METHODS FOR TREATING NON- SMALL CELL LUNG CANCER USING TOR KINASE INHIBITOR COMBINATION THERAPY

[0001] This application claims the benefit of U.S. Provisional Application No. 61/603,012, filed February 24, 2012, claims the benefit of U.S. Provisional Application No. 61/716,424, filed October 19, 2012 and claims the benefit of U.S. Provisional Application No. 61/725,805, filed November 13, 2012, the entire contents of each of which are incorporated herein by reference.

1. FIELD

[0002] Provided herein are methods for treating or preventing advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor and an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer.

2. BACKGROUND

[0003] The connection between abnormal protein phosphorylation and the cause or consequence of diseases has been known for over 20 years. Accordingly, protein kinases have become a very important group of drug targets. *See* Cohen, *Nature*, 1:309-315 (2002). Various protein kinase inhibitors have been used clinically in the treatment of a wide variety of diseases, such as cancer and chronic inflammatory diseases, including diabetes and stroke. *See* Cohen, *Eur. J. Biochem.*, 268:5001-5010 (2001), *Protein Kinase Inhibitors for the Treatment of Disease: The Promise and the Problems*, Handbook of Experimental Pharmacology, Springer Berlin Heidelberg, 167 (2005).

[0004] The protein kinases are a large and diverse family of enzymes that catalyze protein phosphorylation and play a critical role in cellular signaling. Protein kinases may exert positive or negative regulatory effects, depending upon their target protein. Protein kinases are involved in specific signaling pathways which regulate cell functions such as, but not limited to, metabolism, cell cycle progression, cell adhesion, vascular function, apoptosis, and angiogenesis. Malfunctions of cellular signaling have been associated with many diseases, the most characterized of which include cancer and diabetes. The regulation

of signal transduction by cytokines and the association of signal molecules with protooncogenes and tumor suppressor genes have been well documented. Similarly, the connection between diabetes and related conditions, and deregulated levels of protein kinases, has been demonstrated. *See e.g.*, Sridhar *et al. Pharmaceutical Research*, 17(11):1345-1353 (2000). Viral infections and the conditions related thereto have also been associated with the regulation of protein kinases. Park *et al. Cell* 101 (7): 777-787 (2000).

[0005] Because protein kinases regulate nearly every cellular process, including metabolism, cell proliferation, cell differentiation, and cell survival, they are attractive targets for therapeutic intervention for various disease states. For example, cell-cycle control and angiogenesis, in which protein kinases play a pivotal role are cellular processes associated with numerous disease conditions such as but not limited to cancer, inflammatory diseases, abnormal angiogenesis and diseases related thereto, atherosclerosis, macular degeneration, diabetes, obesity, and pain.

[0006] Protein kinases have become attractive targets for the treatment of cancers. Fabbro *et al.*, *Pharmacology & Therapeutics* 93:79-98 (2002). It has been proposed that the involvement of protein kinases in the development of human malignancies may occur by: (1) genomic rearrangements (*e.g.*, BCR-ABL in chronic myelogenous leukemia), (2) mutations leading to constitutively active kinase activity, such as acute myelogenous leukemia and gastrointestinal tumors, (3) deregulation of kinase activity by activation of oncogenes or loss of tumor suppressor functions, such as in cancers with oncogenic RAS, (4) deregulation of kinase activity by over-expression, as in the case of EGFR and (5) ectopic expression of growth factors that can contribute to the development and maintenance of the neoplastic phenotype. Fabbro *et al.*, *Pharmacology & Therapeutics* 93:79-98 (2002).

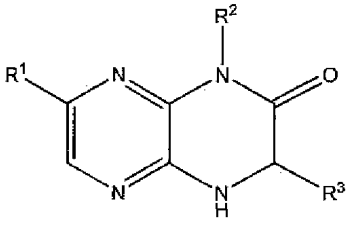
[0007] The elucidation of the intricacy of protein kinase pathways and the complexity of the relationship and interaction among and between the various protein kinases and kinase pathways highlights the importance of developing pharmaceutical agents capable of acting as protein kinase modulators, regulators or inhibitors that have beneficial activity on multiple kinases or multiple kinase pathways. Accordingly, there remains a need for new kinase modulators.

[0008] The protein named mTOR (mammalian target of rapamycin), which is also called FRAP, RAFTI or RAPT1), is a 2549-amino acid Ser/Thr protein kinase, that has been shown to be one of the most critical proteins in the mTOR/PI3K/Akt pathway that regulates cell growth and proliferation. Georgakis and Younes *Expert Rev. Anticancer Ther.* 6(1):131-140 (2006). mTOR exists within two complexes, mTORC1 and mTORC2. While mTORC1 is sensitive to rapamycin analogs (such as temsirolimus or everolimus), mTORC2 is largely rapamycin-insensitive. Notably, rapamycin is not a TOR kinase inhibitor. Several mTOR inhibitors have been or are being evaluated in clinical trials for the treatment of cancer. Temsirolimus was approved for use in renal cell carcinoma in 2007 and sirolimus was approved in 1999 for the prophylaxis of renal transplant rejection. Everolimus was approved in 2009 for renal cell carcinoma patients that have progressed on vascular endothelial growth factor receptor inhibitors, in 2010 for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in patients who require therapy but are not candidates for surgical resection, and in 2011 for progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. There remains a need for TOR kinase inhibitors that inhibit both mTORC1 and mTORC2 complexes.

[0009] 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

[0010] In one aspect, there is provided a use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for treating advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

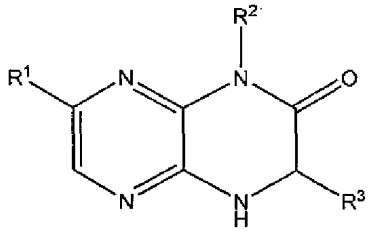
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

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.

Provided herein are methods for treating or preventing advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor and an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer.

[0011] In another aspect, there is provided a use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein:

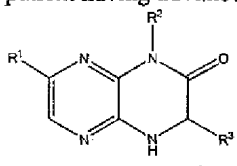
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

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.

In certain examples, provided herein are methods for achieving a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to said patient.

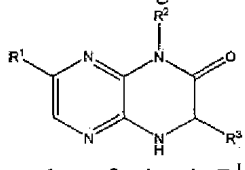
[0012] In one aspect, there is provided Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog in the manufacture of a medicament for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



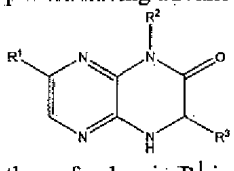
(IV) or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof, wherein R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted 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. In certain examples, provided herein are methods for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to said patient.

[0013] In certain examples, the TOR kinase inhibitor is a compound as described herein.

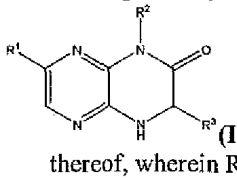
[0014] In one aspect, the present invention refers to use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or azacitidine in the manufacture of a medicament for treating advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV) or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug 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. In another aspect, the present invention refers to use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or azacitidine in the manufacture of a medicament for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV) or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug 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. In a further aspect, the present invention refers to Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or azacitidine in the manufacture of a medicament for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV) or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug 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.

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

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 depicts the viability dose-response curves and isobolograms for Compound 1 and 5-azacitidine for H1755 cells, and the synergy seen for the combination treatment, for 2 combination ratios.

[0016] Figure 2 depicts the viability dose-response curves and isobolograms for Compound 1 and erlotinib for H1755 cells, and the synergy seen for the combination treatment, for 2 combination ratios.

[0017] Figure 3 depicts: A. Impact of sequence of addition and ratio on CI values. CI values of all combinations from each of the three sequences of addition were compared by t-test. Sim: Simultaneously addition of both compounds; SeqM1: Compound 1 first followed by addition of azacitidine; SeqM2: azacitidine first followed by addition of Compound 1. B. Different ratios of azacitidine and Compound 1 do not significantly impact CI values in SeqM2 addition.

[0018] Figure 4 depicts: A. Sequence of addition has no impact on CI values for Compound 1 and erlotinib combination. CI values of all combinations from each of the three sequences of addition were compared by t-test. Sim: Simultaneously addition of both compounds; SeqM1: Compound 1 first followed by addition of azacitidine; SeqM2: azacitidine first followed by addition of Compound 1. B. Different ratios of azacitidine and Compound 1 significantly impact CI values.

[0019] Figures 5A-D depict combination indices of erlotinib treatment in combination with Compound 1 in various cell lines, at various concentrations. Figure 1A depicts the combination indices in A549 cell line. Figure 1B shows the combination indices in H1975 cell line. Figure 1C demonstrates the combination indices in HCC95 cell line. Figure 1D shows the combination indices in H1650 cell line.

[0020] Figure 6 depicts cell cycle analysis in A549 cell line treated with erlotinib, Compound 1, or their combination.

[0021] Figures 7A and 7B show a biomarker analysis using Western blotting. Cell lines were treated with erlotinib, Compound 1, or their combination for 1 or 3 days. Cell lysates were produced and 30 μg protein subjected to SDS-PAGE and Western blotting. The data for cell lines A549 and H1975 is shown in Figure 7A. The data for cell lines H1650 and HCC95 is shown in Figure 7B.

[0022] Figure 8 shows the anti-tumor activity of Compound 1 or erlotinib, when administered orally as single agents, and in combination in A549 xenografts.

[0023] Figure 9 shows the anti-tumor activity of Compound 1 and erlotinib, when administered orally as single agents, and in combination, in H1975 xenografts.

5. DETAILED DESCRIPTION

5.1 DEFINITIONS

[0024] 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, 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

certain embodiments, when the alkyl groups described herein are said to be "substituted," they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; $B(OH)_2$, or O(alkyl)aminocarbonyl.

[0025] An "alkenyl" group is a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms, typically from 2 to 8 carbon atoms, and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_8)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl and the like. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. An alkenyl group can be unsubstituted or substituted.

[0026] A "cycloalkyl" group is a saturated, partially saturated, or unsaturated cyclic alkyl group of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings which can be optionally substituted with from 1 to 3 alkyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms ranges from 3 to 5, 3 to 6, or 3 to 7. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple or bridged ring structures such as adamantyl and the like. Examples of unsaturared cycloalkyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, hexadienyl, among others. A cycloalkyl group can be substituted or unsubstituted. Such substituted cycloalkyl groups include, by way of example, cyclohexanone and the like.

[0027] An "aryl" group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl). In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6 to 10 carbon atoms in the ring portions of the groups. Particular aryls include phenyl, biphenyl, naphthyl and the like. An aryl group can be substituted or unsubstituted. The phrase "aryl groups" also includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like).

[0028] A "heteroaryl" group is an aryl ring system having one to four heteroatoms as ring atoms in a heteroaromatic ring system, wherein the remainder of the atoms are carbon atoms. In some embodiments, heteroaryl groups contain 5 to 6 ring atoms, and in others from 6 to 9 or even 6 to 10 atoms in the ring portions of the groups. Suitable heteroatoms include oxygen, sulfur and nitrogen. In certain embodiments, the heteroaryl ring system is monocyclic or bicyclic. Non-limiting examples include but are not limited to, groups such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl (for example, isobenzofuran-1,3-diimine), indolyl, azaindolyl (for example, pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, benzimidazolyl (for example, 1H-benzo[d]imidazolyl), imidazopyridyl (for example, azabenzimidazolyl, 3H-imidazo[4,5-b]pyridyl or 1H-imidazo[4,5-b]pyridyl), pyrazolopyridyl, triazolopyridyl, benzotriazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, isoxazolopyridyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

[0029] A "heterocyclyl" is an aromatic (also referred to as heteroaryl) or non-aromatic cycloalkyl in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N. In some embodiments, heterocyclyl groups include 3 to10 ring members, whereas other such groups have 3 to 5, 3 to 6, or 3 to 8 ring members. Heterocyclyls can also be bonded to other groups at any ring atom (*i.e.*, at any carbon atom or heteroatom of the heterocyclic ring). A heterocyclylalkyl group can be substituted or unsubstituted. Heterocyclyl groups encompass unsaturated, partially saturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl

and imidazolidinyl groups. The phrase heterocyclyl includes fused ring species, including those comprising fused aromatic and non-aromatic groups, such as, for example, benzotriazolyl, 2,3-dihydrobenzo[1,4]dioxinyl, and benzo[1,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Representative examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidinyl, pyrrolidyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl (for example, tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathiane, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, homopiperazinyl, quinuclidyl, indolyl, indolinyl, isoindolyl, azaindolyl (pyrrolopyridyl), indazolyl, indolizinyl, benzotriazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiinyl, benzoxathiinyl, benzothiazinyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[1,3]dioxolyl, pyrazolopyridyl, imidazopyridyl (azabenzimidazolyl; for example, 1H-imidazo[4,5-b]pyridyl, or 1H-imidazo[4,5-b]pyridin-2(3H)-onyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthalenyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, and tetrahydroquinolinyl groups. Representative substituted heterocyclyl groups may be mono- substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed below.

[0030] A "cycloalkylalkyl" group is a radical of the formula: -alkyl-cycloalkyl, wherein alkyl and cycloalkyl are defined above. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl, or both the alkyl and the cycloalkyl portions of the

group. Representative cycloalkylalkyl groups include but are not limited to cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, and cyclohexylpropyl. Representative substituted cycloalkylalkyl groups may be mono-substituted or substituted more than once.

[0031] An "aralkyl" group is a radical of the formula: -alkyl-aryl, wherein alkyl and aryl are defined above. Substituted aralkyl groups may be substituted at the alkyl, the aryl, or both the alkyl and the aryl portions of the group. Representative aralkyl groups include but are not limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl.

[0032] A "heterocyclylalkyl" group is a radical of the formula: -alkyl-heterocyclyl, wherein alkyl and heterocyclyl are defined above. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl, or both the alkyl and the heterocyclyl portions of the group. Representative heterocylylalkyl groups include but are not limited to 4-ethyl-morpholinyl, 4-propylmorpholinyl, furan-2-yl methyl, furan-3-yl methyl, pyrdine-3-yl methyl, (tetrahydro-2H-pyran-4-yl)methyl, (tetrahydro-2H-pyran-4-yl)ethyl, tetrahydrofuran-2-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

[0033] A "halogen" is fluorine, chlorine, bromine or iodine.

[0034] A "hydroxyalkyl" group is an alkyl group as described above substituted with one or more hydroxy groups.

[0035] An "alkoxy" group is -O-(alkyl), wherein alkyl is defined above.

[0036] An "alkoxyalkyl" group is -(alkyl)-O-(alkyl), wherein alkyl is defined above.

[0037] An "amino" group is a radical of the formula: $-NH_2$.

[0038] An "alkylamino" group is a radical of the formula: -NH-alkyl or $-N(alkyl)_2$, wherein each alkyl is independently as defined above.

[0039] A "carboxy" group is a radical of the formula: -C(O)OH.

[0040] An "aminocarbonyl" group is a radical of the formula: $-C(O)N(R^{\#})_2$, $-C(O)NH(R^{\#})$ or $-C(O)NH_2$, wherein each $R^{\#}$ is independently a substituted or unsubstituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl or heterocyclyl group as defined herein.

[0041] An "acylamino" group is a radical of the formula: $-NHC(O)(R^{\#})$ or $-N(alkyl)C(O)(R^{\#})$, wherein each alkyl and $R^{\#}$ are independently as defined above.

[0042] An "alkylsulfonylamino" group is a radical of the formula: $-NHSO_2(R^{\#})$ or $-N(alkyl)SO_2(R^{\#})$, wherein each alkyl and $R^{\#}$ are defined above.

[0043] A "urea" group is a radical of the formula: $-N(alkyl)C(O)N(R^{\#})_2$, $-N(alkyl)C(O)NH(R^{\#})$, $-N(alkyl)C(O)NH_2$, $-NHC(O)N(R^{\#})_2$, $-NHC(O)NH(R^{\#})$, or $-NH(CO)NHR^{\#}$, wherein each alkyl and $R^{\#}$ are independently as defined above.

[0044] When the groups described herein, with the exception of alkyl group are said to be "substituted," they may be substituted with any appropriate substituent or substituents. Illustrative examples of substituents are those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxygen (=O); $B(OH)_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, or thiazinyl); monocyclic or fused or non-fused polycyclic aryl or heteroaryl (*e.g.*, phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridinyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzothiophenyl, or benzofuranyl) aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclyl alkoxy.

[0045] As used herein, the term "pharmaceutically acceptable salt(s)" refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the TOR kinase inhibitors include, but are not limited to metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids

include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton PA (1995).

[0046] As used herein and unless otherwise indicated, the term "clathrate" means a TOR kinase inhibitor, or a salt thereof, in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within or a crystal lattice wherein a TOR kinase inhibitor is a guest molecule.

[0047] As used herein and unless otherwise indicated, the term "solvate" means a TOR kinase inhibitor, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. In one embodiment, the solvate is a hydrate.

[0048] As used herein and unless otherwise indicated, the term "hydrate" means a TOR kinase inhibitor, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[0049] As used herein and unless otherwise indicated, the term "prodrug" means a TOR kinase inhibitor derivative that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound, particularly a TOR kinase inhibitor. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a TOR kinase inhibitor that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. In certain embodiments, prodrugs of compounds with carboxyl functional

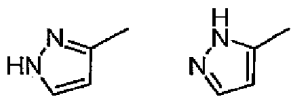
groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by *Burger's Medicinal Chemistry and Drug Discovery* 6th ed. (Donald J. Abraham *ed.*, 2001, Wiley) and *Design and Application of Prodrugs* (H. Bundgaard *ed.*, 1985, Harwood Academic Publishers Gmfh).

[0050] As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of a TOR kinase inhibitor that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The TOR kinase inhibitors can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments 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 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).

[0051] 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, the TOR kinase inhibitors are isolated as either the cis or trans isomer. In other embodiments, the TOR kinase inhibitors are a mixture of the cis and trans isomers.

[0052] "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:



[0053] 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.

[0054] 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 provided herein. In some embodiments, there are provided isotopologues of the TOR kinase inhibitors, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched TOR kinase inhibitors.

[0055] "Treating" as used herein, means an alleviation, in whole or in part, of advanced non-small cell lung cancer or a symptom associated with advanced non-small cell lung cancer, or slowing, or halting of further progression or worsening of those symptoms.

[0056] "Preventing" as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of advanced non-small cell lung cancer, or a symptom thereof.

[0057] The term "effective amount" in connection with an TOR kinase inhibitor, erlotinib or a cytidine analog means an amount alone or in combination capable of alleviating, in whole or in part, a symptom associated with advanced non-small cell lung cancer, or slowing or halting further progression or worsening of those symptoms, or treating or preventing advanced non-small cell lung cancer in a subject having or at risk for having advanced non-small cell lung cancer. The effective amount of the TOR kinase inhibitor, erlotinib or a cytidine analog, 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.

[0058] In one embodiment, erlotinib is TARCEVA®.

