HETEROCYCLIC RIP1 KINASE INHIBITORS

FIELD

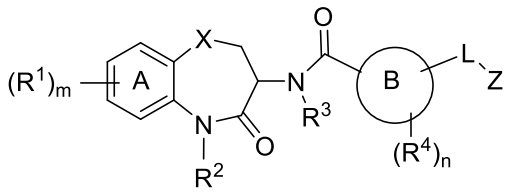
The present disclosure concerns compounds and methods of making and using the compounds, such as for inhibiting receptor-interacting protein-1 ("RIP1") kinase, and for treating diseases and/or conditions related to RIP1.

BACKGROUND

Receptor-interacting protein-1 kinase (referred to herein as "RIP1") belongs to the tyrosine kinase-like family and is a serine/threonine protein kinase involved in innate immune signaling. RIP1 plays a central role in regulating cell signaling and its role in programmed cell death has been linked to various inflammatory diseases, such as inflammatory bowel disease, psoriasis, and other diseases and/or conditions associated with inflammation and/or necroptotic cell death.

SUMMARY

In a first aspect of the present disclosure, there is provided a compound, according to Formula I



Formula I

or a pharmaceutically acceptable salt, N-oxide, solvate, tautomer, or stereoisomer thereof, wherein:

ring B is heteroaryl;

each R^1 independently is halogen or -linker-R^6 group, wherein the linker is a bond or R^a, provided that R^a is not H or D, and R^6 is heterocyclyl, R^b, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

R^2 is R^a;

R^3 is R^a;

if present, each R^4 independently is R^e;

L is a heteroatom or R^a, provided that R^a is not H or D;

X is CH_2 or O;

Z is heteroaryl;

m is 1, 2, 3, or 4;

n is 0, 1 or 2;

R^a is independently for each occurrence H or D, except for embodiments where L is R^a, C_{1-10}aliphatic, C_{1-10}haloaliphatic, C_{5-10}aromatic, C_{3-6}heterocyclic, or C_{3-10}spiroheterocyclic;

R^b is independently for each occurrence -OH, -SH, -OR^c, -SR^c, -NR^dR^d, -$Si(R^a)_3$, -C(O)OH, -$C(O)OR^c$, -$C(O)NR^dR^d$, -$OC(O)NR^dR^d$, -$OC(O)C_{1-10}$alkyl substituted with one or two NR^dR^d, carboxyl, or a combination thereof, and optionally further substituted with an aromatic moiety, -SH, -O-acyl, or -$C(O)NH_2$;

R^c is independently for each occurrence C_{1-10}alkyl, which can be substituted with 1, 2 or 3 R^e, C_{2-10}alkenyl, which can be substituted with 1, 2 or 3 R^e, C_{2-10}alkynyl, which can be substituted with 1, 2 or 3 R^e, C_{3-6}cycloalkyl, which can be substituted with 1, 2 or 3 R^e, or C_{5-10}aromatic, which can be substituted with 1, 2 or 3 R^e;

R^d is independently for each occurrence H; C_{1-6}alkyl, which can be substituted with 1, 2 or 3 R^e or a C_{3-9}heterocyclyl; C_{3-6}cycloalkyl, which can be substituted with 1, 2 or 3 R^e; C_{3-6}heterocyclic, which can be substituted with 1, 2 or 3 R^e; C_{5-10}aryl, which can be substituted with 1, 2 or 3 R^b; C_{5-10}heteroaryl, which can be substituted with 1, 2 or 3 R^e; or two R^d groups together with the nitrogen bound thereto provide a C_{3-9}heterocyclic, which can be substituted with one or more R^e), or a C_{5-10}heteroaryl, which can be substituted with one or more R^e;

R^e is independently for each occurrence halogen, C_{1-6}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{5-10}heteroaryl, or -OR^a; and

R^f is independently for each occurrence –alkyl-phosphate, R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C_{2-6}alkenyl group, a C_{3-6}cycloalkyl group, which can be substituted with one or more R^e, or a C_{3-10}heterocyclic, which can be substituted with one or more R^e or acyl.

In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound as disclosed herein.

In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a composition thereof, in the manufacture of a medicament, wherein the medicament is to be administered to a subject.

In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a composition thereof, in the manufacture of a medicament, wherein the medicament is to be contacted with a receptor-interacting protein-1 (RIP1) kinase.

In another aspect of the present disclosure, there is provided a use of (i) a therapeutically effective amount of the compound as disclosed herein, or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof; or (ii) a therapeutically effective amount of a pharmaceutical composition of the compound, in the manufacture of a medicament for treating a disease in a subject; wherein the subject has, or is suspected of having or developing, the disease, wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase.

In yet another aspect of the present disclosure, there is provided a compound that is

I-51: (*S*)-4-((2-fluoropyridin-3-yl)methyl)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide;

I-52: (*S*)-4-((2-fluoropyridin-3-yl)methyl)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide;

I-53: (*S*)-4-((6-fluoropyridin-2-yl)methyl)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide;

I-54: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-55: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-56: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-57: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-58: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-59: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-60: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-61: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-ylmethyl)picolinamide

I-62: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-ylmethyl)picolinamide

I-63: (*S*)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-64: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-2-ylmethyl)picolinamide

I-65: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-66: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-67: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-68: (*S*)-4-((3,5-dimethylisoxazol-4-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-69: (*S*)-4-((3,5-dimethylisoxazol-4-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-70: (*S*)-4-((1*H*-pyrazol-1-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-71: (*S*)-4-((1*H*-pyrazol-1-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-72: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)methyl)picolinamide

I-73: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)methyl)picolinamide

I-74: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylpyridin-3-yl)oxy)picolinamide

I-75: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylpyridin-3-yl)oxy)picolinamide

I-76: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(thiazol-4-ylmethyl)picolinamide

I-77: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(thiazol-4-ylmethyl)picolinamide

I-78: (*S*)-4-((2,6-dimethylpyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-79: (*S*)-4-((2,6-dimethylpyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-80: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-81: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-82: (*S*)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylpyridin-3-yl)oxy)picolinamide

I-83: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-84: (*S*)-4-((6-fluoropyridin-2-yl)methyl)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-85: (*S*)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-86: (*S*)-4-hydroxy-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-87: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-88: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-89: (*S*)-4-hydroxy-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-90: (*S*)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-91: (*S*)-4-((2-cyanopyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-92: (*S*)-4-((2-cyanopyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-93: (*S*)-4-((6-cyanopyridin-2-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-94: (*S*)-4-((6-cyanopyridin-2-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-95: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-fluoropyridin-3-yl)oxy)picolinamide

I-96: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-97: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)picolinamide

I-98: (*S*)-4-((2-ethylthiazol-4-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-99: (*S*)-4-((2-ethylthiazol-4-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-100: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-101: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((5-fluoropyridin-3-yl)oxy)picolinamide

I-102: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-103: (*S*)-*N*-(7-((3-Hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-104: (*S*)-*N*-(5-Methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-105: (±)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-((3*S*)-5-methyl-4-oxo-7-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-106: (*S*)-*N*-(7-(3,3-Dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-107: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(5-methyl-7-(3-methyl-3-(tetrahydro-2*H*-pyran-4-yl)but-1-yn-1-yl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-108: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-109: (*S*)-*N*-(5-Methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide

I-110: (*S*)-*N*-(7-Bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-2-yl)oxy)-1*H*-pyrazole-1-carboxamide

I-111: (*S*)-4-((6-Fluoropyridin-2-yl)oxy)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-112: (*S*)-4-((6-Fluoropyridin-2-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-113: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-((3-hydroxyoxetan-3-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-114: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-(3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-115: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(8-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide

I-116: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-((4-hydroxytetrahydro-2*H*-pyran-4-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-117: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-((1-hydroxycyclobutyl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-118: (*S*)-*N*-(8-Bromo-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-119: (*S*)-*N*-(8-(3-Hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-120: (*S*)-*N*-(8-((3-Hydroxyoxetan-3-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-121: (*S*)-*N*-(6-Fluoro-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-122: (*S*)-*N*-(6-Fluoro-8-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-123: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)picolinamide

I-124: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)picolinamide

I-125: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-126: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-127: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-128: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-2-yloxy)picolinamide

I-129: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-2-yloxy)picolinamide

I-130: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)oxy)picolinamide

I-131: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)oxy)picolinamide

I-132: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-133: (*S*)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-134: (*S*)-4-((6-fluoropyridin-2-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-135: (*S*)-4-((6-fluoropyridin-2-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-136: (*S*)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-137: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(oxazol-4-ylmethyl)picolinamide

I-138: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(oxazol-4-ylmethyl)picolinamide

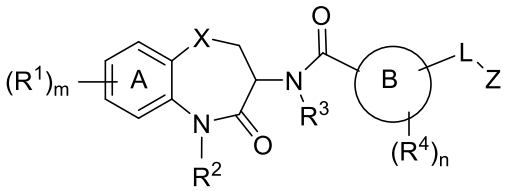
I-139: *tert*-butyl (*S*)-4-((3-(4-((2-fluoropyridin-3-yl)oxy)picolinamido)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-7-yl)ethynyl)piperidine-1-carboxylate

I-140: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-7-((1-methylpiperidin-4-yl)ethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-141: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-4-oxo-7-(piperidin-4-ylethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof; or a pharmaceutical composition of the compound, for use in therapy.

Disclosed compounds according to the present disclosure may have a Formula I



Formula I

or a pharmaceutically acceptable salt, N-oxide, solvate, tautomer, or stereoisomer thereof. With respect to Formula I, ring B is heteroaryl, and may be a monocyclic heteroaryl. In some examples, ring B is a 5-membered or 6-membered heteroaryl, and may be pyrazolyl or pyridinyl.

Each R^1 independently is halogen or -linker-R^6 group, wherein the linker is a bond or R^a, provided that R^a is not H or D, and R^6 is heterocyclyl, R^b, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$; R^2 is R^a; R^3 is R^a and may be H; if present, each R^4 independently is R^e; and L is a heteroatom or R^a, provided that R^a is not H or D.

R^a is independently for each occurrence H or D, except for examples where L is R^a, C_{1-10}aliphatic, C_{1-10}haloaliphatic, C_{5-10}aromatic, C_{3-6}heterocyclic, or C_{3-10}spiroheterocyclic; R^b is independently for each occurrence -OH, -SH, -OR^c, -SR^c, -NR^dR^d, -$Si(R^a)_3$, -C(O)OH, -$C(O)OR^c$, -$C(O)NR^dR^d$, -$OC(O)NR^dR^d$, -$OC(O)C_{1-10}$alkyl substituted with one or two NR^dR^d, carboxyl, or a combination thereof, and optionally further substituted with an aromatic moiety, -SH, -O-acyl, or -$C(O)NH_2$; R^c is independently for each occurrence C_{1-10}alkyl, which can be substituted with 1, 2 or 3 R^e, C_{2-10}alkenyl, which can be substituted with 1, 2 or 3 R^e, C_{2-10}alkynyl, which can be substituted with 1, 2 or 3 R^e, C_{3-6}cycloalkyl, which can be substituted with 1, 2 or 3 R^e, or C_{5-10}aromatic, which can be substituted with 1, 2 or 3 R^e; R^d is independently for each occurrence H; C_{1-6}alkyl, which can be substituted with 1, 2 or 3 R^e or a C_{3-9}heterocyclyl; C_{3-6}cycloalkyl, which can be substituted with 1, 2 or 3 R^e; C_{3-6}heterocyclic, which can be substituted with 1, 2 or 3 R^e; C_{5-10}aryl, which can be substituted with 1, 2 or 3 R^b; C_{5-10}heteroaryl, which can be substituted with 1, 2 or 3 R^e; or two R^d groups together with the nitrogen bound thereto provide a C_{3-9}heterocyclic, which can be substituted with one or more R^e), or a C_{5-10}heteroaryl, which can be substituted with one or more R^e; R^e is independently for each occurrence halogen, C_{1-6}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{5-10}heteroaryl, or -OR^a; and R^f is independently for each occurrence –alkyl-phosphate, R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C_{2-6}alkenyl group, a C_{3-6}cycloalkyl group, which can be substituted with one or more R^e, or a C_{3-10}heterocyclic, which can be substituted with one or more R^e or acyl.

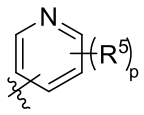
Also with respect to Formula I, X is CH_2 or O; Z is heteroaryl; m is 1, 2, 3, or 4; and n is 0, 1 or 2. In some examples, m is 1, and/or n is 0 or n is 1.

In some examples, R^2 is C_{1-6}alkyl, and may be CH_3 or CD_3.

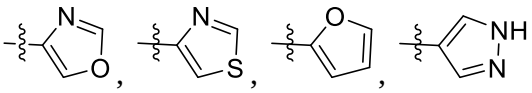
In certain examples, n is 0, but in other examples, n is 1. In such examples, R^4 may be C_{1-6}alkyl, such as methyl.

In certain examples, L is a heteroatom, such as O, but in other examples, L is C_{1-6}alkyl, such as CH_2.

In some examples, Z may be a 6-membered heteroaryl, and may be pyridinyl, pyrimidinyl, or pyridazinyl. In any examples, Z may be unsubstituted or Z may be

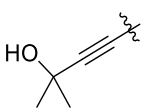
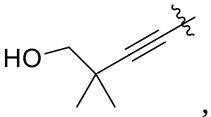
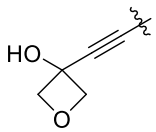
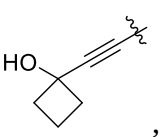
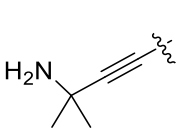
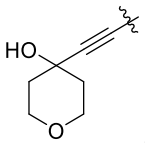
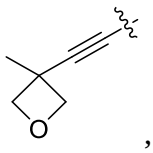
substituted, such as with halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or OH. In some examples, Z is , p is 0, 1, 2, 3, or 4, and if present, each R^5 independently is R^e. Each R^5 independently may be OH, halogen, C_{1-6}alkyl, or C_{1-6}haloalkyl, such as OH, CF_3, methyl or fluoro. And/or in some examples, p is 1, but in other examples, p is 0.

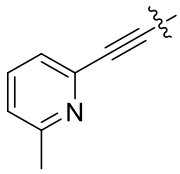
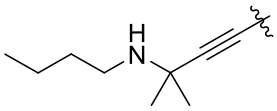
In some examples Z is 5-membered heteroaryl, such as thiazolyl, pyrazolyl, imidazolyl, oxazolyl, furanyl and the like. As with 6-membered heteroaryl Z moieties, 5-membered heteroaryl Z moieties may be substituted with groups such as such as halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or OH.

