V) : m/z=426 $(M + H)^+$.

[0303]

Example 9(4): 6-[9-(4-cyclohexylbutyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-

TLC:Rf 0.24(chloroform: methanol:water=10:1:0.1);
MS (FAB, Pos.) : m/z=462 $(M + H)^+$.

[0561]

Example 18(22): 3-(2-{9-[(5-chloro-2-thienyl)methyl]-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-2-oxoethoxy)-2,2-dimethylpropanoic acid

TLC:Rf 0.33(chloroform: methanol:water=10:1:0.1);
MS (FAB, Pos.) : m/z=462 $(M + H)^+$.

[0562]

Example 18(23): 3-(2-{9-[(2,5-dimethyl-3-thienyl)methyl]-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-2-oxoethoxy)-2,2-dimethylpropanoic acid

TLC:Rf 0.22(chloroform: methanol:water=10:1:0.1);
MS (FAB, Pos.) : m/z=456 $(M + H)^+$.

[0563]

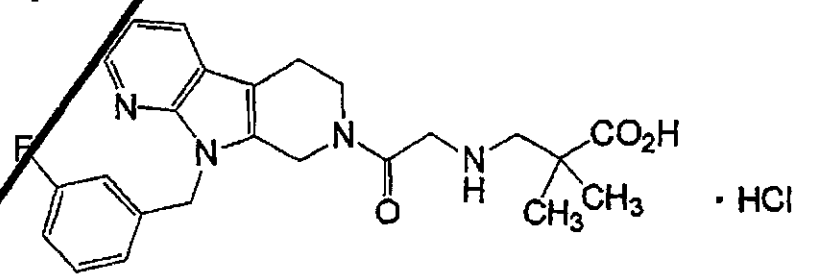
Example 19: methyl 3-[(2-{9-[(3-fluorbenzyl)methyl]-5,6,8,9- tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-2-oxoethoxy)-2,2-dimethylpropanoate

To the compound (72 mg) produced in Example 16 and methyl 3-amino-2,2-dimethylpropanoate hydrochloride (67 mg) in THF solution (5 mL) was added triethylamine (0.14 mL) at 0°C. After stirred at room temperature for 1 hour, tetrabutylammonium bromide (10 mg) was added, and the mixture was stirred at 60°C for 14 hours. The reaction solution was cooled to room temperature, and to the reaction solution was added an aqueous saturated sodium bicarbonate solution, followed by extraction with ethyl acetate. After the extract solution was washed with an aqueous saturated sodium chloride solution (2 L), dried using anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified with a silica gel column (ethyl acetate : methanol = 9 : 1) to obtain the title compound (80 mg) having the following physical property values.
TLC:Rf 0.47 (chloroform: methanol:water=50:10:1);
^{1}H-NMR($CDCl_3$):δ 1.08 - 1.26 (m, 6 H), 2.60 - 2.73 (m, 2 H), 2.74 - 2.90 (m, 2 H), 3.24 - 3.58 (m, 2 H), 3.59 - 3.68 (m, 3 H), 3.66 - 3.96 (m, 2 H), 4.38 - 4.71 (m, 2 H), 5.38 - 5.51 (m, 2 H), 6.69 - 6.99 (m, 3 H), 7.02 - 7.13 (m, 1 H), 7.16 - 7.31 (m, 1 H), 7.73 - 7.86 (m, 1 H), 8.21 - 8.36 (m, 1 H).

[0564]

Example 20: 3-({2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}amino)-2,2-dimethylpropanoic acid hydrochloride

[0565]



[0566]

^{1}H-NMR(DMSO-d_6):δ 0.92 - 1.15 (m, 6 H), 1.20 - 1.55 (m, 10 H), 2.25 - 2.50 (m, 2 H), 3.40 - 3.60 (m, 2 H), 4.45 - 4.65 (m, 2 H), 5.45 - 5.65 (m, 2 H), 7.08 (dd, J=4.8, 7.8 Hz ,1 H), 7.18 - 7.33 (m, 2 H), 7.77 (d, J=8.1 Hz, 2 H), 8.08 (d, J=7.8 Hz, 1 H), 8.17 (d, J=4.8 Hz, 1 H), 12.03 (s, 1 H).

