HETEROCYCLIC COMPOUNDS AS GCN2 AND PERK KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Number 63/285,833 filed December 3, 2021, and U.S. Provisional Application Number 63/348,557 filed June 3, 2022, the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

[0002] Cancer cells need a continuous supply of nutrients to maintain their abnormal growth and rapid division. As part of these nutrients, amino acids are essential to support the high metabolic demands of tumor cells.

[0003] GCN2 is a serine/threonine protein kinase, one of the eukaryotic initiation factor 2α (eIF2α) kinases that are master regulators in the integrated stress response (ISR). The ISR is essential for maintaining cellular homeostasis under a wide range of stressors and is activated when cells adapt to stress conditions such as hypoxia and amino acid deprivation. The ISR is regulated by phosphorylation and activation of eIF2α kinases, including GCN2, that act as early responders to disturbances in cellular homeostasis. In addition to GCN2, there are three other eIF2α kinases family including PKR-like ER kinase (PERK), double-stranded RNA-dependent protein kinase (PKR), and heme-regulated eIF2α kinase (HRI). All four eIF2α kinases share extensive homology in their kinase catalytic domains but possess distinct regulatory domains. Each of the IF2α kinases responds to distinct environmental and physiological stresses, which reflect their unique regulatory mechanisms. PERK kinase is activated under stress conditions including ATP depletion and the unfolded protein response, and like GCN2, PERK kinase activation leads to up-regulation of the key ISR transcription factor ATF4.

[0004] Under conditions of essential amino-acid limitation or other stressors (UV irradiation, redox stress or proteasome inhibition), GCN2 phosphorylates eIF2α, which inhibits the formation of a new ternary complex and hence inhibition of mRNA translation initiation. While decreasing global mRNA translation, in tumor cells eIF2α phosphorylation also increases the translation of the ISR transcription factor ATF4, which increases the expression of many stress response genes including genes dedicated to providing amino acids to the tumor cell: i.e., amino acid synthesis enzymes and transporters that mediate influx of amino acids into the tumor cell. ATF4 is over-expressed in human solid and liquid tumors suggesting an important function in tumor progression.

[0005] Asparagine is an important amino acid involved in several biosynthetic pathways that significantly influence carcinogenesis and tumor biology. All cells need asparagine for their protein

angiogenesis through AAD-mediated VEGF expression. Abrogation of ATF4 or GCN2 expression significantly inhibited tumor growth in vivo.

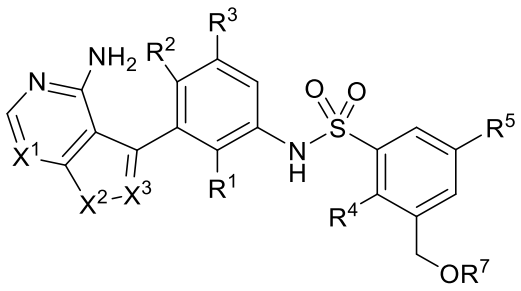
[00012] Therefore, selective inhibition of GCN2 can both increase the activity of the immune system and decrease vascularization in the tumor microenvironment. The GCN2-eIF2α-ATF4 pathway is critical for maintaining metabolic homeostasis in tumor cells under conditions of stress, and for maintaining an immunosuppressed immune cell microenvironment. The PERK-ATF4 pathway is also critical for maintaining homeostasis in tumors cells under conditions of stress. It has been reported that there is cross talk regulation of both the GCN2 and PERK signaling pathways, such that inhibition of GCN2 can activate PERK as a compensatory mechanism, and *vice versa*, that inhibition of PERK an activate GCN2 as a compensatory mechanism.

[00013] There is a need for inhibitors of GCN2 and/or PERK that modulate the pro-tumoral aspects of GCN2 and/or PERK, both in the tumor cell (tumor cell autonomous) and in the tumor immune cell microenvironment.

SUMMARY

[00014] Described herein are compounds that modulate (e.g., inhibit or activate) the GCN2 (general control nonderepressible 2) kinase and/or PERK (PKR-like ER kinase) kinase and methods of use thereof for the treatment of disorders, including GCN2 or PERK associated diseases.

