TREATMENT OF CANCER WITH TOR KINASE INHIBITORS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/611,361, filed March 15, 2012 and claims the benefit of U.S. Provisional Application No. 61/715,323, filed October 18, 2012, the entire contents of each of which are incorporated herein by reference.

1. FIELD

[0002] Provided herein are methods for treating or preventing head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma.

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 additional TOR kinase inhibitors.

[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] Provided herein are methods for treating or preventing head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma.

[0011] In certain embodiments, provided herein are methods for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, comprising

administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma.

[0012] In some embodiments, the TOR kinase inhibitor is a compound as described herein.

[0013] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

4. DETAILED DESCRIPTION

4.1 DEFINITIONS

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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).

[0018] 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.

[0019] 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[l,4]dioxinyl, and benzo[l,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[l,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.

[0020] An "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.

[0021] 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.

[0022] 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.

[0023] A "halogen" is fluorine, chlorine, bromine or iodine.

[0024] A "hydroxyalkyl" group is an alkyl group as described above substituted with one or more hydroxy groups.

[0025] An "alkoxy" group is -O-(alkyl), wherein alkyl is defined above.

[0026] An "alkoxyalkyl" group is -(alkyl)-O-(alkyl), wherein alkyl is defined above.

[0027] An "amino" group is a radical of the formula: $-NH_2$.

[0028] An "alkylamino" group is a radical of the formula: -NH-alkyl or $-N(alkyl)_2$, wherein each alkyl is independently as defined above.

[0029] A "carboxy" group is a radical of the formula: -C(O)OH.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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).

[0036] 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.

[0037] 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.

[0038] 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.

[0039] As used herein and unless otherwise indicated, the term "prodrug" means a TOR kinase inhibitor derivative that can hydrolyze, oxidize, or otherwise react under

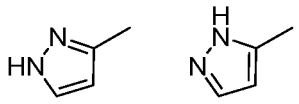
biological conditions (*in vitro* or *in vivo*) to provide an active compound, particularly a TOR kinase inhibitor. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a TOR kinase inhibitor that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable 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).

[0040] 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).

[0041] 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.

[0042] "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:



[0043] 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.

[0044] 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.

[0045] "Treating" as used herein, means an alleviation, in whole or in part, of head and neck squamous cell carcinoma, or a symptom thereof, or slowing, or halting of further progression or worsening of head and neck squamous cell carcinoma or a symptom thereof.

[0046] "Preventing" as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of head and neck squamous cell carcinoma or a symptom thereof.

[0047] The term "effective amount" in connection with an TOR kinase inhibitor means an amount capable of alleviating, in whole or in part, symptoms associated with head and neck squamous cell carcinoma, or slowing or halting further progression or worsening of those symptoms, or treating or preventing head and neck squamous cell carcinoma. The effective amount of the TOR kinase inhibitor, for example in a pharmaceutical composition, may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 100 mg/kg of a patient's body weight in unit dosage for both oral and parenteral administration. As will be apparent to those skilled in the art, it is to be

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

[0048] 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 head and neck squamous cell carcinoma. In one embodiment, a patient is a human having histologically or cytologically-confirmed head and neck squamous cell carcinoma, including subjects who have progressed on (or not been able to tolerate) standard anticancer therapy or for whom no standard anticancer therapy exists.

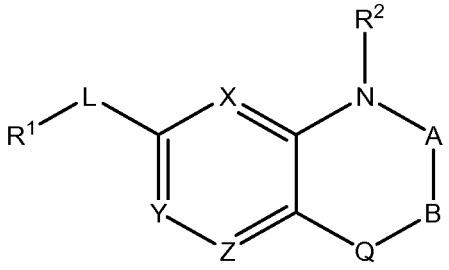
[0049] In the context of head and neck squamous cell carcinoma, treatment may be assessed by inhibition of disease progression, inhibition of tumor growth, reduction of primary and/or secondary tumor(s), relief of tumor-related symptoms, improvement in quality of life, delayed appearance of primary and/or secondary tumor(s), slowed development of primary and/or secondary tumor(s), decreased occurrence of primary and/or secondary tumor(s), slowed or decreased severity of secondary effects of disease, arrested tumor growth and/or regression of tumors, among others. In certain embodiments, treatment of head and neck squamous cell carcinoma may be assessed by the inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in circulating blood and/or tumor cells and/or skin biopsies or tumor biopsies/aspirates, before, during and/or after treatment with a TOR kinase inhibitor. In other embodiments, treatment of head and neck squamous cell carcinoma may be assessed by the inhibition of DNA-dependent protein kinase (DNA-PK) activity in skin samples and/or tumor biopsies/aspirates, such as by assessment of the amount of pDNA-PK S2056 as a biomarker for DNA damage pathways, before, during, and/or after TOR kinase inhibitor treatment. In one embodiment, the skin sample is irradiated by UV light. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident head and neck squamous cell carcinoma altogether

or preventing the onset of a preclinically evident stage of head and neck squamous cell carcinoma. 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 head and neck squamous cell carcinoma.

4.2 TOR KINASE INHIBITORS

[0050] 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).

[0051] 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.

[0052] In one embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -$CH_2C(O)NH$-.

[0053] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -$C(O)CH_2NH$-.

[0054] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-.

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

[0056] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -$C(O)CH_2O$-.

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

[0058] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -$C(O)NR^3$-.

[0059] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein Y is CR^3.

[0060] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CR^3.

[0061] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CH.

[0062] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are CH and Y is N.

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

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

[0065] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[0066] 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.

[0067] 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.

[0068] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^1 is H.

[0069] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is H.

[0074] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein L is a direct bond.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

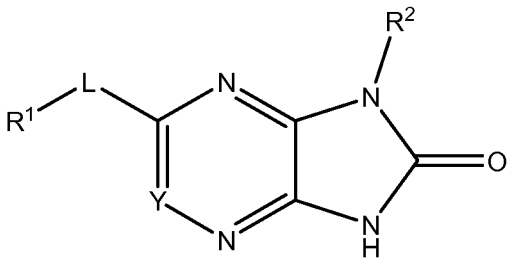
[0088] In another embodiment, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is -C(O)NR^3-, R^2 is

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.

[0089] In another embodiment, the TOR kinase inhibitors of formula (I) do not include compounds wherein R^1 is a substituted or unsubstituted oxazolidinone.

[0090] 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.

[0091] 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.

[0092] In one embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[0093] 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.

[0094] 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.

[0095] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is H.

[0096] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted C_{1-8}alkyl.

[0097] 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.

[0098] 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.

[0099] 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.

[00100] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is H.

[00101] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein Y is CH.

[00102] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein L is a direct bond.

[00103] 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_{1-8}alkyl.

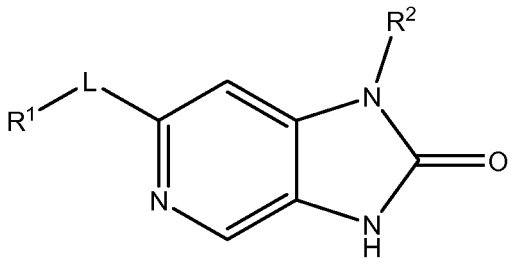
[00104] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is C_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00105] 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.

[00106] 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_{1-8}alkyl substituted with substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[00107] 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.

[00108] In one embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00109] 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.

[00110] 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.

[00111] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is H.

[00112] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted C_{1-8}alkyl.

[00113] 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.

[00114] 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.

[00115] 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.

[00116] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is H.

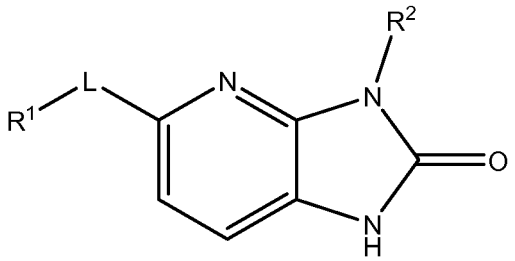
[00117] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein L is a direct bond.

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] In one embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00123] 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.

[00124] 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.

[00125] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is H.

[00126] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted C_{1-8}alkyl.

[00127] 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.

[00128] 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.

[00129] 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.

[00130] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is H.

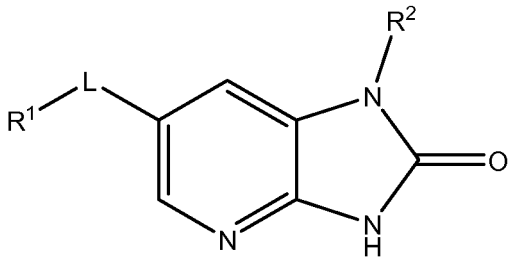
[00131] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein L is a direct bond.

[00132] 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.

[00133] 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.

[00134] 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.

[00135] 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.

[00136] In one embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00137] 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.

[00138] 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.

[00139] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is H.

[00140] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted C_{1-8}alkyl.

[00141] 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.

[00142] 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.

[00143] 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.

[00144] In another embodiment, the Heteroaryl Compounds of formula (Id) are those wherein R^2 is H.