[0589]

Example 23(10): 6-{9-[(2,5-dimethyl-1,3-thiazol-4-yl)methyl]-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-2,2-dimethyl-6-oxohexanoic acid

TLC:Rf 0.35 (methylene chloride: ethyl acetate: methanol=8:4:1);

^{1}H-NMR(DMSO-d_6):δ 0.95 - 1.15 (m, 6 H), 1.20 - 1.40 (m, 6 H), 1.40 - 1.60 (m, 4 H), 2.25 - 2.60 (m, 8 H), 3.35 - 3.55 (m, 2 H), 4.69 (s, 2 H), 5.40 - 5.65 (m, 2 H), 7.07 (dd, J=7.8, 4.8 Hz ,1 H), 8.04 (d, J=7.8 Hz, 1 H), 8.21 (d, J=4.8 Hz, 1 H), 12.05 (s, 1 H).

[0590]

Example 23(11): 6-[9-(4-cyanobenzyl)-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-3,3-dimethyl-6-oxohexanoic acid

TLC:Rf 0.44 (chloroform: methanol=10:1);

MS (FAB, Pos.) : m/z=473 $(M + H)^+$.

[0591]

Example 23(12): 6-{9-[(6-chloro-3-pyridinyl)methyl]-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-3,3-dimethyl-6-oxohexanoic acid

TLC:Rf 0.41 (chloroform: methanol=10:1);

MS (FAB, Pos.) : m/z=483 $(M + H)^+$.

[0592]

Example 23(13): 6-{9-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-3,3-dimethyl-6-oxohexanoic acid

TLC:Rf 0.38 (chloroform: methanol=10:1);

MS (FAB, Pos.) : m/z=466 $(M + H)^+$.

[0593]

Example 23(13): 6-{9-[(2,5-dimethyl-1,3-thiazol-4-yl)methyl]-5,5-dimethyl-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl}-3,3-dimethyl-6-oxohexanoic acid

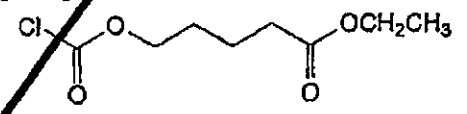
TLC:Rf 0.44 (chloroform: methanol=10:1);

MS (FAB, Pos.) : m/z=483 $(M + H)^+$.

[0594]

Example 24: ethyl 5-((chlorocarbonyl)oxy)pentanoate

[0595]

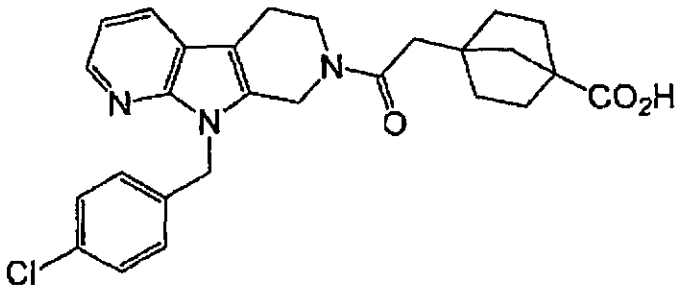


[0596]

Ethyl 5-hydroxypentanoate (1.12 g, 7.66 mmol) was dissolved in 25 mL of methylene chloride, triphosgene (772 mg, 0.34 equivalent), and pyridine (0.743 mL, 1.2 equivalent) were sequentially added while stirred at 0°C, and the mixture was stirred at room temperature for 1 hour. After completion of the reaction, water was added, and extraction operation (methylene chloride) was

Example 31(189): 4-{2-[9-(4-chlorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}bicyclo[2.2.1]heptane-1-carboxylic acid

[0780]



[0781]

TLC:Rf 0.48 (methylene chloride: water=100:10:1);

MS (ESI, Pos. 20 V): m/z=478 (M + H)+.

[0782]

Example 31(190): 4-{2-[9-(3-chlorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}bicyclo[2.2.1]heptane-1-carboxylic acid

TLC:Rf 0.49 (methylene chloride: methanol=9:1);

MS (APCI, Pos. 40 V): m/z=478 $(M + H)^+$.

