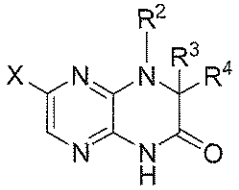
capable of acting as protein kinase modulators, regulators or inhibitors that have beneficial activity on multiple kinases or multiple kinase pathways. Accordingly, there remains a need for new kinase modulators.

[0009] The protein named mTOR (mammalian target of rapamycin), which is also called FRAP, RAFTI or RAPTI), 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. mTORC1 is sensitive to rapamycin analogs (such as temsirolimus or everolimus) and mTORC2 is largely rapamycin-insensitive. 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 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] Citation or identification of any reference in Section 2 of this application is not to be construed as an admission that the reference is prior art to the present application.

3. SUMMARY

[0011] In one aspect, there is provided a compound having formula (III):



(III)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

X is halogen, $B(OR^{+})_2$ or $Sn(R^{++})_3$;

each R^+ is independently hydrogen or substituted or unsubstituted C_{1-3} alkyl, or each R^+, together with the boron atom and the atoms to which they are attached, form a cyclic boronate;

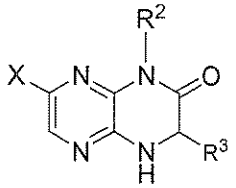
each R^{++} is independently C_{1-4} alkyl;

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

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, or substituted cycloalkylalkyl,

wherein substituted means substituted with a substituent selected from the group consisting of chloro; iodo; bromo; fluoro; alkyl; hydroxy; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; alkylsulfonyl; sulfonamide; acyl; ester; urea; urethane; oxime; hydroxylamine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxo; $B(OH)_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic, or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic; monocyclic or fused or non-fused polycyclic aryl or heteroaryl; aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclylalkoxy.

[0011a] In another aspect, there is provided a compound having formula (VI):



(VI)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

X is halogen, $B(OR^+)_2$ or $Sn(R^{++})_3$;

each R^+ is independently hydrogen or substituted or unsubstituted C_{1-3} alkyl, or each R^+, together with the boron atom and the atoms to which they are attached, form a cyclic boronate;

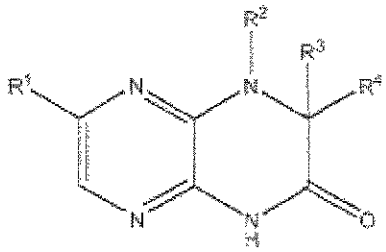
each R^{++} is independently C_{1-3} alkyl;

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

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

wherein substituted means substituted with a substituent selected from the group consisting of chloro; iodo; bromo; fluoro; alkyl; hydroxy; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; alkylsulfonyl; sulfonamide; acyl; ester; urea; urethane; oxime; hydroxylamine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxo; $B(OH)_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic, or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic; monocyclic or fused or non-fused polycyclic aryl or heteroaryl; aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclylalkoxy.

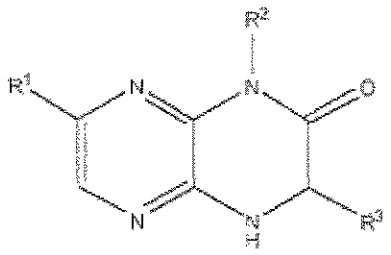
[0011b] Disclosed herein also include compounds having the following formula (I):



(I)

and pharmaceutically acceptable salts, clathrates, solvates, tautomers, stereoisomers and prodrugs thereof, wherein R^1 -R^4 are as defined herein.

[0012] Further disclosed herein are compounds having the following formula (II):



(II)

and pharmaceutically acceptable salts, clathrates, solvates, tautomers, stereoisomers and prodrugs thereof, wherein R^1, R^2 and R^3 are as defined herein.

[0013] Compounds of formula (I) and (II), or pharmaceutically acceptable salts, clathrates, solvates, hydrates, stereoisomers, tautomers, or prodrugs thereof (each being referred to herein as "Heteroaryl Compounds"), are useful for treating or preventing cancer, inflammatory conditions, immunological conditions, neurodegenerative diseases, diabetes, obesity, neurological disorders, age-related diseases, and cardiovascular conditions, and conditions treatable or preventable by inhibition of a kinase pathway. In one example, the kinase pathway is the mTOR/PI3K/Akt pathway. In another example, the kinase pathway is the PI3Kα, PI3Kβ, PI3Kδ, KDR, GSK3α, GSK3β, ATM, ATX, ATR, cFMS, and/or DNA-PK pathway.