[00014a] In a first aspect of the present disclosure, there is provided a compound represented by Formula I-A:



Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^3 are each independently selected from the group consisting of CH and N;

X^2 is selected from the group consisting of NR^6, O, and S;

R^1, R^2, and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

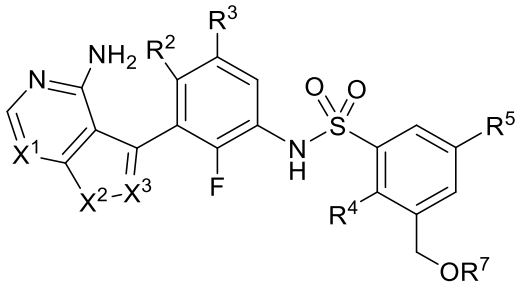
R^4 is selected from the group consisting of halogen, alkoxy and alkyl;

R^5 is selected from the group consisting of H, halogen and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acyl.

[00014b] In another aspect of the present disclosure, there is provided a compound represented by Formula I-B:



Formula I-B

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^3 are each independently selected from the group consisting of CH and N;

X^2 is selected from the group consisting of NR^6, O, and S;

R^2 and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

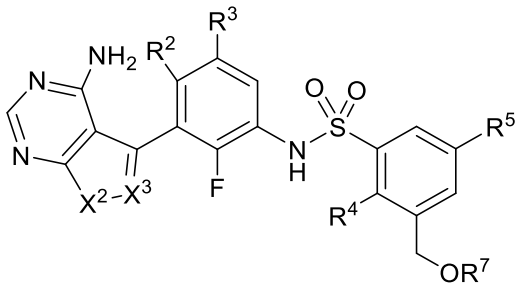
R^4 is selected from the group consisting of halogen, alkoxy and alkyl;

R^5 is selected from the group consisting of H, halogen and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acyl.

[00014c] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-C:



Formula I-C

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of NR^6, O, and S;

X^3 is selected from the group consisting of CH and N;

R^2 and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

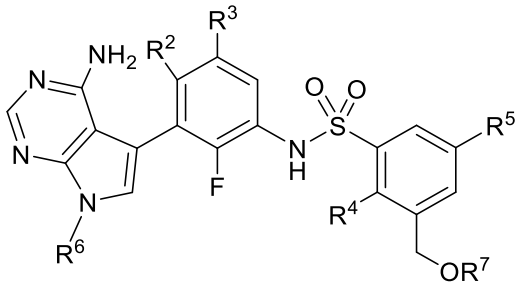
R^4 is selected from the group consisting of halogen, alkoxy, and alkyl;

R^5 is selected from the group consisting of H, halogen, and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acyl.

[00014d] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-D:



Formula I-D

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

R^2 and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

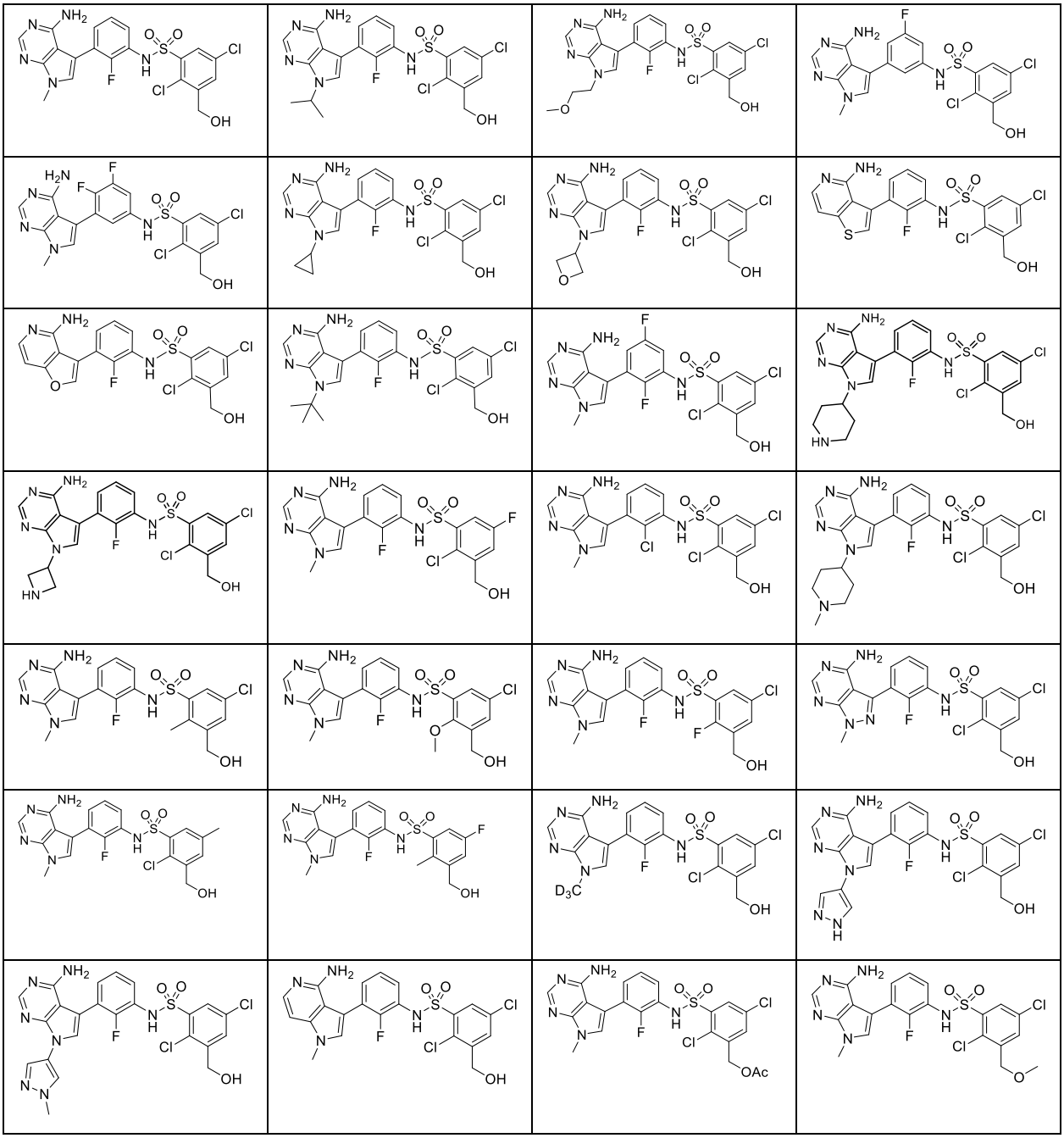
R^4 is selected from the group consisting of halogen, alkoxy and alkyl;

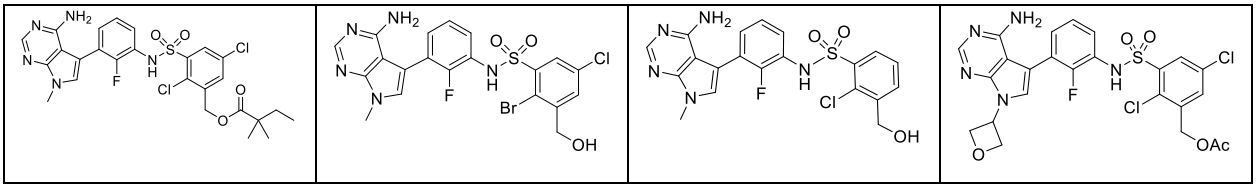
R^5 is selected from the group consisting of H, halogen and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acetate.

[00014e] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:





and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

[00014f] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[00014g] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease caused by a dysregulation of the integrated stress response in a patient in need thereof.

[00014h] In another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for modulating the activity of GCN2 kinase in a patient in need thereof.

[00014i] In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for activating GCN2 kinase in a patient in need thereof.

[00014j] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for modulating the activity of PERK kinase in a patient in need thereof.

[00014k] In another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for activating PERK kinase in a patient in need thereof.

[00014l] In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof.

[00014m] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting the activity of GCN2 kinase in a patient in need thereof.

