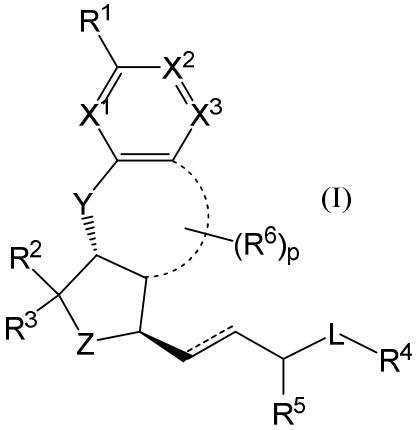
Claims

[Claim 1] A compound represented by general formula (I) or a salt thereof:



(I)

wherein

R^1 represents COOH, $COOR^{11}$, $CONHSO_2R^{12}$ or tetrazolyl,

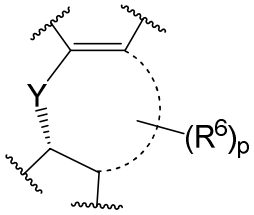
R^{11} represents C1-6 alkyl,

R^{12} represents C1-6 alkyl or phenyl, which phenyl is optionally substituted with 1 to 5 (1) halogen atoms or (2) C1-4 alkyl groups,

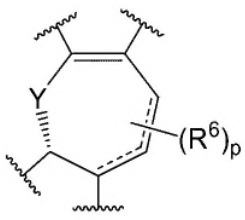
X^1, X^2 and X^3 each independently represent N, CH or CR^{21},

a plurality of R^{21}s each independently represent (1) halogen, (2) C1-4 alkyl, (3) C1-4 haloalkyl, (4) -$(CH_2)_t$-(C3-4 saturated carbocycle), or (5) vinyl optionally substituted with 1 to 3 halogen atoms,

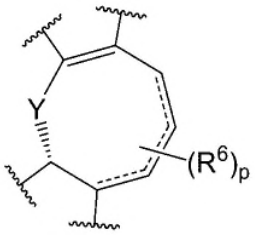
t represents an integer of 0 or 1,



represents



, or



R^6 represents (1) halogen, (2) C1-4 alkyl, (3) C1-4 haloalkyl, or (4) -$(CH_2)_q$-(C3-4 saturated carbocycle),

q represents an integer of 0 or 1,

p represents an integer of 0 to 3,

a plurality of R^6s may form a C3-4 saturated carbocycle optionally substituted with 1 to 6 halogen atoms together with a carbon atom to which each R^6 is bonded,

Y represents an oxygen atom or a sulfur atom,

R^2 and R^3 each independently represent (1) a hydrogen atom, (2) halogen, (3) C1-4 alkyl, or (4) C1-4 haloalkyl,

R^2 and R^3 may form a C3-4 saturated carbocycle optionally substituted with 1 to 6 halogen atoms together with a carbon atom to which R^2 and R^3 are bonded,

Z represents CHR^{10} or an oxygen atom,

R^{10} represents a hydrogen atom, halogen, a hydroxyl group, or a methoxy group,

L represents $-CH_2-$, $-CHR^{L1}-$, $-CR^{L2}R^{L3}-$ or $-C(=CH_2)-$,

R^{L1} represents (1) halogen, (2) C1-4 alkyl, (3) C1-4 haloalkyl, (4) C2-4 alkenyl, (5) C2-4 haloalkenyl, (6) C2-4 alkynyl or (7) C2-4 haloalkynyl,

R^{L2} and R^{L3} each independently represent (1) halogen, (2) C1-4 alkyl, (3) C1-4 haloalkyl, (4) C2-4 alkenyl, (5) C2-4 haloalkenyl, (6) C2-4 alkynyl, (7) C2-4 haloalkynyl or (8) a hydroxyl group, or

R^{L2} and R^{L3} may form (1) a C3-6 saturated carbocycle optionally substituted with 1 to 10 halogen atoms or (2) a 3-6 membered saturated heterocycle optionally substituted with 1 to 8 halogen atoms, together with a carbon atom to which R^{L2} and R^{L3} are bonded,

R^4 represents (1) C3-7 alkyl optionally substituted with 1 to 5 R^{41}s, (2) C3-7 alkenyl optionally substituted with 1 to 5 R^{42}s, (3) C3-7 alkynyl optionally substituted with 1 to 5 R^{43}s, (4) C2-6 alkoxy optionally substituted with 1 to 5 R^{44}s or (5) Cyc^1,

R^{41}, R^{42}, R^{43} and R^{44} each independently represent (1) halogen, (2) a C3-6 carbocycle or (3) a 3-6 membered heterocycle, wherein the C3-6 carbocycle and the 3-6 membered heterocycle is optionally substituted with 1 to 10 (1) halogen atoms or (2) C1-2 alkyl groups,

Cyc^1 represents (1) a C5-10 carbocycle optionally substituted with 1 to 5 R^{51}s or (2) a 5-10 membered heterocycle optionally substituted with 1 to 5 R^{52}s,