[0014] Further provided herein are compositions comprising an effective amount of a Heteroaryl Compound and compositions comprising an effective amount of a Heteroaryl Compound and a pharmaceutically acceptable carrier or vehicle. The compositions are useful for treating or preventing cancer, inflammatory conditions, immunological conditions, neurodegenerative diseases, diabetes, obesity, neurological disorders, age-related diseases, or cardiovascular conditions and conditions treatable or preventable by inhibition of a kinase pathway, in one example, the mTOR/PI3K/Akt pathway.

[0015] Further provided herein are methods for treating or preventing cancer, inflammatory conditions, immunological conditions, neurodegenerative diseases, diabetes,

obesity, neurological disorders, age-related diseases, or cardiovascular conditions and conditions treatable or preventable by inhibition of a kinase pathway, in one example, the mTOR/PI3K/Akt pathway, comprising administering an effective amount of a Heteroaryl Compound to a patient in need of the treating or preventing.

[0016] Also provided herein are methods for inhibiting a kinase in a cell expressing said kinase, comprising contacting the cell with an effective amount of a Heteroaryl Compound as described herein. In one example the kinase is mTOR, DNA-PK, or PI3K or a combination thereof.

[0017] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

4. DETAILED DESCRIPTION

4.1 DEFINITIONS

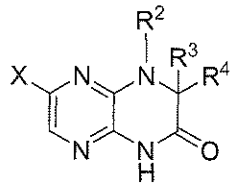
[0018] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl and the like. Examples of unsaturared alkyl groups include, but are not limited to, vinyl, allyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, $-C\equiv CH$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-CH_2C\equiv CH$, $-CH_2C\equiv C(CH_3)$ and $-CH_2C\equiv C(CH_7CH_3)$, among others. An alkyl group can be substituted or unsubstituted.

[0019] 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,

CLAIMS

What is claimed is:

1. A compound having formula (III):



(III)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

X is halogen, $B(OR^{+})_2$ or $Sn(R^{++})_3$;

each R^{+} is independently hydrogen or substituted or unsubstituted C_{1-3} alkyl, or each R^{+}, together with the boron atom and the atoms to which they are attached, form a cyclic boronate;

each R^{++} is independently C_{1-4} alkyl;

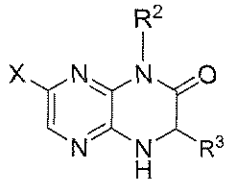
R^2 is H, unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted cycloalkylalkyl; and

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, or substituted cycloalkylalkyl,

wherein substituted means substituted with a substituent selected from the group consisting of chloro; iodo; bromo; fluoro; alkyl; hydroxy; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; alkylsulfonyl; sulfonamide; acyl; ester; urea; urethane; oxime; hydroxylamine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxo; $B(OH)_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic, or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic;

monocyclic or fused or non-fused polycyclic aryl or heteroaryl; aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclylalkoxy.

2. A compound having formula (VI):



(VI)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

X is halogen, $B(OR^{+})_2$ or $Sn(R^{++})_3$;

each R^{+} is independently hydrogen or substituted or unsubstituted C_{1-3} alkyl, or each R^{+}, together with the boron atom and the atoms to which they are attached, form a cyclic boronate;

each R^{++} is independently C_{1-3} alkyl;

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

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

wherein substituted means substituted with a substituent selected from the group consisting of chloro; iodo; bromo; fluoro; alkyl; hydroxy; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; alkylsulfonyl; sulfonamide; acyl; ester; urea; urethane; oxime; hydroxylamine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxo; $B(OH)_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic, or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic; monocyclic or fused or non-fused polycyclic aryl or heteroaryl; aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclylalkoxy.

3. The compound of claim 2, wherein R^2 is substituted cycloalkyl.

4. The compound of claim 3, wherein R^2 is substituted cyclohexyl.

5. The compound of claim 4, wherein R^2 is cyclohexyl substituted with alkoxy.

6. The compound of claim 5, wherein R^2 is cyclohexyl substituted with methoxy.

7. The compound of claim 2, wherein X is halogen.

8. The compound of claim 7, wherein X is Br.

9. The compound of claim 2, wherein R^3 is H.

10. The compound of claim 2, wherein X is halogen, R^2 is substituted cycloalkyl and R^3 is H.

11. The compound of claim 2, wherein the compound has the structure:

