TITLE

IDENTIFICATION OF LKB1 MUTATION AS A PREDICTIVE BIOMARKER FOR SENSITIVITY TO TOR KINASE INHIBITORS

1. CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/301,150, filed February 3, 2010, and claims the benefit of U.S. Provisional Application No. 61/362,982, filed July 9, 2010, the entire contents of each of which are incorporated herein by reference.

2. FIELD

[0002] Provided herein are methods for treating and/or preventing a cancer or a tumor syndrome in a patient, comprising administering an effective amount of a TOR kinase inhibitor to a patient having cancer or a tumor syndrome, characterized by a LKB1 and/or AMPK gene or protein loss or mutation.

3. 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, *Nat. Rev. Drug Disc.*, 1:309-315 (2002), Grimmiger *et al. Nat. Rev. Drug Disc.* 9(12):956-970 (2010). 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 belong to 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. Pharm. Res.* 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] Protein kinases can be divided into broad groups based upon the identity of the amino acid(s) that they target (serine/threonine, tyrosine, lysine, and histidine). For example, tyrosine kinases include receptor tyrosine kinases (RTKs), such as growth factors and non-receptor tyrosine kinases, such as the src kinase family. There are also dual-specific protein kinases that target both tyrosine and serine/threonine, such as cyclin dependent kinases (CDKs) and mitogen-activated protein kinases (MAPKs).

[0006] 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.

[0007] Protein kinases have become attractive targets for the treatment of cancers. Fabbro *et al. Pharm. Ther.* 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.*, *Pharm. Ther.* 93:79-98 (2002).

[0008] 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.

[0009] The protein named mTOR (mammalian target of rapamycin), 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 everolimus was approved in 2009 for renal cell carcinoma patients that have progressed on vascular endothelial growth factor receptor inhibitors. In addition, sirolimus was approved in 1999 for the prophylaxis of renal transplant rejection. The interesting but limited clinical success of these mTORC1 inhibitory compounds demonstrates the usefulness of mTOR inhibitors in the treatment of cancer and transplant rejection, and the increased potential for compounds with both mTORC1 and mTORC2 inhibitory activity.

[0010] Somatic mutations affect key pathways in lung cancer. Accordingly, identification of specific mutations associated with lung cancer may lead to improved therapeutic protocols. Recent studies have uncovered a large number of somatic mutations of the LKB1 gene that are present in lung, cervical, breast, intestinal, testicular, pancreatic and skin cancer

(Distribution of somatic mutations in STK11, Catalogue of Somatic Mutations in Cancer, Wellcome Trust Genome Campus, Hinxton, Cambridge).

[0011] 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.

4. SUMMARY

[0012] In one aspect, the present invention refers to the use of a TOR kinase inhibitor in the manufacture of a medicament for treating non-small cell lung carcinoma, in a patient having non-small cell lung carcinoma characterized by a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In another aspect, the present invention refers to an *in vitro* method for predicting the likelihood of a patient having non-small cell lung carcinoma being responsive to TOR kinase inhibitor therapy, comprising screening said patient's carcinoma for the presence of a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the presence of LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said non-small cell lung carcinoma or cervical cancer, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In yet another aspect, the present invention refers to an *in vitro* method for predicting therapeutic efficacy of treatment of a patient having non-small cell lung carcinoma with a TOR kinase inhibitor, comprising screening said patient's carcinoma or cancer for the presence of a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the presence of LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In yet another aspect, the present invention refers to the use of a TOR kinase inhibitor and use of one or more agents that module AMP levels, glucose uptake, metabolism or a stress response in the manufacture of a medicament for treating non- small cell lung carcinoma, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl) -3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically

acceptable salt, stereoisomer, or tautomer thereof. In yet another aspect, the present invention refers to a kit comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, an AMPK gene loss, AMPK protein loss, AMPK gene mutation, or AMPK protein mutation, or both, relative to wild type, in a patient's cancer or in a patient having a tumor syndrome and instructions for detecting LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, AMPK gene loss, AMPK protein loss, AMPK gene mutation, or AMPK protein mutation, or both, in a patient's cancer or in a patient having a tumor syndrome, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

Provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having a cancer or a tumor syndrome characterized by a LKB1 gene or protein loss or mutation, relative to that of a control patient or wild type.

[0013] Further provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's cancer for the presence of LKB1 gene or protein loss or mutation relative to that of a control patient or wild type and administering an effective amount of a TOR kinase inhibitor to the patient having a cancer characterized by the LKB1 gene or protein loss or mutation.

[0014] Further provided herein are methods for detecting LKB1 gene or protein loss or mutation in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of LKB1 mRNA expression, the level of LKB1 protein expression, determining the methylation status of the LKB1 gene or otherwise identifying the presence of gene or protein loss or mutation (e.g., by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss, or immunohistochemistry (IHC), immunofluorescence (IF) or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a LKB1 gene or protein loss or mutation (wild type); wherein a change in LKB1 mRNA expression, LKB1 protein expression, LKB1 mRNA structure, LKB1 gene methylation status and/or LKB1 protein structure in the biological sample

from the test patient, relative to that of the control patient or wild-type, indicates the presence of LKB1 gene or protein loss or mutation in the test patient's cancer.

[0015] Further provided herein are methods for predicting the likelihood of a patient having a cancer, for example non-small cell lung carcinoma or cervical cancer, being responsive to TOR kinase inhibitor therapy, comprising screening said patient's cancer for the presence of a LKB1 gene or protein loss or mutation relative to that of a control patient or wild type, wherein the presence of LKB1 gene or protein loss or mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said cancer.

[0016] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having cancer, for example non-small cell lung carcinoma or cervical cancer, with a TOR kinase inhibitor, comprising screening said patient's cancer for the presence of LKB1 gene or protein loss or mutation relative to that of a control patient or wild type, wherein the presence of LKB1 gene or protein loss or mutation in the patient's cancer is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[0017] Further provided herein are methods for treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising screening the patient for the presence of a LKB1 gene or protein loss or mutation relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having the LKB1 gene or protein loss or mutation.

[0018] Further provided herein are methods for detecting LKB1 gene or protein loss or mutation in a patient ("test patient") having a tumor syndrome, for example, Peutz-Jeghers Syndrome, comprising: obtaining a biological sample from the test patient; measuring one or more of the level of LKB1 mRNA expression, the level of LKB1 protein expression, determining the methylation status of the LKB1 gene or otherwise identifying the presence of gene or protein loss or mutation (*e.g.*, by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss, or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient ("control patient") without the LKB1 gene or protein loss or mutation (wild type); wherein a change in LKB1 mRNA

expression, LKB1 protein expression, LKB1 mRNA structure, LKB1 gene methylation status and/or LKB1 protein structure in the biological sample from the test patient, relative to that of the control patient or wild-type, indicates the presence of LKB1 gene or protein loss or mutation in the test patient.

[0019] Further provided herein are methods for predicting the likelihood of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, being responsive to TOR kinase inhibitor therapy, comprising screening said patient for the presence of LKB1 gene or protein loss or mutation relative to that of a control patient or wild type, wherein the presence of LKB1 gene or protein loss or mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said tumor syndrome.

[0020] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, with a TOR kinase inhibitor, comprising screening said patient for the presence of LKB1 gene or protein loss or mutation relative to that of a control patient or wild type, wherein the presence of LKB1 gene or protein loss or mutation in the patient is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[0021] Provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having a cancer or a tumor syndrome characterized by AMPK gene or protein loss or mutation, relative to that of a control patient or wild type.

[0022] Provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having a cancer or a tumor syndrome characterized by a reduced level of phospho-AMPK (pAMPK) protein and/or AMPK activity relative to that of a control patient or wild type. In one example, the pAMPK is pAMPK T172.

[0023] Further provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's

cancer for the presence of AMPK gene or protein loss or mutation relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having a cancer characterized by the AMPK gene or protein loss or mutation.

[0024] Further provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's cancer for the presence of a reduced level of pAMPK protein and/or AMPK activity relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having a cancer characterized by a reduced level of pAMPK protein and/or AMPK activity. In one example, the pAMPK is pAMPK T172.

[0025] Further provided herein are methods for detecting AMPK gene or protein loss or mutation in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of AMPK mRNA expression, the level of AMPK protein expression, determining the methylation status of the AMPK gene, or otherwise identifying the presence of gene or protein loss or mutation (e.g., by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss, or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a AMPK gene or protein or mutation (wild type); wherein a change in AMPK mRNA expression, AMPK protein expression, AMPK mRNA structure, AMPK gene methylation, and/or AMPK protein structure in the biological sample from the test patient, relative to that of a control patient or wild type, indicates the presence of AMPK gene or protein loss or mutation in the test patient's cancer.

[0026] Further provided herein are methods for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of, pAMPK protein expression, the level of AMPK activity, or otherwise measuring the level of pAMPK protein (e.g., immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine the

amount of pAMPK protein or the amount of phosphorylation of AMPK at specific sites, for example at the T172 site), and/or the level of AMPK activity (e.g. AMPK kinase assay, see Sanders *et al. Biochem.J.* 403:139-148 (2007)); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a reduced level of pAMPK protein and/or AMPK activity (wild type); wherein a lower level of pAMPK protein and/or AMPK activity in the biological sample from the test patient, relative to that of a control patient or wild type, indicates the presence of a reduced level of pAMPK protein and/or AMPK activity in the test patient's cancer.

[0027] Further provided herein are methods for predicting the likelihood of a patient having a cancer, for example non-small cell lung carcinoma or cervical cancer, being responsive to TOR kinase inhibitor therapy, comprising screening said patient's cancer for the presence of a AMPK gene or protein loss or mutation, relative to that of a control patient or wild type, wherein the presence of AMPK gene or protein loss or mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said cancer.

[0028] Further provided herein are methods for predicting the likelihood of a patient having a cancer, for example non-small cell lung carcinoma or cervical cancer, being responsive to TOR kinase inhibitor therapy, comprising screening said patient's cancer for the presence of a reduced level of pAMPK protein and/or AMPK activity relative to that of a control patient or wild type, wherein the presence of a reduced level of pAMPK protein and/or AMPK activity predicts an increased likelihood that TOR kinase inhibitor therapy will treat said cancer.

[0029] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having cancer, for example non-small cell lung carcinoma or cervical cancer, with a TOR kinase inhibitor, comprising screening said patient's cancer for the presence of AMPK gene or protein loss or mutation relative to that of a control patient or wild type, wherein the presence of AMPK gene or protein loss in the patient's cancer is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[0030] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having cancer, for example non-small cell lung carcinoma or cervical cancer, with a TOR kinase inhibitor, comprising screening said patient's cancer for the presence

of a reduced level of pAMPK protein and/or AMPK activity relative to that of a control patient or wild type, wherein the presence a reduced level of pAMPK protein and/or AMPK activity in the patient's cancer is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[0031] Further provided herein are methods for treating or preventing cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor and an effective amount of one or more agents that modulate AMP levels, glucose uptake, metabolism or a stress response to a patient having cancer or a tumor syndrome.

[0032] Further provided herein are pharmaceutical compositions comprising one or more TOR kinase inhibitors and one or more agents that modulate AMP levels, glucose uptake, metabolism or a stress response and a pharmaceutically acceptable carrier, excipient or diluent.

[0033] Further provided herein are kits comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting LKB1 gene or protein loss or mutation, or AMPK gene or protein loss or mutation, or both, in a patient's cancer or in a patient having a tumor syndrome and instructions for detecting LKB1 gene or protein loss or mutation, or AMPK gene or protein loss or mutation, or both, in a patient's cancer or in a patient having a tumor syndrome.

[0034] Further provided herein are kits comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's cancer or in a patient having a tumor syndrome, and instructions for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's cancer or in a patient having a tumor syndrome.

[0035] In some examples, the TOR kinase inhibitor is a compound as described herein.

[0036] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

5. BRIEF DESCRIPTION OF THE DRAWINGS

[0037] **FIG 1A.** Figure 1 lists the LKB1 mutation status of non small cell lung cancer (NSCLC) cell lines, based on reported DNA sequences, the reported mutation, the presence (positive) or absence (negative) of intact LKB1 protein (as determined by Western immunoblotting as shown in Fig. 1B) and mean IC_{50} values (μM) for growth inhibition by Compound 1 (n is number of replicate IC_{50} determinations).

[0038] **FIG 1B.** Figure 1B illustrates a LI-COR Western blot showing LKB1 protein levels across the panel of NSCLC cell lines from Fig. 1A. The experiment confirms lack of LKB1 protein for lines reported as LKB1 gene mutants.

