R^7 represents a C_1-C_6 alkyl group which may be substituted with one hydroxy group, a hydroxy group, or a hydrogen atom, or

R^6 and R^7 may together form a spiro-linked 4- to 6-membered hydrocarbon ring or a spiro-linked 4- to 6-membered nitrogen-containing heterocyclic ring,

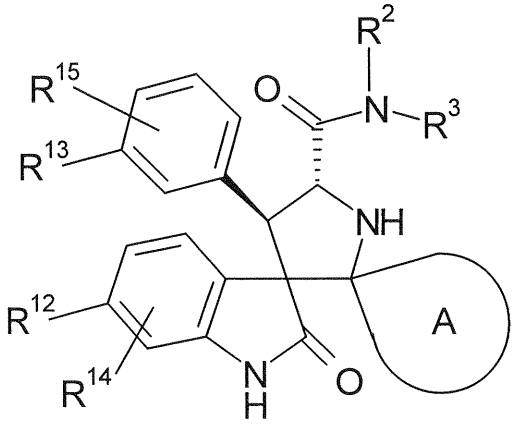
R^8 is absent or represents one or more substituents selected from a hydroxy group, a C_1-C_6 alkyl group, and a C_1-C_6 alkoxy group, and

Z represents CH_2, NH, or an oxygen atom; and

in formula (4),

R^9 represents a C_1-C_6 alkyl group which may have one or more substituents selected from Group 4, a carbamoyl group which may have one or more substituents selected from Group 5, a 5- or 6-membered nitrogen-containing heteroaryl group which may be substituted with an oxo group or one or more C_1-C_6 alkyl groups which may be substituted with an oxo group or one hydroxy group, a hydroxy group, or -NR'R'', wherein

R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, an oxo group, or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may



(5)

[0016]

wherein in formula (5),

ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in [1];

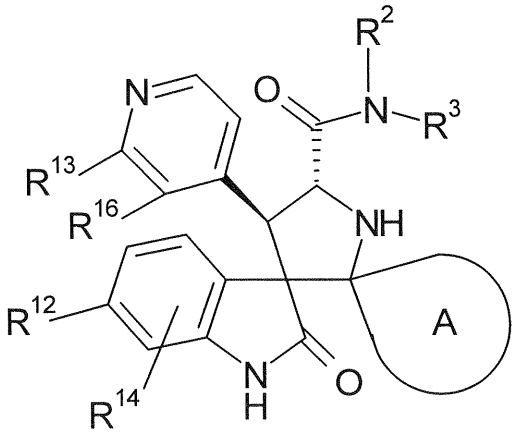
R^{12} and R^{13} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group;

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group; and

R^{15} is absent or represents one or more substituents selected from Group 3 (which has the same meaning as Group 3 in [1]).

[3] A compound according to [1] represented by general formula (6) or a salt thereof:

[0017]



(6)

[0018]

wherein in formula (6),

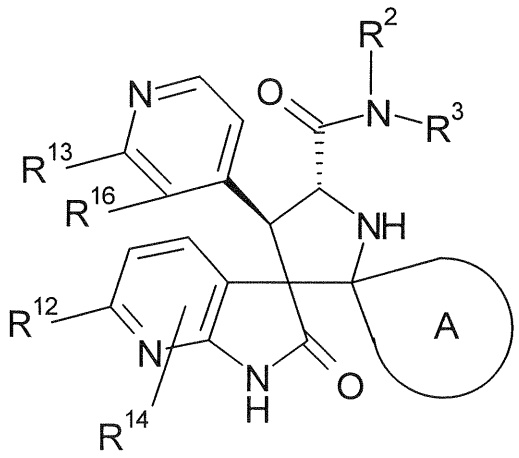
ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in [1];

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group; and

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group.

[4] A compound according to [1] represented by general formula (7) or a salt thereof:

[0019]



(7)

[0020]

wherein in formula (7),

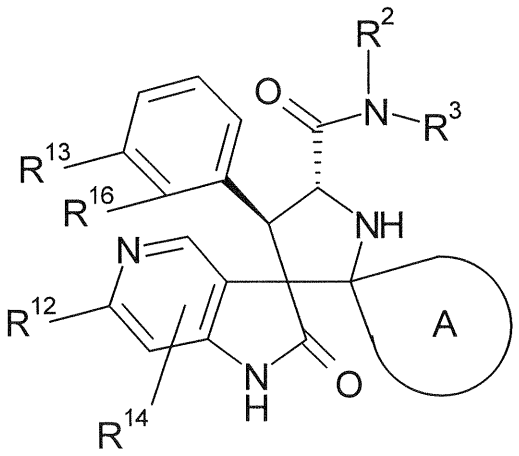
ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in [1];

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group; and

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group.

[5] A compound according to [1] represented by general formula (8) or a salt thereof:

[0021]



(8)

[0022]

wherein in formula (8),

ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in [1];

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group; and

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group.

