What is claimed is:

1. Use of a TOR kinase inhibitor in the manufacture of a medicament for treating E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administration of an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing Ewings sarcoma.

2. The use of claim 1, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

3. The use of claim 2, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

4. The use of claim 1, wherein said patient is to be administered about 0.5 mg/day to about 120 mg/day of a TOR kinase inhibitor.

5. The use of claim 4, wherein said patient is to be administered 0.5 mg/day, 1 mg/day, 2 mg/day, 4 mg/day, 8 mg/day, 16 mg/day, 20 mg/day, 30 mg/day, 45 mg/day, 60 mg/day, 90 mg/day, or 120 mg/day of a TOR kinase inhibitor.

6. The use of claim 1, wherein said patient is to be administered a unit dosage form comprising 0.25 mg, 1.0 mg, 5.0 mg, 7.5 mg, or 10 mg of a TOR kinase inhibitor.

7. A method for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, comprising administration of an effective amount of a TOR kinase inhibitor to a patient having E-twenty six (ETS) overexpressing Ewings sarcoma.

8. The method of claim 7, wherein the ETS overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

9. The method of claim 8, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

10. Use of a TOR kinase inhibitor in the manufacture of a medicament for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administration of an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.

11. The use of claim 10, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

12. The use of claim 11, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

13. Use of a TOR kinase inhibitor in the manufacture of a medicament for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administration of an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated DNA-PK in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.

14. The use of claim 13, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

15. The use of claim 14, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

16. Use of a TOR kinase inhibitor in the manufacture of a medicament for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administration of an effective amount of a TOR kinase inhibitor to said patient, measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of a TOR kinase inhibitor.

17. The use of claim 16, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

18. The use of claim 17, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

19. Use of a TOR kinase inhibitor in the manufacture of a medicament for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administration of an effective amount of a TOR kinase inhibitor to said patient, measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of a TOR kinase inhibitor.

20. The use of claim 19, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

21. The use of claim 20, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

22. A kit comprising a TOR kinase inhibitor and means for monitoring patient response to administration of said TOR kinase inhibitor, wherein said patient has E-twenty six (ETS) overexpressing Ewings sarcoma.

CLAIMS

What is claimed is:

1. Use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof in the manufacture of a medicament for treating E-twenty six (ETS) overexpressing Ewings sarcoma in a patient, wherein the patient is having ETS overexpressing Ewings sarcoma.

2. The use of claim 1, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

3. The use of claim 2, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

4. The use of claim 1, wherein said patient is to be administered about 0.5 mg/day to about 120 mg/day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof.

5. The use of claim 4, wherein said patient is to be administered 0.5 mg/day, 1 mg/day, 2 mg/day, 4 mg/day, 8 mg/day, 16 mg/day, 20 mg/day, 30 mg/day, 45 mg/day, 60 mg/day, 90 mg/day, or 120 mg/day of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof.

6. The use of claim 1, wherein said patient is to be administered a unit dosage form comprising 0.25 mg, 1.0 mg 5.0 mg, 7.5 mg, or 10 mg of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof.

7. Use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof in the manufacture of a medicament for treating E-twenty six (ETS) overexpressing Ewings sarcoma in a patient by improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of said patient.

8. The use of claim 7, wherein the ETS overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

9. The use of claim 8, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

10. An *in vitro method* for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof.

11. The method of claim 10, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

12. The method of claim 11, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

13. An *in vitro* method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample of said patient who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof, and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof.

14. The method of claim 13, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated.

15. The method of claim 14, wherein the E-twenty six (ETS) overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

16. A kit comprising 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof and means for monitoring patient response to administration of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof, wherein said patient has E-twenty six (ETS) overexpressing Ewings sarcoma.

[0010] Citation or identification of any reference in Section 2 of this application is not to be construed as an admission that the reference is prior art to the present application.

3. SUMMARY

[0011] In one aspect, the present disclosure refers to use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof in the manufacture of a medicament for treating E-twenty six (ETS) overexpressing Ewings sarcoma in a patient, wherein the patient is having ETS overexpressing Ewings sarcoma.~~a TOR kinase inhibitor in the manufacture of a medicament for treating E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administration of an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing Ewings sarcoma~~. ~~Provided~~ Disclosed herein are methods for treating or preventing E-twenty six (ETS) overexpressing Ewings sarcoma comprising administering an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing Ewings sarcoma.

[0012] In another aspect, the disclosure refers to the use of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof in the manufacture of a medicament for treating E-twenty six (ETS) overexpressing Ewings sarcoma in a patient by improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of said patient.~~a method for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, comprising administration of an effective amount of a TOR kinase inhibitor to a patient having E-twenty six (ETS) overexpressing Ewings sarcoma~~. In certain examples, ~~provided~~ disclosed herein are methods for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, comprising administering an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing Ewings sarcoma.

~~[0013] In yet another aspect, the disclosure refers to use of a TOR kinase inhibitor in the manufacture of a medicament for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administration of an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition. In some examples, the TOR kinase inhibitor is a compound as described herein.~~

[0014~~0~~0013] ~~In a further aspect, the disclosure refers to use of a TOR kinase inhibitor in the manufacture of a medicament for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having E-twenty six (ETS) overexpressing Ewings sarcoma,~~

~~comprising administration of an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated DNA-PK in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.~~

~~[0014]~~ In one aspect, the present disclosure refers to ~~use of a TOR kinase inhibitor in the manufacture of a medicament~~an *in vitro* method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising ~~administration of an effective amount of a TOR kinase inhibitor to said patient,~~ measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof~~a TOR kinase inhibitor~~. In another aspect, the present disclosure refers to ~~use of a TOR kinase inhibitor in the manufacture of a medicament~~an *in vitro* method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, comprising ~~administration of an effective amount of a TOR kinase inhibitor to said patient,~~ measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample of said patient who was administered an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof, and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof~~a TOR kinase inhibitor~~. In yet another aspect, the present disclosure refers to a kit comprising 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof~~a TOR kinase inhibitor~~ and means for monitoring patient response to administration of 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer or isotopologue thereof~~said TOR kinase inhibitor~~, wherein said patient has E-twenty six (ETS) overexpressing Ewings sarcoma.

The present examples can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting examples.

4. DETAILED DESCRIPTION

4.1 DEFINITIONS

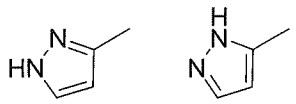
[0015] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some ~~embodiments~~examples, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative

alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl and the like. Examples of unsaturared alkyl groups include, but are not limited to, vinyl, allyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, $-C\equiv CH$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-CH_2C\equiv CH$, $-CH_2C\equiv C(CH_3)$ and $-CH_2C\equiv C(CH_7CH_3)$, among others. An alkyl group can be substituted or unsubstituted. In

included within the ~~embodiments~~examples disclosed herein, including mixtures thereof. The use of stereomerically pure forms of such TOR kinase inhibitors, as well as the use of mixtures of those forms are encompassed by the ~~embodiments~~examples disclosed herein. For example, mixtures comprising equal or unequal amountsv of the enantiomers of a particular TOR kinase inhibitor may be used in methods and compositions disclosed herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al., Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al., Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0042] It should also be noted the TOR kinase inhibitors can include E and Z isomers, or a mixture thereof, and cis and trans isomers or a mixture thereof. In certain ~~embodiments~~examples, the TOR kinase inhibitors are isolated as either the cis or trans isomer. In other ~~embodiments~~examples, the TOR kinase inhibitors are a mixture of the cis and trans isomers.

[0043] "Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



[0044] As readily understood by one skilled in the art, a wide variety of functional groups and other stuctures may exhibit tautomerism and all tautomers of the TOR kinase inhibitors are within the scope of the present invention defined in the claims.

[0045] It should also be noted the TOR kinase inhibitors can contain unnatural proportions of atomic isotopes at one or more of the atoms. For example, the compounds

may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), sulfur-35 (^{35}S), or carbon-14 (^{14}C), or may be isotopically enriched, such as with deuterium (^{2}H), carbon-13 (^{13}C), or nitrogen-15 (^{15}N). As used herein, an "isotopologue" is an isotopically enriched compound. The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term "isotopic composition" refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically encriched compounds are useful as therapeutic agents, e.g., cancer and inflammation therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the TOR kinase inhibitors as described herein, whether radioactive or not, are intended to be encompassed within the scope of the ~~embodiments~~ examples provided herein. In some ~~embodiments~~examples, there are provided isotopologues of the TOR kinase inhibitors, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched TOR kinase inhibitors.

[0046] "Treating" as used herein, means an alleviation, in whole or in part, of ETS overexpressing Ewings sarcoma, or a symptom thereof, or slowing, or halting of further progression or worsening of ETS overexpressing Ewings sarcoma or a symptom thereof.

[0047] "Preventing" as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of ETS overexpressing Ewings sarcoma, or a symptom thereof.

[0048] The term "effective amount" in connection with an TOR kinase inhibitor means an amount capable of alleviating, in whole or in part, symptoms associated with ETS overexpressing Ewings sarcoma, or slowing or halting further progression or worsening of those symptoms, or treating or preventing ETS overexpressing Ewings sarcoma. The effective amount of the TOR kinase inhibitor, for example in a pharmaceutical composition, may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 100 mg/kg of a patient's body weight in unit dosage for both oral and parenteral administration. As will be apparent to those skilled in the art, it is to be

expected that the effective amount of a TOR kinase inhibitor disclosed herein may vary depending on the severity of the indication being treated.

[0049] The terms "patient" and "subject" as used herein include an animal, including, but not limited to, an animal such as a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig, in one ~~embodiment~~example a mammal, in another ~~embodiment~~example a human. In one ~~embodiment~~example, a "patient" or "subject" is a human having ETS overexpressing Ewings sarcoma. In one ~~embodiment~~example, a patient is a human having histologically or cytologically-confirmed ETS overexpressing Ewings sarcoma, including subjects who have progressed on (or not been able to tolerate) standard anticancer therapy or for whom no standard anticancer therapy exists.

