each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, or carbonate;

X is $-(CH(R^9))_z-$;

Y is $-N(R^9)-C(=O)-$, $-C(=O)-N(R^9)-$, $-C(=O)-N(R^9)-(CHR^9)-$, $-N(R^9)-S(=O)-$, $-S(=O)-N(R^9)-$, $-S(=O)_2-N(R^9)-$, $-N(R^9)-C(=O)-N(R^9)$ or $-N(R^9)S(=O)_2-$;

z is an integer of 1, 2, 3, or 4;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro;

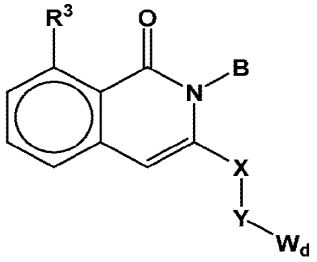
each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or heteroalkyl; or two adjacent occurrences of R^9 together with the atoms to which they are attached form a 4- to 7-membered ring;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl, each of which is substituted with one or more R^{10}, R^{11}, R^{12} or R^{13}, and

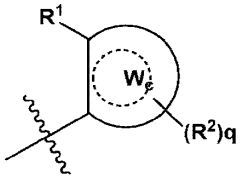
R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate or NR'R" wherein R' and R" are taken together with nitrogen to form a cyclic moiety.

14. The method of paragraph 14, wherein the PI3K inhibitor is:



or its pharmaceutically acceptable salt thereof, wherein

B is:



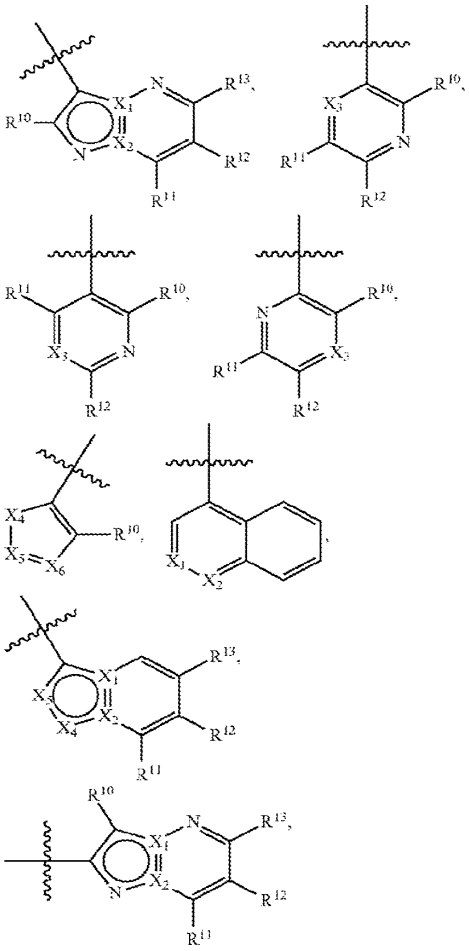
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

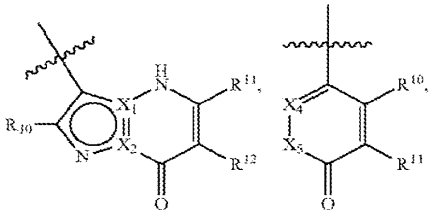
q is an integer of 0, 1, 2, 3, or 4;

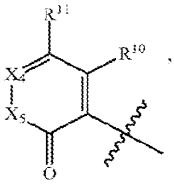
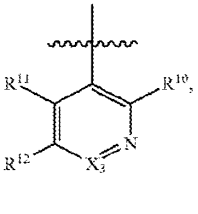
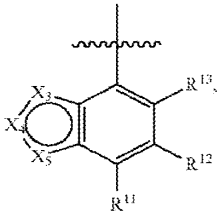
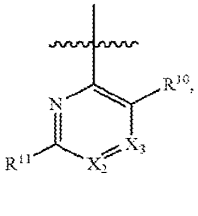
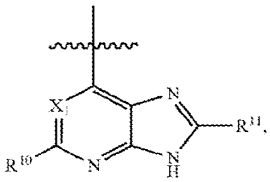
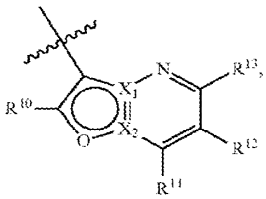
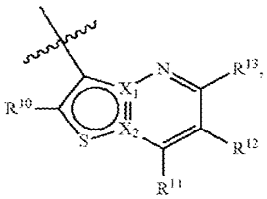
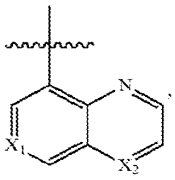
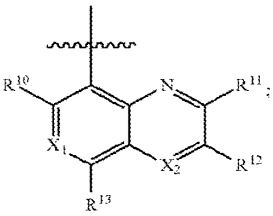
X is a bond or $-(CH(R^9))_z-$, and z is an integer of 1;

Y is $-N(R^9)-$;

W_d is:













or

;

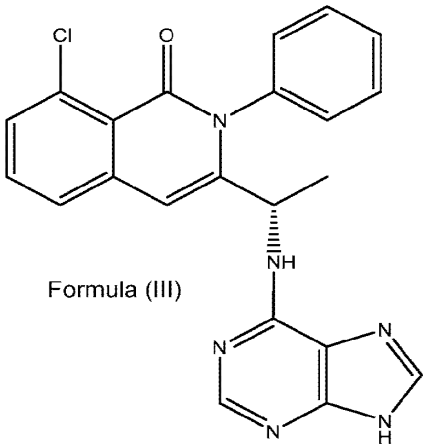
X_1, X_2 and X_3 are each independently C, CR^{13} or N; and X_4, X_5 and X_6 are each independently N, NH, CR^{13}, S or O;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy or nitro; and

each instance of R^9 is independently hydrogen, alkyl, or heterocycloalkyl.

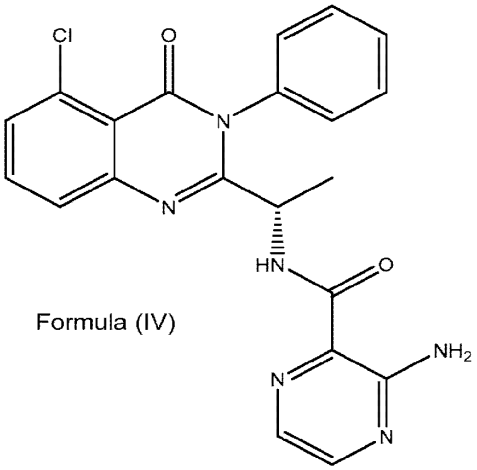
15. The method of paragraph 14, wherein the PI3K inhibitor is



Formula (III)

or a pharmaceutically acceptable salt thereof.

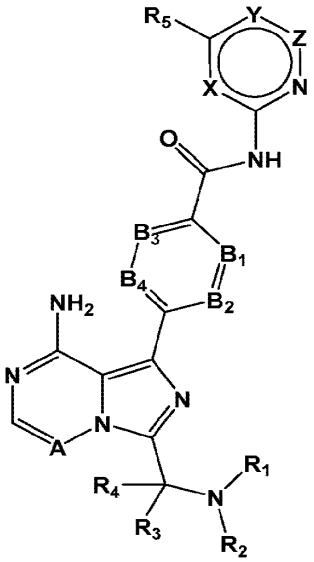
16. The method of paragraph 14, wherein the PI3K inhibitor is



Formula (IV)

or a pharmaceutically acceptable salt thereof.

17. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

X is CH, N, O or S;

Y is $C(R_6)$, N, O or S;

Z is CH, N or bond;

A is CH or N;

B_1 is N or $C(R_7)$;

B_2 is N or $C(R_8)$;

B_3 is N or $C(R_9)$;

B_4 is N or $C(R_{10})$;

R_1 is $R_{11}C(O)$, $R_{12}S(O)$, $R_{13}SO_2$ or (1-6C)alkyl optionally substituted with R_{14};

R_2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R_3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R_2 and R_3 form, together with the N and C atom they are attached to, a (3- 7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R_4 is H or (1-3C)alkyl;

R_5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R_5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R_6 is H or (1-3C)alkyl; or

R_5 and R_6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R_7 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy;

R_8 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy; or

R_7 and R_8 together with the carbon atoms they are attached to, form (6-10C)aryl or (1-9C)heteroaryl;

R_9 is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{10} is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{11} is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or R_{11} is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

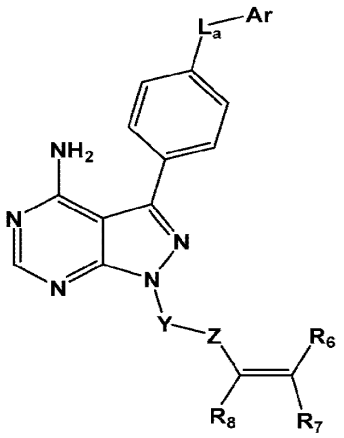
R_{11} is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R_{12} and R_{13} are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano; and

R14 is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl.

18. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

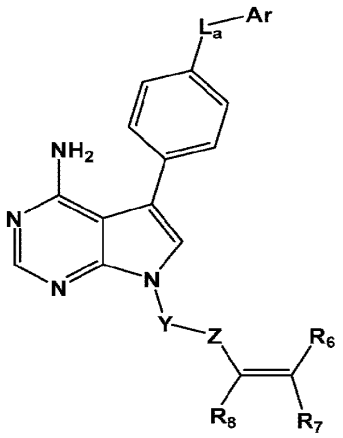
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1-C_6alkyl.

19. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

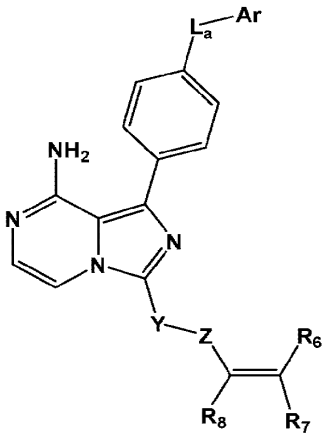
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1-C_6alkyl.

20. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

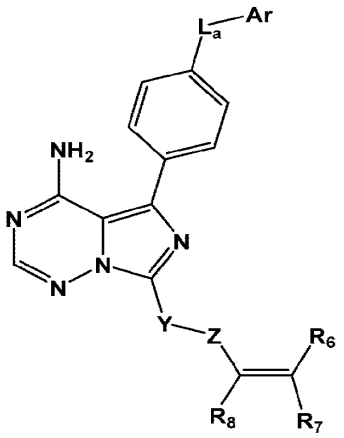
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1-C_6alkyl.

21. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof, wherein

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

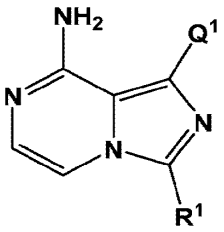
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NRS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are each H; or R_7 and R_8 taken together form a bond;

R_6 is H; and

R is H or C_1-C_6alkyl.

22. The method of paragraph 1, wherein the BTK inhibitor is:



or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is aryl^1, heteroaryl^1, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one to five independent G^1 substituents;

R^1 is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, or heterobicycloalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

G^1 and G^{41} are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, -CN, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C{=}O)R^3$, $NR^2(C{=}O)OR^3$, $NR^2(C{=}O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C{=}S)OR^2$, $-(C{=}O)SR^2$, $-NR^2(C{=}NR^3)NR^{2a}R^{3a}$, $-NR^2(C{=}NR^3)OR^{2a}$, $-NR^2(C{=}NR^3)SR^{3a}$, $-O(C{=}O)OR^2$, $-O(C{=}O)NR^2R^3$, $-O(C{=}O)SR^2$, $-S(C{=}O)OR^2$, $-S(C{=}O)NR^2R^3$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333}a)_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333a}$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents; or $-(X^1)_n-(Y^1)_m-R^4$; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333a}$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally

substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}$, $R^{333}(R^{333a})_{j3a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j3a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j3a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222}aR^{333}a$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333}a$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents;

G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{3a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-CONR^{21}R^{31}$, $-NO_2$, -CN, $-S(O)_{j4}R^{21}$, $-SO_2NR^{21}R^{31}$, $NR^{21}(C=O)R^{31}$, $NR^{21}(C=O)OR^{31}$, $NR^{21}(C=O)NR^{21}R^{31}$, $NR^{21}S(O)_{j4}R^{31}$, $-(C=S)OR^{21}$, $-(C=O)SR^{21}$, $-NR^{21}(C=NR^{31})NR^{2a1}R^{3a1}$, $-NR^{21}(C=NR^{31})OR^{2a1}$, $-NR^{21}(C=NR^{31})SR^{3a1}$, $-O(C=O)OR^{21}$, $-O(C=O)NR^{21}R^{31}$, $-O(C=O)SR^{21}$, $-S(C=O)OR^{21}$, $-S(C=O)NR^{21}R^{31}$, $-P(O)OR^{21}OR^{31}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j4a}R^{3331}$, $-(C=S)OR^{2221}$, $-(C=O)SR^{2221}$, $-NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C=NR^{3331})OR^{222a1}$, $-NR^{2221}(C=NR^{3331})SR^{333a1}$, $-O(C=O)OR^{2221}$, $-O(C=O)NR^{2221}R^{3331}$, $-O(C=O)SR^{2221}$, $-S(C=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C=O)NR^{2221}R^{3331}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j5a}R^{3331}$, $-(C=S)OR^{2221}$, $-(C=O)SR^{2221}$, $-NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C=NR^{3331})OR^{222a1}$, $-NR^{2221}(C=NR^{3331})SR^{333a1}$, $-O(C=O)OR^{2221}$, $-O(C=O)NR^{2221}R^{3331}$, $-O(C=O)SR^{2221}$, $-S(C=O)OR^{2221}$, $-P(O)OR^{2221}R^{3331}$, or $-S(C=O)NR^{2221}R^{3331}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j6a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$,

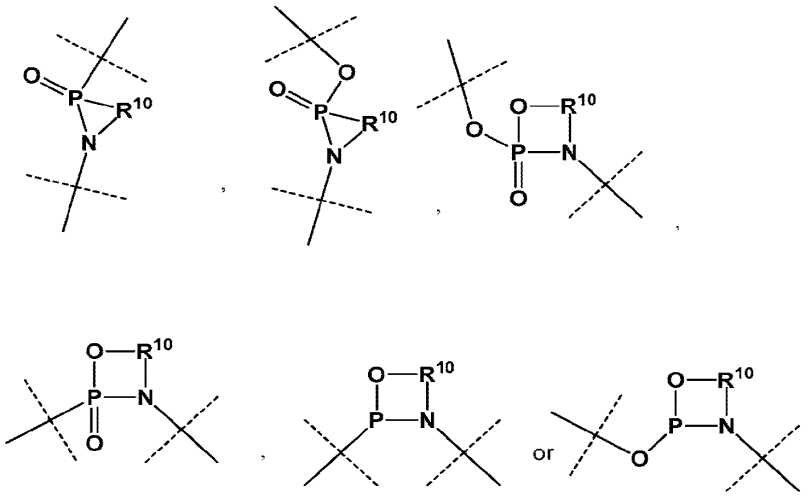
$NR^{2221}(C{=}O)R^{3331}$, $NR^{2221}(C{=}O)OR^{3331}$, $NR^{2221}(C{=}O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j6a}R^{3331}$, $-(C{=}S)OR^{2221}$, $-(C{=}O)SR^{2221}$, $-NR^{2221}(C{=}NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C{=}NR^{3331})OR^{222a1}$, $-NR^{2221}(C{=}NR^{3331})SR^{333a1}$, $-O(C{=}O)OR^{2221}$, $-O(C{=}O)NR^{2221}R^{3331}$, $-O(C{=}O)SR^{2221}$, $-S(C{=}O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C{=}O)NR^{2221}R^{3331}$ substituents; or G^{11} is taken together with the carbon to which it is attached to form a double bond which is substituted with R^5 and G^{111};

R^2, R^{2a}, R^3, R^{3a}, R^{222}, $R^{222}a$, R^{333}, R^{333a}, R^{21}, R^{2a1}, R^{31}, R^{3a1}, R^{2221}, R^{222a1}, R^{3331}, and R^{333a1} are each independently equal to C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or in the case of $-NR^2R^3(R^{3a})_{j1}$ or $-NR^{222}R^{333}(R^{333}a)_{j1}a$ or $-NR^{222}R^{333}(R^{333}a)j2a$ or $-NR^{2221}R^{3331}(R^{333a1})_{j3a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, R^2 and R^3 or R^{222} and $R^{333}3$ or R^{2221} and R^{3331} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted by one or more G^{111} substituents;

X^1 and Y^1 are each independently -O-, $-NR^7-$, $-S(O)_{j7}-$, $-CR^5R^6-$, $-N(C(O)OR^7)-$, $-N(C(O)R^7)-$, $-N(SO_2R^7)-$, $-CH_2O-$, $-CH_2S-$, $-CH_2N(R^7)-$, $-CH(NR^7)-$, $-CH_2N(C(O)R^7)-$, $-CH_2N(C(O)OR^7)-$, $-CH_2N(SO_2R^7)-$, $-CH(NHR^7)-$, $-CH(NHC(O)R^7)-$, $-CH(NHSO_2R^7)-$, $-CH(NHC(O)OR^7)-$, $-CH(OC(O)R^7)-$, $-CH(OC(O)NHR^7)-$, -CH=CH-, -C.ident.C-, $-C(=NOR^7)-$, -C(O)-, $-CH(OR^7)-$, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$ $-OC(O)N(R^7)-$, $-N(R^7)C(O)N(R^7)-$, $-NR^7C(O)O-$, $-S(O)N(R^7)-$, $-S(O)_2N(R^7)-$, $-N(C(O)R^7)S(O)-$, $-N(C(O)R^7)S(O)_2-$, $-N(R^7)S(O)N(R^7)-$, $-N(R^7)S(O)_2N(R^7)-$, $-C(O)N(R^7)C(O)-$, $-S(O)N(R^7)C(O)-$, $-S(O)_2N(R^7)C(O)-$, $-OS(O)N(R^7)-$, $-OS(O)_2N(R^7)-$, $-N(R^7)S(O)O-$, $-N(R^7)S(O)_2O-$, $-N(R^7)S(O)C(O)-$, $-N(R^7)S(O)_2C(O)-$, $-SON(C(O)R^7)-$, $-SO_2N(C(O)R^7)-$, $-N(R^7)SON(R^7)-$, $-N(R^7)SO_2N(R^7)-$,

