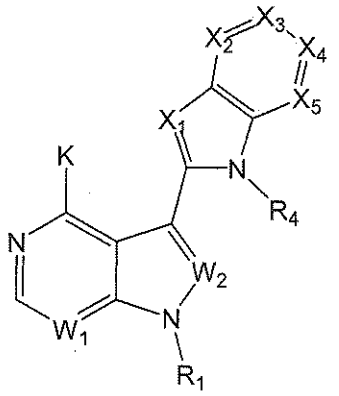
SUMMARY ~~OF THE INVENTION~~

[0013] The disclosure~~In one aspect, the invention~~ provides a compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

wherein K is $NR^{31}R^{32}$, CH_3, CH_2G, CHGG, CGGG, G, or H, wherein G is Cl, Br, or F;

W_1 and W_2 are independently CH, CR_5, or N;

X_1, X_2, X_3, X_4, and X_5 are independently N or CR_2, wherein no more than two adjacent ring atoms are N and the total number of X_1, X_2, X_3, X_4, and X_5 which are N is no more than 4;

R_1 is H, –L-C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, L-C_{1-10}alkylaryl, -L- C_{1-10}alkylhetaryl, -L- C_{1-10}alkylheterocylyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl—L-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl–L-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocylyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, -L-heterocycloalkyl, -L- C_{3-8}cycloalkyl –heterocycloalkyl, or -L- C_{3-8}cycloalkyl –heteroaryl, each of which is unsubstituted or substituted by one or more independent R_3 substituents;

L is absent, C=O, -C(=O)O-, -C(=O) NR^{31}-, -S(O)-, -S-, -$S(O)_2$-, -$S(O)_2NR^{31}$-, or -NR^{31}- ;

each instance of R_2 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

each instance of R_3 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

R_4 is hydrogen, ,–$C(O)R^{31}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, or heteroalkyl;

each instance of R_5 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –

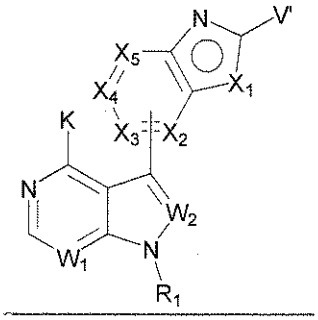
$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

R^{31}, R^{32}, and R^{33}, in each instance, is independently H, C_{1-10}alkyl, -C_{3-8}cycloalkyl , aryl, hetaryl, or heterocycloalkyl; and

wherein when X_1, X_2, X_3, X_4, and X_5 are CH, K is NH_2, R_4 is H, and W_1 is N and W_2 is N, then R_1 is not –cycloC_4H_7.

In one embodiment, K is NH_2, and W_1 and W_2 are N.

[0013a] In a first aspect, there is provided a compound of Formula:



wherein K is $NR^{31}R^{32}$, CH_3, CH_2F, CHF_2, CF_3, F, or H;

V' is NH-R_1 or –NHCO-R_1;

W_1 and W_2 are independently CH, CR_5, or N;

X_1 is S;

X_2, X_3, X_4, and X_5 are independently CR_2;

R_1 is H, –L-C_{1-10}alkyl, –L-C_{3-8}cycloalkyl or -L-heterocycloalkyl, each of which is unsubstituted or substituted by one or more independent R_3 substituents;

L is absent, C=O, -C(=O)O-, -C(=O) NR^{31}-, -S(O)-, -$S(O)_2$-, -$S(O)_2NR^{31}$-, or -NR^{31}- ;

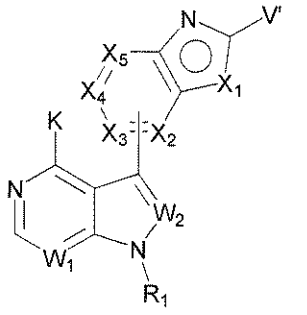
each instance of R_2 is independently hydrogen;

each instance of R_3 is independently hydrogen, halo or –OH;

each instance of R_5 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl; and

R^{31}, R^{32}, and R^{33}, in each instance, is independently H, C_{1-10}alkyl, -C_{3-8}cycloalkyl , aryl, hetaryl, or heterocycloalkyl.

[0014] In an embodiment~~another aspect~~, the disclosure~~invention~~ provides a method of treating a disease or of inhibiting cell proliferation with a compound of Formula:



wherein K is $NR^{31}R^{32}$, CH_3, CH_2F, CHF_2, CF_3, F, or H;

V' is $-(L')_k-R_1$;

W_1 and W_2 are independently CH, CR_5, or N;

X_1 is N, O or S;

X_2, X_3, X_4, and X_5 are independently N or CR_2, wherein no more than two adjacent ring atoms are N and the total number of X_2, X_3, X_4, and X_5 which are N is no more than 3;

R_1 is H, –L-C_{1-10}alkyl, –L-C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, L-C_{1-10}alkylaryl, -L- C_{1-10}alkylhetaryl, -L- C_{1-10}alkylheterocylyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl—L-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl–L-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocylyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, -L-heterocycloalkyl, -L- C_{3-8}cycloalkyl –heterocycloalkyl, or -L- C_{3-8}cycloalkyl –heteroaryl, each of which is unsubstituted or substituted by one or more independent R_3 substituents;

L is absent, C=O, -C(=O)O-, -C(=O) NR^{31}-, -S(O)-, -S-, -$S(O)_2$-, -$S(O)_2NR^{31}$-, or -NR^{31}- ;

L' is –O–, –NR^{31}–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^{31})–, –N(R^{31})C(O)–, –N(R^{31})S(O)–, –N(R^{31})$S(O)_2$–, –C(O)O–, –CH(R^{31})N(C(O)OR^{32})–, –CH(R^{31})N(C(O)R^{32})–, –CH(R^{31})N(SO_2R^{32})–, –CH(R^{31})N(R^{32})–, –CH(R^{31})C(O)N(R^{32})–, –CH(R^{31})N(R^{32})C(O)–, –CH(R^{31})N(R^{32})S(O)–, or –CH(R^{31})N(R^{32})$S(O)_2$–;

k, in each instance, is 0 or 1;

each instance of R_2 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33},–OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

each instance of R_3 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33},–OC(=O)OR^{33}, –

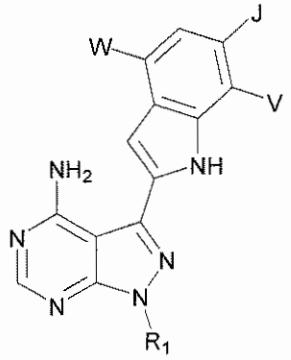
$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

R_4 is hydrogen, ,–$C(O)R^{31}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, or heteroalkyl;

each instance of R_5 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

R^{31}, R^{32}, and R^{33}, in each instance, is independently H, C_{1-10}alkyl, -C_{3-8}cycloalkyl , aryl, hetaryl, or heterocycloalkyl; and wherein the compound inhibits mTorC1 and/or mTorC2 activity relative to one or more type I phosphatidylinositol 3-kinases (PI3-kinase) ascertained by an *in vitro* kinase assay, wherein the one or more type I PI3-kinase is selected from the group consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ.

[0015] In an embodiment~~another aspect~~, the ~~invention~~disclosure additionally provides a compound of Formula:



wherein R_1 is C_{1-10}alkyl, unsubstituted or substituted by one or more independent R_3 substituents;

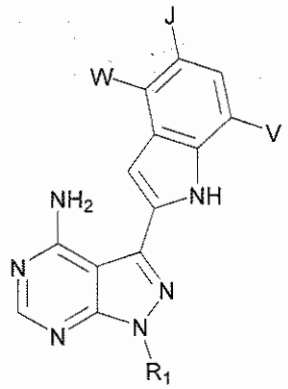
each instance of R_3 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

R_4 is hydrogen, ,–$C(O)R^{31}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, or heteroalkyl;

J, V, and W are independently hydrogen, halo, –OH, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, -$OP(O)(OR^{31})_2$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl and R_1 is H, –L-C_{1-10}alkyl, –L-C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, L-C_{1-10}alkylaryl, -L- C_{1-10}alkylhetaryl, -L- C_{1-10}alkylheterocylyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl—L-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl–L-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocylyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, -L-heterocycloalkyl, -L- C_{3-8}cycloalkyl –heterocycloalkyl, or -L- C_{3-8}cycloalkyl –heteroaryl, each of which is unsubstituted or substituted by one or more independent R_3 substituents, and wherein at least one of J, V, and W is not hydrogen;

R^{31}, R^{32}, and R^{33}, in each instance, is independently H, C_{1-10}alkyl, -C_{3-8}cycloalkyl , aryl, hetaryl, or heterocycloalkyl; wherein R_1 is not –cycloC_4H_7.

[0016] In an embodiment~~a further aspect~~, the ~~invention~~disclosure provides a compound of Formula:



wherein R_1 is C_{1-10}alkyl, unsubstituted or substituted by one or more independent R_3 substituents;

each instance of R_3 is independently hydrogen, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl;

R_4 is hydrogen, ,–$C(O)R^{31}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, or heteroalkyl;

J, V, and W are independently hydrogen, halo, –OH, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$,–$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$,–$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, -$OP(O)(OR^{31})_2$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl and R_1 is H, –L-C_{1-10}alkyl, –L-C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, L-C_{1-10}alkylaryl, -L- C_{1-10}alkylhetaryl, -L- C_{1-10}alkylheterocylyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl–L-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl–L-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocylyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, -L-heterocycloalkyl, -L- C_{3-8}cycloalkyl –heterocycloalkyl, or -L- C_{3-8}cycloalkyl –heteroaryl, each of which is unsubstituted or substituted by one or more independent R_3 substituents and wherein at least two of J, V and W are not hydrogen;

R^{31}, R^{32}, and R^{33}, in each instance, is independently H, C_{1-10}alkyl, -C_{3-8}cycloalkyl , aryl, hetaryl, or heterocycloalkyl; and

wherein R_1 is not –cycloC_4H_7.

[0017] In various embodiments, J is hydrogen, fluoro, chloro, bromo, hydroxy, methoxy, cyano, or amido; V is hydrogen, hetaryl, trifluoromethyl, trifluoromethoxy, methyl, cycloalkyl, cyano, chloro, bromo, fluoro, amido, or sulfonate; and W is hydrogen, hydroxy, methoxy, trifluoromethoxy, fluoro, bromo, chloro, or amido.

[0018] In some embodiments, J, V, and W are independently H, OH, Cl, OMe, or F; and R_1 is C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocycloalkyl. In various embodiments, V is OH, OMe, or Cl. In various embodiments, R_1 is isopropyl. In other embodiments, R_1 is cyclopentyl. In yet other embodiments, R_1 is morpholino or substituted piperidinyl.

[0019] In various embodiments, K is amino, hydrogen or methyl.

[0020] In some embodiments, W_1 and W_2 are CH. In some embodiments, W_1 and W_2 are N. In some embodiments, W_1 is CH, and W_2 is N. In some embodiments, W_1 is N and W_2 is CH.

[0021] In various embodiments, X_1, X_2, X_3, X_4, and X_5 are CR_2; or X_1, is N, and X_2, X_3, X_4, and X_5 are CR_2; or X_2, is N, and X_1, X_3, X_4, and X_5 are CR_2; or X_3, is N, and X_1, X_2, X_4, and X_5 are CR_2; or X_4, is N, and X_1, X_2, X_3, and X_5 are CR_2; or X_5 is N, and X_1, X_2, X_3, and X_4 are CR_2; or $X_1$and X_2 are N, and X_3, X_4, and X_5 are CR_2; or X_1 and X_3 are N, and X_2, X_4, and X_5 are CR_2; or X_1 and X_4 are N, and X_2, X_3, and X_5 are CR_2; or X_1 and X_5 are N, and X_2, X_3, and X_4 are CR_2; or X_2 and X_4 are N, and X_1, X_3, and X_5 are CR_2; or X_3 and X_5 are N, and X_1, X_2, and X_4 are CR_2; or X_2 and X_4 are N, and X_1, X_3, and X_5 are CR_2; or X_1, X_2, and X_4 are N, and X_3 and X_5 are CR_2; or X_2 and X_5 are N, and X_1, X_3, and X_4 are CR_2; or X_1, X_2, and X_5 are N, and X_4 and X_5 are CR_2; or X_3 and X_5 are N, and X_1, X_2, and X_4 are CR_2; or X_1, X_3, and X_5 are N, and X_2 and X_4 are CR_2.

[0022] In various embodiments, each R_2 is independently hydrogen, halo, –OH, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$,–$C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, heterocycloalkyl, aryl, or hetaryl.

[0023] In various embodiments, R_1 is –L-C_{1-10}alkyl, –L-C_{3-8}cycloalkyl, -L-heteroaryl, -L-heterocycloalkyl, -L- C_{1-10}alkylheterocylyl, -L- C_{3-8}cycloalkyl –heterocycloalkyl, or -L- C_{1-10}alkylhetaryl. In various embodiments, L is absent.

[0024] In various embodiments, R_3 is independently halo, –OH, $–NR^{31}R^{32}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$,$–NR^{31}S(O)_{0-2}R^{32}$, C_{1-10}alkyl, C_{3-8}cycloalkyl,–C_{2-10}alkenyl-, –C_{2-10}alkynyl, –C_{1-10}alkoxy, -heterocycloalkyl, aryl, hetaryl, or heteroalkyl.

[0025] In various embodiments, R_4 is hydrogen or C_{1-10}alkyl.

[0026] In anothera ~~further~~ aspect ~~of the invention~~, a pharmaceutical composition is provided, comprising a compound as disclosed above~~of the invention~~ and a pharmaceutically acceptable carrier.

[0027] In an embodiment~~a further aspect of the invention~~, a method is provided of treating a subject suffering from a disease mediated by mTorC1 and/or mTorC2 comprising administering an effective amount of a compound of the invention to the subject. In another aspect, there is provided a compound as defined above for use in treating a subject suffering from a disease mediated by mTorC1 and/or mTorC2, wherein the compound selectively inhibits mTorC1 and/or mTorC2 activity relative to one or more type I phosphatidylinositol 3-kinases (PI3-kinase) ascertained by an *in vitro* kinase assay, wherein the one or more type I PI3-kinase is selected from the group consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In a further aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for treating a subject suffering from a disease mediated by mTorC1 and/or mTorC2, wherein the compound selectively inhibits mTorC1 and/or mTorC2 activity relative to one or more type I phosphatidylinositol 3-kinases (PI3-kinase) ascertained by an *in vitro* kinase assay, wherein the one or more type I PI3-kinase is selected from the group consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ.

[0028] In some embodiments of the methods of the disclosure~~invention~~, the disease is bone disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, respiratory disease, cardiac disease or a neoplastic condition. In some embodiments, the disease is a neoplastic condition such as restenosis. In other embodiments, the neoplastic condition is cancer. In some embodiments, the cancer is selected from B cell lymphoma, T cell lymphoma, non small cell lung carcinoma, and leukemia. In other embodiments, the disease is an autoimmune disorder.