[0783]

Example 31(191): 4-{2-[9-(4-chloro-2-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}bicyclo[2.2.1]heptane-1-carboxylic acid

TLC:Rf 0.50 (chloroform: methanol: water=100:10:1);

MS (ESI, Pos. 20 V):m/z=496 $(M + H)^+$.

[0784]

Example 31(192): 4-{2-[9-(4-chloro-3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}bicyclo[2.2.1]heptane-1-carboxylic acid

TLC:Rf 0.54 (methylene chloride: methanol=9:1);

MS (APCI, Pos. 40 V): m/z=496 $(M + H)^+$.

[0785]

Example 31(193): 4-{2-[9-(3-chloro-4-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}bicyclo[2.2.1]heptane-1-carboxylic acid

TLC:Rf 0.61 (chloroform: methanol: water=50:10:1);

MS (ESI, Pos. 20 V): m/z=496 $(M + H)^+$.

[0786]

Example 31(195): 4-{2-[9-(3,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}bicyclo[2.2.1]heptane-1-carboxylic acid

TLC:Rf 0.61 (methylene chloride: methanol=9:1);

MS (ES, Pos.): m/z=480 $(M+H)^+$.

[0787]

oxoethyl)-4-piperidinecarboxylic acid hydrochloride

TLC:Rf 0.15 (chloroform: methanol: water=50:10:1);

MS (ESI, Pos. 20 V): m/z=472 $(M + H)^+$.

[0863]

Example 35(116): [4-(2-{9-[(5-chloro-2-thienyl)methyl]-1,3,4,9-tetrahydro-2H-beta-carbolin-2-yl}-2-oxoethyl)-1-piperazinyl]acetic acid dihydrochloride

TLC:Rf 0.09 (chloroform: methanol: water=50:10:1);

MS (ESI, Pos. 20 V): m/z=487 $(M + H)^+$.

[0864]

Example 35(118): (2S)-2-amino-6-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-6-oxohexanoic acid hydrochloride

TLC:Rf 0.13 (chloroform: methanol: water=80:20:1);

MS (FAB, Pos.): m/z=425 $(M + H)^+$.

[0865]

Example 35(119): (2S)-2-amino-6-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-6-oxohexanoic acid hydrochloride

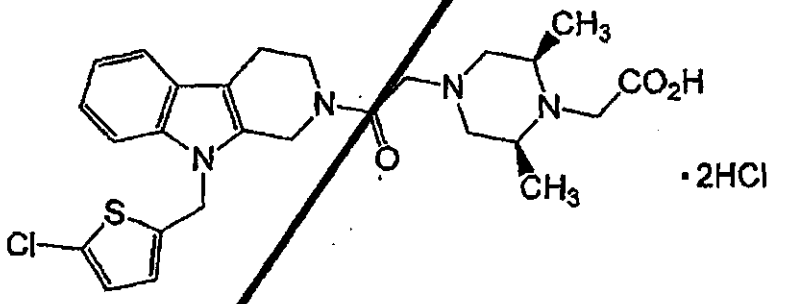
TLC:Rf 0.17 (chloroform: methanol: water=80:20:1);

MS (FAB, Pos.): m/z=443 $(M + H)^+$.

[0866]

Example 35(122): rel-[(2R,6S)-4-(2-{9-[(5-chloro-2-thienyl)methyl]-1,3,4,9-tetrahydro-2H-beta-carbolin-2-yl}-2-oxoethyl)-2,6-dimethyl-1-piperazinyl]acetic acid dihydrochloride

[0867]



[0868]

TLC:Rf 0.51 (chloroform: methanol: water=50:10:1);

MS (ESI, Pos. 20 V): m/z=515 $(M + H)^+$.

[0869]

Example 35(125): 1-(2-{9-[(5-chloro-2-thienyl)methyl]-1,3,4,9-tetrahydro-2H-beta-carbolin-2-yl}-2-oxoethyl)-4-methyl-4-piperidinecarboxylic acid

TLC:Rf 0.30 (chloroform: methanol: water=90:10:1);

MS (FAB, Pos.): m/z=486 $(M + H)^+$.

[0870]

Reference example 1: 3-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-

[0967]

Example 51(3): 2-chloro-4-{2-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid

TLC:Rf 0.28 (methylene chloride: methanol=9:1);

MS (ESI, Pos. 20 V): m/z=496 $(M + H)^+$.