[0050] In the context of ETS overexpressing Ewings sarcoma, treatment may be assessed by inhibition of disease progression, inhibition of tumor growth, reduction of primary and/or secondary tumor(s), relief of tumor-related symptoms, improvement in quality of life, inhibition of tumor secreted factors (including tumor secreted hormones, such as those that contribute to carcinoid syndrome), delayed appearance of primary and/or secondary tumor(s), slowed development of primary and/or secondary tumor(s), decreased occurrence of primary and/or secondary tumor(s), slowed or decreased severity of secondary effects of disease, arrested tumor growth and/or regression of tumors, among others. In certain ~~embodiments~~examples, treatment of ETS overexpressing Ewings sarcoma may be assessed by the inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in circulating blood and/or tumor cells and/or skin biopsies or tumor biopsies/aspirates, before, during, and/or after treatment with a TOR kinase inhibitor. In other ~~embodiments~~examples, treatment of ETS overexpressing Ewings sarcoma may be assessed by the inhibition of DNA-dependent protein kinase (DNA-PK) activity in skin samples and/or tumor biopsies/aspirates, such as by assessment of the amount of pDNA-PK S2056 as a biomarker for DNA damage pathways before, during and/or after TOR kinase inhibitor treatment. In one ~~embodiment~~example, the skin sample is irradiated by UV light. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident ETS overexpressing Ewings sarcoma

altogether or preventing the onset of a preclinically evident stage of ETS overexpressing Ewings sarcoma. Also intended to be encompassed by this definition is the prevention of transformation into malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing ETS overexpressing Ewings sarcoma.

4.2 BRIEF DESCRIPTION OF THE DRAWINGS

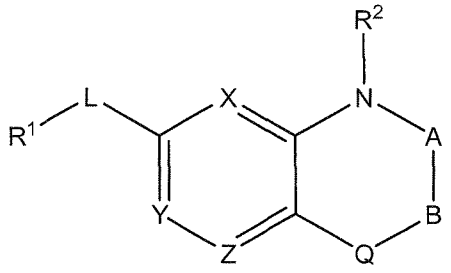
[0051] FIG. 1 provides a clonogenic growth inhibition assay for Compound 1 with ETS positive and ETS negative cell lines.

[0052] FIG. 2 provides the potentiation of DNA damage by Compound 1 in ETS positive cells.

4.3 TOR KINASE INHIBITORS

[0053] The compounds ~~provided~~disclosed herein are generally referred to as "TOR kinase inhibitor(s)." In a specific embodiment, the TOR kinase inhibitors do not include rapamycin or rapamycin analogs (rapalogs).

[0054] ~~In one embodiment, the~~The subject matter of the present invention is as defined in the claims. Also disclosed herein are TOR kinase inhibitors include compounds having the following formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

X, Y and Z are at each occurrence independently N or CR^3, wherein at least one of X, Y and Z is N and at least one of X, Y and Z is CR^3;

-A-B-Q- taken together form $-CHR^4C(O)NH-$, $-C(O)CHR^4NH-$, -C(O)NH-, $-CH_2C(O)O-$, $-C(O)CH_2O-$, -C(O)O- or $C(O)NR^3$;

L is a direct bond, NH or O;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl;

R^3 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclylalkyl, $-NHR^4$ or $-N(R^4)_2$; and

R^4 is at each occurrence independently substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[0055] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-CH_2C(O)NH-$.

[0056] In another example~~embodiment~~, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)CH_2NH-$.

[0057] In another example~~embodiment~~, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-.

[0058] In another example~~embodiment~~, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-CH_2C(O)O-$.

[0059] In another example~~embodiment~~, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)CH_2O-$.

[0060] In another example~~embodiment~~, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)O-.

[0061] In another example~~embodiment~~, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)NR^3-$.

[0062] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein Y is CR^3.

[0063] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CR^3.

[0064] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CH.

[0065] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein X and Z are CH and Y is N.

[0066] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein Y and Z are CH and X is N.

[0067] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein X and Y are CH and Z is N.

[0068] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[0069] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[0070] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[0071] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^1 is H.

[0072] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl.

[0073] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[0074] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[0075] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[0076] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein R^2 is H.

[0077] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein L is a direct bond.

[0078] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-, X and Z are N and Y is CH, R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, L is a direct bond, and R^2 is substituted or unsubstituted C_{1-8}alkyl.

[0079] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-, X and Z are N and Y is CH, R^1 is substituted or unsubstituted aryl, L is a direct bond, and R^2 is substituted or unsubstituted C_{1-8}alkyl.

[0080] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-, X and Z are N and Y is CH, R^1 is substituted or unsubstituted aryl, and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[0081] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-, X and Z are N and Y is CH, R^1 is substituted or unsubstituted aryl, and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[0082] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-, X and Z are N and Y is CH, R^1 is substituted phenyl, L is a direct bond, and R^2 is substituted C_{1-8}alkyl.

[0083] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is -C(O)NH-, L is a direct bond, R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, and R^2 is C_{1-8}alkyl substituted with substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0084] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is -C(O)NH-, L is a direct bond, R^1 is phenyl, naphthyl, indanyl or biphenyl, each of which may be optionally substituted with one or more substituents independently selected from the group consisting substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[0085] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is -C(O)NH-, L is a direct bond, R^1 is phenyl, naphthyl or biphenyl, each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-4}alkyl, amino, aminoC_{1-12}alkyl, halogen, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, $-CF_3$, C_{1-12}alkoxy, aryloxy, arylC_{1-12}alkoxy, -CN, $-OCF_3$, $-COR_g$, $-COOR_g$, $-CONR_gR_h$, $-NR_gCOR_h$, $-SO_2R_g$, $-SO_3R_g$ or $-SO_2NR_gR_h$, wherein each R_g and R_h are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl; or A is a 5- to 6-membered monocyclic heteroaromatic ring having from one, two, three or four heteroatoms independently selected from the group consisting of N, O and S, that monocyclic heteroaromatic ring may be optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, amino, aminoC_{1-12}alkyl, halogen, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-12}alkoxy, aryloxy, aryl C_{1-12}alkoxy, -CN, $-CF_3$, $-OCF_3$, $-COR_i$, $-COOR_i$, $-CONR_iR_j$, $-NR_iCOR_j$, $-NR_iSO_2R_j$, $-SO_2R_i$, $-SO_3R_i$ or $-SO_2NR_iR_j$, wherein each R_i and R_j are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-6}cycloalkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl; or A is a 8- to 10

membered bicyclic heteroaromatic ring from one, two, three or four heteroatoms selected from the group consisting of N, O and S, and may be optionally substituted with one, two or three substituents each independently selected from the group consisting of C_{1-6}alkyl, amino, aminoC_{1-12}alkyl, halogen, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-12}alkoxy, aryloxy, aryl C_{1-12}alkoxy, -CN, -CF_3, -OCF_3, -COR_k, -$COOR_k$, -$CONR_kR_l$, -NR_kCOR_l, -$NR_kSO_2R_l$, -SO_2R_k, -SO_3R_k or -$SO_2NR_kR_l$, wherein each R_k and R_l are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl, and R^2 is C_{1-8}alkyl substituted with substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0086] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Y are both N and Z is CH, -A-B-Q- is -C(O)NH-, L is a direct bond, R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted heteroaryl, and R^2 is substituted or unsubstituted methyl, unsubstituted ethyl, unsubstituted propyl, or an acetamide.

[0087] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Y are both N and Z is CH, -A-B-Q- is -C(O)NH-, L is a direct bond, R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted heteroaryl, and R^2 is an acetamide.

[0088] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X is N and Y and Z are both CH, -A-B-Q- is -C(O)NH-, L is a direct bond, R^1 is a (2,5'-Bi-1H-benzimidazole)-5-carboxamide, and R^2 is H.

[0089] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein one of X and Z is CH and the other is N, Y is CH, -A-B-Q- is -C(O)NH-, L is a direct bond, R^1 is unsubstituted pyridine, and R^2 is H, methyl or substituted ethyl.

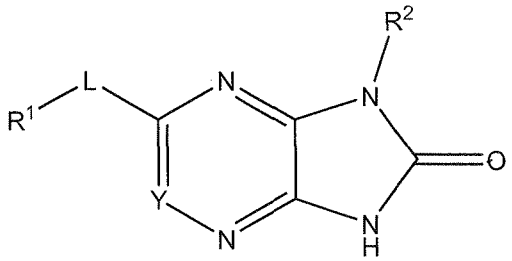
[0090] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is -C(O)NH-, R^1 is H, C_{1-8}alkyl, C_{2-8}alkenyl, aryl or cycloalkyl, and L is NH.

[0091] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is $-C(O)NR^3-$, R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl, and L is NH.

[0092] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include compounds wherein R^1 is a substituted or unsubstituted oxazolidinone.

[0093] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (I) do not include one or more of the following compounds: 1,7-dihydro-2-phenyl-8H-Purin-8-one, 1,2-dihydro-3-phenyl-6H-Imidazo[4,5-e]-1,2,4-triazin-6-one, 1,3-dihydro-6-(4-pyridinyl)-2H-Imidazo[4,5-b]pyridin-2-one, 6-(1,3-benzodioxol-5-yl)-1,3-dihydro-1-[(1S)-1-phenylethyl]- 2H-Imidazo[4,5-b]pyrazin-2-one, 3-[2,3-dihydro-2-oxo-3-(4-pyridinylmethyl)-1H-imidazo[4,5-b]pyrazin-5-yl]-Benzamide, 1-[2-(dimethylamino)ethyl]-1,3-dihydro-6-(3,4,5-trimethoxyphenyl)-2H-Imidazo[4,5-b]pyrazin-2-one, N-[5-(1,1-dimethylethyl)-2-methoxyphenyl]-N'-[4-(1,2,3,4-tetrahydro-2-oxopyrido[2,3-b]pyrazin-7-yl)-1-naphthalenyl]-Urea, N-[4-(2,3-dihydro-2-oxo-1H-imidazo[4,5-b]pyridin-6-yl)-1-naphthalenyl]-N'-[5-(1,1-dimethylethyl)-2-methoxyphenyl]-Urea, 1,3-dihydro-5-phenyl-2H-Imidazo[4,5-b]pyrazin-2-one, 1,3-dihydro-5-phenoxy-2H-Imidazo[4,5-b]pyridin-2-one, 1,3-dihydro-1-methyl-6-phenyl-2H-Imidazo[4,5-b]pyridin-2-one, 1,3-dihydro-5-(1H-imidazol-1-yl) 2H-Imidazo[4,5-b]pyridin-2-one, 6-(2,3-dihydro-2-oxo-1H-imidazo[4,5-b]pyridin-6-yl)-8-methyl-2(1H)-Quinolinone and 7,8-dihydro-8-oxo-2-phenyl-9H-purine-9-acetic acid.

[0094] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (Ia):



(Ia)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

L is a direct bond, NH or O;

Y is N or CR^3;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl;

R^3 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclylalkyl, $-NHR^4$ or $-N(R^4)_2$; and

R^4 is at each occurrence independently substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[0095] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[0096] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[0097] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[0098] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is H.

[0099] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted C_{1-8}alkyl.

[00100] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00101] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00102] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00103] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is H.

[00104] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein Y is CH.

[00105] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein L is a direct bond.