[00014n] In another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting the activity of PERK kinase in a patient in need thereof.

[00014o] In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a cancer in a patient in need thereof.

[00014p] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating amyloidosis in a patient in need thereof.

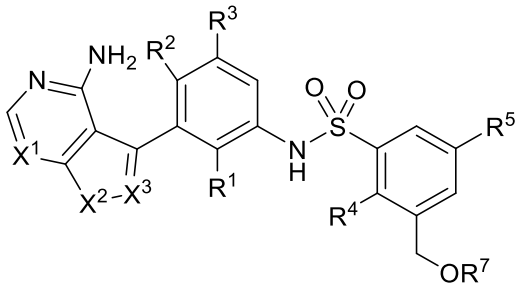
[00014q] In another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating light chain amyloidosis in a patient in need thereof.

[00014r] In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof.

[00014s] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents, in the manufacture of a medicament for treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof.

[00014t] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, for use in therapy.

[00015] In one example, described herein is a compound represented by Formula I-A:



Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: X^1 and X^3 are each independently selected from the group consisting of CH and N; X^2 is selected from the group consisting of NR^6, O, and S; R^1, R^2, and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy; R^4 is selected from the group consisting of halogen, alkoxy and alkyl; R^5 is selected from the group consisting of H, halogen and alkyl; R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and R^7 is selected from the group consisting of H, alkyl, and acyl.

[00016] In another example, described herein is a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formulae I-A, I-B, I-C, and I-D described herein) and a pharmaceutically acceptable carrier or excipient.

[00017] In another example, described herein is a method of treating a disease caused by a dysregulation of an integrated stress response in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00018] In another example, described herein is a method of treating a disease caused by a dysregulation of an integrated stress response and/or an unfolded protein response in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00019] In another example, described herein is a method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00020] In another example, described herein is a method of activating GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00021] In another example, described herein is a method of modulating the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00022] In another example, described herein is a method of activating PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00023] In another example, described herein is a method of inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00024] In another example, described herein is a method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically

effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00025] In another example, described herein is a method of inhibiting the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00026] In another example, described herein is a method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[00027] In another example, described herein is a method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of one or more therapeutic agents.

[00028] In another example, described herein is a method of treating a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formulae I-A, I-B, I-C, and I-D described herein) or a pharmaceutically acceptable salt thereof, or pharmaceutical composition described herein.

[00029] In another example, described herein is a method of treating a disorder selected from the group consisting of melanoma, fibrosarcoma, thyroid cancer, ovarian cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, blood-borne cancers, acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) and other cancers caused by activation of the GCN2 signaling pathway in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formulae I-A, I-B, I-C, and I-D described herein) or a pharmaceutically acceptable salt thereof.

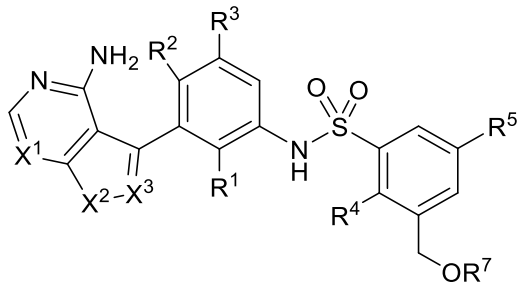
BRIEF DESCRIPTION OF THE DRAWINGS

[00030] FIG. 1 is a graphical representation demonstrating the unexpected stimulation of the UPR/ISR marker ATF4 (black bars) in response to increasing concentrations of Compound 2.

CLAIMS

What is claimed is:

1. A compound represented by Formula I-A:



Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^3 are each independently selected from the group consisting of CH and N;

X^2 is selected from the group consisting of NR^6, O, and S;

R^1, R^2, and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

R^4 is selected from the group consisting of halogen, alkoxy and alkyl;

R^5 is selected from the group consisting of H, halogen and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acyl.

