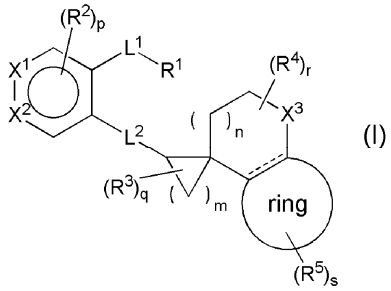
CLAIMS

1. A medicament comprising a combination of a compound represented by formula (I), a salt thereof, an N-oxide thereof, or a solvate thereof, and an immune checkpoint inhibitor,

[Chem. 1]



(I)

wherein R^1 represents $COOR^8$, SO_3H, SO_2NH_2, SO_2NHR^{8-1}, $CONHSO_2R^{8-1}$, SO_2NHCOR^{8-1}, or hydroxamic acid,

wherein R^8 represents a hydrogen atom, C1-4 alkyl, or benzyl, and

R^{8-1} represents C1-4 alkyl, C1-4 haloalkyl, a C3-10 carbon ring, or a three- to ten-membered heterocyclic ring, wherein the C3-10 carbon ring and the three- to ten-membered heterocyclic ring each may be substituted with C1-4 alkyl, C1-4 haloalkyl, C1-4 alkoxy, -O(C1-4 haloalkyl), C1-4 alkylthio, -S(C1-4 haloalkyl), halogen, or nitrile (here and below, "-CN"),

L^1 represents C1-5 alkylene, C2-5 alkenylene, or C2-5 alkynylene,

R^2 represents halogen, C1-4 alkyl, C1-4 alkoxy, C1-4 alkylthio, C2-4 alkenyl, C2-4 alkynyl, -O(C1-4 haloalkyl), -S(C1-4 haloalkyl), -C(O)(C1-4 alkyl), $-SO_2$(C1-4 alkyl), -CONH(C1-4 alkyl), $-CON(C1\text{-}4\ alkyl)_2$, -NHC(O)(C1-4 alkyl), -N(C1-4 alkyl)C(O)(C1-4 alkyl), $-NHSO_2$(C1-4 alkyl), $-N(C1\text{-}4\ alkyl)SO_2$(C1-4 alkyl), $-SO_2NH$(C1-4 alkyl), $-SO_2N(C1\text{-}4\ alkyl)_2$, $-NR^{17}R^{17}$, nitro, nitrile, a hydroxyl group, aldehyde (here and below, formyl), or carboxyl, wherein the C1-4 alkyl groups each may be substituted with halogen, and

the $(C1\text{-}4\ alkyl)_2$ in R^2 represents two independent C1-4 alkyl groups which may be the same or different,

X^1 represents CR^6 or a nitrogen atom, wherein R^6 represents a hydrogen atom or R^2,

X^2 represents CR^7, and R^7 represents a hydrogen atom, halogen or nitrile,

L^2 represents, -NHCO-, -CONH-, $-NHSO_2$-, or $-SO_2NH$-,

R^3 represents C1-4 alkyl or halogen,

R^4 represents halogen, C1-4 alkyl, or C1-4 haloalkyl,

X^3 represents methylene, an oxygen atom, a sulfur atom which may be oxidized, or NR^{10}, wherein R^{10} represents C1-4 alkyl, -C(O)(C1-4 alkyl), -C(O)O(C1-4 alkyl), or -SO_2(C1-4 alkyl), wherein the C1-4 alkyl groups each may be substituted with halogen,

the ring represents a benzene ring or a five- or six-membered monocyclic aromatic heterocyclic ring,

[Chem. 2]

represents a single bond or a double bond,

R^5 represents (1) halogen, (2) C1-4 alkyl, (3) carboxyl, (4) nitrile, (5) -$CONHR^{11}$, (6) -$C(O)R^{12}$, (7) -OR^{14}, (8) -$S(O)_tR^{15}$, (9) -CH_2R^{16}, (10) -$NR^{17}R^{17}$, (11) -$NHCOR^{11}$, (12) a C4-10 carbon ring, or (13) a four- to ten-membered heterocyclic ring, wherein the C4-10 carbon ring or the four- to ten-membered heterocyclic ring may be substituted with one to three R^{18}, wherein, when a plurality of R^{18} exists, the plurality of R^{18} each independently may be the same or different,