[0059] In certain embodiments, the cytidine analog is 5-azacitidine (also known as 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1H)-one; National Service Center designation NSC-102816; CAS Registry Number 320-67-2; azacitidine; Aza and AZA; and currently marketed as VIDAZA®). In certain embodiments, the cytidine analog is 2′-deoxy-5-azacytidine (also known as 5-aza-2'-deoxycytidine, decitabine, 5-aza-CdR, Dac, and DAC, and currently marketed as DACOGEN®). In certain embodiments, the cytidine analog is, for example: 1-β-D-arabinofuranosylcytosine (Cytarabine or ara-C); pseudoiso-cytidine (psi ICR); 5-fluoro-2'-deoxycytidine (FCdR); 2'-deoxy-2',2'-difluorocytidine (Gemcitabine); 5-aza-2'-deoxy-2',2'-difluorocytidine; 5-aza-2'-deoxy-2'-fluorocytidine; 1-β-D-ribofuranosyl-

2(1H)-pyrimidinone (Zebularine); 2',3'-dideoxy-5-fluoro-3'-thiacytidine (Emtriva); 2'-cyclocytidine (Ancitabine); l-β-D-arabinofuranosyl-5-azacytosine (Fazarabine or ara-AC); 6-azacytidine (6-aza-CR); 5,6-dihydro-5-azacytidine (dH-aza-CR); N^4 pentyloxy-carbonyl-5'-deoxy-5-fluorocytidine (Capecitabine); N^4 octadecyl-cytarabine; elaidic acid cytarabine; or a conjugated compound comprising a cytidine analog and a fatty acid (e.g., an azacitidine–fatty acid conjugate, including, but not limited to, CP-4200 (Clavis Pharma ASA) or a compound disclosed in WO 2009/042767, such as aza-C-5′-petroselinic acid ester or aza-C-5′-petroselaidic acid ester).

[0060] In certain embodiments, cytidine analogs provided herein include esterified derivatives of cytidine analogs, such as, e.g., esterified derivatives of 5-azacitidine. In particular embodiments, esterified derivatives are cytidine analogs that contain an ester moiety (e.g., an acetyl group) at one or more positions on the cytidine analog molecule. Esterified derivatives may be prepared by any method known in the art. In certain embodiments, esterified derivatives of a cytidine analog serve as prodrugs of the cytidine analog, such that, e.g., following administration of an esterified derivative, the derivative is deacetylated in vivo to yield the cytidine analog. A particular embodiment herein provides 2′,3′,5′-triacetyl-5-azacytidine (TAC), which possesses favorable physical-chemical and therapeutic properties. See, e.g., International Publication No. WO 2008/092127 (International Application No. PCT/US2008/052124); Ziemba, A.J., et al., "Development of Oral Demethylating Agents for the Treatment of Myelodysplastic Syndrome" (Abstract No. 3369), In: Proceedings of the 100th Annual Meeting of the American Association for Cancer Research; 2009 Apr. 18-22; Denver, Co. Philadelphia (PA): AACR; 2009 (both of which are incorporated by reference herein in their entireties).

[0061] In certain embodiments, the cytidine analogs provided herein include any compound which is structurally related to cytidine or deoxycytidine and functionally mimics and/or antagonizes the action of cytidine or deoxycytidine. Certain embodiments herein provide salts, cocrystals, solvates (e.g., hydrates), complexes, prodrugs, precursors, metabolites, and/or other derivatives of the cytidine analogs provided herein. For example, particular embodiments provide salts, cocrystals, solvates (e.g., hydrates), complexes, precursors, metabolites, and/or other derivatives of 5-azacitidine. Certain embodiments

provide cytidine analogs that are not salts, cocrystals, solvates (e.g., hydrates), or complexes of the cytidine analogs provided herein. For example, particular embodiments provide 5-azacitidine in a non-ionized, non-solvated (e.g., anhydrous), non-complexed form. Certain embodiments herein provide mixtures of two or more cytidine analogs provided herein.

[0062] Cytidine analogs referred to herein may be prepared using synthetic methods and procedures referenced herein or otherwise available in the literature. For example, particular methods for synthesizing 5-azacitidine are taught in, e.g., U.S. Patent No. 7,038,038 and references discussed therein, each of which is incorporated herein by reference. 5-Azacitidine is also available from Celgene Corporation, Warren, NJ. Other cytidine analogs provided herein may be prepared using previously disclosed synthetic procedures available to a person of ordinary skill in the art.

[0063] As used herein, and unless otherwise specified, the term "in combination with" includes the administration of two or more therapeutic agents simultaneously, concurrently, or sequentially within no specific time limits unless otherwise indicated. In one embodiment, a TOR kinase inhibitor is administered in combination with erlotinib or a cytidine analog. In one embodiment, the agents are present in the cell or in the subject's body at the same time or exert their biological or therapeutic effect at the same time. In one embodiment, the therapeutic agents are in the same composition or unit dosage form. In other embodiments, the therapeutic agents are in separate compositions or unit dosage forms. In certain embodiments, a first agent can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), essentially concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent, or any combination thereof. For example, in one embodiment, the first agent can be administered prior to the second therapeutic agent, for e.g. 1 week. In another, the first agent can be

administered prior to (for example 1 day prior) and then concomitant with the second therapeutic agent.

[0064] 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 a mammal, in another embodiment a human. In one embodiment, a "patient" or "subject" is a human having advanced non-small cell lung cancer. In one embodiment, a "patient" or "subject" is a human having Stage IIIB/IV non-small cell lung cancer. In one embodiment, a "patient" or "subject" is a human having advanced non-small cell lung cancer. In one embodiment, a "patient" or "subject" is a human having Stage IIIB/IV non-small cell lung cancer who has failed at least one line of standard therapy. In one embodiment, a patient is a human having histologically or cytologically-confirmed advanced non-small cell lung cancer, including subjects who have progressed on (or not been able to tolerate) standard anticancer therapy or for whom no standard anticancer therapy exists. In one embodiment, the standard anticancer therapy is chemotherapy or EGFR inhibitor therapy,

[0065] In the context of advanced non-small cell lung cancer, inhibition may be assessed by 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), increased Overall Survival (OS), among others. OS as used herein means the time from randomization until death from any cause, and is measured in the intent-to-treat population. TTP as used herein means the time from randomization until objective tumor progression; TTP does not include deaths. As used herein, PFS means the time from randomization until objective tumor progression or death. In one embodiment, PFS rates will be computed using the Kaplan-Meier estimates. 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 advanced non-small cell lung cancer altogether or preventing the onset of a preclinically evident stage of advanced non-small cell lung cancer. 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 advanced non-small cell lung cancer. In certain embodiments, the advanced non-small cell lung cancer can be Stage IIIB or Stage IV non-small cell lung cancer.

[0066] In certain embodiments, the treatment of non-small cell lung cancer may be assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*see* Thereasse P., et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J. of the National Cancer Institute; 2000; (92) 205-216 and 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). Overall responses for all possible combinations of tumor responses in target and non-target lesions with our without the appearance of new lesions are as follows:

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

[0067] With respect to the evaluation of target lesions, complete response (CR) is the disappearance of all target lesions, partial response (PR) is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest

diameter, progressive disease (PD) is at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions and stable disease (SD) is neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

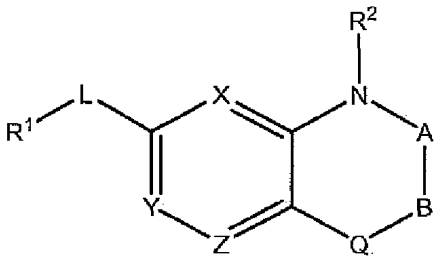
[0068] With respect to the evaluation of non-target lesions, complete response (CR) is the disappearance of all non-target lesions and normalization of tumor marker level; incomplete response/stable disease (SD) is the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits, and progressive disease (PD) is the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

[0069] In certain embodiments, treatment of non-small cell lung cancer may be assessed by the inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in circulating blood and/or tumor cells, or tumor biopsies/aspirates, before, during and/or after treatment with a TOR kinase inhibitor. For example, the inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT is assessed in B-cells, T-cells and/or monocytes.

5.2 TOR KINASE INHIBITORS

[0070] The compounds provided 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).

[0071] In one embodiment, the 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.

[0072] In one embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-CH_2C(O)NH-$.

[0073] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)CH_2NH-$.

[0074] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-.

[0075] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-CH_2C(O)O-$.

[0076] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)CH_2O-$.

[0077] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)O-.

[0078] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)NR^3-$.

[0079] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein Y is CR^3.

[0080] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CR^3.

[0081] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CH.

[0082] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are CH and Y is N.

[0083] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein Y and Z are CH and X is N.

[0084] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Y are CH and Z is N.

[0085] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[0086] In another embodiment, 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.

[0087] In another embodiment, 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.

[0088] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^1 is H.

[0089] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted C_{1-8}alkyl.

[0090] In another embodiment, 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.

[0091] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[0092] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[0093] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is H.

[0094] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein L is a direct bond.

[0095] In another embodiment, 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.

[0096] In another embodiment, 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.

[0097] In another embodiment, 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.

[0098] In another embodiment, 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.

[0099] In another embodiment, 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.

[00100] In another embodiment, 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.

[00101] In another embodiment, 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.

[00102] In another embodiment, 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.

[00103] In another embodiment, 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.

[00104] In another embodiment, 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.

[00105] In another embodiment, 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.

[00106] In another embodiment, 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.

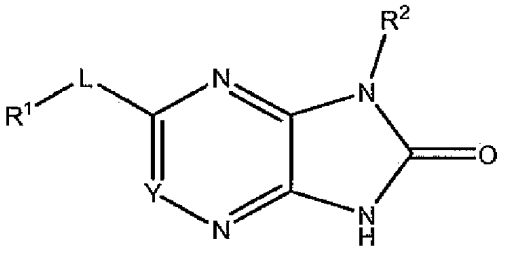
[00107] In another embodiment, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is -C(O)NH-, R^1 is H, C_{1-8}alkyl, C_{2-8}alkenyl, aryl or cycloalkyl, and L is NH.

[00108] In another embodiment, 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.

[00109] In another embodiment, the TOR kinase inhibitors of formula (I) do not include compounds wherein R^1 is a substituted or unsubstituted oxazolidinone.

[00110] In another embodiment, 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.

[00111] In one embodiment, 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.

[00112] In one embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00113] In another embodiment, 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.

[00114] In another embodiment, 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.

[00115] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is H.

[00116] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted C_{1-3}alkyl.

[00117] In another embodiment, 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.

[00118] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00119] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00120] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is H.

[00121] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein Y is CH.

[00122] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein L is a direct bond.

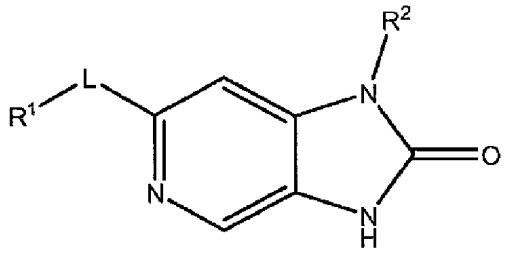
[00123] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted $C_{1\text{-}8}$alkyl.

[00124] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is $C_{1\text{-}8}$alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00125] In another embodiment, 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.

[00126] In another embodiment, 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 $C_{1\text{-}8}$alkyl substituted with substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[00127] In one embodiment, 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.

[00128] In one embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00129] In another embodiment, 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.

[00130] In another embodiment, 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.

[00131] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is H.

[00132] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted C_{1-8}alkyl.

[00133] In another embodiment, 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.

[00134] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00135] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00136] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is H.

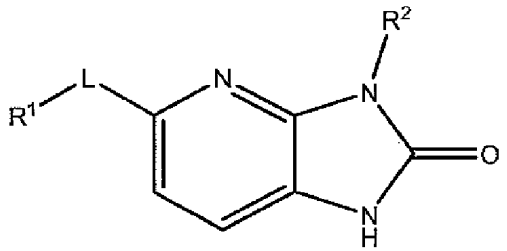
[00137] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein L is a direct bond.

[00138] In another embodiment, 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.

[00139] In another embodiment, 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.

[00140] In another embodiment, 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.

[00141] In one embodiment, 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.

[00142] In one embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00143] In another embodiment, 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.

[00144] In another embodiment, 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.

[00145] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is H.

[00146] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted C_{1-8}alkyl.

[00147] In another embodiment, 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.

[00148] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00149] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00150] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is H.

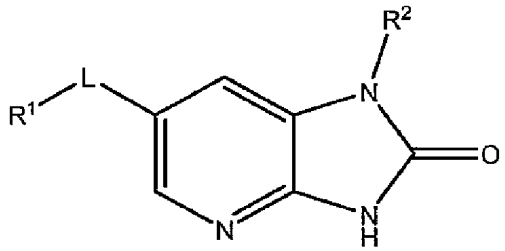
[00151] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein L is a direct bond.

[00152] In another embodiment, 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.

[00153] In another embodiment, 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.

[00154] In another embodiment, 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.

[00155] In one embodiment, 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.

[00156] In one embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00157] In another embodiment, 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.

[00158] In another embodiment, 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.

[00159] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is H.

[00160] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted C_{1-8}alkyl.

[00161] In another embodiment, 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.

[00162] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00163] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00164] In another embodiment, the Heteroaryl Compounds of formula (Id) are those wherein R^2 is H.

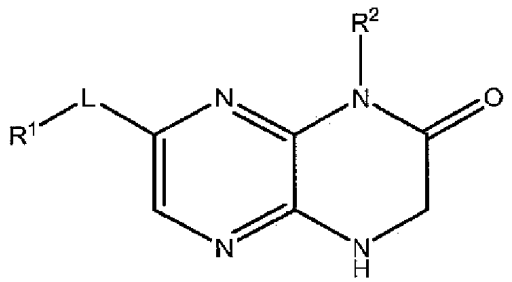
[00165] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein L is a direct bond.

[00166] In another embodiment, 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.

[00167] In another embodiment, 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.

[00168] In another embodiment, 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.

[00169] In one embodiment, 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.

[00170] In one embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00171] In another embodiment, 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.

[00172] In another embodiment, 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.

[00173] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is H.

[00174] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl.

[00175] In another embodiment, 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.

[00176] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00177] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00178] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is H.

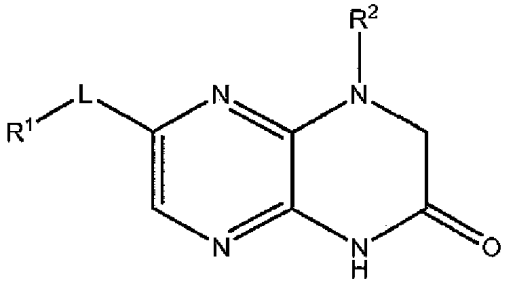
[00179] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein L is a direct bond.

[00180] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted $C_{1\text{-}8}$alkyl.

[00181] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is $C_{1\text{-}8}$alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00182] In another embodiment, 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.

[00183] In one embodiment, 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.

[00184] In one embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00185] In another embodiment, 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.

[00186] In another embodiment, 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.

[00187] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^1 is H.

[00188] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted C_{1-8}alkyl.

[00189] In another embodiment, 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.

[00190] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00191] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00192] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is H.

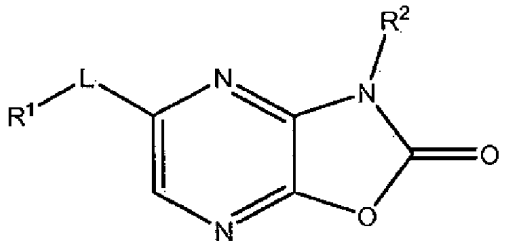
[00193] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein L is a direct bond.

[00194] In another embodiment, 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.

[00195] In another embodiment, 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.

[00196] In another embodiment, 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.

[00197] In one embodiment, 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.

[00198] In one embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00199] In another embodiment, 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.

[00200] In another embodiment, 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.

[00201] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is H.

[00202] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted C_{1-8}alkyl.

[00203] In another embodiment, 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.

[00204] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclylalkyl.

[00205] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00206] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is H.

[00207] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein L is a direct bond.

[00208] In another embodiment, 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.

[00209] In another embodiment, 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.

[00210] In another embodiment, 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.

[00211] Representative TOR kinase inhibitors of formula (I) include compounds from **Table A**.

[00212] **Table A.**

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

6-(4-hydroxyphenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-6-(naphthalen-1-yl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-1-(1-hydroxy-3-methylbutan-2-yl)-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-hydroxy-3-methylbutan-2-yl)-6-phenyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-1-(1-hydroxy-3-methylbutan-2-yl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-hydroxy-3-methylbutan-2-yl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-hydroxy-3-methylbutan-2-yl)-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-benzyl-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(4-methoxybenzyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-isopropyl-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-cyclohexyl-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
5-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-isobutyl-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(2-hydroxyethyl)-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(5-isopropyl-2-methoxyphenyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;
(S)-1-(1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-c]pyridin-2(3H)-one;
3-(1-phenylethyl)-5-(quinolin-5-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one;
(R)-3-(1-phenylethyl)-5-(quinolin-5-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one;

(R)-6-(5-isopropyl-2-methoxyphenyl)-1-(3-methylbutan-2-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-6-(5-isopropyl-2-methoxyphenyl)-1-(tetrahydrofuran-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-6-(5-isopropyl-2-methoxyphenyl)-1-(3-methylbutan-2-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-cyclopentyl-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-6-(5-isopropyl-2-methoxyphenyl)-1-(tetrahydrofuran-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(cyclopropylmethyl)-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(cyclopentylmethyl)-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(cyclohexylmethyl)-6-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(5-isopropyl-2-methoxyphenyl)-1-neopentyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-isopropyl-6-(3-isopropylphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-isopropyl-6-(2-methoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-3-(1-hydroxy-3-methylbutan-2-yl)-5-(5-isopropyl-2-methoxyphenyl)-1H-imidazo[4,5-b]pyridin-2(3H)-one;
(R)-1-(2-hydroxy-1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-1-(2-hydroxy-1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-benzhydryl-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(S)-1-(1-phenylpropyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-phenylpropyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(5-isopropyl-2-methoxyphenyl)-1-(tetrahydro-2H-pyran-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(3-methoxybenzyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-methyl-3-(1-phenylethyl)-5-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