[6] A compound selected from the following group or a salt thereof:

[0023]

[13] (3'R, 4'S, 5'R)-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-N-{(3R, 6S)-6-[1-hydroxyethyl]tetrahydro-2H-pyran-3-yl}-4, 4-dimethyl-2"-oxo-1", 2"-dihydrodispiro[cyclohexane-1, 2'-pyrrolidine-3', 3"-indole]-5'-carboxamide benzenesulfonate.

[14] An inhibitor of Mdm2 comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13].

[15] An inhibitor of Mdm2 ubiquitin ligase comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13].

[16] An inhibitor of p53-Mdm2 binding comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13].

[17] An inhibitor of suppression of p53 transcription activity comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13].

[18] An inhibitor of p53 degradation comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13].

[19] A medicament comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13] as an active ingredient.

[20] An anticancer agent comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13] as an active ingredient.

[21] An anticancer agent according to [20], wherein the cancer is lung cancer, breast cancer, prostate cancer, colon cancer, acute myeloid leukemia, malignant lymphoma,

malignant melanoma, retinoblastoma, neuroblastoma, or sarcoma.

[22] A pharmaceutical composition comprising a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13] and a pharmaceutically acceptable carrier.

~~[23] A method for treating cancer, comprising administering a compound according to any one of [1] to [13] or a salt thereof.~~

~~[24] A method for treating cancer according to [23], wherein the cancer is lung cancer, breast cancer, prostate cancer, colon cancer, acute myeloid leukemia, malignant lymphoma, malignant melanoma, retinoblastoma, neuroblastoma, or sarcoma.~~

[~~25~~23] Use of a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13] for the manufacture of a medicament.

[~~26~~24] Use of a compound according to any one of [1] to [6~~13~~] or a salt thereof or a compound according to any one of [7] to [13] for the manufacture of an anticancer agent.

[Advantages of the Invention]

[0025]

The present invention provides a novel spiroprolinamide derivative represented by the above formula (1), which has Mdm2 inhibiting activity. Such a novel compound is useful as an anti-tumor agent.

[Description of Embodiments]

[0026]

a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group;

R^7 represents a C_1-C_6 alkyl group which may be substituted with one hydroxy group, a hydroxy group, or a hydrogen atom, or

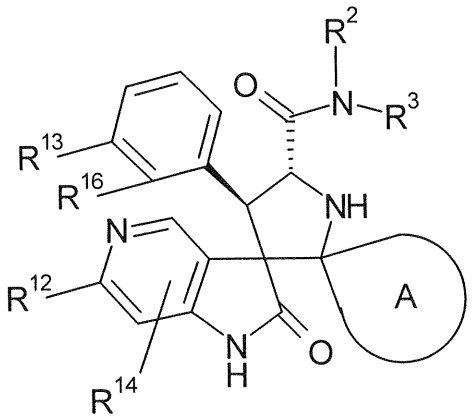
R^6 and R^7 may together form a spiro-linked 4- to 6-membered hydrocarbon ring or a spiro-linked 4- to 6-membered nitrogen-containing heterocyclic ring (wherein "spiro-linked" means that a ring formed by R^6 and R^7 together and the Z-containing 6-membered ring form a spiro ring);

R^8 is absent or represents one or more substituents selected from a hydroxy group, a C_1-C_6 alkyl group, and a C_1-C_6 alkoxy group; and

Z represents CH_2, NH, or an oxygen atom.

[0063]

When R^6 is a "C_1-C_6 alkyl group which may have one or more substituents", examples of the substituent(s) include a halogen atom, a hydroxy group, a carbamoyl group, a morpholino group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylsulfonyl group, and -NR'R''. Here, R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, one to three hydroxy groups, or an oxo group, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms



(8)

[0088]

R^{12}, R^{13}, and R^{16} represents a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group and are preferably a halogen atom or a cyano group, more preferably a halogen atom, yet more preferably a chlorine atom or a fluorine atom.

[0089]

R^{14} represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms ~~or one to three hydroxy groups~~, and a cyano group and is not necessarily required to be present. Preferably, R^{14} is absent or R^{14}, if present, is a fluorine atom. The position of the substituent bonded to the ring is not limited.

[0090]

R^{15} represents one or more substituents selected from Group 3 above and is not necessarily required to be

[0144]

The present invention further includes use of a compound of the present invention, a salt, or a solvate thereof for the manufacture of a medicament.

[0145]

Hereinafter, the present invention will be specifically explained with reference to the Examples. However, the present invention is not limited to these examples, and they should not be construed in any limitative way. Furthermore, reagents, solvents, and starting materials in the specification can be readily obtained from commercially available supply sources unless otherwise specified.

