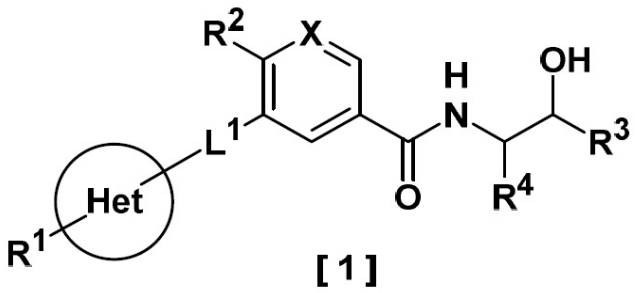
Claims

[Claim 1]

A compound of the formula [1]:



[1]

or a pharmaceutically acceptable salt thereof, or a solvate thereof,

wherein

R^1 is one or two groups selected from the group consisting of hydrogen, halogen, an optionally-substituted alkyl, an optionally-substituted amino, an optionally-substituted alkoxy, an optionally-substituted aryl, haloalkyl, cycloalkyl, an optionally-substituted sulfonyl, cyano, an optionally-substituted carbamoyl, heteroaryl and dialkylphosphoryl;

Het is a 5- to 10-membered heteroaryl;

L^1 is a bond, -CO-NH-, $-CR^a=CR^b-$ or -C≡C-, and the carbonyl group (C=O) in -CO-NH- is bonded to Het and $-CR^a$ in $-CR^a=CR^b-$ is bonded to Het;

R^a is hydrogen or halogen;

R^b is hydrogen or halogen;

X is N or $C-R^c$ wherein R^c is hydrogen or halogen;

R^2 is hydrogen, ethyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl; and

R^3 is hydrogen, and R^4 is hydrogen, an optionally-substituted phenyl or an optionally-substituted alkyl, or

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally-substituted C_3-C_8 cycloalkyl.

[Claim 2]

The compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1 wherein

R^1 is one or two groups selected from the group consisting of hydrogen, halogen, an optionally-substituted alkyl, an optionally-substituted amino, an optionally-substituted alkoxy, an optionally-substituted aryl, haloalkyl and an optionally-substituted carbamoyl;

Het is a 5- to 10-membered heteroaryl;

L^1 is a bond, $-CR^a=CR^b-$, -CO-NH- or $-C\equiv C-$, and the carbonyl group (C=O) in -CO-NH- is bonded to Het and $-CR^a$ in $-CR^a=CR^b-$ is bonded to Het;

R^a is hydrogen or halogen;

R^b is hydrogen or halogen;

X is N or $C-R^c$ wherein R^c is hydrogen or halogen;

R^2 is ethyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl; and

R^3 is hydrogen, and R^4 is hydrogen, an optionally-substituted phenyl or an optionally-substituted alkyl, or

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally-substituted C_3-C_8 cycloalkyl.

[Claim 3]

The compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1 wherein

R^1 is one or two groups selected from the group consisting of hydrogen, an optionally-substituted alkyl, an optionally-substituted amino and an optionally-substituted carbamoyl;

Het is a 5- to 10-membered heteroaryl;

L^1 is a bond, $-CR^a=CR^b-$ or $-C\equiv C-$, and $-CR^a$ in $-CR^a=CR^b-$ is bonded to Het;

R^a is hydrogen;

R^b is halogen;

X is N or $C-R^c$ wherein R^c is hydrogen;

R^2 is C_1–C_6 haloalkoxy or C_1–C_6 haloalkyl; and

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally-substituted C_3–C_8 cycloalkyl.

[Claim 4]

The compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1 wherein

R^1 is one or two groups selected from the group consisting of hydrogen, alkyl, amino and carbamoyl;

Het is pyrimidinyl, pyridyl, pyrazinyl, pyrazolyl, pyridinyl, imidazo[1,5-a]pyridyl, oxazolyl, thiazolyl or pyrazyl;

L^1 is a bond, $-CR^a=CR^b-$ or $-C\equiv C-$, and $-CR^a$ in $-CR^a=CR^b-$ is bonded to Het;

R^a is hydrogen;

R^b is halogen;

X is N or $C-R^c$ wherein R^c is hydrogen;

R^2 is C_1–C_6 fluoroalkoxy, C_1–C_6 difluoroalkoxy, C_1–C_6 trifluoroalkoxy, C_1–C_6 fluoroalkyl, C_1–C_6 difluoroalkyl or C_1–C_6 trifluoroalkyl; and

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally-substituted cyclopentyl, an optionally-substituted cyclohexyl, or an optionally-substituted spiro[2.4]heptanyl.