[0039] **FIG 2A.** Figure 2A illustrates the correlation of sensitivity to TOR kinase inhibitor Compound 1 treatment (IC_{50}) with reported LKB1 gene mutation status, as determined by Kruskal test ($p= 0.0296$).

[0040] **FIG 2B.** Figure 2B illustrates the correlation of sensitivity to TOR kinase inhibitor Compound 1 treatment (IC_{50}) with the presence (positive) or absence (negative) of LKB1 protein as assessed by LI-COR Western immunoblotting, as determined by the Wilcoxon test ($p= 0.0128$).

[0041] **FIG 2C.** Figure 2C illustrates the application of the Fisher test and Wilcoxon test to analyze the correlation between Compound 1 sensitivity (defined as IC_{50} <5 μM) and the presence or absence of intact LKB1 protein (as determined by Western immunoblotting). The resulting p-values indicate that cell lines without intact LKB1 protein are more sensitive to Compound 1.

[0042] FIG 3A. Figure 3A illustrates a LI-COR Western blot showing phospho- AMPK T172, AMPK, LKB1, and actin levels from selected NSCLC cell lines. The LKB1 protein levels are correlated to pAMPK T172 levels except for H1437.

[0043] FIG 3B. Figure 3B illustrates the result of the application of the Wilcoxon test to analyze the correlation between LKB1 status and pAMPK/actin ratio in forty-two NSCLC cell lines. LKB1 status was defined as either negative or positive based on Western immunoblotting. The y-axis is Log_{10} of pAMPK/actin ratio. The correlation between LKB1 protein status and

pAMPK/actin ratio was assessed using Wilcoxon test (p=0.000278), wherein a p value < 0.05 is considered as significant correlation.

6. DETAILED DESCRIPTION

6.1 DEFINITIONS

[0044] 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 unsaturated 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≡CH, -C≡C(CH_3), -C≡C(CH_2CH_3), -CH_2C≡CH, -CH_2C≡C(CH_3) and -CH_2C≡C(CH_7CH_3), among others. An alkyl group can be substituted or unsubstituted. Unless otherwise indicated, 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); 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, or O(alkyl)aminocarbonyl.

[0045] 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.

[0046] 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.

[0047] 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).

[0048] 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.

[0049] A "heterocyclyl" is an aromatic (also referred to as heteroaryl) or non-aromatic cycloalkyl in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N. In some embodiments, heterocyclyl groups include 3 to10 ring members, whereas other such groups have 3 to 5, 3 to 6, or 3 to 8 ring members. Heterocyclyls can also be bonded to other groups at any ring atom (*i.e.*, at any carbon atom or heteroatom of the heterocyclic ring). A heterocyclylalkyl group can be substituted or unsubstituted. Heterocyclyl groups encompass unsaturated, partially saturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl and imidazolidinyl groups. The phrase heterocyclyl includes fused ring species, including those comprising fused aromatic and non-aromatic groups, such as, for example, benzotriazolyl, 2,3-dihydrobenzo[1,4]dioxinyl, and benzo[1,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Representative examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidinyl, pyrrolidyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl (for example, tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathiane, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, homopiperazinyl, quinuclidyl, indolyl, indolinyl, isoindolyl, azaindolyl (pyrrolopyridyl), indazolyl, indolizinyl, benzotriazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiinyl, benzoxathiinyl, benzothiazinyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[1,3]dioxolyl, pyrazolopyridyl,

imidazopyridyl (azabenzimidazolyl; for example, 1H-imidazo[4,5-b]pyridyl, or 1H-imidazo[4,5-b]pyridin-2(3H)-onyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthalenyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, and tetrahydroquinolinyl groups. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed below.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] A "halogen" is fluorine, chlorine, bromine or iodine.

[0054] A "hydroxyalkyl" group is an alkyl group as described above substituted with one or more hydroxy groups.

[0055] An "alkoxy" group is -O-(alkyl), wherein alkyl is defined above.

[0056] An "alkoxyalkyl" group is -(alkyl)-O-(alkyl), wherein alkyl is defined above.

[0057] An "amino" group is a radical of the formula: $-NH_2$.

[0058] An "alkylamino" group is a radical of the formula: -NH-alkyl or $-N(alkyl)_2$, wherein each alkyl is independently as defined above.

[0059] A "carboxy" group is a radical of the formula: -C(O)OH.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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).

[0066] 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.

[0067] 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.

[0068] 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.

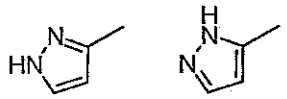
[0069] As used herein and unless otherwise indicated, the term "prodrug" means a TOR kinase inhibitor derivative that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound, particularly a TOR kinase inhibitor. Examples of prodrugs 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).

[0070] 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).

[0071] 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.

[0072] "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:



[0073] 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.

[0074] 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.

[0075] "Treating" as used herein, means an alleviation, in whole or in part, of symptoms associated with a disorder or disease (*e.g.*, cancer or a tumor syndrome), or slowing, or halting of further progression or worsening of those symptoms.

[0076] "Preventing" as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or disorder (*e.g.*, cancer), or a symptom thereof.

[0077] 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 cancer, for example non-small cell lung carcinoma or cervical cancer, or a tumor syndrome, for example Peutz-Jeghers Syndrome, or slowing or halting further progression or worsening of those

symptoms, or preventing or providing prophylaxis for cancer, for example non-small cell lung carcinoma or cervical cancer, or a tumor syndrome, for example Peutz-Jeghers Syndrome in a subject at risk for cancer, for example non-small cell lung carcinoma or cervical cancer, or a tumor syndrome, for example Peutz-Jeghers Syndrome. 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.

[0078] 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.

[0079] As used herein "wild type" refers to the typical or most common form of a characteristic (for example, gene sequence or presence, or protein sequence, presence, level or activity), as it occurs in nature, and the reference against which all others are compared. As will be understood by one skilled in the art, when used herein, wild type refers to the typical sequence of LKB1 gene or protein or AMPK gene or protein, or the typical level of LKB1 gene or protein, AMPK gene or protein, pAMPK protein, or AMPK activity, as it most commonly occurs in nature. Similarly, a "control patient", as used herein, is a patient who possesses the wild type characteristics (presence, sequence, level, activity) for LKB1 and/or AMPK. For example, as used herein "LKB1 gene or protein mutation" refers to, for example, a LKB1 gene mutation resulting in a decrease in LKB1 mRNA expression, a decrease in LKB1 protein production or a non-functional LKB1 protein, as compared to wild type. As used herein "LKB1 gene or protein loss" refers to a reduced level of LKB1 protein or the absence of LKB1 protein, as compared to wild type levels.

[0080] As used herein, "AMPK activity" refers to the activity of AMP-activated protein kinase. As understood by one skilled in the art, AMPK requires activation by phosphorylation to

exert its kinase activity. In the context of AMPK activity, it is understood that AMPK activity and pAMPK activity can be used interchangeably.

[0081] As used herein "reduced level" or "loss" means a reduction in level relative to levels observed in wild type. In one embodiment the reduction is 10% - 50% or 50%-100%. In some embodiments, the reduction is 20%, 30%, 40%, 50%, 60%, 70%, 80%. 90% or 100% (complete loss) relative to wild type.

[0082] In one embodiment, a "patient" or "subject" is a human whose cancer DNA comprises a LKB1 and/or an AMPK gene mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human whose cancer DNA contains a LKB1 and/or an AMPK gene mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human whose cancer DNA comprises a LKB1 and/or an AMPK gene mutation and a KRAS gene mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human having a cancer, for example non-small cell lung carcinoma or cervical cancer, characterized by LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human having a cancer, for example non-small cell lung carcinoma or cervical cancer, characterized by LKB1 and/or AMPK gene or protein loss or mutation and a KRAS gene mutation, relative to that of a control patient or wild type.

[0083] In another embodiment, a "patient" or "subject" is a human whose DNA comprises a LKB1 and/or an AMPK gene mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human whose DNA contains a LKB1 and/or an AMPK gene mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human whose DNA comprises a LKB1 and/or an AMPK gene mutation and a KRAS gene mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human having LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human having LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type, and also having a tumor syndrome, for example Peutz-Jeghers Syndrome. In another embodiment, a "patient" or

"subject" is a human having LKB1 and/or AMPK gene or protein loss or mutation and a KRAS gene mutation, relative to that of a control patient or wild type, wherein said human also has a tumor syndrome, for example Peutz-Jeghers Syndrome.

[0084] In another embodiment, a "patient" or "subject" is a human having a cancer, for example non-small cell lung carcinoma or cervical cancer, characterized by a reduced level of pAMPK protein and/or AMPK activity, relative to that of a control patient or wild type. In another embodiment, a "patient" or "subject" is a human having a cancer, for example non-small cell lung carcinoma or cervical cancer, characterized by a reduced level of pAMPK protein and/or AMPK activity and a KRAS gene mutation, relative to that of a control patient or wild type. In some embodiments, the pAMPK is pAMPK T172.

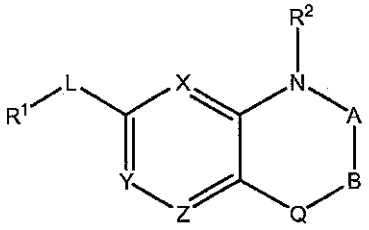
[0085] In another embodiment, a "patient" or "subject" is a human having a reduced level of pAMPK protein and/or AMPK activity, relative to that of a control patient or wild type, and also having a tumor syndrome, for example Peutz-Jeghers Syndrome. In another embodiment, a "patient" or "subject" is a reduced level of pAMPK protein and/or AMPK activity and a KRAS gene mutation, relative to that of a control patient or wild type , wherein said human also has a tumor syndrome, for example Peutz-Jeghers Syndrome. In some embodiments, the pAMPK is pAMPK T172.

[0086] In the context of cancer, for example non-small cell lung carcinoma or cervical cancer, or a tumor syndrome, for example Peutz-Jeghers Syndrome, inhibition may be assessed by 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, among others. 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 cancer, carcinoma or tumor altogether or preventing the onset of a preclinically evident stage of cancer, carcinoma or tumor in individuals at risk. 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 the cancer, carcinoma or tumor.

6.2 TOR KINASE INHIBITORS

[0087] The compounds provided herein are generally referred to as TOR kinase inhibitors or "TORKi." In a specific embodiment, the TORKi do not include rapamycin or rapamycin analogs (rapalogs). In certain embodiments, compounds provided herein are also DNA-PK inhbitors or "DNA-PKi."

[0088] 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.

[0089] In one embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-CH_2C(O)NH-$.

[0090] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)CH_2NH-$.

[0091] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)NH-.

[0092] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-CH_2C(O)O-$.

[0093] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)CH_2O-$.

[0094] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form -C(O)O-.

[0095] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein -A-B-Q- taken together form $-C(O)NR^3-$.

[0096] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein Y is CR^3.

[0097] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CR^3.

[0098] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are N and Y is CH.

[0099] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Z are CH and Y is N.

[00100] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein Y and Z are CH and X is N.

[00101] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein X and Y are CH and Z is N.

[00102] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00103] 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.

[00104] 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.

[00105] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^1 is H.

[00106] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is substituted C_{1-8}alkyl.

[00107] 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.

[00108] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is methyl or ethyl substituted with substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00109] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is C_{1-4}alkyl substituted with substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl.

[00110] 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.

[00111] 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.

[00112] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein R^2 is H.

[00113] In another embodiment, the TOR kinase inhibitors of formula (I) are those wherein L is a direct bond.

[00114] 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.

[00115] 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.

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

[00123] 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.

[00124] 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.

[00125] 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.

[00126] 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, $C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, aryl or cycloalkyl, and L is NH.

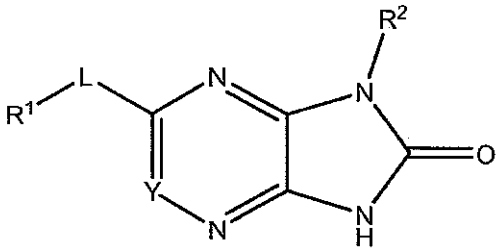
[00127] In another embodiment, the TOR kinase inhibitors of formula (I) do not include compounds wherein X and Z are both N and Y is CH, -A-B-Q- is -C(O)NR^3-, R^2 is H, substituted or unsubstituted $C_{1\text{-}8}$alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclylalkyl, and L is NH.

[00128] In another embodiment, the TOR kinase inhibitors of formula (I) do not include compounds wherein R^1 is a substituted or unsubstituted oxazolidinone.

[00129] 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.

[00130] 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.

[00131] In one embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00132] 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.

[00133] 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.

[00134] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is H.

[00135] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is substituted C_{1-8}alkyl.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^2 is H.