-C(O)O-, -N(R^7)P(OR^8)O-, -N(R^7)P(OR^8)-, -N(R^7)P(O)(OR^8)O-, -N(R^7)P(O)(OR^8)-, -N(C(O)R^7)P(OR^8)O-, -N(C(O)R^7)P(OR^8)-, -N(C(O)R^7)P(O)(OR^8)O-, -N(C(O)R^7)P(OR^8)-, -CH(R^7)S(O)-, -CH(R^7)S$(O)_2$-, -CH(R^7)N(C(O)OR^7)-, -CH(R^7)N(C(O)R^7)-, -CH(R^7)N(SO_2R^7)-, -CH(R^7)O-, -CH(R^7)S-, -CH(R^7)N(R^7)-, -CH(R^7)N(C(O)R^7)-, -CH(R^7)N(C(O)OR^7)-, -CH(R^7)N(SO_2R^7)-, -CH(R^7)C(=NOR^7)-, -CH(R^7)C(O)-, -CH(R^7)CH(OR^7)-, -CH(R^7)C(O)N(R^7)-, -CH(R^7)N(R^7)C(O)-, -CH(R^7)N(R^7)S(O)-, -CH(R^7)N(R^7)S$(O)_2$-, -CH(R^7)OC(O)N(R^7)-, -CH(R^7)N(R^7)C(O)N(R^7)-, -CH(R^7)NR^7C(O)O-, -CH(R^7)S(O)N(R^7)-, -CH(R^7)S$(O)_2$N(R^7)-, -CH(R^7)N(C(O)R^7)S(O)-, -CH(R^7)N(C(O)R^7)S(O)-, -CH(R^7)N(R^7)S(O)N(R^7)-, -CH(R^7)N(R^7)S$(O)_2$N(R^7)-, -CH(R^7)C(O)N(R^7)C(O)-, -CH(R^7)S(O)N(R^7)C(O)-, -CH(R^7)S$(O)_2$N(R^7)C(O)-, -CH(R^7)OS(O)N(R^7)-, -CH(R^7)OS$(O)_2$N(R^7)-, -CH(R^7)N(R^7)S(O)O-, -CH(R^7)N(R^7)S$(O)_2$O-, -CH(R^7)N(R^7)S(O)C(O)-, -CH(R^7)N(R^7)S$(O)_2$C(O)-, -CH(R^7)SON(C(O)R^7)-, -CH(R^7)SO_2N(C(O)R^7)-, -CH(R^7)N(R^7)SON(R^7)-, -CH(R^7)N(R^7)SO_2N(R^7)-, -CH(R^7)C(O)O-, -CH(R^7)N(R^7)P(OR^8)O-, -CH(R^7)N(R^7)P(OR^8)-, -CH(R^7)N(R^7)P(O)(OR^8)O-, -CH(R^7)N(R^7)P(O)(OR^8)-, -CH(R^7)N(C(O)R^7)P(OR^8)O-, -CH(R^7)N(C(O)R^7)P(OR^8)-, -CH(R^7)N(C(O)R^7)P(O)(OR^8)O-, or -CH(R^7)N(C(O)R^7)P(OR^8)-; or

X^1 and Y^1 are each independently represented by one of the following structural formulas:



R^{10}, taken together with the phosphinamide or phosphonamide, is a 5-, 6-, or 7-membered aryl, heteroaryl or heterocyclyl ring system;

R^5, R^6, and G^{111} are each independently a C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}R^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R^{69}; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R^{69};

R^7 and R^8 are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G^{111} substituents;

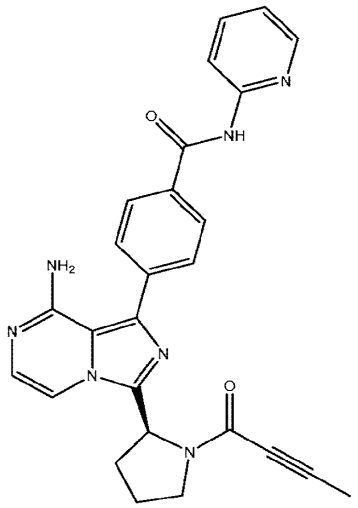
R^4 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G^{41} substituents;

R^{69} is equal to halo, $-OR^{78}$, -SH, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-CONR^{78}R^{88}$, $-NO_2$, -CN, $-S(O)_{j8}R^{78}$, $-SO_2NR^{78}R^{88}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or -N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$ $SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

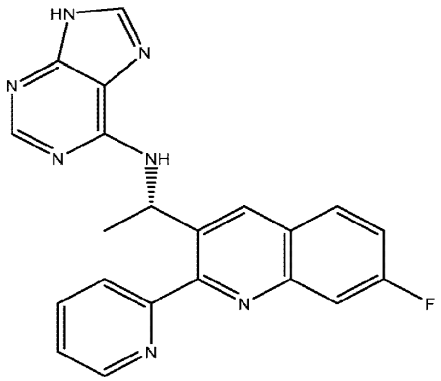
R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, C_{1-10}alkylcarbonyl, C_{2-10}alkenylcarbonyl, C_{2-10}alkynylcarbonyl, C_{1-10}alkoxycarbonyl, C_{1-10}alkoxycarbonylC_{1-10}alkyl, monoC_{1-6}alkylaminocarbonyl, diC_{1-6}alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C_{1-10}alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, -SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl), or -N(C_{0-4}alkyl)(C_{0-4}alkyl) substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(C_{0-4}alkyl), C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, -CON(C_{0-4}alkyl)(C_{0-10}alkyl), -SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl), or -N(C_{0-4}alkyl)(C_{0-4}alkyl) substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(C_{0-4}alkyl), C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, -CON(C_{0-4}alkyl)(C_{0-4}alkyl), -SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl), or -N(C_{0-4}alkyl)(C_{0-4}alkyl) substituents; or mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or -N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(C_{0-4}alkyl), C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, -CON(C_{0-4}alkyl)(C_{0-4}alkyl), -SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl), or -N(C_{0-4}alkyl)(C_{0-4}alkyl) substituents; and

n, m, j1, j1a, j2a, j3a, j4, j4a, j5a, j6a, j7, and j8 are each independently equal to 0, 1, or 2.

23. The method of paragraphs 1, 2, or 3, wherein the BTK inhibitor is:



or a pharmaceutically-acceptable salt thereof, and the PI3K inhibitor is:



or a pharmaceutically-acceptable salt thereof.

24. The method of paragraphs 1, 2, or 3, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or apharmaceutically-acceptable salt thereof, and the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

25. A method of treating a solid tumor cancer in a human comprising administering a

therapeutically effective dose of a BTK inhibitor and a PI3K inhibitor, wherein the dose is effective to inhibit signaling between the cells of the solid tumor cancer and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts.

26. The method of Claim 25, wherein the cancer is a solid tumor cancer, and wherein the solid tumor cancer is selected from the group consisting of colon carcinoma, pancreatic carcinoma, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, and stomach cancer.

27. The method of any of Claims 25-26, wherein the dose is further effective to increase immune system recognition and rejection of the solid tumor by the human.

28. The method of any of Claims 25-27, wherein the PI3K inhibitor is a PI3K-δ inhibitor.

ABSTRACT

[00323] In some embodiments, the invention includes a therapeutic combination of a phosphoinositide 3-kinase (PI3K) inhibitor, including PI3K inhibitors selective for the γ- and δ-isoforms and selective for both γ- and δ-isoforms, and a Bruton's tyrosine kinase (BTK) inhibitor. In some embodiments, the invention includes therapeutic methods of using a BTK inhibitor and a PI3K-δ inhibitor to treat solid tumor cancers by modulation of the tumor microenvironment, including macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts.

Electronic Acknowledgement Receipt	
EFS ID:	19829023
Application Number:	62035777
International Application Number:	
Confirmation Number:	2633
Title of Invention:	Therapeutic Combination of a PI3K Inhibitor and a BTK Inhibitor
First Named Inventor/Applicant Name:	Ahmed Hamdy
Customer Number:	28977
Filer:	Frederick Vogt
Filer Authorized By:	
Attorney Docket Number:	055112-5002-02-PR
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Application Type:	Provisional

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Payment was successfully received in RAM	$660
RAM confirmation Number	3466
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	ProvisionalSB.pdf	1477553 9bd6c35d98c26fad81658799c3ddaf2d98f26ef6	no	4
Warnings:					
Information:					
2	Drawings-only black and white line drawings	DWGS.pdf	655240 5638dbd989f745738bc5b53ef141003355ffacbf	no	41
Warnings:					
Information:					
3		SPEC.pdf	1118854 3dca9991cd91dbbf08057728e0c879d6e3ae750c	yes	146

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	119
Claims	120	145
Abstract	146	146

Warnings:					
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4	Fee Worksheet (SB06)	fee-info.pdf	31180 d859e367e5f1db5a0534524d082593db01c524eb	no	2
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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/IB2015/000645**
International filing date:		**21 January 2015 (21.01.2015)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**US**
	Number:	**62/035,777**
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United States Patent and Trademark Office

February 08, 2015

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APPLICATION NUMBER: ***61/929,742***
FILING DATE: ***January 21, 2014***
RELATED PCT APPLICATION NUMBER: ***PCT/US15/12288***

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS ***US61/929,742***

UNITED STATES PATENT AND TRADEMARK OFFICE · DEPARTMENT OF COMMERCE

Certified by

David J. Kappos

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country i
Ahmed		Hamdy	San Carlos	CA	US

Inventor 2 — Remove

Given Name	Middle Name	Family Name	City	State	Country i
Raquel		Izumi	San Carlos	CA	

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Title of Invention	Methods of Use of ACP-196
Attorney Docket Number (if applicable)	055112-5000

Correspondence Address

Direct all correspondence to (select one):

◉ The address corresponding to Customer Number	○ Firm or Individual Name
Customer Number	28977

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ◉ No.
- ○ Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:
- ○ Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

EFS - Web 1.0.1

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

- ○ Applicant asserts small entity status under 37 CFR 1.27
- ○ Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- ◉ No

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Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Frederick G. Vogt/			Date (YYYY-MM-DD)	2014-01-21
First Name	Frederick	Last Name	Vogt	Registration Number (If appropriate)	70115

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

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6. A record in this system of records may be disclosed, as a routine use, t o a n other federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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A Phase 1, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia

Protocol Number:	ACE-CL-001
IND Number:	118717
Drug Product:	ACP-196
Medical Monitor:	Ahmed Hamdy, MD a.hamdy@acerta-pharma.com 831.421.1757 (cell)
sponsor:	Acerta Pharma, LLC 1509 Industrial Rd San Carlos, CA 94070
Protocol Date:	01 October 2013

Confidentiality Statement

This document contains proprietary and confidential information of Acerta Pharma, LLC that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Acerta Pharma, LLC.

Investigator's Agreement

I have read the attached protocol entitled "A Phase 1, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia" and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Acerta Pharma, LLC.

Signature

Print Name of Principal Investigator | Date (DD Month YYYY)

Signature

Medical Monitor | Oct. 21 – 2013
Date (DD Month YYYY)

Protocol Synopsis

Protocol Number:	ACE-CL-001
Study Drug:	ACP-196
Protocol Title:	A Phase 1, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia
Phase:	Phase 1
Comparator:	None
Background and Rationale for Study	Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton's tyrosine kinase (BTK) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL). Acerta Pharma LLC (Acerta Pharma) has developed a novel second generation BTK inhibitor, ACP-196, that achieves significant oral bioavailability and potency. The purpose of this study is to evaluate the safety and efficacy of ACP-196 in treating subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).
Study Design:	This study is a multicenter, open-label, nonrandomized, sequential group, dose-escalation study. The following dose cohorts will be evaluated: Cohort 1: 100 mg/day for 28 days (= 1 cycle) Cohort 2: 175 mg/day for 28 days (= 1 cycle) Cohort 3: 250 mg/day for 28 days (= 1 cycle) Cohort 4: 350 mg/day for 28 days (= 1 cycle) Cohort 5: 450 mg/day for 28 days (= 1 cycle) Cohort 6: TBD mg/day for 28 days (= 1 cycle) Each cohort will be enrolled sequentially with 6 subjects per cohort. If ≤ 1 dose-limiting toxicity (DLT; see Section 3.8 for definition) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Subjects may be enrolled in the next cohort if 4 of the 6 subjects enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining 2 subjects are completing evaluation. If ≥ 2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the maximum tolerated dose (MTD) will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Dose escalation will end when either the MTD is achieved or at 3 dose levels above full BTK occupancy, whichever occurs first. Full BTK occupancy is

	defined as ACP-196 active-site occupancy of > 80% (average of all subjects in cohort) at 24 hours postdose. Should escalation to Cohort 6 be necessary, the dose will be determined based on the aggregate data from Cohorts 1 to 5, which includes safety, efficacy, and pharmacokinetic (PK)/pharmacodynamic (PD) results. The dose for Cohort 6 will not exceed 900 mg/day. Treatment with ACP-196 may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. Subjects with disease progression will be removed from the study. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. Radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 12 and at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment. All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) due to the pancreatic findings in the 28-day Good Laboratory Practice (GLP) rat toxicity study. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected during the first week of treatment for PK/PD assessments. Electrocardiograms (ECGs) will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6. ECGs are done in triplicate for screening only. Thereafter, single ECGs are done unless a repeat ECG is required (see Section 4.1 for a more detailed description of ECG assessments). Refer to Table 4-1 for a comprehensive list of study assessments and their timing. A study schema is provided at the end of this synopsis.
Definition of Dose-limiting Toxicity	A DLT will be defined as any of the following events (if not related to disease progression): • Any Grade ≥ 3 nonhematologic toxicity (except alopecia) persisting despite receipt of a single course of standard outpatient symptomatic therapy (eg, Grade 3 diarrhea that responds to a single, therapeutic dose of Imodium® would not be considered a DLT) • Grade ≥ 3 prolongation of the corrected QT interval (QTc), as determined by a central ECG laboratory overread • Grade 4 neutropenia (absolute neutrophil count

	[ANC] < 500/μL) lasting > 7 days after discontinuation of therapy without growth factors or lasting > 5 days after discontinuation of therapy while on growth factors (ie, Grade 4 neutropenia not lasting as long as specified will not be considered a DLT) • Grade 4 thrombocytopenia (platelet count < 20,000/μL) lasting > 7 days after discontinuation of therapy or requiring transfusion (ie, Grade 4 thrombocytopenia not lasting as long as specified will not be considered a DLT) • Dosing delay due to toxicity for > 7 consecutive days
Study Objectives:	Primary Objective: • Establish the safety and the MTD of orally administered ACP-196 in subjects with CLL/SLL • Determine the PK of orally administered ACP-196 and identification of its major metabolite • Measure PD parameters including drug occupancy of BTK, the target enzyme, and effect on biologic markers of B-cell function Secondary Objective: Evaluate tumor response
Efficacy Parameters:	• Overall response rate • Duration of response • Progression-free survival
Safety Parameters:	• DLTs and MTD • Frequency, severity, and attribution of adverse events (AEs) based on the Common Terminology Criteria for Adverse Events (CTCAE v4.03) for nonhematologic AEs (See Table 5-1 for the grading scale used for hematologic toxicities)

Pharmacokinetic Parameters:	The plasma PK of ACP-196 and a metabolite will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of ACP-196: • $AUC_{(0-t)}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (Ct). • $AUC_{(0-24)}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation. • $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant. • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • Cl/F: Oral clearance
Pharmacodynamic Parameters:	The occupancy of BTK by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.
Sample Size:	Twenty-four to 36 subjects depending on dose escalation into subsequent cohorts.
Inclusion Criteria:	• Men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL; however, subjects with 17p deletion are eligible if they have relapsed after, or been refractory to, 1 prior treatment for CLL/SLL. • Body weight ≥ 60 kg. • ECOG performance status of ≤ 2. • Agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children. • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing

	capsules without difficulty. • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).
Exclusion Criteria:	• Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor. • A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ACP-196, or put the study outcomes at undue risk. • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification. • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Any immunotherapy within 4 weeks of first dose of study drug. • For subjects with recent chemotherapy or experimental therapy the first dose of study drug must occur after 5 times the half-life of the agent(s). • Relapsed after, or refractory to, prior BTK inhibitor therapy. • Concomitant use of medicines known to cause QT prolongation or Torsades de pointes (see Appendix 1). • Central nervous system (CNS) involvement by lymphoma • Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation. • Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection. • Major surgery within 4 weeks before first dose of study drug.

	• ANC < 0.75 x 10^9/L or platelet count < 50 x 10^9/L unless there is bone marrow involvement. • Creatinine > 1.5 x institutional upper limit of normal (ULN); total bilirubin > 1.5 x ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN unless disease related. • Serum amylase > 1.5 x ULN or serum lipase > 1.5 x ULN. • Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and QTc ≥ 480 ms • Lactating or pregnant.
Dosage Form and Strength:	ACP-196 is provided as 25-mg hard gelatin capsules prepared using standard pharmaceutical grade excipients. The color of the capsules is Swedish orange.
Dose Regimen/Route of Administration:	ACP-196 is an orally administered product. ACP-196 will be administered once daily on an empty stomach defined as no food 2 hours before and 30 minutes after dosing.
Statistics:	No formal statistical tests of hypotheses will be performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate. Twenty-four to 36 evaluable subjects will be enrolled in this study. The trial design is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1.

LIST OF ABBREVIATIONS

λ_z	terminal elimination rate constant
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
Cl/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed drug concentration
CNS	central nervous system
CR	complete remission (response)
CRi	CR with incomplete blood count recovery
CSSF	Clinical Supplies Shipping Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
G-CSF	granulocyte colony-stimulating factor
Hb	hemoglobin
HBV	hepatitis B virus

HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
ICF	informed consent form
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IgHV	immunoglobulin heavy-chain variable
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mos	months
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
PBMCs	peripheral blood mononuclear cells
PE	physical exam
PET	positron emission tomography
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (oral)
PP	per-protocol (analysis set)
PR	partial remission (response)
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SD	stable disease
SLL	small lymphocytic lymphoma
SPD	sum of the product of the diameters
$t_{1/2}$	half life
TBD	to be determined
T_{max}	time to maximum drug concentration
ULN	upper limit of normal
WHO	World Health Organization
XLA	X-linked agammaglobulinemia

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1. INTRODUCTION

1.1. Role of BTK in Lymphoid Cancers

Bruton's tyrosine kinase (BTK) is a non-receptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration [Mohamed 2009, Bradshaw 2010]. Functional null mutations of BTK in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells [Vihinen 2000]. Conversely, BTK activation is implicated in the pathogenesis of several B-cell malignancies [Buggy 2012]. Taken together, these findings have suggested that inhibition of BTK may offer an attractive strategy for treating B-cell neoplasms.