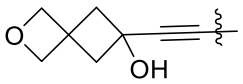
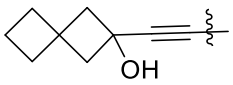
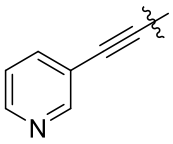
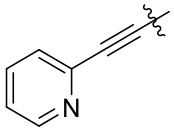
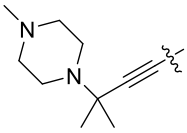
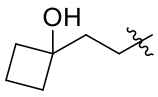
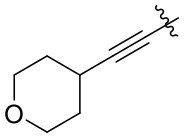
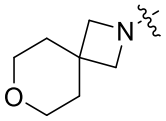
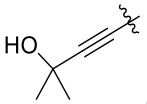
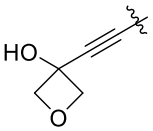
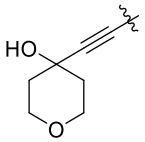
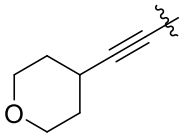
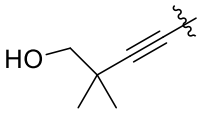
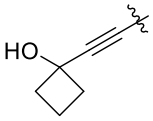
In particular examples, the Z moiety is selected from  each optionally substituted with one, two or three groups selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or OH.

And in any examples, the -L-Z moiety may be (6-fluoropyridin-2-yl)methyl, (6-methylpyridin-2-yl)methyl, (2-methylpyridin-5-yl)oxy, (2-fluoropyridin-5-yl)oxy, pyridin-2-ylmethyl, (6-trifluoromethylpyridin-2-yl)methyl, (6-hydroxypyridin-2-yl)methyl, pyridin-3-ylmethyl, pyridazin-3-ylmethyl, (2-methylpyridin-5-yl)methyl, (2-fluoropyridin-5-yl)methyl, (2-fluoropyridin-3-yl)methyl, (2,6-difluoropyridin-3-yl)methyl, pyrimidin-2-ylmethyl, or pyridin-4-ylmethyl.

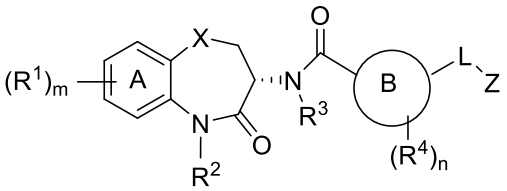
In some examples, ring B is pyrazolyl and in some examples, the -N(R^3)C(O)- moiety is attached to ring B at a ring nitrogen atom on ring B.

At least one R^1 may be halogen, such as Br, and/or at least one R^1 may be -linker-R^6. In some examples, at least one R^1 is 8- to 12-membered spiroheterocyclyl, C_{1-10}alkyl or a C_{2-10}alkyne. And in certain examples, at least one R^1 is , , , , , , ,

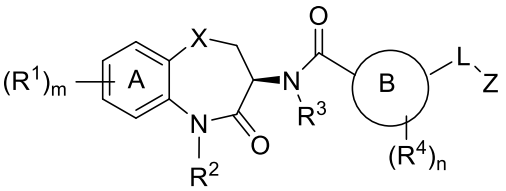

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A person of ordinary skill will appreciate that compounds of all stereoisomers are included in Formula 1, including but not limited to, compounds having a formula



Formula I-1



Formula I-2,

or a pharmaceutically acceptable salt, N-oxide, solvate, tautomer, or stereoisomer thereof.

In particular examples of the compounds according to Formula I, the compound may have a formula as indicated below, including any and all stereoisomers thereof:

or a pharmaceutically acceptable salt, N-oxide, solvate, tautomer, or stereoisomer thereof.

Also disclosed herein are examples of a composition comprising one or more of the disclosed compounds. The composition may further comprise an excipient, a therapeutic agent, or combinations thereof.

Examples of a method of using the disclosed compounds, or composition thereof, also are disclosed herein. In some examples, the method may comprise administering one or more of the disclosed compounds, or a composition thereof, to a subject. The method may be a method for treating a disease in a subject and/or may comprise administering to the subject (i) a therapeutically effective amount of a disclosed compound or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof; or (ii) a therapeutically effective amount of a pharmaceutical composition of the compound. In some examples, the subject may have, or may be suspected of having or developing, the disease, such as a disease involving a receptor-interacting protein-1 (RIP1) kinase. Examples of diseases that can be treated according to this method example include diseases or disorders associated with inflammation, necroptosis, or both. In certain examples, diseases to be treated with the present compounds are inflammatory or immune-regulatory disorders, including autoimmune and proliferative disorders. Exemplary diseases are disclosed herein.

Also disclosed herein are examples of a method comprising contacting a receptor-interacting protein-1 (RIP1) kinase with one or more disclosed compound a pharmaceutical composition thereof. The method may be an *in vitro* method or an *in vivo* method, such as when the RIP1 kinase is in a subject.

The foregoing and other objects and features of the present disclosure will become more apparent from the following detailed description.

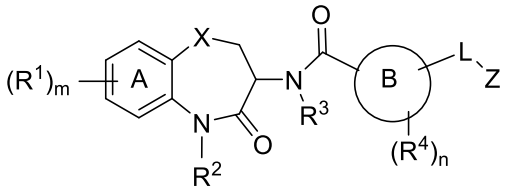
DETAILED DESCRIPTION

I. Overview of Terms

The following explanations of terms and methods are provided to better describe the present disclosure and to guide those of ordinary skill in the art in the practice of the present disclosure. The singular forms “a,” “an,” and “the” refer to one or more than one,

We claim:

1. A compound, according to Formula I



Formula I

or a pharmaceutically acceptable salt, N-oxide, solvate, tautomer, or stereoisomer thereof, wherein:

ring B is heteroaryl;

each R^1 independently is halogen or -linker-R^6 group, wherein the linker is a bond or R^a, provided that R^a is not H or D, and R^6 is heterocyclyl, R^b, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

R^2 is R^a;

R^3 is R^a;

if present, each R^4 independently is R^e;

L is a heteroatom or R^a, provided that R^a is not H or D;

X is CH_2 or O;

Z is heteroaryl;

m is 1, 2, 3, or 4;

n is 0, 1 or 2;

R^a is independently for each occurrence H or D, except for embodiments where L is R^a, C_{1-10}aliphatic, C_{1-10}haloaliphatic, C_{5-10}aromatic, C_{3-6}heterocyclic, or C_{3-10}spiroheterocyclic;

R^b is independently for each occurrence -OH, -SH, $-OR^c$, $-SR^c$, $-NR^dR^d$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^c$, $-C(O)NR^dR^d$, $-OC(O)NR^dR^d$, $-OC(O)C_{1-10}$alkyl substituted with one or two NR^dR^d, carboxyl, or a combination thereof, and optionally further substituted with an aromatic moiety, -SH, -O-acyl, or $-C(O)NH_2$;

R^c is independently for each occurrence C_{1-10}alkyl, which can be substituted with 1, 2 or 3 R^e, C_{2-10}alkenyl, which can be substituted with 1, 2 or 3 R^e, C_{2-10}alkynyl, which

can be substituted with 1, 2 or 3 R^e, C_{3-6}cycloalkyl, which can be substituted with 1, 2 or 3 R^e, or C_{5-10}aromatic, which can be substituted with 1, 2 or 3 R^e;

R^d is independently for each occurrence H; C_{1-6}alkyl, which can be substituted with 1, 2 or 3 R^e or a C_{3-9}heterocyclyl; C_{3-6}cycloalkyl, which can be substituted with 1, 2 or 3 R^e; C_{3-6}heterocyclic, which can be substituted with 1, 2 or 3 R^e; C_{5-10}aryl, which can be substituted with 1, 2 or 3 R^b; C_{5-10}heteroaryl, which can be substituted with 1, 2 or 3 R^e; or two R^d groups together with the nitrogen bound thereto provide a C_{3-9}heterocyclic, which can be substituted with one or more R^e), or a C_{5-10}heteroaryl, which can be substituted with one or more R^e;

R^e is independently for each occurrence halogen, C_{1-6}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{5-10}heteroaryl, or -OR^a; and

R^f is independently for each occurrence –alkyl-phosphate, R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C_{2-6}alkenyl group, a C_{3-6}cycloalkyl group, which can be substituted with one or more R^e, or a C_{3-10}heterocyclic, which can be substituted with one or more R^e or acyl.