[0146]

~~Hereinafter, the present invention will be specifically explained with reference to the Examples. However, the present invention is not limited to these examples, and they should not be construed in any limitative way. Furthermore, reagents, solvents, and starting materials in the specification can be readily obtained from commercially available supply sources unless otherwise specified.~~

Examples

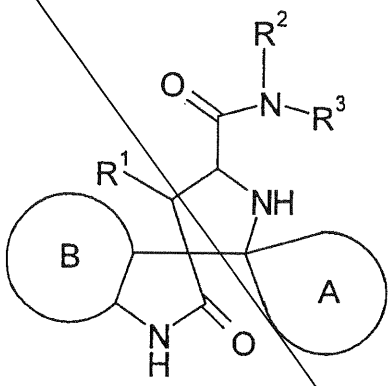
[0147]

Example 1

[0148]

Claims

1. A compound represented by general formula (1) or a salt thereof:



(1)

wherein

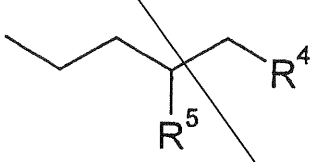
ring A represents a spiro-linked 4- to 6-membered saturated hydrocarbon ring which may have one or more substituents selected from Group 1, or a spiro-linked 6-membered saturated heterocyclic ring which may have one or more substituents selected from Group 1;

ring B represents a benzene ring which may have one or more substituents selected from Group 2, a pyridine ring which may have one or more substituents selected from Group 2, or a pyrimidine ring which may have one or more substituents selected from Group 2;

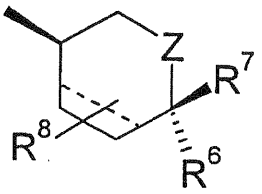
R^1 represents an aryl group which may have one or more substituents selected from Group 3, a heteroaryl group which may have one or more substituents selected from Group 3, a C_3-C_6 cycloalkyl group which may have one or more substituents selected from Group 3, or a C_3-C_6 cycloalkenyl group which may have one or more substituents selected from Group 3;

R^2 represents a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom; and

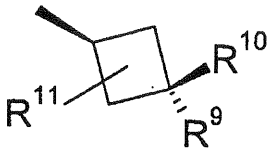
R^3 represents a group represented by the following general formulae (2), (3), or (4):



(2)



(3)



(4)

wherein in formula (2),

R^4 and R^5 each independently represent a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group, or R^4 and R^5 together with the carbon atoms to which the R^4 and R^5 groups are respectively bonded may form a 4- to 6-membered saturated hydrocarbon ring;

in formula (3),

the broken line in the ring structure indicates that the bond may be a double bond,

R^6 represents a C_1-C_6 alkyl group which may have one or more substituents selected from Group 4, a carbamoyl group which may have one or more substituents selected from Group 5, a 5- or 6-membered nitrogen-containing heteroaryl group which may be substituted with an oxo group or one or more C_1-C_6 alkyl groups which may be substituted with an oxo group or one hydroxy group, a hydroxy group, or -NR'R'', wherein

R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, an oxo group, or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group,

R^7 represents a C_1-C_6 alkyl group which may be substituted with one hydroxy group, a hydroxy group, or a hydrogen atom, or

R^6 and R^7 may together form a spiro-linked 4- to 6-membered hydrocarbon ring or a spiro-linked 4- to 6-membered nitrogen-containing heterocyclic ring,

R^8 represents one or more substituents selected from a hydroxy group, a C_1-C_6 alkyl group, and a C_1-C_6 alkoxy group, and

Z represents CH_2, NH, or an oxygen atom; and in formula (4),

R^9 represents a C_1-C_6 alkyl group which may have one or more substituents selected from Group 4, a carbamoyl group which may have one or more substituents selected from Group 5, a 5- or 6-membered nitrogen-containing heteroaryl group which may be substituted with an oxo group or one or more C_1-C_6 alkyl groups which may be

substituted with an oxo group or one hydroxy group, a hydroxy group, or -NR'R'', wherein

R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, an oxo group, or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group,

R^{10} represents a C_1-C_6 alkyl group which may be substituted with one hydroxy group, a hydroxy group, or a hydrogen atom, or

R^9 and R^{10} may together form a spiro-linked 4- to 6-membered hydrocarbon ring or a spiro-linked 4- to 6-membered nitrogen-containing heterocyclic ring, and

R^{11} represents one or more substituents selected from a hydroxy group, a C_1-C_6 alkyl group, and a C_1-C_6 alkoxy group:

Group 1: a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, a C_1-C_6 alkoxy group, and a cyano group,

Group 2: a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, a C_3-C_4 cycloalkyl group which may be substituted with one to

three halogen atoms, a vinyl group, an ethynyl group, a cyano group, and a C_1-C_6 alkoxy group,

Group 3: a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, a vinyl group, an ethynyl group, a cyano group, -OR', -NR'R'', -COOR', and -CONHR', wherein R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group,

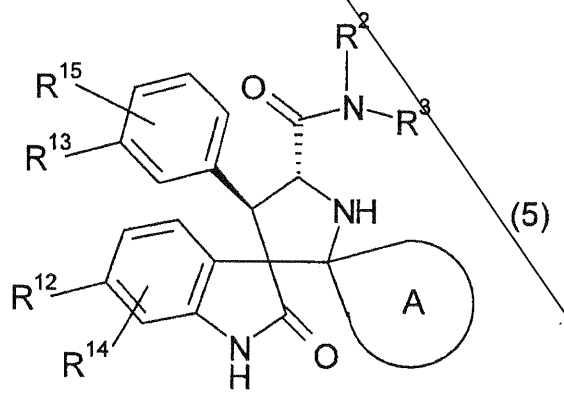
Group 4: a halogen atom, a hydroxy group, a carbamoyl group, a morpholino group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylsulfonyl group, and -NR'R'', wherein

R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, one to three hydroxy groups, or an oxo group, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-

membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group, and

Group 5: a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, one to three hydroxy groups, or a C_1-C_6 alkoxy group, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group, and a tetrahydropyranyl group.