R^{11} represents C1-6 alkyl, C3-6 cycloalkyl, phenyl, or a four- to six-membered heterocyclic ring and may be substituted with one to three R^{13}, wherein, when a plurality of R^{13} exists, the plurality of R^{13} each independently may be the same or different, and

R^{13} represents halogen, C1-6 alkyl, C3-6 cycloalkyl, C1-4 alkoxy, a hydroxyl group, -$NR^{20}R^{21}$, benzene, or a four- to six-membered heterocyclic ring,

wherein R^{20} and R^{21} each independently represent a hydrogen atom or C1-4 alkyl,

R^{12} represents C1-6 alkyl, C3-6 cycloalkyl, benzene, or a four- to six-membered heterocyclic ring, wherein the C3-6 cycloalkyl, the benzene, and the four- to six-membered heterocyclic ring each independently may be substituted with halogen, C1-4 alkyl, or C1-4 alkoxy,

R^{14} represents a hydrogen atom, C1-6 alkyl, C3-6 cycloalkyl, benzene, or benzyl, wherein the C1-6 alkyl may be substituted with one to three R^{19}, wherein, when a plurality of R^{19} exists, the plurality of R^{19} each independently may be the same or different, and

R^{19} represents C1-4 alkoxy, -CONH(C1-4 alkyl), -$CON(C1\text{-}4\ alkyl)_2$, or a five- or six-membered monocyclic aromatic heterocyclic ring which may be substituted with a substituent selected from the group consisting of C1-4 alkyl and C1-4 haloalkyl,

wherein the $(C1\text{-}4\ alkyl)_2$ in R^{19} represents two independent C1-4 alkyl groups which may be the same or different,

R^{15} represents C1-6 alkyl, C3-6 cycloalkyl, benzene, or benzyl,

R^{16} represents a hydroxyl group or C1-4 alkoxy,

each R^{17} independently represents a hydrogen atom, C1-6 alkyl, or C3-6 cycloalkyl, and

R^{18} represents halogen, C1-6 alkyl, C3-6 cycloalkyl, C1-4 alkoxy, oxo, nitrile, a hydroxyl group, hydroxymethyl, 1-methyl-1-hydroxyethyl, (C1-4 alkyl)SO_2-, a four- to six-membered heterocyclic ring, (C1-4 alkyl)NH-, or (C1-4 alkyl)$_2$N-,

wherein the (C1-4 alkyl)$_2$ in R^{18} represents two independent C1-4 alkyl groups which may be the same or different,

m represents an integer of 1 ,

n represents an integer of 0 to 4,

p represents an integer of 0 to 2,

q represents an integer of 0 to 6,

r represents an integer of 0 to 6,

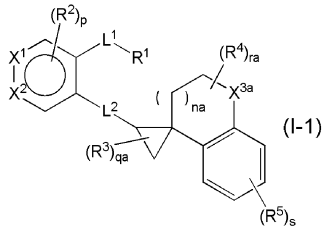
s represents an integer of 0 to 2,

t represents an integer of 0 to 2, and

R^2, R^3, R^4, and R^5 each independently may be the same or different when p, q, r, and s are each an integer of 2 or more.

2. The medicament according to claim 1, wherein the compound represented by formula (I) is a compound represented by formula (I-1),

[Chem. 3]



(I-1)

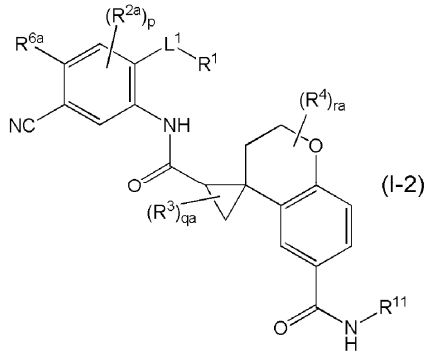
wherein na represents an integer of 0 or 1, qa represents an integer of 0 to 3, ra represents an integer of 0 to 4, X^{3a} represents methylene or an oxygen atom, and the other symbols have the same meanings as the symbols defined in claim 1.

