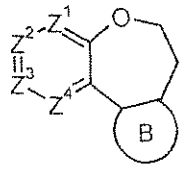
Case 26593

BENZOXAZEPIN PI3K INHIBITOR COMPOUNDS AND METHODS OF USE

The disclosure~~invention~~ relates generally to compounds with anti-cancer activity and more specifically to compounds which inhibit PI3 kinase activity. The disclosure~~invention~~ also relates to methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, or associated pathological conditions.

The present disclosure~~invention~~ provides benzoxazepin compounds, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by PI3 kinases.

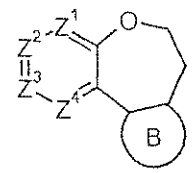
The present disclosure~~In one aspect the present invention~~ provides compounds of Formula I



I

including stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein: Z^1 is CR^1 or N; Z^2 is CR^2 or N; Z^3 is CR^3 or N; Z^4 is CR^4 or N; and B is a pyrazolyl, imidazolyl, or triazolyl ring fused to the benzoxazepin ring. The various substituents are as defined herein.

More specifically, the present disclosure~~invention~~ provides compounds of Formula I:



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stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof, wherein:

Z^1 is CR^1 or N;

Z^2 is CR^2 or N;

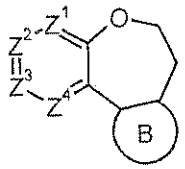
Z^3 is CR^3 or N;

C_1–C_{20} heteroaryl, each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2NH_2$, $-(CH_2)_2N(CH_3)_2$, $-CH_2C_6H_5$, -CN, $-CF_3$, $-CO_2H$, $-C(O)CH_3$, $-C(O)CH(OH)CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, =O (oxo), -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OP(O)(OH)_2$, $-SCH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2N(CH_3)_2$, $-CH_2S(O)_2NHCH_3$, $-CH_2S(O)_2CH_2CH_3$, $-S(O)_2NHCH_3$, $-S(O)_2CH_2CH_3$, pyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, cyclopropyl, cyclopentyl, oxetanyl, 4-methylpiperazin-1-yl, and 4-morpholinyl; or

R^{10} and R^{11} when attached to a nitrogen atom together with the nitrogen atoms to which they are attached form a C_2–C_{20} heterocyclyl ring or C_1–C_{20} heteroaryl each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, –CN, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, –OH, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, $-CH(CH_3)_2$, $-CH_2CF_3$, $-CH_2CH_2OH$ and $-C(CH_3)_2OH$; and

R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, –CN, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

More specifically, the present disclosure~~invention~~ provides compounds of Formula I:



I

stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof, wherein:

Z^1 is CR^1 or N;

Z^2 is CR^2 or N;

Z^3 is CR^3 or N;

Z^4 is CR^4 or N;

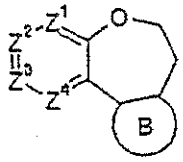
B is a pyrazolyl, imidazolyl, or triazolyl ring fused to the benzoxepin ring and selected from the structures:

$-C(O)CH_3$, $-C(O)CH(OH)CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, =O (oxo), $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OP(O)(OH)_2$, $-SCH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2N(CH_3)_2$, $-CH_2S(O)_2NHCH_3$, $-CH_2S(O)_2CH_2CH_3$, $-S(O)_2NHCH_3$, $-S(O)_2CH_2CH_3$, pyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, cyclopropyl, cyclopentyl, oxetanyl, 4-methyl-piperazin-1-yl, and 4-morpholinyl; or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring or C_1–C_{20} heteroaryl each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, $-CH(CH_3)_2$, $-CH_2CF_3$, $-CH_2CH_2OH$ and $-C(CH_3)_2OH$; and

R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

In a first aspect, there is provided compounds of Formula I:



I

stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof, wherein:

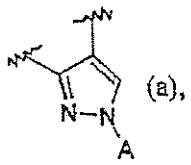
Z^1 is CR^1 or N;