1.2. BTK Inhibition as a Therapy for Lymphoid Cancers

Ibrutinib (PCI-32765), a first-generation oral, small-molecule BTK inhibitor has been developed clinically for the treatment for B-cell malignancies and is currently under review in the United States for marketing approval. The nonclinical and early clinical findings with ibrutinib have created the foundation on which second-generation agents, such as ACP-196, will be developed.

In Phase 1/2 clinical testing as a monotherapy in subjects with hematologic malignancies [Advani 2013, Byrd 2013, Wang 2013], ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating $CD4^+$ cells or serum immunoglobulins were noted. Adverse events with an apparent relationship to study drug included diarrhea and rash.

In subjects with heavily pretreated non-Hodgkin lymphoma (NHL), ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in most subjects. Improvements in disease-associated anemia and thrombocytopenia were observed. The pattern of changes in subjects with CLL was notable. Single-agent ibrutinib caused rapid and substantial reductions in lymph node size concomitant with a redistribution of malignant sites into the peripheral blood. An asymptomatic absolute lymphocyte

count increase was observed that was maximal during the first few months of treatment and generally decreased thereafter but could be persistent in some subjects or could be seen repeatedly in subjects who had interruption and resumption of drug therapy.

Collectively, these data with ibrutinib support the potential benefits of selective BTK inhibition in the treatment of subjects with relapsed lymphoid cancers. However, while highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds [Acerta Pharma data on file]. For example, ibrutinib inhibits epidermal growth factor receptor (EGFR), which may be the cause of ibrutinib-related diarrhea and rash. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5 and 2D6, which increases the possibility of drug-drug interactions. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancers.

1.3. Preclinical Studies

Knowledge of the critical importance of BTK in tumor biology and the clinical profile observed with ibrutinib has encouraged the development of second-generation BTK inhibitors as a therapy for lymphoid cancers. Acerta Pharma, a pharmaceutical company with sites in San Carlos, CA, USA and in Oss, The Netherlands, has identified novel compounds that selectively inhibit BTK. Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of ACP-196, an orally bioavailable, new chemical entity that covalently inhibits BTK and shows encouraging activity and acceptable safety in nonclinical studies. ACP-196 may offer an improved therapeutic index relative to ibrutinib and may be more readily combined with other agents active in the therapy of lymphoid cancers. Summaries of preclinical studies are provided below. For more detailed information please refer to the Investigator's Brochure.

1.3.1. Chemistry

ACP-196 is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and ACP-196 is the S-enantiomer. ACP-196 is orally bioavailable in animals and is suitable for formulating in capsules. For clinical testing, ACP-196 has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

1.3.2. Efficacy Pharmacology

ACP-196 is currently being evaluated in an ongoing study of canine spontaneous B-cell lymphoma. Six dogs have been treated with ACP-196 2.5 mg/kg once daily oral administration for an average of 22 days (range 14 to 42 days). To date, partial remission (PR), per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma [Vali 2010], has been observed in 2 of 6 dogs. No ACP-196-related adverse events have been reported to date in this study. These findings are preliminary and similar to the clinical responses (ie, 3 dogs with PR out of 8 dogs treated) observed with ibrutinib in dogs with spontaneous B-cell lymphoma [Honigberg 2010].

1.3.3. Safety Pharmacology

In vitro and in vivo safety pharmacology studies with ACP-196 have demonstrated a favorable nonclinical safety profile.

When screened at 10 μM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, ACP-196 shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a IC_{50} of 2.7 μM, suggesting a low clinical risk of off-target effects. ACP-196 at 10 μM showed no inhibition of in vitro EGFR phosphorylation in an A431 human epidermoid cancer cell line whereas ibrutinib had an IC_{50} of 66 nM.

The in vitro effect of ACP-196 on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. ACP-196 inhibited hERG channel activity by 25% at 10 μM, suggesting a low clinical risk that ACP-196 would induce clinical QT prolongation as predicted by this assay.

ACP-196 was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of ACP 196 at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT

interval) parameters. The results suggest that ACP-196 is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.3.4. Drug-drug Interaction Potential

In vitro experiments evaluating loss of parent drug as catalyzed by CYPs indicated that ACP-196 is metabolized by CYP3A4.

In vitro metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with ^{14}C-labelled ACP-196 indicated 2 mono-oxidized metabolites and a glutathione conjugate. No unique human metabolite was identified. Preliminary evaluations of metabolism in the plasma, bile, and urine of rats, dogs, and monkeys indicated metabolic processes of oxidation, glutathione binding, and hydrolysis. It was shown that ACP-196 binds to glutathione but does not deplete glutathione in vitro.

Nonclinical CYP interaction studies data indicate that ACP-196 is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYP enzymes.

1.3.5. In Vivo General Toxicology

To date, the toxicology program has included 28-day GLP evaluations in both rats and dogs. In the 28-day study in male and female Sprague-Dawley rats, animals received oral gavage ACP-196 doses of 30, 100, and 300 mg/kg/day. In the 28-day study in male and female beagle dogs, animals received oral ACP-196 doses of 3, 10, and 30 mg/kg/day. Both studies had 28-day recovery periods.

The no observable adverse effect level in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, the 100 mg/kg/day was selected to conservatively represent the highest nonseverely toxic dose (HNSTD). In dogs at 30 mg/kg/day, no adverse effects on the pancreas where observed.

1.3.6. Summary and Conclusions

The design and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with lymphoid cancers; knowledge of the activity and safety of a first-generation BTK inhibitor, ibrutinib, in

subjects with hematologic cancers; and the available nonclinical information regarding ACP-196.

The collective data support the following conclusions:

- BTK expression plays an important role in the biology of lymphoid neoplasms, which represent serious and life-threatening disorders with continuing unmet medical need.
- Clinical evaluation of ACP-196 as a potential treatment for these disorders has sound scientific rationale based on observations that the compound selectively abrogates BTK activity and shows activity in nonclinical models of lymphoid cancers. These data are supported by clinical documentation that ibrutinib, a first-generation BTK inhibitor, is clinically active in these diseases.
- Ibrutinib clinical data and ACP-196 nonclinical safety pharmacology and toxicology studies support the safety of testing ACP-196 in subjects with B-cell malignancies.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- Establish the safety and the MTD of orally administered ACP-196 in subjects with CLL/SLL.
- Determine pharmacokinetics (PK) of orally administered ACP-196 and identification of its major metabolite
- Measure pharmacodynamic (PD) parameters including drug occupancy of BTK, the target enzyme, and effect on biologic markers of B-cell function

2.2. Secondary Objective

Evaluate tumor responses

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This study is a multicenter, open-label, nonrandomized, sequential group, dose-escalation study. The following dose cohorts will be evaluated:

- Cohort 1: 100 mg/day for 28 days (= 1 cycle)
- Cohort 2: 175 mg/day for 28 days (= 1 cycle)
- Cohort 3: 250 mg/day for 28 days (= 1 cycle)
- Cohort 4: 350 mg/day for 28 days (= 1 cycle)
- Cohort 5: 450 mg/day for 28 days (= 1 cycle)
- Cohort 6: TBD mg/day for 28 days (= 1 cycle)

Each cohort will be enrolled sequentially with 6 subjects per cohort. If ≤ 1 dose-limiting toxicity (DLT; see Section 3.8 for definition) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Subjects may be enrolled in the next cohort if 4 of the 6 subjects enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining 2 subjects are completing evaluation. If ≥ 2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the MTD will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Dose escalation will end when either the MTD is achieved or at 3 dose levels above full BTK occupancy, whichever occurs first. Full BTK occupancy is defined as ACP-196 active-site occupancy of > 80% (average of all subjects in cohort) at 24 hours postdose. Should escalation to Cohort 6 be necessary, the dose will be determined based on the aggregate data from Cohorts 1 to 5, which includes safety, efficacy, and PK/PD results. The dose for Cohort 6 will not exceed 900 mg/day.

Treatment with ACP-196 may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. Subjects with disease progression will be removed from the study. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe.

Radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 12 and at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment.

All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) due to the pancreatic findings in the 28-day GLP rat toxicity study. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected during the first week of treatment for PK/PD assessments. ECGs will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6. ECGs are done in triplicate for screening only. Thereafter, single ECGs are done unless a repeat ECG is required (see Section 4.1 for a more detailed description of ECG assessments).

Refer to Table 4-1 for a comprehensive list of study assessments and their timing. A study schema is provided at the end of the protocol synopsis.

The occupancy of BTK by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.

3.2. Study Parameters

3.2.1. Efficacy Parameters

- Overall response rate
- Duration of response
- Progression-free survival

3.2.2. Safety Parameters

- DLTs and MTD
- Frequency, severity, and attribution of adverse events (AEs)

3.2.3. Pharmacokinetic and Pharmacodynamic Parameters

A description of the pharmacokinetic parameters for ACP-196 and its major metabolites in plasma are provided in Section 6.4.4.

The occupancy of BTK by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.

3.3. Rationale for Study Design and Dosing Regimen

The starting ACP-196 dose of 100 mg was selected based on Food and Drug Administration (FDA) Guidances: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (MSSD), and Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9) [FDA 2005 and 2010]. Standard GLP 28-day nonclinical systemic toxicity studies in rats and dogs were conducted in support of this trial. The no observable adverse effect level in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, the 100 mg/kg/day was selected to conservatively represent the HNSTD. Following the S9 guidance and using conversion factors from Table 1 in the MSSD guidance, the conversion factor for mg/kg to mg/m^2 for rodents is 6, which converts to 600 mg/m^2 in rats. The starting human dose for oncology would be one-tenth the HNSTD, 60 mg/m^2, or approximately 100 mg for a 60-kg subject with a body surface area of 1.6 m^2.

3.4. Selection of Study Population

3.4.1. Inclusion Criteria

To be eligible to participate in this study, a subject must meet the following criteria:

1. Men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL; however, subjects with 17p deletion are eligible if they have relapsed after, or been refractory to, 1 prior treatment for CLL/SLL.
2. Body weight ≥ 60 kg.
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

4. Agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children.
5. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
6. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

3.4.2. Exclusion Criteria

A subject meeting any of the following criteria will be excluded from this study:

1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor.
2. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ACP-196, or put the study outcomes at undue risk.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
5. Any immunotherapy within 4 weeks of first dose of study drug.
6. For subjects with recent chemotherapy or experimental therapy the first dose of study drug must occur after 5 times the half-life of the agent(s).
7. Relapsed after, or refractory to, prior BTK inhibitor therapy.
8. Concomitant use of medicines known to cause QT prolongation or Torsades de pointes (see Appendix 1).

9. Central nervous system (CNS) involvement by lymphoma.

10. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.

11. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.

12. Major surgery within 4 weeks before first dose of study drug.

13. Absolute neutrophil count (ANC) < 0.75 x 10^9/L or platelet count < 50 x 10^9/L unless there is bone marrow involvement.

14. Creatinine > 1.5 x institutional upper limit of normal (ULN); total bilirubin > 1.5 x ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN unless disease related.

15. Serum amylase > 1.5 x ULN or serum lipase > 1.5 x ULN.

16. Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and corrected QT interval (QTc) ≥ 480 ms.

17. Lactating or pregnant.

3.4.3. Replacement of Subjects

Subjects who meet any of the following criteria will be replaced:

- Did not receive at least 21 of 28 doses in Cycle 1, unless due to DLT or another safety-related issue
- Did not undergo a DLT assessment at the start of Cycle 2
- Discontinued treatment during Cycle 1 for reasons other than DLT

It is not necessary to replace subjects if ≥ 4 subjects in a cohort have completed Cycle 1 without a DLT.

3.4.4. Enrollment Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

- Notify the sponsor when a clinically eligible subject is identified to receive current dose level information and ensure availability on study.

- After the subject has signed and dated the Informed Consent Form (ICF), eligibility has been confirmed, and all screening procedures have been completed, the subject can be officially enrolled in the study.
- To enroll a subject, the study center will fax/email a completed Enrollment Form to the sponsor. The enrollment date will be the date that the form is faxed/emailed to the sponsor.
- An Enrollment Confirmation Form will be completed and faxed/emailed to the study center by the sponsor within 24 hours.

Treatment must begin within 10 days after the enrollment form is faxed or emailed to the sponsor.

3.5. Study Drug: ACP-196 Hard Gelatin Capsule

3.5.1. Premedications

No premedications are required for administration of ACP-196.

3.5.2. Formulation, Packaging, and Storage

ACP-196 drug substance and drug product are manufactured according to cGMP and will be provided to the investigational site by Acerta Pharma or a designee.

ACP-196 will be provided in capsules intended for oral administration. Each capsule contains 25 mg of ACP-196 drug substance. Capsules also include the following inactive excipients: microcrystalline cellulose, gelatin, and globally acceptable colorant. Capsules are Swedish orange in color.

ACP-196 will be provided in white, high-density polyethylene bottles. Each bottle contains 30 capsules (25 mg per capsule of ACP-196).

Labels for study drug bottles will meet all applicable requirements of the United States FDA, Annex 13 of cGMP (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations, as applicable. Each bottle is closed with a white, continuous-thread, child-resistant, polypropylene screw cap.

Bottles containing ACP-196 will be shipped and stored at controlled room temperature (~15°C to 30°C). While stability of the drug when stored at controlled room temperature has been confirmed, brief excursions to temperatures as high as 40°C or as low as 5°C will not adversely affect the drug substance. Stability data at the start of study will support the use of the drug product capsules for at

least 3 months. Ongoing stabilities studies will support the use of the drug product for longer than 3 months.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and faxed to the sponsor or the sponsor's representative. Refer to the Investigator's Brochure for additional information regarding the drug product to be used in this trial.

3.5.3. Administration of ACP-196

Investigators are prohibited from supplying ACP-196 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators on FDA Form 1572. The investigator must ensure that subjects receive ACP-196 only from personnel who fully understand the procedures for administering the drug.

ACP-196 is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice due to CYP450 3A4 inhibition). **Subjects should be instructed to take each dose of ACP-196 on an empty stomach defined as no food 2 hours before and 30 minutes after dosing.** The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.4. Assuring Subject Compliance

Subjects will receive their first, second, eighth, and fifteenth dose in the clinic, as predose PK/PD measurements and /or ECG assessment are required. For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other treatments will be taken at home. Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules were

administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.6. Returned capsules must not be redispensed to the same subject or to another subject. The study staff will resupply the subject with the correct number of capsules needed for use until the next visit.

3.5.5. Study Treatment Schedule

Subjects will receive study treatment as detailed in Section 3.5.3 and assessments will be performed as outlined in the Schedule of Assessments (Table 4-1). If no DLT is experienced during Cycle 1, subjects with stable disease or tumor response may continue on therapy until disease progression (radiologic or clinical) or until the investigator considers the study treatment to be no longer tolerable or in the subject's best interest.

3.6. Concomitant Therapy

3.6.1. Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards. Use of hematopoietic growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines [Smith 2006].

For subjects considered at risk for tumor lysis syndrome: Administer appropriate hydration, alkalinization of urine, and allopurinol or rasburicase per institutional standards before initiating treatment.

3.6.2. Prohibited Concomitant Therapy

Any chemotherapy (eg, bendamustine, cyclophosphamide, pentostatin, or fludarabine), immunotherapy (eg, rituximab, GA101, alemtuzumab, or ofatumumab), corticosteroids (at dosages equivalent to prednisone > 20 mg/day), kinase inhibitors (eg, ibrutinib and idelalisib), bone marrow transplant, experimental therapy, and radiotherapy are prohibited.

Use of medications known to prolong QTc interval or that may be associated with Torsades de pointes (see Appendix 1) are prohibited within 7 days of starting study drug and during treatment.

3.7. Precautions

3.7.1. Drug-drug Interactions

At the systemic exposure levels expected in this study, ACP-196 inhibition of CYP metabolism is not anticipated.

However, ACP-196 may be metabolized by CYP3A4. Therefore, any medications that are strong inhibitors CYP3A4 (eg, see Appendix 2) should be avoided.

3.7.2. Reproductive Toxicity

Reproductive toxicity studies have not been done with ACP-196. Therefore, subjects with reproductive potential who are sexually active must use reliable, approved methods of contraception during the study and for 30 days after the last dose of ACP-196. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue ACP-196 immediately. Pregnancy in a female subject or a male subject's partner must be reported in the same manner as any serious adverse event (SAE; see Section 5.2).

3.7.3. Overdose Instructions

For any subject experiencing an ACP-196 overdose (administration of a dose ≥1.5 time the intended dose level in the clinical study protocol), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters, and ECGs should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

The Acerta Pharma Medical Monitor should be contacted if a study drug overdose occurs.

3.8. Assessment of Dose Limiting Toxicity (DLT)

A DLT will be defined as any of the following events (if not related to disease progression):

- Any Grade ≥ 3 nonhematologic toxicity (except alopecia) persisting despite receipt of a single course of standard outpatient symptomatic therapy (eg, Grade 3 diarrhea that responds to a single, therapeutic dose of Imodium® would not be considered a DLT)
- Grade ≥ 3 prolongation of the QTc interval, as determined by a central ECG laboratory overread

- Grade 4 neutropenia (ANC < 500/μL) lasting > 7 days after discontinuation of therapy without growth factors or lasting > 5 days after discontinuation of therapy while on growth factors (ie, Grade 4 neutropenia not lasting as long as specified will not be considered a DLT)
- Grade 4 thrombocytopenia (platelet count < 20,000/μL) lasting >7 days after discontinuation of therapy or requiring transfusion (ie, Grade 4 thrombocytopenia not lasting as long as specified will not be considered a DLT)
- Dosing delay due to toxicity for > 7 consecutive days

3.9. Assessment of QTc Interval Prolongation

The potential of ACP-196 to delay cardiac repolarization will be evaluated using ECGs for the measurement of the QTc interval. The study will be carried out in collaboration with a centralized cardiac safety monitoring laboratory that specializes in cardiac monitoring who will provide centralized ECG functions.

Toxicity grading of QTc interval prolongation is defined by the Common Terminology Criteria for Adverse Events (CTCAE) and provided in Table 3-1.

Table 3-1. QTc Toxicity Grading Defined by CTCAE

Grade	Definition
1	QTc 450 to 480 ms
2	QTc 481 to 500 ms
3	QTc ≥ 501 ms on at least 2 separate ECGs
4	QTc ≥ 501 ms or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
5	Death

Refer to Section 4.1 for instructions on ECG evaluation.