3. The medicament according to claim 1 or claim 2, wherein s is an integer of 1 to 2, and at least one R^5 is -CONHR^{11}.

4. The medicament according to any one of claim 1 to claim 3, wherein L^2 is -NHCO- or -CONH-.

5. The medicament according to any one of claim 1 to claim 4, wherein the compound represented by formula (I) is a compound represented by formula (I-2),

[Chem. 4]



wherein R^{2a} represents halogen, R^{6a} represents a hydrogen atom or halogen, and the other symbols have the same meanings as the symbols defined in claim 1 and claim 2.

6. The medicament according to claim 1, wherein the compound represented by formula (I) is

(1) 4-[4-cyano-2-({[(2'R,4S)-6-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(2) 4-{4-cyano-2-[({(2'R,4S)-6-[(cyclopropylmethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(3) 4-{4-cyano-2-[({(2'R,4S)-6-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(4) 4-{4-cyano-2-[({(2'R,4S)-6-[(2-methyl-2-propanyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(5) 4-[4-cyano-2-({[(2'R,4S)-6-{[(2S)-1-methoxy-2-propanyl]carbamoyl}-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(6) 4-{4-cyano-2-[({(2'R,4S)-6-[(1-methyl-1H-pyrazol-3-yl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(7) 4-[4-cyano-2-({[(2'R,4S)-6-(cyclopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(8) 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(9) 4-[4-cyano-2-({[(2'R,4S)-6-(cyclopentylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(10) 4-{2-[({(2'R,4S)-6-[(2S)-2-butanylcarbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]-4-cyanophenyl}butanoic acid,

(11) 4-{4-cyano-2-[({(2'R,4S)-6-[(trans-4-hydroxycyclohexyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(12) 4-{4-cyano-2-[({(2'R,4S)-6-[(cis-4-hydroxycyclohexyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(13) 4-[4-cyano-2-({[(2'R,4S)-6-(2-pyridinylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(14) 4-[4-cyano-2-({[(2'R,4S)-6-(3-pyridazinylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(15) 4-[4-cyano-2-({[(2'R,4S)-6-(cyclobutylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(16) 4-[4-cyano-2-({[(2'R,4S)-6-{[1-(2-methyl-2-propanyl)-1H-pyrazol-4-yl]carbamoyl}-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(17) 4-[4-cyano-2-({[(2'R,4S)-6-(tetrahydro-2H-pyran-4-ylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(18) 4-[4-cyano-2-({[(2'R,4S)-6-(propylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(19) 4-{4-cyano-2-[({(2'R,4S)-6-[(2-ethoxyethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(20) 4-[4-cyano-2-({[(2'R,4S)-6-(ethylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(21) 4-[4-cyano-2-({[(1R,2R)-6'-(methylcarbamoyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl]carbonyl}amino)phenyl]butanoic acid,

(22) 4-{4-cyano-2-[({(1R,2R)-6'-[(2-methoxyethyl)carbamoyl]-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl}carbonyl)amino]phenyl}butanoic acid,

(23) 4-{4-cyano-2-[({(1R,2R)-6'-[(1-methyl-1H-pyrazol-4-yl)carbamoyl]-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl}carbonyl)amino]phenyl}butanoic acid,

(24) 4-[4-cyano-2-({[(2'R,4S)-7-fluoro-6-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(25) 4-{4-cyano-2-[({(2'R,4S)-7-fluoro-6-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(26) 4-[4-cyano-2-({[(2'R,4S)-7-fluoro-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(27) 4-[4-cyano-2-({[(2'R,4S)-7-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(28) 4-{4-cyano-2-[({(2'R,4S)-7-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(29) 4-[4-cyano-2-({[(2'R,4S)-7-methoxy-6-(methylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(30) 4-{4-cyano-2-[({(2'R,4S)-7-methoxy-6-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(31) 4-[4-cyano-2-({[(2'R,3S)-5-(methylcarbamoyl)-2H-spiro[1-benzofuran-3,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(32) 4-{4-cyano-2-[({(2'R,3S)-5-[(2-methoxyethyl)carbamoyl]-2H-spiro[1-benzofuran-3,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(33) 4-[4-cyano-2-({[(1S,2R)-6'-[(2-methoxyethyl)carbamoyl]-3',3'-dimethyl-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl]carbonyl}amino)phenyl]butanoic acid, or