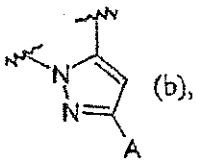
Z^2 is CR^2 or N;

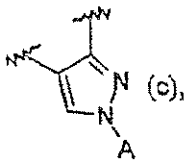
Z^3 is CR^3 or N;

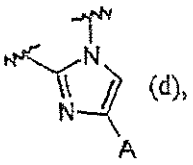
Z^4 is CR^4 or N;

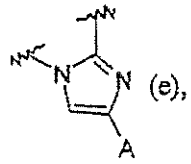
B is a pyrazolyl, or imidazolyl ring fused to the benzoxepin ring and selected from the structures:


(a),


(b),


(c),


(d),


(e),

R^1, R^2, R^3, and R^4 are independently selected from H, F, Cl, Br, I, –CN, $-COR^{10}$, $-CO_2R^{10}$, $-C(=O)N(R^{10})OR^{11}$, $-C(=NR^{10})NR^{10}R^{11}$, $-C(=O)NR^{10}R^{11}$, $-NO_2$, $-NR^{10}R^{11}$, $-NR^{12}C(=O)R^{10}$, $-NR^{12}C(=O)OR^{11}$, $-NR^{12}C(=O)NR^{10}R^{11}$, $-NR^{12}C(=O)(C_1-C_{12}$alkylene)$NR^{10}R^{11}$, $-NR^{12}(C_1-C_{12}$ alkylene)$NR^{10}R^{11}$, $-NR^{12}(C_1-C_{12}$alkylene)OR^{10}, $-NR^{12}(C_1-C_{12}$ alkylene)$C(=O)NR^{10}R^{11}$, $-OR^{10}$, $-S(O)_2R^{10}$, $-C(=O)NR^{10}(C_1-C_{12}$alkylene)$NR^{10}R^{11}$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)$NR^{10}C(=O)OR^{11}$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)$NR^{10}C(=O)R^{11}$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)R^{10}, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryl, C_1-C_{20} heteroaryl, $-(C_3-C_{12}$ carbocyclyl$)-(C_1-C_{12}$ alkyl), $-(C_2-C_{20}$ heterocyclyl$)-(C_1-C_{12}$ alkyl), $-(C_6-C_{20}$ aryl$)-(C_1-C_{12}$ alkyl), $-(C_1-C_{20}$ heteroaryl$)-(C_1-C_{12}$ alkyl), $-(C_1-C_{12}$ alkylene$)-(C_3-C_{12}$

carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–(C_3–C_{12} carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–C(=O)–(C_2–C_{20} heterocyclyl), -(C_1-C_{12}alkylene)–(C_1–C_{20}heteroaryl), –(C_1–C_{12}alkylene)–(C_2–C_{20}heterocyclyl)–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_6–C_{20} aryl)–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl)–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–C(=O)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)C(=O)OR^{10}, –(C_1–C_{12} alkylene)–$NR^{10}R^{11}$, –(C_1–C_{12} alkylene)$NR^{12}C(=O)R^{10}$, –(C_1–C_{12} alkylene)OR^{10}, –(C_1–C_{12} alkylene)–NR^{10}–(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl), –(C_1–C_{12} alkylene)–NR^{10}–(C_1–C_{12} alkylene)–(C_1–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–NR^{10}–(C_1–C_{12} alkylene)–NHC(=O)–(C_1–C_{20} heteroaryl), –(C_1–C_{12} alkylene)-(C_2–C_{20} heterocyclyl)–$NR^{10}R^{11}$, and –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–(C_1–C_{12} alkyl)–$NR^{10}R^{11}$,

where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, R^{10}, –SR^{10}, –$S(O)_2R^{10}$, –$S(O)_2NR^{10}R^{11}$, –$NR^{10}R^{11}$, –$NR^{12}C(O)R^{10}$, –CO_2R^{10}, –$C(O)R^{10}$, –$CONR^{10}R^{11}$, oxo, and –OR^{10};