(S)-1-methyl-3-(1-phenylethyl)-5-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(cyclopentylmethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(2-fluorophenyl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(4-fluorophenyl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-cyclopentyl-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(3-fluorophenyl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(3-methoxyphenyl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(4-methoxyphenyl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(quinolin-5-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(quinolin-5-yl)-1-(tetrahydro-2H-pyran-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-((1s,4s)-4-hydroxycyclohexyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-((1r,4r)-4-hydroxycyclohexyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(isoquinolin-5-yl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-1-(1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one;
1-(1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one;
1-isopropyl-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(4-chlorophenyl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(4-(methylsulfonyl)phenyl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(pyridin-4-yl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
5-methyl-1-((S)-1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
5-methyl-1-((R)-1-phenylethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-phenylethyl)-6-(quinolin-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(3-fluorophenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(2-fluorophenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-phenylethyl)-6-(quinolin-6-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(piperidin-4-ylmethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(pyridin-2-yl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-(pyridin-3-yl)ethyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-((1s,4s)-4-(hydroxymethyl)cyclohexyl)-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
N-(4-(2-oxo-3-(1-phenylethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)phenyl)methanesulfonamide;
6-(3-(methylsulfonyl)phenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(3-aminophenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(3-(dimethylamino)phenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-phenyl-6-(quinolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(1-phenylethyl)-6-(4-(trifluoromethyl)phenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
N-(3-(2-oxo-3-(1-phenylethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)phenyl)methanesulfonamide;
6-(4-(methylsulfonyl)phenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
3-(1-phenylethyl)-5-(quinolin-5-yl)oxazolo[5,4-b]pyrazin-2(3H)-one;
1-(cyclopentylmethyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one
6-(4-hydroxyphenyl)-1-isopropyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-hydroxyphenyl)-1-isobutyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-hydroxyphenyl)-1-((tetrahydro-2H-pyran-3-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(cyclohexylmethyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
5-(3-Hydroxyphenyl)-3-(2-methoxyphenyl)-1H-imidazo[4,5-b]pyridin-2(3H)-one;
4-(3-(3-Methoxybenzyl)-2-oxo-2,3-dihydrooxazolo[5,4-b]pyrazin-5-yl)-N-methyl benzamide;
1-Cyclopentyl-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-Cyclohexyl-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzamide;
Methyl 4-(3-(cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzoate;
1-(Cyclohexylmethyl)-6-(pyridin-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)-N-methylbenzamide;

1-(Cyclohexylmethyl)-6-(4-(hydroxymethyl)phenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(Cyclohexylmethyl)-6-(pyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzonitrile;
1-(Cyclohexylmethyl)-6-(1H-indol-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)-N-isopropylbenzamide;
1-(2-Hydroxyethyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(Cyclohexylmethyl)-6-(1H-indol-6-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
3-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzamide;
6-(4-(Aminomethyl)phenyl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-((1-methylpiperidin-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;;
4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzonitrile;
1-((1s,4s)-4-Hydroxycyclohexyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(Cyclohexylmethyl)-6-(pyridin-2-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)-N-ethylbenzamide;
1-(Cyclohexylmethyl)-6-(4-(2-hydroxypropan-2-yl)phenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(Cyclohexylmethyl)-6-(4-hydroxy-2-methylphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzoic acid;
6-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-(3-methoxypropyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-4-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(4-Hydroxyphenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-phenethyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-((1r,4r)-4-Hydroxycyclohexyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

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

1-(Cyclohexylmethyl)-6-(1H-pyrazol-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(Cyclohexylmethyl)-6-(1H-pyrazol-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(Cyclohexylmethyl)-6-(1-oxoisoindolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

1-(Cyclohexylmethyl)-6-(2-oxoindolin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(Cyclohexylmethyl)-6-(1H-indazol-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(Cyclohexylmethyl)-6-(6-methoxypyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

6-(4-Hydroxyphenyl)-1-(piperidin-4-ylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(((1r,4r)-4-Aminocyclohexyl)methyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(Cyclohexylmethyl)-6-(6-hydroxypyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(Cyclohexylmethyl)-6-(2-methoxypyridin-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

4-(3-((1r,4r)-4-Hydroxycyclohexyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzamide;

2-(4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)phenyl) acetic acid;

2-(4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)phenyl) acetamide;

1-(Cyclohexylmethyl)-6-(2-oxoindolin-6-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

4-(3-(Cyclohexylmethyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)-3-methyl benzoic acid;

N-Methyl-4-(2-oxo-3-((tetrahydro-2H-pyran-4-yl)methyl)-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzamide;

4-(2-oxo-3-((Tetrahydro-2H-pyran-4-yl)methyl)-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzamide;

7-(4-Hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

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

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

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

6-(1H-Benzo[d]imidazol-5-yl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

4-(2-oxo-3-(2-(Tetrahydro-2H-pyran-4-yl)ethyl)-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-5-yl)benzamide;

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

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

6-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-1-((1r,4r)-4-hydroxycyclohexyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

1-(Cyclohexylmethyl)-6-(2-hydroxypyridin-4-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

6-(4-(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;

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

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

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

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

6-(4-(1H-Pyrazol-3-yl)phenyl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(1H-Pyrazol-4-yl)phenyl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(5-(Aminomethyl)-1H-1,2,4-triazol-3-yl)phenyl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one hydrochloride;
1-(Cyclohexylmethyl)-6-(4-(5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl)phenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-((1r,4r)-4-methoxycyclohexyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-((tetrahydrofuran-2-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(3-(1H-1,2,4-Triazol-3-yl)phenyl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-((1r,4r)-4-(Hydroxymethyl)cyclohexyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-((1s,4s)-4-methoxycyclohexyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-((1r,4r)-4-(methoxymethyl)cyclohexyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(1-Methyl-1H-pyrazol-4-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(((1r,4r)-4-Hydroxycyclohexyl)methyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-((tetrahydrofuran-3-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(((1s,4s)-4-Hydroxycyclohexyl)methyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(1H-Benzo[d]imidazol-5-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one hydrochloride;
6-(4-(5-(Morpholinomethyl)-1H-1,2,4-triazol-3-yl)phenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

6-(4-Hydroxyphenyl)-1-(3-(2-oxopyrrolidin-1-yl)propyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-(2-morpholinoethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one hydrochloride;
1-(Cyclohexylmethyl)-6-(4-(oxazol-5-yl)phenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(2-Methyl-1H-benzo[d]imidazol-5-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one hydrocholoride;
6-(4-(5-(Methoxymethyl)-1H-1,2,4-triazol-3-yl)phenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-((1s,4s)-4-(Hydroxymethyl)cyclohexyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(3-Methyl-1H-pyrazol-4-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(1H-Pyrazol-4-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(2-Amino-1H-benzo[d]imidazol-5-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one di hydrochloride;
6-(4-(5-(2-Hydroxypropan-2-yl)-1H-1,2,4-triazol-3-yl)phenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(5-Isopropyl-1H-1,2,4-triazol-3-yl)phenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
4-(2-Methoxy-1-(2-morpholinoethyl)-1H-imidazo[4,5-b]pyrazin-6-yl)benzamide hydrochloride;
4-(1-((1s,4s)-4-Hydroxycyclohexyl)-2-methoxy-1H-imidazo[4,5-b]pyrazin-6-yl) benzamide;
6-(4-Hydroxyphenyl)-1-((1s,4s)-4-(methoxymethyl)cyclohexyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(3H-imidazo[4,5-b]pyridin-6-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

1-(2-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)ethyl)-6-(4-hydroxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

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

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

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

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

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

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

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

6-(4-(1H-1,2,4-Triazol-5-yl)phenyl)-1-(((1s,4s)-4-methoxycyclohexyl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

6-(4-(1H-1,2,4-Triazol-5-yl)phenyl)-1-(((1r,4r)-4-methoxycyclohexyl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

6-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-1-(2-(2-oxopyrrolidin-1-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

6-(4-Hydroxyphenyl)-1-(pyrrolidin-2-ylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one hydrochloride;

6-(2-Aminobenzimidazol-5-yl)-1-(cyclohexylmethyl)-4-imidazolino[4,5-b]pyrazin-2-one di hydrochloride;

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

6-(4-Hydroxyphenyl)-1-(piperidin-3-ylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

6-(4-(4H-1,2,4-triazol-3-yl)phenyl)-1-(2-(piperidin-1-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one hydrochloride;

1-(Cyclohexylmethyl)-6-(2-(methylamino)pyrimidin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

1-(Cyclohexylmethyl)-6-(2-(2-methoxyethylamino)pyrimidin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

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

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;

6-(4-(1H-imidazol-2-yl)phenyl)-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-methyl-2-morpholinopropyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

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

6-(4-(5-(aminomethyl)-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;

6-(5-(Hydroxymethyl)thiophen-2-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(1r,4r)-4-(6-(4-Hydroxyphenyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-1-yl)cyclohexanecarboxamide;
(1s,4s)-4-(6-(4-Hydroxyphenyl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyrazin-1-yl)cyclohexanecarboxamide;
6-(4-(5-methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(2-morpholinoethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(5-Oxopyrrolidin-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(Pyrrolidin-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(1H-benzo[d]imidazol-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(3-(Hydroxymethyl)thiophen-2-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(5-(2-Hydroxyethyl)thiophen-2-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(Cyclohexylmethyl)-6-(pyrimidin-5-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(6-Fluoropyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(6-Aminopyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(5-methyl-1H-imidazol-2-yl)phenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(5-Methyl-1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(2-oxopyrrolidin-1-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(6-(Methylamino)pyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(2-aminopyrimidin-5-yl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

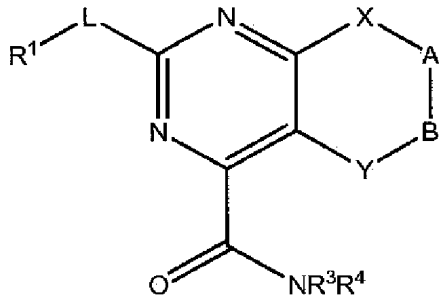
6-(4-(2-hydroxypropan-2-yl)phenyl)-1-(((1r,4r)-4-methoxycyclohexyl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-hydroxyphenyl)-1-((1-methylpiperidin-3-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(cyclohexylmethyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(hydroxymethyl)thiophen-2-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(1H-benzo[d]imidazol-6-yl)-1-(((1r,4r)-4-methoxycyclohexyl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(4,5-dimethyl-1H-imidazol-2-yl)phenyl)-1-(2-morpholinoethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-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;
6-(4-(4H-1,2,4-triazol-3-yl)phenyl)-3-(cyclohexylmethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyridin-2(3H)-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-(1H-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;

6-(3-Methyl-4-(1H-1,2,4-Triazol-3-yl)phenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-B]pyrazin-2(3H)-one;
6-(4-(1H-imidazol-2-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(5-(Aminomethyl)-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;
6-(1H-benzo[d]imidazol-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(2-Aminopyrimidin-5-yl)-1-(cyclohexylmethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-Hydroxyphenyl)-1-((1-methylpiperidin-2-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one hydrochloride;
6-(3-Methyl-4-(1H-1,2,4-Triazol-3-yl)phenyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-B]pyrazin-2(3H)-one;
1-(Cyclohexylmethyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(6-(2-Hydroxypropan-2-yl)pyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-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.

[00213] In one embodiment, 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.

[00214] In one embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)CH_2C(O)NH-$.

[00215] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)CH_2NH-$.

[00216] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -$N(R^2)C(O)NH$-.

[00217] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -$N(R^2)C{=}N$-.

[00218] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -$C(R^2){=}CHNH$-.

[00219] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein L is a direct bond.

[00220] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00221] In another embodiment, 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.

[00222] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00223] In another embodiment, 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.

[00224] In another embodiment, 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.

[00225] In another embodiment, 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.

[00226] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl, such as $-CH_2C_6H_5$.

[00227] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^2 is unsubstituted $C_{1\text{-}8}$alkyl, such as unsubstituted methyl.

[00228] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00229] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00230] In another embodiment, 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.

[00231] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00232] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^3 and R^4 are H.

[00233] In another embodiment, 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.

[00234] In another embodiment, 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.

[00235] In another embodiment, 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.

[00236] In another embodiment, 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.

[00237] In another embodiment, 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.

[00238] In another embodiment, 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.

[00239] In another embodiment, 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.

[00240] In another embodiment, 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.

[00241] In another embodiment, 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.

[00242] In another embodiment, 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-

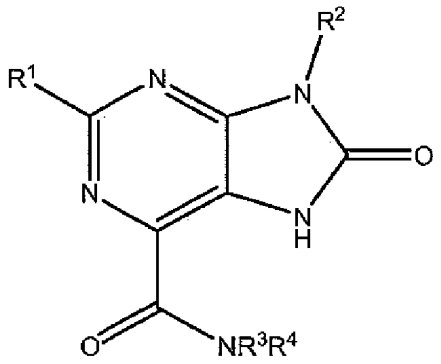
hydroxyethyl)-2-phenyl-9H-purine-6-carboxamide, 9-(3-hydroxypropyl)-2-methyl-9H-purine-6-carboxamide, 9-(3-hydroxypropyl)-2-(trifluoromethyl)-9H-purine-6-carboxamide, 2-methyl-9-phenylmethyl-9H-purine-6-carboxamide or 2-methyl-9-β-D-ribofuranosyl-9H-purine-6-carboxamide.

[00243] In another embodiment, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted furanoside.

[00244] In another embodiment, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00245] In another embodiment, the TOR kinase inhibitors of formula (II) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00246] In one embodiment, 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_{1-8}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.

[00247] In one embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^1 is substituted aryl, substituted or unsubstituted heteroaryl, such as substituted phenyl.

[00248] In another embodiment, 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.

[00249] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00250] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl, such as $-CH_2C_6H_5$.

[00251] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is unsubstituted $C_{1\text{-}8}$alkyl, such as unsubstituted methyl.

[00252] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00253] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00254] In another embodiment, 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.

[00255] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00256] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^3 and R^4 are H.

[00257] In another embodiment, 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-

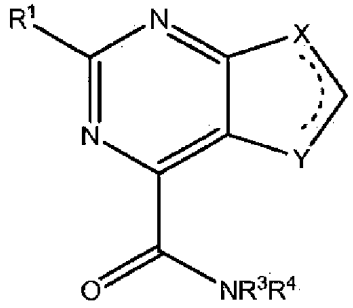
carboxamide, 9-phenylmethyl-9H-purine-2,6-dicarboxamide, or 2-methyl-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide.

[00258] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted furanoside.

[00259] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00260] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00261] In one embodiment, the TOR kinase inhibitors include compounds having the following formula (IIb):



(IIb)

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



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.

[00262] In one embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00263] In another embodiment, 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.

[00264] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00265] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00266] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00267] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00268] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00269] In another embodiment, 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.

[00270] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00271] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^3 and R^4 are H.

[00272] In another embodiment, 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.

[00273] In another embodiment, 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.

[00274] In another embodiment, 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.

[00275] In another embodiment, 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.

[00276] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted cyclobutyl when  is -N(R^2)-CH=N-.

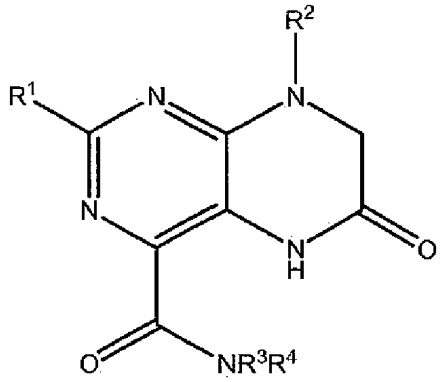
[00277] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is a substituted furanoside when  is -N(R^2)-CH=N-.

[00278] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted pyrimidine when  is -C(R^2)=CH-NH-.

[00279] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted oxetane when  is -N(R^2)-CH=N-.

[00280] In another embodiment, 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-.

[00281] In one embodiment, 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_{1-8}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.

[00282] In one embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00283] In another embodiment, 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.

[00284] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00285] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00286] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00287] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

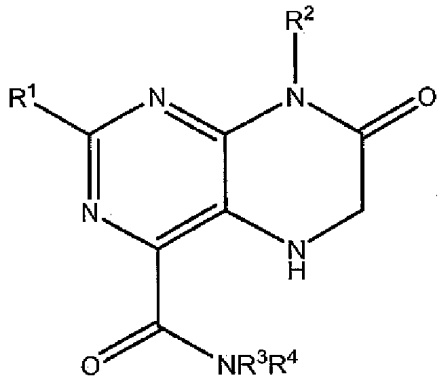
[00288] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00289] In another embodiment, 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.

[00290] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00291] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^3 and R^4 are H.

[00292] In one embodiment, 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.

[00293] In one embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00294] In another embodiment, 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.

[00295] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^1 is substituted or unsubstituted cycloalkyl, such as substituted or unsubstituted cyclopentyl.

[00296] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00297] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00298] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl.

[00299] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00300] In another embodiment, 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.

[00301] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00302] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^3 and R^4 are H.

[00303] Representative TOR kinase inhibitors of formula (II) include compounds from Table B.

[00304] **Table B.**

9-benzyl-8-oxo-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
N-methyl-8-oxo-9-phenyl-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
8-oxo-9-phenyl-2-(pyridin-2-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(2-chloropyridin-3-yl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide;
2-(2-methoxypyridin-3-yl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide;
N,N-dimethyl-8-oxo-9-phenyl-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
9-methyl-8-oxo-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-hydroxyphenyl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-hydroxyphenyl)-8-oxo-9-o-tolyl-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-indol-4-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-indol-6-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-hydroxyphenyl)-9-(4-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(2-hydroxypyridin-4-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-chlorophenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-fluorophenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2,6-difluorophenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-cycloheptyl-8-oxo-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-methoxyphenyl)-8-oxo-2-(quinolin-5-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-cyclopentyl-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-methoxyphenyl)-8-oxo-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-methoxyphenyl)-2-(6-methoxypyridin-3-yl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-hydroxyphenyl)-8-oxo-9-(4-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
9-benzyl-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-hydroxyphenyl)-8-oxo-9-(2-(trifluoromethoxy)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
9-(2,4-dichlorophenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;

9-(2-methoxyphenyl)-2-(3-nitrophenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-cyanophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide;
9-(3-fluorophenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-methoxyphenyl)-8-oxo-2-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(5-fluoropyridin-3-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1-benzylpiperidin-4-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
benzyl 4-(6-carbamoyl-8-oxo-2-(pyridin-3-yl)-7H-purin-9(8H)-yl)piperidine-1-carboxylate;
9-cyclohexyl-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-methoxyphenyl)-8-oxo-2-(3-(trifluoromethoxy)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
9-phenyl-2-(pyridin-3-yl)-9H-purine-6-carboxamide;
6-oxo-8-phenyl-2-(pyridin-3-yl)-5,6,7,8-tetrahydropteridine-4-carboxamide;
6-oxo-8-phenyl-2-(pyridin-4-yl)-5,6,7,8-tetrahydropteridine-4-carboxamide;
2-(3-aminophenyl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-hydroxyphenyl)-9-(2-methoxyphenyl)-9H-purine-6-carboxamide;
9-Cyclopentyl-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-tert-Butyl-2-(3-hydroxy-phenyl)-8-oxo-8,9-dihydo-7H-purine-6-carboxamide;
[2-(3-Hydroxyphenyl)-9-(2-methoxyphenyl)-8-oxo(7-hydropurin-6-yl)]-N-methylcarboxamide;
2-phenyl-5H-pyrrolo[3,2-d]pyrimidine-4-carboxamide;
[2-(3-Hydroxyphenyl)-9-(2-methoxyphenyl)-8-oxo(7-hydropurin-6-yl)]-N,N-dimethyl carboxamide;
2-(3-Hydroxyphenylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-Hydroxyphenylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;

