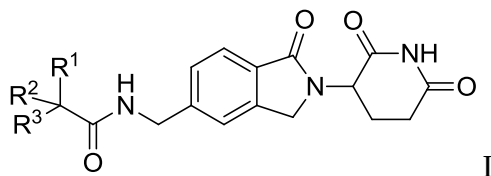


CLAIMS

1. A compound of Formula I:



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

R^1 is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl;

R^2 and R^3 are each halo;

where the substituents on R^1 , when present, are one to three groups Q, where each Q is independently alkyl, halo, haloalkyl, alkoxyalkyl, oxo, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted

heteroaryl, $-R^4OR^5$, $-R^4O-R^4OR^5$, $-R^4N(R^6)(R^7)$, $-R^4SR^5$, $-R^4OR^4N(R^6)(R^7)$, $-R^4OR^4C(J)N(R^6)(R^7)$, $-C(J)R^9$ or $R^4S(O)_2R^8$;

each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclylalkyl, where alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl or heterocyclylalkyl groups in R^5 are each independently optionally substituted with 1-3 Q^1 groups, where each Q^1 is independently alkyl, haloalkyl or halo;

R^6 and R^7 are selected as follows:

i) R^6 and R^7 are each independently hydrogen or alkyl; or

ii) R^6 and R^7 together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two halo, alkyl or haloalkyl;

R^8 is alkyl, haloalkyl, or hydroxyalkyl;

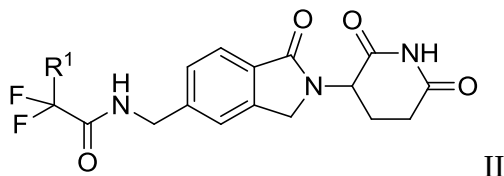
R⁹ is alkyl or aryl;

J is O or S; and

t is 1 or 2.

2. The compound of claim 1, wherein R¹ is optionally substituted aryl.

3 The compound of claim 1 having Formula II:



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

R¹ is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl;

where the substituents on R¹, when present, are one to three groups Q, where each Q is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, -R⁴OR⁵, -R⁴SR⁵, -R⁴N(R⁶)(R⁷), R⁴OR⁴N(R⁶)(R⁷) or R⁴OR⁴C(J)N(R⁶)(R⁷);

J is O or S;

each R⁴ is independently alkylene, alkenylene or a direct bond;

each R⁵ is independently hydrogen, alkyl, haloalkyl or hydroxyalkyl; and

R⁶ and R⁷ are selected as follows:

i) R⁶ and R⁷ are each independently hydrogen or alkyl; or

ii) R⁶ and R⁷ together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two halo, alkyl or haloalkyl.

4. The compound of claim 1, wherein R¹ is optionally substituted aryl;

where the substituents on R¹, when present, are one to three groups Q, where each Q is independently alkyl, halo, haloalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, -R⁴OR⁵, -R⁴SR⁵, -R⁴N(R⁶)(R⁷), R⁴OR⁴N(R⁶)(R⁷) or R⁴OR⁴C(J)N(R⁶)(R⁷);

J is O or S;

each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, haloalkyl or hydroxyalkyl; and

R^6 and R^7 are selected as follows:

i) R^6 and R^7 are each independently hydrogen or alkyl; or

ii) R^6 and R^7 together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two halo, alkyl or haloalkyl.

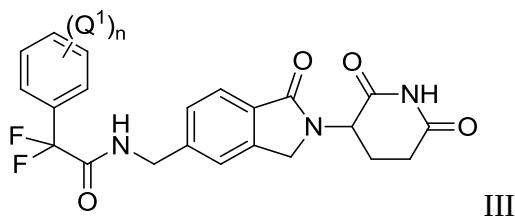
5. The compound of claim 1, wherein R^1 is optionally substituted phenyl, optionally substituted cyclohexyl, optionally substituted piperidinyl, or optionally substituted pyridyl, where the substituents on R^1 , when present, are one to three groups Q, where each Q is independently halo, alkyl, $-R^4OR^5$ or $-R^4N(R^6)(R^7)$; each R^4 is independently a direct bond or alkylene; each R^5 is independently hydrogen, alkyl, or haloalkyl; and R^6 and R^7 are selected as follows:

i) R^6 and R^7 are each independently hydrogen or alkyl; or

ii) R^6 and R^7 together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl ring.

6. The compound of claim 1, wherein R^1 is optionally substituted phenyl, where the substituents on R^1 , when present, are one to three groups Q, where each Q is independently fluoro, chloro, methyl, *tert* butyl, $-R^4OR^5$, $-R^4SR^5$ or $R^4OR^4C(J)N(R^6)(R^7)$; each R^4 is independently a direct bond or methylene; each R^5 is independently hydrogen, methyl, ethyl or trifluoromethyl; and R^6 and R^7 are each independently hydrogen or methyl.