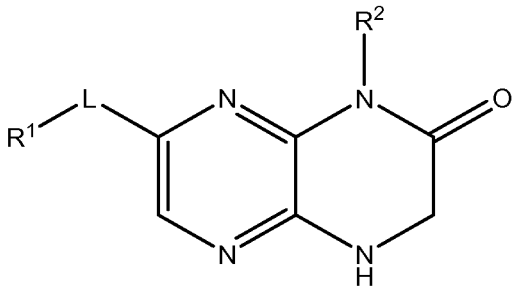
[00145] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein L is a direct bond.

[00146] 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.

[00147] 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.

[00148] 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.

[00149] 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.

[00150] In one embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00151] 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.

[00152] 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.

[00153] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is H.

[00154] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted C_{1-8}alkyl.

[00155] 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.

[00156] 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.

[00157] 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.

[00158] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is H.

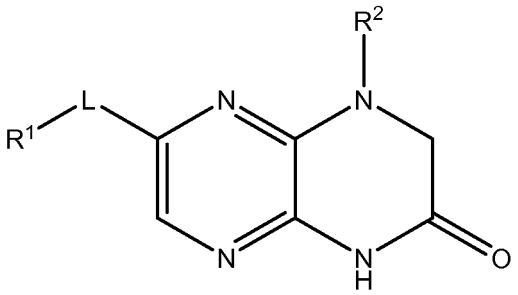
[00159] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein L is a direct bond.

[00160] 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_{1-8}alkyl.

[00161] 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_{1-8}alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00162] 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.

[00163] 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.

[00164] In one embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00165] 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.

[00166] 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.

[00167] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^1 is H.

[00168] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted C_{1-8}alkyl.

[00169] 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.

[00170] 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.

[00171] 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.

[00172] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is H.

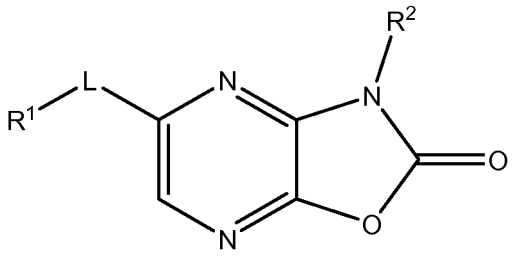
[00173] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein L is a direct bond.

[00174] 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.

[00175] 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.

[00176] 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.

[00177] 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.

[00178] In one embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00179] 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.

[00180] 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.

[00181] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is H.

[00182] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted C_{1-8}alkyl.

[00183] 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.

[00184] 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.

[00185] 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.

[00186] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is H.

[00187] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein L is a direct bond.

[00188] 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.

[00189] 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.

[00190] 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.

[00191] Representative TOR kinase inhibitors of formula (I) include:
(S)-1-(1-hydroxy-3-methylbutan-2-yl)-6-phenyl-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-((tetrahydro-2H-pyran-4-yl)methyl)-6-(3,4,5-trimethoxyphenyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
(R)-6-(naphthalen-1-yl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

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

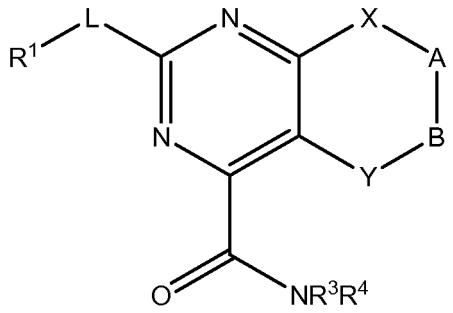
6-(2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
1-(cyclohexylmethyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
6-(4-(hydroxymethyl)thiophen-2-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;
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.

[00192] 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.

[00193] In one embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)CH_2C(O)NH-$.

[00194] 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-.

[00195] 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-.

[00196] 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-.

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

[00198] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein L is a direct bond.

[00199] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00200] 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.

[00201] 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.

[00202] 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.

[00203] 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.

[00204] 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.

[00205] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl, such as $-CH_2C_6H_5$.

[00206] 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.

[00207] 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.

[00208] 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.

[00209] 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.

[00210] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00211] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^3 and R^4 are H.

[00212] 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.

[00213] 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.

[00214] 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.

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

[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-, 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.

[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(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.

[00218] 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.

[00219] 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 $C_{1\text{-}8}$alkyl or substituted or unsubstituted cycloalkyl.

[00220] 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 $C_{1\text{-}8}$alkyl or substituted or unsubstituted cycloalkyl.

[00221] 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-

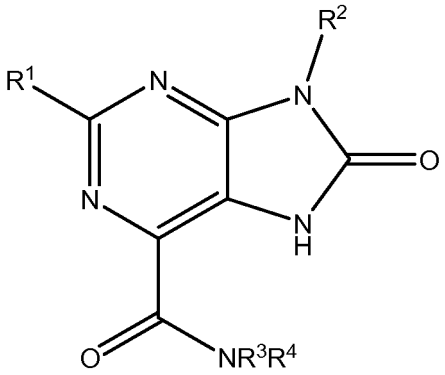
7H-purine-6-carboxamide, 2-(4-nitrophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 9-benzyl-2-(4-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide, 2-methyl-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 9-benzyl-9H-purine-2,6-dicarboxamide, 9-[2,3-bis[(benzoyloxy)methyl]cyclobutyl]-2-methyl-9H-Purine-6-carboxamide, 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.

[00222] In another embodiment, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted furanoside.

[00223] In another embodiment, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00224] In another embodiment, the TOR kinase inhibitors of formula (II) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00225] 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.

[00226] 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.

[00227] 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.

[00228] 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.

[00229] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00230] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00231] 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.

[00232] 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.

[00233] 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.

[00234] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00235] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^3 and R^4 are H.

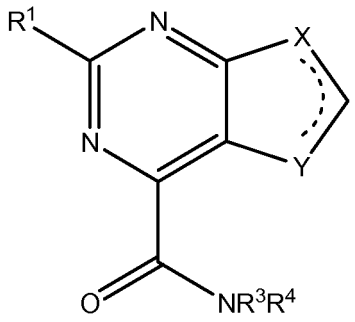
[00236] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 2-(4-cyanophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 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.

[00237] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted furanoside.

[00238] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00239] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00240] 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.

[00241] In one embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00242] 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.

[00243] 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.

[00244] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl, such as $-CH_2C_6H_5$.

[00245] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is unsubstituted $C_{1\text{-}8}$alkyl, such as unsubstituted methyl.

[00246] 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.

[00247] 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.

[00248] 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.

[00249] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00250] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^3 and R^4 are H.

[00251] 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.

[00252] 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.

[00253] 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.

[00254] 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.

[00255] 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-.

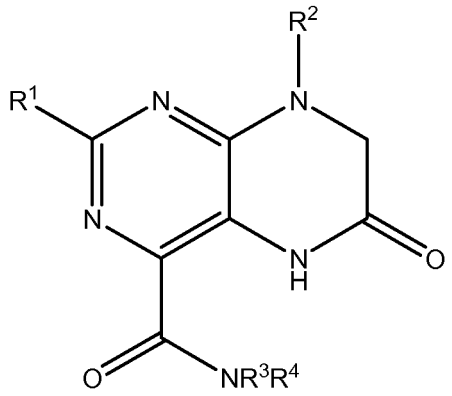
[00256] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is a substituted furanoside when  is -N(R^2)-CH=N-.

[00257] 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-.

[00258] 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-.

[00259] 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-.

[00260] 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.

[00261] In one embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00262] 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.

[00263] 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.

[00264] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl, such as $-CH_2C_6H_5$.

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

[00266] 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.

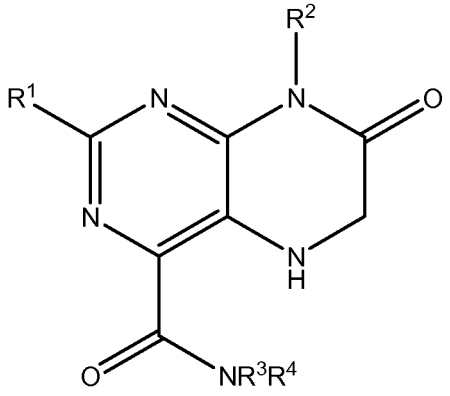
[00267] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00268] 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.

[00269] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00270] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^3 and R^4 are H.

[00271] 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.

[00272] In one embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00273] 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.

[00274] 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.

[00275] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00276] 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.

[00277] 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.

[00278] 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.

[00279] 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.

[00280] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00281] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^3 and R^4 are H.

[00282] Representative TOR kinase inhibitors of formula (IV) include:

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-methylcarbox-amide;

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-carbox-amide;
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;

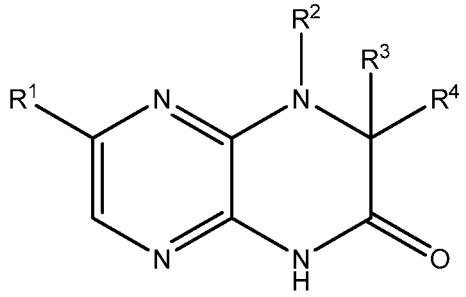
2-(1H-Imidazo[4,5-b]pyridin-6-yl)-9-(cis-4-methoxycyclohexyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide;

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.