[Claim 5]

The compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1 wherein

R^1 is a group selected from the group consisting of hydrogen, alkyl, amino and carbamoyl;

Het is pyrimidinyl, pyridyl, pyrazinyl, pyrazolyl, pyridinyl, imidazo[1,5-a]pyridyl, oxazolyl, thiazolyl or pyrazyl;

L^1 is a bond, $-CR^a=CR^b-$ or $-C\equiv C-$, and $-CR^a$ in $-CR^a=CR^b-$ is bonded to Het;

R^a is hydrogen;

R^b is halogen;

X is N or $C-R^c$ wherein R^c is hydrogen;

R^2 is C_1-C_6 fluoroalkoxy, C_1-C_6 difluoroalkoxy, C_1-C_6 trifluoroalkoxy, C_1-C_6 fluoroalkyl, C_1-C_6 difluoroalkyl or C_1-C_6 trifluoroalkyl; and

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form cyclopentyl substituted with one or two groups selected from the group consisting of halogen and haloalkoxy, cyclohexyl substituted with one or two groups selected from the group consisting of halogen and haloalkoxy, or spiro[2.4]heptanyl substituted with one or two groups selected from the group consisting of halogen and haloalkoxy.

[Claim 6]

The compound according to Claim 1 selected from the group consisting of the following compounds (1) to (47):

(1) 4-(difluoromethoxy)-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]-3-[(pyrimidin-5-yl)ethynyl]benzamide,

(2) 4-(difluoromethoxy)-3-[2-(5-fluoropyridin-3-yl)ethynyl]-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]benzamide,

(3) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]benzamide,

(4) 3-[2-(5-aminopyrazin-2-yl)ethynyl]-4-(difluoromethoxy)-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]benzamide,

(5) 3-[2-(2-amino-4-methoxypyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]benzamide,

(6) 4-(difluoromethoxy)-N-[(1S,2S,4S)-2-hydroxy-4-

(trifluoromethoxy)cyclopentyl]-3-[2-(1-methyl-1H-pyrazol-4-yl)ethynyl]benzamide,
(7) 3-[2-(5-aminopyrazin-2-yl)ethynyl]-4-(difluoromethoxy)-N-[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]benzamide,
(8) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(1S)-1-(3-fluorophenyl)-2-hydroxyethyl]benzamide,
(9) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(2S)-1-hydroxy-3-(4-methoxyphenyl)propan-2-yl]benzamide,
(10) 3-[(1Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-4-(difluoromethoxy)-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]benzamide,
(11) 5-[(1Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-6-ethyl-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]pyridine-3-carboxamide,
(12) 3-[(1Z)-2-(2-aminopyrimidin-5-yl)-1-fluoroethenyl]-4-(difluoromethoxy)-N-[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]benzamide,
(13) 4-(difluoromethoxy)-3-fluoro-5-[(1Z)-1-fluoro-2-(5-methoxypyridin-3-yl)ethenyl]-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]benzamide,
(14) 7-(5-{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl}-2-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine-3-carboxamide,
(15) 5-{3-carbamoylimidazo[1,5-a]pyridin-7-yl}-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]-6-(trifluoromethyl)pyridine-3-carboxamide,
(16) N-(2-ethyl-5-{[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]carbamoyl}phenyl)-2-phenyl-1,3-oxazole-5-carboxamide,
(17) 2-(cyclopropylmethyl)-N-(2-ethyl-5-{[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]carbamoyl}phenyl)-1,3-thiazole-5-carboxamide,
(18) 4-(difluoromethoxy)-N-[(5S,6S)-6-hydroxyspiro[2.4]heptan-5-yl]-3-[2-(pyrimidin-5-

yl)ethynyl]benzamide,
(19) 4-(difluoromethoxy)-3-[2-(5-fluoropyridin-3-yl)ethynyl]-N-[(5S,6S)-6-hydroxyspiro[2.4]heptan-5-yl]benzamide,
(20) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-N-[(1S,2S)-5,5-difluoro-2-hydroxycyclohexyl]-4-(difluoromethoxy)benzamide,
(21) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(5S,6S)-6-hydroxyspiro[2.4]heptan-5-yl]benzamide,
(22) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]benzamide,
(23) 3-[2-(2-amino-4-methoxypyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(5S,6S)-6-hydroxyspiro[2.4]heptan-5-yl]benzamide,
(24) 4-(difluoromethoxy)-N-[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]-3-[2-(1-methyl-1H-pyrazol-4-yl)ethynyl]benzamide,
(25) 3-[(1Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-N-[(1S,2S)-5,5-difluoro-2-hydroxycyclohexyl]-4-(difluoromethoxy)benzamide,
(26) 3-[(1Z)-2-(5-aminopyrazin-2-yl)-2-fluoroethenyl]-4-(difluoromethoxy)-N-[(5S,6S)-6-hydroxyspiro[2.4]heptan-5-yl]benzamide,
(27) 7-(5-{[(1S,2S)-5,5-difluoro-2-hydroxycyclohexyl]carbamoyl}-2-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine-3-carboxamide,
(28) 7-(5-{[(5S,6S)-6-hydroxyspiro[2.4]heptan-5-yl]carbamoyl}-2-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine-3-carboxamide,
(29) 7-(5-{[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]carbamoyl}-2-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine-3-carboxamide,
(30) 5-{3-carbamoylimidazo[1,5-a]pyridin-7-yl}-N-[(2S)-1-

hydroxy-4-(trifluoromethoxy)butan-2-yl]-6-(trifluoromethyl)pyridine-3-carboxamide,