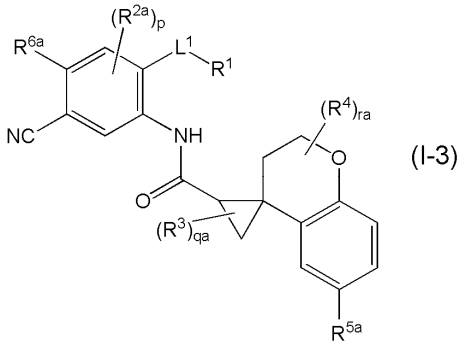
(34) 4-[4-cyano-2-({[(1S,2R)-3',3'-dimethyl-6'-(methylcarbamoyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl]carbonyl}amino)phenyl]butanoic acid.

7. The medicament according to claim 1 or claim 2, wherein s is an integer of 1 to 2, and at least one R^5 is a C4-10 carbon ring which may be substituted with one to three R^{18} or a four- to ten-membered heterocyclic ring which may be substituted with one to three R^{18}, wherein, when a plurality of R^{18} exists, the plurality of R^{18} each independently may be the same or different.

8. The medicament according to claim 7, wherein L^2 is -NHCO- or -CONH-.

9. The medicament according to any one of claim 1, claim 2, claim 7, and claim 8, wherein the compound represented by formula (I) is a compound represented by formula (I-3),

[Chem. 5]



(I-3)

wherein R^{5a} is a C4-10 carbon ring which may be substituted with one to three R^{18} or a four- to ten-membered heterocyclic ring which may be substituted with one to three R^{18}, wherein, when a plurality of R^{18} exists, the plurality of R^{18} each independently may be the same or different, and the other symbols have the same meanings as the symbols defined in claim 1, claim 2, and claim 5.

10. The medicament according to claim 1, wherein the compound represented by formula (I) is

(1) 4-[4-cyano-2-({[(2'R,4S)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(2) 4-[4-cyano-2-({[(2'R,4S)-6-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(3) 4-[4-cyano-2-({[(2'R,4S)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(4) 4-[4-cyano-2-({[(2'R,4S)-6-(3-pyridinyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(5) 4-[4-cyano-2-({[(2'R,4S)-6-(1H-pyrazol-1-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(6) 4-[4-cyano-2-({[(2'R,4S)-6-(1H-pyrazol-5-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(7) 4-[4-cyano-2-({[(2'R,4S)-6-(4-pyridazinyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(8) 4-[4-cyano-2-({[(2'R,4S)-6-(2-oxo-1-pyrrolidinyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(9) 4-[4-cyano-2-({[(2'R,4S)-6-(6-methoxy-3-pyridinyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(10) 4-{4-cyano-2-[({(2'R,4S)-6-[6-(1H-pyrazol-1-yl)-3-pyridinyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(11) 4-{4-cyano-2-[({(2'R,4S)-6-[6-(dimethylamino)-3-pyridinyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(12) 4-[4-cyano-2-({[(2'R,4S)-6-(6-methyl-3-pyridinyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(13) 4-{4-cyano-2-[({(2'R,4S)-6-[6-(methylamino)-3-pyridinyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid,

(14) 4-[4-cyano-2-({[(2'R,4S)-6-(2-pyridinyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(15) 4-[4-cyano-2-({[(2'R,4S)-6-(1,3-thiazol-2-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(16) 4-[4-cyano-2-({[(2'R,4S)-6-(1,3-oxazol-2-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(17) 4-[4-cyano-2-({[(2'R,4S)-6-(1-methyl-1H-1,2,3-triazol-4-yl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(18) 4-[4-cyano-2-({[(2'R,4S)-6-(3-pyridazinyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid,

(19) 4-[4-cyano-2-({[(2'R,3S)-5-(3-pyridinyl)-2H-spiro[1-benzofuran-3,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid, or

(20) 4-[4-cyano-2-({[(1S,2R)-3',3'-dimethyl-6'-(3-pyridinyl)-2',3'-dihydrospiro[cyclopropane-1,1'-inden]-2-yl]carbonyl}amino)phenyl]butanoic acid.