[00283] 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:

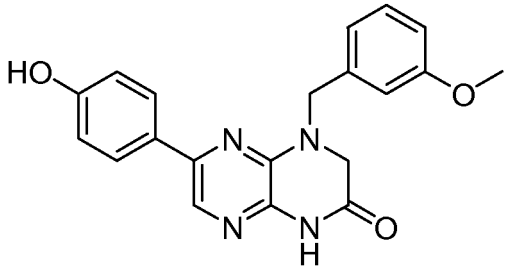
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

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;

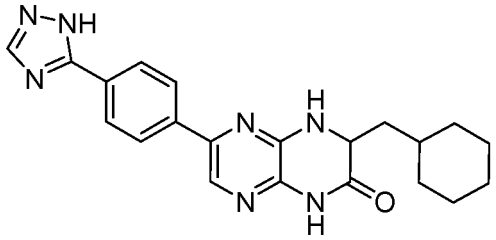
R^3 and R^4 are each independently H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, substituted or 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:

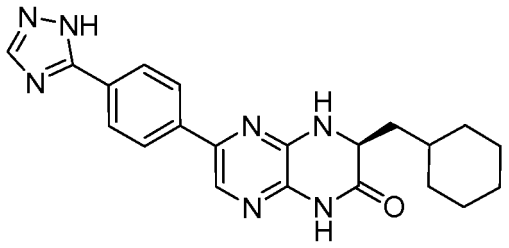


6-(4-hydroxyphenyl)-4-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;



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

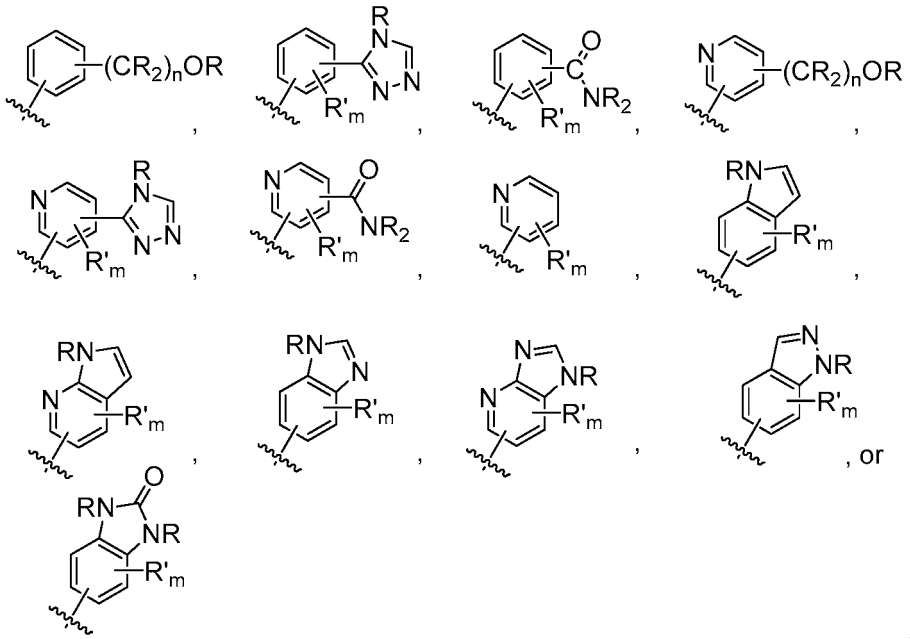
or,



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

[00284] 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.

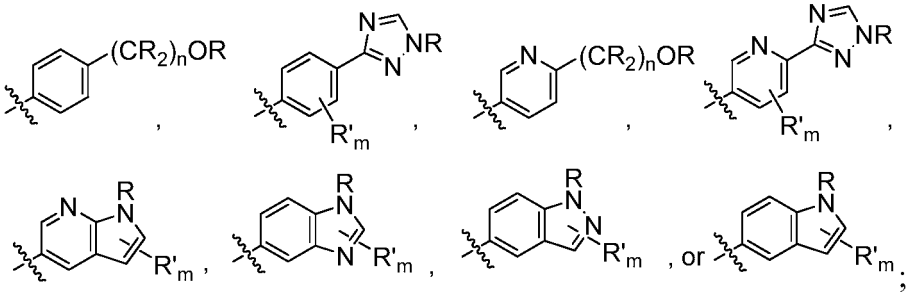
[00285] In some embodiments of compounds of formula (III), R^1 is



;

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.

[00286] In some embodiments of compounds of formula (III), R^1 is

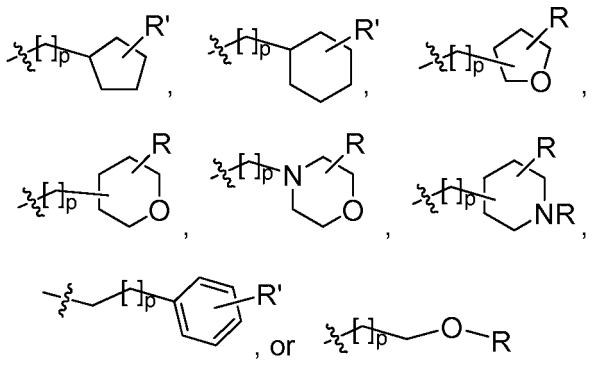


;

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.

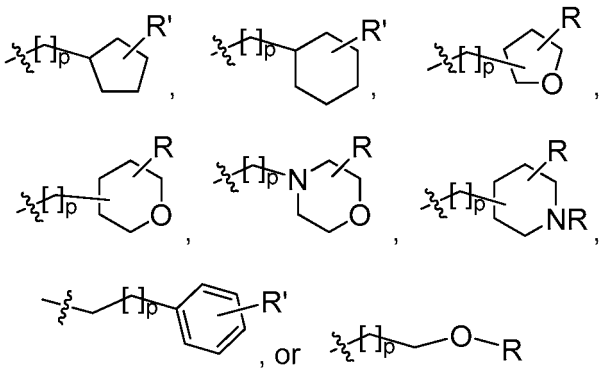
[00287] In some embodiments of compounds of formula (III), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, 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.

[00288] In other embodiments, R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



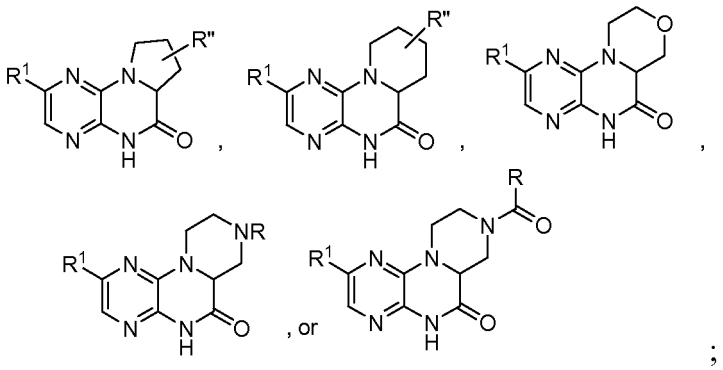
wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently H, -OR, cyano, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); and p is 0-3.

[00289] 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.

[00290] 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.

[00291] 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).

[00292] 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

[00293] In certain embodiments, the compounds of formula (III) have an R^1 group set forth herein and an R^2 group set forth herein.

[00294] 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.

[00295] Representative TOR kinase inhibitors of formula (III) include: 6-(1H-pyrrolo[2,3-b]pyridin-3-yl)-4-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

6-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-4-((*trans*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
6-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-4-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
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;

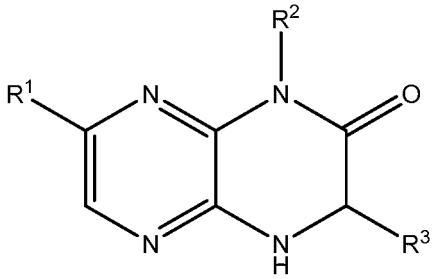
9-(6-(4H-1,2,4-triazol-3-yl)-2-methyl-3-pyridyl)-6,11,4a-trihydromorpholino[4,3-e]pyrazino[2,3-b]pyrazin-5-one;
4-(*trans*-4-hydroxycyclohexyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(*cis*-4-hydroxycyclohexyl)-6-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
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.