(31) 7-(5-{[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]carbamoyl}-2-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine-3-carboxamide,

(32) N-(2-ethyl-5-{[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]carbamoyl}phenyl)-5-(3-fluorophenyl)pyridine-3-carboxamide,

(33) N-(2-ethyl-5-{[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]carbamoyl}phenyl)-5-(3-fluorophenyl)pyridine-3-carboxamide,

(34) 3-[(1Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-(difluoromethoxy)-N-[(1S)-1-(3-fluorophenyl)-2-hydroxyethyl]benzamide,

(35) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-N-[(2S)-1-(4-chlorophenyl)-3-hydroxypropan-2-yl]-4-(difluoromethoxy)benzamide hydrochloride,

(36) 3-[2-(2-aminopyrimidin-5-yl)ethynyl]-4-(difluoromethoxy)-N-[(1S)-2-hydroxy-1-phenylethyl]benzamide hydrochloride,

(37) 3-[(1Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-N-[(1S,2S)-5,5-difluoro-2-hydroxycyclohexyl]-4-(difluoromethoxy)benzamide,

(38) 3-[(1Z)-2-(2-aminopyrimidin-5-yl)-2-fluoroethenyl]-4-(difluoromethoxy)-N-[(1S,2S)-2-hydroxycyclohexyl]benzamide,

(39) 3-[(1Z)-2-(2-aminopyrimidin-5-yl)-1-fluoroethenyl]-4-(difluoromethoxy)-N-[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]benzamide,

(40) 3-[(1Z)-2-(2-aminopyrimidin-5-yl)-1-fluoroethenyl]-4-(difluoromethoxy)-N-[(5S,6S)-6-hydroxyspiro[2.4]heptan-5-yl]benzamide,

(41) 5-{3-carbamoylimidazo[1,5-a]pyridin-7-yl}-N-[(1S,2S)-5,5-difluoro-2-hydroxycyclohexyl]-6-(trifluoromethyl)pyridine-3-carboxamide,

(42) 5-(cyclopropylmethoxy)-N-(2-ethyl-5-{[(1S,2S,4S)-2-hydroxy-4-

(trifluoromethoxy)cyclopentyl]carbamoyl}phenyl)pyridine-3-carboxamide,
(43) 5-(cyclopropylmethoxy)-N-(2-ethyl-5-{[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]carbamoyl}phenyl)pyridine-3-carboxamide,
(44) 2-[(cyclopropylmethyl)amino]-N-(2-ethyl-5-{[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]carbamoyl}phenyl)-1,3-thiazole-5-carboxamide,
(45) 2-[(cyclopropylmethyl)amino]-N-(2-ethyl-5-{[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]carbamoyl}phenyl)-1,3-thiazole-5-carboxamide,
(46) 2-cyclopropyl-N-(2-ethyl-5-{[(1S,2S,4S)-2-hydroxy-4-(trifluoromethoxy)cyclopentyl]carbamoyl}phenyl)-1,3-thiazole-5-carboxamide, and
(47) 2-(cyclopropylmethyl)-N-(2-ethyl-5-{[(2S)-1-hydroxy-4-(trifluoromethoxy)butan-2-yl]carbamoyl}phenyl)-1,3-thiazole-5-carboxamide,
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[Claim 7]
A pharmaceutical composition containing the compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1, as an active ingredient.

[Claim 8]
A DDR1 kinase inhibiting agent containing the compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1, as an active ingredient.

[Claim 9]
A prophylactic or therapeutic agent, containing the compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1, for use as a medicament.

[Claim 10]

Use of a prophylactic or therapeutic agent containing the compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, according to Claim 1, in the manufacture of a medicament for inhibiting DDR1 kinase in a subject in need thereof with diseases in which DDR1 kinase is involved.

[Claim 11]

The use of Claim 10, wherein the diseases in which DDR1 kinase is involved comprises: Alport syndrome, IgA nephropathy, Goodpasture syndrome, anti-glomerular basement membrane nephritis, lupus nephritis, ANCA-related nephritis, diabetic nephropathy, purpura nephritis, focal segmental glomerulosclerosis, chronic renal failure, microvascular nephrotic syndrome, mesangial proliferative glomerulonephritis, membranous proliferative glomerulonephritis, semilunar glomerulonephritis, membranous nephropathy, pulmonary fibrosis, myelofibrosis, liver fibrosis, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoid leukemia, chronic lymphoid leukemia, Hodgkin lymphoma, non-Hodgkin's lymphoma, glioma, non-small cell lung cancer, small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, colon cancer or osteoarthritis.