[00140] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein Y is CH.

[00141] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein L is a direct bond.

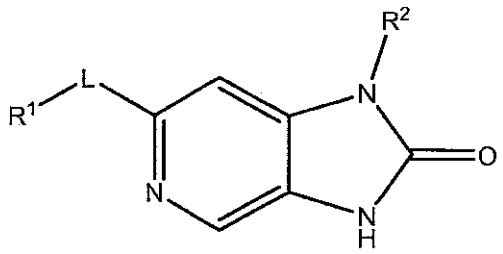
[00142] In another embodiment, the TOR kinase inhibitors of formula (Ia) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted C_{1-8}alkyl.

[00143] 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.

[00144] 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.

[00145] 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.

[00146] 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.

[00147] In one embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00148] 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.

[00149] 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.

[00150] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^1 is H.

[00151] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is substituted C_{1-8}alkyl.

[00152] 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.

[00153] 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.

[00154] 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.

[00155] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein R^2 is H.

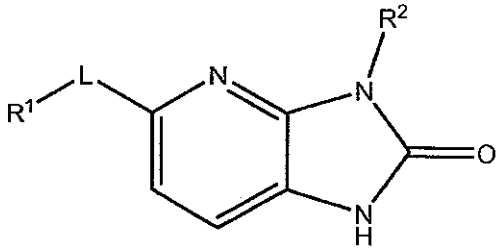
[00156] In another embodiment, the TOR kinase inhibitors of formula (Ib) are those wherein L is a direct bond.

[00157] 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.

[00158] 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.

[00159] 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.

[00160] 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.

[00161] In one embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00162] 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.

[00163] 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.

[00164] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is H.

[00165] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is substituted $C_{1\text{-}8}$alkyl.

[00166] 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.

[00167] 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.

[00168] 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.

[00169] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^2 is H.

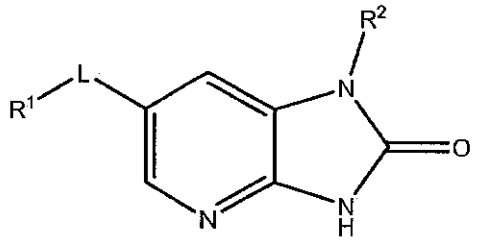
[00170] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein L is a direct bond.

[00171] 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 $C_{1\text{-}8}$alkyl.

[00172] In another embodiment, the TOR kinase inhibitors of formula (Ic) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is $C_{1\text{-}8}$alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00173] 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.

[00174] 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.

[00175] In one embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00176] 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.

[00177] 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.

[00178] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^1 is H.

[00179] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein R^2 is substituted C_{1-8}alkyl.

[00180] 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.

[00181] 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.

[00182] 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.

[00183] In another embodiment, the Heteroaryl Compounds of formula (Id) are those wherein R^2 is H.

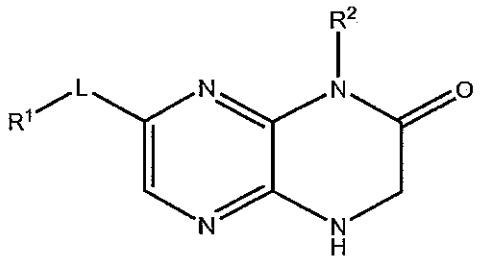
[00184] In another embodiment, the TOR kinase inhibitors of formula (Id) are those wherein L is a direct bond.

[00185] 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.

[00186] 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.

[00187] 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.

[00188] 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.

[00189] In one embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00190] 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.

[00191] 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.

[00192] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is H.

[00193] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is substituted C_{1-8}alkyl.

[00194] 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.

[00195] 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.

[00196] 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.

[00197] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^2 is H.

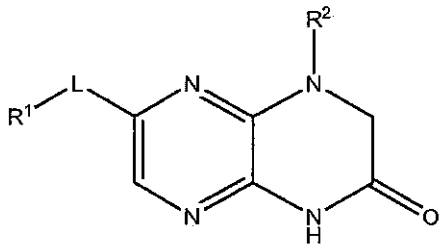
[00198] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein L is a direct bond.

[00199] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is unsubstituted $C_{1\text{-}8}$alkyl.

[00200] In another embodiment, the TOR kinase inhibitors of formula (Ie) are those wherein R^1 is substituted or unsubstituted aryl and R^2 is $C_{1\text{-}8}$alkyl substituted with one or more substituents selected from alkoxy, amino, hydroxy, cycloalkyl, or heterocyclylalkyl.

[00201] 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.

[00202] 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.

[00203] In one embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00204] 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.

[00205] 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.

[00206] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^1 is H.

[00207] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is substituted C_{1-8}alkyl.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein R^2 is H.

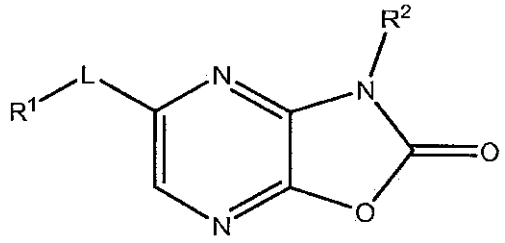
[00212] In another embodiment, the TOR kinase inhibitors of formula (If) are those wherein L is a direct bond.

[00213] 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.

[00214] 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.

[00215] 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.

[00216] 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.

[00217] In one embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00218] 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.

[00219] 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.

[00220] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^1 is H.

[00221] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is substituted C_{1-8}alkyl.

[00222] 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.

[00223] 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.

[00224] 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.

[00225] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein R^2 is H.

[00226] In another embodiment, the TOR kinase inhibitors of formula (Ig) are those wherein L is a direct bond.

[00227] 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.

[00228] 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.

[00229] 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.

[00230] 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;

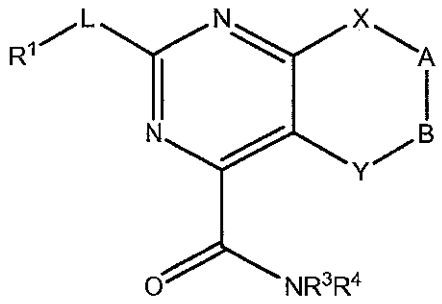
(S)-6-(4-(4H-1,2,4-Triazol-3-yl)phenyl)-1-(1-phenylethyl)-1H-imidazo[4,5-b]pyrazin-2(3H)-one;

(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.

[00231] 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.

[00232] In one embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)CH_2C(O)NH-$.

[00233] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)CH_2NH-$.

[00234] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)NH-$.

[00235] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C=N-$.

[00236] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-C(R^2)=CHNH-$.

[00237] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein L is a direct bond.

[00238] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00239] 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.

[00240] 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.

[00241] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form $-N(R^2)C(O)NH-$ and R^1 is substituted aryl, such as phenyl.

[00242] 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.

[00243] 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.

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

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

[00246] 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.

[00247] 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.

[00248] 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.

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

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

[00251] 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.

[00252] 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.

[00253] 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.

[00254] 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.

[00255] 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.

[00256] 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.

[00257] 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.

[00258] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted heteroaryl, L is a direct bond and R^2 is substituted or unsubstituted C_{1-8}alkyl or substituted or unsubstituted cycloalkyl.

[00259] In another embodiment, the TOR kinase inhibitors of formula (II) are those wherein -X-A-B-Y- taken together form -N(R^2)C(O)NH-, R^1 is substituted or unsubstituted aryl, L is a direct bond and R^2 is substituted or unsubstituted C_{1-8}alkyl or substituted or unsubstituted cycloalkyl.

[00260] 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-

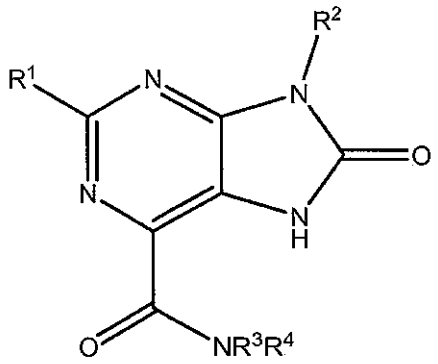
benzyl-2-(4-methoxyphenyl)-8-oxo-8,9-dihydro-7H-purine-6-carboxamide, 2-methyl-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 9-benzyl-9H-purine-2,6-dicarboxamide, 9-[2,3-bis[(benzoyloxy)methyl]cyclobutyl]-2-methyl-9H-Purine-6-carboxamide, 9-benzyl-2-methyl-9H-purine-6-carboxamide, 9-(2-hydroxyethyl)-2-methyl-9H-purine-6-carboxamide,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

[00261] In another embodiment, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted furanoside.

[00262] In another embodiment, the TOR kinase inhibitors of formula (II) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00263] In another embodiment, the TOR kinase inhibitors of formula (II) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00264] 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.

[00265] 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.

[00266] 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.

[00267] 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.

[00268] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00269] 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.

[00270] 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.

[00271] 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.

[00272] 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.

[00273] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00274] In another embodiment, the TOR kinase inhibitors of formula (IIa) are those wherein R^3 and R^4 are H.

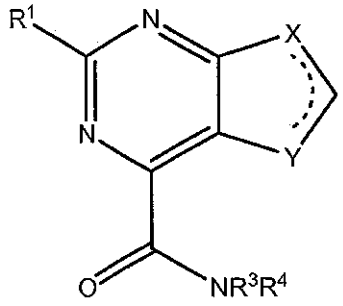
[00275] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 8,9-dihydro-8-oxo-9-phenyl-2-(3-pyridinyl)-7H-Purine-6-carboxamide, 2-(4-cyanophenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide, 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.

[00276] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted furanoside.

[00277] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include compounds wherein R^2 is a substituted or unsubstituted furanoside.

[00278] In another embodiment, the TOR kinase inhibitors of formula (IIa) do not include (2′R)-2′-deoxy-2′-fluoro-2′-*C*-methyl nucleosides.

[00279] 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.

[00280] In one embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00281] 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.

[00282] 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.

[00283] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00284] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00285] 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.

[00286] 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.

[00287] 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.

[00288] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00289] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^3 and R^4 are H.

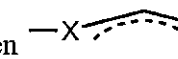
[00290] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein  is $-C(R^2)=CH-NH-$ and R^2 is substituted aryl, such as substituted phenyl.

[00291] 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.

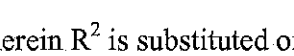
[00292] In another embodiment, the TOR kinase inhibitors of formula (IIb) are those wherein R^1 is substituted aryl, such as phenyl, and R^2 is substituted aryl, such as substituted phenyl.

[00293] 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.

[00294] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted cyclobutyl when  is $-N(R^2)-CH=N-$.

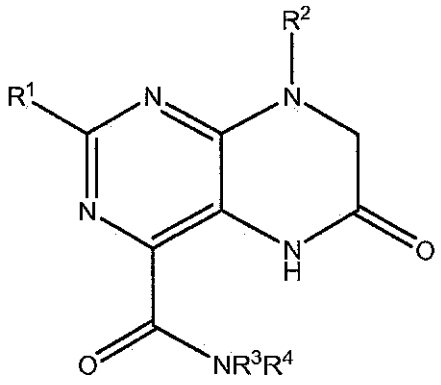
[00295] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is a substituted furanoside when  is $-N(R^2)-CH=N-$.

[00296] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted pyrimidine when  is $-C(R^2)=CH-NH-$.

[00297] In another embodiment, the TOR kinase inhibitors of formula (IIb) do not include compounds wherein R^2 is substituted oxetane when  is $-N(R^2)-CH=N-$.

[00298] 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 $-N(R^2)-CH=N-$.

[00299] 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.

[00300] In one embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00301] 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.

[00302] 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.

[00303] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00304] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is unsubstituted C_{1-8}alkyl, such as unsubstituted methyl.

[00305] 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.

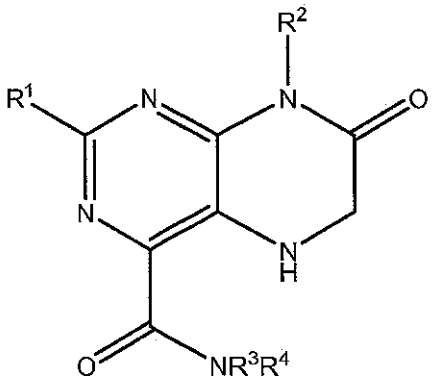
[00306] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted aryl, such as halo, haloalkyl or alkoxy substituted phenyl.

[00307] 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.

[00308] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00309] In another embodiment, the TOR kinase inhibitors of formula (IIc) are those wherein R^3 and R^4 are H.

[00310] 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.

[00311] In one embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^1 is substituted aryl, such as substituted phenyl.