[00296] In one embodiment, the TOR kinase inhibitors include compounds having the following formula (IV):



(IV)

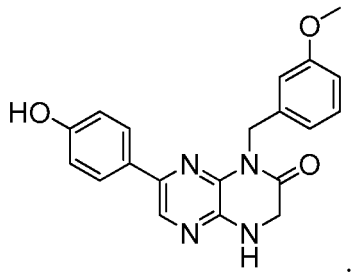
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

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,

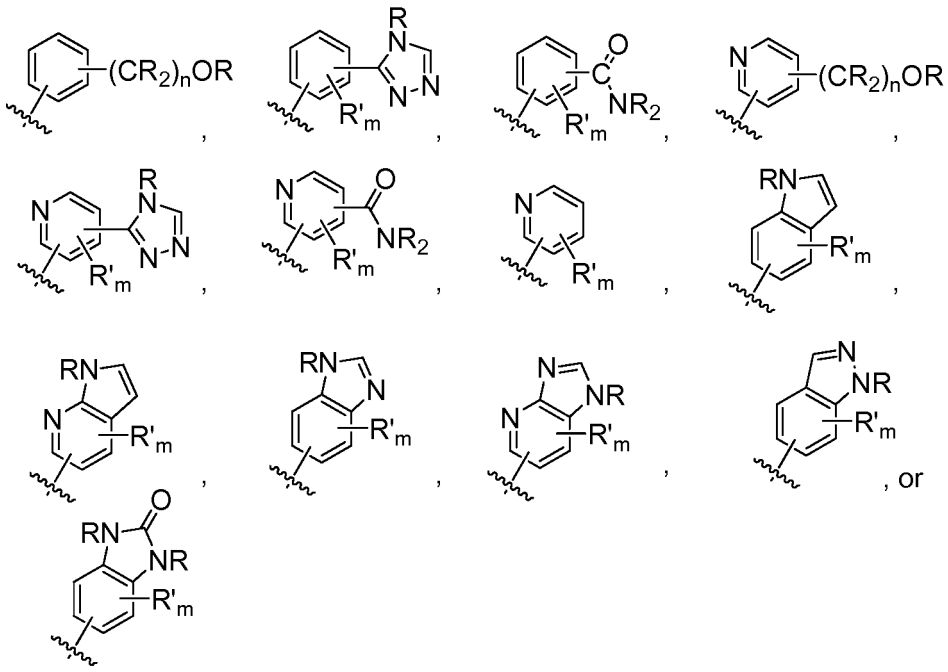
wherein in certain embodiments, the TOR kinase inhibitors do not include 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one, depicted below:



[00297] 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.

[00298] In some embodiments, R^1 is

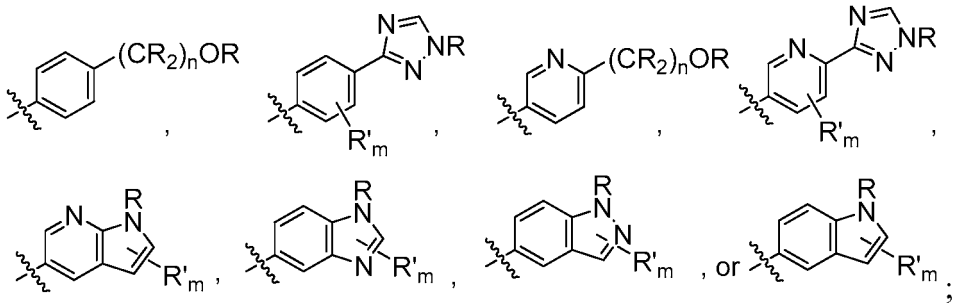


;

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.

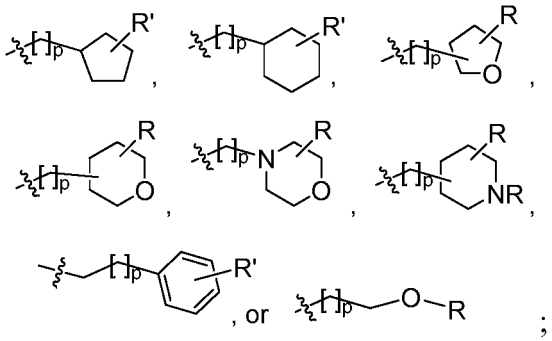
[00299] In some embodiments of compounds of formula (IV), R^1 is



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.

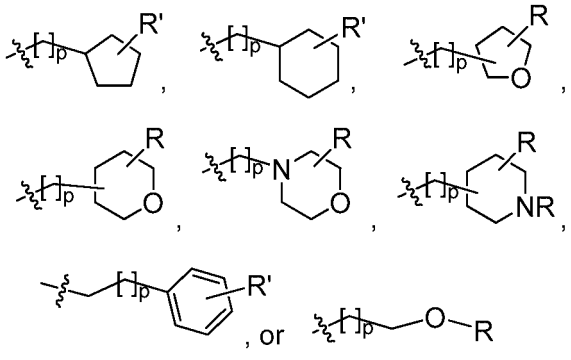
[00300] In some embodiments of compounds of formula (IV), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, 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.

[00301] 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.

[00302] 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.

[00303] In other embodiments of compounds of formula (IV), R^3 is H.

[00304] 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.

[00305] In certain embodiments, the compounds of formula (IV) have an R^1 group set forth herein and an R^2 group set forth herein.

[00306] 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.

[00307] Representative TOR kinase inhibitors of formula (IV) include:
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(*cis*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-pyrrolo[2,3-b]pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(1H-pyrrolo[3,2-b]pyridin-5-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-benzo[d]imidazol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*trans*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
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.

4.3 METHODS FOR MAKING TOR KINASE INHIBITORS

[00308] 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.

[00309] Particular methods for preparing compounds of formula (I) are disclosed in U.S. Patent No. 7,981,893, issued July 19, 2011, incorporated by reference herein in its entirety. Particular methods for preparing compounds of formula (II) are disclosed in U.S. Patent No. 7,968,556, issued June 28, 2011, incorporated by reference herein in its entirety. Particular methods for preparing compounds of formula (III) and (IV) are disclosed in U.S. Patent No. 8,110,578, issued February 7, 2012, and U.S. Publication No. 2011/0137028, filed October 25, 2010, incorporated by reference herein in its entirety.

4.4 METHODS OF USE

[00310] Provided herein are methods for treating or preventing head and neck squamous cell carcinoma (also known as HNSCC), comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma. In certain embodiments, a TOR kinase inhibitor is administered to a patient who has locally advanced, recurrent or metastatic, squamous cell carcinoma of the head and neck not amenable to curative surgical resection. In another embodiment, a TOR kinase inhibitor is administered to a patient who has received at least one prior line of platinum based chemotherapy. In some embodiments, a TOR kinase inhibitor is administered to a patient who has a tumor showing DNA-PK overexpression.

[00311] In one embodiment, provided herein are methods for treating or preventing head and neck squamous cell carcinoma that has metastasized, comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma that has metastasized. In particular embodiments, the head and neck squamous cell carcinoma that has metastasized has metastasized to an axilliary node, the palate, the a neck lymph node, the lung, a superior segment, the nose or nasal passageway, the neck, the skull base, the cervix, the chest wall, pleural fluid, a latisimal muscle, a tonsil or a location as set forth in Table 3.

[00312] In some embodiments, provided herein are methods for treating head and neck squamous cell carcinoma, the methods comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma, 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.

[00313] In one embodiment, provided herein are methods for preventing metastasis of head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma.

[00314] In one embodiment, provided herein are methods for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*see* Eisenhauer E.A., Therasse P., Bogaerts J., et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European J. Cancer*; 2009; (45) 228–247) of a patient comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma.

[00315] In one embodiment, provided herein are methods for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient. In some such embodiments, the inhibition of phosphorylation is assessed in a biological sample of the patient, such as in circulating blood and/or tumor cells, skin biopsies and/or tumor biopsies or aspirate. In such embodiments, the amount of inhibition of phosphorylation is assessed by comparison of the amount of phospho- S6RP, 4E-BP1 and/or AKT before and after administration of the TOR kinase inhibitor. In certain embodiments, provided herein are methods for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient, measuring the amount of phosphorylated S6RP, 4E BP1 and/or AKT in said patient, and comparing said amount of phosphorylated S6RP, 4E BP1 and/or AKT to that of said patient prior to administration of an effective amount of a TOR kinase inhibitor.

[00316] In certain embodiments, provided herein are methods for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a

TOR kinase inhibitor to said patient and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.

[00317] In one embodiment, provided herein are methods for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient. In some embodiments, DNA-PK inhibition is assessed in the skin of the patient having head and neck squamous cell carcinoma, in one example in a UV light-irradiated skin sample of said patient. In another embodiment, DNA-PK inhibition is assessed in a tumor biopsy or aspirate of a patient having head and neck squamous cell carcinoma. In one embodiment, inhibition is assessed by measuring the amount of phosphorylated DNA-PK S2056 (also known as pDNA-PK S2056) before and after administration of the TOR kinase inhibitor. In certain embodiments, provided herein are methods for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient, measuring the amount of phosphorylated DNA-PK S2056 present in the skin sample and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of a TOR kinase inhibitor. In one embodiment, the skin sample is irradiated with UV light.

[00318] In certain embodiments, provided herein are methods for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated DNA-PK in a

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

[00319] 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 $C_{16}H_{16}N_8O$). In one embodiment, Compound 1 is 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one.

[00320] A TOR kinase inhibitor can be combined with radiation therapy or surgery. In certain embodiments, a TOR kinase inhibitor is administered to patient who is undergoing radiation therapy, has previously undergone radiation therapy or will be undergoing radiation therapy. In certain embodiments, a TOR kinase inhibitor is administered to a patient who has undergone tumor removal surgery.

