RIP1K INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the earlier filing date of U.S. Provisional Application No. 63/004,404, filed on April 2, 2020.

FIELD

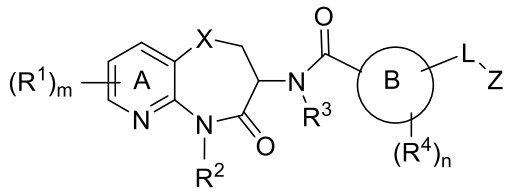
The present disclosure concerns compounds and methods of making and using the compounds, such as for inhibiting receptor-interacting protein-1 kinase ("RIP1"), and for treating diseases and/or conditions related to RIP1.

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



wherein ring B is 5-membered or 6-membered heteroaryl;

X is CH_2 or O;

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

Z is C_{1-10}aliphatic (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-6}cycloalkyl); aryl or heteroaryl, each optionally substituted with one or more R^5 group;

R^1 is independently for each occurrence $-NR^dR^d$ wherein the two R^d groups together with the nitrogen bound thereto provide a C_{3-10}heterocyclic group; $-C{\equiv}CH$, or a -linker-R^6 group, wherein the linker is a divalent C_{1-10}aliphatic moiety (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl) or C_{1-10}cycloaliphatic moiety, and R^6 is R^b, $-C(R^f)_3$, or $-C(R^f){=}C(R^f)_2$; C_{5-10}aromatic, or C_{3-6}heterocyclic, each linker optionally substituted with one or more halo, R^a, or both;

R^2 and R^3 independently are R^a;

R^4 and R^5 independently are, for each occurrence, R^e;

R^a is independently for each occurrence hydrogen, C_{1-10}aliphatic, C_{1-10}haloaliphatic, C_{5-10}aromatic, or C_{3-6}heterocyclic;

R^b is independently for each occurrence -OH, -SH, -OR^c, -SR^c, -NR^eR^e, -$Si(R^a)_3$, -C(O)OH, -C(O)OR^c, or -C(O)NR^eR^e

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

R^d is C_{1-9}aliphatic optionally substituted with 1, 2, or 3 R^a, R^b and/or R^e groups;

R^e is independently for each occurrence oxo (=O), -OR^a, $N(R^a)_2$, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or two R^e groups join together to provide a C_{3-10}heterocyclic group with a nitrogen to which the two R^e groups are bound;

m is 1 to 4; and

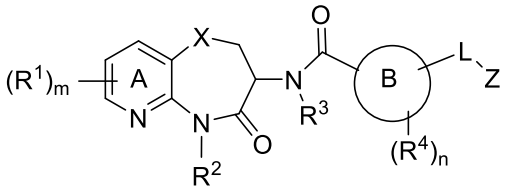
n is 0, 1 or 2.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in inhibiting a RIP kinase.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for the treatment of a disease, wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in the treatment of a disease, wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase.

Disclosed herein are compounds according to Formula I



wherein ring B is 5-membered or 6-membered heteroaryl;

X is CH_2 or O;

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

Z is C_{1-10}aliphatic (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-6}cycloalkyl); aryl or heteroaryl, each optionally substituted with one or more R^5 group;

R^1 is independently for each occurrence -NR^dR^d wherein the two R^d groups together with the nitrogen bound thereto provide a C_{3-10}heterocyclic group; -C≡CH, or a -linker-R^6 group, wherein the linker is a divalent C_{1-10}aliphatic moiety (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl) or C_{1-10}cycloaliphatic moiety, and R^6 is R^b, -$C(R^f)_3$, or -$C(R^f)$=$C(R^f)_2$; C_{5-10}aromatic, or C_{3-6}heterocyclic, each linker optionally substituted with one or more halo, R^a, or both;

R^2 and R^3 independently are R^a In some ~~embodiment~~examples, R^2 is hydrogen or C_{1-10}aliphatic, such as H or C_{1-6}alkyl, and in certain ~~embodiment~~examples, R^2 is C_{1-6}alkyl, such as CH_3 or CD_3;

R^4 and R^5 independently are, for each occurrence, R^e;

R^a is independently for each occurrence hydrogen, C_{1-10}aliphatic (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, or C_{3-6}cycloalkyl), C_{1-10}haloaliphatic, C_{5-10}aromatic, or C_{3-6}heterocyclic;

R^b is independently for each occurrence -OH, -SH, -OR^c, -SR^c, -NR^eR^e, -$Si(R^a)_3$, -C(O)OH, -$C(O)OR^c$, or -$C(O)NR^eR^e$

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

R^d is C_{1-9}aliphatic optionally substituted with 1, 2, or 3 R^a, R^b and/or R^e groups;

R^e is independently for each occurrence oxo (=O), -OR^a, $N(R^a)_2$, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or two R^e groups join together to provide a C_{3-10}heterocyclic group with a nitrogen to which the two R^e groups are bound;

m is 1 to 4; and

n is 0, 1 or 2.

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

DETAILED DESCRIPTION

I. Overview of Terms

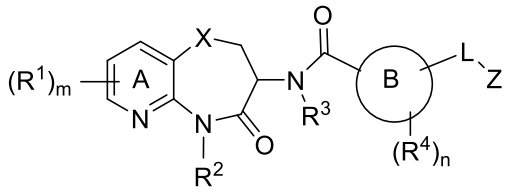
The following explanations of terms and methods are provided to better describe the present disclosure and to guide those of ordinary skill in the art in the practice of the present disclosure. The singular forms “a,” “an,” and “the” refer to one or more than one, unless the context clearly dictates otherwise. The term “or” refers to a single element of stated alternative elements or a combination of two or more elements, unless the context clearly indicates otherwise. As used herein, “comprises” means “includes.” Thus, “comprising A or B,” means “including A, B, or A and B,” without excluding additional elements. All references, including patents and patent applications cited herein, are incorporated by reference.

Unless otherwise indicated, all numbers expressing quantities of components, molecular weights, percentages, temperatures, times, and so forth, as used in the specification or claims are to be understood as being modified by the term “about.” Accordingly, unless otherwise indicated, implicitly or explicitly, the numerical parameters set forth are approximations that may depend on the desired properties sought and/or limits of detection under standard test conditions/methods. When directly and explicitly distinguishing embodiments from discussed prior art, the embodiment numbers are not approximates unless the word “about” is expressly recited.

Unless explained otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the

We claim:

1. A compound according to Formula I



wherein ring B is 5-membered or 6-membered heteroaryl;

X is CH_2 or O;

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

Z is C_{1-10}aliphatic (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-6}cycloalkyl); aryl or heteroaryl, each optionally substituted with one or more R^5 group;

R^1 is independently for each occurrence $-NR^dR^d$ wherein the two R^d groups together with the nitrogen bound thereto provide a C_{3-10}heterocyclic group; $-C{\equiv}CH$, or a -linker-R^6 group, wherein the linker is a divalent C_{1-10}aliphatic moiety (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl) or C_{1-10}cycloaliphatic moiety, and R^6 is R^b, $-C(R^f)_3$, or $-C(R^f){=}C(R^f)_2$; C_{5-10}aromatic, or C_{3-6}heterocyclic, each linker optionally substituted with one or more halo, R^a, or both;

R^2 and R^3 independently are R^a;

R^4 and R^5 independently are, for each occurrence, R^e;

R^a is independently for each occurrence hydrogen, C_{1-10}aliphatic, C_{1-10}haloaliphatic, C_{5-10}aromatic, or C_{3-6}heterocyclic;

R^b is independently for each occurrence -OH, -SH, $-OR^c$, $-SR^c$, $-NR^eR^e$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^c$, or $-C(O)NR^eR^e$

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

R^d is C_{1-9}aliphatic optionally substituted with 1, 2, or 3 R^a, R^b and/or R^e groups;

R^e is independently for each occurrence oxo (=O), $-OR^a$, $N(R^a)_2$, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or two R^e groups join together to provide a C_{3-10}heterocyclic group with a nitrogen to which the two R^e groups are bound;

m is 1 to 4; and

n is 0, 1 or 2.

2. The compound according to claim 1~~A method~~ for use in inhibiting a RIP kinase~~, comprising contacting the kinase with a compound according to claim 1~~.

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

4. The compound of claim 1, wherein ring B is a 5-membered heteroaryl.

5. The compound of claim 4, wherein ring B is a triazole, a diazole, an oxazole or an oxadiazole.

6. 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.

7. The compound of claim 1, wherein ring B is 6-membered heteroaryl.

8. The compound of claim 7, wherein ring B is pyridinyl.

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

10 The compound of claim 1, wherein R^2 is methyl.

11. The compound of claim 10, wherein R^2 is CD_3.

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

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

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

15. The compound of claim 1, wherein at least one R^4 is C_{1-6}alkyl.

16. The compound of claim 1, wherein at least one R^4 is fluoro.

17. The compound of claim 14, wherein R^4 is C_{1-6}alkyl or fluoro.

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

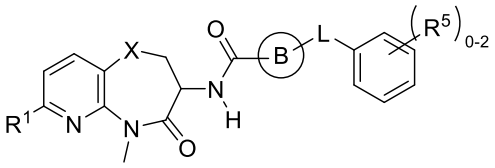
19. The compound of claim 1, wherein X is -CH_2-.

20. The compound of claim 1, wherein L is a heteroatom.

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

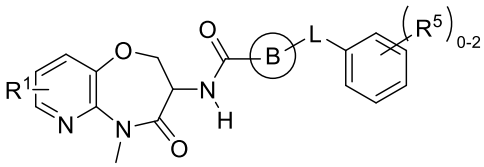
22. The compound of claim 1, wherein L is $C_{1\text{-}6}$alkyl.

23. The compound of claim 1, having Formula II



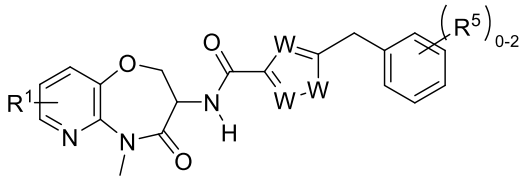
Formula II.

24. The compound of claim 1, having Formula IIA

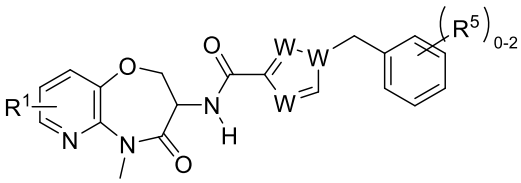


Formula IIA.

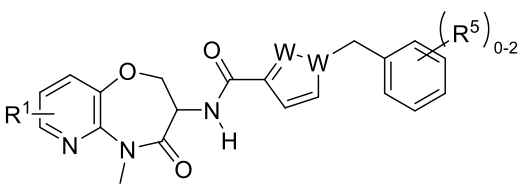
25. The compound of claim 1, having Formula IIB, IIC, IID or IIE



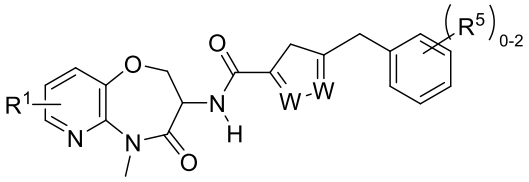
Formula IIB



Formula IIC



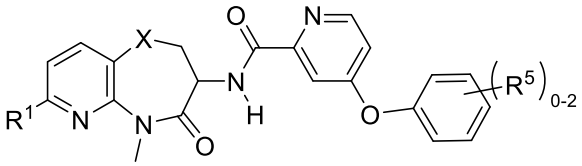
Formula IID



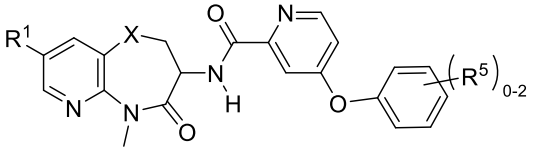
Formula IIE

wherein each W is independently N or O.

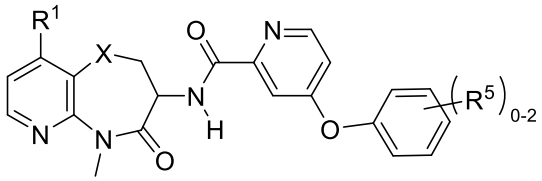
26. The compound of claim 1, having Formula IIF, IIG, IIH



Formula IIF

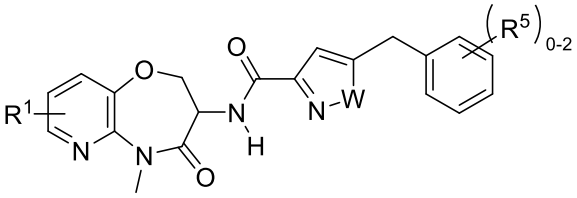


Formula IIG.



Formula IIH.

27. The compound of claim 1, having Formula IIK



Formula IIK.

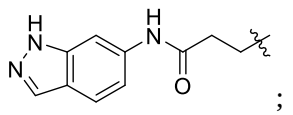
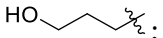
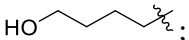
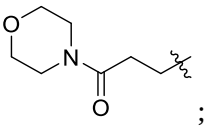
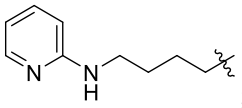
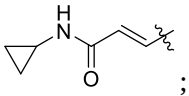
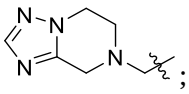
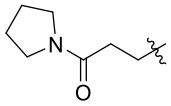
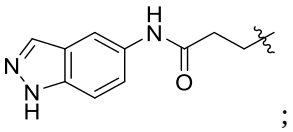
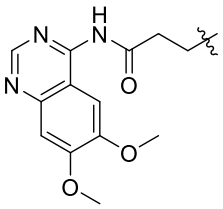
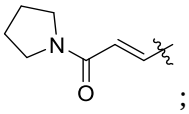
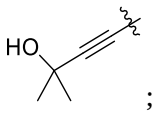
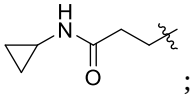
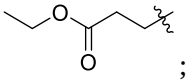
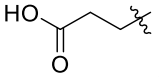
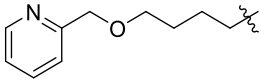
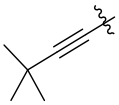
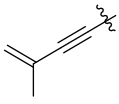
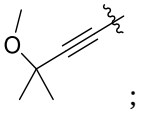
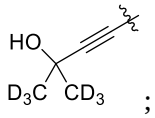
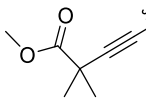
28. The compound of claim 1, wherein m is 1.

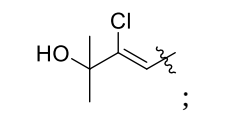
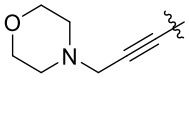
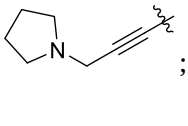
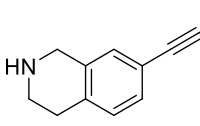
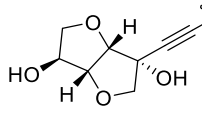
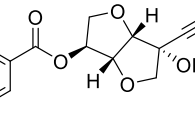
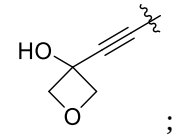
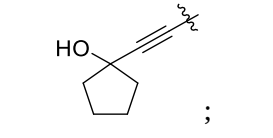
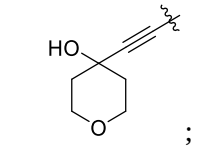
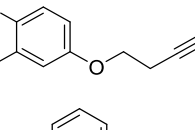
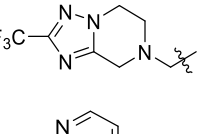
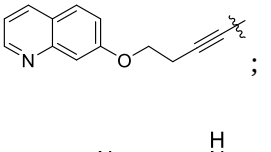
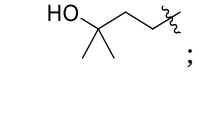
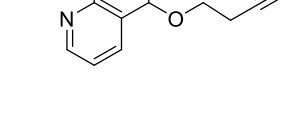
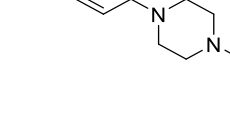
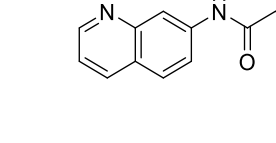
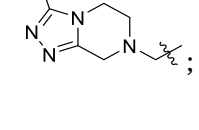
29. The compound of claim 1, wherein at least one R^1 is halogen.

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

31. 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.

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


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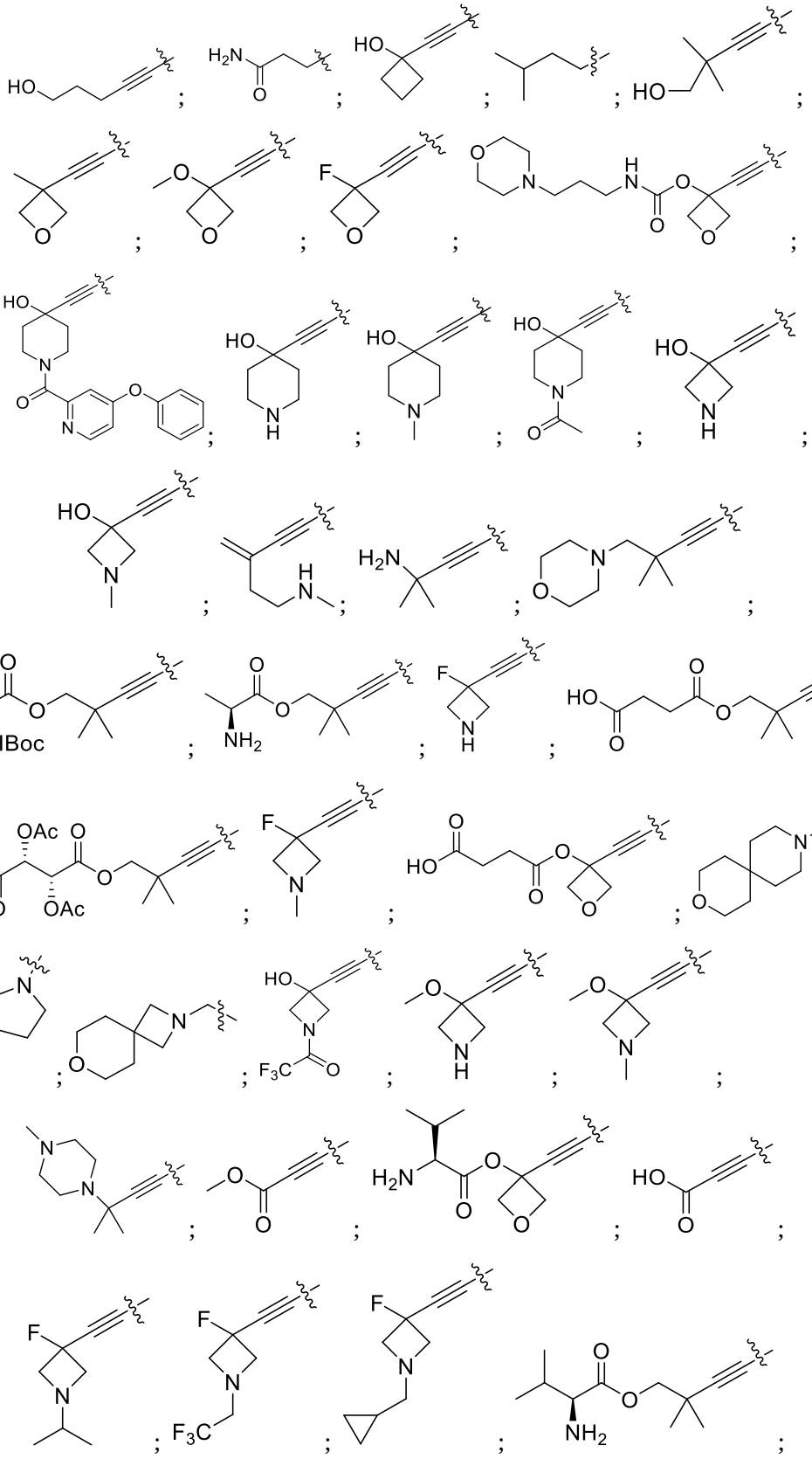
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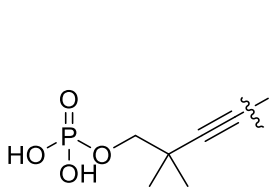
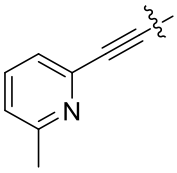
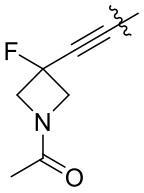
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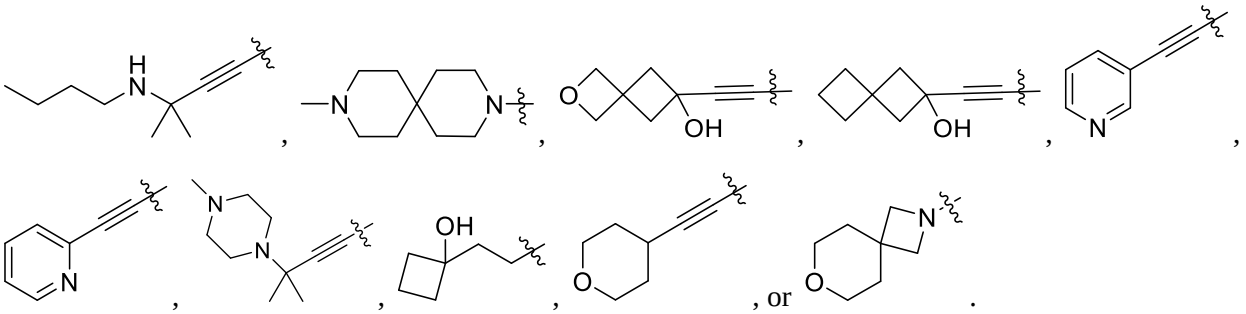
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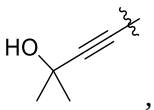
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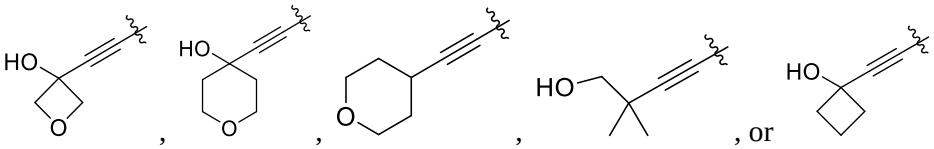
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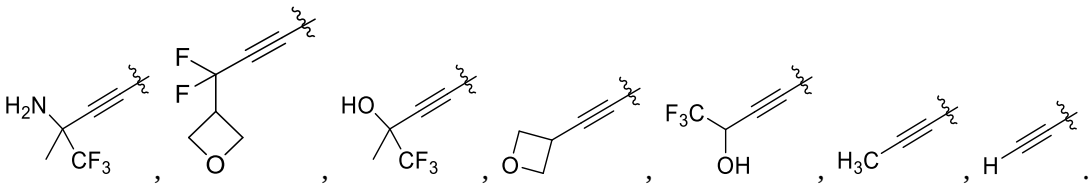