A is selected from –$C(=O)NR^5R^6$, –NR^5R^6, C_2–C_{20} heterocyclyl and C_1–C_{20} heteroaryl wherein heterocyclyl and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, –COR^{10}, –CO_2R^{10}, –$C(=O)N(R^{10})OR^{11}$, –$C(=NR^{10})NR^{10}R^{11}$, –$C(=O)NR^{10}R^{11}$, –NO_2, –$NR^{10}R^{11}$, –$NR^{12}C(=O)R^{10}$, –$NR^{12}C(=O)OR^{11}$, –$NR^{12}C(=O)NR^{10}R^{11}$, –$NR^{12}C(=O)$($C_1$–$C_{12}$alkylene)$NR^{10}R^{11}$, –$NR^{12}$($C_1$–$C_{12}$ alkylene)$NR^{10}R^{11}$, -NR^{12}(C_1-C_{12}alkylene)OR^{10}, -NR^{12}(C_1-C_{12}alkylene)$C(=O)NR^{10}R^{11}$, –OR^{10}, –$S(O)_2R^{10}$, –$C(=O)NR^{10}$(C_1–C_{12} alkylene)$NR^{10}R^{11}$, –$C(=O)NR^{10}$(C_1–C_{12} alkylene)$NR^{10}C(=O)OR^{11}$, –$C(=O)NR^{10}$(C_1–C_{12} alkylene)$NR^{10}C(=O)R^{11}$, –$C(=O)NR^{10}$(C_1–C_{12} alkylene)R^{10}, C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, C_1–C_{20} heteroaryl, –(C_3–C_{12} carbocyclyl)–(C_1–C_{12} alkyl), –(C_2–C_{20} heterocyclyl)–(C_1–C_{12} alkyl), –(C_6–C_{20} aryl)–(C_1–C_{12} alkyl), –(C_1–C_{20} heteroaryl)–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–(C_3–C_{12}

carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–C(=O)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)-(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_6–C_{20} aryl)–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl)–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–C(=O)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)C(=O)OR^{10}, –(C_1–C_{12} alkylene)–$NR^{10}R^{11}$, –(C_1–C_{12} alkylene)$NR^{12}C(=O)R^{10}$, –(C_1–C_{12} alkylene)OR^{10}, -(C_1-C_{12} alkylene)–NR^{10}–(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl), –(C_1–C_{12} alkylene)–NR^{10}–(C_1–C_{12} alkylene)–(C_1–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–NR^{10}–(C_1–C_{12} alkylene)–NHC(=O)–(C_1–C_{20} hetero-aryl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl)–$NR^{10}R^{11}$, and –(C_1–C_{12} alkylene)-(C_2–C_{20} hetero-cyclyl)–(C_1–C_{12} alkyl)–$NR^{10}R^{11}$,

where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, R^{10}, –SR^{10}, –$S(O)_2R^{10}$, –$NR^{10}R^{11}$, –$NR^{12}C(O)R^{10}$, –CO_2R^{10}, –$C(O)R^{10}$, -$CONR^{10}R^{11}$, and –OR^{10};

R^5 is selected from H, and C_1–C_{12} alkyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NH_2, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, and –$S(O)_2CH_3$;

R^6 is selected from C_1–C_{12} alkyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and C_6–C_{20} aryl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_3, –CH_2OH, –$CH_2C_6H_5$, –CN, –CF_3, –CO_2H, –$C(O)CH_3$, –NH_2, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, oxo, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, –$S(O)_2CH_3$, –$C(=O)NR^{10}$(C_1–C_{12} alkylene)$NR^{10}R^{11}$, phenyl, pyridinyl, tetrahydro-furan-2-yl, 2,3-dihydro-benzofuran-2-yl, 1-isopropyl-pyrrolidin-3-ylmethyl, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, -C≡CR^{13}, -CH=CHR^{13}, and –$C(=O)NR^{10}R^{11}$; or

R^5 and R^6 together with the nitrogen atom to which they are attached form C_2–C_{20} heterocyclyl or C_1–C_{20} heteroaryl, optionally substituted with one or more groups selected from F, Cl, Br, I, CH_3, $C(CH_3)_3$, –CH_2OH, -CH_2CH_2OH, –$CH_2C_6H_5$, pyridin-2-yl, 6-methyl-pyridin-2-yl,

pyridin-4-yl, pyridin-3-yl, pyrimidin-2-yl, pyrazin-2-yl, tetrahydrofuran-carbonyl, 2-methoxy-phenyl, benzoyl, cyclopropylmethyl, (tetrahydrofuran-2-yl)methyl, 2,6-dimethyl-morpholin-4-yl, 4-methyl-piperazine-carbonyl, pyrrolidine-1-carbonyl, cyclopropanecarb-onyl, 2,4-difluoro-phenyl, pyridin-2-ylmethyl, morpholin-4-yl, –CN, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-COCF_3$, $-COCH_3$, $-COCH(CH_3)_2$, $-NO_2$, $NHCH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-NHCOCH_3$, $-NCH_3COCH_3$, $-NHS(O)_2CH_3$, –OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2S(O)_2NHCH_3$, $-CH_2S(O)_2CH_2CH_3$, $-S(O)_2NHCH_3$, $-S(O)_2CH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2N(CH_3)_2$ and $-S(O)_2CH_3$;

R^{10}, R^{11} and R^{12} are independently selected from H, C_1-C_{12} alkyl, -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_6-C_{20} aryl), -(C_1-C_{12} alkylene)-(C_3-C_{12} carbocyclyl), C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2NH_2$, $-(CH_2)_2N(CH_3)_2$, $-CH_2C_6H_5$, –CN, $-CF_3$, $-CO_2H$, $-C(O)CH_3$, $-C(O)CH(OH)CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, =O (oxo), –OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OP(O)(OH)_2$, $-SCH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2N(CH_3)_2$, $-CH_2S(O)_2NHCH_3$, $-CH_2S(O)_2CH_2CH_3$, $-S(O)_2NHCH_3$, $-S(O)_2CH_2CH_3$, pyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, cyclopropyl, cyclopentyl, oxetanyl, 4-methylpiperazin-1-yl, and 4-morpholinyl; or

R^{10} and R^{11} when attached to a nitrogen atom together with the nitrogen atoms to which they are attached form a C_2–C_{20} heterocyclyl ring or C_1–C_{20} heteroaryl each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, –CN, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, –OH, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, $-CH(CH_3)_2$, $-CH_2CF_3$, $-CH_2CH_2OH$ and $-C(CH_3)_2OH$; and

R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, –CN, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

In a second aspect, there is provided a pharmaceutical composition comprised of a compound as defined above and a pharmaceutically acceptable carrier, glidant, diluent, or excipient, optionally further comprising an additional therapeutic agent selected from a chemotherapeuttc agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

In a third aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.

In a fourth aspect, there is provided a compound as defined above for use in the prophylactic or therapeutic treatment of cancer.

In a fifth aspect, there is provided a kit for treating a PI3K-mediated condition, comprising (a) a first pharmaceutical composition comprising a compound as defined above; and (b) instructions for use.

Reference will now be made in detail to certain embodiments of the disclosure~~invention~~, examples of which are illustrated in the accompanying structures and formulas. While the disclosure~~invention~~ will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the disclosure~~invention~~ to those embodiments. On the contrary, the disclosure~~invention~~ is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present disclosure~~invention~~ as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present disclosure~~invention~~. The present disclosure~~invention~~ is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkyl groups include, but are not limited to, methyl (Me, -CH_3), ethyl (Et,