2. A compound according to claim 1 represented by general formula (5) or a salt thereof:



wherein

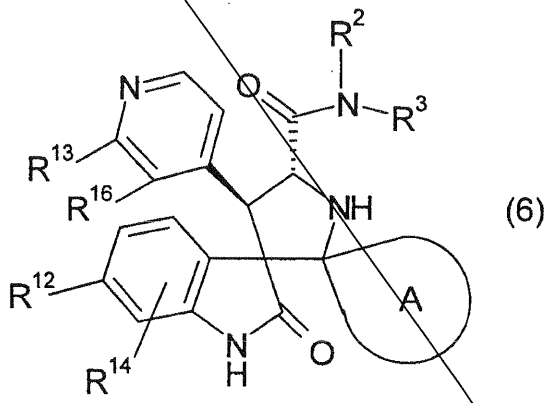
ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12} and R^{13} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group;

R^{14} represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group; and

R^{15} represents one or more substituents selected from Group 3 (which has the same meaning as Group 3 in claim 1).

3. A compound according to claim 1 represented by general formula (6) or a salt thereof:



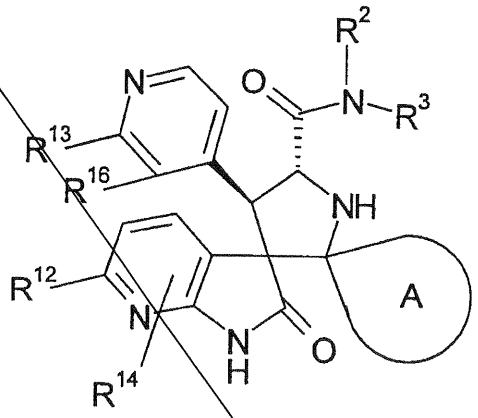
wherein

ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group; and

R^{14} represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group.

4. A compound according to claim 1 represented by general formula (7) or a salt thereof:



(7)

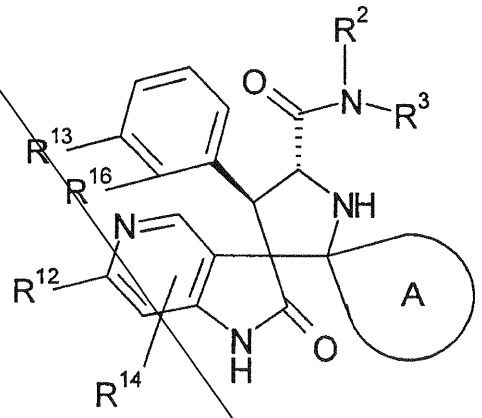
wherein

ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group; and

R^{14} represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group.

5. A compound according to claim 1 represented by general formula (8) or a salt thereof:



(8)