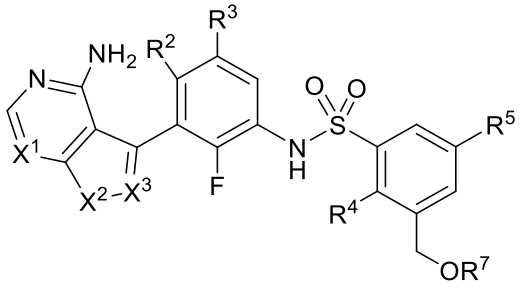
2. The compound of claim 1, wherein at least one of R^1, R^2, and R^3 is halogen.

3. The compound of claim 1 or 2, wherein at least one of R^1, R^2, and R^3 is fluoro.

4. The compound of any one of claims 1-3, wherein R^1 is fluoro.

5. The compound of any one of claims 1-4, wherein X^1 is N.

6. A compound represented by Formula I-B:



Formula I-B

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 and X^3 are each independently selected from the group consisting of CH and N;

X^2 is selected from the group consisting of NR^6, O, and S;

R^2 and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

R^4 is selected from the group consisting of halogen, alkoxy and alkyl;

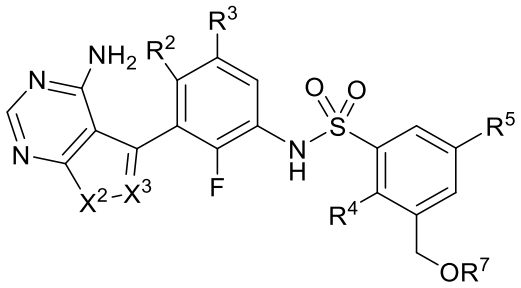
R^5 is selected from the group consisting of H, halogen and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acyl.

7. The compound of claim 6, wherein X^1 is N.

8. A compound represented by Formula I-C:



Formula I-C

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of NR^6, O, and S;

X^3 is selected from the group consisting of CH and N;

R^2 and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

R^4 is selected from the group consisting of halogen, alkoxy, and alkyl;

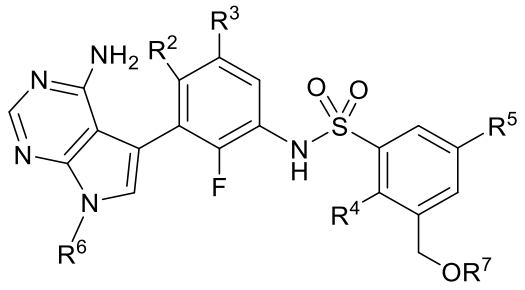
R^5 is selected from the group consisting of H, halogen, and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acyl.

9. The compound of claim 8, wherein X^2 is NR^6.

10. A compound represented by Formula I-D:



Formula I-D

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

R^2 and R^3 are each independently selected from the group consisting of H, halogen, cyano, and alkoxy;

R^4 is selected from the group consisting of halogen, alkoxy and alkyl;

R^5 is selected from the group consisting of H, halogen and alkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl; and

R^7 is selected from the group consisting of H, alkyl, and acetate.

11. The compound of any one of claims 6-10, wherein R^2 is H and R^3 is H.

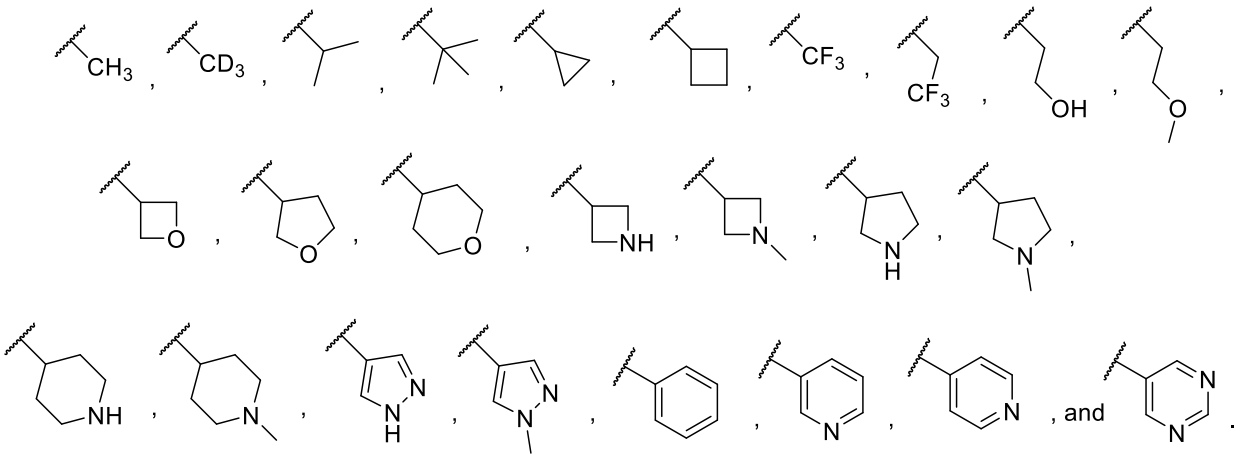
12. The compound of any one of claims 6-10, wherein R^2 is F and R^3 is H.