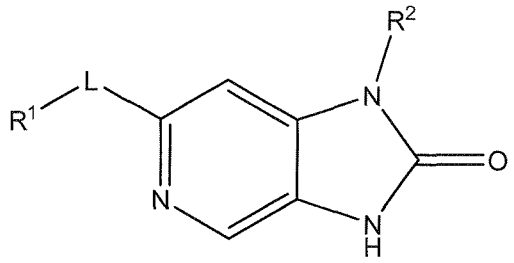
[00106] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00107] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00108] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00109] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ia) do not include compounds wherein Y is CH, L is a direct bond, R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, and R^2 is C_{1-8}alkyl substituted with substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[00110] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (Ib):



(Ib)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

L is a direct bond, NH or O;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl; and

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00111] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00112] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[00113] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[00114] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is H.

[00115] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted C_{1-8}alkyl.

[00116] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00117] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00118] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00119] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is H.

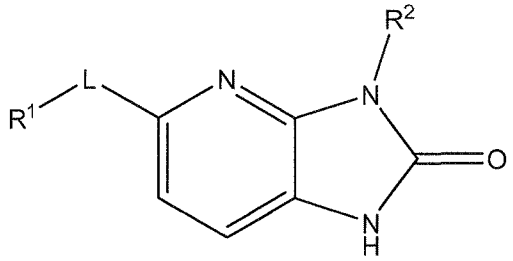
[00120] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein L is a direct bond.

[00121] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00122] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00123] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00124] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (Ic):



(Ic)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

L is a direct bond, NH or O;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl; and

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00125] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00126] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[00127] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[00128] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is H.

[00129] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted C_{1-8}alkyl.

[00130] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00131] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00132] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00133] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is H.

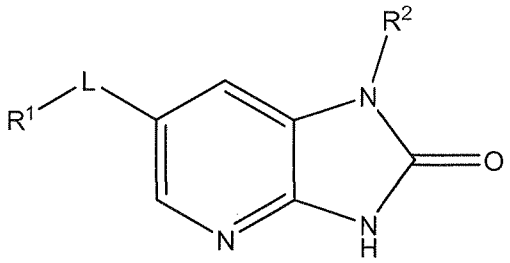
[00134] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein L is a direct bond.

[00135] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00136] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00137] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00138] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (Id):



(Id)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

L is a direct bond, NH or O;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl; and

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00139] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00140] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[00141] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[00142] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is H.

[00143] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted C_{1-8}alkyl.

[00144] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00145] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00146] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00147] In another ~~embodiment~~example, the Heteroaryl Compounds of formula (Id) are those wherein R^2 is H.

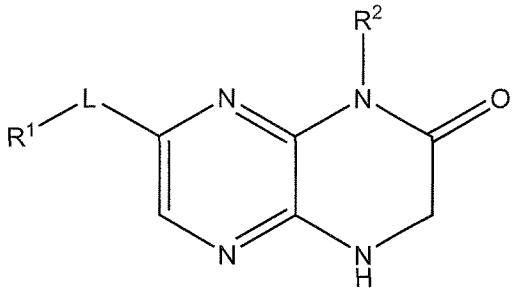
[00148] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein L is a direct bond.

[00149] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00150] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00151] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00152] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (Ie):



(Ie)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

L is a direct bond, NH or O;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl; and

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00153] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00154] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[00155] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[00156] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is H.

[00157] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted C_{1-8}alkyl.

[00158] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00159] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00160] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00161] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is H.

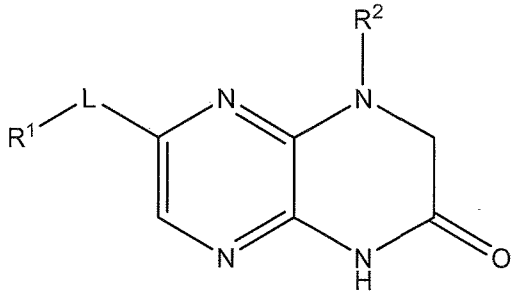
[00162] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein L is a direct bond.

[00163] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00164] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00165] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00166] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (If):



(If)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

L is a direct bond, NH or O;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl; and

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00167] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00168] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[00169] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[00170] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^1 is H.

[00171] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted C_{1-8}alkyl.

[00172] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00173] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00174] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00175] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^2 is H.

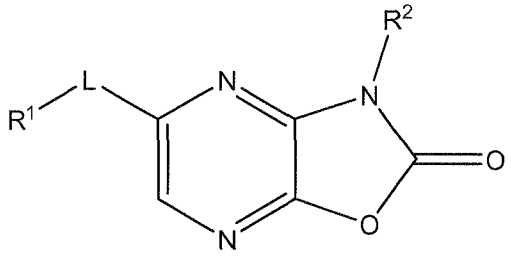
[00176] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein L is a direct bond.

[00177] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00178] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00179] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00180] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (Ig):



(Ig)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

L is a direct bond, NH or O;

R^1 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted C_{2-8}alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl; and

R^2 is H, substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00181] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00182] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

[00183] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted quinoline, substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted indole, or substituted or unsubstituted thiophene.

[00184] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is H.

[00185] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted C_{1-8}alkyl.

[00186] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00187] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00188] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00189] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is H.

[00190] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein L is a direct bond.

[00191] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00192] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00193] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00194] Representative TOR kinase inhibitors of formula (I) include:

(S)-1-(1-hydroxy-3-methylbutan-2-yl)-6-phenyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

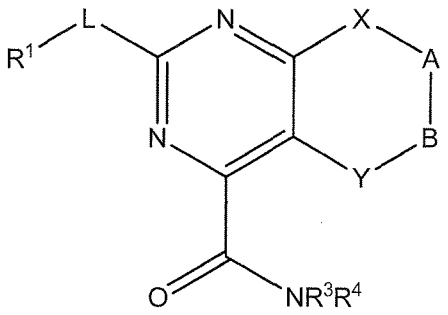
1-((tetrahydro-2H-pyran-4-yl)methyl)-6-(3,4,5-trimethoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

(R)-6-(naphthalen-1-yl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(3-methoxybenzyl)-6-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

6-(6-(2-Hydroxypropan-2-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(4H-1,2,4-Triazol-3-yl)phenyl)-1-(2-morpholino-2-oxoethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-6-(4-(4H-1,2,4-Triazol-3-yl)phenyl)-3-(cyclohexylmethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(R)-6-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-B]pyrazin-2(3H)-one;
(S)-6-(4-(4H-1,2,4-Triazol-3-yl)phenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(1r,4r)-4-(6-(4-(2-Hydroxypropan-2-yl)phenyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-1-yl)cyclohexanecarboxamide; and
6-(4-(5-Methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one,
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof.

[00195] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (II):



(II)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl;

-X-A-B-Y- taken together form $-N(R^2)CH_2C(O)NH-$, $-N(R^2)C(O)CH_2NH-$, $-N(R^2)C(O)NH-$, $-N(R^2)C=N-$, or $-C(R^2)=CHNH-$;

L is a direct bond, NH or O;

R^2 is substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl; and

R^3 and R^4 are independently H or C_{1-8}alkyl.

[00196] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)CH_2C(O)NH-$.

[00197] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)CH_2NH-$.

[00198] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)NH-$.

[00199] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C=N-$.

[00200] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-C(R^2)=CHNH-$.

[00201] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein L is a direct bond.

[00202] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00203] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, substituted or unsubstituted indole or substituted or unsubstituted quinoline.

[00204] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00205] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)NH-$ and R^1 is substituted aryl, such as phenyl.

[00206] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)NH-$ and R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, substituted or unsubstituted indole or substituted or unsubstituted quinoline.

[00207] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)NH-$ and R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00208] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00209] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00210] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00211] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00212] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclohexyl or substituted or unsubstituted cycloheptyl.

[00213] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00214] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein R^3 and R^4 are H.

[00215] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH- and R^2 is unsubstituted aryl, such as unsubstituted phenyl.

[00216] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, and R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00217] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl, and R^3 and R^4 are H.

[00218] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, L is a direct bond, R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl, and R^3 and R^4 are H.

[00219] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl, and R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00220] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl, R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl, and R^3 and R^4 are H.

[00221] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, L is a direct bond, R^1 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl, R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl, and R^3 and R^4 are H.

[00222] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted heteroaryl, L is a direct bond and R^2 is substituted or unsubstituted C_{1-8}alkyl or substituted or unsubstituted cycloalkyl.

[00223] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted aryl, L is a direct bond and R^2 is substituted or unsubstituted C_{1-8}alkyl or substituted or unsubstituted cycloalkyl.

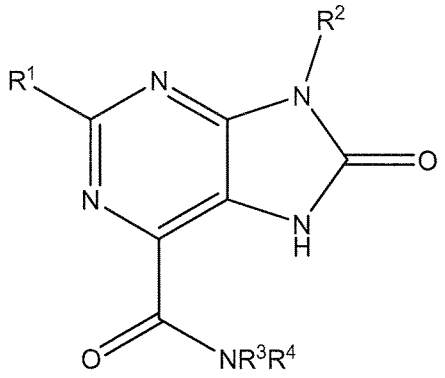
[00224] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) do not include 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-purine-6-carboxamide, 2-(4-cyanophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 2-(4-nitrophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 9-benzyl-2-(4-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide, 2-methyl-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 9-benzyl-9H-purine-2,6-dicarboxamide, 9-[2,3-bis[(benzoyloxy)methyl]cyclobutyl]-2-methyl-9H-Purine-6-carboxamide, 9-benzyl-2-methyl-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-methyl-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-(trifluoromethyl)-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-(prop-1-enyl)-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-phenyl-9H-purine-6-carboxamide, 9-(3-hydroxypropyl)-2-methyl-9H-purine-6-carboxamide, 9-(3-hydroxypropyl)-2-(trifluoromethyl)-9H-purine-6-carboxamide, 2-methyl-9-phenylmethyl-9H-purine-6-carboxamide or 2-methyl-9-β-D-ribofuranosyl-9H-purine-6-carboxamide.

[00225] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted furanoside.

[00226] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00227] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (II) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00228] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (IIa):



(IIa)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

R^1 is substituted or unsubstituted $C_{1\text{-}8}$alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is substituted or unsubstituted $C_{1\text{-}8}$alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl; and

R^3 and R^4 are independently H or $C_{1\text{-}8}$alkyl.

[00229] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^1 is substituted aryl, substituted or unsubstituted heteroaryl, such as substituted phenyl.

[00230] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, substituted or unsubstituted indole or substituted or unsubstituted quinoline.

[00231] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00232] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl, such as $-CH_2C_6H_5$.

[00233] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is unsubstituted $C_{1\text{-}8}$alkyl, such as unsubstituted methyl.