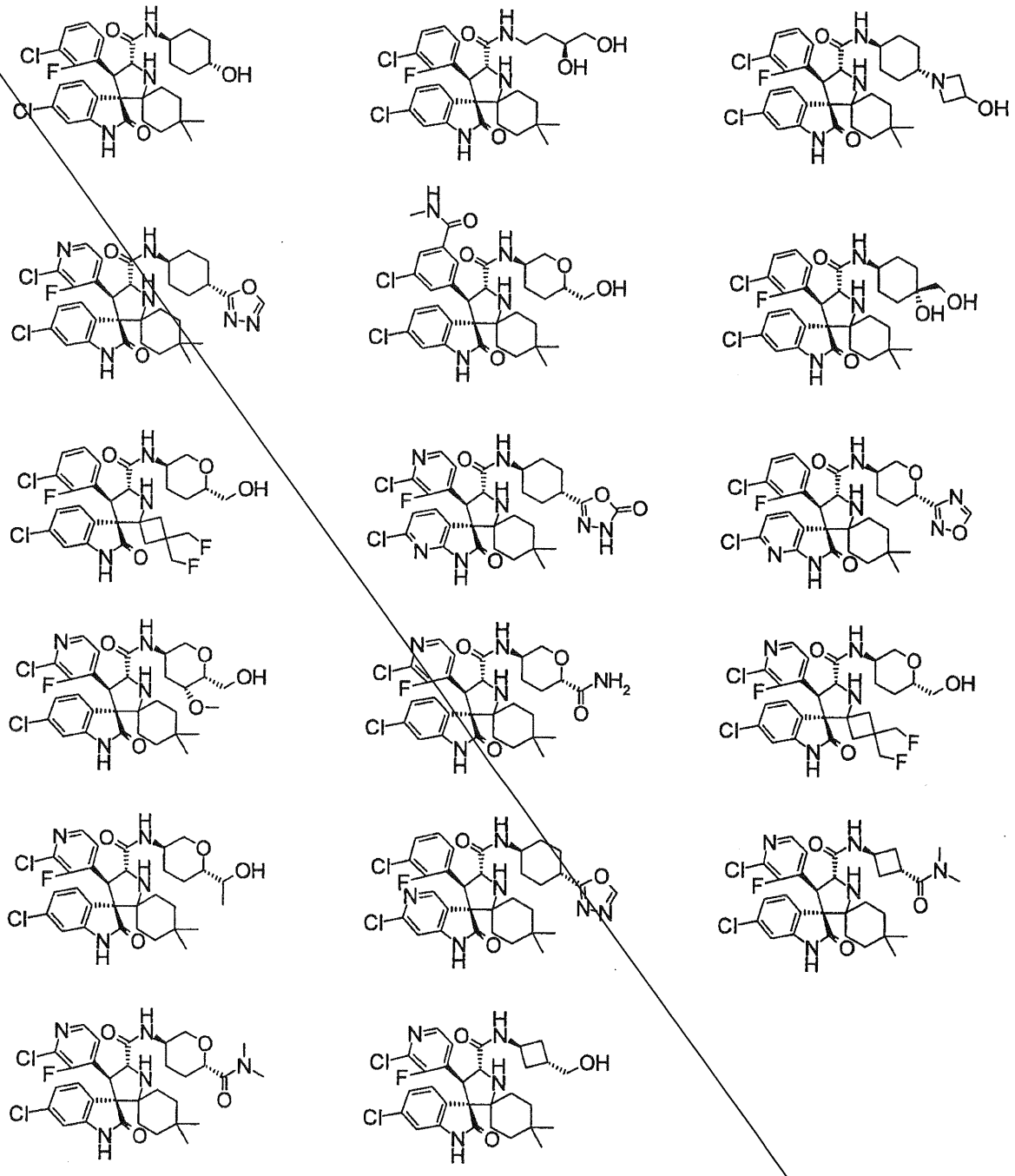
wherein

ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group; and

R^{14} represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, and a cyano group.

6. A compound selected from the following group or a salt thereof:



7. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-

1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide hydrochloride.

8. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide sulfate.

9. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide methanesulfonate.

10. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide ethanesulfonate.

11. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide benzenesulfonate.

12. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-

4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide p-toluenesulfonate.

13. (3'R,4'S,5'R)-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-N-{(3R,6S)-6-[1-hydroxyethyl]tetrahydro-2H-pyran-3-yl}-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide benzenesulfonate.

14. An inhibitor of Mdm2 comprising a compound according to any one of claims 1 to 13 or a salt thereof.

15. An inhibitor of Mdm2 ubiquitin ligase comprising a compound according to any one of claims 1 to 13 or a salt thereof.

16. An inhibitor of p53-Mdm2 binding comprising a compound according to any one of claims 1 to 13 or a salt thereof.

17. An inhibitor of suppression of p53 transcription activity comprising a compound according to any one of claims 1 to 13 or a salt thereof.

18. An inhibitor of p53 degradation comprising a compound according to any one of claims 1 to 13 or a salt thereof.

19. A medicament comprising a compound according to any one of claims 1 to 13 or a salt thereof as an active ingredient.

20. An anticancer agent comprising a compound according to any one of claims 1 to 13 or a salt thereof as an active ingredient.

21. An anticancer agent according to claim 20, wherein the cancer is lung cancer, breast cancer, prostate cancer, colon cancer, acute myeloid leukemia, malignant lymphoma, malignant melanoma, retinoblastoma, neuroblastoma, or sarcoma.

22. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 or a salt thereof and a pharmaceutically acceptable carrier.

23. A method for treating cancer, comprising administering a compound according to any one of claims 1 to 13 or a salt thereof.

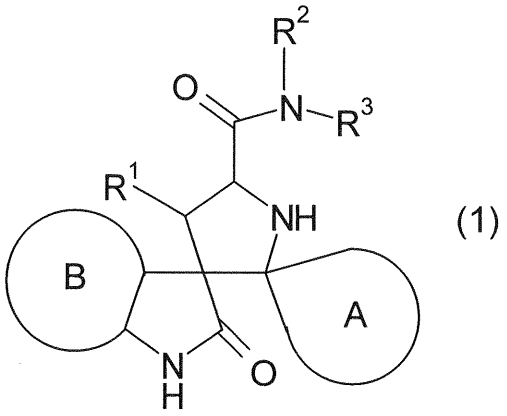
24. A method for treating cancer according to claim 23, wherein the cancer is lung cancer, breast cancer, prostate cancer, colon cancer, acute myeloid leukemia, malignant lymphoma, malignant melanoma, retinoblastoma, neuroblastoma, or sarcoma.