2. The compound of claim 1, wherein ring B is 5-membered or 6-membered heteroaryl.

3. The compound of claim 1, wherein ring B is pyrazolyl or pyridinyl.

4. The compound of claim 1, wherein ring B is pyrazolyl, and the -$N(R^3)C(O)$- moiety is attached to ring B at a ring nitrogen atom on ring B.

5. The compound of claim 1, wherein R^2 is C_{1-6}alkyl.

6. The compound of claim 1, wherein R^2 is CH_3 or CD_3.

7. The compound of claim 1, wherein R^3 is H.

8. The compound of claim 1, wherein n is 0.

9. The compound of claim 1, wherein n is 1.

10. The compound of claim 9, wherein R^4 is C_{1-6}alkyl.

11. The compound of claim 1, wherein X is O.

12. The compound of claim 1, wherein X is CH_2.

13. The compound of claim 1, wherein L is heteroatom.

14. The compound of claim 13, wherein L is O.

15. The compound of claim 1, wherein L is C_{1-6}alkyl.

16. The compound of claim 15, wherein L is CH_2.

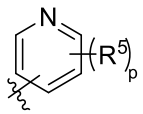
17. The compound of claim 16, wherein Z is 6-membered heteroaryl.

18. The compound of claim 17, wherein Z is pyridinyl, pyrimidinyl or pyridazinyl.

19. The compound of claim 1, wherein Z is unsubstituted.

20. The compound of claim 1, wherein Z is substituted with halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or OH.

21. The compound of claim 1, wherein:

Z is ;

p is 0, 1, 2, 3, or 4; and

if present, each R^5 independently is R^e.

22. The compound of claim 21, wherein each R^5 independently is OH, halogen, C_{1-6}alkyl, or C_{1-6}haloalkyl.

23. The compound of claim 21, wherein each R^5 independently is OH, CF_3, methyl or fluoro.

24. The compound of claim 21, wherein p is 1.

25. The compound of claim 21, wherein p is 0.

26. The compound of claim 1, wherein the -L-Z moiety is (6-fluoropyridin-2-yl)methyl, (6-methylpyridin-2-yl)methyl, (2-methylpyridin-5-yl)oxy, (2-fluoropyridin-5-yl)oxy, pyridin-2-ylmethyl, (6-trifluoromethylpyridin-2-yl)methyl, (6-hydroxypyridin-2-yl)methyl, pyridin-3-ylmethyl, pyridazin-3-ylmethyl, (2-methylpyridin-5-yl)methyl, (2-fluoropyridin-5-yl)methyl, (2-fluoropyridin-3-yl)methyl, (2,6-difluoropyridin-3-yl)methyl, pyrimidin-2-ylmethyl, or pyridin-4-ylmethyl.

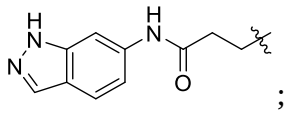
27. The compound of claim 1, wherein m is 1.

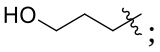
28. The compound of claim 1, wherein at least one R^1 is halogen.

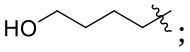
29. The compound of claim 1, wherein at least one R^1 is -linker-R^6.

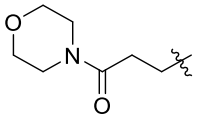
30. The compound of claim 29, wherein at least one R^1 is 8- to 12-membered spiroheterocyclyl, C_{1-10}alkyl or a C_{2-10}alkyne.

31. The compound of claim 1, wherein at least one R^1 is selected from the following:

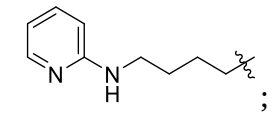
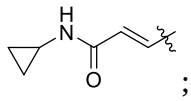
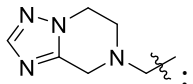


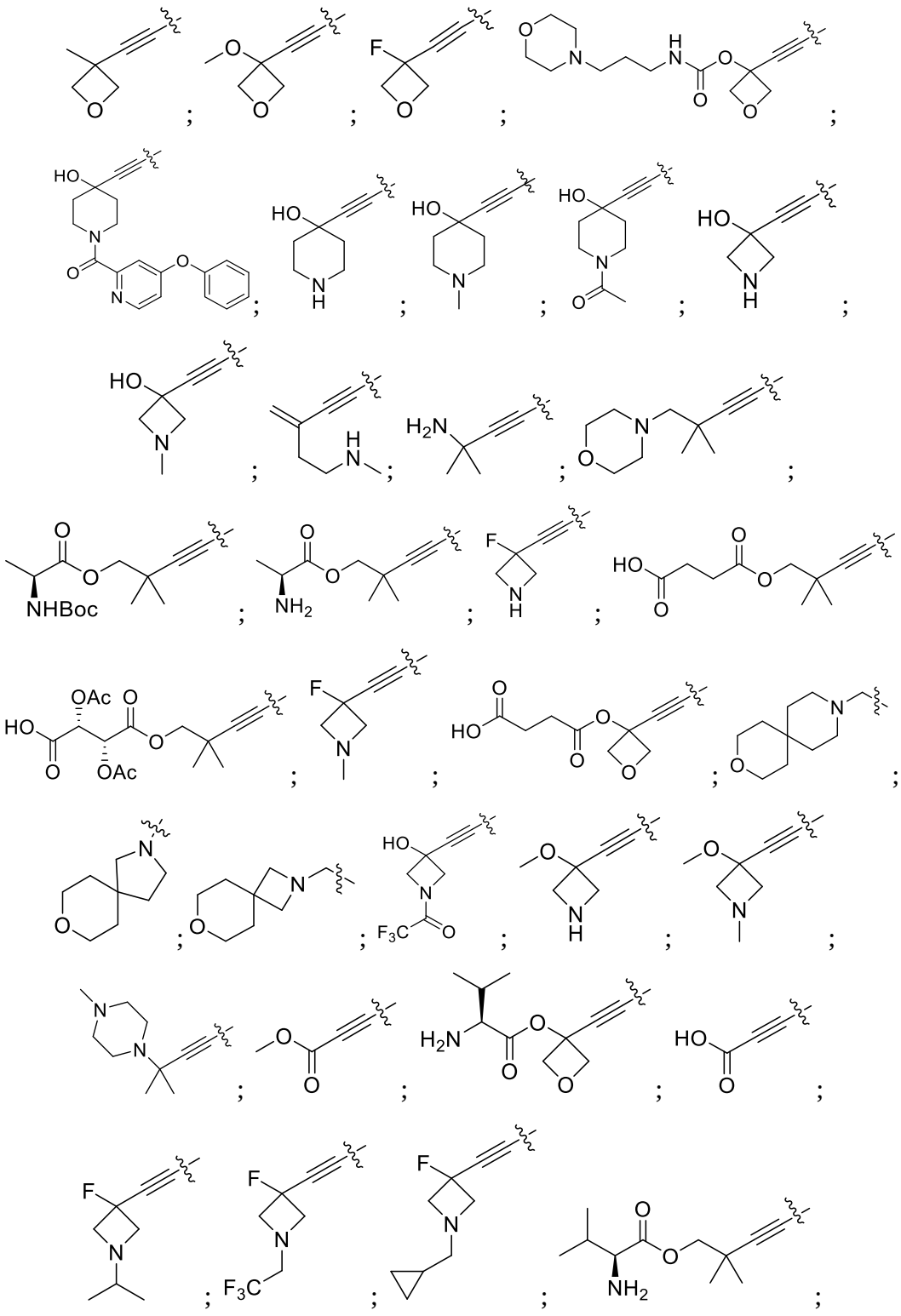
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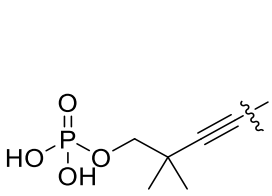
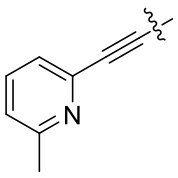
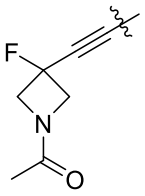
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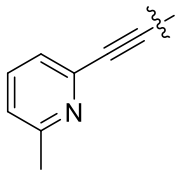
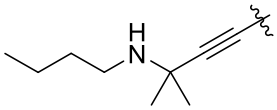
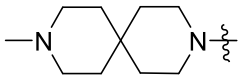
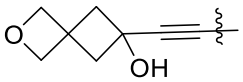
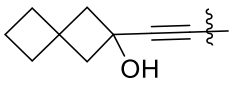
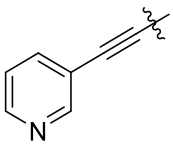
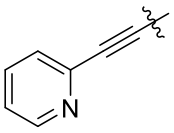
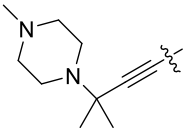
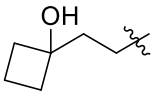
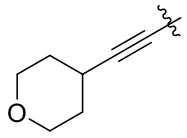
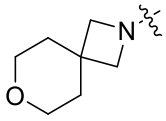
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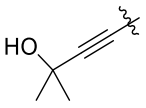