7. The compound of claim 1, wherein the compound has formula III



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

each Q^1 is independently alkyl, halo, haloalkyl, alkoxyalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, $-R^4OR^5$, $-R^4SR^5$, $-R^4N(R^6)(R^7)$, $R^4OR^4N(R^6)(R^7)$ or $R^4OR^4C(J)N(R^6)(R^7)$;

J is O or S;

each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, or haloalkyl;

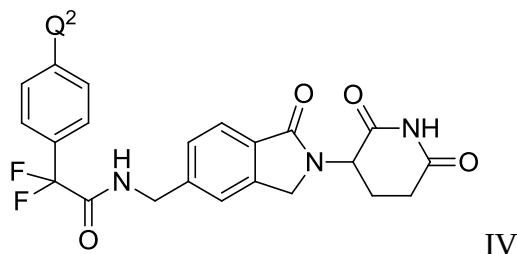
R^6 and R^7 are selected as follows:

i) R^6 and R^7 are each independently hydrogen or alkyl; or

ii) R^6 and R^7 together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two halo, alkyl or haloalkyl; and

n is 0-3.

8. The compound of claim 1, wherein the compound has formula IV



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

Q^2 is hydrogen, alkyl, halo, haloalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, $-R^4OR^5$, $-R^4SR^5$, $-R^4N(R^6)(R^7)$, $R^4OR^4N(R^6)(R^7)$ or $R^4OR^4C(J)N(R^6)(R^7)$;

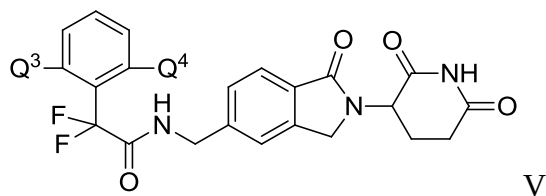
J is O or S;

each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, haloalkyl or hydroxyalkyl; and

R^6 and R^7 are each independently hydrogen or alkyl.

9. The compound of claim 1, wherein the compound has formula V



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

Q^3 and Q^4 are each independently hydrogen, alkyl, halo, haloalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, $-R^4OR^5$, $-R^4SR^5$, $-R^4N(R^6)(R^7)$, $R^4OR^4N(R^6)(R^7)$ or $R^4OR^4C(J)N(R^6)(R^7)$;

J is O or S;

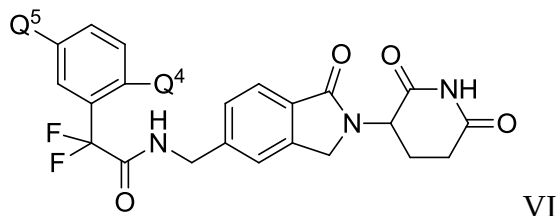
each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, or alkoxyalkyl;

and

R^6 and R^7 are each independently hydrogen or alkyl.

10. The compound of claim 1, wherein the compound has formula VI



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

Q^4 and Q^5 are each independently hydrogen, alkyl, halo, haloalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, $-R^4OR^5$, $-R^4SR^5$, $-R^4N(R^6)(R^7)$, $R^4OR^4N(R^6)(R^7)$ or $R^4OR^4C(J)N(R^6)(R^7)$;

J is O or S;

each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, haloalkyl, alkoxyalkyl or hydroxyalkyl;

and

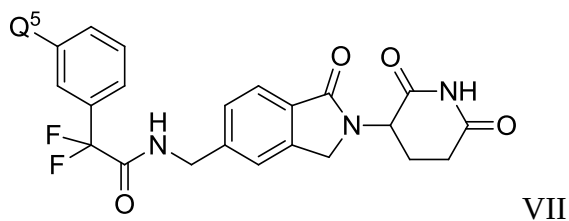
R^6 and R^7 are selected as follows:

i) R^6 and R^7 are each independently hydrogen or alkyl; or

ii) R^6 and R^7 together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two halo, alkyl or haloalkyl.

11. The compound of claim 10, wherein Q^4 and Q^5 are each independently hydrogen, halo, alkyl, alkoxyalkyl, $-R^4N(R^6)(R^7)$, or $-R^4OR^5$; R^4 is a direct bond or alkylene; R^5 is hydrogen, alkyl or haloalkyl; and R^6 and R^7 together with the nitrogen atom on which they are substituted form a 6-membered heterocyclyl.