[0968]

Example 51(5): 2-fluoro-4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}benzoic acid

TLC:Rf 0.29 (methylene chloride: methanol=9:1);

MS (ESI, Pos. 20 V): m/z=462 $(M + H)^+$.

[0969]

Example 51(6): 4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-3-methylbenzoic acid

TLC:Rf 0.40 (methylene chloride: methanol=9:1);

MS (ESI, Pos. 20 V): m/z=458 $(M + H)^+$.

[0970]

Example 51(7): 4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-2-methoxybenzoic acid

TLC:Rf 0.45 (methylene chloride: methanol=9:1);

MS (APCI, Pos. 20 V): m/z=474 $(M + H)^+$.

[0971]

Example 51(8): 4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-3-methoxybenzoic acid

TLC:Rf 0.40 (methylene chloride: methanol=9:1);

MS (APCI, Pos. 20 V): m/z=474 $(M + H)^+$.

[0972]

Example 51(9): 4-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-2-methylbenzoic acid

TLC:Rf 0.52 (methylene chloride: methanol=9:1);

MS (APCI, Pos. 20 V): m/z=458 $(M + H)^+$.

[0973]

Example 51(10): 4-{2-[9-(2,4-difluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-2-fluorobenzoic acid

TLC:Rf 0.28 (methylene chloride: methanol=9:1);

MS (APCI, Pos. 20 V): m/z=480 $(M + H)^+$.

[0974]

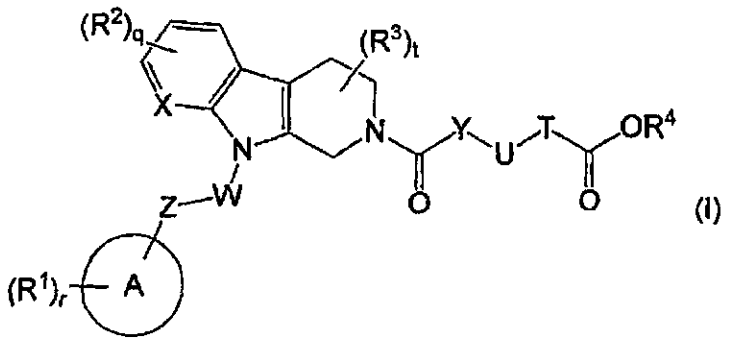
Example 51(12): 5-{2-[9-(3-fluorobenzyl)-5,6,8,9-tetrahydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-b]pyridin-7-yl]-2-oxoethyl}-2-thiophenecarboxylic acid

TLC:Rf 0.10 (ethyl acetate);

MS (ESI, Pos. 20 V): m/z=450 $(M + H)^+$.

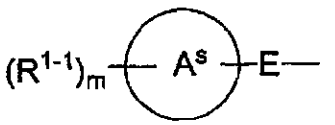
CLAIMS

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



(I)

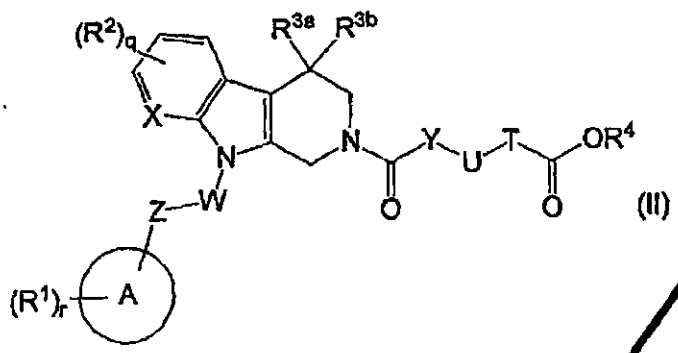
[wherein R^1 represents a halogen atom, a C1-4 alkyl group, a C1-4 alkoxy group, a C1-4 haloalkyl group, a C1-4 haloalkoxy group, a carboxyl group, a cyano group, a C1-3 alkylsulfonyl group, a carbamoyl group or