13. The compound of any one of claims 6-10, wherein R^2 is H and R^3 is F.

14. The compound of any one of claims 1-13, wherein R^6 is selected from the group consisting of (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkenyl-(C_1-C_4)alkyl, (C_2-C_8)alkynyl, (C_2-C_8)alkynyl-(C_1-C_4)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl-(C_1-C_4)alkyl, (C_3-C_8)alkoxy-(C_1-C_4)alkyl, (C_3-C_8)cycloalkenyl, (C_3-C_8)cycloalkenyl-(C_1-C_4)alkyl, heterocyclyl, heterocyclyl-(C_1-C_4)alkyl, aryl, heteroaryl, and heteroaryl-(C_1-C_4)alkyl.

15. The compound of any one of claims 1-14, wherein R^6 is selected from the group consisting of (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)alkoxy-(C_1-C_4)alkyl, heterocyclyl, and heteroaryl.

16. The compound of any one of claims 1-14, wherein R^6 is selected from the group consisting of



17. The compound of any one of claims 1-16, wherein R^4 is selected from the group consisting of halogen, (C_1-C_6)alkoxy and (C_1-C_6)alkyl.

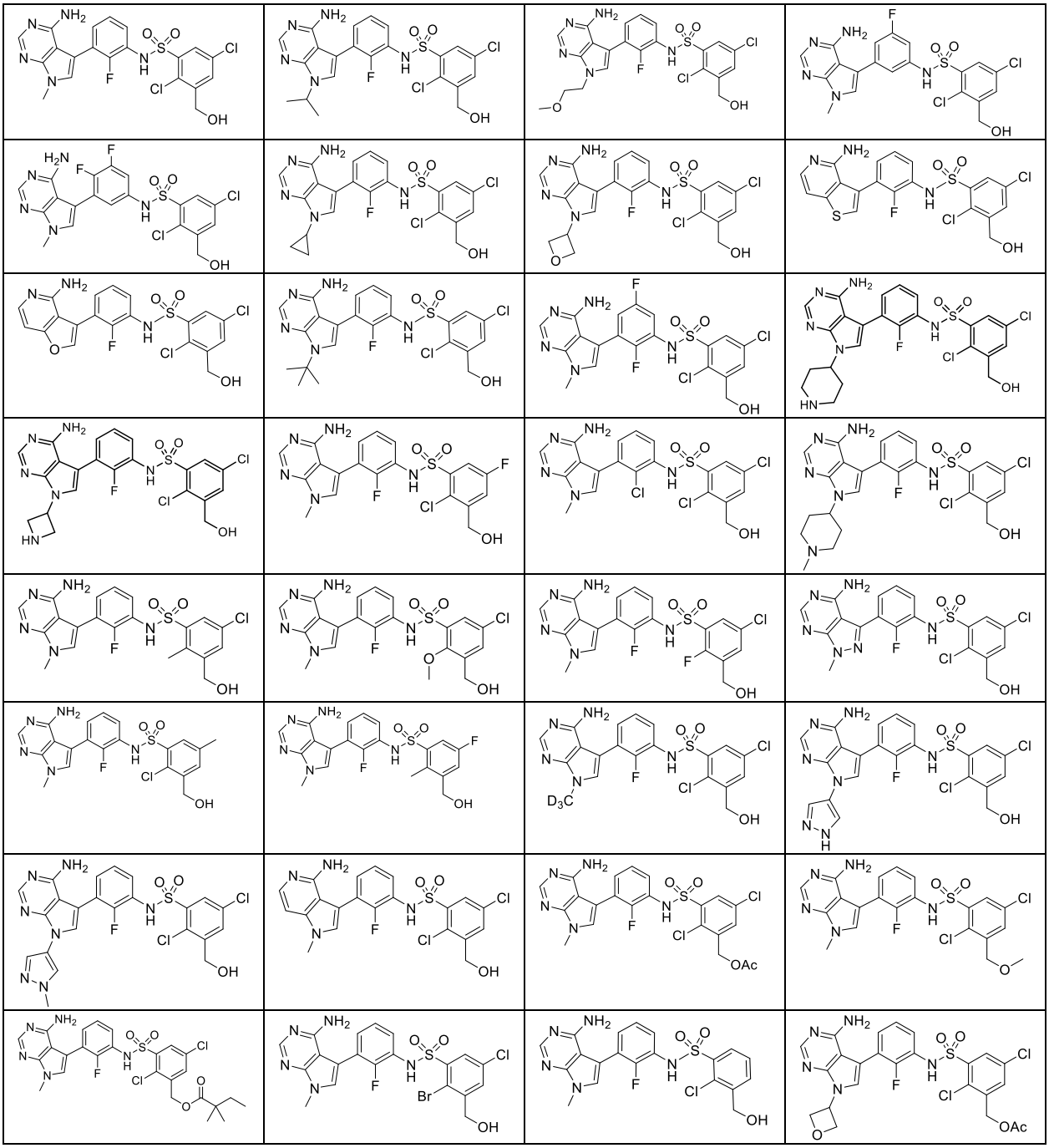
18. The compound of any one of claims 1-17, wherein R^4 is selected from the group consisting of chloro, fluoro, methoxy, and methyl.