[00321] Further provided herein are methods for treating patients who have been previously treated for head and neck squamous cell carcinoma, but are non-responsive to standard therapies, 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 the condition at issue, as well as those who have not. Because patients with head and neck squamous cell carcinoma may have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with head and neck squamous cell carcinoma.

[00322] In one embodiment, the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated. In certain embodiments, the head and neck

squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

4.5 PHARMACEUTICAL COMPOSITIONS AND ROUTES OF ADMINISTRATION

[00323] Provided herein are compositions, comprising an effective amount of a TOR kinase inhibitor, and compositions comprising an effective amount of a TOR kinase inhibitor and a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutical compositions described herein are suitable for oral, parenteral, mucosal, transdermal or topical administration.

[00324] The TOR kinase inhibitors can be administered to a patient orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions and syrups. Suitable formulations can be prepared by methods commonly employed using conventional, organic or inorganic additives, such as an excipient *(e.g.,* sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder *(e.g.,* cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator *(e.g.,* starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant *(e.g.,* magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent *(e.g.,* citric acid, menthol, glycine or orange powder), a preservative *(e.g,* sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer *(e.g.,* citric acid, sodium citrate or acetic acid), a suspending agent *(e.g.,* methylcellulose, polyvinyl pyrroliclone or aluminum stearate), a dispersing agent *(e.g.,* hydroxypropylmethylcellulose), a diluent *(e.g.,* water), and base wax *(e.g.,* cocoa butter, white petrolatum or polyethylene glycol). The effective amount of the TOR kinase inhibitor in the pharmaceutical composition may be at a level that will exercise the desired

effect; for example, about 0.005 mg/kg of a patient's body weight to about 10 mg/kg of a patient's body weight in unit dosage for both oral and parenteral administration.

[00325] The dose of a TOR kinase inhibitor to be administered to a patient is rather widely variable and can be subject to the judgment of a health-care practitioner. In general, the TOR kinase inhibitors can be administered one to four times a day in a dose of about 0.005 mg/kg of a patient's body weight to about 10 mg/kg of a patient's body weight in a patient, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration. In one embodiment, the dose is about 0.01 mg/kg of a patient's body weight to about 5 mg/kg of a patient's body weight, about 0.05 mg/kg of a patient's body weight to about 1 mg/kg of a patient's body weight, about 0.1 mg/kg of a patient's body weight to about 0.75 mg/kg of a patient's body weight, about 0.25 mg/kg of a patient's body weight to about 0.5 mg/kg of a patient's body weight, or about 0.007 mg/kg of a patient's body weight to about 1.7 mg/kg of patient's body weight. In one embodiment, one dose is given per day. In another embodiment, two doses are given per day. In any given case, the amount of the TOR kinase inhibitor administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

[00326] In another embodiment, provided herein are methods for the treatment or prevention of head and neck squamous cell carcinoma, comprising the administration of about 0.375 mg/day to about 750 mg/day, about 0.75 mg/day to about 375 mg/day, about 3.75 mg/day to about 75 mg/day, about 7.5 mg/day to about 55 mg/day, about 18 mg/day to about 37 mg/day, about 0.5 mg/day to about 60 mg/day, or about 0.5 mg/day to about 128 mg/day of a TOR kinase inhibitor to a patient in need thereof. In another embodiment, provided herein are methods for the treatment or prevention of head and neck squamous cell carcinoma, comprising the administration of about 0.5 mg/day to about 1200 mg/day, about 10 mg/day to about 1200 mg/day, about 100 mg/day to about 1200 mg/day, about 400 mg/day to about 1200 mg/day, about 600 mg/day to about 1200 mg/day, about 400 mg/day to about 800 mg/day or about 600 mg/day to about 800 mg/day of a TOR

kinase inhibitor to a patient in need thereof. In a particular embodiment, the methods disclosed herein comprise the administration of 0.5 mg/day, 1 mg/day, 2 mg/day, 4 mg/day, 8 mg/day, 16 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, 45 mg/day, 60 mg/day, 90 mg/day, 120 mg/day or 128 mg/day of a TOR kinase inhibitor to a patient in need thereof.

[00327] In another embodiment, provided herein are unit dosage formulations that comprise between about 0.1 mg and about 2000 mg, about 1 mg and 200 mg, about 35 mg and about 1400 mg, about 125 mg and about 1000 mg, about 250 mg and about 1000 mg, or about 500 mg and about 1000 mg of a TOR kinase inhibitor.

[00328] In a particular embodiment, provided herein are unit dosage formulation comprising about 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 45 mg, 50 mg, 60 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 600 mg or 800 mg of a TOR kinase inhibitor.

[00329] In another embodiment, provided herein are unit dosage formulations that comprise 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 50 mg, 70 mg, 100 mg, 125 mg, 140 mg, 175 mg, 200 mg, 250 mg, 280 mg, 350 mg, 500 mg, 560 mg, 700 mg, 750 mg, 1000 mg or 1400 mg of a TOR kinase inhibitor. In a particular embodiment, provided herein are unit dosage formulations that comprise 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 45 mg or 60 mg of a TOR kinase inhibitor.

[00330] A TOR kinase inhibitor can be administered once, twice, three, four or more times daily.

[00331] A TOR kinase inhibitor can be administered orally for reasons of convenience. In one embodiment, when administered orally, a TOR kinase inhibitor is administered with a meal and water. In another embodiment, the TOR kinase inhibitor is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a suspension. In another embodiment, when administered orally, a TOR kinase inhibitor is administered in a fasted state.

[00332] The TOR kinase inhibitor can also be administered intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, rectally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the health-care practitioner, and can depend in-part upon the site of the medical condition.

[00333] In one embodiment, provided herein are capsules containing a TOR kinase inhibitor without an additional carrier, excipient or vehicle.

[00334] In another embodiment, provided herein are compositions, comprising an effective amount of a TOR kinase inhibitor and a pharmaceutically acceptable carrier or vehicle, wherein a pharmaceutically acceptable carrier or vehicle can comprise an excipient, diluent, or a mixture thereof. In one embodiment, the composition is a pharmaceutical composition.

[00335] 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.

[00336] 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.

[00337] 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.

[00338] When it is desired to administer a TOR kinase inhibitor 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.

[00339] The effect of the TOR kinase inhibitor can be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the TOR kinase inhibitor 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 oily or emulsified vehicles that allow it to disperse slowly in the serum.

4.6 KITS

[00340] In certain embodiments, provided herein are kits comprising a TOR kinase inhibitor.

[00341] In other embodiments, provide herein are kits comprising a TOR kinase inhibitor and means for monitoring patient response to administration of said TOR kinase inhibitor. In certain embodiments, the patient has head and neck squamous cell carcinoma. In particular embodiments, the patient response measured is inhibition of disease progression, inhibition of tumor growth, reduction of primary and/or secondary tumor(s), relief of tumor-related symptoms, improvement in quality of life, delayed appearance of primary and/or secondary tumors, slowed development of primary and/or secondary tumors, decreased occurrence of primary and/or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth or regression of tumor.

[00342] In other embodiments, provided herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in a patient. In certain embodiments, the kits comprise means for measuring inhibition of phosphorylation of S6RP, 4E-BP1 and/or AKT in circulating blood or tumor cells and/or skin biopsies or tumor biopsies/aspirates of a patient. In certain embodiments, provided herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of inhibition of phosphorylation as assessed by comparison of the amount of phospho- S6RP, 4E-BP1 and/or AKT before, during and/or after administration of the TOR kinase inhibitor. In certain embodiments, the patient has head and neck squamous cell carcinoma.

[00343] In other embodiments, provided herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of inhibition of DNA-dependent protein kinase (DNA-PK) activity in a patient. In certain embodiments, the kits comprise means for

measuring the amount of inhibition of DNA-dependent protein kinase (DNA-PK) activity in a skin sample and/or a tumor biopsy/aspirate of a patient. In one embodiment, the kits comprise a means for measuring the amount of pDNA-PK S2056 in a skin sample and/or a tumor biopsy/aspirate of a patient. In one embodiment, the skin sample is irradiated by UV light. In certain embodiments, provided herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of inhibition of DNA-dependent protein kinase (DNA-PK) activity before, during and/or after administration of the TOR kinase inhibitor. In certain embodiments, provided herein are kits comprising a TOR kinase inhibitor and means for measuring the amount of phosphorylated DNA-PK S2056 before, during and/or after administration of the TOR kinase inhibitor. In certain embodiments, the patient has head and neck squamous cell carcinoma.

[00344] In certain embodiments, the kits provided herein comprise an amount of a TOR kinase inhibitor effective for treating or preventing head and neck squamous cell carcinoma. In certain embodiments, the kits provided herein comprise a TOR kinase inhibitor having molecular formula $C_{16}H_{16}N_8O$. In certain embodiments, the kits provided herein comprise Compound 1.

[00345] In certain embodiments, the kits provided herein further comprise instructions for use, such as for administering a TOR kinase inhibitor and/or monitoring patient response to administration of a TOR kinase inhibitor.