[00312] 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.

[00313] 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.

[00314] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted C_{1-8}alkyl, such as $-CH_2C_6H_5$.

[00315] 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.

[00316] 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.

[00317] 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.

[00318] 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.

[00319] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^2 is substituted heterocyclylalkyl, such as substituted piperidine.

[00320] In another embodiment, the TOR kinase inhibitors of formula (IId) are those wherein R^3 and R^4 are H.

[00321] Representative TOR kinase inhibitors of formula (II) 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;

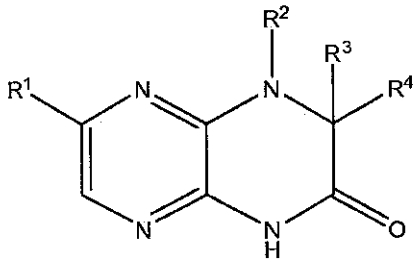
2-(3-Hydroxyphenyl)-8-oxo-9-(2-phenoxyphenyl)-8,9-dihydro-7H-purine-6-carboxamide;

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.

[00322] 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:

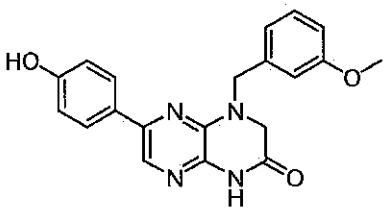
R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

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;

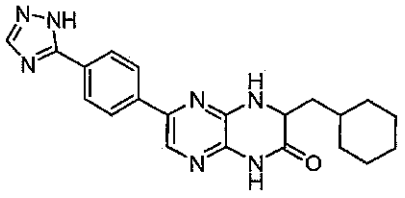
R^3 and R^4 are each independently H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, substituted or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

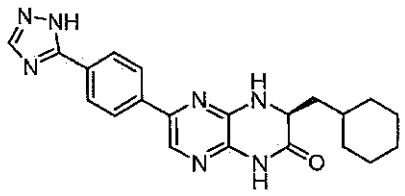


6-(4-hydroxyphenyl)-4-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;



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

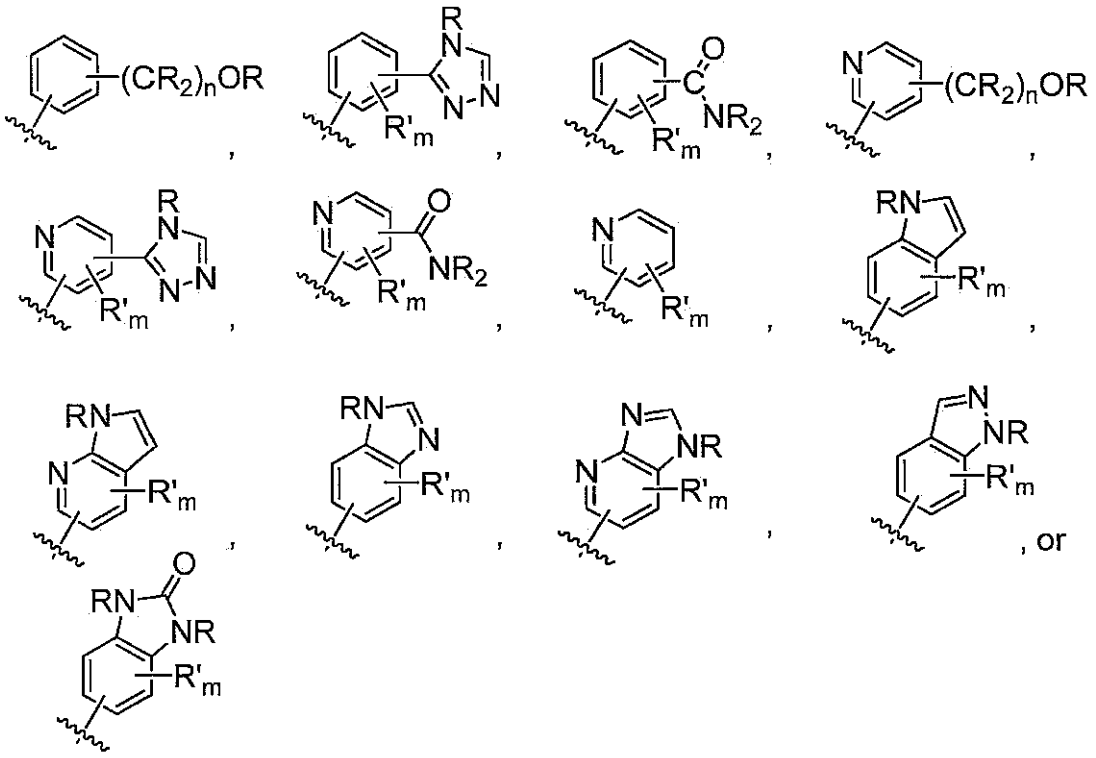
or,



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

[00323] 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.

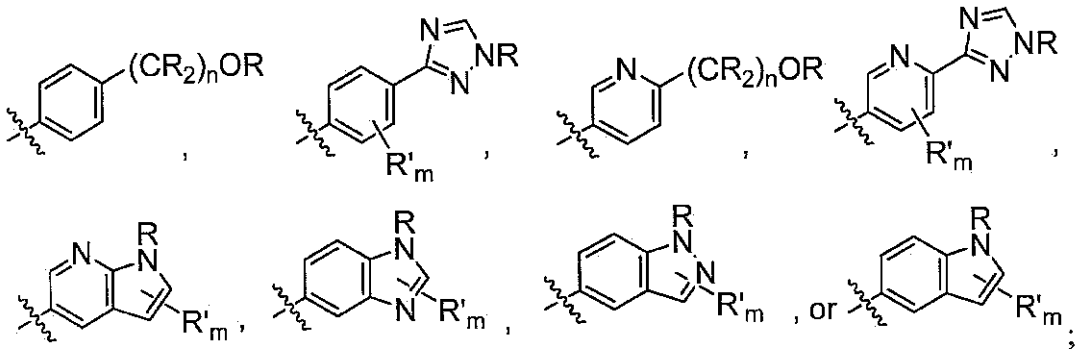
[00324] In some embodiments of compounds of formula (III), R^1 is



;

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.

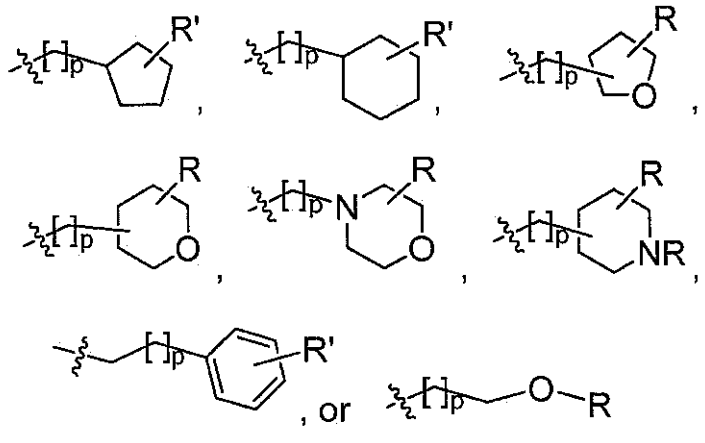
[00325] In some embodiments of compounds of formula (III), R^1 is



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.

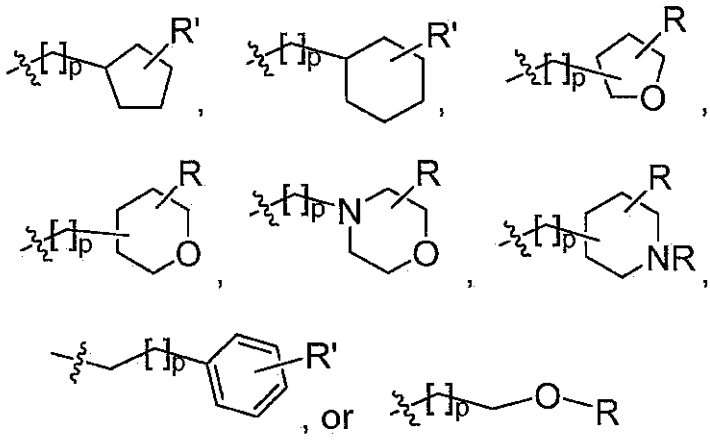
[00326] In some embodiments of compounds of formula (III), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, 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.

[00327] In other embodiments, R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



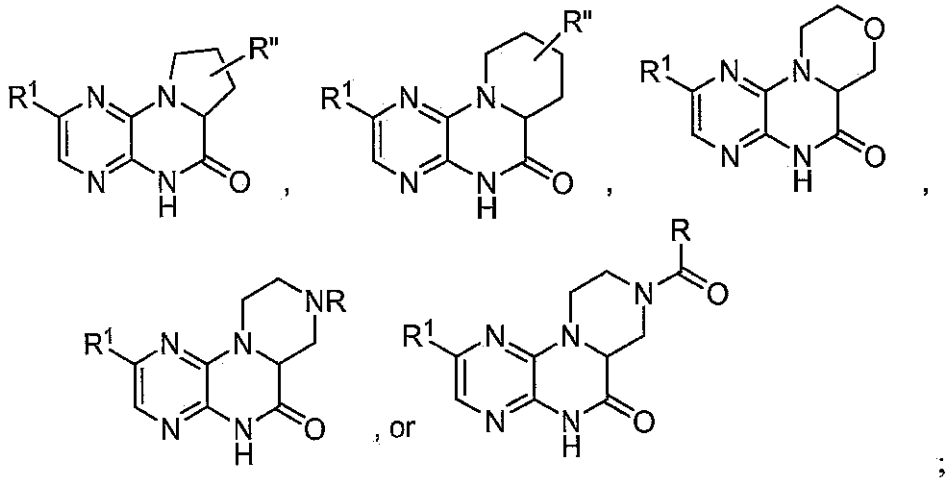
wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently H, -OR, cyano, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); and p is 0-3.

[00328] 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.

[00329] 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.

[00330] 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).

[00331] 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.

[00332] In certain embodiments, the compounds of formula (III) have an R^1 group set forth herein and an R^2 group set forth herein.

[00333] 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.

[00334] 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;

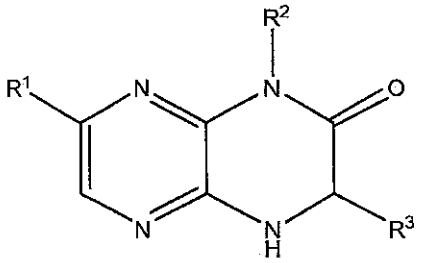
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-3-(2-methoxyacetyl)-6,11,4a-trihydropiperazino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-6,11,4a-trihydropiperazino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;
9-(4-(4H-1,2,4-triazol-3-yl)-2-methylphenyl)-3-(2-methoxyethyl)-6,11,4a-trihydropiperazino[1,2-e]pyrazino[2,3-b]pyrazin-5-one;
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.