R^{51} and R^{52} each independently represent (1) halogen, (2) C1-4 alkyl, (3) C1-4 haloalkyl, (4) C2-4 alkenyl, (5) C2-4 haloalkenyl, (6) C2-4 alkynyl, (7) C2-4 haloalkynyl, (8) C1-4 alkoxy, (9) C1-4 haloalkoxy, (10) a hydroxyl group, (11) a C3-6 saturated carbocycle or (12) a 3-6 membered saturated heterocycle,

R^{L1} and R^{51} may form (1) a C3-6 saturated carbocycle or (2) a 3-6 membered saturated heterocycle, together with a carbon atom to which R^{L1} and R^{51} are bonded,

R^5 represents a hydrogen atom or a hydroxyl group,

wherein a plurality of R^6s, R^{41}s, R^{42}s, R^{43}s, R^{44}s, R^{51}s and R^{52}s may be the same or different,



represents a single bond or a double bond, provided that adjacent



are not simultaneously a double bond,



represents a bond beyond the sheet surface (that is, an α configuration),



represents a bond in front of the sheet surface (that is, a β configuration),

wherein



bonded to an asymmetric atom represents the α configuration, the β configuration, or a mixture of the α configuration and the β configuration in any ratio, unless otherwise indicated.

[Claim 2] The compound or the salt thereof according to claim 1, wherein X^1, X^2 and X^3 are each independently CH or CR^{21}.

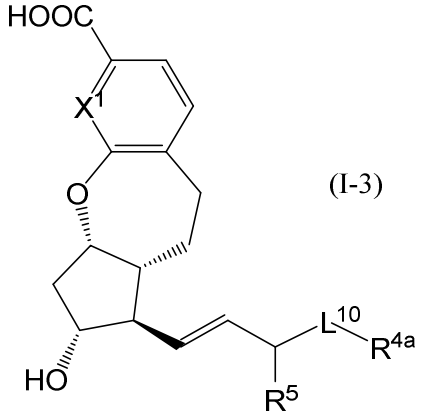
[Claim 3] The compound or the salt thereof according to claim 1 or 2, wherein Y is an oxygen atom.

[Claim 4] The compound or the salt thereof according to any one of claims 1 to 3, wherein R^4 is C3-7 alkyl optionally substituted with 1 to 3 R^{41}s, C3-7 alkenyl optionally substituted with 1 to 3 R^{42}s, or Cyc^1.

[Claim 5] The compound or the salt thereof according to any one of claims 1 to 4, wherein Z is CHR^{10}, and R^{10} is a hydroxyl group.

[Claim 6] The compound or the salt thereof according to any one of claims 1 to 5, wherein R^1 is COOH.

[Claim 7] The compound or the salt thereof according to claim 1, wherein general formula (I) is represented by general formula (I-3)



(I-3)

wherein L^{10} represents $-CHR^{L1}-$ or $-CR^{L2}R^{L3}-$, R^{4a} represents C3-7 alkyl optionally substituted with 1 to 3 R^{41}s, C3-7 alkenyl optionally substituted with 1 to 3 R^{42}s, or Cyc^1, and other symbols represent identical meanings to those in claim 1.

[Claim 8] The compound or the salt thereof according to claim 1, wherein the compound represented by general formula (I) or the salt thereof is

(1) (1R,2R,3aS,10aR)-1-[(1E,3R,4S)-4-(2,4-difluorophenyl)-3-hydroxy-1-penten-1-yl]-5-fluoro-2-hydroxy-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(2) (1R,2R,3aS,10aR)-5-fluoro-1-[(1E)-4-(2-fluorophenyl)-3-hydroxy-1-penten-1-yl]-2-hydroxy-