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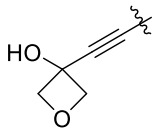
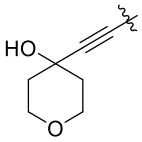
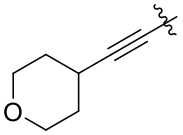
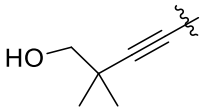
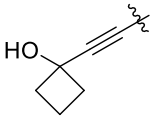



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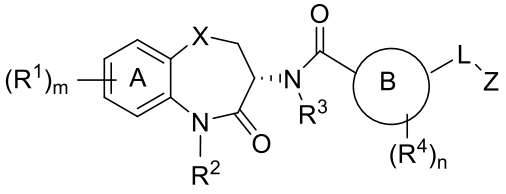
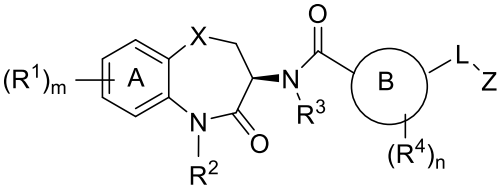
, or .

33. The compound of claim 1, wherein at least one R^1 is ,

, , , , or .

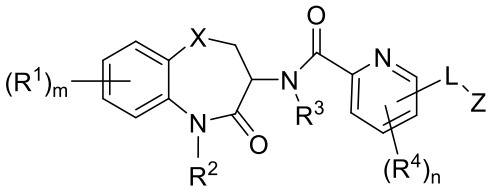
34. The compound of claim 1, wherein the compound has a formula selected from

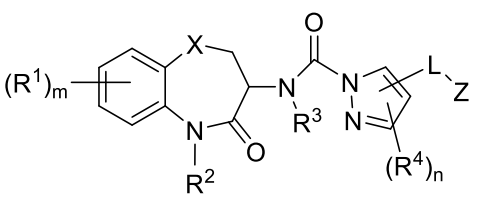
Formula I-1 Formula I-2,

or a pharmaceutically acceptable salt, N-oxide, solvate, tautomer, or stereoisomer thereof.

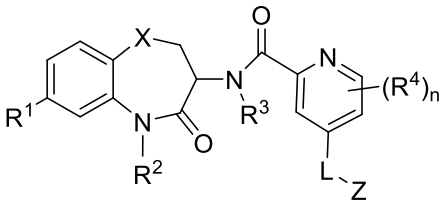
35. The compound of claim 1, wherein the compound has a formula selected from



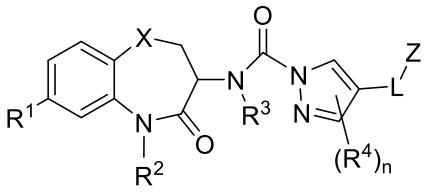
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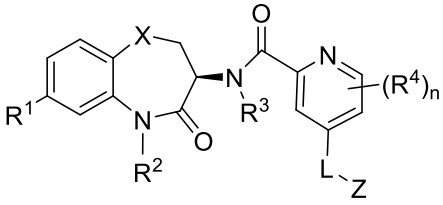
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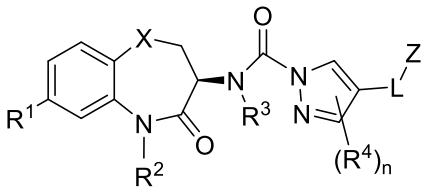
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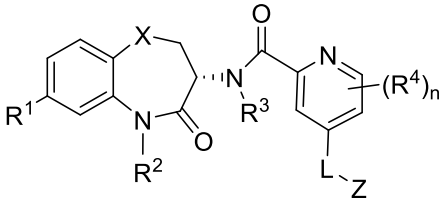
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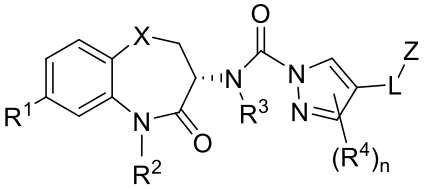
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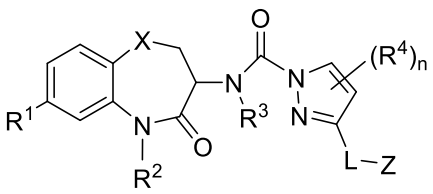
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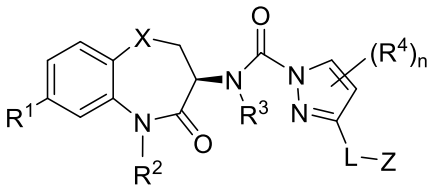
Formula I-9 ,



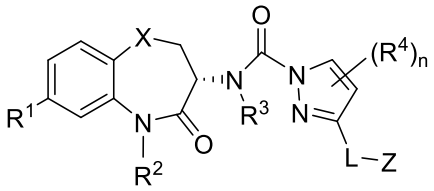
Formula I-10 ,



Formula I-11 ,



Formula I-12 , or



Formula I-13 ,

or a pharmaceutically acceptable salt, N-oxide, solvate, tautomer, or stereoisomer thereof.

36. The compound of claim 1, wherein the compound is:

I-1: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-2: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide;

I-3: (S)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)oxy)picolinamide;

I-4: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)oxy)picolinamide;

I-5: (S)-4-((6-fluoropyridin-3-yl)oxy)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide;

I-6: (S)-4-((6-fluoropyridin-3-yl)oxy)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide;

I-7: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide;

I-8: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridin-2-ylmethyl)-1H-pyrazole-1-carboxamide;

I-9: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide;

I-10: (S)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-hydroxypyridin-2-yl)methyl)picolinamide;

I-11: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)picolinamide;

I-12: (S)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)picolinamide;

I-13: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide;

I-14: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridin-3-ylmethyl)-1H-pyrazole-1-carboxamide;

I-15: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)methyl)-1H-pyrazole-1-carboxamide;

I-16: (S)-4-((6-fluoropyridin-3-yl)methyl)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-17: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridazin-3-ylmethyl)-1H-pyrazole-1-carboxamide;

I-18: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridin-2-ylmethyl)-1H-pyrazole-1-carboxamide;

I-19: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide;

I-20: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide;

I-21: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide;

I-22: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridin-3-ylmethyl)-1H-pyrazole-1-carboxamide;

I-23: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)methyl)-1H-pyrazole-1-carboxamide;

I-24: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-3-yl)methyl)-1H-pyrazole-1-carboxamide;

I-25: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridazin-3-ylmethyl)-1H-pyrazole-1-carboxamide;

I-26: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide;

I-27: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)picolinamide;

I-28: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridin-4-ylmethyl)-1H-pyrazole-1-carboxamide;

I-29: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyridin-4-ylmethyl)-1H-pyrazole-1-carboxamide;

I-30: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyrimidin-2-ylmethyl)-1H-pyrazole-1-carboxamide;

I-31: (S)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(pyrimidin-2-ylmethyl)-1H-pyrazole-1-carboxamide;

I-32: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-33: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(7-((4-hydroxytetrahydro-2H-pyran-4-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-34: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(5-methyl-4-oxo-7-((tetrahydro-2H-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-35: (S)-N-(8-bromo-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide;

I-36: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(8-((3-hydroxyoxetan-3-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide;

I-37: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(7-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-38: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(8-(3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide;

I-39: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(8-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide;

I-40: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(8-((4-hydroxytetrahydro-2H-pyran-4-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide;

I-41: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(8-((1-hydroxycyclobutyl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide;

I-42: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((2-fluoropyridin-3-yl)methyl)-1H-pyrazole-1-carboxamide;

I-43: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-44: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(7-((4-hydroxytetrahydro-2H-pyran-4-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-45: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(5-methyl-4-oxo-7-((tetrahydro-2H-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-46: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(7-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-47: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-48: (S)-4-((2-fluoropyridin-3-yl)methyl)-N-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide;

I-49: (S)-N-(7-bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-((2,6-difluoropyridin-3-yl)methyl)-1H-pyrazole-1-carboxamide; or

I-50: (S)-4-((2,6-difluoropyridin-3-yl)methyl)-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide.

37. A pharmaceutical composition, comprising a compound according claim 1.

38. The composition according to claim 37 comprising an excipient, a therapeutic agent, or combinations thereof.

39. Use of a compound according to claim 1 or a composition thereof, in the manufacture of a medicament, wherein the medicament is to be administered to a subject.

40. Use of a compound according to claim 1 or a composition thereof, in the manufacture of a medicament, wherein the medicament is to be contacted with a receptor-interacting protein-1 (RIP1) kinase.

41. Use of (i) a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof; or (ii) a therapeutically effective amount of a pharmaceutical composition of the compound, in the manufacture of a medicament for treating a disease in a subject; wherein the subject has, or is suspected of having or developing, the disease, wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase.

42. The use according to claim 41, wherein the disease is an inflammatory or immune-regulatory disorder.

43. The use according to claim 41, wherein the disease is an aging disorder.

44. The use according to claim 41, wherein the disease is selected from amyotrophic lateral sclerosis (ALS), an autoimmune syndrome, rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel diseases, including Crohn’s disease and ulcerative colitis, biliary cirrhosis, multiple sclerosis, Wegener's granulomatosis, ichthyosis, asthma, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, allergic rhinitis, spondyloarthritis, ankylosing spondylitis, autoimmune hepatitis, autoimmune hepatobiliary diseases, cerebrovascular accident, allergic diseases, chronic obstructive pulmonary disease, pulmonary emphysema, Friedreich’s ataxia, Lewy body disease, diabetic neuropathy, polyglutamine (polyQ) diseases, Fahr disease, Menke’s disease, Wilson’s disease, prion disorder, destructive bone disorders such as bone resorption disease, multiple myeloma-related bone disorder; benign tumor, proliferative disorders, inflammatory and hyperproliferative skin disorders, an epidermal hyperproliferation, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, pustular psoriasis, bullous dermatitis, dermatitis erythema multiforme, linear IgA bullous dermatitis, cement dermatitis, gingivitis, periodontitis, lesions of gingiva, alveolar bone, substantia ossea dentis, sepsis, pancreatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, adiposis, eosinophilic fascitis, acne, alopecia areata, male pattern alopecia, alopecia senilis, keratoconjunctivitis, vernal conjunctivitis, corneal alkali burn, Behcet's disease, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Vogt-Koyanagi-Harada syndrome, hematological disorders, hematological malignancies, lymphomas, Hodgkins lymphoma, non-Hodgkins lymphoma, mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, ABC diffuse large B-cell lymphoma

(DLBCL), Waldenström's macroglobulinemia, primary cutaneous T-cell lymphoma, smoldering or indolent multiple myeloma, leukemia, acute myeloid leukemia (AML), DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, myelodysplastic syndromes (MDS), myelofibrosis, polycythemia vera, Kaposi’s sarcoma, splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, intravascular large B-cell lymphoma, IL-1 driven disorders, MyD88 driven disorders, drug resistant malignancies, such as JAK inhibitor-resistant malignancies and ibrutinib resistant malignancies, for example ibrutinib resistant hematological malignancies, ibrutinib resistant CLL and ibrutinib resistant Waldenström's macroglobulinemia, acute myelogenous leukemia, chronic myelogenous leukemia; angiogenic disorders such as angiogenic disorders including solid tumors, ocular neovascularization, hemangiomas, such as infantile hemangiomas; sepsis, septic shock, shigellosis; migraine, bronchitis, gastric ulcers, necrotizing enterocolitis, intestinal lesions associated with thermal burns, celiac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, interleukin-1 converting enzyme-associated associated fever syndrome, tumor necrosis factor receptor-associated periodic syndrome, NEMO-deficiency syndrome, HOIL-1 deficiency, linear ubiquitin chain assembly complex deficiency syndrome, a lysosomal storage disease, Gaucher disease, GM2 gangliosidosis, alpha-mannosidosis, aspartylglucosaminuria, cholesteryl ester storage disease, chronic hexosaminidase A deficiency, cystinosis, Danon disease, Fabry disease, Farber disease, fucosidosis, galactosialidosis, GM1 gangliosidosis, mucolipidosis, infantile free sialic acid storage disease, juvenile hexosaminidase A deficiency, Krabbe disease, lysosomal acid lipase deficiency, metachromatic leukodystrophy, mucopolysaccharidoses disorders, multiple sulfatase deficiency, Niemann-Pick disease, neuronal ceroid lipofuscinoses, Pompe disease, pycnodysostosis, Sandhoff disease, Schindler disease, sialic acid storage disease, Tay-Sachs disease, Wolman disease, Huntington’s disease, Parkinson's disease, neurodegenerative diseases, Huntington’s disease, Parkinson’s disease, metastatic melanoma, neurodegeneration associated with HIV infection and CMV retinitis, such as associated neurocognitive disorders or dementia, fibrotic conditions such as, nonalcoholic steatohepatitis and cardiac conditions such as, ischemia reperfusion; allergies, adult respiratory distress