[00335] In one embodiment, the TOR kinase inhibitors include compounds having the following formula (IV):



(IV)

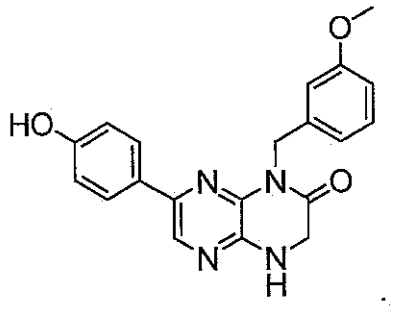
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, and prodrugs thereof, wherein:

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;

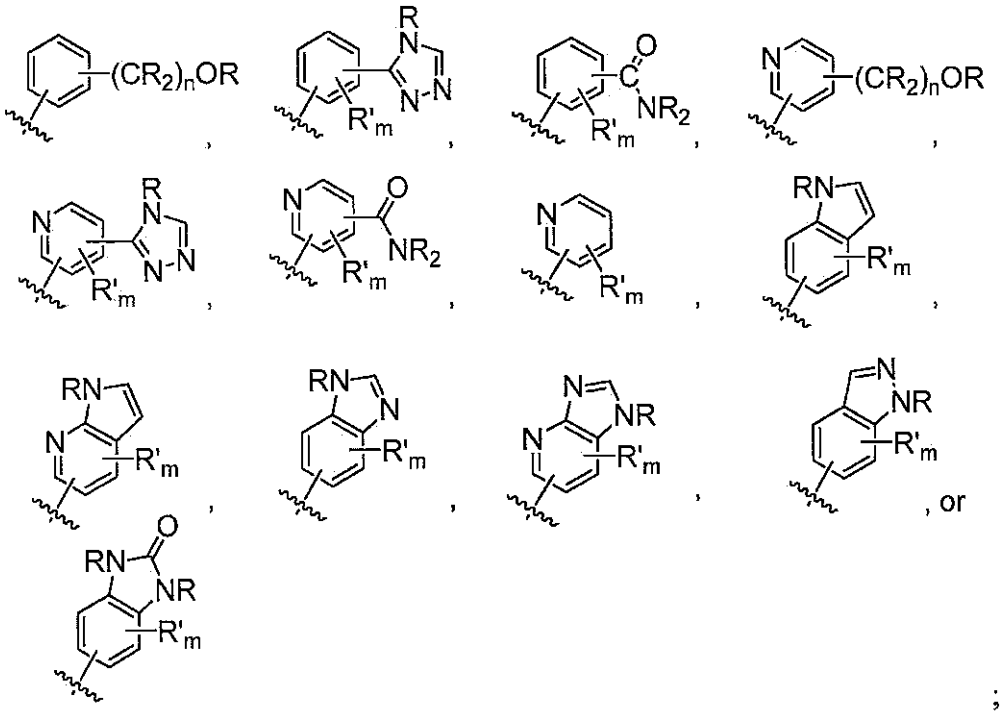
R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

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:



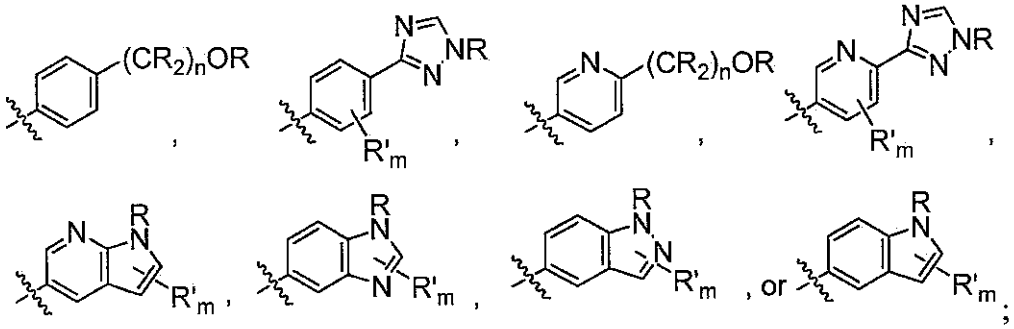
[00336] In some embodiments of compounds of formula (IV), R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. For example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, 1H-pyrrolo[2,3-b]pyridyl, indazolyl, indolyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 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.

[00337] 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.

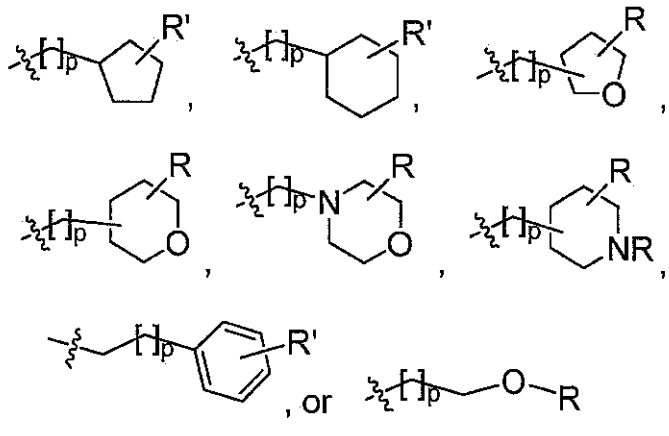
[00338] In some embodiments of compounds of formula (IV), R^1 is



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.

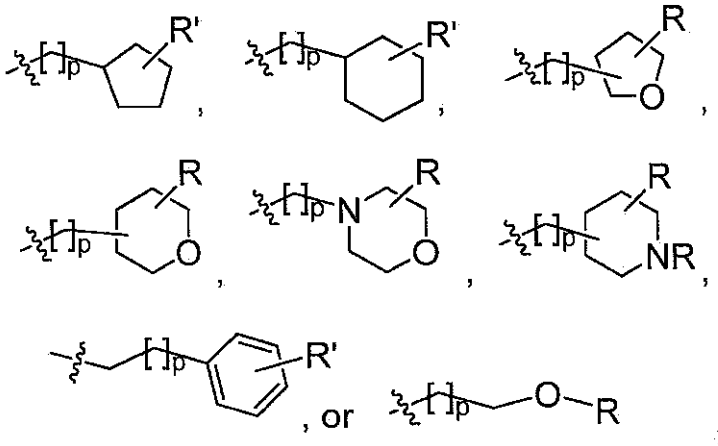
[00339] In some embodiments of compounds of formula (IV), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, 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.

[00340] 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.

[00341] 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.

[00342] In other embodiments of compounds of formula (IV), R^3 is H.

[00343] 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.

[00344] In certain embodiments, the compounds of formula (IV) have an R^1 group set forth herein and an R^2 group set forth herein.

[00345] 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.

[00346] 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;

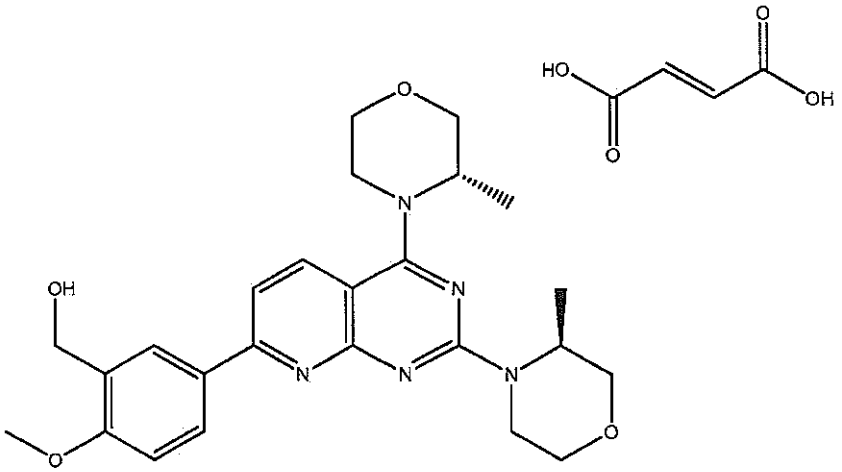
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

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;

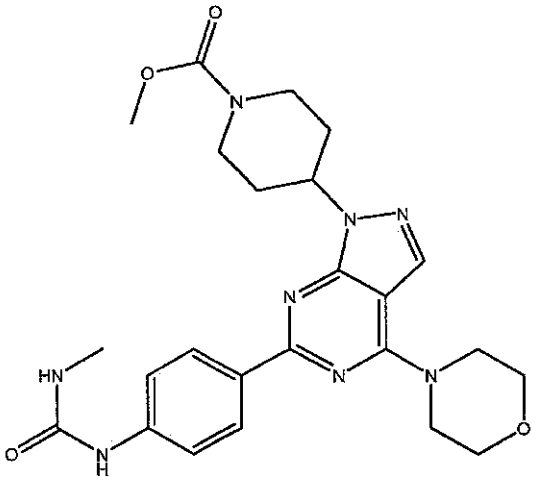
7-(2-amino-4-methyl-1H-benzo[d]imidazol-6-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(R)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-methyl-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[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.

[00347] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



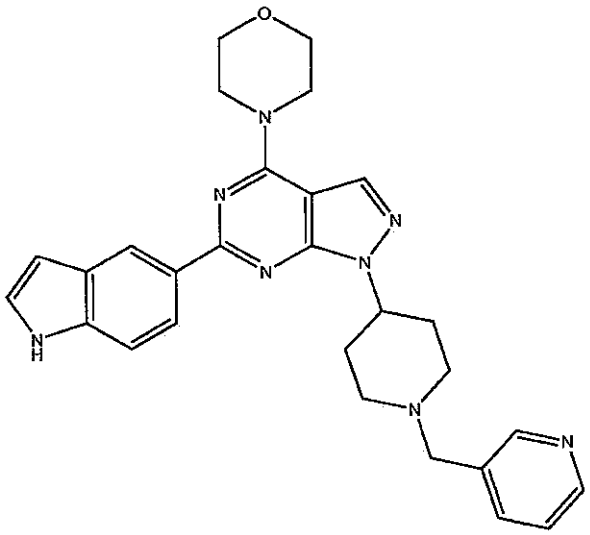
or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof.

[00348] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



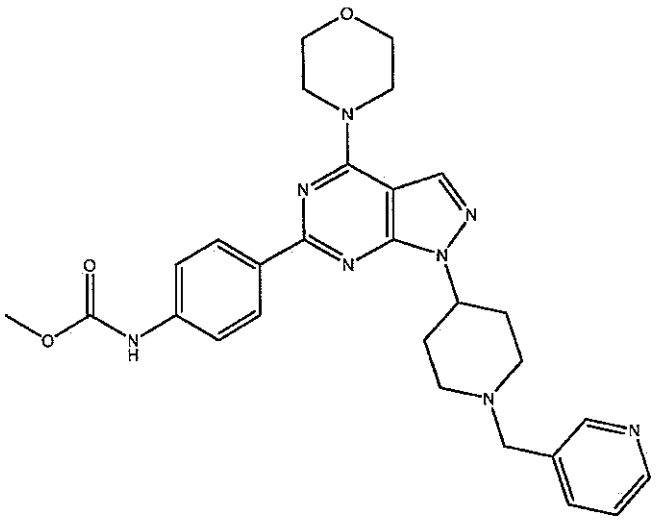
or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof.

[00349] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



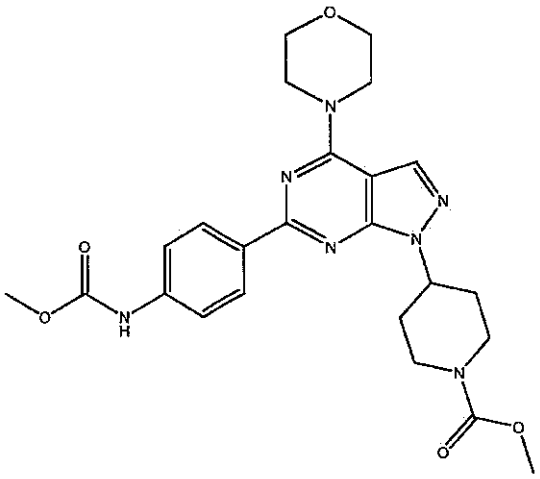
or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof.

[00350] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



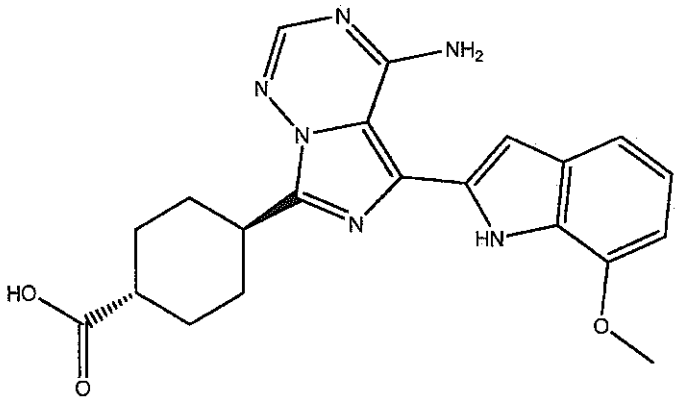
or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof.

[00351] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



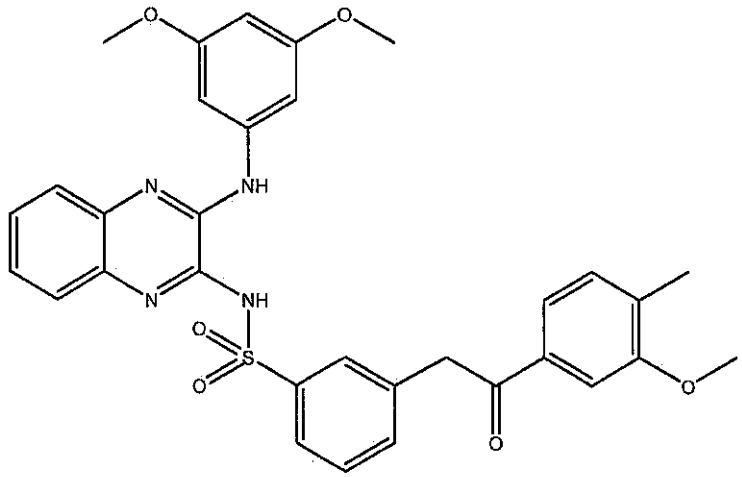
or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof.