5. EXAMPLES

5.1 BIOLOGICAL EXAMPLES

5.1.1 Biochemical assays

[00346] **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:

[00347] "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.

[00348] 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.

[00349] 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).

[00350] 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).

[00351] 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.

[00352] **DNA-PK assay**. DNA-PK assays were performed using the procedures supplied in the Promega DNA-PK assay kit (catalog # V7870). DNA-PK enzyme was purchased from Promega (Promega cat#V5811).

[00353] Selected TOR kinase inhibitors as described herein have, or are expected to have, an IC_{50} below 10 μM in this assay, with some TOR kinase inhibitors as described herein having an IC_{50} below 1 μM, and others having an IC_{50} below 0.10 μM.

5.1.2 Cell based assays

[00354] **Growth inhibition assay for Head and Neck (HN) Cancer Cell lines.** Compound 1 (a TOR kinase inhibitor set forth herein having molecular formula $C_{16}H_{16}N_8O$) was dissolved in dimethyl sulfoxide (DMSO) to prepare a 10 mM stock solution. A serial titration was performed to produce a working concentration range of 1.5 μM to 10 mM. Aliquots to produce final concentrations of 1.5 nM to 10 μM were spotted via an acoustic dispenser (EDC ATS-100) into an empty 384-well plate. Compound 1 was spotted in a 10-point serial dilution fashion (3-fold dilution) in duplicate within the plate. The DMSO concentration was kept constant for a final assay concentration of 0.1% DMSO. Plates were replicated for use with different cell lines and testing periods. After compound plate replication, all plates were sealed (Agilent ThermoLoc) and stored at -20°C for up to 1 month. Repeat testing of Compound 1 in the control cell line (A549) resulted in consistent GI_{50} and IC_{50} values regardless of plate replication sequence or storage time at -20°C, suggesting Compound 1 is stable under the storage conditions used in the current study for at least 1 month. When ready for testing, plates were removed from the freezer, thawed, and unsealed just prior to the addition of the test cells. Prior to testing, cells were grown and expanded in culture flasks to provide sufficient amounts of starting material. Cells were then diluted to the appropriate densities and added directly to the compound-spotted 384-well plates. Cells were allowed to grow for 72 hours at 37 °C/5% CO_2. At the time when compound was added (t_0), initial cell number was assessed via a viability assay (Cell Titer-Glo) by quantifying the level of luminescence generated by ATP present in viable cells. After 72 hours, cell viability of compound-treated cells was assessed via Cell Titer-Glo and luminescence measurement. Cell lines were assayed for growth inhibition by Compound 1 in at least 3 independent tests. A control cell line (the lung tumor cell line, A549) was included in each of the assays. The compound response against this control cell

line was monitored closely to enable comparison of the data generated through the assay period. All data were normalized and presented as a percentage of the DMSO-treated cells. Results were then expressed as a GI_{50} value. The GI_{50} value corrects for the cell count at time zero. In addition, the IC_{50} value of Compound 1 for each cell line was calculated. Results for Compound 1 for selected HN cell lines are set forth in Table 1.

Table 1

HNC Cell Lines	n	GI_{50} (μM)	GI_{50} SD	GI_{50} SEM	IC_{50} (μM)	IC_{50} SD	IC_{50} SEM	n	Cal_X
A253	3	0.3028	0.056	0.0323	0.3779	0.0925	0.0534	1	10
BHY	2	0.0395	0.0135	0.0096	0.2104	0.0736	0.0521	1	10
CAL-27	3	0.1442	0.0367	0.0212	0.1768	0.057	0.0329	1	10
CAL-33	3	0.0427	0.0041	0.0024	0.0698	0.0089	0.0051	1	0.8764
Detroit562	3	0.1691	0.0506	0.0292	0.2539	0.0477	0.0275	1	10
FADU	3	0.7925	0.0893	0.0516	1.162	0.0219	0.0127	1	10
HN	3	0.1166	0.0156	0.009	0.1777	0.0183	0.0106	1	10
RPMI-2650	3	0.2187	0.0615	0.0355	0.3888	0.0841	0.0486	1	10
SCC-15	3	0.0568	0.0147	0.0085	0.6792	0.2094	0.1209	1	10
SCC-25	3	0.1271	0.0419	0.0242	0.1788	0.044	0.0254	1	10
SCC-9	3	0.1292	0.06	0.0346	0.3625	0.0936	0.054	1	10

SD = Standard deviation.
SEM = Standard error of the mean.

[00355] **Apoptosis assay for HN Cancer Cell lines.** Prior to testing, cells were grown and expanded in culture flasks to provide sufficient amounts of starting material. Cells were then diluted to their desired densities and added directly to compound-spotted 384-well plates. Cells were allowed to grow for 24 hours in 5% CO_2 at 37°C. The apoptotic response was assessed by quantifying the activities of caspase 3 and caspase 7 (Caspase 3/7-Glo) in treated cells and control cells at the 24-hour time point. All data was normalized and represented as a value relative to the DMSO-treated cells. Results were then expressed

as CalX, which is the minimum compound concentration required to double the levels of caspase 3/7 relative to those of the DMSO-treated cells during their treatment period.

[00356] Results for Compound 1 for induction of apoptosis in selected HN cancer cell lines are set forth in Table 2.

Table 2

HNC Cell Line	n	CalX μM
A253	1	>10
BHY	1	>10
CAL-27	1	>10
CAL-33	1	0.8764
Detroit562	1	>10
FADU	1	>10
HN	1	>10
RPMI-2650	1	>10
SCC-15	1	>10
SCC-25	1	>10
SCC-9	1	>10

[00357] **Proliferation and apoptosis assay using patient tumor cells**. Cryopreserved patient-derived tumor cells were resurrected from liquid nitrogen storage and conditioned on coated plates prior to drug treatment. Anti-proliferative potential of the compound was assessed by adding 3 fold dilutions of an initial concentration (30 μM) of the compound, for example, Compound 1. The mitotic activity of the cells was assessed by measuring ethynyl dioxyuridine (EdU) incorporation during S-phase. The untreated control wells received medium containing DMSO (vehicle used to dissolve each compound and EdU). Potential apoptosis activation by the compound was analyzed by adding 10 fold dilutions of an initial concentration of the compound (e.g. Compound 1) at 10 μM. The apoptotic activity of the cells was assessed by measuring CellEvent incorporation due to caspase 3 and 7 activation. The untreated control wells received medium containing DMSO (vehicle used to dissolve each compound and CellEvent). After conditioning, cell lines were plated on a 3D matrix in two 96-well plates. The cells were allowed to settle and form

spheroid structures for 48 hours. Then, 48 hours after plating, the cells were treated with compound.

[00358] **Proliferation Assay.** The cells were treated only on Day 1. For the last 48 hours of the treatment, EdU was added to measure the cell proliferation. At the end of the treatment, plates were fixed, permeabilized and stained for EdU uptake (proliferation marker) and DAPI (nuclear marker). Plates were imaged at 4X magnification using ImageXpress Micro (Molecular Devices, Sunnyvale, CA). Seven z-stacks at 5 sites per well were captured and deconvoluted to create the images for analysis. For the proliferation assay, images were analyzed using a Multi Wave Scoring Algorithm (Molecular Devices, Sunnyvale, CA) to quantify mean fluorescent intensities (MFI) of each well for EdU. The EdU MFI's for the treated wells were normalized to those of the untreated wells to generate the compound response curves. As shown in Table 3, Compound 1 showed inhibition of proliferation of patient tumor cells, with IC_{50} values ranging from ~100 to 1800 nM.

Apoptosis Assay. The cells were treated only on Day 1. After 48 hours of compound treatment, CellEvent was added to measure the apoptotic activity in cells. After 1 hour of incubation with CellEvent, cells were stained with Hoechst (nuclear staining) for 15 minutes. Plates were imaged at 4X magnification using ImageXpress Micro (Molecular Devices, Sunnyvale, CA). Seven z-stacks at 3 sites per well are captured and deconvoluted to create the images for analysis. For the Apoptosis assay, images were analyzed using a Multi Wavelength Scoring Algorithm (Molecular Devices, Sunnyvale, CA) to quantify mean fluorescent intensities (MFI) of each well for activated caspase 3 and 7 using CellEvent. The CellEvent mean fluorescence intensities (MFI) of treated wells and untreated controls were averaged and plotted. Apoptosis was observed in some patient-derived samples treated with compound 1 at a concentration between 0.1 – 10 μM.