[00234] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00235] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00236] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclohexyl or substituted or unsubstituted cycloheptyl.

[00237] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00238] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) are those wherein R^3 and R^4 are H.

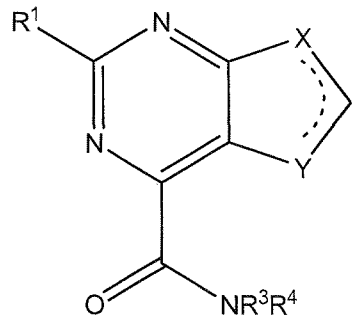
[00239] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) do not include 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 2-(4-cyanophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 2-(4-nitrophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 9-benzyl-2-(4-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide, 9-phenylmethyl-9H-purine-2,6-dicarboxamide, or 2-methyl-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide.

[00240] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted furanoside.

[00241] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00242] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIa) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00243] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (IIb):



(IIb)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

—X⌒Y— is $-C(R^2)=CH-NH-$ or $-N(R^2)-CH=N-$;

R^1 is substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl; and

R^3 and R^4 are independently H or C_{1-8}alkyl.

[00244] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00245] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, substituted or unsubstituted indole or substituted or unsubstituted quinoline.

[00246] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00247] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00248] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00249] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00250] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00251] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclohexyl or substituted or unsubstituted cycloheptyl.

[00252] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00253] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^3 and R^4 are H.

[00254] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein  is $-C(R^2)=CH-NH-$ and R^2 is substituted aryl, such as substituted phenyl.

[00255] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein  is $-N(R^2)-CH=N-$ and R^2 is substituted aryl, such as substituted phenyl.

[00256] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted aryl, such as phenyl, and R^2 is substituted aryl, such as substituted phenyl.

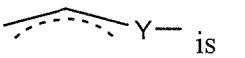
[00257] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) do not include 9-benzyl-9H-purine-2,6-dicarboxamide, 9-[2,3-bis[(benzoyloxy)methyl]cyclobutyl]-2-methyl-9H-Purine-6-carboxamide, 9-benzyl-2-methyl-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-methyl-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-(trifluoromethyl)-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-(prop-1-enyl)-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-phenyl-9H-purine-6-carboxamide, 9-(3-hydroxypropyl)-2-methyl-9H-

purine-6-carboxamide, 9-(3-hydroxypropyl)-2-(trifluoromethyl)-9H-purine-6-carboxamide, 9-phenylmethyl-9H-purine-2,6-dicarboxamide, 2-methyl-9-phenylmethyl-9H-purine-6-carboxamide or 2-methyl-9-β-D-ribofuranosyl-9H-purine-6-carboxamide.

[00258] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted cyclobutyl when  is $-N(R^2)-CH=N-$.

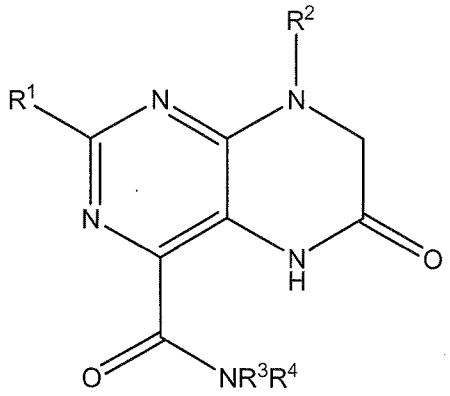
[00259] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is a substituted furanoside when  is $-N(R^2)-CH=N-$.

[00260] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted pyrimidine when  is $-C(R^2)=CH-NH-$.

[00261] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted oxetane when  is $-N(R^2)-CH=N-$.

[00262] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted cyclopentyl or a heterocyclopentyl when  is $-N(R^2)-CH=N-$.

[00263] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (IIc):



(IIc)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

R^1 is substituted or unsubstituted $C_{1\text{-}8}$alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is substituted or unsubstituted $C_{1\text{-}8}$alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl; and

R^3 and R^4 are independently H or $C_{1\text{-}8}$alkyl.

[00264] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00265] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, substituted or unsubstituted indole or substituted or unsubstituted quinoline.

[00266] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00267] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl, such as $-CH_2C_6H_5$.

[00268] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00269] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

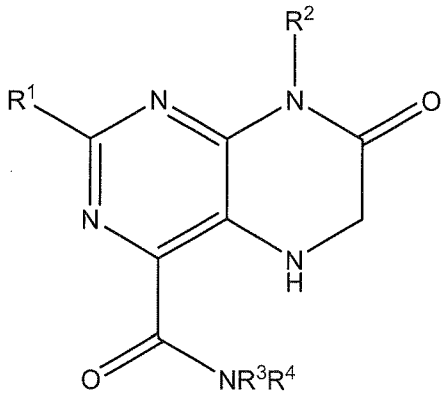
[00270] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00271] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclohexyl or substituted or unsubstituted cycloheptyl.

[00272] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00273] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IIc) are those wherein R^3 and R^4 are H.

[00274] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (IId):



(IId)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is substituted or unsubstituted C_{1-8}alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl; and

R^3 and R^4 are independently H or C_{1-8}alkyl.

[00275] In one ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00276] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^1 is substituted or unsubstituted heteroaryl, such as substituted or unsubstituted pyridine, substituted or unsubstituted indole or substituted or unsubstituted quinoline.

[00277] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00278] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00279] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00280] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00281] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00282] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclohexyl or substituted or unsubstituted cycloheptyl.

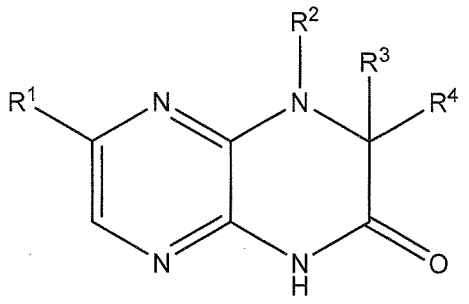
[00283] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00284] In another ~~embodiment~~example, the TOR kinase inhibitors of formula (IId) are those wherein R^3 and R^4 are H.

[00285] Representative TOR kinase inhibitors of formula (IV) include:

9-benzyl-8-oxo-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;

[00286] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (III):



(III)

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

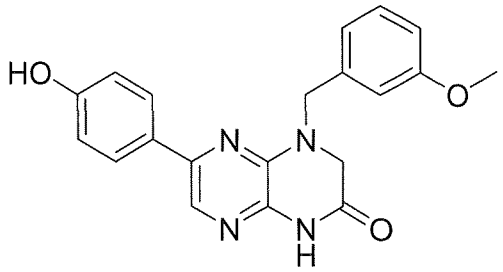
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

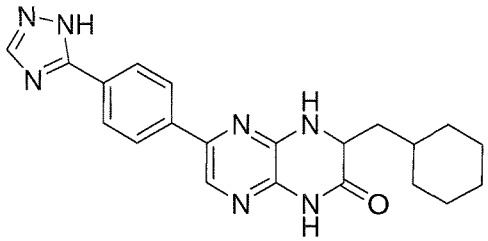
R^3 and R^4 are each independently H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkylalkyl, or R^3 and R^4, together with the atoms to which they are attached, form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclyl;

or R^2 and one of R^3 and R^4, together with the atoms to which they are attached, form a substituted or unsubstituted heterocyclyl,

wherein in certain ~~embodiments~~examples, the TOR kinase inhibitors do not include the compounds depicted below, namely:

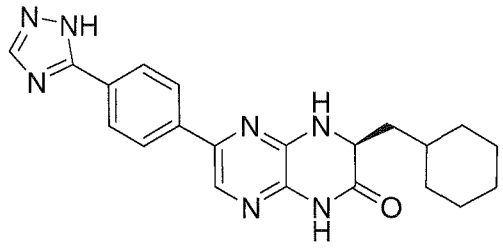


6-(4-hydroxyphenyl)-4-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;



6-(4-(1H-1,2,4-triazol-5-yl)phenyl)-3-(cyclohexylmethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

or,

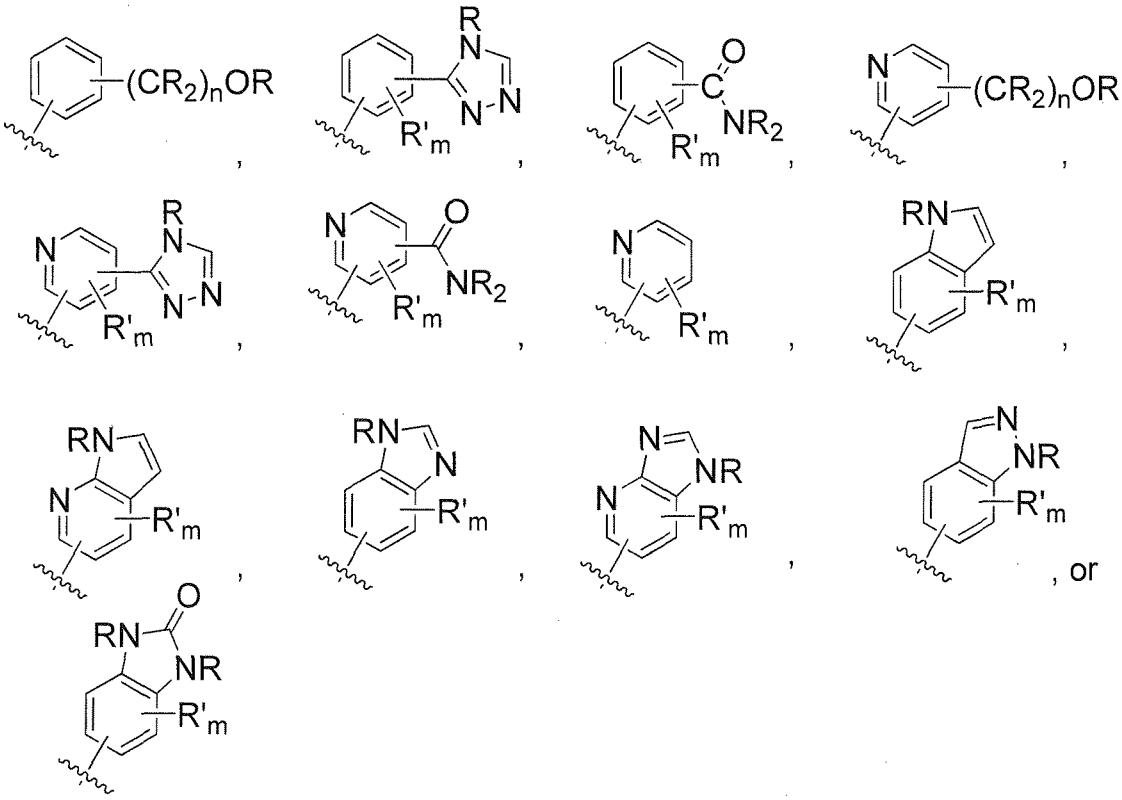


(R)-6-(4-(1H-1,2,4-triazol-5-yl)phenyl)-3-(cyclohexylmethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

[00287] In some ~~embodiments~~examples of compounds of formula (III), R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In one ~~embodiment~~example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, indolyl, indazolyl, 1H-pyrrolo[2,3-b]pyridyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 3H-imidazo[4,5-b]pyridyl, or pyrazolyl, each optionally substituted. In some ~~embodiments~~examples, R^1 is phenyl substituted with one or more substituents independently selected from the group consisting of

substituted or unsubstituted C_{1-8} alkyl (for example, methyl), substituted or unsubstituted heterocyclyl (for example, substituted or unsubstituted triazolyl or pyrazolyl), halogen (for example, fluorine), aminocarbonyl, cyano, hydroxyalkyl (for example, hydroxypropyl), and hydroxy. In other ~~embodiments~~examples, R^1 is pyridyl substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted heterocyclyl (for example, substituted or unsubstituted triazolyl), halogen, aminocarbonyl, cyano, hydroxyalkyl, -OR, and $-NR_2$, wherein each R is independently H, or a substituted or unsubstituted C_{1-4} alkyl. In yet other ~~embodiments~~examples, R^1 is 1H-pyrrolo[2,3-b]pyridyl or benzimidazolyl, each optionally substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, and $-NR_2$, wherein each R is independently H, or a substituted or unsubstituted C_{1-4} alkyl.