[00352] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



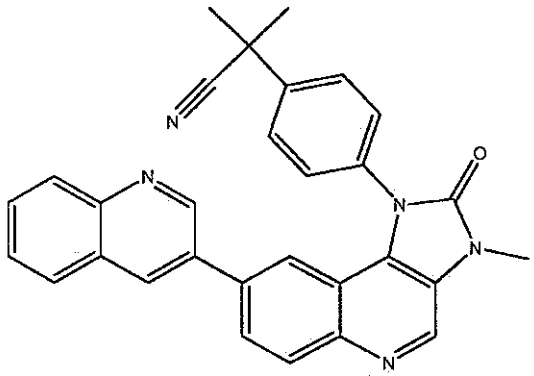
or a pharmaceutically acceptable salt, clathrate, solvate, stereoisomer, tautomer, or prodrug thereof.

[00353] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



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

[00354] In one embodiment, the TOR kinase inhibitor is a compound having the following formula:



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

[00355] In one embodiment, the TOR kinase inhibitor is a compound disclosed in WO 2008/023161 (see, *e.g.*, page 5, line 5 to page 11, line 15), WO 2009/007751 (see, *e.g.*, page 9, line 8 to page 26, line 8), WO 2009/007749 (see, *e.g.*, page 9, line 21 to page 29, line 23), WO 2009/007750 (see, *e.g.*, page 9, line 21 to page 32, line 22), WO 2009/007748 (see, *e.g.*, page 9, line 6 to page 42, line 28), WO 2008/032028 (see, *e.g.*, page 11, line 13 to page 21, line 13), WO

2008/032086 (see, *e.g.*, page 10 line 21 to page 15, line 22), WO 2008/032072 (see, *e.g.*, page 11, line 11 to page 16, line 13), WO 2008/032033 (see, *e.g.*, page 11, line 3 to page 16, line 5), WO 2008/032089 (see, *e.g.*, page 11, line 11 to page 16, line 13), WO 2008/032060 (see, *e.g.*, page 11, line 3 to page page 16, line 6), WO 2008/032091 (see, *e.g.*, page 11, line 11 to page 16, line 13), WO 2008/032036 (see, *e.g.*, page 11, line 13 to page 21, line 13), WO 2008/032077 (see, *e.g.*, page 10, line 21 to page 15, line 22), WO 2008/032064 (see, *e.g.*, page 11, line 3 to page 16, line 5), WO 2008/032027 (see, *e.g.*, page 10, line 21 to page 15, line 22), WO 2007/135398 (see, *e.g.*, page 11, line 28 to page 16, line 6), WO 2007/129052 (see, *e.g.*, page 10, line 8 to page 13, line 5), WO 2007/129044 (see, *e.g.*, page 10, line 22 to page 13, line 20), WO 2007/080382 (see, *e.g.*, page 9, line 20 to page 32, line 32), WO 2007/066102 (see, *e.g.*, page 9, line 22 to page 14, line 17), WO 2007/066099 (see, *e.g.*, page 9, line 22 to page 14, line 14), WO 2007/066103 (see, *e.g.*, page 9, line 22 to page 14, line 16), WO 2007/060404 (see, *e.g.*, 5, line 4 to page 7, line 25), WO 2006/090169 (see, *e.g.*, page 4, lines 1-25), WO 2006/090167 (see, *e.g.*, page 3, line 33 to page 6, line 23), WO 2008/115974 (see, *e.g.*, page 4, paragraph [0012] to page 127, paragraph [0257]), WO 2009/052145 (see, *e.g.*, page 5, paragraph [0015] to page 81, paragraph [0082]), WO 2010/006072 (see, *e.g.*, page 28, line 1 to page 34, line 1), WO 2007/044698 (see, *e.g.*, page 3, paragraph [0010] to the bottom of page 7), WO 2007/044813 (see, *e.g.*, page 3, paragraph [0010] to the middle of page 7), WO 2007/044729 (see, *e.g.*, page 3, paragraph [0010] to the bottom of page 10), WO 2007/129161 (see, *e.g.*, page 2, line 10 to page 9, line 19), WO 2006/046031 (see, *e.g.*, page 2, line 15 to page 4, line 12), WO 2003/072557 (see, *e.g.*, page 1, line 4 to page 2, line 27), WO 2004/048365 (see, *e.g.*, page 1, line 4 to page 4, line 17), WO 2004/078754 (see, *e.g.*, page 1, line 4 to page 2, line 21), WO 2004/096797 (see, *e.g.*, page 1, line 4 to page 2, line 34), WO 2005/021519 (see, *e.g.*, page 1, line 4 to page 4, line 17) or US 2007/112005 (see, *e.g.*, page 2, paragraph [0012] to page 22, paragraph [0065]), each of which is incorporated by reference herein in its entirety.

6.3 METHODS FOR MAKING TOR KINASE INHIBITORS

[00356] 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.

[00357] Particular methods for preparing compounds of formula (I) are disclosed in U.S. Application No. 11/975,652, filed October 18, 2007, incorporated by reference herein in its entirety. Particular methods for preparing compounds of formula (II) are disclosed in U.S. Application No. 11/975,657, filed October 18, 2007, incorporated by reference herein in its entirety. Particular methods for preparing compounds of formula (III) and (IV) are disclosed in U.S. Application No. 12/605,791, filed October 26, 2009, incorporated by reference herein in its entirety.

6.4 METHODS OF USE

[00358] Without being limited by theory, it is believed that LKB1 plays an important role in the nutrient sensing arm of the mTOR pathway. In particular, it is believed that LKB1 is a negative regulator of the mTOR pathway under stress conditions, such as hypoxia and low glucose. LKB1 suppresses mTOR activity via its downsteam kinase, AMP-activated protein kinase (AMPK). In response to energy stress, LKB1 phosphorylates the AMPK catalytic subunit at T172 and this phosphorylation is essential for activation of AMPK. Activated AMPK phosphorylates TSC2 and raptor, and suppresses mTOR activity [Shackelford DB and Shaw JS, *Nat. Rev Cancer* 9:563 (2009)]. Therefore, phosphorylation or activity of AMPK can be used as a marker for LKB1 status. In basal conditions, it is believed that loss of LKB1 and/or AMPK can result in activation of the mTOR pathway. In cancer cells, under stress conditions, it is believed that the LKB1/AMPK pathway may actually play a protective role by causing cells to slow down their proliferation and thus evade apoptosis induced by the stress condition. However, it is believed that in LKB1 mutant cancer cells (*e.g.*, cells harboring a LKB1 gene mutation resulting in a decrease in LKB1 mRNA expression, a decrease in LKB1 protein

production or a non-functional LKB1 protein), in the absence of the negative signal to mTOR, the cancer cells continue to proliferate and undergo metabolic catastrophe. Accordingly, without being limited by theory, it is believed that TOR kinase inhibitors by their effects on cell metabolism cause a stress response in cancer cells and in LKB1 mutant cancer cells, and in the absence of a negative signal to slow the growth of the cells, result in cell death.

[00359] Provided herein are methods for treating or preventing cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having cancer, for example non-small cell lung carcinoma or cervical cancer, or a tumor syndrome, for example Peutz-Jeghers Syndrome, characterized by loss of LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type.

[00360] Provided herein are methods for treating or preventing a cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor to a patient having a cancer or a tumor syndrome characterized by a reduced level of phospho-AMPK (pAMPK) protein or AMPK activity, relative to that of a control patient or wild type. In one embodiment, the pAMPK is pAMPK T172.

[00361] Further provided herein are methods for treating or preventing cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's cancer for the presence of LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having cancer, for example non-small cell lung carcinoma or cervical cancer, characterized by the LKB1 and/or AMPK gene or protein loss or mutation.

[00362] Further provided herein are methods for treating or preventing cancer, for example non-small cell lung carcinoma or cervical cancer, comprising screening a patient's cancer for the presence of a reduced level of pAMPK protein or AMPK activity relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having cancer, for example non-small cell lung carcinoma or cervical

cancer, characterized by a reduced level of pAMPK protein or AMPK activity. In one embodiment, the pAMPK is pAMPK T172.

[00363] Further provided herein are methods for detecting LKB1 gene or protein loss or mutation in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of LKB1 mRNA expression, the level of LKB1 protein expression, determining the methylation status of the LKB1 gene or otherwise identifying the presence of LKB1 gene or protein loss or mutation (*e.g.*, by cDNA or direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a LKB1 gene or protein loss or mutation (wild type); wherein a change in LKB1 mRNA expression, LKB1 protein expression, LKB1 mRNA structure, LKB1 gene methylation status and/or LKB1 protein structure in the biological sample from the test patient, relative to that of a control patient or wild-type, indicates the presence of LKB1 gene or protein loss or mutation in the test patient's cancer.

[00364] Further provided herein are methods for detecting AMPK gene or protein loss or mutation in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of AMPK mRNA expression, the level of AMPK protein expression, determining the methylation status of the AMPK gene or otherwise identifying the presence of AMPK gene or protein loss or mutation (*e.g.*, by cDNA or direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a AMPK gene or protein loss or mutation (wild type); wherein a change in AMPK mRNA expression, AMPK protein expression, AMPK mRNA structure, AMPK gene methylation status and/or AMPK protein structure in the

biological sample from the test patient, relative to that of a control patient or wild-type, indicates the presence of LKB1 gene or protein loss or mutation in the test patient's cancer.

[00365] Further provided herein are methods for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's ("test patient") cancer, for example non-small cell lung carcinoma or cervical cancer, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of, pAMPK protein expression, the level of AMPK activity, or otherwise measuring the level of pAMPK protein (*e.g.*, immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine the amount of pAMPK protein or the amount of phosphorylation of AMPK at specific sites, for example at the T172 site), and/or the level of AMPK activity (e.g. AMPK kinase assay, see Sanders *et al. Biochem.J.* 403:139-148 (2007)); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a reduced level of pAMPK protein and/or AMPK activity (wild type); wherein a lower level of pAMPK protein and/or AMPK activity in the biological sample from the test patient, relative to that of a control patient or wild type, indicates the presence of a reduced level of pAMPK protein and/or AMPK activity in the test patient's cancer. In one embodiment, the pAMPK is pAMPK T172.

[00366] Further provided herein are methods for predicting the likelihood of a patient ("test patient") having cancer, for example non-small cell lung carcinoma or cervical cancer, being responsive to TOR kinase inhibitor therapy, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of LKB1 mRNA expression, the level of LKB1 protein expression, determining the methylation status of the LKB1 gene or otherwise identifying the presence of LKB1 gene or protein loss or mutation (*e.g.*, by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a LKB1 gene or protein loss or mutation; wherein a change in LKB1 mRNA expression, LKB1 protein expression, LKB1 mRNA structure, LKB1 gene methylation status and/or LKB1 protein structure in the biological sample from the test patient, relative to that of a control patient or

wild-type, predicts an increased likelihood that TOR kinase inhibitor therapy will treat said cancer, for example non-small cell lung carcinoma or cervical cancer.

[00367] Further provided herein are methods for predicting the likelihood of a patient ("test patient") having cancer, for example non-small cell lung carcinoma or cervical cancer, being responsive to TOR kinase inhibitor therapy, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of AMPK mRNA expression, the level of AMPK protein expression, determining the methylation status of the AMPK gene or otherwise identifying the presence of AMPK gene or protein loss or mutation (*e.g.*, by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by loss of AMPK gene or protein loss or mutation; wherein a change in AMPK mRNA expression, AMPK protein expression, AMPK mRNA structure, AMPK gene methylation and/or AMPK protein structure in the biological sample from the test patient, relative to that of a control patient or wild-type, predicts an increased likelihood that TOR kinase inhibitor therapy will treat said cancer, for example non-small cell lung carcinoma or cervical cancer.

[00368] Further provided herein are methods for predicting the likelihood of a patient ("test patient") having cancer, for example non-small cell lung carcinoma or cervical cancer, being responsive to TOR kinase inhibitor therapy, comprising: obtaining a biological sample from the test patient's cancer; measuring one or more of the level of pAMPK protein expression, the level of AMPK activity, or otherwise measuring the level of pAMPK protein (*e.g.*, immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine the amount of pAMPK protein, or the amount of phosphorylation of AMPK at specific sites, for example at the T172 site), and/or the level of AMPK activity (e.g. AMPK kinase assay, see Sanders *et al. Biochem.J.* 403:139-148 (2007)); and comparing said measurement with a control measurement from a patient's ("control patient") cancer which is not characterized by a reduced level of pAMPK protein and/or AMPK activity (wild type); wherein a lower level of pAMPK protein and/or AMPK activity in the biological sample from the test patient, relative to that of a

control patient or wild type, predicts an increased likelihood that TOR kinase inhibitor therapy will treat said cancer, for example non-small cell lung carcinoma or cervical cancer. In one embodiment, the pAMPK is pAMPK T172.