[0029] In some embodiments of the methods of the disclosure~~invention~~, the method further comprises administering a second therapeutic agent. In some embodiments, the compound substantially inhibits full activation of Akt in a cell and the second therapeutic agent is an anti-cancer agent, and further the efficacy of said treatment is enhanced through a synergistic effect of the compound and the anti-cancer agent. For example, the anti-cancer agent is selected from the group consisting of rapamycin, Gleevec, or derivative thereof that inhibits a mammalian target of rapamycin or Gleevec. In some embodiments, the compound or the second therapeutic agent is administered parenterally, orally, intraperitoneally, intravenously, intraarterially, transdermally, intramuscularly, liposomally, via local delivery by catheter or stent, subcutaneously, intraadiposally, or intrathecally.

[0030] In some embodiments, one or more of the subject compounds yield selective inhibition of mTor-mediated signal transduction without affecting upstream PI3K. In some other embodiments, the compounds provided herein

can inhibit mTor-mediated activity more effectively than rapamycin, hence providing an alternative treatment for rapamycin-resistant conditions.

[0031] In some embodiments, one or more of the subject compound selectively inhibits both mTorC1 and mTorC2 activity relative to all type I phosphatidylinositol 3-kinases (PI3-kinase) consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ.

[0032] In some embodiments, one or more of the subject compound selectively inhibits both mTor activity with an IC50 value of about 100 nM, 50 nM, 10 nM, 5 nM, 100 pM, 10 pM or even 1 pM, or less as ascertained in an *in vitro* kinase assay.

[0033] In some embodiments, one or more of the subject compound is substantially ineffective in inhibiting a type I PI3-kinase at a concentration of 100nM, 200nM, 500nM, or 1uM, 5 uM or 10uM, or higher in an *in vitro* kinase assay.

[0034] In some embodiments, one or more of the subject compound inhibits phosphorylation of Akt (S473) and Akt (T308) more effectively than rapamycin when tested at a comparable molar concentration in an *in vitro* kinase assay.

[0035] In some embodiments, one or more of the subject compound competes with ATP for binding to ATP-binding site on mTorC1 and/or mTorC2.

[0036] In some embodiments, one or more of the subject compound causes apoptosis of said cell or cell cycle arrest.

[0037] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a method for inhibiting cell proliferation comprising contacting a cell with a compound of the ~~invention~~disclosure that selectively inhibits mTorC1 and/or mTorC2 activity relative to one or more type I phosphatidylinositol 3-kinases (PI3-kinase) ascertained by an *in vitro* kinase assay, wherein the one or more type I PI3-kinase is selected from the group consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In some embodiments, the compound of the ~~invention~~disclosure selectively inhibits both mTorC1 and mTorC2 activity, and simultaneously inhibits Akt phosphorylation at residues S473 and T308. In other embodiments, the compound selectively inhibits both mTorC1 and mTorC2 activity relative to all type I phosphatidylinositol 3-kinases (PI3-kinase) consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In other embodiments, the compound of the ~~invention~~disclosure inhibits phosphorylation of Akt (S473) and Akt (T308) more effectively than rapamycin when tested at a comparable molar concentration in an *in vitro* kinase assay.

[0038] In some embodiments, the inhibition of cell-proliferation is evidenced by an assay selected from the group consisting of an MTS cell proliferation assay, a resazurin assay, a colony formation assay, flow cytometry, a cell division tracker dye assay, immunoblotting, and a phosflow assay. In other embodiments, the inhibition takes place *in vitro*.

[0039] In some embodiments, the compound competes with ATP for binding to ATP-binding site on mTorC1 and/or mTorC2. In other embodiments, the compound inhibits phosphorylation of S473 of Akt more effectively than phosphorylation of T308 of Akt when tested at a comparable molar concentration. In yet other embodiments, the cell is a neoplastic cell and wherein the compound inhibits full activation of Akt in a cell and wherein the compound is an anti-cancer agent, wherein said inhibition of cell proliferation is enhanced through a synergistic effect of said compound and said anti-cancer agent. In some embodiments, the inhibition causes apoptosis of said cell or cell cycle arrest. In specific embodiments, the cell is rapamycin-resistant.