3.10. Stopping Rules

Subjects with stable disease or tumor response may continue on therapy until disease progression (radiologic or clinical) or until the investigator considers the study treatment to be no longer tolerable or in the subject's best interest.

Treatment of subjects with study drug is terminated if:

- A DLT(s) occurs in Cycle 1 (28 days of treatment).
- Dosing delayed due to study drug-related toxicity for > 7 consecutive days.
- Disease progression.
- Subject decides to withdraw from the study.
- Intercurrent illness develops which compromises further participation in the study.
- Investigator determines that continuation on study is no longer in the best interest of the subject or change in the subject's condition renders them ineligible for further treatment.

3.11. Dosing Delays and Modifications

Clinical judgment should be used to determine appropriate management of the subject during any adverse event. Temporary interruption or permanent discontinuation of the study drug should be considered if clinically indicated.

Subjects who experience a non-DLT adverse event resulting in interruption of treatment for ≤ 7 missed doses, may restart treatment at the original dose if the abnormality returns to baseline or Grade 1.

3.12. Data and Safety Monitoring

This trial will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Monthly conference calls with the investigators will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs, and deaths). In addition, mandatory safety calls will occur before enrollment of subjects into the next cohort level.

4. STUDY ACTIVITIES AND ASSESSMENTS

The schedules of events are shown in Schedule of Assessments. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

Table 4-1. Schedule of Assessments

	Screening[a]	Cycle 1						Cycle 2				Cycle 3	Cycle 4	Cycles 5-24[b]	Follow Up[c]
		Days (± 2)						Day(s) (±2)				Day(s) (±2)	Day(s) (±2)	Day(s) (±2)	30 days after last dose
		1	2	8	15	22	28	1-14	15	16-27	28	28	28	28	
Informed consent	x														
Confirm eligibility	x														
Medical history	x														
PE[d]/Vital signs[e]/Weight	x	x		x	x	x	x		x		x	x	x	x	x
ECOG status	x	x		x	x	x	x		x		x	x	x	x	x
ECG[f]	x	x	x	x	x	x	x		x		x	x	x	x	x
Lab assessments:															
Urine pregnancy test[g]	x														x
Hematology[h]	x			x	x	x	x		x		x	x	x	x	x
Serum chemistry[i]	x			x	x	x	x		x		x	x	x	x	x
Amylase & Lipase	x	x					x				x	x	x	x	x
Urinalysis[j]	x														
T/B/NK/monocyte cell count[k]		x									x			Every 6 mos	
Serum Ig[l]		x									x			Every 6 mos	
Bone marrow (aspirate/biopsy)														Cycle 12 only	
Pharmacodynamics		x[m]	x[n]	x[m]											x
Pharmacokinetics[o]		x	x	x	x	x	x								
Molecular markers[p]	x														
ACP-196 dispensed[q]		x	x	x	x	x	x				x	x	x	x	
Study drug compliance		x	x	x	x	x	x		x		x	x	x	x	
Tumor assessment	x[r]										x[s]		x[s]	x[s]	
Concomitant medications	x	x		x	x	x	x		x		x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, Ig = immunoglobulin; mos = months; PE = physical exam

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Footnotes for ACE-CL-001 Schedule of Study Activities:

a. Screening tests should be performed within 7 (±3) days before the first administration of study drug, unless otherwise indicated.
b. Any subjects who have not progressed while receiving study drug treatment, may be eligible to enroll into a long-term follow up study and continue to receive ACP-196.
c. A 30-day (± 7 days) safety follow-up visit is required when subjects discontinue study drug unless they start another anticancer therapy within that timeframe.
d. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter.
e. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
f. 12-lead electrocardiogram (ECG) will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. On Cycle 1 Day 1 and Cycle 1 Day 8, single ECGs are done predose and at 1, 2, 4, and 6 h postdose. The single ECG on Cycle 1 Day 2 is done predose. On Cycle 1 Day 15, Day 22, and Day 28, a single ECG is done 2 h postdose. Starting with Cycle 2, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review.
g. Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
h. Hematology includes complete blood count with differential and platelet and reticulocyte counts.
i. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.
j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
k. T/B/NK/monocyte cell count (ie, CD3, CD4, CD8, CD14, CD19, CD19, CD16/56)
l. Serum immunoglobulin: IgG, IgM, IgA, and total immunoglobulin
m. Pharmacodynamic samples are drawn predose and 4 hours (±10 minutes) postdose on the days indicated.
n. Pharmacodynamic samples are drawn predose on the day indicated.
o. Pharmacokinetic samples for Cycle 1 Day 1 are drawn predose and at 0.5, 1, 2, 4, 6 and 24 h (before dose on Day 2) postdose. Samples for Cycle 1 Day 8 are drawn predose and at 0.5, 1, 2, 4, and 6 h postdose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn predose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 h postdose.
p Includes, but is not limited to, interphase cytogenetics, stimulated karyotype, IgHV mutational status, Zap-70 methylation, and beta-2 microglobulin levels
q. **ACP-196: For Cycle 1 Day 1, 2, 8, 15, 22, and 28 study drug is administered at the site. Therefore, only dispense enough study drug for the days between visits**. Thereafter, starting with the end of Cycle 1, dispense enough capsules for 1 complete cycle.
r. Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis. In addition a positron emission tomography (PET) or PET/CT must done for subjects with SLL.
s. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (- 7days), and Cycle 12 (-7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a complete response (CR). Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter.

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4.1. Description of Procedures

Informed Consent
Screening

The subject must read, understand and sign the Institutional Review Board (IRB)-approved ICF confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information.

Medical History
Screening

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

Adverse Events
At all visits

The accepted regulatory definition for an AE is provided in Section 5.1. All medical occurrences from the time of signing the ICF that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 5.6.

Concomitant Medications and Therapy
At all visits

Document all concomitant medications and procedures from within 14 days before the start of ACP-196 administration through 30 days after the last dose of ACP-196.

Confirmation of Eligibility
Screening

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion. Screening evaluations must be completed within 7 (+3) days before the subject's first dose of ACP-196.

Physical Examination & Vital Signs & Weight
Per Table 4-1

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination

of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period and at the safety follow-up visits.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position. Vital signs and weight will be measured at every visit.

ECOG Performance Status
At all visits

The ECOG performance index is provided in Appendix 3.

Electrocardiogram
Per Table 4-2

A centralized cardiac safety monitoring laboratory will be used in this study. The service provider will provide the ECG equipment (12-lead surface), instructions, and training (when requested). At screening, results from the central ECG reader (ie, 3 ECGs) will be averaged to determine eligibility and must meet the eligibility criteria of QTc < 480 ms. Thereafter single ECGs are done at each timepoint. However, if a machine read ECG registers a QTc (either Bazett's or Fredericia's) of ≥ 501 ms or > 60 ms above baseline then a second ECG must be done after 5 minutes. If at any point, a subject experiences a Grade 3 QTc prolongation (ie, 2 consecutive ECGs taken at least 5 minutes apart with QTc that are both ≥ 501 ms and/or > 60 ms change from baseline), per the machine on site, the dose must be held pending the QTc results from the centralized review. If centralized review confirms both ECG QTc readings are ≥ 501 ms or > 60 ms change from baseline then the subject must be withdrawn from the study. Conversely, if the centralized review shows that both ECG QTc readings are ≤ 500 ms and ≤ 60 ms change from baseline, dosing may be restarted at the same dose level, but missed doses will not be made up.

Table 4-2. ECG Acquisition Times

Study Segment	Day	ECG Acquisition Times
Screening	--	Triplicate at least 1 min apart
Cycle 1	1-2	Single ECG predose, and 1, 2, 4, 6, and 24 h (before Day 2 dose) after 1st dose; window for ECGs at 1, 2, 4, 6 h is ±10 min. The 24-h ECG must be predose on Day 2.
Cycle 1	8	Single ECG predose, and 1, 2, 4, and 6 h after 8th dose; window for ECGs at 1, 2, 4, 6 h is ±10 min
Cycle 1	15, 22, 28	Single ECG 2 h (±30 min) postdose
Cycle 2	15, 28	Single ECG anytime during the visit
Cycles 3 to 6	28	Single ECG anytime during the visit
30-day follow up	--	Single ECG anytime during the visit

Urine Pregnancy Test
Screening and safety follow-up visit

Pregnancy tests are required only for women with childbearing potential.

Hematology
Screening, then all visits starting with Cycle 1 Day 8

Hematology studies must include complete blood count (CBC) with differential and platelet and reticulocyte counts. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Chemistry
Screening, then all visits starting with Cycle 1 Day 8

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time,

then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Amylase and Lipase
Screening, then all visits starting with Cycle 1 Day 8
Serum amylase and serum lipase testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Urinalysis
Screening
Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

T/B/NK/Monocyte Cell Count
Screening; end of Cycle 2 then every 6 months thereafter
Flow cytometry testing for $CD3^+$, $CD4^+$, $CD8^+$, $CD14^+$, $CD19^+$, $CD16/56^+$ cells. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Serum Immunoglobulin
Screening; end of Cycle 2 then every 6 months thereafter
Testing for IgG, IgM, IgA and total immunoglobulin levels. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Pharmacodynamics
Per Table 4-1
Blood samples will be used for PD testing (eg, BTK occupancy and B-cell activation) as well as for the investigation of marker(s) predictive of response to ACP-196. Refer to the laboratory binder for instructions on collecting and processing these samples.

Pharmacokinetics
Per Table 4-3

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory.

Table 4-3. Pharmacokinetic Sample Schedule

		HOURS POSTDOSE						
Cycle	**Day**	**Predose**	**0.5 (±5 min)**	**1 (±10 min)**	**2 (±10 min)**	**4 (±10 min)**	**6 (±10 min)**	**24 (±30 min)**
1	**1**	X	X	X	X	X	X	X*before Day 2 dose
	8	X	X	X	X	X	X	
	15, 22, 28	Predose and 2 h (±30 min)						

Molecular Testing
Screening

Blood will be drawn for molecular testing including, but not limited to, interphase cytogenetics, stimulated karyotype, IgHV mutational status, ZAP-70 methylation, and beta-2 microglobulin levels. Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at central clinical laboratories.

Bone Marrow
Cycle 12 and to confirm CR

Bone marrow aspirate/biopsy is required to confirm a CR. A mandatory bone marrow aspirate/biopsy is required at the end of Cycle 12 concurrent with the radiologic tumor assessment as outlined below. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Tumor Assessment
Screening and end of Cycle 2/Cycle 4/Cycle 12

See Section 4.2 for response assessment criteria. Pretreatment tumor assessment should be performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is

required of the chest, abdomen, and pelvis for the pretreatment tumor assessment for subjects with CLL. In addition, positron emission tomography (PET)/CT is required for subjects with SLL. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (- 7days) and Cycle 12 (-7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a CR. Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter or as clinically indicated.

Study Drug Accountability
Cycle 1 Day 1, 2, 8, 15, 22, and 28, and end of every cycle
See Section 7.6.

4.2. Investigator's Assessment of Response to Treatment

The investigator must rate the subject's response to treatment based on recent guidelines for CLL (Table 4-4) and SLL (Table 4-5).

Table 4-4. Response Assessment Criteria for CLL [Hallek 2008]

Response	Peripheral Blood	Bone Marrow if done	Nodes, Liver, and Spleen[a]
CR	Lymphocytes <4 x 10^9/L ANC >1.5 x 10^9/L[b] Platelets >100 x 10^9/L[b] Hemoglobin >11.0 g/dL (untransfused)[b]	Normocellular <30% lymphocytes No B-lymphoid nodules	Normal (eg, no lymph nodes >1.5 cm)
CRi	Lymphocytes <4 x 10^9/L Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity	Hypocellular <30% lymphocytes	Normal (eg, no lymph nodes >1.5 cm)
PR	Lymphocytes ≥50% decrease from baseline ANC >1.5 x 10^9/L Or Platelets >100 x 10^9/L or 50% improvement over baseline[b] Or Hemoglobin >11.0 g/dL or 50% improvement over baseline (untransfused)[b]	Not assessed	≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement

ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission

a Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation

b without need for exogenous growth factors

c in the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

Table 4-5. Response Assessment Criteria for SLL [Cheson 2007]

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥ 1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or progressive disease	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET (b) Variably FDG avid or PET negative; no change in size of previous lesions on CT		

Abbreviations: CR = complete remission, CT = computed tomography, FDG = [^{18}F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

4.3. Safety Follow-up Visit

The safety follow-up visit is conducted 30 (±7) days after the last ACP-196 dose unless a subject receives a new anticancer therapy within this timeframe. Refer to Table 4-1 for the assessments done at these visits.

4.4. Missed Evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

5.1. Definitions

5.1.1. Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL/SLL that were not present before the AE reporting period (see Section 5.3)
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values should not be reported as adverse events; however, any clinical consequences of the abnormality (eg, withdrawal from study) should be reported as adverse events

5.1.2. Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not

severity) serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

5.1.3. Severity

Definitions found in the CTCAE version 4.03 (CTCAE v4.03) or later will be used for grading the severity (intensity) of **nonhematologic** AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any nonhematologic AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

The grading scale for hematologic toxicity in subjects with CLL is in Table 5-1.

Table 5-1. Grading Scale for Hematologic Toxicity in CLL [Halleck 2008]

Grade[1]	Decrease in platelets[2] or Hb[3] (nadir) from pretreatment value	Absolute neutrophil count/μL[4] (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

1. Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as Grade 5.
2. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 10^9/L (20,000/μL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, < 20 x 10^9/L [20,000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
3. Hemoglobin (Hb) levels must be below normal levels for Grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
4. If the ANC reaches < 1 x 10^9/L (1000/μL), it should be judged to be Grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity, but should be documented.

5.2. Documenting and Reporting of Adverse and Serious Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are

recorded on the electronic CRF (eCRF). All SAEs also must be reported on the SAE/Product Compliant form (see Section 5.6).

5.3. Adverse Event Reporting Period

The AE reporting period for this study begins when the subject signs informed consent and ends with the safety follow-up visit. Fatal AEs occurring 30 days after the last dose of ACP-196 ***AND*** assessed by the investigator as related to ACP-196 must be reported as an SAE.

5.4. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test (ie, requiring change in study drug dose or discontinuation of study drug or any other medical intervention), or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE/Product Compliant form.

Disease progression itself is not considered an adverse event; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The relationship of adverse events to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' Answer Yes or No.

See Appendix 4 for more detail on assessing relationship.

5.5. Pregnancy

Report any pregnancy that occurs in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Acerta Pharma Drug Safety, or designee, within 24 hours of learning of the event. After the birth of the baby, additional information on the mother, pregnancy and baby will be

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collected by completing the Pregnancy Report Form Part II. Abortion, whether therapeutic, elective or spontaneous, will be reported as an SAE.

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug. Any female subjects receiving ACP-196 who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

5.6. Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on an SAE/Product Compliant form and faxed or emailed to Acerta Pharma Drug Safety, or designee, within 24 hours of the discovery of the event or information. Acerta Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes, and laboratory results).

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the study drug and is not listed in the current investigator's Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the SAE to all investigators. Each investigator must then notify his or her IRB of the SAE.

Drug Safety Contact Information	
Fax:	+1.650.591.2816
Email:	DrugSafety@acerta-pharma.com

5.7. Type and Duration of Follow-up of Subjects After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

6. STATISTICAL METHODS OF ANALYSIS

6.1. General Considerations and Determination of Sample Size

No formal statistical tests of hypotheses will be performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate.

Twenty-four to 36 evaluable subjects will be enrolled in this study. The trial design is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1.

6.2. Definition of Analysis Sets

The following definitions will be used for the safety and efficacy analysis sets.

- **Safety analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug.
- **Per-protocol (PP) analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug and with ≥ 1 tumor response assessment after treatment.

The safety analysis set will be used for evaluating the safety parameters in this study. The PP analysis sets will be analyzed for efficacy parameters in this study.

6.3. Missing Data Handling

No imputation of values for missing data will be performed except for missing or partial start and end dates for adverse events and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

6.4. Endpoint Data Analysis

6.4.1. Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent adverse events will

be reported in each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Vital signs, ECGs, and physical exams will be tabulated and summarized.

6.4.2. Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

6.4.3. Analysis of Efficacy Parameters

Overall Response Rate

The point estimate of the overall response rate will be calculated for the PP analysis set. The corresponding 95% confidence interval also will be derived.

Duration of Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median).

Progression-free Survival

Progression-free survival is measured from the time of first study drug administration until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier

methodology will be used to estimate the event-free curves and corresponding quantiles (including the median).

6.4.4. Analysis of Pharmacokinetic/Pharmacodynamic Parameters

The plasma PK of ACP-196 and a metabolite will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of ACP-196:

- $AUC_{(0-t)}$ Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t).
- $AUC_{(0-24)}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation.
- $AUC_{(0-\infty)}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- Cl/F Oral clearance

Missing dates or times may be imputed for PK and PD samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. If PK and PD sampling for a given subject is not performed according to protocol instructions that subject may be excluded from the PK and PD analyses.

The PK parameters will be tabulated and summarized using descriptive statistics. Pharmacokinetic relationships to PD measures of efficacy or toxicity may also be

explored. Additional PK or PD analyses may be performed, as deemed appropriate.

7. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1. Institutional Review Board and Independent Ethics Committee

The investigator will submit this protocol, the informed consent, Investigator's Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB approval of the protocol and informed consent; and a statement that the IRB is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed FDA 1572 form (Statement of Investigator) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB and local regulatory agency, as appropriate, before the implementation of changes in this study.

7.2. Informed Consent and Protected Subject Health Information Authorization

A copy of the IRB-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as

defined in §21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs. As the study sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.3. Subject Screening Log

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.4. Case Report Forms

Authorized study site personnel (see Section 7.11) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed within 5 days of each subject's visit. The investigator will ensure that source documents that are required to verify the validity and

completeness of data transcribed on the eCRFs are never obliterated or destroyed.

7.5. Study Monitoring Requirements

Representatives of Acerta Pharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.6. Investigational Study Drug Accountability

ACP-196 must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply ACP-196 to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Acerta Pharma.

ACP-196 accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.

Each shipment of ACP-196 will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. Additionally a Drug Re-order Form for requesting more ACP-196 is provided in

the pharmacy binder. If it is used, then the Drug Re-order Form must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of ACP-196. The person receiving the shipment and inspecting it must complete and sign the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/email address listed on the form.

