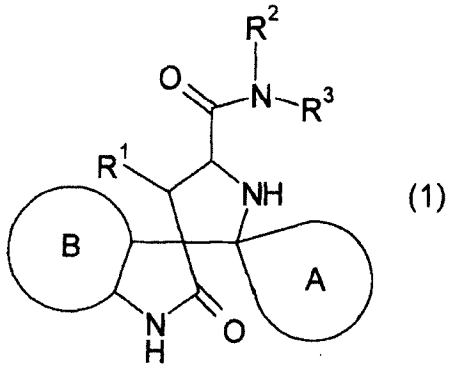
Claims

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 that are each independently a Group 1 substituent; or a spiro-linked 6-membered saturated heterocyclic ring which may have one or more substituents that are each independently a Group 1 substituent;

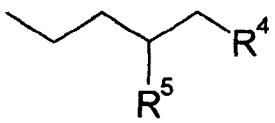
ring B represents a benzene ring which may have one or more substituents that are each independently a Group 2 substituent; a pyridine ring which may have one or more substituents that are each independently a Group 2 substituent; or a pyrimidine ring which may have one or

more substituents that are each independently a Group 2 substituent;

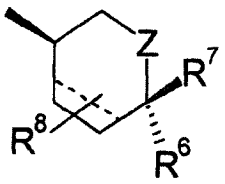
R^1 represents an aryl group which may have one or more substituents that are each independently a Group 3 substituent; a heteroaryl group which may have one or more substituents that are each independently a Group 3 substituent; a C_3-C_6 cycloalkyl group which may have one or more substituents that are each independently a Group 3 substituent; or a C_3-C_6 cycloalkenyl group which may have one or more substituents that are each independently a Group 3 substituent;

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

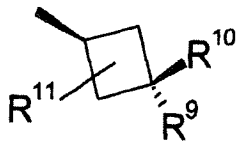
R^3 represents a group represented by the following general formulae (2), (3), or (4):



(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 that are each independently a Group 4 substituent; a carbamoyl group which may have one or more substituents that are each independently a Group 5 substituent; 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 that are each independently a C_1-C_6 alkyl group or 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 that are each independently a hydroxy group, a C_1-C_6 alkyl group, or 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 that are each independently a Group 4 substituent; a carbamoyl group which may have one or more substituents that are each independently a Group 5 substituent; 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 that are each independently a C_1-C_6 alkyl group or 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} is absent or represents one or more substituents that are each independently a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group;

wherein a Group 1 substituent is: 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, or a cyano group,

wherein a Group 2 substituent is: 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, or a C_1-C_6 alkoxy group,

wherein a Group 3 substituent is: 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', or -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 that are each independently a C_1-C_6 alkyl group or a hydroxy group,

wherein a Group 4 substituent is: 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, 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, 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 that are each independently a C_1-C_6 alkyl group or a hydroxy group, and

wherein a Group 5 substituent is: 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.

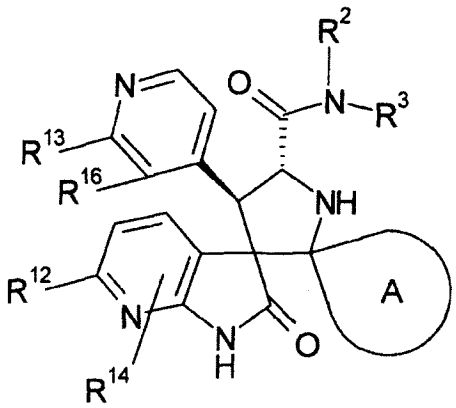
2. A compound according to claim 1 in which ring B represents a benzene ring which may have one or two substituents bonded to the 5- or 6-position that are each independently a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, a cyano group, or a C_1-C_6 alkoxy group.

3. A compound according to claim 1 in which ring B represents a pyridine ring which may have one substituent bonded to the 6-position that is a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, a cyano group, or a C_1-C_6 alkoxy group.

4. A compound according to any one of claims 1 to 3 in which R^1 represents a phenyl group which may have one chlorine atom bonded to the 3-position or a chlorine atom and a fluorine atom bonded to the 3- and 2-positions respectively.

5. A compound according to any one of claims 1 to 3 in which R^1 represents a pyridyl group which may have one chlorine atom bonded to the 2-position or a chlorine atom and a fluorine atom bonded to the 2- and 3-positions respectively.