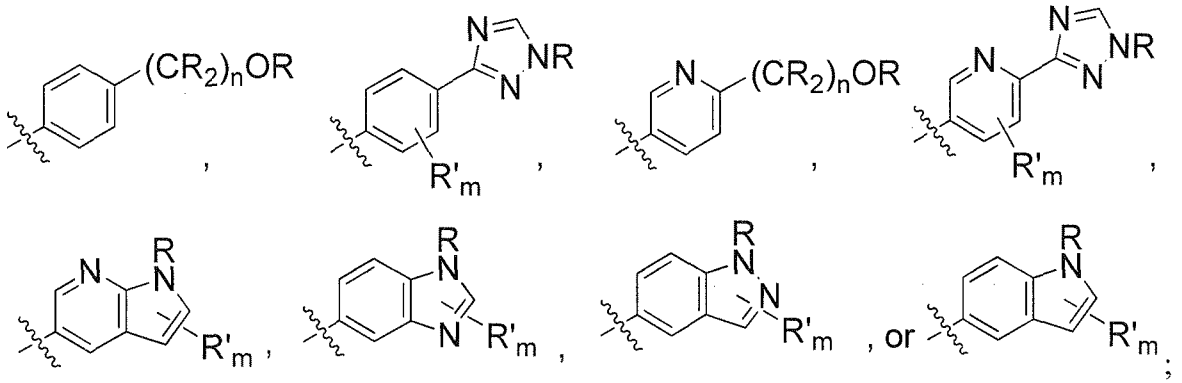
[00288] In some ~~embodiments~~examples of compounds of formula (III), R^1 is



;

wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently a substituted or unsubstituted C_{1-4} alkyl, halogen (for example, fluorine), cyano, -OR, or $-NR_2$; m is 0-3; and n is 0-3. It will be understood by those skilled in the art that any of the subsitutuents R' may be attached to any suitable atom of any of the rings in the fused ring systems. It will also be understood by those skilled in the art that the connecting bond of R^1 (designated by the bisecting wavy line) may be attached to any of the atoms in any of the rings in the fused ring systems.

[00289] In some ~~embodiments~~examples of compounds of formula (III), R^1 is

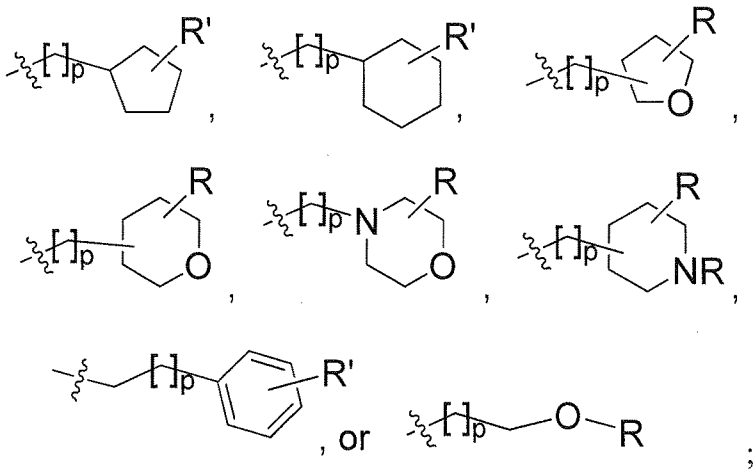


wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl; R' is at each occurrence independently a substituted or unsubstituted C_{1-4} alkyl, halogen, cyano, -OR, or $-NR_2$; m is 0-3; and n is 0-3.

[00290] In some ~~embodiments~~examples of compounds of formula (III), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, or substituted or unsubstituted C_{1-4} alkyl-cycloalkyl. For example, R^2 is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, *sec*-butyl, isobutyl, *tert*-butyl, n-pentyl, isopentyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, (C_{1-4} alkyl)-phenyl, (C_{1-4} alkyl)-cyclopropyl, (C_{1-4} alkyl)-cyclobutyl, (C_{1-4} alkyl)-cyclopentyl, (C_{1-4} alkyl)-cyclohexyl, (C_{1-4} alkyl)-pyrrolidyl,

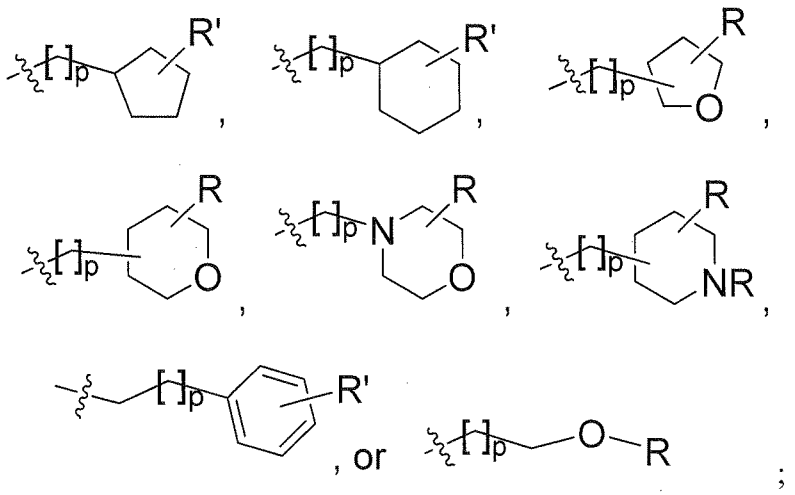
(C_{1-4} alkyl)-piperidyl, (C_{1-4} alkyl)-piperazinyl, (C_{1-4} alkyl)-morpholinyl, (C_{1-4} alkyl)-tetrahydrofuranyl, or (C_{1-4} alkyl)-tetrahydropyranyl, each optionally substituted.

[00291] In other ~~embodiments~~examples, R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



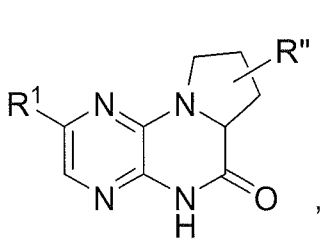
wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently H, -OR, cyano, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); and p is 0-3.

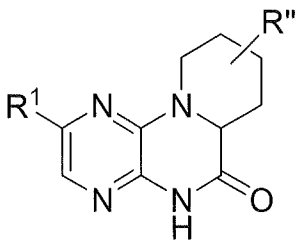
[00292] In some such ~~embodiments~~examples, R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),

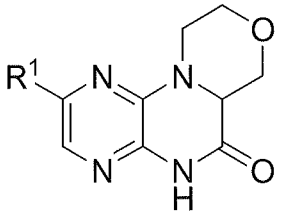


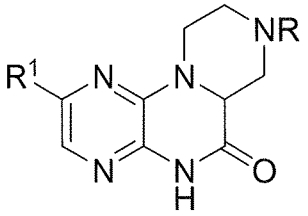
wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-2} alkyl; R' is at each occurrence independently H, -OR, cyano, or a substituted or unsubstituted C_{1-2} alkyl; and p is 0-1.

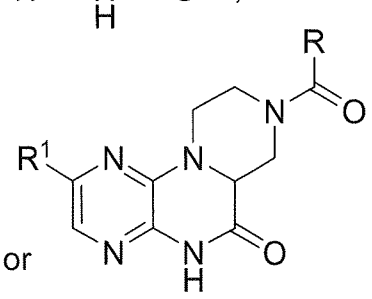
[00293] In some other ~~embodiments~~examples of compounds of formula (III), R^2 and one of R^3 and R^4 together with the atoms to which they are attached form a substituted or unsubstituted heterocyclyl. For example, in some ~~embodiments~~examples, the compound of formula (III) is



,


,


,


, or


;

wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl; R" is H, OR, or a substituted or unsubstituted C_{1-4} alkyl; and R^1 is as defined herein.

[00294] In some ~~embodiments~~examples of compounds of formula (III), R^3 and R^4 are both H. In others, one of R^3 and R^4 is H and the other is other than H. In still others, one of R^3 and R^4 is C_{1-4} alkyl (for example, methyl) and the other is H. In still others, both of R^3 and R^4 are C_{1-4} alkyl (for example, methyl).

[00295] In some such ~~embodiments~~examples described above, R^1 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. For example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, indolyl, indazolyl, 1H-pyrrolo[2,3-b]pyridyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 3H-imidazo[4,5-b]pyridyl, or pyrazolyl, each optionally substituted. In some ~~embodiments~~examples, R^1 is phenyl substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted heterocyclyl, halogen, aminocarbonyl, cyano, hydroxyalkyl and hydroxy. In others, R^1 is

pyridyl substituted with one or more substituents independently selected from the group consisting of cyano, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted heterocyclyl, hydroxyalkyl, halogen, aminocarbonyl, -OR, and $-NR_2$, wherein each R is independently H, or a substituted or unsubstituted C_{1-4} alkyl. In others, R^1 is 1H-pyrrolo[2,3-b]pyridyl or benzimidazolyl, optionally substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, and $-NR_2$, wherein R is independently H, or a substituted or unsubstituted C_{1-4} alkyl

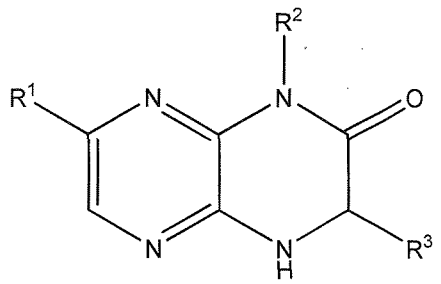
[00296] In certain ~~embodiments~~examples, the compounds of formula (III) have an R^1 group set forth herein and an R^2 group set forth herein.

[00297] In some ~~embodiments~~examples of compounds of formula (III), the compound at a concentration of 10 μM inhibits mTOR, DNA-PK, or PI3K or a combination thereof, by at least about 50%. Compounds of formula (III) may be shown to be inhibitors of the kinases above in any suitable assay system.

[00298] Representative TOR kinase inhibitors of formula (III) include:
6-(1H-pyrrolo[2,3-b]pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-((*trans*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof.

[00299] In one ~~embodiment~~example, the TOR kinase inhibitors include compounds having the following formula (IV):



(IV)

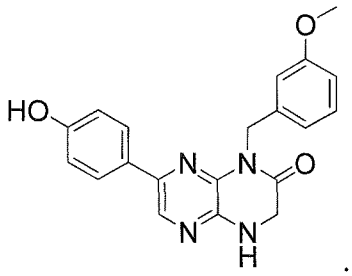
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

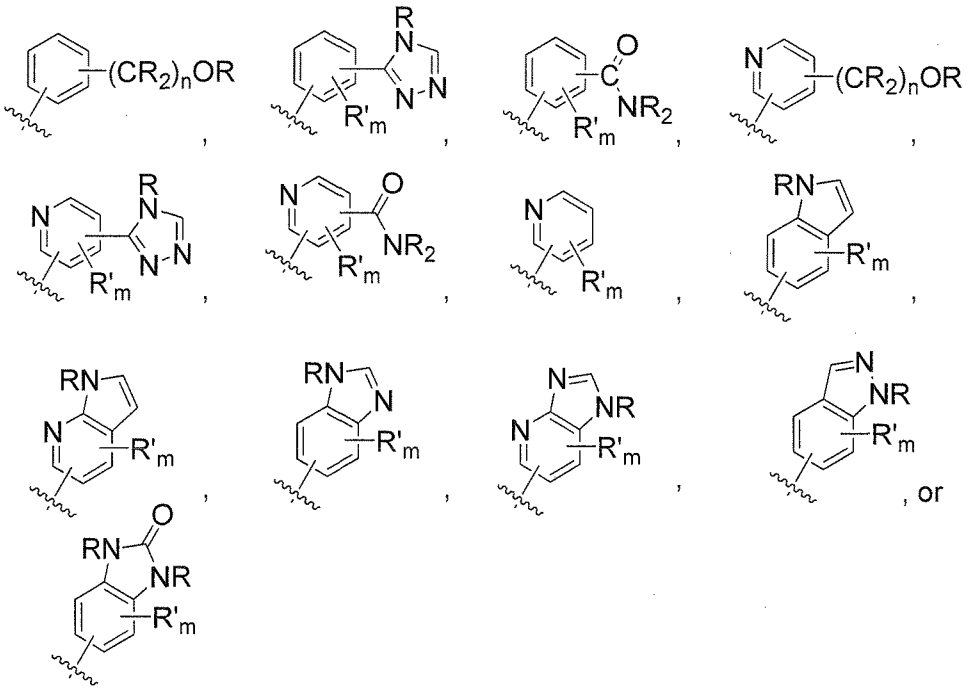
R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

wherein in certain ~~embodiments~~examples, the TOR kinase inhibitors do not include 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one, depicted below:



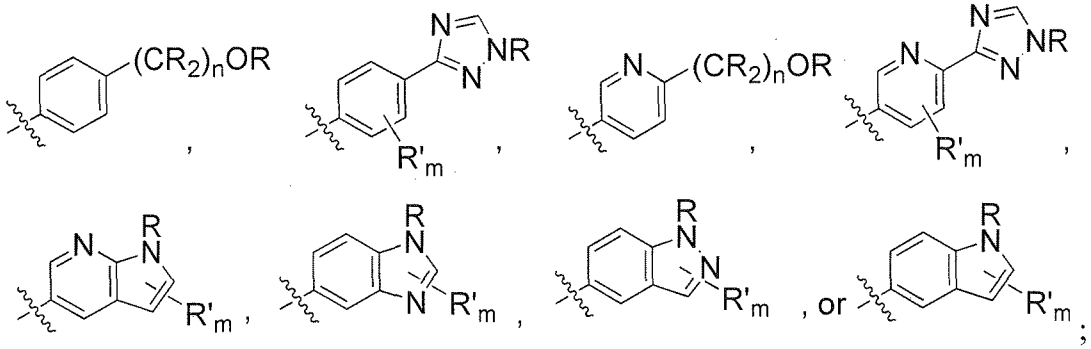
[00300] In some ~~embodiments~~examples of compounds of formula (IV), R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. For example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, 1H-pyrrolo[2,3-b]pyridyl, indazolyl, indolyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 3H-imidazo[4,5-b]pyridyl, or pyrazolyl, each optionally substituted. In some ~~embodiments~~examples, R^1 is phenyl substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl (for example, methyl), substituted or unsubstituted heterocyclyl (for example, a substituted or unsubstituted triazolyl or pyrazolyl), aminocarbonyl, halogen (for example, fluorine), cyano, hydroxyalkyl and hydroxy. In other ~~embodiments~~examples, R^1 is pyridyl substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl (for example, methyl), substituted or unsubstituted heterocyclyl (for example, a substituted or unsubstituted triazolyl), halogen, aminocarbonyl , cyano, hydroxyalkyl (for example, hydroxypropyl), -OR, and $-NR_2$, wherein each R is independently H, or a substituted or unsubstituted C_{1-4} alkyl. In some ~~embodiments~~examples, R^1 is 1H-pyrrolo[2,3-b]pyridyl or benzimidazolyl, optionally substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, and $-NR_2$, wherein R is independently H, or a substituted or unsubstituted C_{1-4} alkyl.

[00301] In some ~~embodiments~~examples, R^1 is



wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently a substituted or unsubstituted C_{1-4} alkyl (for example, methyl), halogen (for example, fluoro), cyano, -OR, or $-NR_2$; m is 0-3; and n is 0-3. It will be understood by those skilled in the art that any of the subsitutuents R' may be attached to any suitable atom of any of the rings in the fused ring systems.

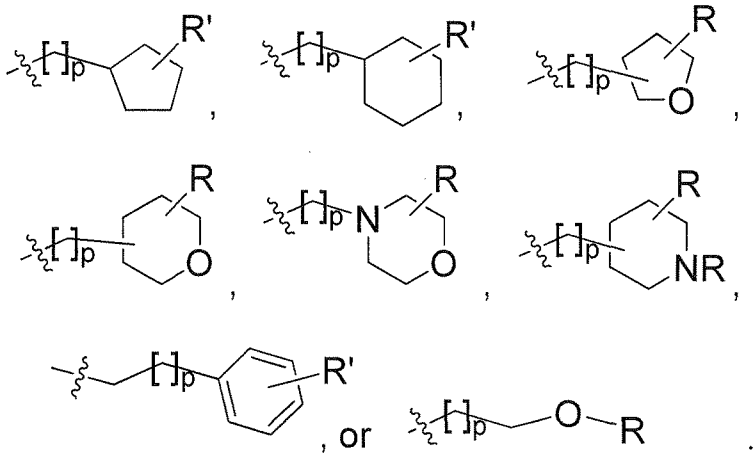
[00302] In some ~~embodiments~~examples of compounds of formula (IV), R^1 is



wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl; R' is at each occurrence independently a substituted or unsubstituted C_{1-4} alkyl, halogen, cyano, -OR or $-NR_2$; m is 0-3; and n is 0-3.

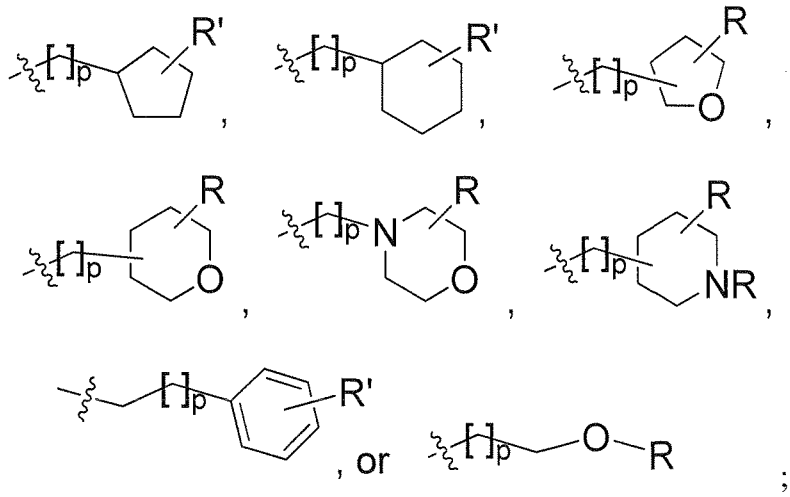
[00303] In some ~~embodiments~~examples of compounds of formula (IV), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, or substituted or unsubstituted C_{1-4} alkyl-cycloalkyl. For example, R^2 is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, *sec*-butyl, isobutyl, *tert*-butyl, n-pentyl, isopentyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, (C_{1-4} alkyl)-phenyl, (C_{1-4} alkyl)-cyclopropyl, (C_{1-4} alkyl)-cyclobutyl, (C_{1-4} alkyl)-cyclopentyl, (C_{1-4} alkyl)-cyclohexyl, (C_{1-4} alkyl)-pyrrolidyl, (C_{1-4} alkyl)-piperidyl, (C_{1-4} alkyl)-piperazinyl, (C_{1-4} alkyl)-morpholinyl, (C_{1-4} alkyl)-tetrahydrofuranyl, or (C_{1-4} alkyl)-tetrahydropyranyl, each optionally substituted.

[00304] In other ~~embodiments~~examples, R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently H, -OR, cyano,or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); and p is 0-3.

[00305] In other ~~embodiments~~examples of compounds of formula (IV), R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-2} alkyl; R' is at each occurrence independently H, -OR, cyano, or a substituted or unsubstituted C_{1-2} alkyl; and p is 0-1.

[00306] In other ~~embodiments~~examples of compounds of formula (IV), R^3 is H.

[00307] In some such ~~embodiments~~examples described herein, R^1 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. For example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, 1H-pyrrolo[2,3-b]pyridyl, indazolyl, indolyl, 1H-imidazo[4,5-b]pyridine, pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 3H-imidazo[4,5-b]pyridyl, or pyrazolyl, each optionally substituted. In some ~~embodiments~~examples, R^1 is phenyl substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted heterocyclyl, aminocarbonyl, halogen, cyano, hydroxyalkyl and hydroxy. In others, R^1 is pyridyl substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, substituted or unsubstituted heterocyclyl, halogen, aminocarbonyl, cyano, hydroxyalkyl, -OR, and $-NR_2$, wherein each R is independently H, or a substituted or unsubstituted C_{1-4} alkyl. In still others, R^1 is 1H-pyrrolo[2,3-b]pyridyl or benzimidazolyl, optionally substituted with one or more substituents independently selected from the group

consisting of substituted or unsubstituted C_{1-8} alkyl, and $-NR_2$, wherein R is independently H, or a substituted or unsubstituted C_{1-4} alkyl.

[00308] In certain ~~embodiments~~examples, the compounds of formula (IV) have an R^1 group set forth herein and an R^2 group set forth herein.

[00309] In some ~~embodiments~~examples of compounds of formula (IV), the compound at a concentration of 10 μM inhibits mTOR, DNA-PK, PI3K, or a combination thereof by at least about 50%. Compounds of formula (IV) may be shown to be inhibitors of the kinases above in any suitable assay system.

[00310] Representative TOR kinase inhibitors of formula (IV) include:

7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(*cis*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(1H-pyrrolo[2,3-b]pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

1-ethyl-7-(1H-pyrrolo[3,2-b]pyridin-5-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(1H-benzo[d]imidazol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*trans*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

4.4 METHODS FOR MAKING TOR KINASE INHIBITORS

[00311] The TOR kinase inhibitors can be obtained via standard, well-known synthetic methodology, see *e.g.*, March, J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure, 4th ed., 1992. Starting materials useful for preparing compounds of formula (III) and intermediates therefore, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents.

[00312] Particular methods for preparing compounds of formula (I) are disclosed in U.S. Patent No. 7,981,893, issued July 19, 2011, incorporated by reference herein in its entirety. Particular methods for preparing compounds of formula (II) are disclosed in U.S. Patent No. 7,968,556, issued June 28, 2011, incorporated by reference herein in its entirety. Particular methods for preparing compounds of formula (III) and (IV) are disclosed in U.S. Patent No. 8,110,578, issued February 7, 2012, and U.S. Publication No. 2011/0137028, filed October 25, 2010, incorporated by reference herein in its entirety.

4.5 METHODS OF USE

[00313] Provided herein are methods for treating or preventing E-twenty six (ETS) overexpressing Ewings sarcoma, comprising administering an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing Ewings sarcoma. In certain ~~embodiments~~examples, a TOR kinase inhibitor is administered to a patient who has locally advanced, recurrent or metastatic, ETS overexpressing Ewings sarcoma not amenable to curative surgical resection. In another ~~embodiment~~example, a TOR kinase inhibitor is administered to a patient who has received at least one prior line of platinum based chemotherapy. In some ~~embodiments~~examples, a TOR kinase inhibitor is administered to a patient who has a tumor showing DNA-PK overexpression.

[00314] In some ~~embodiments~~examples, ~~provided~~disclosed herein are methods for treating E-twenty six (ETS) overexpressing Ewings sarcoma, the methods comprising administering an effective amount of a TOR kinase inhibitor to a patient having E-twenty six (ETS) overexpressing Ewings sarcoma, wherein the treatment results in one or more of

inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors (including tumor secreted hormones, such as those that contribute to carcinoid syndrome), delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), and/or increased Overall Survival (OS), among others.

[00315] In one ~~embodiment~~example, ~~provided~~disclosed herein are methods for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*see* Eisenhauer E.A., Therasse P., Bogaerts J., et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European J. Cancer*; 2009; (45) 228–247) of a patient comprising administering an effective amount of a TOR kinase inhibitor to a patient having ETS overexpressing Ewings sarcoma.

[00316] In one ~~embodiment~~example, provided herein are methods for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a patient having ETS overexpressing Ewings sarcoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient. In some such ~~embodiments~~examples, the inhibition of phosphorylation is assessed in a biological sample of the patient, such as in circulating blood and/or tumor cells, skin biopsies and/or tumor biopsies or aspirate. In such ~~embodiments~~examples, the amount of inhibition of phosphorylation is assessed by comparison of the amount of phospho- S6RP, 4E-BP1 and/or AKT before and after administration of the TOR kinase inhibitor. In certain ~~embodiments~~examples, provided herein are methods for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having ETS overexpressing Ewings sarcoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient, measuring the amount of phosphorylated S6RP, 4E BP1 and/or AKT in said patient, and comparing said amount of phosphorylated S6RP, 4E BP1 and/or AKT to that of said patient prior to administration of an effective amount of a TOR kinase inhibitor.

[00317] In certain ~~embodiments~~examples, ~~provided~~disclosed herein are methods for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having ETS overexpressing Ewings sarcoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.

[00318] In one ~~embodiment~~example, ~~provided~~disclosed herein are methods for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a patient having ETS overexpressing Ewings sarcoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient. In some ~~embodiments~~examples, DNA-PK inhibition is assessed in the skin of the patient having ETS overexpressing Ewings sarcoma, in one example in a UV light-irradiated skin sample of said patient. In another ~~embodiment~~example, DNA-PK inhibition is assessed in a tumor biopsy or aspirate of a patient having ETS overexpressing Ewings sarcoma. In one ~~embodiment~~example, inhibition is assessed by measuring the amount of phosphorylated DNA-PK S2056 (also known as pDNA-PK S2056) before and after administration of the TOR kinase inhibitor. In certain ~~embodiments~~examples, ~~provided~~disclosed herein are methods for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having ETS overexpressing Ewings sarcoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient, measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of a TOR kinase inhibitor. In one ~~embodiment~~example, the skin sample is irradiated with UV light.

[00319] In certain ~~embodiments~~examples, ~~provided~~disclosed herein are methods for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having ETS overexpressing Ewings sarcoma, comprising administering an effective amount of a TOR

kinase inhibitor to said patient and comparing the amount of phosphorylated DNA-PK in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated DNA-PK in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated DNA-PK in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.

[00320] In some ~~embodiments~~examples, the TOR kinase inhibitor is a compound as described herein. In one embodiment, the TOR kinase inhibitor is Compound 1 (a TOR kinase inhibitor set forth herein having molecular formula $C_{16}H_{16}N_8O$). In one embodiment, Compound 1 is 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

[00321] A TOR kinase inhibitor can be combined with radiation therapy or surgery. In certain ~~embodiments~~examples, a TOR kinase inhibitor is administered to patient who is undergoing radiation therapy, has previously undergone radiation therapy or will be undergoing radiation therapy. In certain ~~embodiments~~examples, a TOR kinase inhibitor is administered to a patient who has undergone tumor removal surgery.

[00322] Further ~~provided~~disclosed herein are methods for treating patients who have been previously treated for ETS overexpressing Ewings sarcoma, but are non-responsive to standard therapies, as well as those who have not previously been treated. Further ~~provided~~disclosed herein are methods for treating patients who have undergone surgery in an attempt to treat the condition at issue, as well as those who have not. Because patients with ETS overexpressing Ewings sarcoma may have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with ETS overexpressing Ewings sarcoma.

[00323] In certain ~~embodiments~~examples, the ETS overexpressing Ewings sarcoma is Ewing's sarcoma of the bone, extraosseus Ewing's sarcoma (also known as extraskeletal Ewing's

sarcoma), primitive neuroectodermal tumor (PNET), peripheral neuroepithelioma, Askin's tumor (also known as chest wall Ewing's sarcoma) or atypical Ewing's sarcoma.

[00324] In one ~~embodiment~~example, the ETS overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated. In certain ~~embodiments~~examples, the ETS overexpressing Ewings sarcoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

4.6 PHARMACEUTICAL COMPOSITIONS AND ROUTES OF ADMINISTRATION

[00325] ~~Provided~~Disclosed herein are compositions, comprising an effective amount of a TOR kinase inhibitor, and compositions comprising an effective amount of a TOR kinase inhibitor and a pharmaceutically acceptable carrier or vehicle. In some ~~embodiments~~examples, the pharmaceutical compositions described herein are suitable for oral, parenteral, mucosal, transdermal or topical administration.

[00326] The TOR kinase inhibitors can be administered to a patient orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions and syrups. Suitable formulations can be prepared by methods commonly employed using conventional, organic or inorganic additives, such as an excipient *(e.g.,* sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder *(e.g.,* cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator *(e.g.,* starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant *(e.g.,* magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent *(e.g.,* citric acid, menthol, glycine or orange powder), a preservative *(e.g,* sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer *(e.g.,* citric acid, sodium citrate or acetic acid), a suspending agent *(e.g.,* methylcellulose, polyvinyl pyrroliclone or aluminum stearate), a dispersing agent *(e.g.,* hydroxypropylmethylcellulose), a diluent *(e.g.,* water), and base wax *(e.g.,* cocoa

butter, white petrolatum or polyethylene glycol). The effective amount of the TOR kinase inhibitor in the pharmaceutical composition may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a patient's body weight to about 10 mg/kg of a patient's body weight in unit dosage for both oral and parenteral administration.

[00327] The dose of a TOR kinase inhibitor to be administered to a patient is rather widely variable and can be subject to the judgment of a health-care practitioner. In general, the TOR kinase inhibitors can be administered one to four times a day in a dose of about 0.005 mg/kg of a patient's body weight to about 10 mg/kg of a patient's body weight in a patient, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration. In one ~~embodiment~~example, the dose is about 0.01 mg/kg of a patient's body weight to about 5 mg/kg of a patient's body weight, about 0.05 mg/kg of a patient's body weight to about 1 mg/kg of a patient's body weight, about 0.1 mg/kg of a patient's body weight to about 0.75 mg/kg of a patient's body weight, about 0.25 mg/kg of a patient's body weight to about 0.5 mg/kg of a patient's body weight, or about 0.007 mg/kg of a patient's body weight to about 1.7 mg/kg of patient's body weight. In one ~~embodiment~~example, one dose is given per day. In another ~~embodiment~~example, two doses are given per day. In any given case, the amount of the TOR kinase inhibitor administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

[00328] In another ~~embodiment~~example, provided herein are methods for the treatment or prevention of ETS overexpressing Ewings sarcoma, comprising the administration of about 0.375 mg/day to about 750 mg/day, about 0.75 mg/day to about 375 mg/day, about 3.75 mg/day to about 75 mg/day, about 7.5 mg/day to about 55 mg/day, about 18 mg/day to about 37 mg/day, about 0.5 mg/day to about 60 mg/day, or about 0.5 mg/day to about 128 mg/day of a TOR kinase inhibitor to a patient in need thereof. In another ~~embodiment~~example, ~~provided~~disclosed herein are methods for the treatment or prevention of ETS overexpressing Ewings sarcoma, comprising the administration of about 0.5 mg/day to about 1200 mg/day, about 10 mg/day to about 1200 mg/day, about 100 mg/day to about 1200 mg/day, about 400 mg/day to about 1200 mg/day, about 600 mg/day to about 1200 mg/day, about

400 mg/day to about 800 mg/day or about 600 mg/day to about 800 mg/day of a TOR kinase inhibitor to a patient in need thereof. In a particular ~~embodiment~~example, the methods disclosed herein comprise the administration of 0.5 mg/day, 1 mg/day, 2 mg/day, 4 mg/day, 8 mg/day, 16 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, 45 mg/day, 60 mg/day, 90 mg/day, or 120 mg/day of a TOR kinase inhibitor to a patient in need thereof.