9-(trans-4-Hydroxycyclohexyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(trans-4-Hydroxycyclohexyl)-8-oxo-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
9-(trans-4-Hydroxycyclohexyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(trans-4-Hydroxycyclohexyl)-8-oxo-2-(pyridin-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenylamino)-9-(2-methoxyphenyl)-9H-purine-6-carboxamide;
9-Isopropyl-2-(3-hydroxy-phenyl)-8-oxo-8,9-dihydo-7H-purine-6-carboxamide;
Methyl 4-(6-carbamoyl-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purin-2-yl) benzoate;
2-(2-Chloro-3-hydroxyphenyl)-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carbox amide;
2-(3-Cyanophenyl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(2-Hydroxyphenylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-9-(4-methoxy-2-methylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-8-oxo-9-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-Cyano-phenyl)-9-(2-methoxy-phenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
4-[6-Carbamoyl-9-(2-methoxy-phenyl)-8-oxo-8,9-dihydro-7H-purin-2-yl]-benzoic acid;
Methyl 3-(6-carbamoyl-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)benzoate;
3-(6-Carbamoyl-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purin-2-yl)benzoic acid;
2-(3-Hydroxyphenyl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Indazol-6-yl)-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(4-Carbamoylphenyl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Ethylphenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2,5-Dichlorophenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;

2-(3-Carbamoylphenyl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carbox amide;
9-(2,6-Dichlorophenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(2-Hydroxyphenyl)-9-(2-methoxyphenyl)purine-6-carboxamide;
2-(1H-Indazol-5-yl)-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2,3-Dichlorophenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-[4-(Hydroxymethyl)phenyl]-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carbox-amide;
2-[3-(Hydroxymethyl)phenyl]-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carbox-amide;
9-(2-Methoxyphenyl)-8-oxo-2-(pyridin-4-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-Fluoro-3-hydroxyphenyl)-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carbox-amide;
2-(2-Fluoro-3-hydroxyphenyl)-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carbox-amide;
2-[4-(1-Hydroxy-isopropyl)phenyl]-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-[3-(1-Hydroxy-isopropyl)phenyl]-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2-Methoxyphenyl)-2-(2-nitrophenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2-Methoxyphenyl)-2-(4-nitrophenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2-Methoxyphenyl)-2-(2-nitrophenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2,4-Difluorophenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2-Methoxyphenyl)-2-{3-[(methylsulfonyl)amino]phenyl}-8-oxo-7-hydropurine-6-carboxamide;
9-(4-Chloro-2-fluorophenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2-Chlorophenyl)-8-oxo-2-(3-pyridyl)-7-hydropurine-6-carboxamide;
8-Oxo-2-(3-pyridyl)-9-[2-(trifluoromethyl)phenyl]-7-hydropurine-6-carboxamide;
9-(3-Chloro-2-fluorophenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2-Fluoro-3-trifluoromethylphenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(2, 3, 4-Trifluorophenyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(1H-Benzo[d]imidazol-6-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;

2-[3-(Acetylamino)phenyl]-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(3-hydroxyphenyl)-8-(2-methoxyphenyl)-6-oxo-5,6,7,8-tetrahydropteridine-4-carboxamide;
9-(2-Methoxyphenyl)-8-oxo-2-pyrazol-4-yl-7-hydropurine-6-carboxamide;
9-(2-Methoxyphenyl)-8-oxo-2-pyrazol-3-yl-7-hydropurine-6-carboxamide;
9-(4-Aminocyclohexyl)-2-(3-hydroxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-[3-(Difluoromethyl)phenyl]-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carbox-amide;
2-[5-(Difluoromethyl)-2-fluorophenyl]-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(1H-benzo[d]imidazol-4-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(6-Hydroxypyridin-3-yl)-8-oxo-9-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-benzo[d]imidazol-6-yl)-9-(2-fluorophenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-Benzimidazol-6-yl-8-oxo-9-[2-(trifluoromethyl)phenyl]-7-hydropurine-6-carboxamide;
2-(5-Chloropyridin-3-yl)-8-oxo-9-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
trans-4-(6-Carbamoyl-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purin-2-ylamino) cyclohexyl carbamate;
(R)-9-(2-Methoxyphenyl)-8-oxo-2-(pyrrolidin-3-ylamino)-8,9-dihydro-7H-purine-6-carboxamide;
(S)-9-(2-Methoxyphenyl)-8-oxo-2-(pyrrolidin-3-ylamino)-8,9-dihydro-7H-purine-6-carboxamide;
(cis)-4-(6-Carbamoyl-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purin-2-ylamino) cyclohexyl carbamate;
2-(trans-4-Hydroxycyclohexylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-Chloropyridin-3-yl)-8-oxo-9-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;

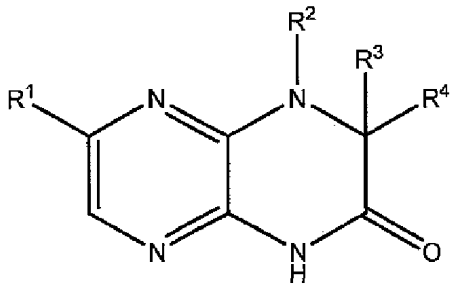
2-(cis-4-Hydroxycyclohexylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-((1H-Imidazol-1-yl)methyl)phenylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-Hydroxypyridin-3-yl)-8-oxo-9-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
(R)-9-(2-Methoxyphenyl)-8-oxo-2-(pyrrolidin-2-ylmethylamino)-8,9-dihydro-7H-purine-6-carboxamide;
(S)-9-(2-Methoxyphenyl)-8-oxo-2-(pyrrolidin-2-ylmethylamino)-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(2-Hydroxyethylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide ;
9-(2-Methoxyphenyl)-8-oxo-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-(1H-1,2,4-Triazol-3-yl)phenyl)-9-(2-methoxyphenyl)-8-oxo-7-hydropurine-6-carboxamide;
9-(Biphenyl-2-yl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-9-(2-fluorophenyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Methoxyphenyl)-2-(2-methyl-1H-benzo[d]imidazol-6-yl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-(Hydroxymethyl)phenylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(2-(Hydroxymethyl)phenylamino)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-tert-Butylphenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;

2-(3-Hydroxyphenyl)-8-oxo-9-(2-phenoxyphenyl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Benzo[d]imidazol-6-yl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Indazol-4-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(2-Hydroxypyridin-3-yl)-8-oxo-9-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Imidazo[4,5-b]pyridin-6-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-(1H-Imidazol-1-yl)phenyl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Cyclohexylphenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-(1H-Imidazol-2-yl)phenyl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Benzo[d]imidazol-1-yl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Imidazo[4,5-b]pyridin-6-yl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Isopropylphenyl)-8-oxo-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Imidazo[4,5-b]pyridin-6-yl)-8-oxo-9-(2-(trifluoromethyl)phenyl)-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Methoxyphenyl)-2-(2-(methylthio)-1H-benzo[d]imidazol-5-yl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Indol-5-yl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(Cyclohexylmethyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2,3-Dihydro-1H-inden-1-yl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-9-isobutyl-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;

9-(trans-4-Methoxycyclohexyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(cis-4-Methoxycyclohexyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-8-oxo-9-(5,6,7,8-tetrahydronaphthalen-1-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-9-cyclohexyl-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-9-(1H-indol-4-yl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Fluoro-3-methoxyphenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Fluoro-5-methoxyphenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
9-Cyclohexyl-2-(1H-imidazo[4,5-b]pyridin-6-yl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-8-oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-8-oxo-9-((tetrahydro-2H-pyran-4-yl)methyl)-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Cyclopentylphenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-8-oxo-9-(piperidin-4-yl)-8,9-dihydro-7H-purine-6-carboxamide;
9-(2-Fluoro-4-methoxyphenyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-benzo[d]imidazol-6-yl)-9-cyclohexyl-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-Benzimidazol-6-yl-9-(trans-4-methoxycyclohexyl)-8-oxo-7-hydropurine-6-carboxamide;
2-(4-(Aminomethyl)phenyl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-9-(cis-4-(methoxymethyl)cyclohexyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;

9-(trans-4-Aminocyclohexyl)-2-(3-hydroxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-9-(2-isobutylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
(R)-2-(3-Hydroxyphenyl)-8-oxo-9-(tetrahydrofuran-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
(S)-2-(3-Hydroxyphenyl)-8-oxo-9-(tetrahydrofuran-3-yl)-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-(Aminomethyl)phenyl)-9-(2-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-(1H-1,2,3-Triazol-5-yl)phenyl)-9-(2-isopropylphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(4-(1H-1,2,4-Triazol-3-yl)phenyl)-9-(cis-4-methoxycyclohexyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Benzo[d]imidazol-6-yl)-9-(cis-4-methoxycyclohexyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(1H-Imidazo[4,5-b]pyridin-6-yl)-9-(cis-4-methoxycyclohexyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;
2-(3-Hydroxyphenyl)-9-((1r,4r)-4-(methoxymethyl)cyclohexyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide; and
9-(2-Isopropylphenyl)-2-(4-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide,
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof.

[00305] In one embodiment, the TOR kinase inhibitors include compounds having the following formula (III):



(III)

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

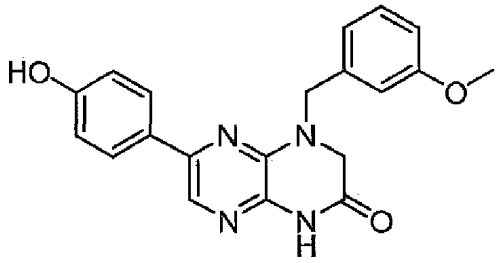
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

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;

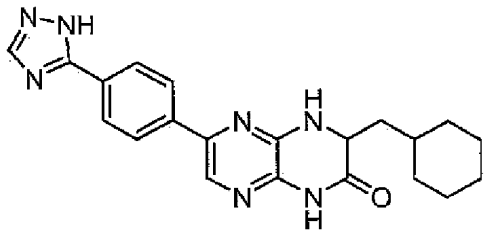
R^3 and R^4 are each independently H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, substituted or 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, the TOR kinase inhibitors do not include the compounds depicted below, namely:

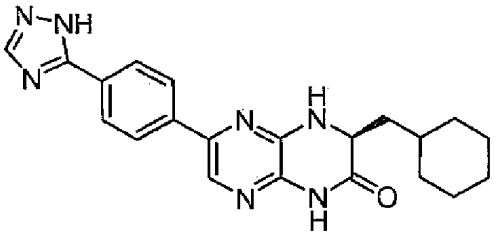


6-(4-hydroxyphenyl)-4-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;



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

or,

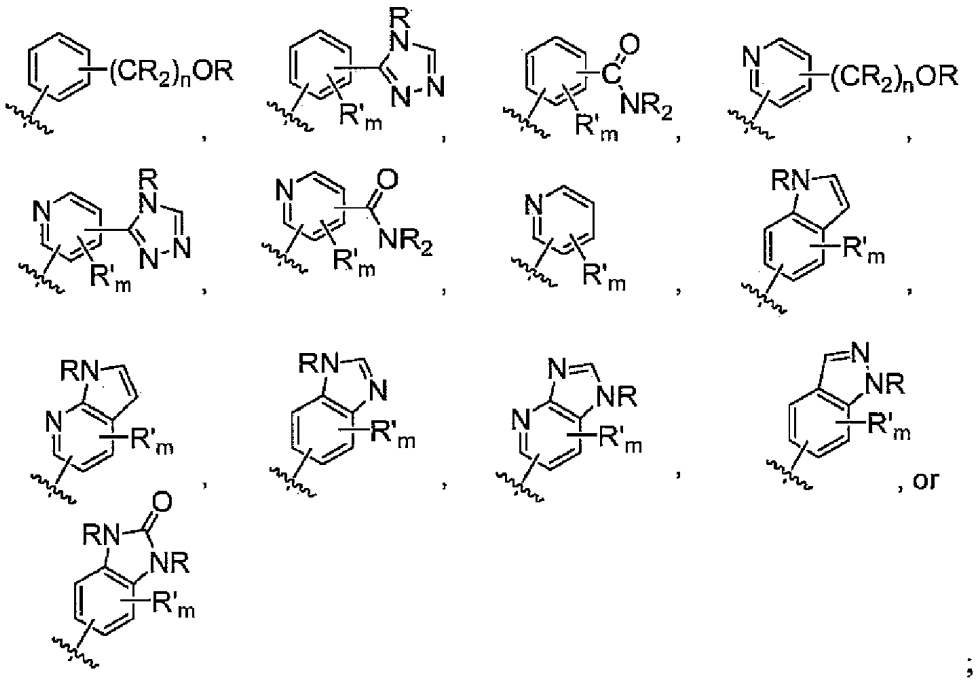


(R)-6-(4-(1H-1,2,4-triazol-5-yl)phenyl)-3-(cyclohexylmethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

[00306] In some embodiments of compounds of formula (III), R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In one embodiment, 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, 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, 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, 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.

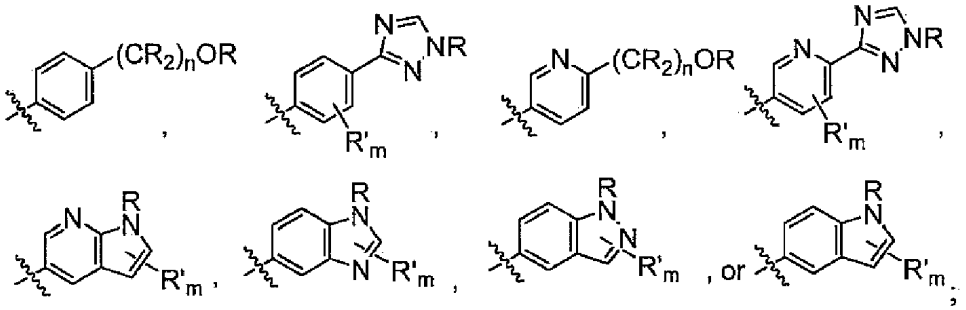
[00307] In some embodiments of compounds of formula (III), R^1 is



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.

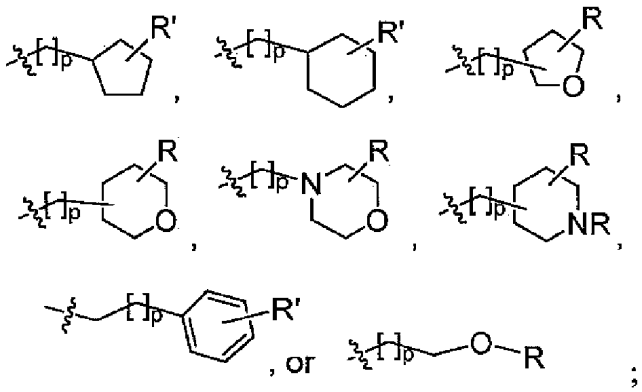
[00308] In some embodiments of compounds of formula (III), R^1 is



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.

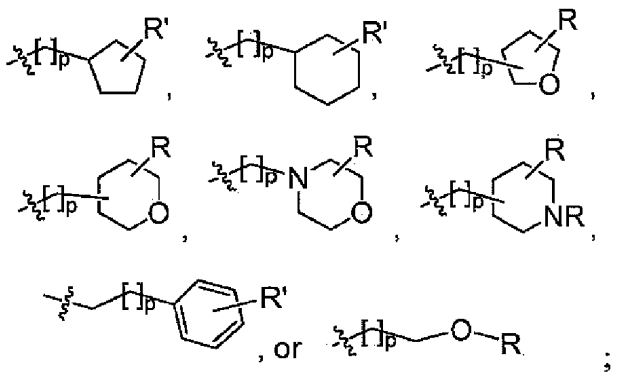
[00309] In some embodiments of compounds of formula (III), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, 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.

[00310] In other embodiments, R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



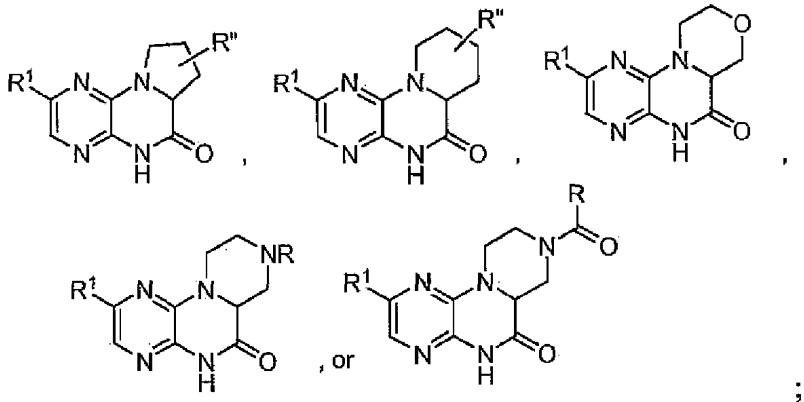
wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently H, -OR, cyano, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); and p is 0-3.

[00311] In some such embodiments, 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.

[00312] In some other embodiments 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, the compound of formula (III) is



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.

[00313] In some embodiments 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).

[00314] In some such embodiments 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, 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

[00315] In certain embodiments, the compounds of formula (III) have an R^1 group set forth herein and an R^2 group set forth herein.

[00316] In some embodiments 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.

[00317] Representative TOR kinase inhibitors of formula (III) include compounds from Table C.

[00318] **Table C.**

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;

6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-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-hydroxycyclohexyl)-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-hydroxycyclohexyl)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)-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)-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-hydroxycyclohexyl)-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-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)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-isopropyl-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-hydroxycyclohexyl)-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)-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-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-ethyl-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)-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-(tetrahydro-2H-pyran-4-yl)-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-isopropyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-ethyl-6-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-(*cis*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(2-methoxyethyl)-6-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-(1H-1,2,4-triazol-5-yl)phenyl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
5-(8-(2-methoxyethyl)-6-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;
3-(6-oxo-8-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)benzamide;
3-(6-oxo-8-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)benzonitrile;
5-(8-(*trans*-4-methoxycyclohexyl)-6-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;
6-(1H-imidazo[4,5-b]pyridin-6-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(1H-indazol-6-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-((1R,3S)-3-methoxycyclopentyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

4-((1S,3R)-3-methoxycyclopentyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-((1R,3R)-3-methoxycyclopentyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-((1S,3S)-3-methoxycyclopentyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-ethyl-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(1H-pyrrolo[2,3-b]pyridin-5-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(1H-indol-6-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(1H-indol-5-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(((1R,3S)-3-methoxycyclopentyl)methyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(((1S,3R)-3-methoxycyclopentyl)methyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-fluoro-2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-fluoro-2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3,3-dimethyl-6-(4-methyl-6-(4H-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-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((1R,3S)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((1S,3R)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(((1S,3S)-3-methoxycyclopentyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(((1R,3R)-3-methoxycyclopentyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((1S,3S)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((1R,3R)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(((1R,3S)-3-methoxycyclopentyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(((1S,3R)-3-methoxycyclopentyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-fluoro-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(3-fluoro-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7'-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-1'-((tetrahydro-2H-pyran-4-yl)methyl)-1'H-spiro[cyclopentane-1,2'-pyrazino[2,3-b]pyrazin]-3'(4'H)-one;
7'-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-1'-((tetrahydro-2H-pyran-4-yl)methyl)-1'H-spiro[cyclobutane-1,2'-pyrazino[2,3-b]pyrazin]-3'(4'H)-one;
4-(cyclopropylmethyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7'-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-1'H-spiro[cyclopentane-1,2'-pyrazino[2,3-b]pyrazin]-3'(4'H)-one;
7'-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-1'H-spiro[cyclobutane-1,2'-pyrazino[2,3-b]pyrazin]-3'(4'H)-one;
7'-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-1'H-spiro[cyclopropane-1,2'-pyrazino[2,3-b]pyrazin]-3'(4'H)-one;
(R)-6-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-((tetrahydrofuran-2-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-6-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-((tetrahydrofuran-2-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

6-(1H-indazol-5-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(6-oxo-8-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)benzamide;
4-(2-methoxyethyl)-3,3-dimethyl-6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-ethyl-3,3-dimethyl-6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3,3-dimethyl-6-(2-methyl-6-(4H-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;
(R)-6-(6-(1-hydroxyethyl)pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3,3-dimethyl-6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)-4-methylpyridin-3-yl)-4-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)-4-methylpyridin-3-yl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3,3-dimethyl-6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3,3-dimethyl-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)-2-methylpyridin-3-yl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)-2-methylpyridin-3-yl)-4-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-6-(6-(1-hydroxyethyl)pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

3,3-dimethyl-6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,3-dimethyl-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(4-(2-hydroxypropan-2-yl)phenyl)-4-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(4-(2-hydroxypropan-2-yl)phenyl)-4-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(*cis*-4-methoxycyclohexyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(*trans*-4-methoxycyclohexyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(4-(2-hydroxypropan-2-yl)phenyl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(2-methoxyethyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
9-(6-(4H-1,2,4-triazol-3-yl)-3-pyridyl)-6,11,4a-trihydromorpholino[4,3-e]pyrazino[2,3-b]pyrazin-5-one;
6-(2-methyl-6-(4H-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;
5-(8-(*cis*-4-methoxycyclohexyl)-6-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-6-methylpicolinonitrile;
6-(6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-3-(2-methoxyacetyl)-6,11,4a-trihydropiperazino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-6,11,4a-trihydropiperazino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-3-(2-methoxyethyl)-6,11,4a-trihydropiperazino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;

4-(cyclopentylmethyl)-6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
9-(6-(4H-1,2,4-triazol-3-yl)-2-methyl-3-pyridyl)-6,11,4a-trihydromorpholino[4,3-e]pyrazino[2,3-b]pyrazin-5-one;
4-(*trans*-4-hydroxycyclohexyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(*cis*-4-hydroxycyclohexyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((tetrahydrofuran-3-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(cyclopentylmethyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-neopentyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-isobutyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3-methyl-6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(piperidin-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-3-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
8-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)(3aS,2R)-2-methoxy-5,10,3a-trihydropyrazino[2,3-b]pyrrolidino[1,2-e]pyrazin-4-one;
8-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)(2R,3aR)-2-methoxy-5,10,3a-trihydropyrazino[2,3-b]pyrrolidino[1,2-e]pyrazin-4-one;
8-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)(2S,3aR)-2-methoxy-5,10,3a-trihydropyrazino[2,3-b]pyrrolidino[1,2-e]pyrazin-4-one;
8-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)(2S,3aS)-2-methoxy-5,10,3a-trihydropyrazino[2,3-b]pyrrolidino[1,2-e]pyrazin-4-one;

6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(3-methoxypropyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((tetrahydrofuran-2-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(R)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((tetrahydrofuran-2-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-3-methyl-6,11,4a-trihydropiperazino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;
9-(4-(4H-1,2,4-triazol-3-yl)phenyl)-6,11,4a-trihydromorpholino[4,3-e]pyrazino[2,3-b]pyrazin-5-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-6,11,4a-trihydropiperidino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(*cis*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(2-morpholinoethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-phenethyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(cyclohexylmethyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

(R)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(tetrahydrofuran-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(tetrahydrofuran-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-phenyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-methyl-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
9-[6-(1-hydroxy-isopropyl)-3-pyridyl]-6,11,4a-trihydromorpholino[4,3-e]pyrazino[2,3-b]pyrazin-5-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(2-amino-7-methyl-1H-benzo[d]imidazol-5-yl)-4-(3-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(3-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-6,11,4a-trihydromorpholino[4,3-e]pyrazino[2,3-b]pyrazin-5-one;
6-(4-methyl-2-(methylamino)-1H-benzo[d]imidazol-6-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
8-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-5,10,3a-trihydropyrazino[2,3-b]pyrrolidino[1,2-e]pyrazin-4-one;
6-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-ethyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(4-(4H-1,2,4-triazol-3-yl)phenyl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

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

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

6-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

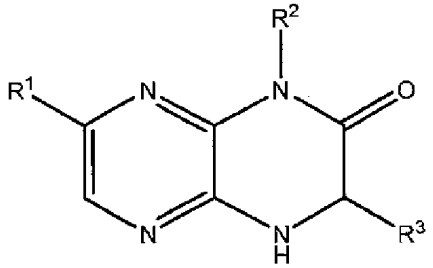
6-(4-methyl-1H-benzo[d]imidazol-6-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

6-(4-(2-hydroxypropan-2-yl)phenyl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one; and

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

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

[00319] In one embodiment, the TOR kinase inhibitors include compounds having the following formula (IV):



(IV)

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

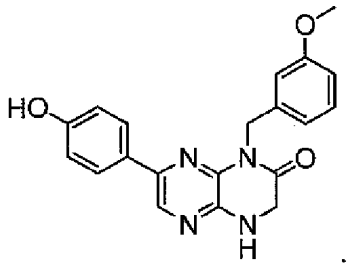
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

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;

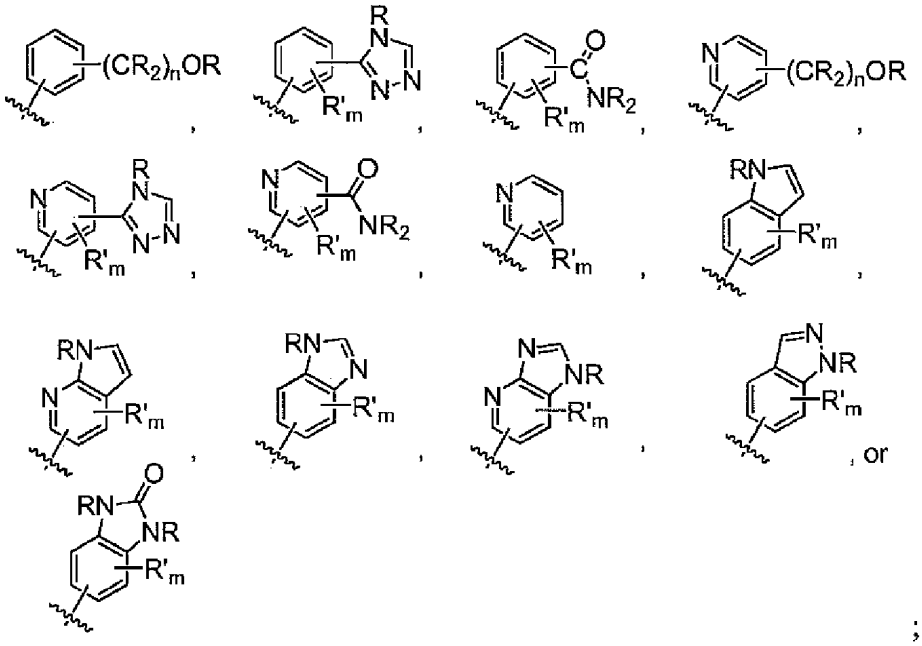
R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

wherein in certain embodiments, 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:



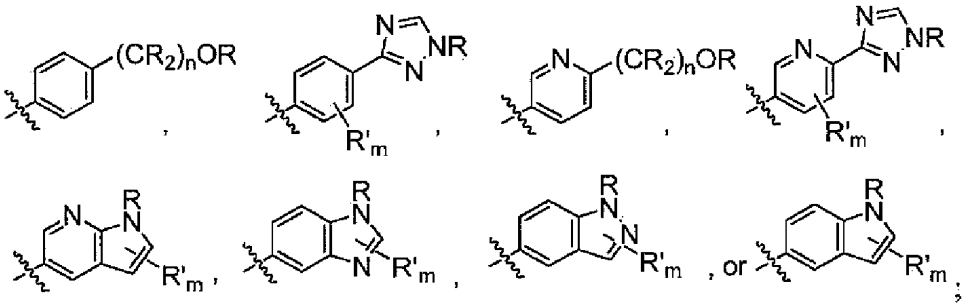
[00320] In some embodiments of compounds of formula (IV), R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. For example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, 1H-pyrrolo[2,3-b]pyridyl, indazolyl, indolyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 3H-imidazo[4,5-b]pyridyl, or pyrazolyl, each optionally substituted. In some embodiments, 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, 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, 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.

[00321] In some embodiments, 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.

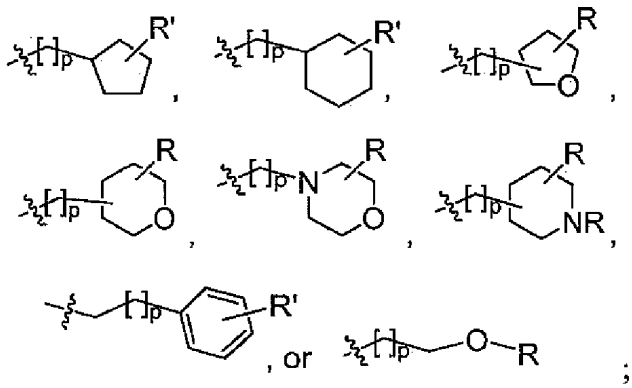
[00322] In some embodiments of compounds of formula (IV), R^1 is



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.

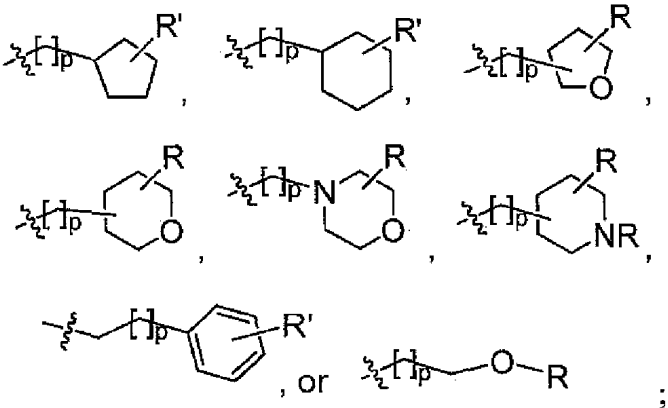
[00323] In some embodiments of compounds of formula (IV), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, 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.

[00324] In other embodiments, 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.

[00325] In other embodiments 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.

[00326] In other embodiments of compounds of formula (IV), R^3 is H.

[00327] In some such embodiments 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, 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.

[00328] In certain embodiments, the compounds of formula (IV) have an R^1 group set forth herein and an R^2 group set forth herein.

[00329] In some embodiments 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.

[00330] Representative TOR kinase inhibitors of formula (IV) include compounds from Table D.

[00331] **Table D.**

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;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(*cis*-4-hydroxycyclohexyl)-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-hydroxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-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-hydroxycyclohexyl)methyl)-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-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indol-4-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-((*trans*-4-hydroxycyclohexyl)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-hydroxycyclohexyl)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)-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)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-isopropyl-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-(*trans*-4-methoxycyclohexyl)-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-(*trans*-4-hydroxycyclohexyl)-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-(2-methoxyethyl)-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-isopropyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-hydroxypyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-isopropyl-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
5-(8-isopropyl-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;
7-(1H-indazol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-aminopyrimidin-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-aminopyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(methylamino)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-hydroxypyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(1H-pyrazol-3-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indazol-4-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indazol-6-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(pyrimidin-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-methoxypyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

1-(2-methoxyethyl)-7-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(1H-indazol-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(pyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-aminopyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-methyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
2-(2-hydroxypropan-2-yl)-5-(8-(*trans*-4-methoxycyclohexyl)-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)pyridine 1-oxide;
4-methyl-5-(7-oxo-8-((tetrahydro-2H-pyran-4-yl)methyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)picolinamide;
5-(8-((*cis*-4-methoxycyclohexyl)methyl)-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;
7-(1H-pyrazol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-methoxycyclohexyl)-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3-((7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-2-oxo-3,4-dihydropyrazino[2,3-b]pyrazin-1(2H)-yl)methyl)benzonitrile;
1-((*trans*-4-methoxycyclohexyl)methyl)-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3-(7-oxo-8-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)benzamide;
5-(8-((*trans*-4-methoxycyclohexyl)methyl)-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;
3-((7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-2-oxo-3,4-dihydropyrazino[2,3-b]pyrazin-1(2H)-yl)methyl)benzonitrile;

7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1R,3R)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1S,3R)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1S,3S)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1R,3S)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indazol-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-hydroxycyclohexyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*cis*-4-hydroxycyclohexyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-isopropyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-imidazo[4,5-b]pyridin-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((*cis*-4-methoxycyclohexyl)methyl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-hydroxycyclohexyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*cis*-4-hydroxycyclohexyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(7-oxo-8-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)benzamide;

7-(1H-indazol-5-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-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((1S,3R)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((1R,3R)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((1R,3S)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((1S,3S)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indol-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indol-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(2-hydroxypropan-2-yl)phenyl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((*trans*-4-methoxycyclohexyl)methyl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(2-methoxyethyl)-7-(4-methyl-2-(methylamino)-1H-benzo[d]imidazol-6-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(7-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(2-methoxyethyl)-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-benzyl-7-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(3-fluoro-4-(4H-1,2,4-triazol-3-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(3-fluoro-4-(4H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(3-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-methoxycyclohexyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(3-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(2-methoxyethyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(cyclopentylmethyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(2-hydroxypropan-2-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

(S)-7-(6-(1-hydroxyethyl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(R)-7-(6-(1-hydroxyethyl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(2-hydroxypropan-2-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(4-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(3-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(3-methoxypropyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-methyl-2-(methylamino)-1H-benzo[d]imidazol-6-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-amino-4-methyl-1H-benzo[d]imidazol-6-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(R)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-methyl-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-methyl-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,3-dimethyl-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-amino-4-methyl-1H-benzo[d]imidazol-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(1H-1,2,4-triazol-5-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(1-hydroxypropan-2-yl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one; and
1-(2-hydroxyethyl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one,
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof.

5.3 METHODS FOR MAKING TOR KINASE INHIBITORS

[00332] 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.

[00333] 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 their entirety.

5.4 METHODS OF USE

[00334] Provided herein are methods for treating or preventing advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor and an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine. In certain embodiments, advanced non-small cell lung cancer is non-small-cell lung carcinoma, Stage IIIB non-small cell lung cancer or Stage IV non-small cell lung cancer. In certain embodiments, the patient has failed at least one line of standard therapy. In one embodiment the standard therapy is chemotherapy or treatment with an EGFR inhibitor, for example, erlotinib. In one embodiment, the advanced non-small cell lung cancer is EGFR inhibitor resistant, for example, erlotinib resistant. In one such embodiment, the advanced non-small cell lung cancer is characterized by a EGFR inhibitor resistant mutation, for example, T790M EGFR mutation. In another embodiment, the advanced non-small cell lung cancer has an EGFR activating mutation, for example, L858R EGFR mutation. In some embodiments, the methods further comprise screening the patient's non-small cell lung cancer for an EGFR inhibitor resistant mutation, for example, an erlotinib resistant mutation. In another the methods further comprise screening the patient's non-small cell lung cancer for an EGFR activating mutation.

[00335] Also provided are methods for predicting therapeutic efficacy of treatment of a patient having advanced non-small cell lung cancer with a TOR kinase inhibitor in combination with erlotinib or a cytidine analog, comprising obtaining a biological sample of the patient's cancer, and screening said patient's cancer for the presence of an EGFR mutation, wherein the presence of an mutation is predictive of therapeutic efficacy of treatment with the TOR kinase inhibitor in combination with erlotinib or a cytidine analog. In one such embodiment, the mutation is an activating mutation. In another, the mutation results in EGFR inhibitor resistance. As is well known in the art, screening for an EGFR mutation can be performed by, for example, EGFR gene sequencing.

[00336] In certain embodiments, provided herein are methods for achieving a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of complete response, partial response or stable disease, comprising administering an effective amount

of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine.

[00337] In certain embodiments, provided herein are methods for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to said patient. In certain embodiments, the cytidine analog is oral azacitidine.

[00338] In one embodiment, provided herein are methods for preventing or delaying a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of progressive disease in a patient, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine. In one embodiment the prevention or delaying of progressive disease is characterized or achieved by a change in overall size of the target lesions, of for example, between -30% and +20% compared to pre-treatment. In another embodiment, the change in size of the target lesions is a reduction in overall size of more than 30%, for example, more than 50% reduction in target lesion size compared to pre-treatment. In another, the prevention is characterized or achieved by a reduction in size or a delay in progression of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by a reduction in the number of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by a reduction in the number or quality of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by the absence or the disappearance of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by the absence or the disappearance of non-target lesions compared to pre-treatment. In another embodiment, the prevention is achieved or characterized by the prevention of new lesions compared to pre-treatment. In yet another embodiment, the prevention is achieved or characterized by the prevention of clinical signs or symptoms of disease progression compared to pre-treatment, such as cancer-related cachexia or increased pain.

[00339] In certain embodiments, provided herein are methods for decreasing the size of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine.

[00340] In certain embodiments, provided herein are methods for decreasing the size of a non-target lesion in a patient compared to pre-treatment, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine.

[00341] In certain embodiments, provided herein are methods for achieving a reduction in the number of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine.

[00342] In certain embodiments, provided herein are methods for achieving a reduction in the number of non-target lesions in a patient compared to pre-treatment, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine.

[00343] In certain embodiments, provided herein are methods for achieving an absence of all target lesions in a patient, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine.

[00344] In certain embodiments, provided herein are methods for achieving an absence of all non-target lesions in a patient, comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer. In certain embodiments, the cytidine analog is oral azacitidine.

[00345] In certain embodiments, provided herein are methods for treating non-small cell lung cancer, the methods comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer, wherein the treatment results in a complete response, partial response or stable disease, as determined by Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1).

[00346] In certain embodiments, provided herein are methods for treating non-small cell lung cancer, the methods comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer, wherein the treatment results in a reduction in target lesion size, a reduction in non-target lesion size and/or the absence of new target and/or non-target lesions, compared to pre-treatment.

[00347] In certain embodiments, provided herein are methods for treating non-small cell lung cancer, the methods comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer, wherein the treatment results in prevention or retarding of clinical progression, such as cancer-related cachexia or increased pain.

[00348] In some embodiments, provided herein are methods for treating non-small cell lung cancer, the methods comprising administering an effective amount of a TOR kinase inhibitor in combination with an effective amount of erlotinib or a cytidine analog to a patient having advanced non-small cell lung cancer, 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.

[00349] In some embodiments, 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 $C_{21}H_{27}N_5O_3$). In one embodiment, Compound 1 is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1r,4r)-4-methoxycyclohexyl)-3,4-dihydropyrazino-[2,3-b]pyrazin-2(1H)-one.

[00350] A TOR kinase inhibitor administered in combination with erlotinib or a cytidine analog can be further combined with radiation therapy or surgery. In certain embodiments, a TOR kinase inhibitor is administered in combination with erlotinib or a cytidine analog to patient who is undergoing radiation therapy, has previously undergone radiation therapy or will be undergoing radiation therapy. In certain embodiments, a TOR kinase inhibitor is administered in combination with erlotinib or a cytidine analog to a patient who has undergone surgery, such as tumor removal surgery. In certain embodiments, the cytidine analog is oral azacitidine.

[00351] Further provided herein are methods for treating patients who have been previously treated for advanced non-small cell lung cancer, as well as those who have not previously been treated. Further provided herein are methods for treating patients who have undergone surgery in an attempt to treat advanced non-small cell lung cancer, as well as those who have not. Because patients with advanced non-small cell lung cancer 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 advanced non-small cell lung cancer.

[00352] In certain embodiments, a TOR kinase inhibitor is administered in combination with a cytidine analog or erlotinib to a patient in cycles. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance, avoid or reduce the side effects, and/or improves the efficacy of the treatment.

[00353] In one embodiment, a TOR kinase inhibitor is administered in combination with a cytidine analog or erlotinib daily in single or divided doses for about 3 days, about 5 days, about one week, about two weeks, about three weeks, about four weeks (e.g., 28 days), about five weeks, about six weeks, about seven weeks, about eight weeks, about ten weeks, about fifteen weeks, or about twenty weeks, followed by a rest period of about 1 day to about ten weeks. In one embodiment, the methods provided herein contemplate cycling treatments of about one week, about two weeks, about three weeks, about four weeks, about five weeks, about six weeks, about eight weeks, about ten weeks, about fifteen weeks, or about twenty weeks. In some embodiments, a TOR kinase inhibitor is administered in combination with a cytidine analog or erlotinib in single or divided doses for about 3 days, about 5 days, about one week, about two weeks, about three weeks, about four weeks (e.g., 28 days), about five weeks, or about six weeks with a rest period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 29, or 30 days. In some embodiments, the rest period is 1 day. In some embodiments, the rest period is 3 days. In some embodiments, the rest period is 7 days. In some embodiments, the rest period is 14 days. In some embodiments, the rest period is 28 days. The frequency, number and length of dosing cycles can be increased or decreased.

[00354] In one embodiment, the methods provided herein comprise: i) administering to the subject a first daily dose of a TOR kinase inhibitor in combination with a cytidine analog or erlotinib; ii) optionally resting for a period of at least one day where a cytidine analog or erlotinib is not administered to the subject; iii) administering a second dose of a TOR kinase inhibitor in combination with a cytidine analog or erlotinib to the subject; and iv) repeating steps ii) to iii) a plurality of times.

[00355] In one embodiment, the methods provided herein comprise administering to the subject a dose of a cytidine analog or erlotinib on day 1, followed by administering a TOR kinase inhibitor in combination with a cytidine analog or erlotinib to the subject on day 2 and subsequent days.

[00356] In certain embodiments, a TOR kinase inhibitor in combination with a cytidine analog or erlotinib is administered continuously for between about 1 and about

52 weeks. In certain embodiments, a TOR kinase inhibitor in combination with a cytidine analog or erlotinib is administered continuously for about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. In certain embodiments, a TOR kinase inhibitor in combination with a cytidine analog or erlotinib is administered continuously for about 7, about 14, about 21, about 28, about 35, about 42, about 84, or about 112 days.

[00357] In certain embodiments, when a TOR kinase inhibitor is administered in combination with a cytidine analog, the TOR kinase inhibitor is administered continuously for 28 days, while a cytidine analog is administered continuously for 21 days followed by 7 days without administration of a cytidine analog. In one embodiment, in a 28 day cycle, the cytidine analog is administered alone on Day 1, the cytidine analog and the TOR kinase inhibitor are administered in combination on Days 2-21 and the TOR kinase inhibitor is administered alone on Days 22-28. In some such embodiments, starting with Cycle 2 both the cytidine analog and the TOR kinase inhibitor are administered on Day 1, the cytidine analog is continued through Day 21, while the TOR kinase inhibitor is continued through Day 28. The 28 day cycles, as described above, can be continued for as long needed, such as for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months or longer.

[00358] In certain embodiments, when a TOR kinase inhibitor is administered in combination with a cytidine analog, in a 28 day cycle, the cytidine analog is administered alone on Days 1-7 and the TOR kinase inhibitor is administered alone on Days 8-28. Such 28 day cycles can be continued for as long needed, such as for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months or longer.

[00359] In certain embodiments, when a TOR kinase inhibitor is administered in combination with a cytidine analog, the TOR kinase inhibitor is administered at an amount of about 5 mg to about 50 mg (such as about 10 mg, about 15 mg, about 30 mg or about 45 mg) and a cytidine analog is administered at an amount of about 50 mg to about 350 mg (such as about 100 mg, about 200 mg or about 300 mg). In certain embodiments, about 10 mg of a TOR kinase inhibitor is administered in combination with about 100 mg, about 200 mg or about 300 mg of a cytidine analog. In certain embodiments, about 15 mg of a TOR kinase inhibitor is administered in combination with about 100 mg, about 200 mg or

about 300 mg of a cytidine analog. In certain embodiments, about 30 mg of a TOR kinase inhibitor is administered in combination with about 100 mg, about 200 mg or about 300 mg of a cytidine analog. In certain embodiments, about 45 mg of a TOR kinase inhibitor is administered in combination with about 100 mg, about 200 mg or about 300 mg of a cytidine analog.

[00360] In certain embodiments, when a TOR kinase inhibitor is administered in combination with a cytidine analog, the TOR kinase inhibitor:cytidine analog ratio is from about 1:1 to about 1:10. In certain embodiments, when a TOR kinase inhibitor is administered in combination with a cytidine analog, the TOR kinase inhibitor:cytidine analog ratio is less than about 1:1, less than about 1:3 or less than about 1:10. In certain embodiments, when a TOR kinase inhibitor is administered in combination with a cytidine analog, the TOR kinase inhibitor:cytidine analog ratio is about 1:1, about 1:3 or about 1:10.

[00361] In certain embodiments, when a TOR kinase inhibitor is administered in combination with erlotinib, the TOR kinase inhibitor is administered at an amount of about 5 mg to about 50 mg (such as about 10 mg, about 15 mg, about 30 mg or about 45 mg) and erlotinib is administered at an amount of about 50 mg to about 200 mg (such as about 75 mg, about 100 mg or about 150 mg). In certain embodiments, about 10 mg of a TOR kinase inhibitor is administered in combination with about 75 mg, about 100 mg or about 150 mg of erlotinib. In certain embodiments, about 15 mg of a TOR kinase inhibitor is administered in combination with about 75 mg, about 100 mg or about 150 mg of erlotinib. In certain embodiments, about 30 mg of a TOR kinase inhibitor is administered in combination with about 75 mg, about 100 mg or about 150 mg of erlotinib. In certain embodiments, about 45 mg of a TOR kinase inhibitor is administered in combination with about 75 mg, about 100 mg or about 150 mg of erlotinib.

[00362] In certain embodiments, when a TOR kinase inhibitor is administered in combination with erlotinib, the TOR kinase inhibitor:erlotinib ratio is from about 1:1 to about 1:30. In certain embodiments, when a TOR kinase inhibitor is administered in combination with erlotinib, the TOR kinase inhibitor:erlotinib ratio is less than about 1:1, less than about 1:10 or less than about 1:30. In certain embodiments, when a TOR kinase

inhibitor is administered in combination with erlotinib, the TOR kinase inhibitor:erlotinib ratio is about 1:1, about 1:10 or about 1:30.

[00363] In some embodiments, when a TOR kinase inhibitor is administered in combination with erlotinib, the TOR kinase inhibitor and erlotinib are taken on an empty stomach, for example, at least 1 hour before and 2 hours after eating.

5.5 PHARMACEUTICAL COMPOSITIONS AND ROUTES OF ADMINISTRATION

[00364] Provided herein are compositions comprising an effective amount of a TOR kinase inhibitor and an effective amount of erlotinib or a cytidine analog and compositions, comprising an effective amount of a TOR kinase inhibitor and erlotinib or a cytidine analog and a pharmaceutically acceptable carrier or vehicle. In certain embodiments, the cytidine analog is oral azacitidine.

[00365] In some embodiments, the pharmaceutical compositions described herein are suitable for oral, parenteral, mucosal, transdermal or topical administration.

[00366] The compositions 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.

[00367] The dose of a TOR kinase inhibitor and the dose of erlotinib or a cytidine analog 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, erlotinib and a cytidine analog 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, 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 or about 0.25 mg/kg of a patient's body weight to about 0.5 mg/kg of a patient's body weight. In one embodiment, one dose is 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.

[00368] In another embodiment, provided herein are methods for the treatment or prevention of advanced non-small cell lung cancer 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 or about 18 mg/day to about 37 mg/day of a TOR kinase inhibitor in combination with erlotinib or a cytidine analog to a patient in need thereof.

[00369] In another embodiment, provided herein are methods for the treatment or prevention of advanced non-small cell lung cancer comprising the administration of about 1 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 in combination with erlotinib or a cytidine analog to a

patient in need thereof. In a particular embodiment, the methods disclosed herein comprise the administration of 10 mg/day, 15 mg/day, 30 mg/day, 45 mg/day, 100 mg/day, 200 mg/day, 300 mg/day, 400 mg/day, 600 mg/day or 800 mg/day of a TOR kinase inhibitor in combination with erlotinib or a cytidine analog to a patient in need thereof. In one embodiment, the methods disclosed herein comprise the administration of 10 mg/day, 15 mg/day, 30 mg/day, or 45 mg/day, of a TOR kinase inhibitor in combination with erlotinib or a cytidine analog to a patient in need thereof.

[00370] In certain embodiments, the methods provided herein comprise the administration of between about 100 mg and about 400 mg, about 150 mg and about 350 mg or about 175 mg and about 325 mg of a cytidine analog alone or in combination with a TOR kinase inhibitor. In another embodiment, the methods provided herein comprise the administration of about 100 mg, about 200 mg or about 300 mg of a cytidine analog alone or in combination with a TOR kinase inhibitor. In a particular embodiment, the cytidine analog is oral azacitidine.

[00371] In another embodiment, the methods provided herein comprise the administration of between about 1 mg and about 200 mg, about 10 mg and about 175 mg or about 25 mg and about 150 mg of erlotinib alone or in combination with a TOR kinase inhibitor. In another embodiment, the methods provided herein comprise the administration of about 25 mg, about 75 mg, about 100 mg or about 150 mg of erlotinib alone or in combination with a TOR kinase inhibitor.

[00372] In another embodiment, provided herein are unit dosage formulations that comprise between about 1 mg and about 2000 mg, about 1 mg and about 200 mg, about 35 mg and about 1400 mg, about 125 mg and about 1000 mg, about 250 mg and about 1000 mg, about 500 mg and about 1000 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg or about 2.5 mg to about 20 mg of a TOR kinase inhibitor alone or in combination with erlotinib or a cytidine analog. In another embodiment, provided herein are unit dosage formulations that comprise 1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 45 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 alone or in combination with erlotinib or a cytidine analog. In another

embodiment, provided herein are unit dosage formulations that comprise between about 2.5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg or about 45 mg of a TOR kinase inhibitor alone or in combination with erlotinib or a cytidine analog.

[00373] In another embodiment, provided herein are unit dosage formulations that comprise between about 25 mg and about 200 mg, about 50 mg and about 150 mg or about 75 mg and about 150 mg of a cytidine analog alone or in combination with a TOR kinase inhibitor. In another embodiment, provided herein are unit dosage formulations that comprise about 100 mg of a cytidine analog alone or in combination with a TOR kinase inhibitor.

[00374] In another embodiment, provided herein are unit dosage formulations that comprise between about 1 mg and about 200 mg, about 10 mg and about 175 mg or about 25 mg and about 150 mg of erlotinib alone or in combination with a TOR kinase inhibitor. In another embodiment, provided herein are unit dosage formulations that comprise about 25 mg, about 100 mg or about 150 mg of erlotinib alone or in combination with a TOR kinase inhibitor.

[00375] In a particular embodiment, provided herein are unit dosage formulations comprising about 10 mg, about 15 mg, about 30 mg, about 45 mg, about 50 mg, about 75 mg, about 100 mg or about 400 mg of a TOR kinase inhibitor in combination with erlotinib or a cytidine analog.

[00376] In certain embodiments, provided herein are unit dosage formulations wherein the TOR kinase inhibitor:cytidine analog ratio is from about 1:1 to about 1:10. In certain embodiments, provided herein are unit dosage formulations wherein the TOR kinase inhibitor:cytidine analog ratio is less than about 1:1, less than about 1:3 or less than about 1:10. In certain embodiments, provided herein are unit dosage formulations wherein the TOR kinase inhibitor:cytidine analog ratio is about 1:1, about 1:3 or about 1:10.

[00377] In certain embodiments, provided herein are unit dosage formulations wherein the TOR kinase inhibitor:erlotinib ratio is from about 1:1 to about 1:30. In certain embodiments, provided herein are unit dosage formulations wherein the TOR kinase inhibitor:erlotinib ratio is less than about 1:1, less than about 1:10 or less than about 1:30.

In certain embodiments, provided herein are unit dosage formulations wherein the TOR kinase inhibitor:erlotinib ratio is about 1:1, about 1:10 or about 1:30.

[00378] A TOR kinase inhibitor can be administered in combination with erlotinib or a cytidine analog once, twice, three, four or more times daily.

[00379] In certain embodiments, the methods provided herein comprise administration of about 5 mg to about 100 mg, about 5 mg to about 50 mg, about 10 mg to about 50 mg or about 15 mg to about 45 mg of a TOR kinase inhibitor in combination with about 50 mg to about 200 mg, about 75 mg to about 175 mg or about 100 mg to about 150 mg of erlotinib. In certain embodiments, the methods provided herein comprise administration of about 10 mg, about 15 mg, about 30 mg or about 45 mg of a TOR kinase inhibitor in combination with about 75 mg, about 100 mg or about 150 mg of erlotinib.

[00380] In certain embodiments, the methods provided herein comprise administration of about 5 mg to about 100 mg, about 5 mg to about 50 mg, about 10 mg to about 50 mg or about 15 mg to about 45 mg of a TOR kinase inhibitor in combination with about 50 to about 350 mg, about 75 mg, to about 350 mg, about 100 mg to about 350 mg, about 150 mg to about 350 mg, about 175 mg to about 325 mg or about 200 mg to about 300 mg of a cytidine analog. In certain embodiments, the methods provided herein comprise administration of about 10 mg, about 15 mg, about 30 mg or about 45 mg of a TOR kinase inhibitor in combination with about 100 mg, about 200 mg or about 300 mg of a cytidine analog, such as oral azacitidine.

[00381] In certain embodiments, the methods provided herein comprise administration of about 10 mg, about 15 mg, about 30 mg or about 45 mg of a TOR kinase inhibitor in combination with about 75 mg, about 100 mg or about 150 mg of erlotinib.

[00382] In certain embodiments, the methods provided herein comprise administration of about 10 mg, about 15 mg, about 30 mg or about 45 mg of a TOR kinase inhibitor in combination with about 100 mg, about 200 mg or about 300 mg of a cytidine analog.

[00383] A TOR kinase inhibitor can be administered in combination with erlotinib or a cytidine analog orally for reasons of convenience. In one embodiment, when administered orally, a TOR kinase inhibitor in combination with erlotinib or a cytidine analog is

administered with a meal and water. In another embodiment, the TOR kinase inhibitor in combination with erlotinib or a cytidine analog is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a suspension. In another embodiment, when administered orally, a TOR kinase inhibitor in combination with erlotinib or a cytidine analog is administered in a fasted state.

[00384] The TOR kinase inhibitor can also be administered in combination with a cytidine analog intravenously, such as intravenous infusion, or subcutaneously, such as subcutaneous injection. 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.

[00385] In one embodiment, provided herein are capsules containing a TOR kinase inhibitor in combination with erlotinib or a cytidine analog without an additional carrier, excipient or vehicle.

[00386] In another embodiment, provided herein are compositions comprising an effective amount of a TOR kinase inhibitor, an effective amount of erlotinib or a cytidine analog, 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, the composition is a pharmaceutical composition.

[00387] 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, 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.

[00388] 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, the pharmaceutical composition is lactose-free. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders. Illustrative tablet formulations comprising Compound 1 are set forth in Tables 2 and 3.

[00389] A lubricant might be necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant can be chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils. Tablet disintegrators are substances that swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethyl cellulose, for example, can be used as well as sodium lauryl sulfate. Tablets can be coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compositions can also be formulated as chewable tablets, for example, by using substances such as mannitol in the formulation.

[00390] When it is desired to administer a TOR kinase inhibitor in combination with erlotinib or a cytidine analog as a suppository, typical bases can be used. Cocoa butter is a traditional suppository base, which can be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

[00391] The effect of the TOR kinase inhibitor in combination with erlotinib or a cytidine analog can be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the TOR kinase inhibitor in combination with erlotinib or a cytidine analog

can be prepared and incorporated in a tablet or capsule, or as a slow-release implantable device. The technique also includes making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules can be coated with a film that resists dissolution for a predictable period of time. Even the parenteral preparations can be made long-acting, by dissolving or suspending the TOR kinase inhibitor in combination with erlotinib or a cytidine analog in oily or emulsified vehicles that allow it to disperse slowly in the serum.

[00392] In certain embodiments, the TOR kinase inhibitor is administered in a formulation set forth in U.S. Provisional Application No. 61/566,109, filed December 2, 2011, which is incorporated herein in its entirety (see particularly page 22, paragraph [0067] to page 38, paragraph [00162] and page 55, paragraph [00216] to page 68, paragraph [00226]).

6. EXAMPLES

6.1 BIOCHEMICAL ASSAYS

[00393] **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:

[00394] "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.

[00395] 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.

[00396] Detection reagent solution: 50 mM HEPES, pH 7.4, 0.01% Triton X-100, 0.01% BSA, 0.1 mM EDTA, 12.7 μg/mL Cy5-αGST Amersham (Cat#PA92002V), 9 ng/mL α–phospho p70S6 (Thr389) (Cell Signaling Mouse Monoclonal #9206L), 627 ng/mL α–mouse Lance Eu (Perkin Elmer Cat#AD0077).

[00397] To 20 μL of the Simple mTor buffer is added 0.5 μL of test compound in DMSO. To initiate the reaction 5 μL of ATP/Substrate solution was added to 20 μL of the Simple TOR buffer solution (control) and to the compound solution prepared above. The assay was stopped after 60 min by adding 5 μL of a 60 mM EDTA solution; 10 μL of detection reagent solution was then added and the mixture was allowed to sit for at least 2 hours before reading on a Perkin-Elmer Envision Microplate Reader set to detect LANCE Eu TR-FRET (excitation at 320 nm and emission at 495/520 nm).

[00398] TOR kinase inhibitors were tested in the mTor HTR-FRET assay and were found to have activity therein, with certain compounds having an IC_{50} below 10 μM in the assay, with some compounds having an IC_{50} between and 0.005 nM and 250 nM, others having an IC_{50} between and 250 nM and 500 nM, others having an IC_{50} between 500 nM and 1 μM, and others having an IC_{50} between 1 μM and 10 μM.

6.2 CELL BASED ASSAYS

[00399] **Cell viability assay for cell lines.** Compound 1 and second agent (azacitidine or erlotinib) were added to a 384-well flat, clear bottom, black polystyrene, TC-Treated plate (Cat#3712, Corning, MA) via an acoustic dispenser (EDC Biosystems). Both Compound 1 and the second agent were serially diluted 3-fold across the plate for ten concentrations in triplicate at 3 different compound ratios. Both compounds were also added alone to determine their affects as single agents. DMSO (no compound) was used as control for 100% viability and background (no cells). Final assay DMSO concentration was 0.2% (v/v). Three different combinatory sequence of additions were tested. In the first instance, both Compound 1 and the second agent were added simultaneously (Sim) into an empty plate. Cells were then added directly on top of the compounds at an optimized density to ensure that the cell growth was within the linear detection range of the assay after three days in culture. In the second instance, Compound 1 was added into an empty plate followed immediately with the addition of cells. After 24 hours in culture, the second agent was then added to the previous plate and allowed to incubate for an additional 48 hours (SeqM1). Thus the treatment time for Compound 1 and the second agent were 72 and 48

hours, respectively. In the third instance, the second agent was added into an empty plate followed immediately with the addition of cells. After 24 hours in culture, Compound 1 was then added to the previous plate and allowed to incubate for an additional 48 hours (SeqM2). Thus the treatment time for Compound 1 and the second agent were 48 and 72 hours, respectively. After 72 hours of total incubation, cell viability was determined using Promega's CellTiter-Glo Luminescent Cell Viability Assay (Cat#G7573, Promega, WI) using the manufacturer's standard operating procedures. Background subtracted luminescence counts were converted to percentages of cell viability with respect to DMSO treated control cells.

[00400] Dose response curves were generated using XLFit4 (IDBS, UK) by fitting the percentage of control data at each concentration using a 4 Parameter Logistic Model/Sigmoidal Dose-Response Model [y = (A+((B-A)/(1+((C/x)^D))))]. To evaluate the combinatory effect of the two agents on a cell line, data was analyzed by comparing its combinatory response against the theoretical additive response of the two agents alone. The expected additive effect of two agents (A and B) can be calculated using the fractional product method (Webb 1961, Enzyme and Metabolic Inhibitors, New York: Academic Press): (*fu*)A,B = (*fu*)A x (*fu*)B where *fu*=fraction unaffected by treatment. Synergism of a combination is determined when the observed fraction unaffected in combination is less than (*fu*)A,B, while an additive effect is determined when the observed fraction unaffected in combination = (*fu*)A,B.

[00401] Alternatively, the calculation of combination index (CI) based off of Chou-Talalay mathematical modeling was used to evaluate the combinatory effect of the two agents. IC_{50} values, which are the effective dose at which a 50% inhibition is achieved, were calculated for each single agent as well as the combined agents and used to calculated their respective CI values. The CI value indicates synergism as shown in Table 1 below (Chou and Talalay, 1983, Trends Pharmacol. Sci. (4) 450-454).

[00402] **Table 1**

Index (CI)	**Description**
<0.1	Very strong synergism

Index (CI)	Description
0.1-0.3	Strong synergism
0.3-0.7	Synergism
0.7-0.85	Moderate synergism
0.85-0.90	Slight synergism
0.90-1.10	Nearly additive
1.10-1.20	Slight antagonism
1.20-1.45	Moderate antagonism
1.45-3.3	Antagonism
3.3-10	Strong antagonism
>10	Very strong antagonism

[00403] Results (CI values) are set forth in Table 2-4 and Figures 1-4. Synergy is observed for many of the combinations of Compound 1 + azacitidine and Compound 1 + erlotinib.

[00404] **Table 2: Simultaneous compound addition**

NSCLC Cell Line	Comp. 1 : azacitidine ratio			Comp. 1 : erlotinib ratio		
	1:1	1:3	1:10	1:1	1:10	1:30
A549	0.95	0.87	0.80	0.82	0.63	0.56
H1755	0.90	0.73	0.72	1.13	0.79	0.60
H460	1.17	0.85	0.82	1.47	0.89	0.60
H838	1.09	0.90	0.93	0.73	0.92	0.59
H1792	0.78	0.70	0.71	1.75	1.00	0.69
H1975	1.25	1.09	0.95	1.16	0.94	0.62
H226	0.96	0.84	0.91	1.20	0.74	0.49
Hop92	1.05	0.61	0.63	1.87	1.18	0.82

NSCLC Cell Line	Comp. 1 : azacitidine ratio			Comp. 1 : erlotinib ratio		
	1:1	1:3	1:10	1:1	1:10	1:30
Median CI	1.01	0.85	0.81	1.18	0.91	0.60

[00405] **Table 3: Compound 1 first followed by second agent (SeqM1)**

NSCLC Cell Line	Comp. 1 : azacitidine ratio			Comp. 1 : erlotinib ratio		
	1:1	1:3	1:10	1:1	1:10	1:30
A549	1.05	0.92	0.78	0.90	0.72	0.65
H1755	0.82	0.67	0.61	0.81	0.64	0.47
H460	0.80	0.80	0.90	1.08	0.81	0.60
H838	1.09	0.99	0.88	1.01	0.90	0.65
H1792	0.63	0.56	0.60	1.04	0.90	0.60
H1975	1.00	0.98	0.99	1.05	0.75	0.54
H226	1.06	1.02	0.98	0.82	0.91	0.74
Hop92	0.86	0.73	0.80	1.23	0.71	0.49
Median CI	0.93	0.86	0.84	1.03	0.78	0.60

[00406] **Table 4: Second agent first followed by Compound 1 (SeqM2)**

NSCLC Cell Line	Comp. 1 : azacitidine ratio			Comp. 1 : erlotinib ratio		
	1:1	1:3	1:10	1:1	1:10	1:30
A549	0.85	0.70	0.69	1.01	0.73	0.60
H1755	0.60	0.60	0.65	0.89	0.78	0.74
H460	0.73	0.74	0.79	2.14	0.81	0.59
H838	0.66	0.68	0.85	1.04	0.83	0.75
H1792	0.73	0.68	0.66	0.79	0.64	0.43
H1975	0.63	0.65	0.66	1.32	0.69	0.60
H226	0.41	0.46	0.54	0.46	0.74	0.64

NSCLC Cell Line	Comp. 1 : azacitidine ratio			Comp. 1 : erlotinib ratio		
	1:1	1:3	1:10	1:1	1:10	1:30
Hop92	0.51	0.47	0.52	2.73	0.82	0.57
Median CI	0.64	0.66	0.66	1.02	0.76	0.60

[00407] As can be seen in the tables and figures, both 5-azacitidine and erlotinib showed synergy with Compound 1 in multiple NSCLC lines in vitro. The sequence of addition affected the combinatorial effect for Compound 1 and the 5-azacitidine combination. The best combinatorial effect was observed when 5- azacitidine was added prior to treatment with Compound 1. For the Compound 1 and erlotinib combination, the ratio of two agents instead of sequence of addition affected the CI values. The best molar ratio was 1:30 for Compound1: erlotinib.

6.3 IN VIVO ASSAYS

[00408] **DM179 - Non Small Cell Lung Cancer Primary TumorGraft.** DM179 is a primary tumorgraft model derived from tumor tissues obtained from a NSCLC patient. Compound 1 and the second agents are tested as single agents and Compound 1 is tested in combination with the second agent (erlotinib or azacitidine) in the model. Nude mice are inoculated subcutaneously with DM179 low passage tumor fragments in the flank region. Following inoculation of the animals, the tumors are allowed to grow to about 200 mm^3 prior to randomization. Animals bearing DM179 tumors of about 200 mm^3 are pooled together and randomized into various treatment groups. Compound 1 is formulated in 0.5% CMC and 0.25% Tween 80 in water (as a suspension). The animals are orally administered vehicle (CMC-Tween) or Compound 1 alone or in combination with the second agent, for example, once daily (QD) for up to 21 days. Treatment with Compound 1 and the second agents is either simultaneous or staggered. Doses of Compound 1 can range between 1 and 10 mg/kg and doses for the second agent or the combination are determined based on single agent experiment results or literature reports. The positive control paclitaxel (20 mg/kg,

Q7Dx4) is administered via intravenous (IV) route. Tumors are measured twice a week using calipers and tumor volumes are calculated using the formula of $W^2 \times L/2$ (W = width, L = length).

[00409] BML-5—Non Small Cell Lung Cancer Primary TumorGraft. BML-5 is a primary tumorgraft model derived from tumor tissues obtained from NSCLC patient. Compound 1 and the second agents are tested as single agents and Compound 1 is tested in combination with the second agent (erlotinib or azacitidine) in the model. Nude mice are inoculated subcutaneously with BML-5 low passage tumor fragments in the flank region. Following inoculation of the animals, the tumors are allowed to grow to about 200 mm^3 prior to randomization. Animals bearing BML-5 tumors of about 200 mm^3 are pooled together and randomized into various treatment groups. Compound 1 is formulated in 0.5% CMC and 0.25% Tween 80 in water (as a suspension). The animals are orally administered vehicle (CMC-Tween), Compound 1 alone or in combination with the second agent, for example, once daily (QD) for up to 21 days. Treatment with Compound 1 and the second agents is either simultaneous or staggered. Doses of Compound 1 can range between 1 and 10 mg/kg and doses for the second agent or the combination are determined based on single agent experiment results or literature reports. The positive control Docetaxel (20 mg/kg, Q7Dx3) is administered via intravenous (IV) route. Tumors are measured twice a week using calipers and tumor volumes are calculated using the formula of $W^2 \times L/2$.

[00410] ST140—Non Small Cell Lung Cancer Primary TumorGraft. ST140 is a primary tumorgraft model derived from tumor tissues obtained from NSCLC patient. Compound 1 and the second agents are tested as single agents and Compound 1 is tested in combination with the second agent (erlotinib or azacitidine) in the model. Nude mice are inoculated subcutaneously with ST-140 low passage tumor fragments in the flank region. Following inoculation of animals, the tumors are allowed to grow to about 200 mm^3 prior to randomization. Animals bearing ST140 tumors of about 200 mm^3 are pooled together and randomized into various treatment groups. Compound 1 is formulated in 0.5% CMC and 0.25% Tween 80 in water (as a suspension). The animals are orally administered vehicle (CMC-Tween), Compound 1 alone or in combination with the second agent, for example, once daily (QD) for up to 21 days. Treatment with Compound 1 and the second agents is

either simultaneous or staggered. Doses of Compound 1 can range between 1 and 10 mg/kg and doses for the second agent or the combination are determined based on single agent experiment results or literature reports. The positive control Docetaxel (20 mg/kg, Q7Dx3) is administered via intravenous (IV) route. Tumors are measured twice a week using calipers and tumor volumes are calculated using the formula of $W^2 \times L / 2$

[00411] Selected TOR kinase inhibitors show, or are expected to show, synergy in the models when used in combination with erlotinib or azacitidine.

6.4 ALTERNATIVE COMBINATION STUDIES WITH COMPOUND 1

[00412] **Proliferation Assays.** NSCLC cell lines and their sensitivies expressed as IC_{50} values for erlotinib and the TOR kinase inhibitor Compound 1 are shown in Table 5.

[00413] Table 5

Cell Line	Histology	KRAS	EGFR	Erlotinib IC50	Compound 1 IC50
A549	ACA	MUT G12S	WT	R >10 μM (25.2)	IC50 9.58 μM
Calu-3	ACA	WT	wt (HER2+)	I, 7.09 μM	IC50 0.184 μM
H1299	Large Cell Neuroendocrine	WT	WT	I, IC50>10 μM	IC50 3.09 μM
H157	SQC	MUT - [c.35G>C]	WT	R, IC50>10 mM	IC50 2.61 μM
H1650	ACA	WT	E746_A750del (exon 19)	I, IC50 2.84 μM	IC50 5.20 μM
H1703	SQC	WT	WT	R >10 μM	IC50 1.64 μM
H1975	ACA	WT	L858R,T790M	I (8.>10 μM	IC50 0.25 μM
H2009	ACA	MUT	WT	R, IC50>10 μM (15.8)	IC50 5.05 μM
H2122	ACA	MUT	WT	R, IC50>10 μM	IC50 1.59 μM
H2126	ACA	WT	WT	R, IC>10 μM (15.8)	IC50 0.214 μM
H226	SQC	WT	WT	R, IC50>10 μM	IC50 1.98 μM
H322c	ACA	WT	WT	R	
H3255	ACA	WT	L858R	S, 0.206 μM	IC50 11.87 μM
H441	ACA,BAC	MUT	WT	R, IC50>10 μM	IC50 0.323 μM
H460	LCC	MUT Q61H	WT	R, IC50>10 μM (15.0)	IC50 0.153 μM
H520	SQC	WT	WT	R, IC50>10 μM	IC50 0.347 μM
H720	carcinoid				
H727	carcinoid	MUT	WT		
H820	ACA	WT	(L747_A750 del, T790M (exon 1	I	
HCC15	SQC	WT	WT	R, IC50>10 μM	IC50 6.37 μM
HCC193	ACA	WT	WT		
HCC4006	ACA	WT	L747_E749del, A750P	S	
HCC95	SQC	WT	WT	I (8.45 μM)	IC50 0.734 μM
NCI-H23	ACA	MUT 13 mutation G12C		R, IC50>10 μM (22.8)	IC50 3.30 μM

[00414] Compound 1 and erlotinib demonstrated anti-proliferative activity in a panel of NSCLC cell lines with various degrees of sensitivity as reflected in different IC_{50} values.

[00415] **Combination Indices.** This study was performed using erlotinib resistant cell lines A549, H1975, H1650, and HCC95. These cell lines display different degrees of erlotinib resistance and possess different genetic backgrounds with regard to mutation status in EGFR and KRAS. In combination with erlotinib, Compound 1 showed synergistic anti-proliferative effects in NSCLC cell lines resistant to erlotinib. The results are shown in Figures 5A-5D. The synergy was more pronounced at lower concentrations displaying combination indices down to 0.1-0.2, indicating strong synergy (for CI value interpretation, see Table 1). These results indicate that Compound 1 is capable of overcoming drug resistance to erlotinib in NSCLC cells showing synergistic effects with combination treatment.

[00416] Table 6 shows the levels of synergy for the combination of erlotinib and Compound 1, in a NSCLC wild-type cell line (A549), a cell line (H3255) with an EGFR activating mutant (L858R), and in a cell line (H1975) with a mutation of EGFR (T790M), which is erlotinib resistant. As can be seen, synergy, as defined by Table 1, was observed in all cell types, including the erlotinib resistant cell line H1975 (ND = not determined).

[00417] **Table 6**

Erlotinib concentration (μM)	Compound 1 concentration (μM)	CI in A549 (WT)	CI in H3255 (EGFR act. mutant)	CI in H1975 (EGFRi resistant)
0.1	0.01		41.958	
0.1	0.1		14.01	
0.1	0.3		0.195	
0.1	0.6		0.224	
0.1	1	ND	0.34	ND
0.1	3		0.89	
0.1	6		1.308	
0.1	10		2.921	
0.1	15		3.621	
0.5	0.01	0.656	1.23	1.497
0.5	0.1	0.402	0.06	0.518
0.5	0.3	0.419	0.125	0.262

Erlotinib concentration (μM)	Compound 1 concentration (μM)	CI in A549 (WT)	CI in H3255 (EGFR act. mutant)	CI in H1975 (EGFRi resistant)
0.5	0.6	0.347	0.136	0.223
0.5	1	0.342	0.265	0.22
0.5	3	0.592	0.635	0.628
0.5	6	1.132	1.926	1.722
0.5	10	1.782	2.258	1.9
0.5	15	2.253	3.242	1.86
1	0.01	0.439	0.239	0.614
1	0.1	0.243	0.175	1.385
1	0.3	0.255	0.201	0.298
1	0.6	0.179	0.163	0.307
1	1	0.245	0.266	0.373
1	3	0.274	0.721	1.06
1	6	0.531	1.694	1.587
1	10	0.963	3.261	1.297
1	15	1.251	3.996	1.32
5	0.01	0.664		0.97
5	0.1	0.355		0.712
5	0.3	0.364		0.452
5	0.6	0.302		0.358
5	1	0.242	ND	0.585
5	3	0.289		1.165
5	6	0.598		3.139
5	10	0.992		1.456
5	15	1.344		1.512

[00418] **Cell Cycle Analysis.** In cell cycle analysis, the use of propidium iodide staining showed increased cell cycle arrest for the combination treatment using Compound 1 and erlotinib with a decrease of the S-phase and an increase of the G0/G1 phase. The results of these studies are shown in Figure 6. These results indicate that Compound 1 in combination with erlotinib caused cell cycle arrest in NSCLC cells.

[00419] **Biomarker Analysis Using Western Blotting.** Data for pathway inhibition analyses are shown in Figures 7A and 7B in several cell types. The data indicate that the

combination of Compound 1 and erlotinib demonstrated inhibition of a signaling component in the mTOR pathway, namely p4EBP1.

[00420] In Vivo Studies of Compound 1 alone or in Combination with Erlotinib in A549 and H1975 Xenografts in Nude Mice. A549 adenocarcinoma or H1975 cells in single cell suspension were implanted into the posterior flanks of athymic nude mice. The control group was treated with vehicle, the other groups were treated with erlotinib at 40 mg/kg 3x per week oral gavage, Compound 1 at 5 mg/kg/daily oral gavage, or a combination of erlotinib at 40 mg/kg and Compound 1 at 5 mg/kg. For the A549 xenograft, the treatments were started on Day 26 after implantation and were stopped on day 53, while for the H1975 xenograft, the treatments were started on day 17 after implantation and were stopped on day 30.

[00421] As can be seen in Fig. 8, when compared to the untreated control group, the A549 xenograft was resistant to the treatment with erlotinib at 40 mg/kg 3x per week. When Compound 1 was combined with erlotinib at 40 mg/kg 3x per week, tumor growth was effectively suppressed. The tumor growth increased when the treatment with combination of Compound 1 and erlotinib was stopped, but at a considerably slower rate compared to the single treatment groups.

[00422] As can be seen in Fig. 9, when compared to the control group, the H1975 xenograft was moderately sensitive to the treatment with erlotinib at 40 mg/kg 3x per week. When Compound 1 was combined with erlotinib at 40 mg/kg 3x per week, tumor growth was inhibited.

[00423] Conclusions. Compound 1 demonstrated anti-proliferative activity in a panel of NSCLC cell lines. In NSCLC cells resistant to the EGFR tyrosine kinase inhibitor erlotinib, Compound 1 combined with erlotinib demonstrated synergistic anti-proliferative effects. Synergistic effects of Compound 1 and erlotinib were also demonstrated in suppression of tumor growth in A549 xenografts. Synergistic effects of Compound 1 and erlotinib were also demonstrated in the growth imhibition of H1975 xenografts. The mechanism for the synergistic effects were found to involve changes in cell cycle arrest. Analyses of signaling pathway inhibition using the drug combinations showed inhibition of signaling components in the mTOR pathway.

6.5 CLINICAL STUDY

[00424] **A Phase 1b, Multi-Center, Open-Label Study Of The mTOR Kinase Inhibitor Compound 1 In Combination With Erlotinib Or Oral Azacitidine In Advanced Non-Small Cell Lung Cancer.** This will be a Phase 1b, multi-center, open-label study of the TOR Kinase Inhibitor Compound 1 in combination with erlotinib or oral azacitidine in advanced non-small cell lung cancer.

[00425] The primary objectives of the study are to determine the safety and tolerability of Compound 1 when administered orally in combination with either erlotinib or oral azacitidine and to define the non-tolerated dose (NTD) and the maximum tolerated dose (MTD) of each combination using NCI CTCAE v4; and to characterize the pharmacokinetics (PK) of Compound 1 and azacitidine following oral administration as single agents and after combination treatment. The secondary objectives of the study are to evaluate the effect of study drugs on mTORC1 and mTORC2 pathway biomarkers in blood and tumor; provide information on the preliminary efficacy of each drug combination; and characterize the PK of Compound 1 M1 metabolite after oral administration of Compound 1 as a single agent and in combination with erlotinib or oral azacitidine.

[00426] This is a clinical study of Compound 1 administered orally in combination with either oral erlotinib or oral azacitidine in subjects with Stage IIIB/IV NSCLC who have failed at least one line of standard therapy. It is a Phase 1b dose escalation and expansion study evaluating escalating dose levels of Compound 1 in combination with two dose levels of erlotinib (Arm A) or two dose levels of oral azacitidine administered either concurrently with Compound 1 (Arm B), or sequentially with Compound 1 (Arm C), followed by expansion of each combination cohort at one or more selected doses.

[00427] In Arm A, cohorts will receive escalating continuous daily doses (15 mg, 30 mg, and 45 mg) of Compound 1 in capsules concurrently with at least two different daily dose levels of erlotinib tablets (100 mg and 150 mg) in 28 day cycles after an initial single dose of Compound 1 seven days before, and a single dose of erlotinib on the first day of, the first cycle.

[00428] In Arm B, cohorts will receive escalating continuous daily dose levels of Compound 1 (15 mg, 30 mg, and 45 mg) concurrently with one or more dose levels of oral azacitidine (200 mg or 300 mg, as two or three 100 mg tablets) administered on Day 1 to 21 of each 28-day cycle after an initial single dose of Compound 1 seven days before, and a single dose of oral azacitidine on the first day of, the first cycle.

[00429] In Arm C, cohorts will receive escalating daily dose levels of Compound 1 (15 mg, 30 mg, and 45 mg) administered on Day 8 to 28 after one or more dose levels of oral azacitidine (200 mg or 300 mg, as two or three 100 mg tablets) administered on Day 1 to 7 of each 28-day cycle after an initial single dose of Compound 1 seven days before the first cycle.

[00430] A standard "3 + 3" dose escalation design will be used to identify initial toxicity of each combination. Subjects will be assigned to study treatment arms based on Investigator choice and open slots. Cohorts of 3 subjects will take study drugs in defined dose increments and, in the event of dose-limiting toxicity (DLT) in 1 of 3 evaluable subjects, cohorts will be expanded to 6 subjects.

[00431] An evaluable subject for DLT is defined as one that received at least 20 of the 27 planned doses of Compound 1, and 21 of the 28 planned doses of erlotinib, during Cycle 1 in Arm A; received at least 20 of the 27 planned doses of Compound 1, and 14 of 21 planned doses of oral azacitidine, during Cycle 1 in Arm B; received at least 14 of 21 planned doses of Compound 1, and 6 of 7 planned doses of oral azacitidine, during Cycle 1 in Arm C; experienced study drug-related DLT after receiving at least one dose.

[00432] Non-evaluable subjects not due to DLT will be replaced. Additional subjects within any dose cohort may be enrolled at the discretion of the Safety Review Committee (SRC).

[00433] A dose will be considered the NTD when 2 of 6 evaluable subjects in a cohort experience drug-related DLT in Cycle 1. The MTD is defined as the last dose level below the NTD with 0 or 1 out of 6 evaluable subjects experiencing DLT during Cycle 1. If 2 of 6 DLT are observed at the first dose level with either combination, a lower dose combination may be explored at the discretion of the SRC. An intermediate dose of

Compound 1 (one between the NTD and the last dose level before the NTD) may be evaluated to accurately determine the MTD of the combination.

[00434] Following completion of dose escalation, each combination treatment arm will be expanded with approximately 10 additional evaluable subjects. Expansion may occur at the MTD established in the dose escalation phase, or at an alternative tolerable combination dose level, based on the review of safety, PK and PD data.

[00435] Tumor biopsy for analysis of genetic mutations and biomarkers of treatment activity is optional in the dose escalation phase but mandatory during the dose expansion phase. Paired tumor biopsies to evaluate tumor biomarkers of Compound 1, erlotinib and/or oral azacitidine activity will be required in the expansion cohorts.

[00436] The study population will consist of men and women, 18 years or older, with Stage IIIB/IV NSCLC, with disease progression following at least one standard first-line treatment regimen. First-line treatment may include either chemotherapy or an EGFR inhibitor.

[00437] Enrollment is expected to take approximately 15 months (9 months for dose escalation, 6 months for expansion). Completion of active treatment and post treatment follow-up is expected to take 6 - 12 additional months.

[00438] Dose levels to be explored in this Phase 1b study are shown below.

	Arm A		**Arm B and C**	
Dose Level	**Cmpd 1 (mg daily)**	**Erlotinib (mg daily)**	**Cmdp 1 (mg) Arm B: D-7, D2-28 Arm C: D-7, D8-28**	**Oral Azacitidine (mg) Arm B: D1-21 Arm C: D1-D7**
1	15	100	15	200
2a	15	150	15	300
2b	30	100	30	200
3a	30	150	30	300
3b	45	100	45	200
4	45	150	45	300

[00439] If unacceptable toxicity occurs at dose level 1, only one dose reduction for each drug is allowed: Compound 1 10 mg, erlotinib 75 mg, and oral azacitidine 100 mg.

[00440] Dose levels 2a and 2b and dose levels 3a and 3b have comparable dose intensity and may be enrolled concurrently.

[00441] Treatment is administered in 28-day cycles. Compound 1 and erlotinib will be dosed daily in Arm A; oral azacitidine will be dosed concurrent with daily Compound 1 for the first 21 of 28 days in Arm B; oral azacitidine will be dosed only for 7 days before dosing with Compound 1 alone for 21 of 28 days in Arm C. For both the dose escalation and expansion phases, slight modifications to the dosing schedule will occur prior to and during Cycle 1 in order to facilitate PK and PD evaluation of each drug alone and in combination. Administration of study drugs is described below:

- In Arm A ,B and C:
  - One week (Day -7) prior to Cycle 1, a single dose of Compound 1 will be administered followed by PK and PD sampling.
- In Arm A:
  - During Cycle 1, a single oral dose of erlotinib will be administered on Day 1. Combined administration with Compound 1 will start on Day 2 and continue through Day 28.
  - Starting with Cycle 2 and thereafter, both drugs will start on Day 1 and continue through Day 28.
- In Arm B:
  - During Cycle 1, a single dose of oral azacitidine will be administered on Day 1. Combined administration with Compound 1 will start on Day 2. Oral azacitidine will continue through Day 21 and Compound 1 through Day 28.
  - Starting with Cycle 2 and thereafter, both drugs will start on Day 1. Oral azacitidine will continue through Day 21 and Compound 1 through Day 28.
- In Arm C:
  - During all cycles, oral azacitidine will be administered on Day 1 through 7 and Compound 1 will be administered on Day 8 through 28.

[00442] After the first dose is administered on Day 1 in any cohort, subjects will be observed for at least 28 days before the next higher protocol-specified dose cohort can

begin. Intra-subject dose escalation of study drugs is not permitted during Cycle 1 but may be permitted in cycles beyond Cycle 1 if approved by the SRC. Dose reduction and temporary interruption of one or both drugs due to toxicity is allowed, but dose reduction during Cycle 1 will constitute DLT.

[00443] Study drugs are taken together at approximately the same time each morning. Due to a significant interaction of erlotinib with food, subjects in Arm A must take study drugs on an empty stomach at least 1 hour before and 2 hours after eating. There are no such food restrictions for subjects taking Compound 1 or oral azacitidine in Arms B and C.

[00444] Study treatment may be discontinued if there is evidence of disease progression, unacceptable toxicity or subject/physician decision to withdraw. Subjects may continue to receive study drugs beyond disease progression at the discretion of the Investigator.

[00445] The estimated total number of subjects to be enrolled during dose escalation is 54 to 108, depending on cohort size. Approximately 30 additional subjects (10 per regimen) will be evaluated for safety, PK, PD and preliminary antitumor effects during the expansion phase.

[00446] Subjects will be evaluated for efficacy after every 2 cycles through Cycle 6 and every 3 cycles thereafter. All treated subjects will be included in the efficacy analysis. The primary efficacy variable is tumor response rate and by progression-free survival at the end of 4 cycles of treatment. Tumor response will be determined by the Investigator, based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1; 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)).

[00447] Secondary and exploratory endpoints include evaluation of mTOR, EGFR, and oral azacitidine biomarkers in blood and/or tumor and exploration of PK, PD, toxicity, and activity relationships.

[00448] The safety variables for this study are adverse events (AEs), safety clinical laboratory variables, 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) assessments, physical examinations, vital signs, exposure to study treatment,

assessment of concomitant medications, and pregnancy testing for females of child bearing potentials (FCBP).

[00449] During dose escalation, the decision to either evaluate a higher dose level or declare an MTD will be determined by the SRC, based on their review of all available clinical and laboratory safety data for a given dose cohort.

[00450] The SRC will also select the dose and schedule of Compound 1 in combination with erlotinib and oral azacitidine appropriate for cohort expansion. One or both schedules of Compound 1 and oral azacitidine may be selected for cohort expansion. The SRC will continue to review safety data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate.

[00451] The concentration-time profiles of Compound 1, M1, erlotinib and oral azacitidine will be determined from serial blood samples collected after administration of study drugs as single agents and after combination treatment. The pharmacokinetics (PK) of Compound 1 and azacitidine will be determined after oral administration of each drug as a single agent and after combination treatment (Compound 1/oral azacitidine) using: (1) Maximum observed concentration in plasma (C_{max}), (2) Area under the concentration-time curve (AUC), (3) Time to maximum concentration (t_{max}), (4) Terminal half-life ($T_{1/2}$), (5) Apparent total body clearance (CL/F) and (6) Apparent volume of distribution (Vz/F).

[00452] The effect of erlotinib and oral azacitidine on Compound 1 and M1 PK will be assessed, as will the effect of Compound 1 on the PK of erlotinib and oral azacitidine. Systemic exposure of Compound 1 after administration of Compound 1 as a single agent and in combination with erlotinib or oral azacitidine will be correlated with safety, PD and activity outcomes. The principal metabolites of Compound I, including M1, will be quantified in plasma. The PK of the M1 metabolite after oral administration of Compound I as a single agent and in combination with erlotinib or oral azacitidine will be characterized.

[00453] Biomarker evaluation will include analysis of mTOR pathway biomarkers, and other signaling pathways when possible, in blood and tumor after both single agent and combination treatment. In some instances, the changes of each biomarker will be determined by comparing the levels of biomarkers in pre- and on-treatment samples and, where possible, correlate these with PK findings and tumor response over time.

[00454] Assessment of gene DNA methylation and expression status in blood and tumor (when available) will be assessed at baseline and during combination drug treatment in Arm B and C to explore potential predictors of sensitivity to the Compound 1 plus oral azacitidine combination and effect of combination treatment on DNA methylation and expression.

[00455] Tumor gene sequencing will be performed at baseline on archival or Screening tumor biopsies to test for multiple genomic abnormalities.

[00456] Inclusion criteria for the study are: (1) Men and women, 18 years or older, with histologically or cytologically-confirmed, Stage IIIB/IV Non-Small Cell Lung Cancer with tumor progression following at least one prior treatment regimen (either chemotherapy or an Epidermal Growth Factor Receptor inhibitor for advanced disease), (2) Eastern Cooperative Oncology Group Performance Score of 0 or 1, (3) the following laboratory values: Absolute Neutrophil Count (ANC) $\geq 1.0 \times 10^9$/L; hemoglobin (Hgb) ≥ 9 g/dL; platelets (plt) $\geq 100 \times 10^9$/L; potassium within normal limits or correctable with supplements; AST/SGOT and ALT/SGPT ≤ 2.5 x Upper Limit of Normal (ULN) or ≤ 5.0 x ULN if liver tumor is present; serum bilirubin ≤ 1.5 x ULN; estimated serum creatinine clearance of ≥ 60 mL/min/1.73m^2 using the Cockcroft-Gault equation; subjects who complete Cycle 1 must meet the following hematologic criteria at the beginning of each subsequent cycle: ANC $> 1.0 \times 10^9$/L; and platelets $> 75 \times 10^9$/L.; and if the hematologic criteria are not met, the start of oral azacitidine in subsequent cycles may be delayed for up to 7 days to allow recovery. If recovery has not occurred after 7 days, this will be considered a DLT, (4) Adequate contraception (if appropriate), (5) Consent to retrieve archival tumor tissue, and (6) Consent to repeated tumor biopsy (dose expansion phase).

[00457] Exclusion criteria for the study are: (1) Prior systemic cancer-directed treatments or investigational drugs within 4 wks or 5 half lives, whichever is shorter, (2) Symptomatic central nervous system metastases, (3) Known acute or chronic pancreatitis, (4) Subjects with persistent diarrhea or malabsorption $\geq$ NCI CTCAE grade 2, despite medical management, (5) Impaired cardiac function or significant cardiac disease, , including any of the following: LVEF $< 45\%$ as determined by MUGA or ECHO; complete left bundle branch or bifascicular block; congenital long QT syndrome; persistent or

clinically meaningful ventricular arrhythmias; QTcF > 460 msec on Screening ECG (mean of triplicate recordings); unstable angina pectoris or myocardial infarction ≤ 3 months prior to starting study drugs; uncontrolled hypertension (blood pressure ≥ 160/95 mmHg); (6) Diabetes on active treatment with either of the following: Fasting blood glucose (FBG) >126 mg/dL (7.0 mmol/L) or HbA1c ≥ 6.5%, (7) Known Human Immunodeficiency Virus infection, chronic active hepatitis B or C virus infection, (8) Prior treatment with an investigational dual TORC1/TORC2, PI3K, or AKT inhibitor, (9) Major surgery ≤ 2 weeks prior to starting study drugs; no specific wash out is required for radiotherapy. Subjects must have recovered from any effects of recent therapy that might confound the safety evaluation of study drug, (10) Women who are pregnant or breast feeding. Adults of reproductive potential not employing two forms of birth control, and (11) history of concurrent second cancers requiring ongoing systemic treatment.

[00458] In some embodiments, 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, 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 combination with an effective amount of erlotinib or oral azacytidine. In certain embodiments, patients undergoing the clinical protocol provided herein will show increased survival without tumor progression. In some embodiments, 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.

6.6 COMPOUND 1 FORMULATIONS

[00459] Illustrative formulations of Compound 1 useful in the methods provided herein are set forth in Tables 7 and 8, below.

[00460] **Table 7**

Ingredients	Amounts	
	mg	%
Compound 1	20.0	15.38
Lactose monohydrate, NF (Fast Flo 316)	63.98	49.22
Microcrystalline cellulose, NF (Avicel pH 102)	40.30	31.00
Croscarmellose sodium, NF (Ac-Di-Sol)	3.90	3.00
Stearic acid, NF	0.52	0.40
Magnesium Stearate, NF	1.30	1.00
Total	130.0	100
Opadry yellow 03K12429	4% weight gain	

[00461] **Table 8**

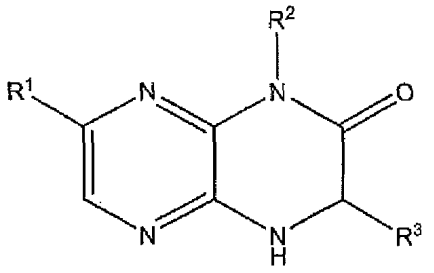
Ingredients	Amounts	
	mg	%
Compound 1	5.0	3.80
Lactose monohydrate, NF (Fast Flo 316)	78.98	60.70
Microcrystalline cellulose, NF (Avicel pH 102)	40.30	31.00
Croscarmellose sodium, NF (Ac-Di-Sol)	3.90	3.00
Stearic acid, NF	0.52	0.40
Magnesium Stearate, NF	1.30	1.00
Total	130.0	100
Opadry II pink 85F94211	5.2	4% weight gain

[00462] 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.

What is claimed is:

1. Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or azacitidine in the manufacture of a medicament for treating advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug 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;

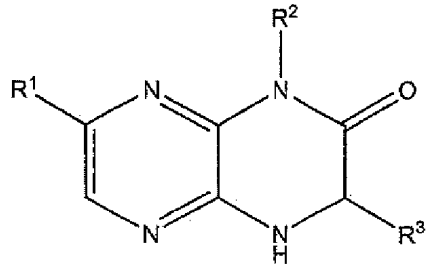
R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

2. The use of claim 1, wherein a TOR kinase inhibitor is to be used in combination with an effective amount of erlotinib.

3. The use of claim 1, wherein a TOR kinase inhibitor is to be used in combination with an effective amount of azacitidine.

4. The use of claim 3, wherein the azacitidine is oral azacitidine.

5. Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or azacitidine in the manufacture of a medicament for achieving a Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of complete response, partial response or stable disease in a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug 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;

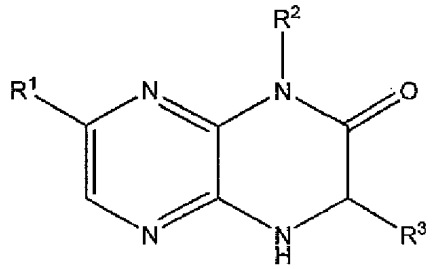
R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl.

6. The use of claim 5, wherein a TOR kinase inhibitor is to be used in combination with an effective amount of erlotinib.

7. The use of claim 5, wherein a TOR kinase inhibitor is to be used in combination with an effective amount of azacitidine.

8. The use of claim 7, wherein the azacitidine is oral azacitidine.

9. Use of a TOR kinase inhibitor in combination with an effective amount of erlotinib or azacitidine in the manufacture of a medicament for increasing survival without tumor progression of a patient having advanced non-small cell lung cancer, wherein the TOR kinase inhibitor has the following formula (IV):



(IV)

or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug 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.

10. The use of claim 9, wherein a TOR kinase inhibitor is to be used in combination with an effective amount of erlotinib.

11. The use of claim 9, wherein a TOR kinase inhibitor is to be used in combination with an effective amount of azacitidine.

12. The use of claim 11, wherein the azacitidine is oral azacitidine.

13. The use of any one of claims 1 – 12, wherein the TOR kinase inhibitor is a compound from Table D.