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



(7)

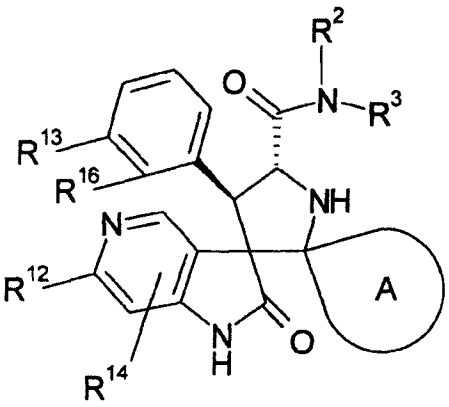
wherein

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} each independently represent a group which is a halogen atom, a C_1-C_6 alkyl group which may be substituted with one to three halogen atoms, or a cyano group; and

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

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



(8)

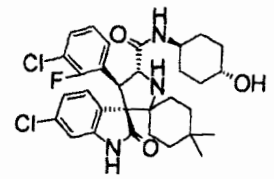
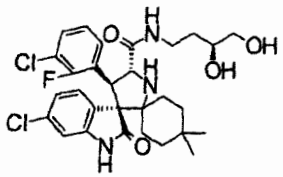
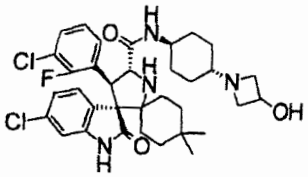
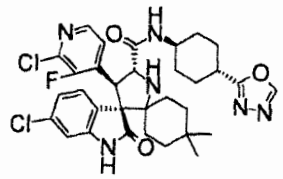
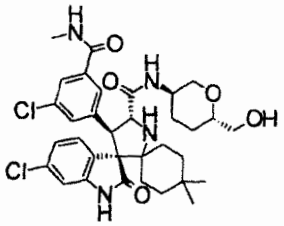
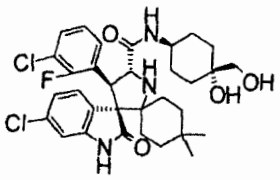
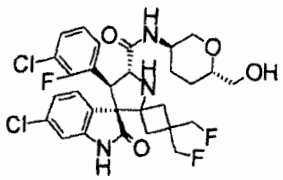
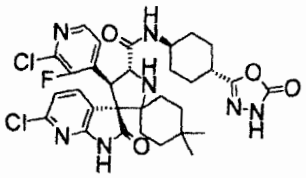
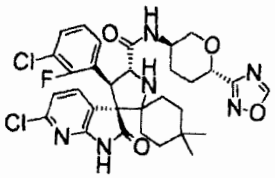
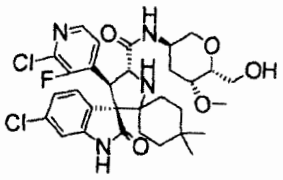
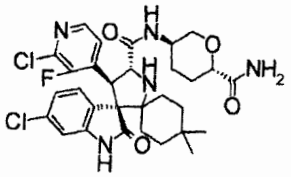
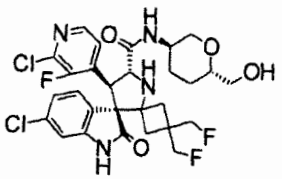
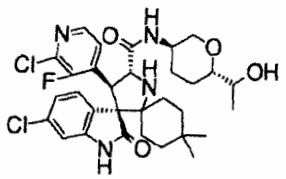
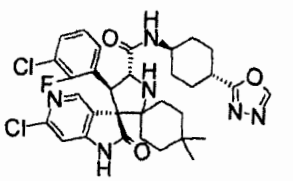
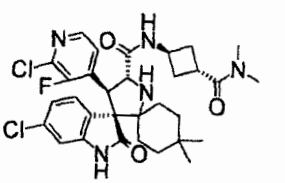
wherein

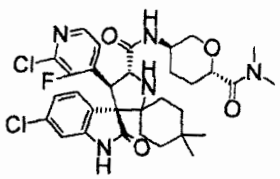
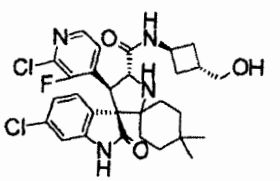
ring A, R^2, and R^3 have the same meanings as ring A, R^2, and R^3, respectively, in claim 1;

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

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

8. A compound which is:

or

or a salt thereof.

9. (2S,5R)-5-({[(3'R,4'S,5'R)-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'-yl]carbonyl}amino)tetrahydro-2H-pyran-2-carboxylic acid.

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 hydrochloride.

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 sulfate.

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 methanesulfonate.

13. (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.

14. (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.

15. (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.

16. (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.

17. An inhibitor of Mdm2 comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16.

18. An inhibitor of Mdm2 ubiquitin ligase comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16.

19. An inhibitor of p53-Mdm2 binding comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16.

20. An inhibitor of suppression of p53 transcription activity comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16.

21. An inhibitor of p53 degradation comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16.

22. A medicament comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16.

23. An anticancer agent comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16.

24. An anticancer agent 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. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16 and a pharmaceutically acceptable carrier.

26. Use of a compound as defined in any one of claims 1 to 8 or a salt thereof or a compound as defined in any one of claims 9 to 16 for the manufacture of an anticancer agent.