Table 3

Age/Gender	**Clinical Diagnosis**	**Collection Site**	**Prolif IC_{50} (nM)**

71 y, male	Squamous cell tongue	Right axilliary node	317.9
77 y, male	Squamous cell H&N	Right pleural biopsy	441.1
Unknown	Not specified	Left palate	546.9
60 y, male	Squamous cell H&N	Left neck lymph node	498.9
67 y, male	H&N carcinoma	Lung	341.9
70 y, male	H&N carcinoma	Left superior segment	260.0
54 y, male	Squamous carcinoma H&N	Right nasal	240.5
54 y, female	Squamous cell H&N	Cervical lymph node	145.7
45 y, female	Tongue	Left neck mass	376.8
54 y, male	Squamous cell H&N	Mass, skull base excision	157.2
44 y, female	Squamous cell H&N	Left neck, cervical	428.7
74 y, female	Squamous cell H&N	Right lower lobe lung	322.2
56 y, male	Squamous carcinoma H&N	Right lower lobe lung	139.3
51 y, male	Squamous carcinoma H&N	Neck	1717.0
44 y, male	Squamous cell H&N	Left chest wall	156.6
63 y, male	Squamous cell H&N	Pleural fluid	536.4
53 y, male	Larynx carcinoma	Left side neck	103.4
36 y, female	Squamous cell H&N	Mass, left latisimal muscle	115.4
43 y, male	Squamous cell H&N	Left tonsil	161.9

5.1.3 5.1.3 In vivo Assays:

[00359] Xenograft studies are conducted with different head and neck squamous cell carcinoma (HNSCC) tumor-bearing mice. SCID or nude mice are inoculated subcutaneously with HNSCC cells (eg. FaDu, Cal-33, Cal-27) in the flank region above the right hind leg. Following inoculation of the animals, the tumors are allowed to grow to about 150 - 200 mm^3 prior to randomization. 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 once daily (QD) for 26 - 40 days. Doses of Compound 1 can range between 1 and 5 mg/kg. Tumors are measured twice a week using calipers and tumor volumes are calculated using the formula of $W^2 \times L / 2$ (wherein "W" is tumor width and "L" is tumor length).

5.1.4 Clinical Study

[00360] Phase 1A/1B, Multi-Center, Open-Label, Dose Finding Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Compound 1 Administered Orally to Subjects with Head and Neck Squamous Cell Carcinoma

[00361] Compound 1 will be administered orally to subjects with head and neck squamous cell carcinoma. The safety and tolerability of Compound 1 in humans, as well as the efficacy, will be evaluated in this study. The study will be conducted in two parts: dose escalation (Part A) and dose expansion (Part B). Subjects will be enrolled sequentially in Part A. Enrollment in Part B will be stratified by tumor type.

[00362] Compound 1 will be available in three strengths (0.25 mg, 1.0 mg and 5.0 mg) presented in gelatin capsules containing only the active pharmaceutical ingredient. The capsules will be packaged in high density polyethylene (HDPE) bottles, fitted with induction seals and child-resistant polypropylene closures. Research pharmacists will repackage and dispense appropriately for each subject.

[00363] Between 30 and 60 subjects will be enrolled in Part A, designed to establish initial toxicity.

[00364] Part B will consist of approximately 100 subjects with prespecified types of tumors, including head and neck squamous cell carcinoma, to further assess the safety profile of Compound 1 and provide efficacy information. Tumor response rate will be assessed by tumor type and dose level. The Part B population will be defined by the efficacy seen during Part A and by data from ongoing preclinical studies.

[00365] The overall study design will be comprised of a Screening Period (Day -28 to Day 1), a Treatment and Evaluation Period (28-day QD (and/or BID) cycles until tumor

progression, unacceptable toxicity or subject/physician decision to discontinue administration of Compound 1) and an End of Treatment and Follow-up Period (end of treatment procedures within 21 days of last dose; follow-up for 28 days after last dose for final safety assessment).

[00366] Subjects will start Compound 1 QD or BID dosing (or other suitable regimen) on Cycle 1 Day 1 and receive daily treatment in 28-day cycles. Compound 1 may be discontinued when there is evidence of tumor progression, but subjects can continue to receive study drug as long as the Investigator considers they are deriving benefit. Compound 1 administration will be discontinued when there is unacceptable toxicity, or the subject decides to withdraw from the study.

[00367] Compound 1 will be administered orally either once or twice daily (or other suitable dosing regimen) with no rest period between cycles. Each QD dose will be taken in the morning with at least 200 mL of water, with the subject having fasted overnight (minimum of 6 hours). Food intake will be delayed until at least 90 minutes after dosing on the days Compound 1 is taken at home. On clinic visit days, the morning Compound 1 dose will be administered in the clinic after any predose tests have been completed. Food may be taken after all fasting tests have been completed but in no case earlier than 90 minutes after dosing (3 hours after dosing on Day 15). For subjects receiving Compound 1 QD where troublesome related GI symptoms, fatigue or other symptoms persist beyond the end of Cycle 1, dosing may be moved to later in the day providing the subject can maintain a 3-hour separation between Compound 1 administration and the last intake of food and a 90-minute delay before ingesting further food. Compound 1 may be taken up to 12 hours late if dosing has been delayed on a single day; otherwise that dose should be omitted.

[00368] Compound 1 will be administered initially as a QD regimen.

[00369] Doses will be administered in an escalating manner following satisfactory review of safety data from the lower doses. There will be a minimum of 28 days after the first dose has been administered to the last subject between dose escalations. Within each

cohort, enrollment will be staggered so that there is a minimum of 24 hours between Cycle 1 Day 1 for each subject in order to evaluate initial toxicity.

[00370] Each cycle of Compound 1 lasts 28 days and there is no rest period between cycles. Subjects may continue to receive Compound 1 for as long as they derive benefit from treatment, as judged by the Investigator. Compound 1 administration will be discontinued when there is evidence of disease progression, unacceptable toxicity or when either the subject or Investigator decides to discontinue it.

[00371] In Part A, cohorts of subjects will initially receive QD ascending doses of Compound 1 to measure PK and to identify the MTD. In Part A, 0.5 mg QD is the Compound 2 starting dose. A modified accelerated titration design (Simon, R., Freidlin, B., Rubinstein, L., et al. Accelerated titration designs for Phase I clinical. trials in oncology, *J Nat Canc Institute* 1997;.89, (15): 1138-1147) will be used to establish initial toxicity. During the accelerated phase, initial cohorts of one subject will be given Compound 1 at dose increments of 100% until the first instance of first-Cycle grade 2 or higher toxicity suspected to be drug-related, at which point the accelerated phase will stop and this particular cohort will be expanded to a total of 6 subjects. Subsequently, a standard escalation dosing schedule with approximately 50% dose increments and 6 subjects per cohort will be initiated in order to establish the NTD and MTD. Smaller increments and additional subjects within a dose cohort may also be evaluated, if necessary, based on toxicity, PK/PD results or tumor biopsy findings.

[00372] Based on interim PK and PD results from initial dose cohorts, a twice-daily (BID) dosing regimen will also be evaluated in part A. This will be initiated in cohorts of 6 subjects at or below a total daily dose level already shown to be tolerable, but divided into two equal doses administered approximately 12 hours apart. Thereafter, dose escalation for QD and BID dosing cohorts may occur independently. Intermittent dosing schedules of comparable or lower dose intensity than continuous daily dosing may also be considered for evaluation.

[00373] A dose will be considered to be non-tolerated if 2 or more out of 6 evaluable subjects in a dose cohort experience DLT during Cycle 1. When a NTD is defined, dose escalation will be stopped. The MTD will be defined as the last dose tested below the NTD with 0 or 1 out of 6 evaluable subjects experiencing DLT during Cycle 1. An intermediate dose (*i.e.*, one between the NTD and the last dose level before the NTD) or additional subjects within any dose cohort may be required to more precisely determine the MTD more precisely, as may alternate regimens if emerging PK-PD results suggest these may be appropriate.

[00374] In Part B, subjects may start Compound 1 on a QD or BID regimen at the MTD and/or lower dose levels based on safety, PK and PD data from Part A. In Part B, approximately 100 subjects will be evaluated for safety and antitumor activity after every two cycles of therapy.

[00375] All subjects who receive at least one dose of Compound 1 will be evaluable for safety. In Part A, a subject evaluable for dose-limiting toxicity (DLT) is defined as one who, in the first 28 days after Cycle 1 dosing began, either (a) received at least 21 of the planned 28 doses of Compound 1 at the cohort-specified dose and has sufficient data for safety evaluation by the SRC, or (b) experienced study drug-related DLT. Non-evaluable subjects will be replaced in the dosing cohort. In Part B, an efficacy evaluable subject for tumor response is defined as one who received at least one cycle of Compound 1, and have baseline and at least one post-baseline efficacy assessment.

[00376] In Parts A and B, dose reductions are permitted in any cycle, including Cycle 1. Dose reductions that occur in Cycle 1 during Part A will constitute DLT, but subjects will be allowed to continue on study drug at the reduced dose. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4, 2009 will be used to grade AEs.

[00377] When a dose reduction is indicated, the next lower dose level will be on a QD or BID schedule will be selected. For BID dose reductions below the starting dose of 10 mg BID, 8 mg BID and 4 mg BID will be selected. Two dose reductions are allowed.

Additional PK evaluations may be conducted at modified dose level(s) in order to characterize intrasubject PK profiles with alternate doses.