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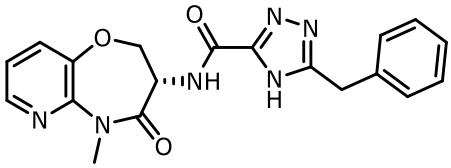
34. The compound of claim 1, wherein at least one R^1 is selected from ,

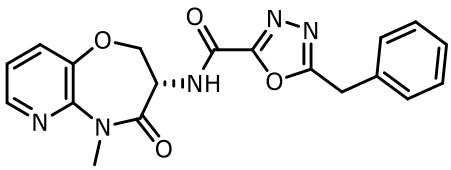


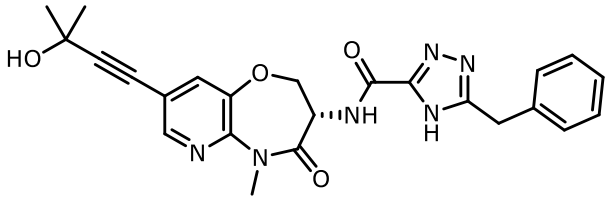
35. The compound of claim 1, wherein at least one R^1 is selected from

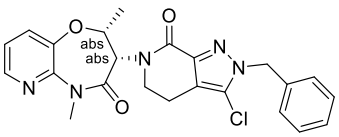


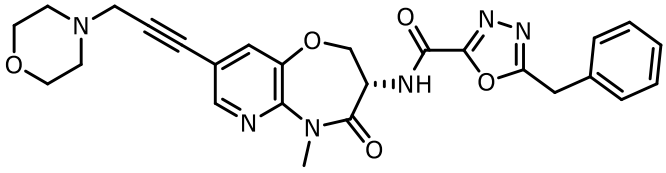
36. The compound of claim 1, having the formula