11. A medicament comprising a combination of 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino)phenyl]butanoic acid, a salt thereof, or a solvate thereof, and an immune checkpoint inhibitor.

12. A medicament comprising a combination of 4-{4-cyano-2-[({(2'R,4S)-6-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid, a salt thereof, or a solvate thereof, and an immune checkpoint inhibitor.

13. The medicament according to any one of claim 1 to claim 12, wherein the immune checkpoint inhibitor is an inhibitor of an immune checkpoint molecule selected from the group

consisting of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM3, BTLA, B7H3, B7H4, CD160, CD39, CD73, A2aR, KIR, VISTA, IDO1, Arginase I, TIGIT, and CD115.

14. The medicament according to any one of claim 1 to claim 13, wherein the immune checkpoint inhibitor is an anti-PD-1 antibody.

15. The medicament according to any one of claim 1 to claim 13, wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody.

16. The medicament according to any one of claim 1 to claim 15 for use in the treatment of cancer.

17. Use of the medicament according to any one of claims 1 to claim 15, in the manufacture of a medicament for the treatment of malignant lymphoma, head and neck cancer, esophageal cancer, stomach cancer, colorectal cancer, pancreatic cancer, lung cancer, renal cancer, or malignant melanoma.

18. A therapeutic agent against cancer comprising a combination of the compound represented by formula (I) according to claim 1, a salt thereof, a solvate thereof, or an N-oxide thereof, and an immune checkpoint inhibitor.

19.A combination of the compound represented by formula (I) according to claim 1, a salt thereof, a solvate thereof, or an N-oxide thereof, and an immune checkpoint inhibitor for use in the treatment of cancer.

20. Use of a combination of the compound represented by formula (I) according to claim 1, a salt thereof, a solvate thereof, or an N-oxide thereof, and an immune checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer.

21. Use of a combination of 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4, 1'-cyclopropan]-2'-yl]carbonyl}amino) phenyl]butanoic acid, a salt thereof, or a solvate thereof, and an immune checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer.

22. Use of a combination of 4-{4-cyano-2-[({(2'R,4S)-6-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro [chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid, a salt

thereof, or a solvate thereof, and an immune checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer.

23. Use of the compound represented by formula (I) according to claim 1, a salt thereof, an N-oxide thereof, or a solvate thereof in the manufacture of a medicament for the treatment of cancer wherein the medicament is to be administered in combination with an immune checkpoint inhibitor.

24. Use of 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino) phenyl]butanoic acid, a salt thereof, or a solvate thereof, in the manufacture of a medicament for the treatment of cancer wherein the medicament is to be administered in combination with an immune checkpoint inhibitor.

25. Use of 4-{4-cyano-2-[({(2'R,4S)-6-[(2-methoxyethyl)carbamoyl]-2,3-dihydrospiro [chromene-4,1'-cyclopropan]-2'-yl}carbonyl)amino]phenyl}butanoic acid, a salt thereof, or a solvate thereof in the manufacture of a medicament for the treatment of cancer wherein the medicament is to be administered in combination with an immune checkpoint inhibitor.

26. Use of an immune checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer wherein the medicament is to be administered in combination with 4-[4-cyano-2-({[(2'R,4S)-6-(isopropylcarbamoyl)-2,3-dihydrospiro[chromene-4,1'-cyclopropan]-2'-yl]carbonyl}amino) phenyl]butanoic acid, a salt thereof, or a solvate thereof.

27. The use according to any one of claim 20 to claim 26, wherein the immune checkpoint inhibitor is an inhibitor of an immune checkpoint molecule selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM3, BTLA, B7H3, B7H4, CD160, CD39, CD73, A2aR, KIR, VISTA, IDO1, Arginase I, TIGIT, and CD115.

28. The use according to any one of claim 20 to claim 27, wherein the immune checkpoint inhibitor is an anti-PD-1 antibody.

29. The use according to any one of claim 20 to claim 27, wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody.

30. The use according to any one of claim 20 to claim 29, wherein the cancer is malignant

lymphoma, head and neck cancer, esophageal cancer, stomach cancer, colorectal cancer, pancreatic cancer, lung cancer, renal cancer, or malignant melanoma.