syndrome, chronic obstructive pulmonary disease, glomerulonephritis, erythematosis, chronic thyroiditis, Graves' disease, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, graft versus host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, Reiter's syndrome, rubella arthritis, acute synovitis, pancreatic β-cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis, psoriatic arthritis, and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, allograft rejection, bone marrow rejection, fever and myalgias due to infection, keloid formation, scar tissue formation, pyresis, influenza, chronic myelogenous leukemia; angiogenic disorders including solid tumors; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), AIDS, ARC or malignancy, herpes; stroke, myocardial infarction, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardial ischemia, ischemia in stroke heart attacks, organ hypoxia, vascular hyperplasia, cardiac and renal reperfusion injury, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, cardiac hypertrophy, thrombin-induced platelet aggregation, endotoxemia and/or toxic shock syndrome, conditions associated with prostaglandin endoperoxidase syndase-2, pemphigus vulgaris, autoimmune/multiple myositis, dermatomyositis, leukoderma vulgaris, photoallergic sensitivity, ischemia reperfusion injury, cardiac ischemia reperfusion injury arising from myocardial infarction, multiple system atrophy, Parkinson-plus syndromes, frontotemporal dementia, intracranial hemorrhage, cerebral hemorrhage, progressive muscular atrophy, pseudobulbar palsy, progressive bulbar palsy, spinal muscular atrophy, inherited muscular atrophy, peripheral neuropathies, progressive supranuclear palsy, corticobasal degeneration, demyelinating diseases, systemic onset juvenile idiopathic arthritis (SoJIA) or Still's disease, systemic lupus erythematosus (SLE), Sjögren's syndrome, anti-phospholipid syndrome (APS), primary sclerosing cholangitis (PSC), renal transplant, surgery, acute kidney injury (AKI), systemic inflammatory response syndrome (SIRS), cytokine release syndrome (CRS), acute respiratory distress syndrome (ARDS), ARDS resulting from COVID-19, postinfectious autoimmune diseases, rheumatic fever, post-infectious glomerulonephritis, systemic sclerosis, cerebrovascular

accident (CVA), chronic obstructive pulmonary disease (COPD), NEMO- deficiency syndrome (F-kappa-B essential modulator gene (also known as IKK gamma or IKKG) deficiency syndrome), solid organ malignancies, lysosomal storage diseases, glaucoma, retinal degenerative disease, retinal ischemia/reperfusion injury, renal ischemia reperfusion injury, cataracta, siderosis, retinitis pigmentosa, retinal degeneration, retinal detachment, senile macular degeneration, vitreal scarring, anthrax lethal toxin induced septic shock, cell death induced by LPS, infectious encephalopathy, encephalitis, allergic encephalomyelitis, autoimmune uveoretinitis, giant cell arteritis, regional enteritis, granulomatous enteritis, distal ileitis, regional ileitis, terminal ileitis, insulin-dependent diabetes mellitus, scleroderma, systemic scleroderma, macular edema, diabetic retinopathy, central areolar choroidal dystrophy, BEST disease, adult vitelliform disease, pattern dystrophy, myopic degeneration, central serous retinopathy, Stargardt's disease, Cone-Rod dystrophy, North Carolina dystrophy, infectious retinitis, inflammatory retinitis, uveitis, posterior uveitis, toxic retinitis and light-induced toxicity, macular edema, central areolar choroidal dystrophy, BEST disease, adult vitelliform disease, pattern dystrophy, optic nerve injury, optic neuritis, optic neuropathies, central retinal artery occlusion, ischemic optic neuropathy (e.g., arteritic or non-arteritic anterior ischemic neuropathy and posterior ischemic optic neuropathy), compressive optic neuropathy, infiltrative optic neuropathy, traumatic optic neuropathy, mitochondrial optic neuropathy (e.g., Leber's optic neuropathy), nutritional optic neuropathy, toxic optic neuropathy and hereditary optic neuropathy, Dominant Optic Atrophy, Behr's syndrome, Creutzfeldt-Jakob disease), progressive supranuclear palsy, hereditary spastic paresis, subarachnoid hemorrhage, perinatal brain injury, subclinical brain injury, spinal cord injury, anoxic-ischemic brain injury, cerebral ischemia, focal cerebral ischemia, global cerebral ischemia, and hypoxic hypoxia, peritoneal damage caused by peritoneal dialysis fluid (PDF) and PD-related side effects, glomerular diseases, tubulointerstitial diseases, interstitial nephritis, obstruction, polycystic kidney disease), focal glomerulosclerosis, immune complex nephropathy, diabetic nephropathy, Goodpasture's syndrome, hepatocellular cancer, pancreatic cancer, urological cancer, bladder cancer, colorectal cancer, colon cancer, breast cancer, prostate cancer, prostate hyperplasia, renal cancer, kidney carcinoma, liver carcinoma, adrenal gland carcinoma, thyroid cancer, gall bladder cancer, peritoneal cancer, ovarian cancer, cervical cancer, gastric cancer, endometrial

cancer, esophageal cancer, stomach cancer, head and neck cancer, neuroendocrine cancer, CNS cancer, brain tumors (e.g., carcinoma of the brain, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, soft tissue sarcoma, retinoblastomas, neuroblastomas, peritoneal effusions, malignant pleural effusions, mesotheliomas, Wilms tumors, trophoblastic neoplasms, epithelial neoplasia, stomach carcinoma, carcinoma of the ovaries, rectum carcinoma, prostate carcinoma, carcinoma of the pancreas, lung carcinoma, carcinoma of the vagina, carcinoma of the cervix, carcinoma of the testis, carcinoma of the genitourinary tract, carcinoma of the esophagus, carcinoma of the larynx, carcinoma of the skin, carcinoma of the bone, carcinoma of the thyroid, sarcoma, glioblastomas, neuroblastomas, gastrointestinal cancer, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, colon carcinoma, colorectal adenoma, hemangiopericytomas, myxoid carcinoma, round cell carcinoma, squamous cell carcinomas, esophageal squamous cell carcinomas, oral carcinomas, vulval cancer, cancers of the adrenal cortex, ACTH producing tumors, and leukemia, respiratory infectious viruses, such as influenza virus, rhinovirus, corona virus, parainfluenza virus, RS virus, adeno virus, reo virus and the like), herpes zoster caused by herpes virus, diarrhea caused by rotavirus, viral hepatitis, AIDS, bacterial infectious diseases, such as *Bacillus cereus*, *Vibrio parahaemolyticus*, *Enterohemorrhagic Escherichia coli*, *Staphylococcus aureus*, MRS A, *Salmonella*, *Botulinus*, *Candida*, Paget's disease, achondroplasia, osteochodrytis, hyperparathyroidism, osteogenesis imperfecta, partial liver resection, acute liver necrosis, necrosis caused by toxin, necrosis caused by viral hepatitis, necrosis caused by shock, necrosis caused by anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic liver disease, alcoholic cirrhosis, alcoholic steatohepatitis, non-alcoholic steatohepatitis (NASH), acetaminophen toxicity, hepatotoxicity, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, chronic kidney diseases, kidney damage/injury, kidney damage/injury caused by nephritis, kidney damage/injury caused by renal transplant, kidney damage/injury caused by surgery, kidney damage/injury caused by administration of nephrotoxic drugs, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, chronic bacterial infection, diseases caused by environmental pollution, aging, hypobaropathy, disease

caused by histamine or leukotriene-C4 release, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, congenital hypophosphatasia, fibromatous lesions, fibrous displasia, bone turnover, osteolytic bone disease, treating post-traumatic bone surgery, treating post-prosthetic joint surgery, treating post-plastic bone surgery, treating post-dental surgery, bone chemotherapy treatment or bone radiotherapy treatment, bone cancer, fragile plaque, disorder, occlusive disorder, stenosis, coronary artery disorders, peripheral arterial disorders, arterial occlusion, aneurysm formation, post-traumatic aneurysm formation, restenosis, post-operative graft occlusion, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, autoimmune idiopathic thrombocytopenic purpura (autoimmune ITP), membranous nephritis, autoimmune thyroiditis, Hashimoito’s thyroiditis, myasthenia gravis, cold and warm agglutinin diseases, Evan's syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, or a combination thereof.