A Study Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-CL-001)
2. subject identification number
3. lot number(s) of ACP-196 dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for study drug disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its representative, for return of unused study drug. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.7. Record Retention

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or return to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

7.8. Protocol Amendments

Acerta Pharma coordinate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.9. Publication of Study Results

Acerta Pharma may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis

by an investigator. The study is being conducted as part of a multicenter clinical trial. Data from all study centers shall be pooled and analyzed for publication in a final report (Primary Publication). The investigator agrees that the Primary Publication, which will be coordinated by Acerta Pharma, will be the first publication to present the pooled study results. After the Primary Publication, or if the Primary Publication is not published within 1 year of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement subject to providing Acerta Pharma with the opportunity to review the contents of any proposed presentation, abstract or publication about such work, including any results of this study, 90 days in advance of any presentation or submission for publication. Within that 90-day period, Acerta Pharma may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, Acerta Pharma may elect an additional review period not to exceed 60 days.

In most cases, the principal investigators, at the sites with the highest accruals of eligible subjects, who have provided significant intellectual input into the study design shall be listed as lead authors on manuscripts and reports of study results. Given their contribution to the project, the Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Acerta Pharma.

7.10. Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.11. General investigator Responsibilities

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.

3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB according to the guidelines at each study site.
10. eCRF pages are completed within 5 days of each subject's visit.
11. All Safety Reports are submitted promptly to the IRB.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge and to the IRB per their requirements.

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Appendix 1. Risk Factors for Drug-induced Torsades de Pointes

- History of congenital long QT syndrome
- Baseline QTc prolongation (> 450 ms)
- Hypokalemia (potassium ≤ 3.0 mEq/L)
- Severe hypomagnesemia (magnesium ≤ 1.2 mEq/L)
- Bradycardia (resting heart rate < 55 beats per minute)
- Current or recent past use (within 7 days before study entry) of drugs known to prolong QTc interval and may be associated with Torsades de Pointes (listed below)

amiodarone, dofetilide, ibutilide, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, droperidol, quetiapine, thioridazine, ziprasidone, risperidone, indapamide, levofloxacin, ciprofloxacin, gatifloxacin, moxifloxacin, clarithromycin, erythromycin, ketoconazole, itraconazole, amitriptyline, desipramine, imipramine, doxepin, fluoxetine, sertraline, venlafaxine, cisapride, sumatriptan, zolmitriptan, arsenic, dolasetron, methadone, chloroquine, chlorpromazine, astemizole, halofantrine, levomethadyl, mesoridazine, pentamidine, pimozide, domperidone, procainamide, quinidine, sparfloxacin

This list is not exhaustive and new information regarding drugs with dysrhythmic potential emerges on a regular basis. Please refer to the following site (or similar sites) for additional information on drugs with dysrhythmic potential:

http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.

Appendix 2. Inhibitors of CYP3A4

A strong inhibitor is one that causes a > 5-fold increase in plasma AUC values or > 80% decrease in clearance.

http://www.medicine.iupui.edu/Flockhart/table.htm

Strong inhibitors are highlighted in **BOLD** below.

HIV antivirals:
INDINAVIR
NELFINAVIR
RITONAVIR

Strong inhibitors:
CLARITHROMYCIN
ITRACONAZOLE
KETOCONAZOLE
NEFAZODONE

Moderate inhibitors:
erythromycin
grapefruit juice
verapamil
diltiazem

Weak inhibitors:
cimetidine

All other inhibitors:
amiodarone
fluvoxamine
mibefradil
troleandomycin

Appendix 3. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

Appendix 4. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either "yes" or "no":

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

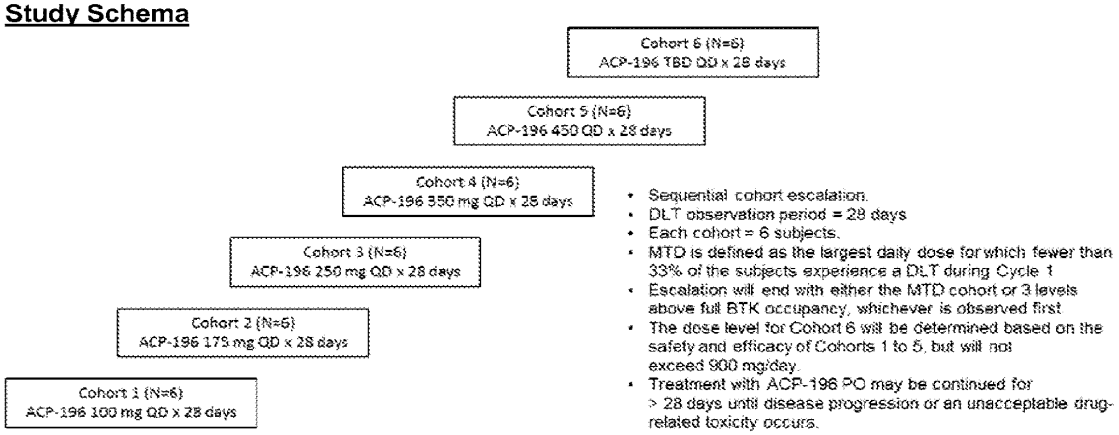
- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject's clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Study Schema



BTK = Bruton's tyrosine kinase; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; PO = per os (oral); TBD = to be determined; QD= once daily

Electronic Acknowledgement Receipt	
EFS ID:	17975130
Application Number:	61929742
International Application Number:	
Confirmation Number:	7002
Title of Invention:	Methods of Use of ACP-196
First Named Inventor/Applicant Name:	Ahmed Hamdy
Customer Number:	28977
Filer:	Frederick Vogt
Filer Authorized By:	
Attorney Docket Number:	055112-5000
Receipt Date:	21-JAN-2014
Filing Date:	
Time Stamp:	16:18:16
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$260
RAM confirmation Number	2596
Deposit Account	500310
Authorized User	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	20140121_Coversheet.pdf	1477302 912a43066431b32ecd62a72b6b70972736071665	no	3
Warnings:					
Information:					
2	Specification	20140121_Specification_asfiled.pdf	601159 fb48b4693309bd4fb72d7a134f97ae12f2f5d2ed	no	65
Warnings:					
Information:					
3	Drawings-only black and white line drawings	20140121_Drawings_asfiled.pdf	92827 e20efec61e695ea746c63ae0912172ebe03367d9	no	1
Warnings:					
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4	Fee Worksheet (SB06)	fee-info.pdf	28918 6eae79eb1715d566589fc957c89089320c241c2f	no	2
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International application number:		**PCT/IB2015/000645**
International filing date:		**21 January 2015 (21.01.2015)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**US**
	Number:	**61/929,742**
	Filing date:	**21 January 2014 (21.01.2014)**
Date of receipt at the International Bureau:		**09 February 2015 (09.02.2015)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

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683620

THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 08, 2015

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APPLICATION NUMBER: ***61/974,665***
FILING DATE: ***April 03, 2014***
RELATED PCT APPLICATION NUMBER: ***PCT/US15/12288***

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS ***US61/974,665***

UNITED STATES PATENT AND TRADEMARK OFFICE · DEPARTMENT OF COMMERCE

Certified by

David J. Kappos

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country
Ahmed		HAMDY	San Carlos	CA	US

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Title of Invention	Therapeutic Combination of a PI3K Inhibitor and a BTK Inhibitor
Attorney Docket Number (if applicable)	055112-5002-PR1

Correspondence Address

Direct all correspondence to (select one):

◉ The address corresponding to Customer Number	○ Firm or Individual Name
Customer Number	28977

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ◉ No.
- ○ Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:
- ○ Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

EFS - Web 1.0.1

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

- ○ Applicant asserts small entity status under 37 CFR 1.27
- ○ Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- ◉ No

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Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Frederick G. Vogt/			Date (YYYY-MM-DD)	2014-04-03
First Name	Frederick G.	Last Name	Vogt	Registration Number (If appropriate)	70115

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

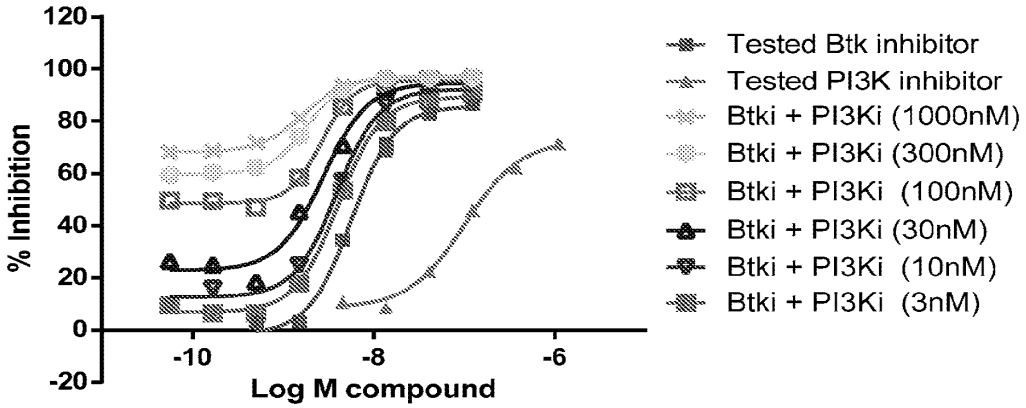
120
100
80
60
40
20
0
-20
% Inhibition
-10
-8
-6
Log M compound
Tested Btk inhibitor
Tested PI3K inhibitor
Btki + PI3Ki (1000nM)
Btki + PI3Ki (300nM)
Btki + PI3Ki (100nM)
Btki + PI3Ki (30nM)
Btki + PI3Ki (10nM)
Btki + PI3Ki (3nM)

FIG. 1

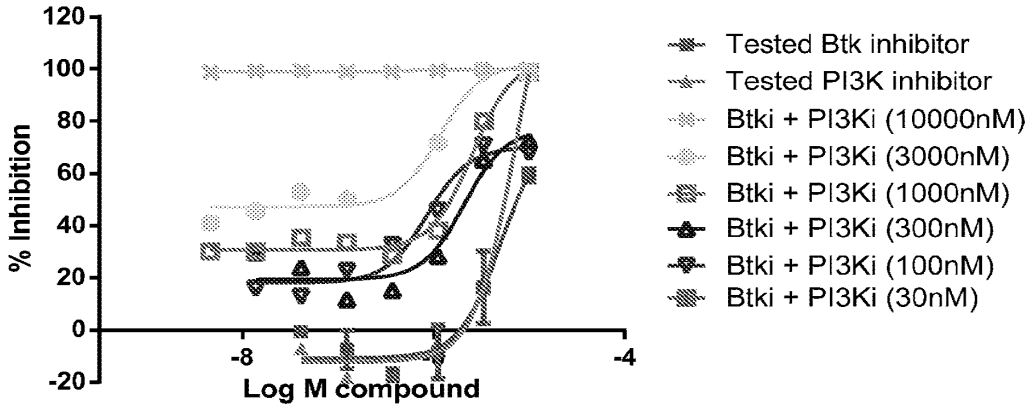
120
100
80
60
40
20
0
-20
% Inhibition
-8
-4
Log M compound
Tested Btk inhibitor
Tested PI3K inhibitor
Btki + PI3Ki (10000nM)
Btki + PI3Ki (3000nM)
Btki + PI3Ki (1000nM)
Btki + PI3Ki (300nM)
Btki + PI3Ki (100nM)
Btki + PI3Ki (30nM)

FIG. 2

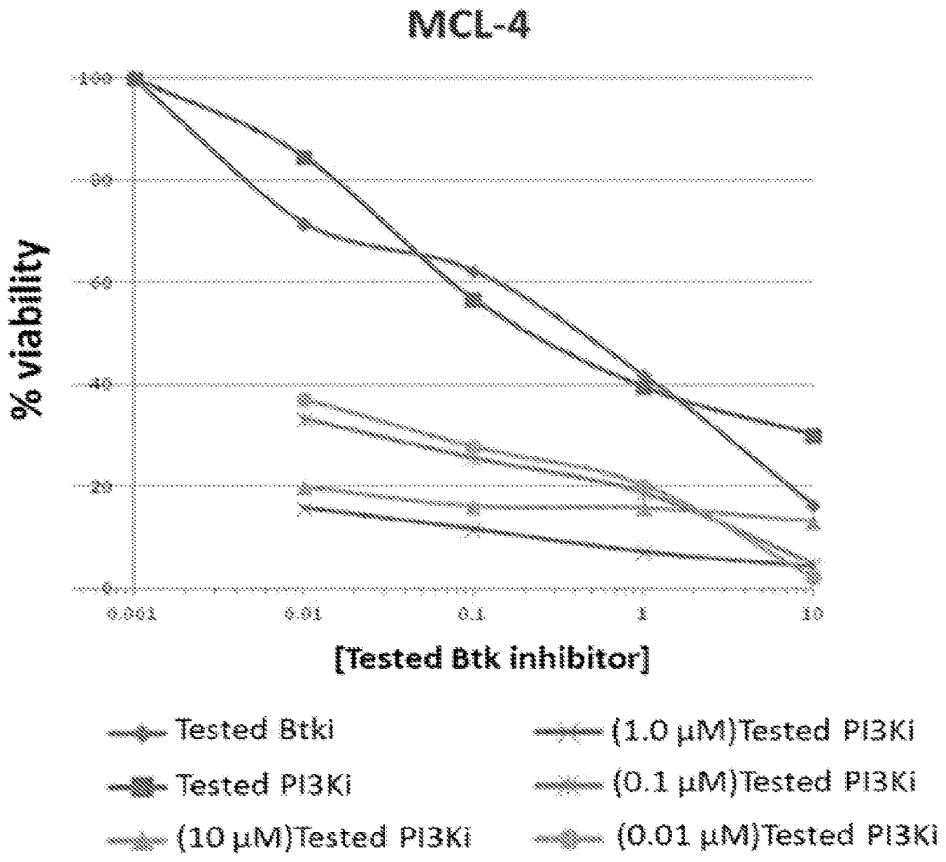
MCL-4
% viability
100
80
60
40
20
0
0.001
0.01
0.1
1
10
[Tested Btk inhibitor]
Tested Btki
Tested PI3Ki
(10 μM)Tested PI3Ki
(1.0 μM)Tested PI3Ki
(0.1 μM)Tested PI3Ki
(0.01 μM)Tested PI3Ki

FIG. 3

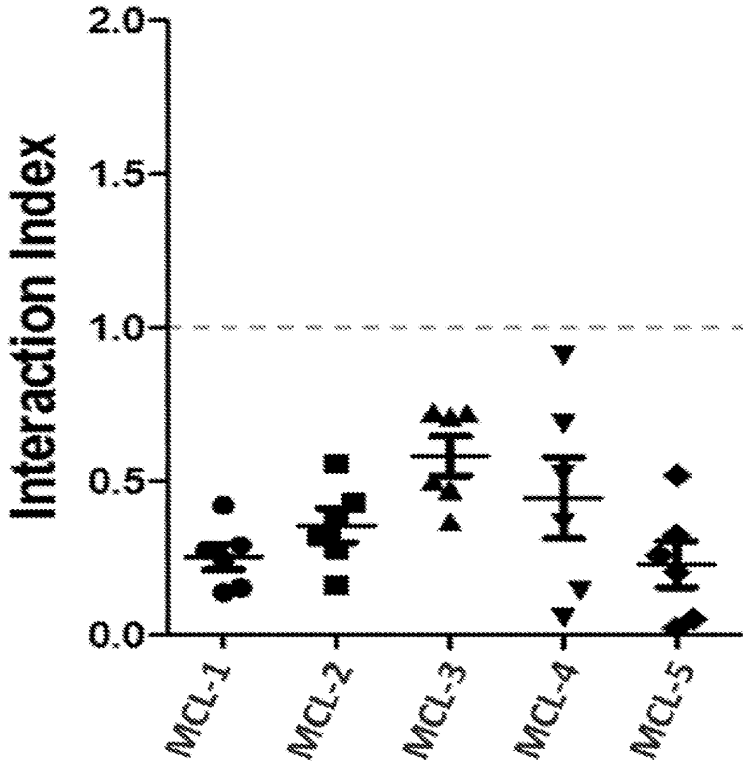

FIG. 4

Electronic Acknowledgement Receipt	
EFS ID:	18659888
Application Number:	61974665
International Application Number:	
Confirmation Number:	8182
Title of Invention:	Therapeutic Combination of a PI3K Inhibitor and a BTK Inhibitor
First Named Inventor/Applicant Name:	Ahmed Hamdy
Customer Number:	28977
Filer:	Frederick Vogt
Filer Authorized By:	
Attorney Docket Number:	055112-5002-PR1
Receipt Date:	03-APR-2014
Filing Date:	
Time Stamp:	15:06:41
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$660
RAM confirmation Number	1359
Deposit Account	500310
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	20140403PROVTRANS.PDF	88450 0ae864b0f7237490a222b14da2ed7b029e1ef0ba	no	3
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This is not a USPTO supplied Provisional Cover Sheet SB16 form.					
Information:					
2	Drawings-only black and white line drawings	20140403DWGS.pdf	257147 b395f04093eedf9ed7e8d69c658fad47ae231ee3	no	4
Warnings:					
Information:					
3	Specification	20140403APPL.pdf	1065418 7def9ff33783f484cfcad7b4a66425444fce4f4f	no	132
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	31182 a353de4f3c60d5583236781f54189a8467983083	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1442197		

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THERAPEUTIC COMBINATION OF A PI3K INHIBITOR AND A BTK INHIBITOR

FIELD OF THE INVENTION

[001] A therapeutic combination of a phosphoinositide 3-kinase (PI3K) inhibitor and a Bruton's Tyrosine Kinase (BTK) inhibitor and uses of the therapeutic combination are disclosed herein.

BACKGROUND OF THE INVENTION

[002] PI3K inhibitors are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. PI3K inhibitors are key signaling enzymes that relay signals from cell surface receptors to downstream effectors. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3K inhibitors (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases.

[003] The PI3K signaling pathway is known to be one of the most highly mutated in human cancers. PI3K signaling is also a key factor in disease states including hematologic malignancies, non-Hodgkin lymphoma (such as diffuse large B-cell lymphoma), allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome. The role of PI3K in cancer has been discussed, for example, in J. A. Engleman, *Nat. Rev. Cancer* **2009,** *9,* 550-562. The PI3K-δ and PI3K-γ isoforms are preferentially expressed in normal and malignant leukocytes.

