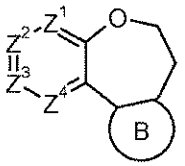
Claims

1. Compounds of Formula I:



I

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

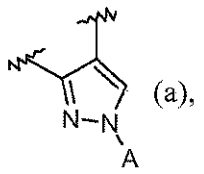
Z^1 is CR^1 or N;

Z^2 is CR^2 or N;

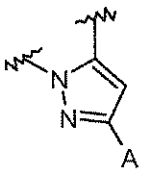
Z^3 is CR^3 or N;

Z^4 is CR^4 or N;

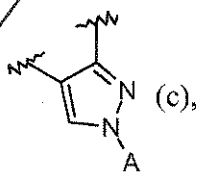
B is a pyrazolyl, imidazolyl, or triazolyl ring fused to the benzoxepin ring and selected from the structures:



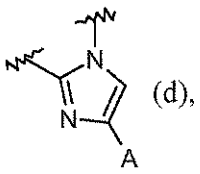
(a),



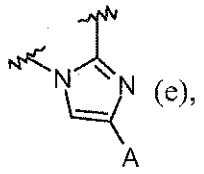
(b),



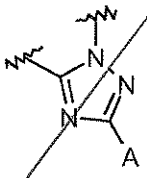
(c),



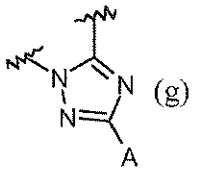
(d),



(e),



(f),



(g)

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

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_6–C_{20} aryl, C_2–C_{20} heterocyclyl and C_1–C_{20} heteroaryl wherein aryl, 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} 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} 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, $-C{\equiv}CR^{13}$, $-CH=CHR^{13}$, 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, cyclopropanecarbonyl, 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 $-S(O)_2CH_3$.

2. The compounds of claim 1 wherein Z^1 is CR^1; Z^2 is CR^2; Z^3 is CR^3; and Z^4 is CR^4.

3. The compounds of claim 1 or 2 wherein B is a structure of formula (a), (b), (d), (e), (f) or (g).

4. The compounds of any one of claims 1 to 3 wherein A is $-C(=O)NR^5R^6$ wherein R^5 is CH_3 and R^6 is phenyl substituted with one or more F or a group of formula (ii), (iii), (iv), (v) or (vi):

8. A pharmaceutical composition comprised of a compound of any one of claims 1 to 7 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient, optionally further comprising an additional therapeutic agent selected from a chemotherapeutic 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.

9. A method of treating cancer in a mammal comprised of administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 7.

10. The use of a compound according to any one of claims 1 to 7 for treating cancer.

11. The use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.

12. A compound according to any one of claims 1 to 7 for use in the prophylactic or therapeutic treatment of cancer.

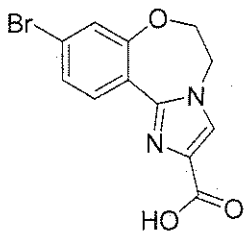
13. A kit for treating a PI3K-mediated condition, comprising (a) a first pharmaceutical composition comprising a compound of any one of claims 1 to 6; and (b) instructions for use.

14. A process for the preparation of a compound according to any one of claims 1 to 6

15. The invention as hereinbefore described.

Claims

1. A compound having the structure:



2. A pharmaceutical composition comprised of a compound of claim 1 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient, optionally further comprising an additional therapeutic agent selected from a chemotherapeutic 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.

3. The use of a compound of claim 1 in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.

4. A compound of claim 1 for use in the prophylactic or therapeutic treatment of cancer.

5. A kit for treating a PI3K-mediated condition, comprising (a) a first pharmaceutical composition comprising a compound of claim 1; and (b) instructions for use.

6. A process for the preparation of a compound according to any one of claims 1 to 6.