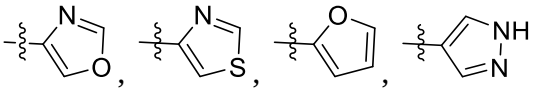
45. The use of claim 41, wherein the disease is atopic dermatitis, rheumatoid arthritis, or ankylosing spondylitis.

46. The use of claim 41, wherein the disease is myelodysplastic syndrome.

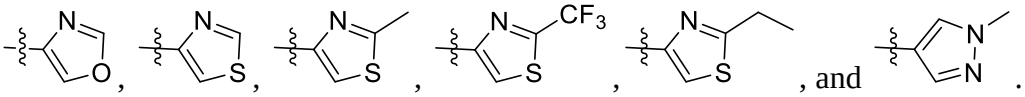
47. The compound according to any one of claims 1 – 16 wherein Z is a 5-membered heteroaryl.

48. The compound according to any one of claims 1 – 16 wherein Z is selected from the group consisting of thiazolyl, pyrazolyl, imidazolyl, oxazolyl and furanyl wherein each Z is optionally substituted with one, two or three groups selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl and OH.

49. The compound according to any one of claims 1 – 16 wherein the Z moiety is selected from


each optionally substituted with one, two or three groups selected from halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, or OH.

50. The compound according to any one of claims 1 – 16 wherein the Z moiety is selected from the group consisting of


, and

.

51. A compound that is

I-51: (*S*)-4-((2-fluoropyridin-3-yl)methyl)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide;

I-52: (*S*)-4-((2-fluoropyridin-3-yl)methyl)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide;

I-53: (*S*)-4-((6-fluoropyridin-2-yl)methyl)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide;

I-54: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-55: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-56: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-57: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-58: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-59: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-60: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-61: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-ylmethyl)picolinamide

I-62: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-ylmethyl)picolinamide

I-63: (*S*)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-64: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-2-ylmethyl)picolinamide

I-65: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-66: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-67: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-68: (*S*)-4-((3,5-dimethylisoxazol-4-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-69: (*S*)-4-((3,5-dimethylisoxazol-4-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-70: (*S*)-4-((1*H*-pyrazol-1-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-71: (*S*)-4-((1*H*-pyrazol-1-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-72: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)methyl)picolinamide

I-73: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-3-yl)methyl)picolinamide

I-74: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylpyridin-3-yl)oxy)picolinamide

I-75: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylpyridin-3-yl)oxy)picolinamide

I-76: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(thiazol-4-ylmethyl)picolinamide

I-77: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(thiazol-4-ylmethyl)picolinamide

I-78: (*S*)-4-((2,6-dimethylpyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-79: (*S*)-4-((2,6-dimethylpyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-80: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-81: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-82: (*S*)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylpyridin-3-yl)oxy)picolinamide

I-83: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-84: (*S*)-4-((6-fluoropyridin-2-yl)methyl)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-85: (*S*)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-86: (*S*)-4-hydroxy-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-87: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-88: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)pyridin-3-yl)oxy)picolinamide

I-89: (*S*)-4-hydroxy-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-90: (*S*)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-91: (*S*)-4-((2-cyanopyridin-3-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-92: (*S*)-4-((2-cyanopyridin-3-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-93: (*S*)-4-((6-cyanopyridin-2-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-94: (*S*)-4-((6-cyanopyridin-2-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-95: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-fluoropyridin-3-yl)oxy)picolinamide

I-96: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-methylthiazol-4-yl)methyl)picolinamide

I-97: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)picolinamide

I-98: (*S*)-4-((2-ethylthiazol-4-yl)methyl)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-99: (*S*)-4-((2-ethylthiazol-4-yl)methyl)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-100: (*S*)-4-((5-fluoropyridin-3-yl)oxy)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-101: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((5-fluoropyridin-3-yl)oxy)picolinamide

I-102: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-3-yloxy)picolinamide

I-103: (*S*)-*N*-(7-((3-Hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-104: (*S*)-*N*-(5-Methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-105: (±)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-((3*S*)-5-methyl-4-oxo-7-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-106: (*S*)-*N*-(7-(3,3-Dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-107: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(5-methyl-7-(3-methyl-3-(tetrahydro-2*H*-pyran-4-yl)but-1-yn-1-yl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-108: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(5-methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-109: (*S*)-*N*-(5-Methyl-7-(oxetan-3-ylethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1H-pyrazole-1-carboxamide

I-110: (*S*)-*N*-(7-Bromo-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-fluoropyridin-2-yl)oxy)-1*H*-pyrazole-1-carboxamide

I-111: (*S*)-4-((6-Fluoropyridin-2-yl)oxy)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-112: (*S*)-4-((6-Fluoropyridin-2-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-113: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-((3-hydroxyoxetan-3-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-114: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-(3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-115: (S)-4-((6-fluoropyridin-2-yl)methyl)-N-(8-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide

I-116: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-((4-hydroxytetrahydro-2*H*-pyran-4-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-117: (*S*)-4-((6-Fluoropyridin-2-yl)methyl)-*N*-(8-((1-hydroxycyclobutyl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-1*H*-pyrazole-1-carboxamide

I-118: (*S*)-*N*-(8-Bromo-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[b]azepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-119: (*S*)-*N*-(8-(3-Hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-120: (*S*)-*N*-(8-((3-Hydroxyoxetan-3-yl)ethynyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-methylpyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-121: (*S*)-*N*-(6-Fluoro-8-(3-hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-122: (*S*)-*N*-(6-Fluoro-8-(4-hydroxy-3,3-dimethylbut-1-yn-1-yl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)-4-((6-fluoropyridin-2-yl)methyl)-1*H*-pyrazole-1-carboxamide

I-123: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)picolinamide

I-124: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)picolinamide

I-125: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-126: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-127: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-128: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-2-yloxy)picolinamide

I-129: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(pyridin-2-yloxy)picolinamide

I-130: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)oxy)picolinamide

I-131: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((6-methylpyridin-2-yl)oxy)picolinamide

I-132: (*S*)-*N*-(7-(3,3-dimethylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-133: (*S*)-*N*-(7-((1-hydroxycyclobutyl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)picolinamide

I-134: (*S*)-4-((6-fluoropyridin-2-yl)oxy)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-135: (*S*)-4-((6-fluoropyridin-2-yl)oxy)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-136: (*S*)-4-((1-methyl-1*H*-pyrazol-4-yl)oxy)-*N*-(5-methyl-4-oxo-7-((tetrahydro-2*H*-pyran-4-yl)ethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-137: (*S*)-*N*-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(oxazol-4-ylmethyl)picolinamide

I-138: (*S*)-*N*-(7-((3-hydroxyoxetan-3-yl)ethynyl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)-4-(oxazol-4-ylmethyl)picolinamide

I-139: *tert*-butyl (*S*)-4-((3-(4-((2-fluoropyridin-3-yl)oxy)picolinamido)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-7-yl)ethynyl)piperidine-1-carboxylate

I-140: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-7-((1-methylpiperidin-4-yl)ethynyl)-4-oxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

I-141: (*S*)-4-((2-fluoropyridin-3-yl)oxy)-*N*-(5-methyl-4-oxo-7-(piperidin-4-ylethynyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)picolinamide

52. A compound according to claim 1, or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof; or a pharmaceutical composition of the compound, for use in therapy.