[004] The delta (δ) isoform of class I PI3K (PI3K-δ) is involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its role in immune system function, PI3K-δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis,

auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. The gamma (γ) isoform of class I PI3K (PI3K-γ) is also involved in immune system functions and plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

[005] Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family and has been implicated in a wide range of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been reported in various types of cancer.

[006] In view of the above, PI3K inhibitors are prime targets for drug development, as described in J. E. Kurt and I. Ray-Coquard, *Anticancer Res.* **2012,** *32,* 2463-70. Several PI3K inhibitors are known, including those those that are PI3K-δ inhbitors, PI3K-γ inhibitors and those that are PI3K-δ,γ inhibitors.

[007] Bruton's Tyrosine Kinase (BTK) is a Tec family non-receptor protein kinase expressed in B cells and myeloid cells. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease characterized by a defect in B cell development with a block between pro- and pre-B cell stages. The result is an almost complete absence of B lymphocytes, causing a pronounced reduction of serum immunoglobulin of all classes. These findings support a key role for BTK in the regulation of the production of auto-antibodies in autoimmune diseases.

[008] Other diseases with an important role for dysfunctional B cells are B cell malignancies. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies, as described in O. Cruz et al., *OncoTargets and Therapy* **2013,** *6,* 161-176.

[009] The present invention includes the unexpected discovery that the combination of a PI3K inhibitor with a BTK inhibitor is effective in the treatment of any of several types of cancers such as leukemia, lymphoma and solid tumor cancers.

SUMMARY OF THE INVENTION

[0010] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K inhibitor and a BTK inhibitor.

[0011] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ inhibitor and a BTK inhibitor.

[0012] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-δ inhibitor and a BTK inhibitor.

[0013] In an embodiment, the invention includes a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor and a BTK inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[0015] FIG. 1 illustrates the sensitivity of the TMD8 diffuse large B cell lymphoma (DLBCL) cell line to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[0016] FIG. 2 illustrates the sensitivity of the MINO mantle cell lymphoma cell to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The concentration of the first agent in the combination (the BTK inhibitor) and the concentration of the individual agents is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[0017] FIG. 3 illustrates the proprofliferative activity in primary mantle cell lymphoma cells of Formula XVIII ("Tested Btki") and Formula IX ("Tested PI3Ki"). The percentage viability of cells ("% viability", y-axis) is plotted versus the concentration of the Formula XVIII ("[Tested Btk Inhibitor]", x-axis). The concentration of the individual BTK and PI3K inhibitors (i.e. not in combination) are also given on the x-axis.

[0018] FIG. 4 illustrates the interaction index of the combination of the BTK inhibitor of Formula XVIII and the PI3K inhibitor of Formula IX in primary mantle cell lymphoma cells.

DETAILED DESCRIPTION OF THE INVENTION

[0019] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

[0020] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[0021] The terms "co-administration" and "administered in combination with" as used herein, encompass administration of two or more agents to a subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0022] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, *etc.* which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0023] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0024] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and

basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In selected embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0025] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

[0026] "Prodrug" is intended to describe a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers the advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgaard, H., Design of Prodrugs (1985) (Elsevier, Amsterdam). The term "prodrug" is also intended to include any covalently bonded carriers, which release the active compound *in vivo* when administered to a subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to yield the active parent compound. Prodrugs include, for example, compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetates, formates and benzoate derivatives of an alcohol, various ester derivatives of a carboxylic acid, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound.

[0027] The term "*in vivo*" refers to an event that takes place in a subject's body.

[0028] The term "*in vitro*" refers to an event that takes places outside of a subject's body. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

[0029] Unless otherwise stated, the chemical structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds where one or more hydrogen atoms is replaced by deuterium or tritium, or wherein one or more carbon atoms is replaced by ^{13}C- or ^{14}C-enriched carbons, are within the scope of this invention.

[0030] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that "consist of" or "consist essentially of" the described features.

[0031] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C_1-C_{10} alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl and decyl. The alkyl moiety may be attached to the rest of the molecule by a single bond, such as for example, methyl (Me), ethyl (Et), n-propyl (Pr), 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is

optionally substituted by one or more of substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$ where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0032] "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0033] "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0034] "Alkylheterocycloalkyl" refers to an -(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

[0035] An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0036] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, C_2-C_{10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkenyl moiety may be attached to the rest of the molecule by a single bond, such as for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl and penta-1,4-dienyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally

substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0037] "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cyclo alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

[0038] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e. C_2-C_{10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0039] "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

[0040] "Carboxaldehyde" refers to a -(C=O)H radical.

[0041] "Carboxyl" refers to a -(C=O)OH radical.

[0042] "Cyano" refers to a -CN radical.

[0043] "Cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (i.e. C_2-C_{10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - *e.g.*, "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloseptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0044] "Cycloalkyl-alkenyl" refers to a -(cycloalkyl)alkenyl radical where cycloalkyl and alkenyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkenyl, respectively.

[0045] "Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl)heterocycloalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heterocycloalkyl, respectively.

[0046] "Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heteroaryl, respectively.

[0047] The term "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy and cyclohexyloxy. "Lower alkoxy" refers to alkoxy groups containing one to six carbons.

[0048] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (*i.e.*, -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0049] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C_1-C_6 alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group.

[0050] The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,

hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0051] "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)- and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the alkyl, aryl or heteroaryl moiety of the acyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0052] "Acyloxy" refers to a R(C=O)O- radical wherein "R" is alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl, which are as described herein. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is

independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0053] "Amino" or "amine" refers to a $-N(R^a)_2$ radical group, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a $-N(R^a)_2$ group has two R^a substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, $-N(R^a)_2$ is intended to include, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0054] The term "substituted amino" also refers to N-oxides of the groups $-NHR^d$, and NR^dR^d each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid.

[0055] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R)_2$ or $-NHC(O)R$, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The R_2 of $-N(R)_2$ of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound of Formula (I), thereby forming a prodrug. The procedures and specific groups to make such amides are known to those of skill in the art and

can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

[0056] "Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms (*e.g.*, C_6-C_{10} aromatic or C_6-C_{10} aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group may consist of 6 ring atoms, 7 ring atoms, *etc.*, up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0057] "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl-radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

[0058] "Ester" refers to a chemical radical of formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The procedures and specific groups to make

esters are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0059] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

[0060] "Halo", "halide", or, alternatively, "halogen" is intended to mean fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

[0061] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given - *e.g.*, C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -

$N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0062] "Heteroalkylaryl" refers to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl, respectively.

[0063] "Heteroalkylheteroaryl" refers to an -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl, respectively.

[0064] "Heteroalkylheterocycloalkyl" refers to an -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl, respectively.

[0065] "Heteroalkylcycloalkyl" refers to an -(heteroalkyl)cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl, respectively.

[0066] "Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (*e.g.*, C_5-C_{13} heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range - *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical - *e.g.*, a pyridyl group with two points of attachment is a pyridylidene. A N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical are

optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl(benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen,

alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0067] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl N-oxides.

[0068] "Heteroarylalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

[0069] "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range - *e.g.*, "3 to 18 ring atoms" means that the heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, *etc.*, up to and including 18 ring atoms. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen,

alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0070] "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

[0071] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - *i.e.*, having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0072] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For

example, if a compound, which may potentially have an (R)- or an (S)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (R)- or (S)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (S)- and 20% (R)-, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or the Pirkle alcohol, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[0073] "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0074] "Nitro" refers to the $-NO_2$ radical.

[0075] "Oxa" refers to the -O- radical.

[0076] "Oxo" refers to the =O radical.

[0077] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[0078] The terms "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (R)-enantiomer, such as at least 75% by weight, such as at least 80% by weight. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, such as at least 90% by weight, such as at least 95% by weight.

[0079] In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); and E. L. Eliel, Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962).

[0080] A "leaving group or atom" is any group or atom that will, under selected reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Examples of such groups, unless otherwise specified, include halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[0081] "Protecting group" is intended to mean a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and the group can then be readily removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999).

[0082] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[0083] "Substituted" means that the referenced group may have attached one or more additional moieties individually and independently selected from, for example, acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and protected derivatives thereof. The substituents themselves may be substituted, for example, a cycloalkyl substituent may itself have a halide substituent at one or more of its ring carbons.

[0084] "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

[0085] "Sulfinyl" refers to groups that include -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl) and -S(O)-(optionally substituted heterocycloalkyl).

[0086] "Sulfonyl" refers to groups that include $-S(O_2)-H$, $-S(O_2)$-(optionally substituted alkyl), $-S(O_2)$-(optionally substituted amino), $-S(O_2)$-(optionally substituted aryl), $-S(O_2)$-(optionally substituted heteroaryl), and $-S(O_2)$-(optionally substituted heterocycloalkyl).

[0087] "Sulfonamidyl" or "sulfonamido" refers to a $-S(=O)_2-NRR$ radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in -NRR of the $-S(=O)_2-NRR$ radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[0088] "Sulfoxyl" refers to a $-S(=O)_2OH$ radical.

[0089] "Sulfonate" refers to a $-S(=O)_2-OR$ radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[0090] Compounds of the invention also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" are intended to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to.

Co-administration of compounds

[0091] An aspect of the invention is a composition, such as a pharmaceutical composition, comprising a combination of a PI3K inhibitor and a BTK inhibitor.

[0092] Another aspect of the invention is a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination of a PI3K inhibitor and a BTK inhibitor.

[0093] In an exemplary embodiment, the PI3K inhibitor is a PI3K-γ inhibitor.

[0094] In an exemplary embodiment, the PI3K inhibitor is a PI3K-δ inhibitor.

[0095] In an exemplary embodiment, the PI3K inhibitor is a PI3K-γ,δ inhibitor.

[0096] In an exemplary embodiment, the PI3K inhibitor is a selective PI3K inhibitor.

[0097] In an exemplary embodiment, the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers.

[0098] In an exemplary embodiment, the leukemia is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL).

[0099] In an exemplary embodiment, the combination of the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor with the BTK inhibitor is administered by intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

[00100] In an exemplary embodiment, the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is in the form of a pharmaceutically acceptable salt.

[00101] In an exemplary embodiment, the BTK inhibitor is in the form of a pharmaceutically acceptable salt.

[00102] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is administered to the subject before administration of the BTK inhibitor.

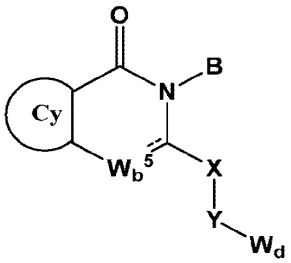
[00103] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is administered concurrently with the administration of the BTK inhibitor.

[00104] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, PI3K-γ,δ inhibitor is administered to the subject after administration of the BTK inhibitor.

[00105] In an exemplary embodiment, the subject is a mammal, such as a human.

PI3K Inhibitors

[00106] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 8,193,182 and 8,569,323, and U.S. Patent Application Publication Nos. 2012/0184568 A1, 2013/0344061 A1, and 2013/0267521 A1, the disclosures of which are incorporated by reference herein. In an exemplary embodiment, the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

Cy is aryl or heteroaryl substituted by 0 or 1 occurrences of R^3 and 0, 1, 2, or 3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, 3, or 4 occurrences of R^2;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, or carbonate;

X is $-(CH(R^9))_z-$;

Y is $-N(R^9)-C(=O)-$, $-C(=O)-N(R^9)-$, $-C(=O)-N(R^9)-(CHR^9)-$, $-N(R^9)-S(=O)-$, $-S(=O)-N(R^9)-$, $S(=O)_2-N(R^9)-$, $-N(R^9)-C(=O)-N(R^9)$ or $-N(R^9)S(=O)_2-$;

z is an integer of 1, 2, 3, or 4;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro;

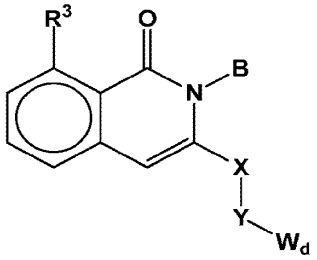
each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or heteroalkyl; or two adjacent occurrences of R^9 together with the atoms to which they are attached form a 4- to 7-membered ring;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl, each of which is substituted with one or more R^{10}, R^{11}, R^{12} or R^{13}, and

R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate or NR'R" wherein R' and R" are taken together with nitrogen to form a cyclic moiety.

[00107] In an exemplary embodiment, the the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (I-1):

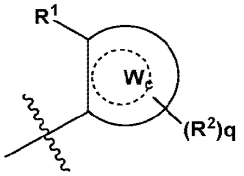


Formula (I-1)

or a pharmaceutically acceptable salt thereof,

wherein:

B is a moiety of Formula (II):



Formula (II) ;

W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

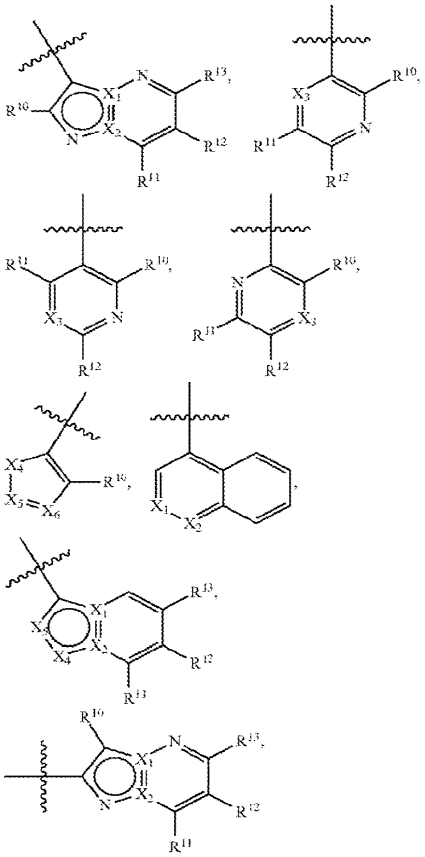
q is an integer of 0, 1, 2, 3, or 4;

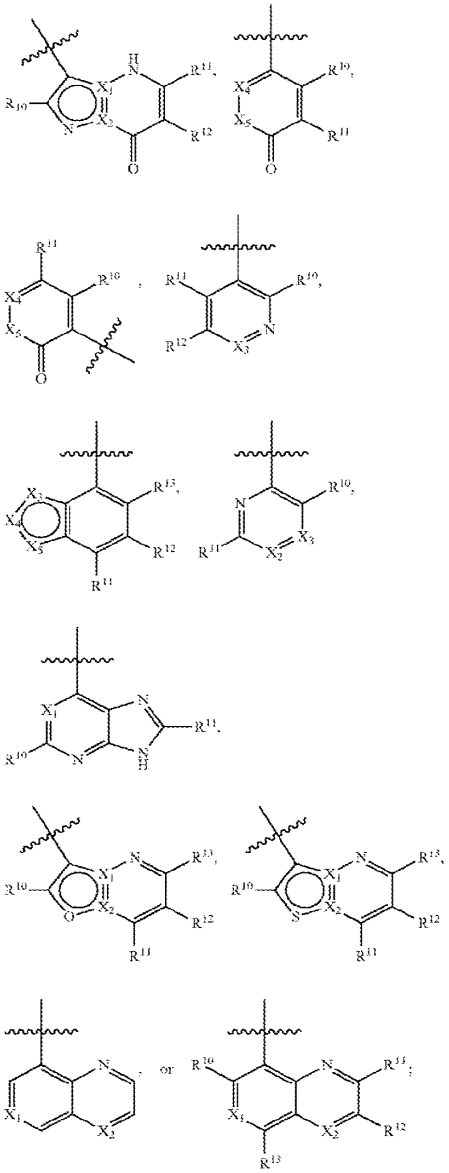
X is a bond or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3 or 4;

Y is a bond, $-N(R^9)-$, -O-, -S-, -S(=O)-, $-S(=O)_2$, -C(=O)-, $-C(=O)(CHR^9)_z-$, $-N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$ or $-N(R^9)C(R^9)_2-$;

z is an integer of 1, 2, 3, or 4;

W_d is:





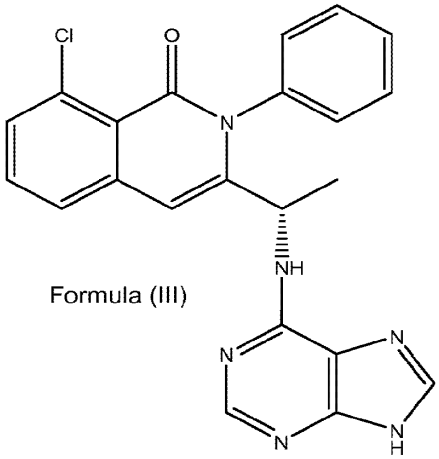
X_1, X_2 and X_3 are each independently C, CR^{13} or N; and X_4, X_5 and X_6 are each independently N, NH, CR^{13}, S or O;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

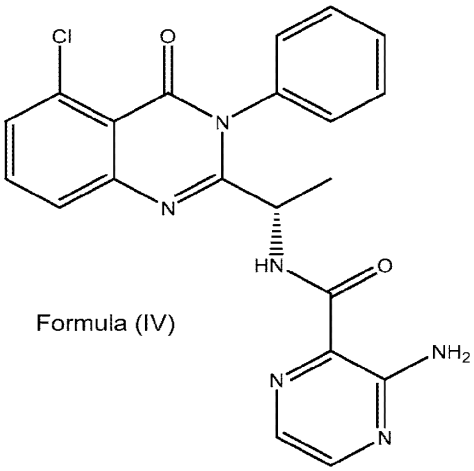
R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; R.sup.3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy or nitro; and

each instance of R^9 is independently hydrogen, alkyl, or heterocycloalkyl.

[00108] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is a compound of Formula (III) or Formula (IV):



Formula (III)



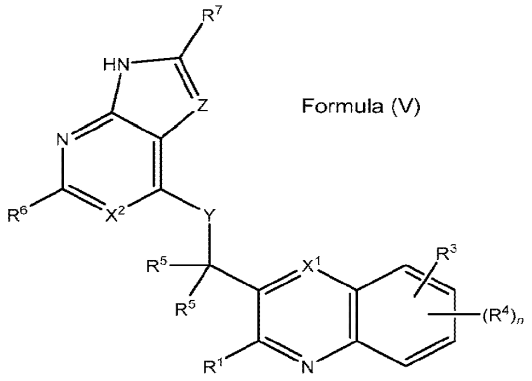
Formula (IV)

or a pharmaceutically acceptable salt thereof.

[00109] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is (S)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one or a pharmaceutically acceptable salt thereof.