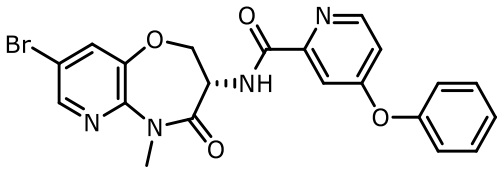
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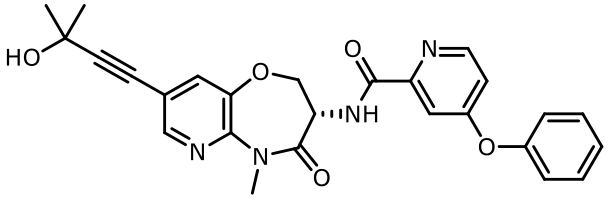
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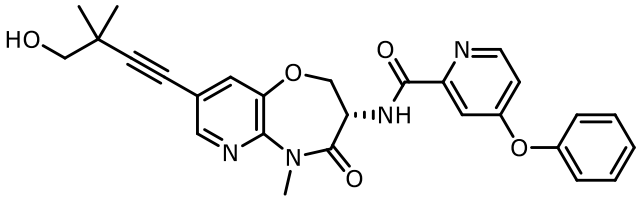
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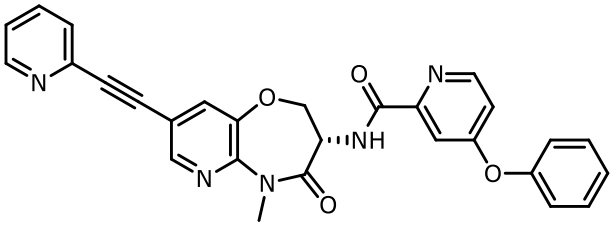
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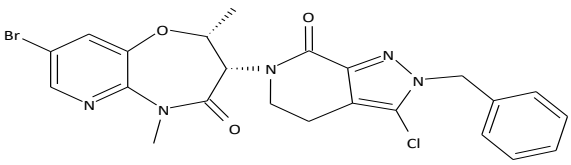
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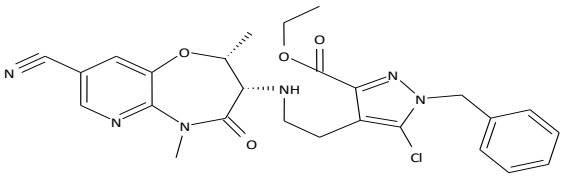
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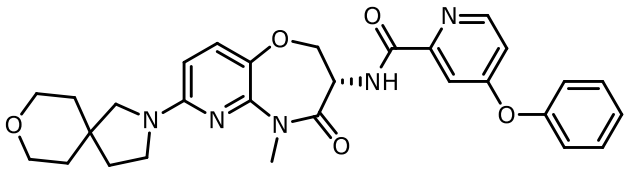
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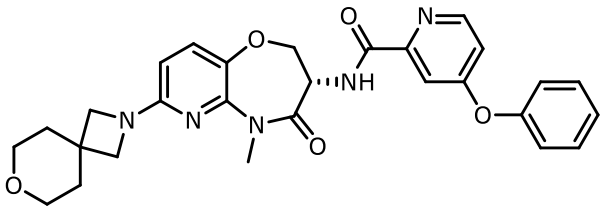
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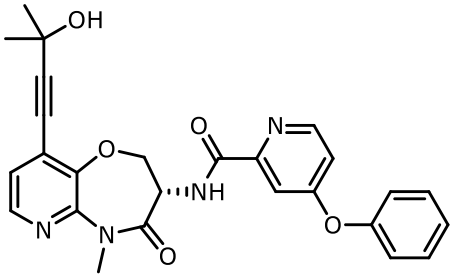
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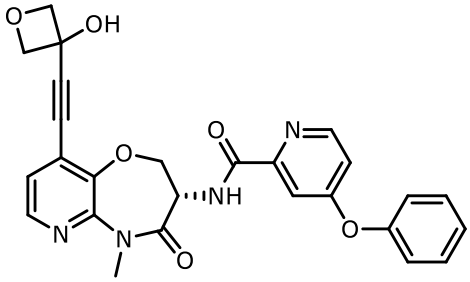
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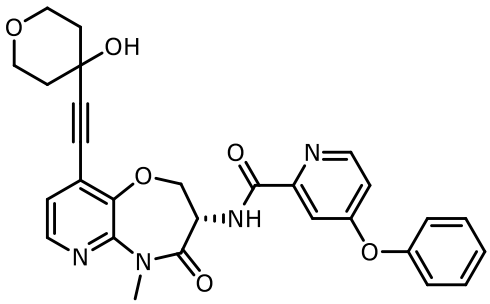
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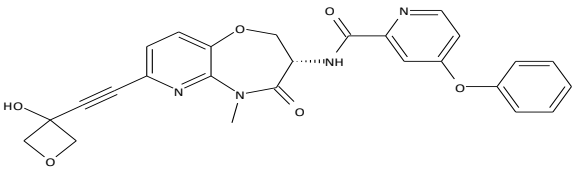
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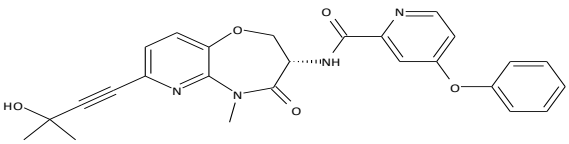
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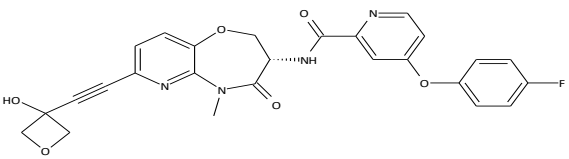
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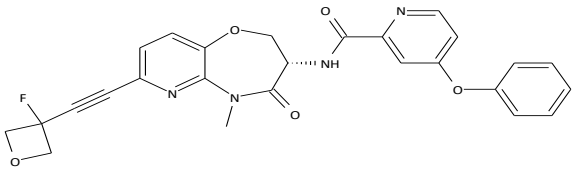
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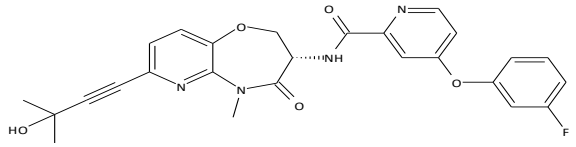
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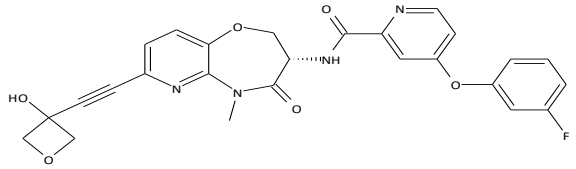
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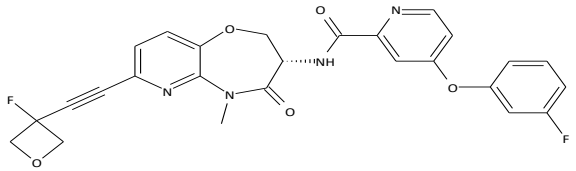
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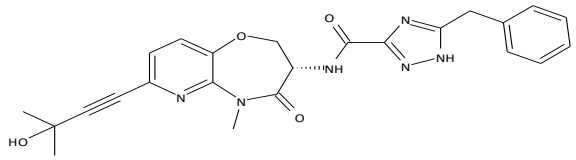
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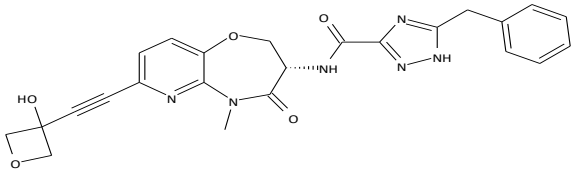
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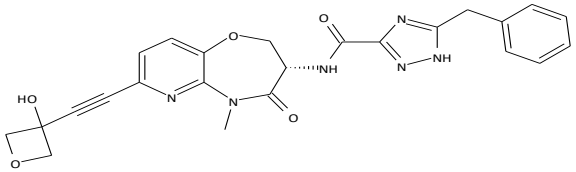
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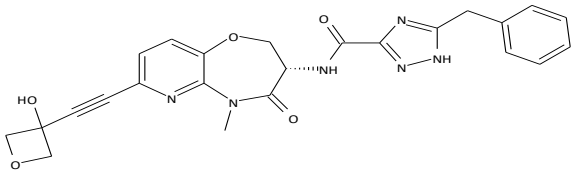
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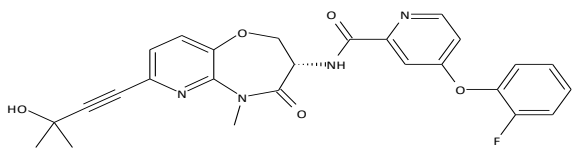
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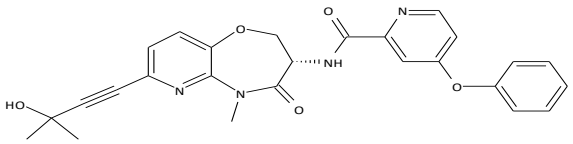
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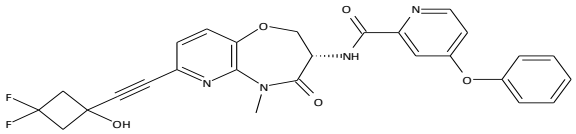
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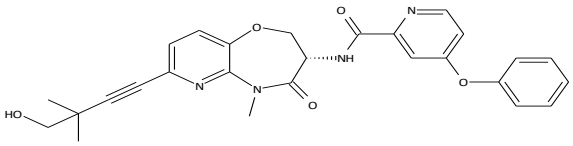
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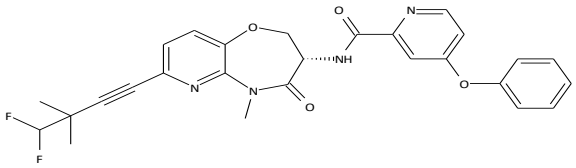
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I-29 