19. The compound of any one of claims 1-18, wherein R^5 is selected from the group consisting of H, halogen, and (C_1-C_6)alkyl.

20. The compound of any one of claims 1-19, wherein R^5 is selected from the group consisting of chloro, fluoro, and methyl.

21. The compound of any one of claims 1-20, wherein R^7 is H.

22. A compound selected from the group consisting of:



and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

23. A pharmaceutical composition comprising a compound according to any one of claims 1-22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

24. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for

treating a disease caused by a dysregulation of the integrated stress response in a patient in need thereof.

25. The use of claim 24, wherein the dysregulation of the integrated stress response and/or an unfolded protein response is caused by a kinase selected from the group consisting of PERK kinase and GCN2 kinase.

26. The use of claim 24 or 25, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by GCN2 kinase.

27. The use of claim 24 or 25, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by PERK kinase.

28. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for modulating the activity of GCN2 kinase in a patient in need thereof.

29. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for activating GCN2 kinase in a patient in need thereof.

30. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for modulating the activity of PERK kinase in a patient in need thereof.

31. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for activating PERK kinase in a patient in need thereof.

32. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof.

33. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for inhibiting the activity of GCN2 kinase in a patient in need thereof.

34. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for inhibiting the activity of PERK kinase in a patient in need thereof.

35. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating a cancer in a patient in need thereof.

36. The use of claim 35, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, light chain amyloidosis, and malignant lymphoma.

37. The use of claim 36 or 37, wherein the cancer is leukemia.

38. The use of claim 36 or 37, wherein the cancer is acute myeloid leukemia.

39. The use of claim 36 or 37, wherein the cancer is acute lymphoblastic leukemia.

40. The use of claim 36 or 37, wherein the cancer is fibrosarcoma.

41. The use of claim 36 or 37, wherein the cancer is multiple myeloma.

42. The use of claim 36 or 37, wherein the cancer is lymphoma.

43. The use of claim 127 or 128, wherein the cancer is B-cell lymphoma.

44. The use of claim 36 or 37, wherein the cancer is T cell lymphoma.

45. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating amyloidosis in a patient in need thereof.

46. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating light chain amyloidosis in a patient in need thereof.

47. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof.

48. The use of claim 47, wherein the disease is a GCN2 associated disease.

49. The use of claim 47, wherein the disease is a PERK associated disease.

50. The use of any one of claims 47-49, wherein the disease is a cancer.

51. The use of claim 50, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, Mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.

52. The use of claim 50 or 51, wherein the cancer is leukemia.

53. The use of claim 50 or 51, wherein the cancer is acute myeloid leukemia.

54. The use of claim 50 or 51, wherein the cancer is acute lymphoblastic leukemia.

55. The use of claim 50 or 51, wherein the cancer is fibrosarcoma.

56. The use of claim 50 or 51, wherein the cancer is multiple myeloma.

57. The use of claim 50 or 51, wherein the cancer is lymphoma.

58. The use of claim 50 or 51, wherein the cancer is B-cell lymphoma.

59. The use of claim 50 or 51, wherein the cancer is T cell lymphoma.

60. The use of claim 47, wherein the disease is amyloidosis.

61. The use of claim 47, wherein the disease is light chain amyloidosis.

62. Use of the compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents, in the manufacture of a medicament for treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof.

63. The use of claim 62, wherein the disease is a GCN2 associated disease.

64. The use of claim 62, wherein the disease is a PERK associated disease.

65. The use of any one of claims 62-64, wherein the disease is a cancer.

66. The use of claim 65, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer,

esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, light chain amyloidosis, and malignant lymphoma.

67. The use of claim 65 or 66, wherein the cancer is leukemia.

68. The use of claim 65 or 66, wherein leukemia is acute myeloid leukemia.

69. The use of claim 65 or 66, wherein leukemia is acute lymphoblastic leukemia.

70. The use of claim 65 or 66, wherein the cancer is fibrosarcoma.

71. The use of claim 65 or 66, wherein the cancer is multiple myeloma.

72. The use of claim 65 or 66, wherein the cancer is lymphoma.

73. The use of claim 65 or 66, wherein the cancer is B-cell lymphoma.

74. The use of claim 65 or 66, wherein the cancer is T cell lymphoma.

75. The use of claim 62, wherein the disease is amyloidosis.

76. The use of claim 62, wherein the disease is light chain amyloidosis.

77. The use of any one of claims 62-76, wherein the one or more therapeutic agents is selected from the group consisting of an IMiD agent, a proteasome inhibitor, a steroid, an anti-CD38 agent, an anti-CD20 agent, a Bcl-2 inhibitor, a PI3K inhibitor, a bi-specific antibody, a nucleoside analog, a BTK inhibitor, a DNA alkylating agent, an EZH2 inhibitor, an anthracycline, a topoisomerase inhibitor, a platin, a tyrosine kinase inhibitor, an HDAC inhibitor, a nuclear export inhibitor, an anti-

microtubule agent, L-asparaginase, pegylated asparaginase, a PERK inhibitor, a mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor.

78. The use of any one of claims 62-76, wherein the one or more therapeutic agents is selected from the group consisting of L-asparaginase, pegaspargase, calaspargase pegol – mnkl, bortezomib, carfilzomib, ixazomib, thalidomide, pomalidomide, lenalidomide, dexamethasone, prednisone, daratumumab, daratumumab / hyaluronidase, isatuximab, rituximab, obinutuzumab, venetoclax, idelalisib, copanlisib, duvelisib, umbralisib, gemcitabine, cytarabine, ibrutinib, acalabrutinib, zanubrutinib, bendamustine, cyclophosphamide, tazemetostat, doxorubicin, daunorubicin, etoposide, oxaloplatin, carboplatin, cisplatin, bosutinib, dasatinib, imatinib, nilotinib, ponatinib, panobinostat, selinexor, vincristine, JZP-458, eryaspase, PF745 (JZP-341), asparaginase *Erwinia chrysanthemi* (crisantaspase), *Escherichia coli* asparaginase (colaspase), an anti-PD1 agent, an anti-PDL1 agent, and an anti-CTLA4 agent.

79. A compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 23, for use in therapy.