[00110] In an exemplary embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is (S)-3-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide or a pharmaceutically acceptable salt thereof.

[00111] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 8,193,199 and 8,586,739, the disclosure of which is incorporated by reference herein. In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (V):



Formula (V)

or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R_{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one 0 or S, wherein the available carbon atoms of the ring are

substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}, $N(C_{1-4}alkyl)C_{1-4}alkyl$ and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a. —OC(=O)N(R^a)S(=O)$_2R^a$, —$OC_{2-6}alkylNR^aR^a$, —$OC_{2-6}alkylOR^a$, —SR^a, OS(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2NR^aR^a$, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2NR^aR^a$, —NR^aC_{2-6} alkylNR^aR^a and —N$R^aC_{2-6}alkylOR^a$; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C_{1-3}alkyl)heteroaryl, —(C_{1-3}alkyl)heterocycle, —O(C_{1-3}alkyl)heteroaryl, —O(C_{1-3}alkyl)heterocycle, —NR^a(C_{1-3}alkyl)heteroaryl, —NR^a(C_{1-3}alkyl)heterocycle, —(C_{1-3}alkyl)phenyl, —O(C_{1-3}alkyl)phenyl and —NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)R^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^2$, —$OC_{2-6}alkylNR^aR^a$, —$OC_{2-6}alkylOR^a$, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2NR^aR^a$, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2NR^aNR^aR^a$, —N$R^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}alkyl$ or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}alkyl$; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}alkyl$;

R^6 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

R^7 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^aC(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(O)NR^aR^aN(R^aC(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —N$R^a$$C_{2-6}$alkylN$R^aR^a$, —N$R^a$$C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —N$R^a$$C_{2-6}$alkylO$R^a$, —N$R^a$$C_{2-6}$alkylO$R^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —

$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}alkylNR^aR^a$ and —$NR^aC_{2-6}alkylOR^a$;

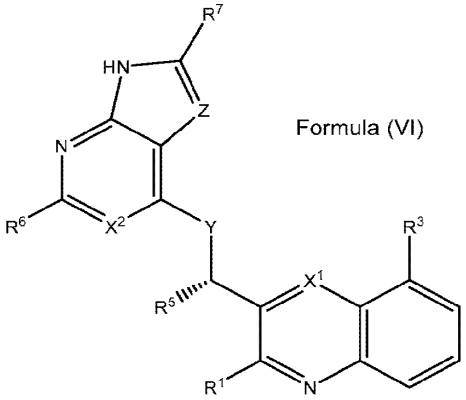
R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

R^{11} is H or C_{1-4}alkyl;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6} alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3} haloalkyl, —OC_{1-4}alkyl, —NH_2, —NHC_{1-4}alkyl, —$N(C_{1-4}alkyl)C_{1-4}$alkyl.

[00112] In another exemplary embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VI):



Formula (VI)

or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}$alkyl$)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6} alkylNR^aR^a and —NR^aC_{2-6}alkylOR^a; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C_{1-3}alkyl)heteroaryl, —(C_{1-3}alkyl)heterocycle, —O(C_{1-3}alkyl)heteroaryl, —O(C_{1-3}alkyl)heterocycle, —NR^a(C_{1-3}alkyl)heteroaryl, —NR^a(C_{1-3}alkyl)heterocycle, —(C_{1-3}alkyl)phenyl, —O(C_{1-3}alkyl)phenyl and —NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, C(=O)NR^aR^aC(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6}alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, N(C_{1-4}alkyl)C_{1-4}alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl,

OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

R^7 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^aS(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6} alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6}alkylNR^aR^a, —NR^aC_{2-6}alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6}alkylNR^a, —NR^aC_{2-6}alkylOR^a; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1,

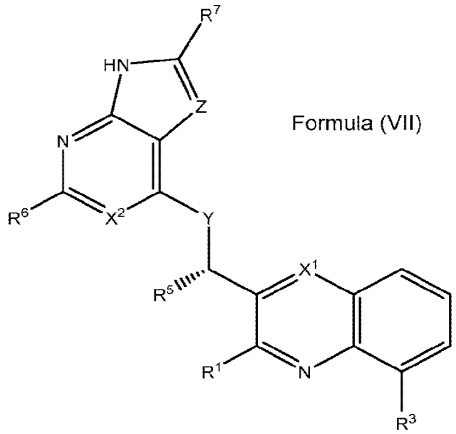
2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)N$R^a$$R^a$, —C(=N$R^a$)N$R^a$$R^a$, —O$R^a$, —OC(=O)$R^a$, —OC(=O)N$R^a$$R^a$, —OC(=O)N($R^a$)S(=O)$_2$$R^a$, —O$C_{2-6}$alkylO$R^a$, —S$R^a$, —S(=O)$R^a$, —S(=O)$_2$$R^a$, —S(=O)$_2NR^a$$R^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)O$R^a$, —S(=O)$_2$N($R^a$)C(=O)N$R^a$$R^a$, —N$R^a$$R^a$, —N($R^a$)C(=O)$R^a$, —N($R^a$)C(=O)O$R^a$, —N($R^a$)C(=O)N$R^a$$R^a$, —N($R^a$)C(=N$R^a$)N$R^a$$R^a$, —N($R^a$)S(=O)$_2$$R^a$, —N($R^a$)S(=O)$_2NR^a$$R^a$, —N$R^a$$C_{2-6}$ alkylN$R^a$$R^a$ and —N$R^a$$C_{2-6}$alkylO$R^a$;

R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, C(=O)N$R^a$$R^a$, —C(=N$R^a$)N$R^a$$R^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)O$R^a$, —S(=O)$_2$N($R^a$)C(=O)N$R^a$$R^a$, —S(=O)$R^b$, S(=O)$_2$$R^b$ or S(=O)$_2$N$R^a$$R^a$; —$R^{11}$ is H or C_{1-4}alkyl;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6} alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3} haloalkyl, —OC_{1-4}alkyl, —NH_2, —NHC_{1-4}alkyl, —N(C_{1-4}alkyl)C_{1-4}alkyl.

[00113] In another exemplary embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VII):



Formula (VII)

or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is C(R^9) or N;

X^2 is C(R^{10}) or N;

Y is N(R^{11}), O or S;

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6} alkylNR^aR^a and —NR^aC_{2-6}alkylOR^a; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C_{1-3}alkyl)heteroaryl, —(C_{1-3}alkyl)heterocycle, —O(C_{1-3}alkyl)heteroaryl, —O(C_{1-3}alkyl)heterocycle, —NR^a(C_{1-3}alkyl)heteroaryl, —NR^a(C_{1-3}alkyl)heterocycle, —(C_{1-3}alkyl)phenyl, —O(C_{1-3}alkyl)phenyl and —NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^1, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6}alkylNR^aR^a, —NR^aC_{2-6}alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^aS(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

R^7 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —S(=O)R^aS(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6}alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^8, —OC(=O)R^8, —OC(=O)NR^2R^8, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^8$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —

$NR^aC_{2-6}alkylNR^aR^a$, —$NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}alkylNR^aR^a$, —$OC_{2-6}alkylOR^a$, —SR^a, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}alkylNR^aR^a$ and —$NR^aC_{2-6}alkylOR^a$;

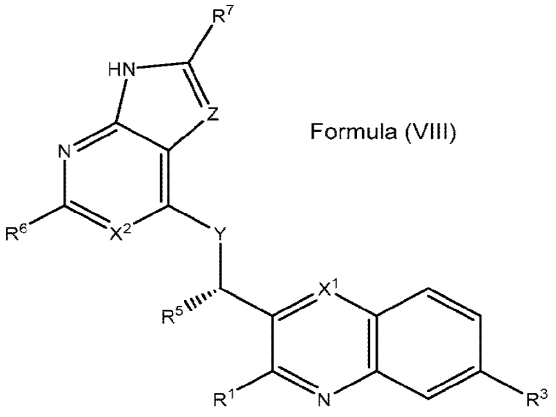
R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

R^{11} is H or C_{1-4}alkyl;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6}alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3}haloalkyl, —OC_{1-4}alkyl, —NH_2, —NHC_{1-4}alkyl, —$N(C_{1-4}alkyl)C_{1-4}alkyl$.

[00114] In another exemplary embodiment, the the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (VIII):



Formula (VIII)

or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}$alkyl$)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$—$C(=NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —OC_{2-6}alkylOR^a, —SR^a, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}$ alkylNR^aR^a and —NR^aC_{2-6}alkylOR^a; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C_{1-3}alkyl)heteroaryl, —(C_{1-3}alkyl)heterocycle, —O(C_{1-3} alkyl)heteroaryl, —O(C_{1-3}alkyl)heterocycle, —NR^a(C_{1-3}alkyl)heteroaryl, —NR^a(C_{1-3} alkyl)heterocycle, —(C_{1-3}alkyl)phenyl, —O(C_{1-3}alkyl)phenyl and —NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$—$C(=NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —OC_{2-6}alkylOR^a, —SR^a, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aNR^a$, —

NR^a, —$NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$;

R^7 is selected from H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6} alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}alkylNR^aR^a$, —$OC_{2-6}alkylOR^a$, —SR^a, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}alkylNR^aR^a$, —$NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, $OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}alkylOR^a$, —SR^a, —$S(=O)R^a$, —

$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}alkylNR^aR^a$, —$NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —$C(O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —OR^a, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}alkylNR^aR^a$, —$OC_{2-6}alkylOR^a$, —SR^a, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^aC_{2-6}$ $alkylNR^aR^a$ and —$NR^aC_{2-6}alkylOR^a$;

R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, —$S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

R^{11} is H or C_{1-4}alkyl;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6} alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3} haloalkyl, —OC_{1-4}alkyl, —NH_2, —NHC_{1-4}alkyl, —$N(C_{1-4}alkyl)C_{1-4}$alkyl.

[00115] In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $C(R^9)$ and X^2 is N.

[00116] In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $C(R^9)$ and X^2 is $C(R^{10})$.

[00117] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl substituted by 0 or 1 R^2 substituents, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00118] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl.

[00119] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl substituted by R^2, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00120] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is selected from 2-methylphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-fluorophenyl and 2-methoxyphenyl.

[00121] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenoxy.

[00122] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00123] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00124] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or

1 R^2 substituents, and the ring is additionally substituted by 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

[00125] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S.

[00126] In another embodiment, in conjunction with any of the above or below embodiments, R^1 is selected from pyridyl and pyrimidinyl.

[00127] In another embodiment, in conjunction with any of the above or below embodiments, R^3 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —NR^aC_{2-6}alkylNR^aR^a, —NR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl.

[00128] In another embodiment, in conjunction with any of the above or below embodiments, R^3 is H.

[00129] In another embodiment, in conjunction with any of the above or below embodiments, R^3 is selected from F, Cl, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl.

[00130] In another embodiment, in conjunction with any of the above or below embodiments, R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-}

$_6$spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl.

[00131] In another embodiment, in conjunction with any of the above or below embodiments, R^5 is H.

[00132] In another embodiment, in conjunction with any of the above or below embodiments, one R^5 is S-methyl, the other is H.

[00133] In another embodiment, in conjunction with any of the above or below embodiments, at least one R^5 is halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl.

[00134] In another embodiment, in conjunction with any of the above or below embodiments, R^6 is H.

[00135] In another embodiment, in conjunction with any of the above or below embodiments, R^6 is F, Cl, cyano or nitro.

[00136] In another embodiment, in conjunction with any of the above or below embodiments, R^7 is H.

[00137] In another embodiment, in conjunction with any of the above or below embodiments, R^7 is F, Cl, cyano or nitro.

[00138] In another embodiment, in conjunction with any of the above or below embodiments, R^8 is selected from H, CF_3, C_{1-3}alkyl, Br, Cl and F.

[00139] In another embodiment, in conjunction with any of the above or below embodiments, R^8 is selected from H.

[00140] In another embodiment, in conjunction with any of the above or below embodiments, R^8 is selected from CF_3, C_{1-3}alkyl, Br, Cl and F.

[00141] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is H.

[00142] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —N$R^a$$C_{2-6}$alkylN$R^aR^a$, —N$R^a$$C_{2-6}$alkylO$R^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —N$R^a$$C_{2-6}$alkylN$R^aR^a$, —N$R^a$$C_{2-6}$alkylO$R^a$.

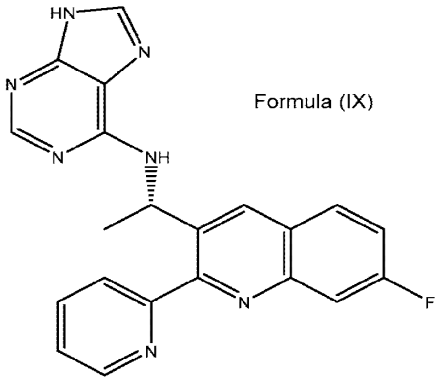
[00143] In another embodiment, in conjunction with any of the above or below embodiments, R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, —C(=O)R^a, —C(=O)OR^a, —C(=O)NR^aR^a, —C(=NR^a)NR^aR^a, —OR^a, —OC(=O)R^a, —OC(=O)NR^aR^a, —OC(=O)N(R^a)S(=O)$_2R^a$, —OC_{2-6}alkylNR^aR^a, —OC_{2-6}alkylOR^a, —SR^a, —S(=O)R^a, —S(=O)$_2R^a$, —S(=O)$_2$NR^aR^a, —S(=O)$_2$N(R^a)C(=O)R^a, —S(=O)$_2$N(R^a)C(=O)OR^a, —S(=O)$_2$N(R^a)C(=O)NR^aR^a, —NR^aR^a, —N(R^a)C(=O)R^a, —N(R^a)C(=O)OR^a, —N(R^a)C(=O)NR^aR^a, —N(R^a)C(=NR^a)NR^aR^a, —N(R^a)S(=O)$_2R^a$, —N(R^a)S(=O)$_2$NR^aR^a, —N$R^a$$C_{2-6}$alkylN$R^aR^a$ and —N$R^a$$C_{2-6}$alkylO$R^a$.

[00144] In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is H.

[00145] In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $—C(=NR^a)NR^aR^a$, $—S(=O)_2N(R^a)C(=O)R^a$, $—S(=O)_2N(R^a)C(=O)OR^a$, $—S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$.

[00146] In another embodiment, in conjunction with any of the above or below embodiments, R^{11} is H.

[00147] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (IX):

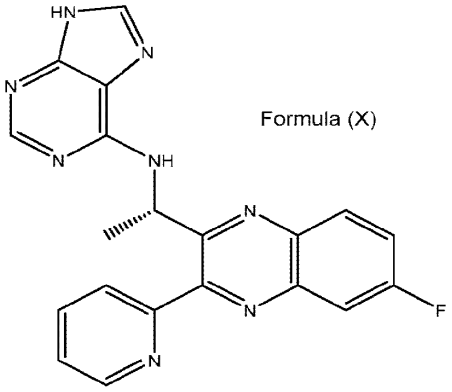


Formula (IX)

or a pharmaceutically-acceptable salt thereof

[00148] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00149] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (X):

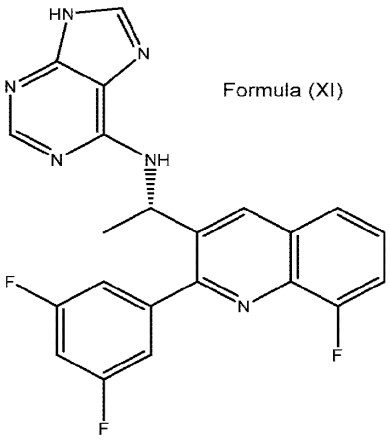


Formula (X)

or a pharmaceutically-acceptable salt thereof

[00150] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(6-fluoro-3-(pyridin-2-yl)quinoxalin-2-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00151] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XI):

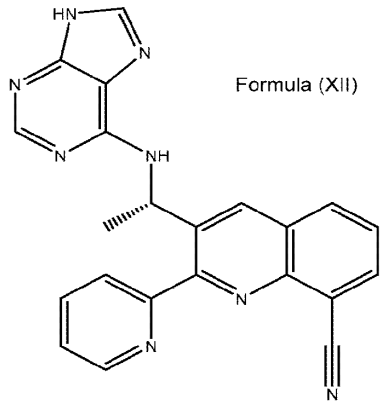


Formula (XI)

or a pharmaceutically-acceptable salt thereof.

[00152] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(2-(3,5-difluorophenyl)-8-fluoroquinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00153] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XII):

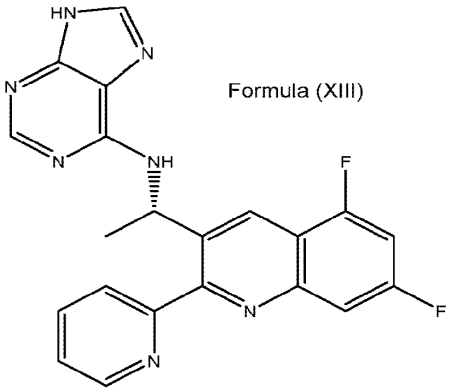


Formula (XII)

or a pharmaceutically-acceptable salt thereof

[00154] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-2-(pyridin-2-yl)quinoline-8-carbonitrile or a pharmaceutically-acceptable salt thereof.

[00155] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XIII):



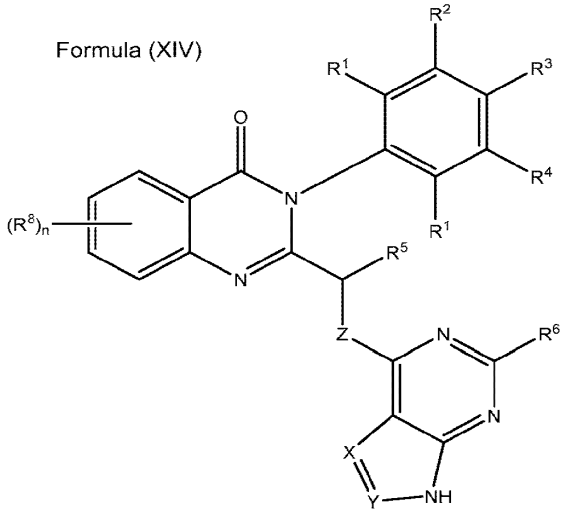
Formula (XIII)

or a pharmaceutically-acceptable salt thereof

[00156] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(5,7-difluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt thereof.