(wherein the ring A^S represents a 5- to 7-membered monocycle, E represents a bond, a methylene group or an oxygen atom, R^{1-1} represents a halogen atom, a C1-4 alkyl group, a C1-4 alkoxy group, a C1-4 haloalkyl group or a C1-4 haloalkoxy group, and m represents an integer of 0 to 3, provided that groups represented by a plurality of R^{1-1}s may be the same or different, respectively),
R^2 represents a hydrogen atom, a halogen atom, a C1-4 alkyl group, a C1-4 alkoxy group or a C1-4 haloalkyl group, R^3 represents a C1-4 alkyl group, R^4 represents a hydrogen atom or a C1-4 alkyl group,
the ring A represents (i) a C3-7 monocyclic carbon ring, (ii) a C8-10 bicyclic carbon ring, (iii) a 4- to 7-membered monocyclic heterocyclic ring containing one to four heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom or (iv) a 8- to 10-membered bicyclic heterocyclic ring containing one to four heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,
X represents a nitrogen atom or a carbon atom, T represents a bond, or a straight C1-4 alkylene group, a C2-4 alkenylene group or a C2-4 alkynylene group, optionally substituted with one or two R^5s (in the groups, R^5 represents a C1-4 alkyl group, a hydroxy group or an amino group), U represents (i) a methylene group, (ii) an oxygen atom, (iii) $-NR^6-$ (in the group, R^6 represents a hydrogen atom or a methyl group) or (iv) a 3- to 7-membered monocycle, a C5-10 bridged carbon ring or a 5- to 10-membered bridged heterocyclic ring, optionally substituted with one to five R^7s (in the groups, R^7 represents a halogen atom, a C1-4 alkyl group, a hydroxy group, an oxo group, a C1-4 alkoxy group, a C1-4 haloalkoxy group, a cyano group or a benzyloxy group), Y represents (i) a bond or (ii) a straight C1-3 alkylene group or a C2-3 alkenylene group, optionally substituted with one or two R^8s (in the groups, R^8 represents a methyl group), W represents a bond or a straight C1-3 alkylene group, Z represents a methylene group, an oxygen atom or an optionally oxidized sulfur atom, q represents an

integer of 1 to 4, r represents an integer of 0 to 5, and t represents an integer of 0 to 2, provided that groups represented by a plurality of R^1s, R^2s, R^3s, R^5s, R^7s and R^8s may be the same or different, respectively, and two R^3s and R^5s bound to the same carbon atom may be taken together with a carbon atom to form C3-5 cycloalkyl, respectively], a salt thereof, a solvate thereof or a prodrug thereof.

2. The compound according to claim 1, which is represented by the general formula (II):



[wherein R^{3a} and R^{3b} each represent independently a hydrogen atom or a methyl group, and other symbols are as defined in claim 1, provided that R^{3a} and R^{3b} may be taken together with a carbon atom to which they are bound, to form cyclopropyl].

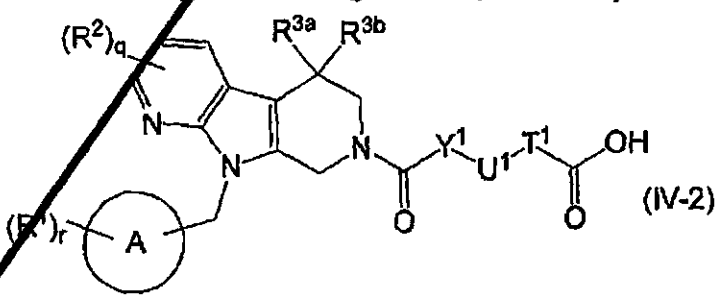
3. The compound according to claim 2, wherein Y is a straight C1-3 alkylene group optionally substituted with one or two R^8s (in the group, R^8 is as defined in claim 1).

4. The compound according to claim 3, wherein X is a nitrogen atom.

5. The compound according to claim 3, wherein X is a carbon atom.

6. The compound according to claim 4 or 5, wherein R^4 is a hydrogen atom.

7. The compound according to claim 6, which is represented by the general formula (IV-2):



[wherein U^1 represents a 5- to 7-membered monocycle or a C5-10 bridged carbon ring, optionally substituted with one to five R^7s (in the groups, R^7 is as defined in claim 1), Y^1 represents a methylene group or an ethylene group, optionally substituted with one or two R^8s, T^1 represents a bond, or a