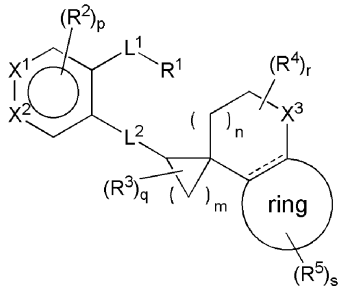
CLAIMS

[Claim 1]

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

[Chem. 1]



(I)

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

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

$R^{8\text{-}1}$ 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 or a nitrogen atom, wherein R^7 represents a hydrogen atom, R^2, or $-L^3\text{-}R^9$, wherein L^3 represents methylene, an oxygen atom, or a sulfur atom which may be

oxidized, and R^9 represents a four- to ten-membered heterocyclic ring which may be substituted with a substituent selected from the group consisting of halogen, C1-4 alkyl, and C1-4 haloalkyl,

L^2 represents $-CH_2CH_2-$, -CH=CH-, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$, $-SCH_2-$, $-CH_2S(O)-$, $-S(O)CH_2-$, $-CH_2SO_2-$, $-SO_2CH_2-$, $-CH_2NH-$, $-NHCH_2-$, -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(C1-4 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 (C1-4 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 to 4,

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 4,

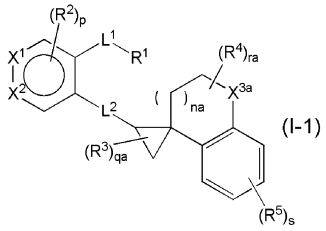
t represents an integer of 0 to 2, and

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.)

[Claim 2]

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

[Chem. 3]



(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.)

[Claim 3]

The medicament according to claim 1 or claim 2, wherein s is an integer of 1 to 4, and at least one R^5 is -CONHR^{11}.

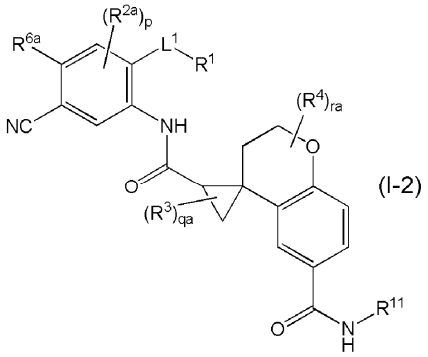
[Claim 4]

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

[Claim 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.)

[Claim 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.

[Claim 7]

The medicament according to claim 1 or claim 2, wherein s is an integer of 1 to 4, 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.

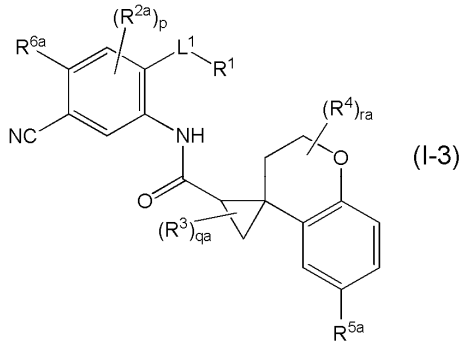
[Claim 8]

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

[Claim 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.)

[Claim 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.

[Claim 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, a solvate thereof, or a prodrug of these and an immune checkpoint inhibitor.

[Claim 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, a solvate thereof, or a prodrug of these and an immune checkpoint inhibitor.

[Claim 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.

[Claim 14]

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

[Claim 15]

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

[Claim 16]

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

[Claim 17]

Use of the medicament according to any one of claims 1-15, in the manufacture of a medicament for the treatment of stomach cancer, colorectal cancer, lung cancer, renal cancer, or malignant melanoma.

[Claim 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, an N-oxide thereof, or a prodrug of these and an immune checkpoint inhibitor.

[Claim 19]

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

[Claim 20]

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

[Claim 21]

A medicament for use in the treatment of cancer wherein the medicament is to be administered as a combination of the compound represented by formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof, or a prodrug of these and an immune checkpoint inhibitor.

[Claim 22]

A therapeutic agent against cancer containing the compound represented by formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof, or a prodrug of these as an active ingredient wherein the agent is to be administered in combination with an immune checkpoint inhibitor.

[Claim 23]

A therapeutic agent against cancer containing an immune checkpoint inhibitor as an active ingredient wherein the agent is to be administered in combination with the compound represented by formula (I) according to claim 1, a salt thereof, an N-oxide thereof, a solvate thereof, or a prodrug of these.

[Claim 24]

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

[Claim 25]

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, a solvate thereof, or a prodrug of these and an immune checkpoint inhibitor in the manufacture of a therapeutic agent for the treatment of cancer.

[Claim 26]

A therapeutic agent against cancer containing 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, a solvate thereof, or a prodrug of these as an active

ingredient wherein the agent is to be administered in combination with an immune checkpoint inhibitor.

[Claim 27]

A therapeutic agent against cancer containing 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, a solvate thereof, or a prodrug of these as an active ingredient wherein the agent is to be administered in combination with an immune checkpoint inhibitor.

[Claim 28]

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, a solvate thereof, or a prodrug of these in the manufacture of a therapeutic agent for the treatment of cancer wherein the therapeutic agent is to be administered in combination with an immune checkpoint inhibitor.

[Claim 29]

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, a solvate thereof, or a prodrug of these in the manufacture of a therapeutic agent for the treatment of cancer wherein the therapeutic agent is to be administered in combination with an immune checkpoint inhibitor.