25. Use of a compound according to any one of claims 1 to 13 or a salt thereof for the manufacture of a medicament.

26. Use of a compound according to any one of claims 1 to 13 or a salt thereof for the manufacture of an anticancer agent.

Claims

1. A compound represented by general formula (1) or a salt thereof:



(1)

wherein

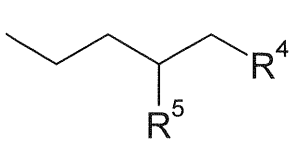
ring A represents a spiro-linked 4- to 6-membered saturated hydrocarbon ring which may have one or more substituents selected from Group 1, or a spiro-linked 6-membered saturated heterocyclic ring which may have one or more substituents selected from Group 1;

ring B represents a benzene ring which may have one or more substituents selected from Group 2, a pyridine ring which may have one or more substituents selected from Group 2, or a pyrimidine ring which may have one or more substituents selected from Group 2;

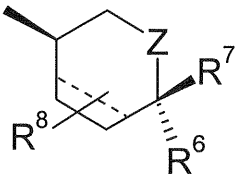
R^1 represents an aryl group which may have one or more substituents selected from Group 3, a heteroaryl group which may have one or more substituents selected from Group 3, a C_3-C_6 cycloalkyl group which may have one or more substituents selected from Group 3, or a C_3-C_6 cycloalkenyl group which may have one or more substituents selected from Group 3;

R^2 represents a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom; and

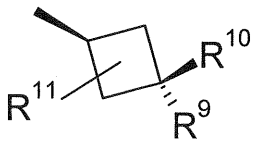
R^3 represents a group represented by the following general formulae (2), (3), or (4):



(2)



(3)



(4)

wherein in formula (2),

R^4 and R^5 each independently represent a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group, or R^4 and R^5 together with the carbon atoms to which the R^4 and R^5 groups are respectively bonded may form a 4- to 6-membered saturated hydrocarbon ring;

in formula (3),

the broken line in the ring structure indicates that the bond may be a double bond,

R^6 represents a C_1-C_6 alkyl group which may have one or more substituents selected from Group 4, a carbamoyl group which may have one or more substituents selected from Group 5, a 5- or 6-membered nitrogen-containing heteroaryl group which may be substituted with an oxo group or one or more C_1-C_6 alkyl groups which may be substituted with an oxo group or one hydroxy group, a hydroxy group, or -NR'R'', wherein

R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, an oxo group, or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group,

R^7 represents a C_1-C_6 alkyl group which may be substituted with one hydroxy group, a hydroxy group, or a hydrogen atom, or

R^6 and R^7 may together form a spiro-linked 4- to 6-membered hydrocarbon ring or a spiro-linked 4- to 6-membered nitrogen-containing heterocyclic ring,

R^8 is absent or represents one or more substituents selected from a hydroxy group, a C_1-C_6 alkyl group, and a C_1-C_6 alkoxy group, and

Z represents CH_2, NH, or an oxygen atom; and in formula (4),

R^9 represents a C_1-C_6 alkyl group which may have one or more substituents selected from Group 4, a carbamoyl group which may have one or more substituents selected from Group 5, a 5- or 6-membered nitrogen-containing heteroaryl group which may be substituted with an oxo group or one or more C_1-C_6 alkyl groups which may be

substituted with an oxo group or one hydroxy group, a hydroxy group, or -NR'R'', wherein

R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, an oxo group, or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group,

R^{10} represents a C_1-C_6 alkyl group which may be substituted with one hydroxy group, a hydroxy group, or a hydrogen atom, or

R^9 and R^{10} may together form a spiro-linked 4- to 6-membered hydrocarbon ring or a spiro-linked 4- to 6-membered nitrogen-containing heterocyclic ring, and

R^{11} represents one or more substituents selected from a hydroxy group, a C_1-C_6 alkyl group, and a C_1-C_6 alkoxy group:

Group 1: a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, a C_1-C_6 alkoxy group, and a cyano group,

Group 2: a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, a C_3-C_4 cycloalkyl group which may be substituted with one to

three halogen atoms, a vinyl group, an ethynyl group, a cyano group, and a C_1-C_6 alkoxy group,

Group 3: a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, a vinyl group, an ethynyl group, a cyano group, -OR', -NR'R'', -COOR', and -CONHR', wherein R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group,

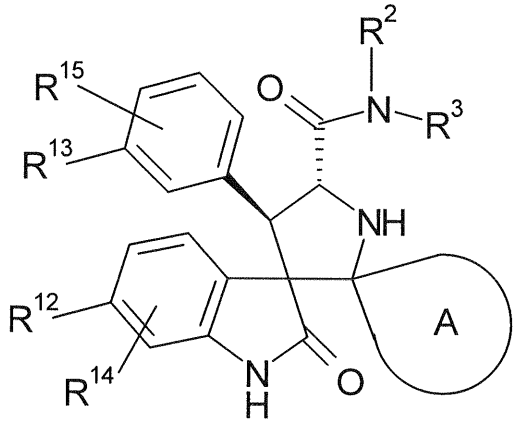
Group 4: a halogen atom, a hydroxy group, a carbamoyl group, a morpholino group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylsulfonyl group, and -NR'R'', wherein