[00369] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having cancer, for example non-small cell lung carcinoma or cervical cancer, with a TOR kinase inhibitor, comprising: screening said patient's cancer for the presence of LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type, wherein the presence of said LKB1 and/or AMPK gene or protein loss or mutation in the patient's cancer is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[00370] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having cancer, for example non-small cell lung carcinoma or cervical cancer, with a TOR kinase inhibitor, comprising: screening said patient's cancer for the presence of a reduced level of pAMPK protein and/or AMPK activity, relative to that of a control patient or wild type, wherein the presence of said reduced level of pAMPK protein and/or AMPK activity in the patient's cancer is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor. In one embodiment, the pAMPK is pAMPK T172.

[00371] Further provided herein are methods for treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising screening the patient for the presence of a LKB11 and/or AMPK gene or protein loss or mutation , relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having the LKB1 and/or AMPK gene or protein loss or mutation.

[00372] Further provided herein are methods for treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising screening the patient for the presence of a reduced level of pAMPK protein and/or AMPK activity, relative to that of a control patient or wild type, and administering an effective amount of a TOR kinase inhibitor to the patient having the reduced level of pAMPK protein and/or AMPK activity. In one embodiment, the pAMPK is pAMPK T172.

[00373] Further provided herein are methods for detecting LKB1 gene or protein loss or mutation in a patient ("test patient") having a tumor syndrome, for example, Peutz-Jeghers Syndrome, comprising: obtaining a biological sample from the test patient; measuring one or more of the level of LKB1 mRNA expression, the level of LKB1 protein expression, determining the methylation status of the LKB1 gene or otherwise identifying the presence of gene or protein loss or mutation (*e.g.*, by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss, or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient ("control patient") without the LKB1 gene or protein loss or mutation (wild type); wherein a change in LKB1 mRNA expression, LKB1 protein expression, LKB1 mRNA structure, LKB1 gene methylation status and/or LKB1 protein structure in the biological sample from the test patient, relative to that of a control patient or wild-type, indicates the presence of LKB1 gene or protein loss or mutation in said the test patient. Examples of biological samples include but are not limited to, tissue samples, blood, saliva, hair, disease tissue samples, buccal smears or tumor samples.

[00374] Further provided herein are methods for detecting AMPK gene or protein loss or mutation in a patient ("test patient") having a tumor syndrome, for example, Peutz-Jeghers Syndrome, comprising: obtaining a biological sample from the test patient; measuring one or more of the level of AMPK mRNA expression, the level of AMPK protein expression, determining the methylation status of the AMPK gene or otherwise identifying the presence of gene or protein loss or mutation (*e.g.*, by direct cDNA or exon DNA sequencing or SNP analysis or multiple ligation probe amplification (MLPA) to identify copy number loss, or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine loss of protein); and comparing said measurement with a control measurement from a patient ("control patient") without the AMPK gene or protein loss or mutation (wild type); wherein a change in AMPK mRNA expression, AMPK protein expression, AMPK mRNA structure, AMPK gene methylation status and/or AMPK protein structure in the biological sample from the test patient, relative to that of a control patient or wild-type, indicates the presence of AMPK gene or protein

loss or mutation in the test patient. Examples of biological samples include but are not limited to, tissue samples, blood, saliva, hair, disease tissue samples, buccal smears or tumor samples.

[00375] Further provided herein are methods for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient ("test patient") having a tumor syndrome, for example, Peutz-Jeghers Syndrome, comprising: obtaining a biological sample from the test patient; measuring one or more of the level of, pAMPK protein expression, the level of AMPK activity, or otherwise measuring the level of pAMPK protein (*e.g.*, immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot to determine the amount of pAMPK protein or the amount of phosphorylation of AMPK at specific sites, for example at the T172 site), and/or the level of AMPK activity (e.g. AMPK kinase assay, see Sanders *et al. Biochem.J.* 403:139-148 (2007)); and comparing said measurement with a control measurement from a patient's ("control patient") without a reduced level of pAMPK protein and/or AMPK activity (wild type); wherein a lower level of pAMPK protein and/or AMPK activity in the biological sample from the test patient, relative to that of a control patient or wild type, indicates the presence of a reduced level of pAMPK protein and/or AMPK activity in the test patient. In one embodiment, the pAMPK is pAMPK T172. Examples of biological samples include but are not limited to, tissue samples, blood, saliva, hair, disease tissue samples, buccal smears or tumor samples.

[00376] Further provided herein are methods for predicting the likelihood of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, being responsive to TOR kinase inhibitor therapy, comprising screening said patient for the presence of LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type, wherein the presence of LKB1 and/or AMPK gene or protein loss or mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said tumor syndrome.

[00377] Further provided herein are methods for predicting the likelihood of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, being responsive to TOR kinase inhibitor therapy, comprising screening said patient for the presence of a reduced level of pAMPK protein and/or AMPK activity, relative to that of a control patient or wild type, wherein the presence of a reduced level of pAMPK protein and/or AMPK activity predicts an increased

likelihood that TOR kinase inhibitor therapy will treat said tumor syndrome. In one embodiment, the pAMPK is pAMPK T172.

[00378] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, with a TOR kinase inhibitor, comprising screening said patient for the presence of LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type, wherein the presence of LKB1 and/or AMPK gene or protein loss or mutation in the patient is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor.

[00379] Further provided herein are methods for predicting therapeutic efficacy of treatment of a patient having a tumor syndrome, for example Peutz-Jeghers Syndrome, with a TOR kinase inhibitor, comprising screening said patient for the presence of a reduced level of pAMPK protein and/or AMPK activity, relative to that of a control patient or wild type, wherein the presence of a reduced level of pAMPK protein and/or AMPK activity in the patient is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor. In one embodiment, the pAMPK is pAMPK T172.

[00380] Further provided herein are methods for treating or preventing cancer, for example non-small cell lung carcinoma or cervical cancer, or treating a tumor syndrome, for example Peutz-Jeghers Syndrome, comprising administering an effective amount of a TOR kinase inhibitor and an effective amount of one or more agents that modulate AMP levels, glucose uptake, metabolism or a stress response to a patient having cancer, for example non-small cell lung carcinoma or cervical cancer, or a tumor syndrome, for example Peutz-Jeghers Syndrome.

[00381] Further provided herein are kits comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting LKB1 gene or protein loss or mutation, or AMPK gene or protein loss or mutation, or both, in a patient's cancer or in a patient having a tumor syndrome, and instructions for detecting LKB1 gene or protein loss or mutation, or AMPK gene or protein loss or mutation, or both, in a patient's cancer or in a patient having a tumor syndrome. In one embodiment, the kit further comprises

instructions for administering a TOR kinase inhibitor or a pharmaceutical composition thereof to a patient in need thereof.

[00382] Further provided herein are kits comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's cancer or in a patient having a tumor syndrome, and instructions for detecting a reduced level of pAMPK protein and/or AMPK activity in a patient's cancer or in a patient having a tumor syndrome. In one embodiment, the kit further comprises instructions for administering a TOR kinase inhibitor or a pharmaceutical composition thereof to a patient in need thereof.

[00383] In one embodiment, the LKB1 gene mutation or loss results in a decrease in LKB1 mRNA expression (*e.g.*, relative to wild-type). In another embodiment, the LKB1 gene mutation or loss results in a change in LKB1 mRNA structure (*e.g.*, relative to wild-type). In another embodiment, the LKB1 gene mutation or loss results in a decrease in LKB1 protein production (*e.g.*, relative to wild-type). In another embodiment, the LKB1 gene mutation or loss results in a change in LKB1 protein structure (*e.g.*, relative to wild-type). Types of gene mutations contemplated include mutations of the LKB1 DNA sequence in which the number of bases is altered, categorized as insertion or deletion mutations (frameshift mutations), and mutations of the DNA that change one base into another, categorized as missense mutations, which are subdivided into the classes of transitions (one purine to another purine, or one pyrimidine to another pyrimidine) and transversions (a purine to a pyrimidine, or a pyrimidine to a purine) and nonsense mutations, wherein a codon encoding an amino acid is changed to a stop codon, thus resulting in truncated protein.

[00384] In one embodiment, the LKB1 gene mutation or loss results in a decrease in AMPK phosphorylation (*e.g.* relative to wild type). In another embodiment, the LKB1 gene mutation or loss results in a decrease in AMPK phosphorylation at T172. (*e.g.* relative to wild type). In another embodiment, the the LKB1 gene mutation or loss results in a decrease in the level pAMPK protein (*e.g.* relative to wild type). In another embodiment, the LKB1 gene mutation or loss results in a decrease in AMPK activity (i.e. kinase activity) (*e.g.* relative to wild type).

[00385] In one embodiment, the AMPK gene mutation or loss results in a decrease in AMPK mRNA expression (*e.g.*, relative to wild-type). In another embodiment, the AMPK gene mutation or loss results in a change in AMPK mRNA structure (*e.g.*, relative to wild-type). In another embodiment, the AMPK gene mutation or loss results in a decrease in AMPK protein production (*e.g.*, relative to wild-type). In another embodiment, the AMPK gene mutation or loss results in a change in AMPK protein structure (*e.g.*, relative to wild-type). Types of gene mutations contemplated include mutations of the AMPK DNA sequence in which the number of bases is altered, categorized as insertion or deletion mutations (frameshift mutations), and mutations of the DNA that change one base into another, categorized as missense mutations, which are subdivided into the classes of transitions (one purine to another purine, or one pyrimidine to another pyrimidine) and transversions (a purine to a pyrimidine, or a pyrimidine to a purine) and nonsense mutations, wherein a codon encoding an amino acid is changed to a stop codon, thus resulting in truncated protein.

[00386] In certain embodiments, the cancer, for example non-small cell lung carcinoma or cervical cancer, or the tumor syndrome, for example Peutz-Jeghers Syndrome, results directly or indirectly from LKB1 and/or AMPK gene or protein loss or mutation, relative to that of a control patient or wild type.

[00387] In one embodiment, the LKB1 and/or AMPK gene mutation is a somatic mutation.

[00388] In one embodiment, a patient or a patient's cancer is screened for LKB1 and/or AMPK gene or protein loss or mutation by obtaining a biological sample from said patient or said patient's cancer, and analyzing said sample *ex vivo*. In certain embodiments, the *ex vivo* analysis is performed by LKB1 gene direct cDNA or exon DNA sequencing, SNP analysis or multiple ligation probe amplification (MLPA) (*e.g.*, to identify copy number loss) or immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot (*e.g.*, to determine loss of protein). In certain embodiments, the *ex vivo* analysis is performed by AMPK gene direct cDNA or exon DNA sequencing, SNP analysis or multiple ligation probe amplification (MLPA) (*e.g.*, to identify copy number loss) or immunohistochemistry (IHC) or Western Blot (*e.g.*, to determine loss of protein). In another embodiment, a patient or a patient's cancer is screened for

a reduced level of pAMPK protein and/or AMPK activity by obtaining a biological sample from said patient or said patient's cancer, and analyzing said sample *ex vivo*. In certain embodiments, the *ex vivo* analysis is performed by immunohistochemistry (IHC), immunofluorescence (IF), or Western Blot (e.g. to determine the amount of pAMPK protein or the amount of phosphorylation of AMPK at specific sites, for example at the T172 site), or by a AMPK kinase assay (e.g. to determine the level of AMPK activity).

[00389] A TOR kinase inhibitor can be combined with other pharmacologically active compounds ("second active agents") in methods and compositions described herein. It is believed that certain combinations may work in the treatment of particular types of diseases or disorders, and conditions and symptoms associated with such diseases or disorders. A TOR kinase inhibitor can also work to alleviate adverse effects associated with certain second active agents, and vice versa.

[00390] One or more second active ingredients or agents can be used in the methods and compositions described herein. Second active agents can be large molecules (*e.g.*, proteins) or small molecules (*e.g.*, synthetic inorganic, organometallic, or organic molecules).

[00391] Examples of second active agents include, but are not limited to, agents that modulate AMP levels (*e.g.*, an AMP activator), glucose uptake, metabolism or a stress response. In one embodiment, the second active agent is 2-deoxyglucose. In one embodiment, the second active agent is metformin. In one embodiment, the second active agent is phenformin. In another embodiment, the second active agent is pemetrexed (*e.g.*, ALIMTA®).

[00392] Administration of a TOR kinase inhibitor and one or more second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for a TOR kinase inhibitor is oral. Preferred routes of administration for the second active agents or ingredients of the invention are known to those of ordinary skill in the art. *See, e.g., Physicians' Desk Reference*, 1755-1760 (56th ed., 2002).