[00378] In Part A, intrasubject dose escalation beyond the dose initially assigned to a subject is not permitted in Cycle 1. Those continuing to take Compound 1 beyond Cycle 1 may, following approval by the SRC, have the dose level increased providing the alternative dose level has been shown to be well tolerated by at least one cohort of other subjects in this study. In these instances, additional PK evaluation at the higher dose level may be conducted. In Part B, no dose escalation beyond the MTD is allowed.

[00379] The primary objectives of this Phase 1a/1b study are to determine the safety, tolerability, NTD and MTD of Compound 1 when administered orally to adult subjects and to determine the PK characteristics of oral Compound 1. The secondary objectives are to evaluate the extent of inhibition of phosphorylation of S6RP and/or 4E-BP1 for mTORC1 activity and AKT and/or other relevant biomarkers for mTORC2 activity in blood, skin and/or tumor biopsies/aspirates and to explore the antitumor activity of Compound 1 at selected dose levels/regimens by tumor type. Further secondary objectives are to evaluate the inhibition of DNA-PK activity in skin samples irradiated by UV light and/or tumor biopsies/aspirates using pDNA-PK S2056 and other relevant biomarkers for DNA damage pathways before and during Compound 1 treatment.

[00380] In the following, statistical analyses will be performed by study phase, dose level, dosing regimen and tumor cohort as needed or applicable.

[00381] The study population definitions are as follows: (a) Intent-to-Treat (ITT) Population – All subjects who take at least one dose of Compound 1; (b) Safety Population – All subjects who take at least one dose of Compound 1, which is the same as ITT population for this study; (c) Efficacy Evaluable (EE) Population – All ITT subjects who meet eligibility criteria, complete at least one cycle of Compound 1, and have baseline and at least one valid post-baseline efficacy assessment.

[00382] Subject enrollment will be curtailed when up to 20 evaluable subjects have been enrolled in each tumor type and dose level/regimen. In Part B as a whole, sample sizes

are not based on statistical calculation but rather on clinical empirical and practical considerations traditionally used for Phase 1 studies of this kind.

[00383] All efficacy evaluable subjects in the Part B portion will be included for efficacy analysis. Efficacy will be analyzed by each tumor type once all subjects have withdrawn from the study or completed 6 cycles. Two-sided ninety-five percent confidence intervals of the response rate will be provided by tumor type. A case-by-case description of all subjects who exhibited a complete or partial response during the Part A segment will be provided. A descriptive analysis of other evidence of anti-tumor activity will be provided based on clinical, radiographic, and biologic assessments of efficacy.

[00384] Subjects will be evaluated for efficacy during even-numbered cycles. The primary efficacy variable is response rate. Tumor response will be based on RECIST 1.1. Other supplementary efficacy variables, including CTC assessments, will be summarized using frequency tabulations for categorical variables or descriptive statistics for continuous variables.

[00385] For both the dose escalation and dose expansion parts of this protocol, inclusion criteria are: (a) Understand and voluntarily sign an informed consent document before any study-related assessments/procedures are conducted; (b) Men and women, 18 years or older, with histological or cytological confirmation of head and neck squamous cell carcinoma; (c) Consent to screening tumor biopsy; (d) ECOG PS of 0 or 1; (e) The following laboratory values: (1) Absolute neutrophil count (ANC) $\geq$ 1.5 x 109/L; (2) Hemoglobin (Hgb) $\geq$ 9 g/dl; (3) Platelets (plt) $\geq$ 100 x 109/L; (4) Potassium within normal range, or correctable with supplements; (5) AST/SGOT and ALT/SGPT $\leq$ 2.5 x Upper Limit of Normal (ULN) or $\leq$ 5.0 x ULN if liver tumor is present; (6) Serum total bilirubin $\leq$ 1.5 x ULN; (7) Serum creatinine $\leq$ 1.5 x ULN, or 24-hr clearance $\geq$ 50 mL/min; and (8) Negative serum or urine pregnancy test within 72 hrs before starting study treatment in females of childbearing potential; and (f) Able to adhere to the study visit schedule and other protocol requirements.

[00386] For the dose expansion part (Part B) of this protocol, inclusion criteria are: (a) Subject consent to retrieve formalin-fixed, paraffin-embedded (FFPE) archival tumor tissue, either in tumor blocks or sectioned/mounted specimens; and (b) Histologically-confirmed head and neck squamous cell carcinoma (locally advanced, recurrent or metastatic, squamous cell carcinoma of the head and neck not amenable to curative surgical resection; measurable disease according to RECIST v1.1; must have received at least one prior line of platinum-based chemotherapy; cohort may be expanded to enroll a minimum of 5 subjects with tumors with DNA-PK overexpression; and consent to undergo paired (screening and on-treatment) tumor biopsies).

[00387] For both the dose escalation and dose expansion parts of this protocol, exclusion criteria are: (a) Symptomatic central nervous system metastases; (b) Known acute or chronic pancreatitis; (c) Any peripheral neuropathy ≥ NCI CTCAE grade 2; (d) Persistent diarrhea or malabsorption ≥ NCI CTCAE grade 2, despite medical management. Impaired ability to swallow; (e) Impaired cardiac function or clinically significant cardiac diseases; (f) Diabetes mellitus on active treatment; (g) Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol; (h) Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half lives or 4 weeks, whichever is shorter, prior to starting study drug or who have not recovered from side effects of such therapy; (i) Major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy; (j) Pregnancy or breast feeding; (k) Adults of reproductive potential not employing two forms of birth control; (l) Known HIV infection; (m) Known chronic hepatitis B or C virus (HBV/HCV) infection, unless this is comorbidity in subjects with HCC; (n) Any significant medical condition, laboratory abnormality, or psychiatric illness, including the inability to swallow capsules, that would prevent subjects from participating in the study; (o) Any condition including the presence of laboratory abnormalities, which places subjects at unacceptable risk if they were to participate in the study; (p) Any condition that confounds the ability to interpret study data; or (q) Concurrent

active second malignancy for which the subject is receiving therapy, excluding non-melanomatous skin cancer or carcinoma in situ of the cervix.

[00388] For the dose expansion part (Part B) of this protocol, exclusion criteria are: Prior treatment with agents targeting both mTOR complexes (dual TORC1+TORC2 inhibitors) and/or PI3K/AKT pathways. However, prior treatment with isolated TORC1 inhibitors (e.g., rapalogs) is allowed in both parts of this study.

[00389] 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 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.

[00390] 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.

CLAIMS

What is claimed is:

1. A method for treating head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma.

2. The method of claim 1, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated.

3. The method of claim 2, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

4. The method of claim 1, wherein said patient is administered about 0.5 mg/day to about 128 mg/day of a TOR kinase inhibitor.

5. The method of claim 4, wherein said patient is administered 0.5 mg/day, 1 mg/day, 2 mg/day, 4 mg/day, 8 mg/day, 16 mg/day, 20 mg/day, 30 mg/day, 45 mg/day, 60 mg/day, 90 mg/day, 120 mg/day or 128 mg/day of a TOR kinase inhibitor.

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

7. A method for improving the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) of a patient, comprising administering an effective amount of a TOR kinase inhibitor to a patient having head and neck squamous cell carcinoma.

8. The method of claim 7, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated.

9. The method of claim 8, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

10. A method for inhibiting phosphorylation of S6RP, 4E-BP1 and/or AKT in a biological sample of a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in a biological sample of a patient obtained prior to and after administration of said TOR kinase inhibitor, wherein less phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained after administration of said TOR kinase inhibitor relative to the amount of phosphorylated S6RP, 4E-BP1 and/or AKT in said biological sample obtained prior to administration of said TOR kinase inhibitor indicates inhibition.

11. The method of claim 10, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated.

12. The method of claim 11, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

13. A method for inhibiting DNA-dependent protein kinase (DNA-PK) activity in a skin sample of a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient and comparing the amount of phosphorylated DNA-PK in a biological sample of a patient obtained prior to

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

14. The method of claim 13, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated.

15. The method of claim 14, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

16. A method for measuring inhibition of phosphorylation of S6RP, 4E-BP1 or AKT in a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient, measuring the amount of phosphorylated S6RP, 4E-BP1 or AKT in said patient, and comparing said amount of phosphorylated S6RP, 4E-BP1 or AKT to that of said patient prior to administration of an effective amount of a TOR kinase inhibitor.

17. The method of claim 16, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated.

18. The method of claim 17, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

19. A method for measuring inhibition of phosphorylation of DNA-PK S2056 in a skin sample of a patient having head and neck squamous cell carcinoma, comprising administering an effective amount of a TOR kinase inhibitor to said patient, measuring the

amount of phosphorylated DNA-PK S2056 present in the skin sample and comparing said amount of phosphorylated DNA-PK S2056 to that in a skin sample from said patient prior to administration of an effective amount of a TOR kinase inhibitor.

20. The method of claim 19, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated.

21. The method of claim 20, wherein the head and neck squamous cell carcinoma is that in which the PI3K/mTOR pathway is activated due to PTEN loss, a PIK3Ca mutation or EGFR overexpression, or a combination thereof.

22. A kit comprising a TOR kinase inhibitor and means for monitoring patient response to administration of said TOR kinase inhibitor, wherein said patient has head and neck squamous cell carcinoma.