R' and R'' each independently represent a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, one to three hydroxy groups, or an oxo group, a C_3-C_4 cycloalkyl group which may be substituted with one to three halogen atoms or one to three hydroxy groups, or a hydrogen atom, or R' and R'' together with the nitrogen atom to which R' and R'' are bonded may form a 4- to 7-

membered nitrogen-containing heterocyclic group which may have one or more substituents selected from a C_1-C_6 alkyl group and a hydroxy group, and

Group 5: a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, one to three hydroxy groups, or a C_1-C_6 alkoxy group, a C_3-C_6 cycloalkyl group, a C_1-C_6 alkoxy group, and a tetrahydropyranyl group.

2. A compound according to claim 1 represented by general formula (5) or a salt thereof:



(5)

wherein

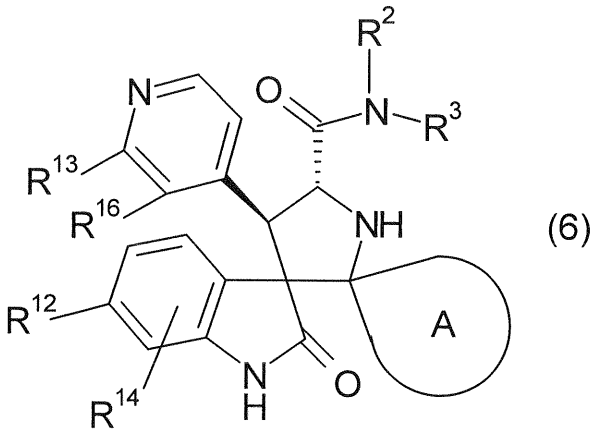
ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12} and R^{13} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group;

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group; and

R^{15} is absent or represents one or more substituents selected from Group 3 (which has the same meaning as Group 3 in claim 1).

3. A compound according to claim 1 represented by general formula (6) or a salt thereof:



(6)

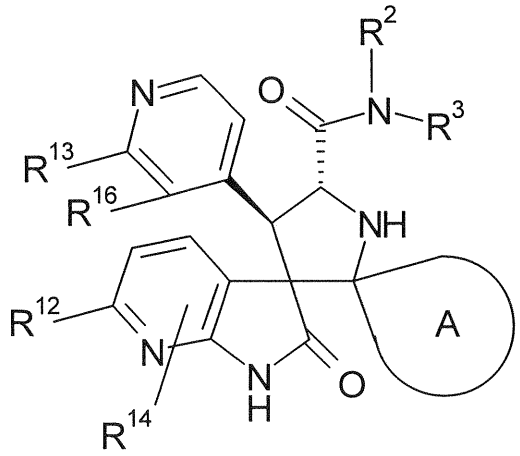
wherein

ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group; and

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group.

4. A compound according to claim 1 represented by general formula (7) or a salt thereof:



(7)

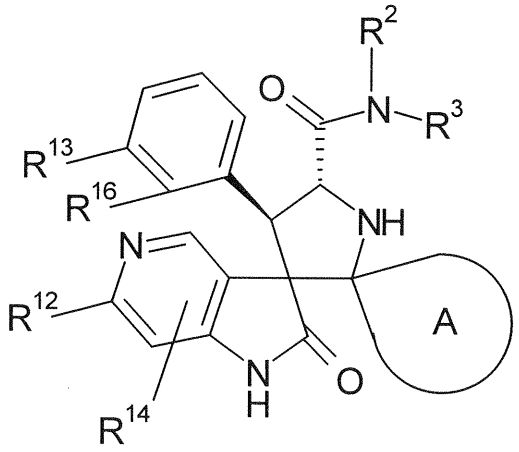
wherein

ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group; and

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group.

5. A compound according to claim 1 represented by general formula (8) or a salt thereof:



(8)