I-30 

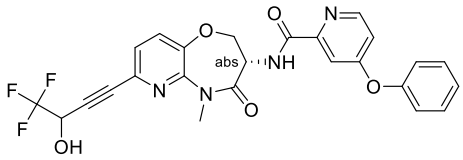
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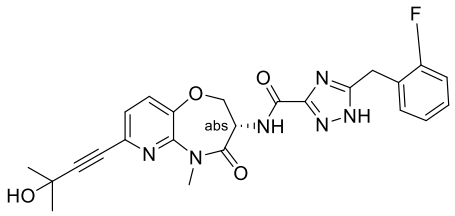
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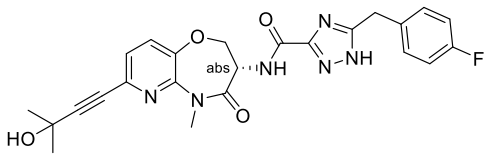
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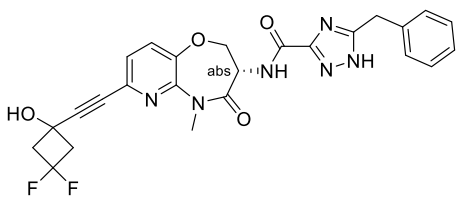
.

37. The compound of claim 1, having the formula

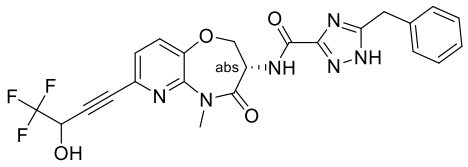
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I-34 

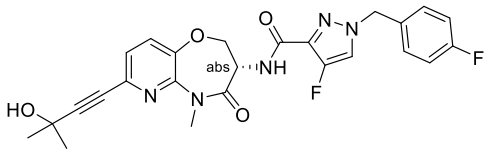
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I-36 

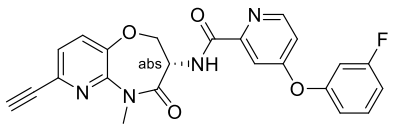
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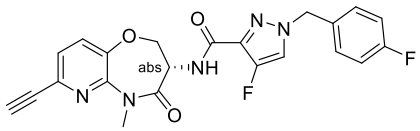
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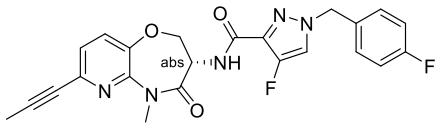
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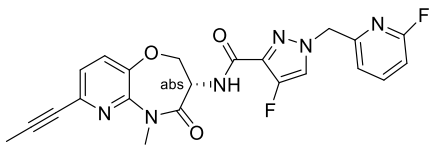
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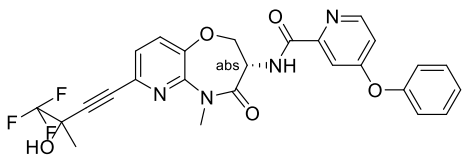
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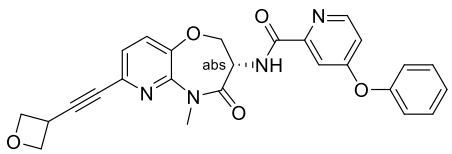
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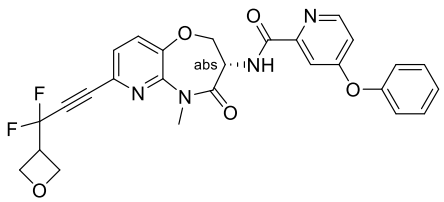
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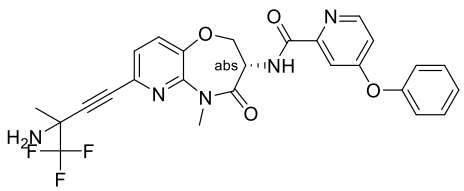
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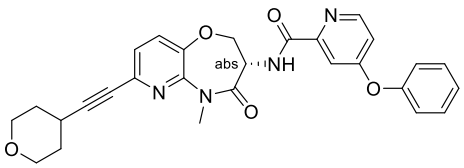