2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(3) (1R,2R,3aS,10aR)-1-{(1E,3ξ)-3-[1-(4-fluorophenyl)cyclobutyl]-3-hydroxy-1-propen-1-yl}-2-hydroxy-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(4) (1R,2R,3aS,10aR)-1-{(1E,3ξ)-3-[1-(2,5-difluorophenyl)cyclobutyl]-3-hydroxy-1-propen-1-yl}-2-hydroxy-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(5) (1R,2R,3aS,10aR)-5-chloro-1-[(1E,3ξ)-4-(2,6-difluorophenyl)-4,4-difluoro-3-hydroxy-1-buten-1-yl]-2-hydroxy-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(6) (1R,2R,3aS,10aR)-1-{(1E,3ξ)-3-[1-(4-fluorophenyl)cyclobutyl]-3-hydroxy-1-propen-1-yl}-2-hydroxy-5-methyl-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(7) (1R,2R,3aS,10aR)-1-[(1E,3ξ,4ξ)-4-ethyl-3-hydroxy-7-methyl-1-octen-1-yl]-2-hydroxy-5-methyl-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(8) (1R,2R,3aS,10aR)-2-hydroxy-5-methyl-1-[(1E,4S)-7,8,8-trifluoro-4-hydroxy-4-methyl-1,7-octadien-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(9) (1R,2R,3aS,10aR)-2-hydroxy-5-methyl-1-[(1E,4S)-8,8,8-trifluoro-4-hydroxy-4-methyl-1-octen-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(10) (1R,2R,3aS,10aR)-2-hydroxy-1-[(1E,4ξ)-4-hydroxy-4,7-dimethyl-1-octen-1-yl]-5-methyl-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(11) (1R,3aS,10aR)-5-fluoro-1-[(1E,3ξ)-3-hydroxy-4-methyl-4-phenyl-1-penten-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(12) (1R,3aS,10aR)-1-{(1E,3ξ)-3-[1-(2-fluorophenyl)cyclobutyl]-3-hydroxy-1-propen-1-yl}-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(13) (1R,3aS,10aR)-5-chloro-1-{(1E,3ξ)-3-[1-(2-fluorophenyl)cyclobutyl]-3-hydroxy-1-propen-1-yl}-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(14) (1R,3aS,10aR)-5-chloro-1-[(1E,3ξ)-3-hydroxy-6-methoxy-4-methylene-1-hexen-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(15) (1R,3aS,10aR)-5-chloro-1-[(1E,3ξ,4S)-4-ethyl-3-hydroxy-1-octen-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(16) (1R,3aS,10aR)-5-chloro-1-[(1E,3ξ)-3-hydroxy-3-(3-phenyl-3-oxetanyl)-1-propen-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(17) (1R,2R,3aS,10aR)-2,5-difluoro-1-[(1E,3ξ)-3-hydroxy-4-methyl-4-phenyl-1-penten-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(18) (1R,2R,3aS,10aR)-2,5-difluoro-1-[(1E,3ξ)-3-hydroxy-3-(3-phenyl-3-oxetanyl)-1-propen-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(19) (1R,2R,3aS,10aR)-2-chloro-5-fluoro-1-{(1E,3ξ)-3-[3-(2-fluorophenyl)-3-oxetanyl]-3-hydroxy-1-propen-1-yl}-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(20) (1R,2R,3aS,10aR)-2-chloro-5-fluoro-1-{(1E,3ξ)-3-hydroxy-3-[(2ξ)-2-phenyl-2-oxetanyl]-1-propen-1-yl}-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

(21) (1R,3aR,10aR)-1-[(1E,3ξ,4S)-3-hydroxy-4-methyl-1-octen-1-yl]-5-methyl-1,3,3a,9,10,10a-hexahydrofuro[3,4-b][1]benzoxepine-6-carboxylic acid,

(22) (1R,3aR,10aR)-1-[(1E,3ξ)-3-hydroxy-3-(1-phenoxycyclobutyl)-1-propen-1-yl]-5-methyl-1,3,3a,9,10,10a-hexahydrofuro[3,4-b][1]benzoxepine-6-carboxylic acid,

(23) (1R,2R,3aS,10aR)-5-fluoro-2-hydroxy-1-{(1E,3ξ)-3-hydroxy-3-[1-(2-methylphenyl)cyclopropyl]-1-propen-1-yl}-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid, or

(24) (1R,2R,3aS,10aR)-2-hydroxy-1-[(1E,3R)-3-hydroxy-3-(1-phenylcyclopropyl)-1-propen-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid,

or a salt thereof.

[Claim 9] A pharmaceutical composition comprising the compound or the salt thereof according to any one of claims 1 to 8.

[Claim 10] An EP3 agonist comprising the compound or the salt thereof according to any one of claims 1 to 8.

[Claim 11] Use of the compound or the salt thereof according to any one of claims 1 to 8 in the manufacture of a medicament for preventing and/or treating a renal disease.

[Claim 12] The use according to claim 11, wherein the renal disease is a chronic renal disease.

[Claim 13] The use according to claim 12, wherein the chronic renal disease is diabetic renal disease, nephrosclerosis, IgA nephropathy, GBM nephritis, ANCA-associated nephritis, mesangial proliferative nephritis, lupus nephritis, minimal change nephrotic syndrome, focal segmental glomerulosclerosis, membranous nephropathy, Alport syndrome, or polycystic kidney disease.

[Claim 14] The use according to claim 11, wherein the renal disease is an acute renal damage.

[Claim 15] The use according to claim 14, wherein the acute renal damage is acute renal damage associated with organ surgery, acute renal damage associated with sepsis, acute renal damage associated with kidney transplantation, acute renal damage associated with rhabdomyolysis, contrast nephropathy, or drug-induced renal damage.

[Claim 16] The compound or the salt thereof according to any one of claims 1 to 8 for use in therapy.

[Claim 17] A compound (1R,2R,3aS,10aR)-2-hydroxy-5-methyl-1-[(1E,4S)-8,8,8-trifluoro-4-hydroxy-4-methyl-1-octen-1-yl]-2,3,3a,9,10,10a-hexahydro-1H-benzo[b]cyclopenta[f]oxepine-6-carboxylic acid, or a salt thereof.

[Claim 18] The compound or the salt therefore according to claim 17 for use in therapy.

[Claim 19] Use of the compound or the salt thereof according to claim 17 in the manufacture of a medicament for preventing and/or treating a renal disease.