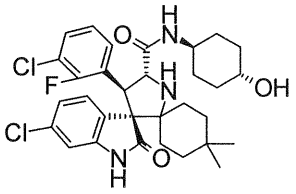
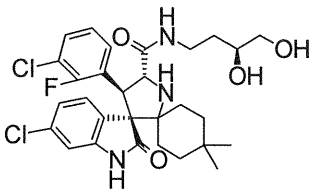
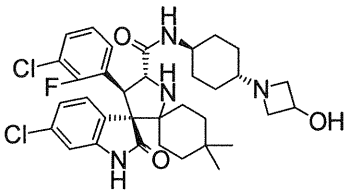
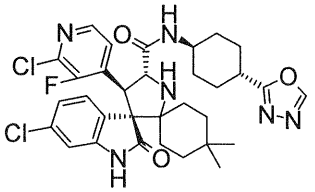
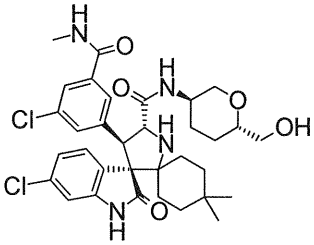
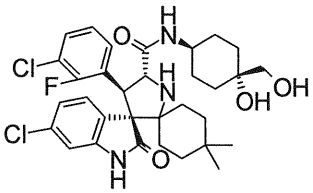
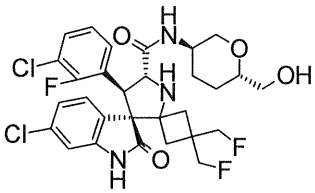
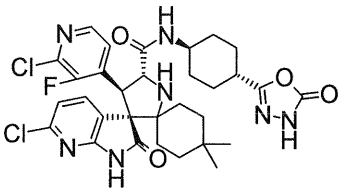
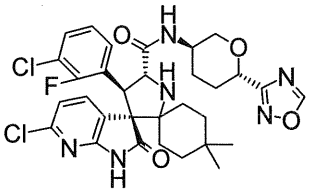
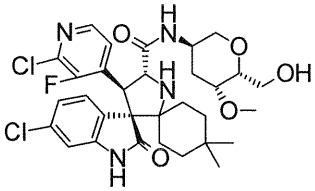
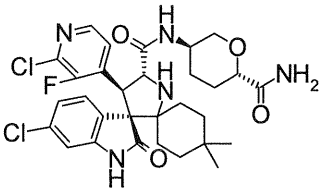
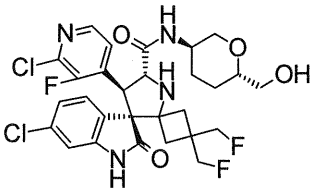
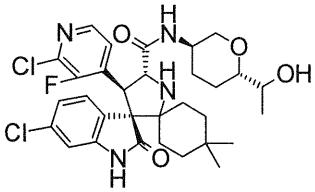
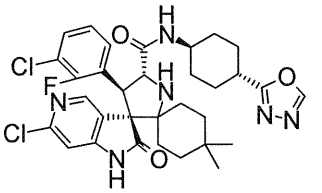
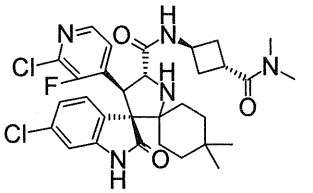
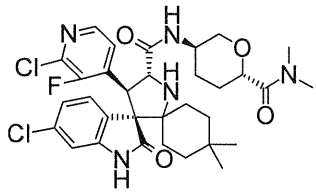
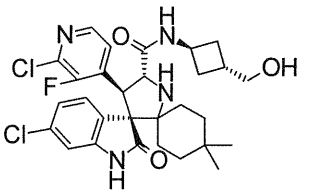
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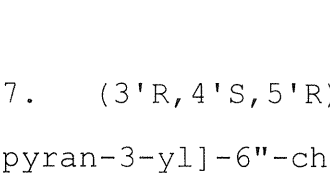
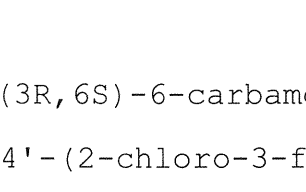
ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

R^{12}, R^{13}, and R^{16} represent a group selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group; and

R^{14} is absent or represents one or more substituents selected from a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, and a cyano group.

6. A compound selected from the following group or a salt thereof:

7. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-

1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide hydrochloride.

8. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide sulfate.

9. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide methanesulfonate.

10. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide ethanesulfonate.

11. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide benzenesulfonate.

12. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-

4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide p-toluenesulfonate.

13. (3'R,4'S,5'R)-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-N-{(3R,6S)-6-[1-hydroxyethyl]tetrahydro-2H-pyran-3-yl}-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide benzenesulfonate.

14. An inhibitor of Mdm2 comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13.

15. An inhibitor of Mdm2 ubiquitin ligase comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13.

16. An inhibitor of p53-Mdm2 binding comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13.

17. An inhibitor of suppression of p53 transcription activity comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13.

18. An inhibitor of p53 degradation comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13.

19. A medicament comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13 as an active ingredient.

20. An anticancer agent comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13 as an active ingredient.

21. An anticancer agent according to claim 20, wherein the cancer is lung cancer, breast cancer, prostate cancer, colon cancer, acute myeloid leukemia, malignant lymphoma, malignant melanoma, retinoblastoma, neuroblastoma, or sarcoma.

22. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13 and a pharmaceutically acceptable carrier.

23. Use of a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13 for the manufacture of a medicament.

24. Use of a compound according to any one of claims 1 to 6 or a salt thereof or a compound according to any one of claims 7 to 13 for the manufacture of an anticancer agent.