[00329] In another ~~embodiment~~example, provided herein are unit dosage formulations that comprise between about 0.1 mg and about 2000 mg, about 1 mg and 200 mg, about 35 mg and about 1400 mg, about 125 mg and about 1000 mg, about 250 mg and about 1000 mg, or about 500 mg and about 1000 mg of a TOR kinase inhibitor.

[00330] In a particular ~~embodiment~~example, ~~provided~~disclosed herein are unit dosage formulation comprising about 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 45 mg, 50 mg, 60 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 600 mg or 800 mg of a TOR kinase inhibitor.

[00331] In another ~~embodiment~~example, ~~provided~~disclosed herein are unit dosage formulations that comprise 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 50 mg, 70 mg, 100 mg, 125 mg, 140 mg, 175 mg, 200 mg, 250 mg, 280 mg, 350 mg, 500 mg, 560 mg, 700 mg, 750 mg, 1000 mg or 1400 mg of a TOR kinase inhibitor. In a particular ~~embodiment~~example, ~~provided~~disclosed herein are unit dosage formulations that comprise 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 45 mg or 60 mg of a TOR kinase inhibitor.

[00332] A TOR kinase inhibitor can be administered once, twice, three, four or more times daily.

[00333] A TOR kinase inhibitor can be administered orally for reasons of convenience. In one ~~embodiment~~example, when administered orally, a TOR kinase inhibitor is administered with a meal and water. In another ~~embodiment~~example, the TOR kinase inhibitor is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a suspension. In another ~~embodiment~~example, when administered orally, a TOR kinase inhibitor is administered in a fasted state.

[00334] The TOR kinase inhibitor can also be administered intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously,

intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, rectally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the health-care practitioner, and can depend in-part upon the site of the medical condition.

[00335] In one ~~embodiment~~example, ~~provided~~disclosed herein are capsules containing a TOR kinase inhibitor without an additional carrier, excipient or vehicle.

[00336] In another ~~embodiment~~example, ~~provided~~disclosed herein are compositions, comprising an effective amount of a TOR kinase inhibitor and a pharmaceutically acceptable carrier or vehicle, wherein a pharmaceutically acceptable carrier or vehicle can comprise an excipient, diluent, or a mixture thereof. In one ~~embodiment~~example, the composition is a pharmaceutical composition.

[00337] The compositions can be in the form of tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions and the like. Compositions can be formulated to contain a daily dose, or a convenient fraction of a daily dose, in a dosage unit, which may be a single tablet or capsule or convenient volume of a liquid. In one ~~embodiment~~example, the solutions are prepared from water-soluble salts, such as the hydrochloride salt. In general, all of the compositions are prepared according to known methods in pharmaceutical chemistry. Capsules can be prepared by mixing a TOR kinase inhibitor with a suitable carrier or diluent and filling the proper amount of the mixture in capsules. The usual carriers and diluents include, but are not limited to, inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[00338] Tablets can be prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. In one ~~embodiment~~example, the pharmaceutical composition is lactose-free. Typical tablet binders are

[00342] In certain ~~embodiments~~examples, ~~provided~~disclosed herein are kits comprising a TOR kinase inhibitor.

[00343] In other ~~embodiments~~examples, ~~provide~~disclosed herein are kits comprising a TOR kinase inhibitor and means for monitoring patient response to administration of said TOR kinase inhibitor. In certain ~~embodiments~~examples, the patient has ETS overexpressing Ewings sarcoma. In particular ~~embodiments~~examples, the patient response measured is inhibition of disease progression, inhibition of tumor growth, reduction of primary and/or secondary tumor(s), relief of tumor-related symptoms, improvement in quality of life, delayed appearance of primary and/or secondary tumors, slowed development of primary and/or secondary tumors, decreased occurrence of primary and/or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth or regression of tumor.

[00344] In other ~~embodiments~~examples, ~~provided~~disclosed herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in a patient. In certain ~~embodiments~~examples, the kits comprise means for measuring inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in circulating blood or tumor cells and/or skin biopsies or tumor biopsies/aspirates of a patient. In certain ~~embodiments~~examples, provided herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of inhibition of phosphorylation as assessed by comparison of the amount of phospho- S6RP, 4E-BP1 and/or AKT before, during and/or after administration of the TOR kinase inhibitor. In certain ~~embodiments~~examples, the patient has ETS overexpressing Ewings sarcoma.

[00345] In other ~~embodiments~~examples, ~~provided~~disclosed herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of inhibition of DNA-dependent protein kinase (DNA-PK) activity in a patient. In certain ~~embodiments~~examples, the kits comprise means for measuring the amount of inhibition of DNA-dependent protein kinase (DNA-PK) activity in a skin sample and/or a tumor biopsy/aspirate of a patient. In one ~~embodiment~~example, the kits comprise a means for measuring the amount of pDNA-PK S2056 in a skin sample and/or a tumor biopsy/aspirate of a patient. In one ~~embodiment~~example, the skin sample is irradiated by UV light. In certain ~~embodiments~~examples, ~~provided~~disclosed herein are kits comprising a TOR kinase inhibitor

and means for measuring the amount of inhibition of DNA-dependent protein kinase (DNA-PK) activity before, during and/or after administration of the TOR kinase inhibitor. In certain ~~embodiments~~examples, ~~provided~~ disclosed herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of phosphorylated DNA-PK S2056 before, during and/or after administration of the TOR kinase inhibitor. In certain ~~embodiments~~examples, the patient has ETS overexpressing Ewings sarcoma.

[00346] In certain ~~embodiments~~examples, the kits ~~provided~~disclosed herein comprise an amount of a TOR kinase inhibitor effective for treating or preventing ETS overexpressing Ewings sarcoma. In certain ~~embodiments~~examples, the kits ~~provided~~disclosed herein comprise a TOR kinase inhibitor having molecular formula $C_{16}H_{16}N_8O$. In certain ~~embodiments~~examples, the kits ~~provided~~disclosed herein comprise Compound 1.

[00347] In certain ~~embodiments~~examples, the kits provided herein further comprise instructions for use, such as for administering a TOR kinase inhibitor and/or monitoring patient response to administration of a TOR kinase inhibitor.

5. EXAMPLES

5.1 BIOLOGICAL EXAMPLES

5.1.1 Biochemical assays

[00348] **mTOR HTR-FRET Assay**. The following is an example of an assay that can be used to determine the TOR kinase inhibitory activity of a test compound. TOR kinase inhibitors were dissolved in DMSO and prepared as 10 mM stocks and diluted appropriately for the experiments. Reagents were prepared as follows:

[00349] "Simple TOR buffer" (used to dilute high glycerol TOR fraction): 10 mM Tris pH 7.4, 100 mM NaCl, 0.1% Tween-20, 1 mM DTT. Invitrogen mTOR (cat#PV4753) was diluted in this buffer to an assay concentration of 0.200 μg/mL.

[00350] ATP/Substrate solution: 0.075 mM ATP, 12.5 mM $MnCl_2$, 50 mM Hepes, pH 7.4, 50 mM β-GOP, 250 nM Microcystin LR, 0.25 mM EDTA, 5 mM DTT, and 3.5 μg/mL GST-p70S6.

bisphosphonates or denusomab are allowed in stable doses; and optional paired tumor biopsies if tumor is accessible).

[00388] For both the dose escalation and dose expansion parts of this protocol, exclusion criteria are: (a) Symptomatic central nervous system metastases; (b) Known acute or chronic pancreatitis; (c) Any peripheral neuropathy ≥ NCI CTCAE grade 2; (d) Persistent diarrhea or malabsorption ≥ NCI CTCAE grade 2, despite medical management. Impaired ability to swallow; (e) Impaired cardiac function or clinically significant cardiac diseases; (f) Diabetes mellitus on active treatment; (g) Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol; (h) Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half lives or 4 weeks, whichever is shorter, prior to starting study drug or who have not recovered from side effects of such therapy; (i) Major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy; (j) Pregnancy or breast feeding; (k) Adults of reproductive potential not employing two forms of birth control; (l) Known HIV infection; (m) Known chronic hepatitis B or C virus (HBV/HCV) infection, unless this is comorbidity in subjects with HCC; (n) Any significant medical condition, laboratory abnormality, or psychiatric illness, including the inability to swallow capsules, that would prevent subjects from participating in the study; (o) Any condition including the presence of laboratory abnormalities, which places subjects at unacceptable risk if they were to participate in the study; (p) Any condition that confounds the ability to interpret study data; or (q) Concurrent active second malignancy for which the subject is receiving therapy, excluding non-melanomatous skin cancer or carcinoma in situ of the cervix.

[00389] For the dose expansion part (Part B) of this protocol, exclusion criteria are: Prior treatment with agents targeting both mTOR complexes (dual TORC1+TORC2 inhibitors) and/or PI3K/AKT pathways. However, prior treatment with isolated TORC1 inhibitors (e.g., rapalogs) is allowed in both parts of this study.

[00390] In some ~~embodiments~~examples, patients undergoing the clinical protocol provided herein will show a positive tumor response, such as inhibition of tumor growth or a

reduction in tumor size. In certain ~~embodiments~~examples, patients undergoing the clinical protocol provided herein will achieve a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of complete response, partial response or stable disease after administration of an effective amount of Compound 1. In certain ~~embodiments~~examples, patients undergoing the clinical protocol provided herein will show increased survival without tumor progression. In some ~~embodiments~~examples, patients undergoing the clinical protocol provided herein will show inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors (including tumor secreted hormones, such as those that contribute to carcinoid syndrome), delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), and/or increased Overall Survival (OS), among others.

~~**[00391]** A number of references have been cited, the disclosures of which are incorporated herein by reference in their entirety. The embodiments disclosed herein are not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the disclosed embodiments and any embodiments that are functionally equivalent are encompassed by the present disclosure. Indeed, various modifications of the embodiments disclosed herein are in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.~~