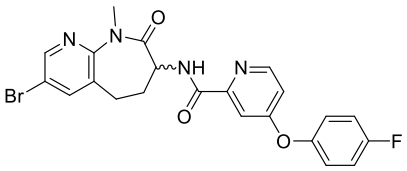
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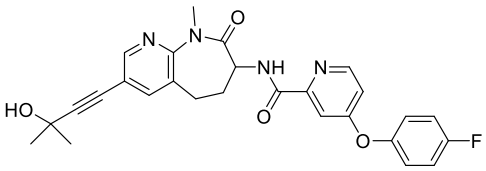


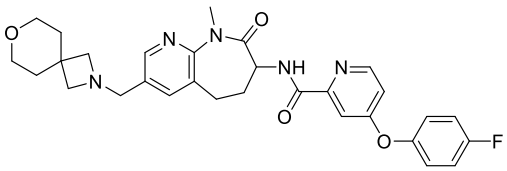
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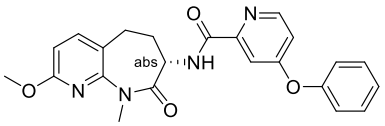


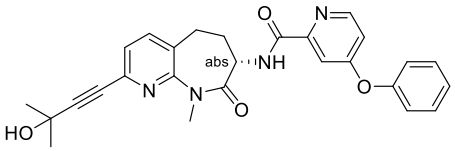
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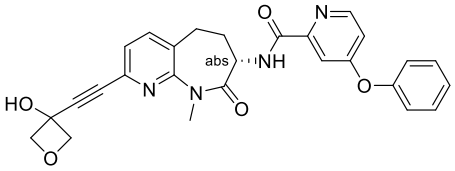
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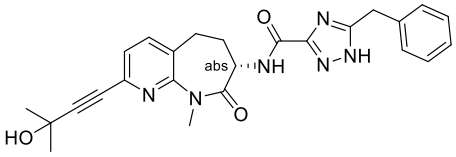
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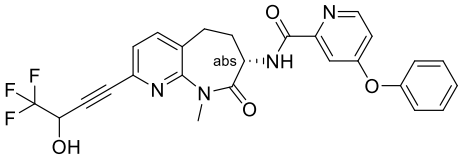
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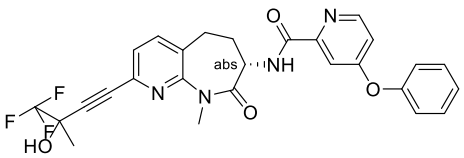
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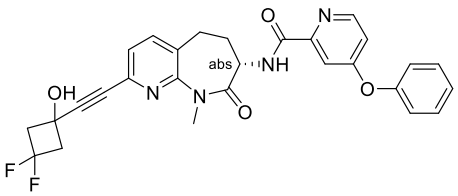
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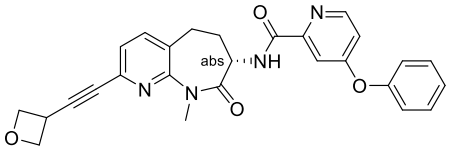
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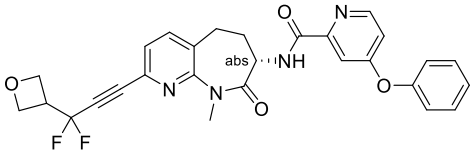
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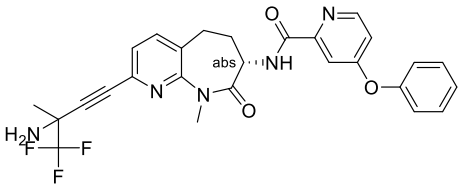
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I-59  or

I-60 .

38. Use ~~A method for treating a disease in a subject, comprising administering to the subject (i) a therapeutically effective amount~~ of a compound according to any one of claims 1 – 37,~~38; or (ii) a therapeutically effective amount of a pharmaceutical composition of the compound; wherein the subject has, or is suspected of having or developing, the~~ in the manufacture of a medicament for the treatment of a disease, wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase.

39. The use~~method~~ according to claim 38, wherein the disease is an inflammatory or immune-regulatory disorder.

40. The use~~method~~ according to claim 38, wherein the disease is an aging disorder.

41. The use~~method~~ according to claim 38, 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, chronic myeloid leukemia (CML), 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.

42. The use~~method~~ of claim 37, wherein the disease is atopic dermatitis, rheumatoid arthritis, or ankylosing spondylitis.

43. The use~~method~~ of claim 37, wherein the disease is myelodysplastic syndrome.

~~44.~~ The compound of any one of claims 1-37 for use in the treatment of a disease, wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase.

45. The compound for use according to claim 44, wherein the disease is an inflammatory or immune-regulatory disorder.

46. The compound for use according to claim 44, wherein the disease is an aging disorder.

47. The compound for use according to claim 44, 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, chronic myeloid leukemia (CML), 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.

48. The compound for use of claim 44, wherein the disease is atopic dermatitis, rheumatoid arthritis, or ankylosing spondylitis.

49. The compound for use of claim 44, wherein the disease is myelodysplastic syndrome.