12. The compound of claim 1, wherein the compound has formula VII



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

Q^5 is hydrogen, alkyl, halo, haloalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, $-R^4OR^5$, $-R^4SR^5$, $-R^4N(R^6)(R^7)$, $R^4OR^4N(R^6)(R^7)$ or $R^4OR^4C(J)N(R^6)(R^7)$;

J is O or S;

each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, haloalkyl, alkoxyalkyl or hydroxyalkyl;

and

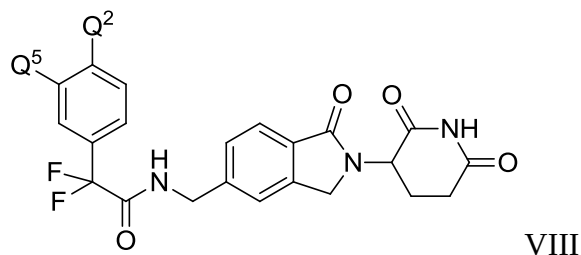
R^6 and R^7 are selected as follows:

i) R^6 and R^7 are each independently hydrogen or alkyl; or

ii) R^6 and R^7 together with the nitrogen atom on which they are substituted form a 5 or 6-membered heterocyclyl or heteroaryl ring, optionally substituted with one or two halo, alkyl or haloalkyl.

13. The compound of claim 12, wherein Q^5 is hydrogen, halo, alkyl, alkoxyalkyl, $-R^4N(R^6)(R^7)$ or $-R^4OR^5$; R^4 is a direct bond or alkylene; and R^5 is hydrogen, alkyl or haloalkyl; and R^6 and R^7 together with the nitrogen atom on which they are substituted form a 6-membered heterocyclyl.

14. The compound of claim 1, wherein the compound has formula VIII



or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein:

Q^2 and Q^5 are each independently hydrogen, alkyl, halo, haloalkyl, hydroxyl, alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, $-R^4OR^5$, $-R^4SR^5$, $-R^4N(R^6)(R^7)$, $R^4OR^4N(R^6)(R^7)$ or $R^4OR^4C(J)N(R^6)(R^7)$;

J is O or S;

each R^4 is independently alkylene, alkenylene or a direct bond;

each R^5 is independently hydrogen, alkyl, haloalkyl or hydroxyalkyl; and

R^6 and R^7 are each independently hydrogen or alkyl, or R^6 and R^7 together with the nitrogen atom on which they are substituted form a 6-membered heterocyclyl.

15. The compound claim 14, wherein Q^2 and Q^5 are each independently hydrogen, halo, alkyl, alkoxyalkyl, optionally substituted aryl, or $-R^4OR^5$; R^4 is a direct bond or alkylene; and R^5 is hydrogen, alkyl or haloalkyl.

16. The compound of claim 1, wherein the compound is selected from Table 1.

17. The compound of claim 16 selected from

N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoro-2-(4-methoxyphenyl)acetamide;

2-(4-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoroacetamide;

2-(3-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoroacetamide;

N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoro-2-(4-fluorophenyl)acetamide; and

2-(2-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoroacetamide.

18. The compound of claim 16, wherein the compound is N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoro-2-(4-methoxyphenyl)acetamide.

19. The compound of claim 16, wherein the compound is 2-(4-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoroacetamide.

20. The compound of claim 16, wherein the compound is 2-(3-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoroacetamide.

21. The compound of claim 16, wherein the compound is N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoro-2-(4-fluorophenyl)acetamide.

22. The compound of claim 16, wherein the compound is 2-(2-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)-2,2-difluoroacetamide.

23. A compound of any one of claims 1-22 for use as a medicament.

24. A compound of any one of claims 1-22 for use in a method of treating cancer, comprising administering to a mammal having cancer a therapeutically effective amount of the compound.

25. The compound for use according to claim 24, wherein the cancer is leukemia.

26. The compound for use according to claim 25, wherein the leukemia is chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia or acute myeloid leukemia.

27. The compound for use according to claim 25, wherein the leukemia is an acute myeloid leukemia.

28. The compound for use according to any one of claims 25-27, wherein the leukemia is relapsed, refractory or resistant to conventional therapy.

29. The compound for use according to any one of claims 23-28, for administering in combination with a therapeutically effective amount of another second active agent or a support care therapy.

30. The compound for use according to claim 29, wherein the other second active agent is a therapeutic antibody that specifically binds to a cancer antigen, hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, cox-2 inhibitor, immunomodulatory agent, immunosuppressive agent, corticosteroid or a pharmacologically active mutant or derivative thereof.

31. The compound for use according to claim 24, wherein the cancer is a solid tumor

32. The compound for use according to claim 24, wherein the cancer is a cancer of bladder, bone, blood, brain, breast, cervix, chest, colon, endometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, or uterus.

33. The compound for use according to claim 31, wherein the cancer is metastatic.

34. The compound for use according to claim 31, wherein the cancer is drug-resistant.

35. The compound according to any one of claims 1-16 for use in a method for treating a disease selected from amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastases, glioblastoma multiforme, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade

follicular lymphoma, malignant melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma.

36. The compound for use according to claim 35, for administering with a second active agent or a support care therapy.

37. The compound for use according to claim 36, wherein the second active agent is a therapeutic antibody that specifically binds to a cancer antigen, a hematopoietic growth factor, a cytokine, an anti-cancer agent, an antibiotic, a cox-2 inhibitor, an immunomodulatory agent, an immunosuppressive agent, a corticosteroid or a pharmacologically active mutant or derivative thereof.