[00393] In one embodiment, a second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of a TOR kinase inhibitor and any optional additional active agents concurrently administered to the patient.

[00394] Further provided herein are methods of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. TOR kinase inhibitors and other active ingredients can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

6.5 PHARMACEUTICAL COMPOSITIONS AND ROUTES OF ADMINISTRATION

[00395] 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 composition described herein are suitable for oral, parenteral, mucosal, transdermal or topical administration.

[00396] 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.

[00397] The dose of a TOR kinase inhibitorto be administered to a patient is rather widely variable and can be patient 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 or about 0.25 mg/kg of a patient's body weight to about 0.5 mg/kg of a patient's body weight. In one embodiment, one dose is given per day. In any given case, the amount of the TOR kinase inhibitor administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

[00398] In another embodiment, provided herein are methods for the treatment or prevention of a disase or disorder comprising the administration of about 0.375 mg/day to about 750 mg/day, about 0.75 mg/day to about 375 mg/day, about 3.75 mg/day to about 75 mg/day, about 7.5 mg/day to about 55 mg/day or about 18 mg/day to about 37 mg/day of a TOR kinase inhibitor to a patient in need thereof.

[00399] In another embodiment, provided herein are methods for the treatment or prevention of a disase or disorder comprising the administration of about 1 mg/day to about 1200 mg/day, about 10 mg/day to about 1200 mg/day, about 100 mg/day to about 1200 mg/day, about 400 mg/day to about 1200 mg/day, about 600 mg/day to about 1200 mg/day, about 400 mg/day to about 800 mg/day or about 600 mg/day to about 800 mg/day of a TOR kinase inhibitor to a patient in need thereof. In a particular embodiment, the methods disclosed herein comprise the administration of 400 mg/day, 600 mg/day or 800 mg/day of a TOR kinase inhibitor to a patient in need thereof.

[00400] In another embodiment, provided herein are unit dosage formulations that comprise between about 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.

[00401] In a particular embodiment, provided herein are unit dosage formulation comprising about 100 mg or 400 mg of a TOR kinase inhibitor.

[00402] In another embodiment, provided herein are unit dosage formulations that comprise 1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 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.

[00403] A TOR kinase inhibitor can be administered once, twice, three, four or more times daily.

[00404] 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.

[00405] 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.

[00406] In one embodiment, provided herein are capsules containing a TOR kinase inhibitor without an additional carrier, excipient or vehicle.

[00407] 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 a further embodiment, provided herein are compositions comprising an effective amount of a TOR kinase inhibitor, and a pharmaceutically acceptable carrier or vehicle, and one or more agents that modulate AMP levels, glucose uptake, metabolism or a stress response. In one embodiment, the composition is a pharmaceutical composition.

[00408] 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.

[00409] 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.

[00410] 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.

[00411] 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.

[00412] 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.

7. EXAMPLES

7.1 BIOLOGICAL EXAMPLES

7.1.1 Biochemical assays

[00413] **TOR 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. TORKi were dissolved in DMSO and prepared as 10 mM stocks and diluted appropriately for the experiments. Reagents were prepared as follows:

[00414] "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 recombinant TOR enzyme (cat#PR8683A) was diluted in this buffer to an assay concentration of 0.200 μg/mL.

[00415] 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.

[00416] 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).

[00417] To 20 μL of the Simple TOR 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).

[00418] TORKi were tested in the TOR 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.

[00419] **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).

[00420] Selected TORKi have, or are expected to have, an IC_{50} below 10 μM in this assay, with some TORKi having an IC_{50} below 1 μM, and others having an IC_{50} below 0.10 μM

7.1.2 Cell based assays

[00421] **Materials and Methods.** Cell lines and cell culture: Human lung cancer cell lines were purchased from American Type Culture Collection (ATCC) and maintained in RPMI 1640 plus 10% bovine calf serum (FCS) or special culture medium recommended by ATCC. The non-small cell lung cancer cells (NSCLC cancer panel) include the following cell lines NCI-H460, NCI-H838, NCI-H1792, NCI-H520, NCI-H1993, NCI-H1944, NCI-H1975, NCI-H1395, A549, NCI-H2122, NCI-H1703, NCI-H1299, NCI-H647, NCI-H358, SK-LU-1, NCI-H1734, NCI-H1693, NCI-H226, NCI-H23, NCI-H2030, NCI-H1755, Calu-6,Calu-1, SW1573, NCI-H2009, NCI-H441, HOP92, NCI-H2110, NCI-H727, NCI-H1568, Calu-3, NCI-H2228, NCI-H2444, NCI-H1563, NCI-H1650, NCI-H1437, NCI-H650, NCI-H1838, NCI-H2291, NCI-H28 and NCI-H596. Additional cell lines that TOR kinase inhibitors can be tested against include HT-3, HeLaSF, Hela S3, SKG-IIIa, SiHa, MS751, BOKU, C-33-A, C-4-II, Ca-Ski, DoTc2-4510, ME-180, OMC-1. SW756, and TC-YIK.

[00422] **Cell viability assay.** A representative TOR kinase inhibitor ("Compound 1") was used in the following biochemical assay. Cell viability was assessed using the Cell Titer-Glo Luminescent Cell Viability from Promega. The assay is a homogenous method of determining the number of viable cells in culture based on quantitation of the adenosine triphosphate (ATP) present, an indicator of metabolically active cells. The homogenous assay procedure involves adding the single reagent (CellTiter-Glo Reagent) directly to cells cultured in serum-supplemented medium. Cells were plated into a 96-well flat bottom plate (Costar Catalog Number 33595) at densities that were previously optimized for each cell line. The cells were

incubated overnight in 5% CO_2 at 37 °C. The following day, compound dilutions were prepared from a 30 mM stock. Compound 1 was first diluted in 100% DMSO and then diluted 1:50 into growth media. Next, Compound 1 was added to the appropriate well at a dilution of 1:10 (*i.e.*, ten microliters (10 µL) of the diluted Compound 1 was added to 90 µL of culture media in each well). The final dilution of Compound 1 was 1:500, which yielded a final DMSO concentration of 0.2% in each well. All concentrations were performed in triplicate. The cells were incubated with Compound 1 in 5% CO_2 at 37 °C for 3 days. After a 3-day incubation period, 100 µL of CellTiter-Glo reagent was added to each well for 2 minutes with shaking and further incubated for 10 minutes (no shaking) at room temperature to stabilize the signal. The luminescence was measured on the VICTOR *X*2 multilabel plate reader. The percent growth inhibition was calculated using the DMSO control response as 100% cell growth in the same plate. The average values from triplicates were plotted to obtain IC_{50} values using software XLfit from IDBS. The formula used for determining IC_{50} in XLfit was model number 205, which utilizes a 4 Parameter Logistic Model or Sigmoidal Dose-Response Model to calculate the IC_{50} values. All IC_{50} values are reported as an average from either two or three independent experiments.

[00423] LKB1 protein expression analysis. The whole lysates were prepared in radio-immunoprecipitation assay buffer [10 mmol/L Tris (pH 7.4), 100 mmol/L NaCl, 1 mmol/L EDTA, 1 mmol/L EGTA, 1 mmol/L NaF, 20 mmol/L $Na_4P_2O_7$, 2 mmol/L Na_3CO_4, 0.1% SDS, 0.5% sodium deoxycholate, 1% Triton X-100, 10% glycerol] containing protease inhibitors. Cell lysates containing 50 µg of protein were fractionated on 4-12% Nu-PAGE® gels and transferred to nitrocellulose membrane. The membrane was incubated with anti-LKB1 antibody (#3050, Cell Signaling Technology) overnight at 4 °C. The membrane was washed three times with PBS + 0.1% Tween before incubation with anti-rabbit secondary antibody for 1 hour at room temperature. The membrane was washed three times with PBS + 0.1% Tween before scanning on the LI-COR Odyssey® scanner at 700 nm and 800 nm wavelengths.

[00424] Statistical Analysis. The correlation between IC_{50} values across different mutation status were assessed using either Wilcoxon test, where the number of groups equals to 2, or Kruskal-Wallis test, where the number of groups is bigger than 2. P value < 0.05 is considered as significant correlation.

[00425] **Phospho AMPK T172 protein expression analysis.** The whole lysates were prepared in radio-immunoprecipitation assay buffer [10 mmol/L Tris (pH 7.4), 100 mmol/L NaCl, 1 mmol/L EDTA, 1 mmol/L EGTA, 1 mmol/L NaF, 20 mmol/L $Na_4P_20_7$, 2 mmol/L Na_3CO_4, 0.1% SDS, 0.5% sodium deoxycholate, 1% Triton X-100, 10% glycerol] containing protease inhibitors. Cell lysates containing 50 μg of protein were fractionated on 4-12% Nu-PAGE® gels and transferred to nitrocellulose membrane. The membrane was incubated with anti-phospho-AMPK T172 (#4188, Cell Signaling Technology, Danvers, MA) anti-AMPK alpha (#2793, Cell Signaling Technology, Danvers, MA) and anti β-actin (#1978, Sigma-Aldrich, St.Louis, MO) overnight at 4 °C. The membrane was washed three times with PBS + 0.1% Tween before incubation with anti-rabbit secondary antibody for 1 hour at room temperature. The membrane was washed three times with PBS + 0.1% Tween before scanning on the LI-COR Odyssey® scanner at 700 nm and 800 nm wavelengths. The levels of pAMPK T172, AMPK and actin were quantitated using LI-COR Odyssey® software. The ratio of pAMPK T172 vs. actin (pAMPK/actin) was applied to Wilcoxon statistical analysis.

[00426] **Statistical analysis.** The correlation between phospho-AMPK T172 expression level and LKB1 protein expression level status was assessed using Wilcoxon test. LKB1 protein expression level status was defined as "Neg" or "Pos" based on Western Blot results. p value < 0.05 is considered as significant correlation.

7.1.3 Xenograft models

[00427] Tumor samples from primary patient biopsies are propagated in immunocompromised animals to create an animal model that may more closely resemble the human disease (eg. John *et al, Clin. Cancer Res.* 17(1):134-141 (2011); de Plater *et al, Br. J. Cancer* 103(8): 1192-1200 (2010)). Tumors from lung cancer patient biopsies propagated in vivo are characterized for the mutational status of LKB1 by gene sequencing techniques. In addition, the expression of the protein in these samples is analyzed by Western blot techniques, IHC, or IF. Four of these cancer animal models are chosen, two that express wild type LKB1 and two that express mutant LKB1, to confirm that the LKB1 mutant tumor models are more sensitive to TORK inhibition compared to the wild type. A compound as described herein (e.g. Compound

1) is tested in these xenograft models derived from primary human cancer biopsies, for example lung cancer biopsies. Compounds provided herein show or are expected to show increased activity in xenograft models that express mutant LKB1.

[00428] 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.

[00429] A number of references have been cited, the disclosures of which are incorporated herein by reference in their entirety.

CLAIMS

What is claimed is:

1. Use of a TOR kinase inhibitor in the manufacture of a medicament for treating non-small cell lung carcinoma, in a patient having non-small cell lung carcinoma characterized by a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

2. An *in vitro* method for predicting the likelihood of a patient having non-small cell lung carcinoma being responsive to TOR kinase inhibitor therapy, comprising screening said patient's carcinoma for the presence of a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the presence of LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation predicts an increased likelihood that TOR kinase inhibitor therapy will treat said non-small cell lung carcinoma or cervical cancer, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

3. An *in vitro* method for predicting therapeutic efficacy of treatment of a patient having non-small cell lung carcinoma with a TOR kinase inhibitor, comprising screening said patient's carcinoma or cancer for the presence of a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, relative to wild type, wherein the presence of LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation is predictive of therapeutic efficacy of treatment with a TOR kinase inhibitor, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

4. Use of a TOR kinase inhibitor and use of one or more agents that module AMP levels, glucose uptake, metabolism or a stress response in the manufacture of a medicament for treating non- small cell lung carcinoma, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

5. A kit comprising one or more containers filled with a TOR kinase inhibitor or a pharmaceutical composition thereof, reagents for detecting a LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, an AMPK gene loss, AMPK protein loss, AMPK gene mutation, or AMPK protein mutation, or both, relative to wild type, in a patient's cancer or in a patient having a tumor syndrome and instructions for detecting LKB1 gene loss, LKB1 protein loss, LKB1 gene mutation, or LKB1 protein mutation, AMPK gene loss, AMPK protein loss, AMPK gene mutation, or AMPK protein mutation, or both, in a patient's cancer or in a patient having a tumor syndrome, wherein the TOR kinase inhibitor is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.