[00157] In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 7,932,260 and 8,207,153, the disclosure of which is incorporated by reference herein. In an exemplary embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XIV):

Formula (XIV)



wherein

X and Y, independently, are N or CRC;

Z is N—R^7 or O;

R^1 are the same and are hydrogen, halo, or C_{1-3}alkyl;

R^2 and R^3, independently, are hydrogen, halo, or C_{1-3}alkyl;

R^4 is hydrogen, halo, OR^a, CN, C_{2-6}alkynyl, $C(=O)R^a$, $C(=O)NR^aR^b$, C_{3-6}heterocycloalkyl, C_{1-3} alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyleneOR^a, OC_{1-3}alkyleneNR^aR^b, OC_{1-3}alkyleneC_{3-6} cycloalkyl, OC_{3-6}heterocycloalkyl, OC_{1-3}alkylene$C{\equiv}CH$, or OC_{1-3}alkylene$C(=O)NR^aR^b$;

R^5 is C_{1-3}alkyl, CH_2CF_3, phenyl, $CH_2C{\equiv}CH$, C_{1-3}alkyleneOR^e, C_{1-4}alkyleneNR^aR^b, or C_{1-4} alkylene$NHC(=O)OR^a$,

R^6 is hydrogen, halo, or NR^aR^b;

R^7 is hydrogen or R^5 and R^7 are taken together with the atoms to which they are attached to form a five- or six-membered saturated ring;

R^8 is C_{1-3}alkyl, halo, CF_3, or CH_2C_{3-6}heterocycloalkyl;

n is 0, 1, or 2;

R^a is hydrogen, C_{1-4}alkyl, or $CH_2C_6H_5$;

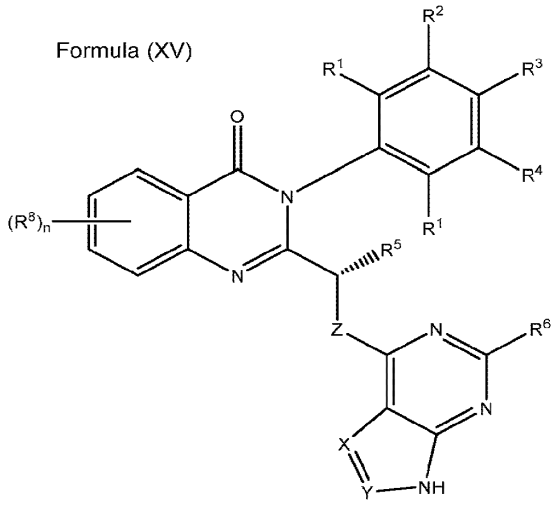
R^b is hydrogen or C_{1-3}alkyl; and

R^c is hydrogen, C_{1-3}alkyl, or halo,

wherein when the R^1 groups are different from hydrogen, R^2 and R^4 are the same; or a pharmaceutically acceptable salt, or prodrug, or solvate (e.g., hydrate) thereof.

[00158] In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is an enantiomer of Formula (XIV), as shown in Formula (XV):

Formula (XV)



wherein X, Y, Z, R^1 through R^8, R^a, R^b, R^c, and n are as defined above for Formula (XIV).

[00159] In various embodiments exhibiting increased potency relative to other compounds, R^8 is C_{1-3}alkyl, F, Cl, or CF_3. Alternatively, in such embodiments, n is 0 (such that there is no R^8 substituent).

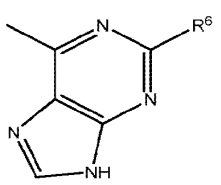
[00160] In other embodiments exhibiting such increased potency, X and Y, independently, are N or CH. In further embodiment exhibiting increased potency, X is N and Y is CH.

Alternatively, X and Y may also both be CH. In further embodiments exhibiting increased potency, R^6 is hydrogen, halo, or NH_2.

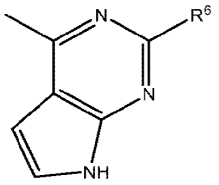
[00161] Unexpectedly, potency against PI3K-δ is conserved when R^1 is the same. In structural formulae (I) and (II), R^2 and R^4 may differ provided that R^1 is H. When R^1 is H, free rotation is unexpectedly permitted about the bond connecting the phenyl ring substituent to the quinazoline ring, and the compounds advantageously do not exhibit atropisomerism (i.e., multiple diasteromer formation is avoided). Alternatively, R^2 and R^4 can be the same such that the compounds advantageously do not exhibit atropisomerism.

[00162] As used with respect to Formula (XIV) and Formula (XV), the term "alkyl" is defined as straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms, e.g., methyl, ethyl, and straight chain and branched propyl and butyl groups. The terms "C_{1-3}alkylene" and "C_{1-4}alkylene" are defined as hydrocarbon groups containing the indicated number of carbon atoms and one less hydrogen than the corresponding alkyl group. The term "C_{2-6}alkynyl" is defined as a hydrocarbon group containing the indicated number of carbon atoms and a carbon-carbon triple bond. The term "C_{3-6}cycloalkyl" is defined as a cyclic hydrocarbon group containing the indicated number of carbon atoms. The term "C_{2-6}heterocycloalkyl" is defined similarly as cycloalkyl except the ring contains one or two heteroatoms selected from the group consisting of O, NR^a, and S. The term "halo" is defined as fluoro, bromo, chloro, and iodo.

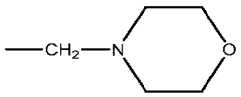
[00163] In preferred embodiments, Z is N—R^7, and the bicyclic ring system containing X and Y is:



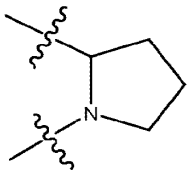
or



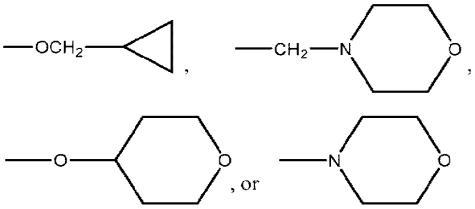
[00164] In other preferred embodiments, R^1 is hydrogen, fluoro, chloro, methyl, or



and R^2 is hydrogen, methyl, chloro, or fluoro; R^3 is hydrogen or fluoro; R^6 is NH_2, hydrogen, or fluoro; R^7 is hydrogen or R^5 and R^7 are taken together to form

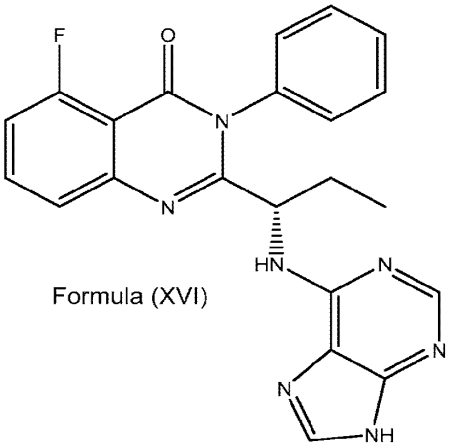


R^8 is methyl, trifluoromethyl, chloro, or fluoro; R^4 is hydrogen, fluoro, chloro, OH, OCH_3, $OCH_2C{\equiv}CH$, $O(CH_2)_2N(CH_3)_2$, $C(=O)CH_3$, $C{\equiv}CH$, CN, $C(=O)NH_2$, $OCH_2C(=O)NH_2$, $O(CH_2)_2OCH_3$, $O(CH_2)_2N(CH_3)_2$,



and R^5 is methyl, ethyl, propyl, phenyl, CH_2OH, $CH_2OCH_2C_6H_5$, CH_2CF_3, $CH_2OC(CH_3)_3$, $CH_2C{\equiv}CH$, $(CH_2)_3N(C_2H_5)_2$, $(CH_2)_3NH_2$, $(CH_2)_4NH_2$, $(CH_2)_3NHC(=O)OCH_2C_6H_5$, or $(CH_2)_4NHC(=O)OCH_2C_6H_5$; R^c is hydrogen, methyl, fluoro, or bromo; and n is 0 or 1.

[00165] In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is the compound of Formula (XVI):



Formula (XVI)

or a pharmaceutically-acceptable salt thereof.

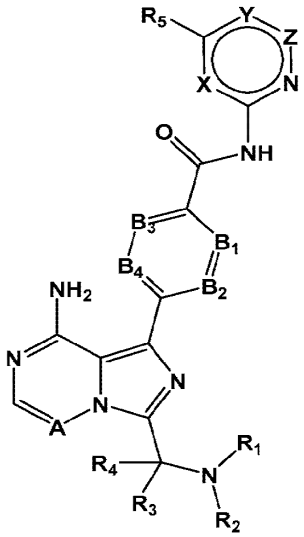
[00166] In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one or a pharmaceutically-acceptable salt thereof.

[00167] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is 4(3*H*)-quinazolinone, 5-fluoro-3-phenyl-2-[(1*S*)-1-(9*H*-purin-6-ylamino)propyl]-5-fluoro-3-phenyl-2-{(1*S*)-1-[(7*H*-purin-6-yl)amino]propyl}quinazolin-4(3*H*)-one or or a pharmaceutically-acceptable salt thereof

[00168] Other PI3K inhibitors suitable for use in the described combination with a BTK inhibitor also include, but are not limited to, those described in, for example, U.S. Patent No. 8,193,182 and U.S. Published Application Nos. 2013/0267521; 2013/0053362; 2013/0029984; 2013/0029982; 2012/0184568; and 2012/0059000, the disclosures of each of which are incorporated by reference in their entireties.

BTK Inhibitors

[00169] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XVII):



Formula (XVII)

or a pharmaceutically acceptable salt thereof,

wherein:

X is CH, N, O or S;

Y is $C(R_6)$, N, O or S;

Z is CH, N or bond;

A is CH or N;

B_1 is N or $C(R_7)$;

B_2 is N or $C(R_8)$;

B_3 is N or $C(R_9)$;

B_4 is N or $C(R_{10})$;

R_1 is $R_{11}C(=O)$, $R_{12}S(=O)$, $R_{13}S(=O)_2$ or (1-6C)alkyl optionally substituted with R_{14};

R_2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R_3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R_2 and R_3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R_4 is H or (1-3C)alkyl;

R_5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R_5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R_6 is H or (1-3C)alkyl; or

R_5 and R_6 together may form a (3-7C)cycloalkenyl or (2-6C)heterocycloalkenyl, each optionally substituted with (1-3C)alkyl or one or more halogens;

R_7 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy;

R_8 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy; or

R_7 and R_8 together with the carbon atoms they are attached to, form (6-10C)aryl or (1-9C)heteroaryl;

R_9 is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{10} is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{11} is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl, where each alkyl, alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl; or R_{11} is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

R_{11} is (1-5C)heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen or cyano;

R_{12} and R_{13} are independently selected from the group consisting of (2-6C)alkenyl or (2-6C)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl; or a (1-5C)heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen and cyano; and

R_{14} is independently selected from the group consisting of halogen, cyano, (2-6C)alkenyl and (2-6C)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl and (3-7C)heterocycloalkyl;

with the proviso that:

0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;

when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;

when Z is C or N then Y is C(R6) or N and X is C or N;

0 to 2 atoms of B1, B2, B3 and B4 are N;

with the terms used having the following meanings:

(1-2C)alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl,

(1-3C)alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

(1-4C)alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (1-3C)alkyl groups being preferred;

(1-5C)alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and isopentyl, (1-4C)alkyl groups being preferred. (1-6C)Alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (1-5C)alkyl groups are preferred, (1- 4C)alkyl being most preferred;

(1-2C)alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

(1-3C)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-2C)alkoxy groups are preferred;

(1-4C)alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-3C)alkoxy groups are preferred, (1-2C)alkoxy groups being most preferred;

(2-4C)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;

(2-6C)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, (2-4C)alkenyl groups being most preferred;

(2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;

(2-6C)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl. (2-4C)alkynyl groups are preferred; (3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

(3-7C)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

(2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; also preferred are piperidine, morpholine, pyrrolidine and piperazine; with the most preferred (2-6C)heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;

(3-7C)heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O; preferred (3-7C) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (3-7C)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(3-7C)cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

(6-10C)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred (6-10C)aryl group is phenyl;

(1-5C)heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (1-5C)heteroaryl may optionally be substituted; preferred (1-5C)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, a more preferred (1-5C)heteroaryl is pyrimidyl;

(1-9C)heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (1-9C)heteroaryl may optionally be substituted; preferred (1-9C)heteroaryl groups are quinoline, isoquinoline and indole;

[(1-4C)alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; preferred [(1-4C)alkyl]amino group is methylamino;

di[(1-4C)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; preferred di[(1-4C)alkyl]amino group is dimethylamino;

halogen means means fluorine, chlorine, bromine or iodine;

(1-3C)alkyl-C(0)-S-(1-3C)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

(3-7C)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred (3-7C)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; cyclohexenyl groups are most preferred;

(2-6C)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; preferred (2-6C)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl group.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula (XVII) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

The term "substituted" means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. "Stable compound" or "stable structure" is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

[00170] In an exemplary embodiment of Formula (XVII), B_1 is $C(R_7)$; B_2 is $C(R_8)$; B_3 is $C(R_9)$; B_4 is $C(R_{10})$; R_7, R_9, and R_{10} are each H; and R_8 is hydrogen or methyl.

[00171] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

[00172] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyridazyl.

[00173] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

[00174] In an exemplary embodiment of Formula (XVII), the ring containing X, Y and Z is pyridyl.

[00175] In an exemplary embodiment of Formula (XVII), R_5 is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

[00176] In an exemplary embodiment of Formula (XVII), R_5 is hydrogen.

[00177] In an exemplary embodiment of Formula (XVII), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl and morpholinyl, optionally substituted with one or more of fluoro, hydroxyl, (1-3C)alkyl and (1-3C)alkoxy.

[00178] In an exemplary embodiment of Formula (XVII), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

[00179] In an exemplary embodiment of Formula (XVII), R_2 and R_3 together form a pyrrolidinyl ring.

[00180] In an exemplary embodiment of Formula (XVII), R_1 is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (1-4C)alkyl, (3-

7C)cycloalkyl, [(l-4C)alkyl]amino, di[(l-4C)alkyl] amino, (l-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl and (3-7C)heterocycloalkyl.

[00181] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X is N; Y and Z are CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

[00182] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

[00183] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-ethenyl.

[00184] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is H; A is CH; R_2 and R_3 together form a pyrrolidinyl ring; R_4 is H; and R_1 is CO-propynyl.

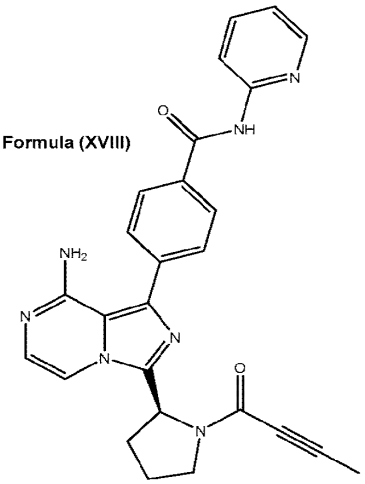
[00185] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-propynyl.

[00186] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is H; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-ethenyl.

[00187] In an exemplary embodiment of Formula (XVII), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-propynyl.

[00188] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XVIII):

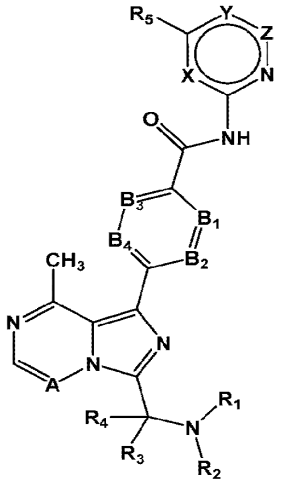
Formula (XVIII)



or a pharmaceutically-acceptable salt thereof. The preparation of this compound is described at Example 6 of International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference. The preparation of this compound and related structures are described in the Examples of International Patent Application Publication No. WO 2013/010868, the disclosure of which is incorporated herein by reference.

[00189] In an exemplary embodiment, the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or pharmaceutically-acceptable salt therof.

[00190] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XIX) or a pharmaceutically-acceptable salt of a compound of Formula (XIX):



Formula (XIX)

In Formula (XIX) the substituents are defined as

X is CH, N, O or S;

Y is $C(R_6)$, N, O or S;

Z is CH, N or bond;

A is CH or N;

B_1 is N or $C(R_7)$;

B_2 is N or $C(R_8)$;

B_3 is N or $C(R_9)$;

B_4 is N or $C(R_{10})$;

R_1 is $R_{11}C(0)$, $R_{12}S(O)$, $R_{13}SO_2$ or (1-6C)alkyl optionally substituted with R_{14};

R_2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R_3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R_2 and R_3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R_4 is H or (1-3C)alkyl;

R_5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl; all alkyl groups of R5 are optionally substituted with one or more halogen; or R_5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R_6 is H or (1-3C)alkyl; or R_5 and R_6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R_7 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy;

R_8 is H, halogen, CF_3, (1-3C)alkyl or (1-3C)alkoxy; or

R_7 and R_8 together with the carbon atoms they are attached to, form (6-10C)aryl or (1-5C)heteroaryl;

R_9 is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{10} is H, halogen, (1-3C)alkyl or (1-3C)alkoxy;

R_{11} is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl, or

R_{11} is (1-3C)alkyl-C(0)-S-(1-3C)alkyl; or

R_{11} is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

R_{12} and R_{13} are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R_{14} is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
- when Z is C or N then Y is $C(R_6)$ or N and X is C or N;
- 0 to 2 atoms of B_1, B_2, B_3 and B_4 are N;

with the terms used having the following meanings:

(1-3C)alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

(1-4C)alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (1-3C)alkyl groups being preferred;

(1-6C)alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (1-5C)alkyl groups are preferred, (1-4C)alkyl being most preferred;

(1-2C)alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

(1-3C)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined, with (1-2C)alkoxy groups preferred;

(2-3C)alkenyl means an alkenyl group having 2-3 carbon atoms, such as ethenyl or 2- propenyl;

(2-4C)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;

(2-6C)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, with (2-4C)alkenyl groups preferred, and (2-3C)alkenyl groups even more preferred;

(2-4C)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;

(2-3C)alkynyl means an alkynyl group having 2-3 carbon atoms, such as ethynyl or 2-propynyl;

(2-6C)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl, wtih (2-4C)alkynyl groups preferred, and (2-3C)alkynyl groups more preferred;

(3-6C)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

(3-7C)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

(2-6C)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3- 5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O;

preferred groups are piperidine, morpholine, pyrrolidine and piperazine; a most preferred (2-6C)heterocycloalkyl is pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(3-7C)heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3- 5 carbon atoms, and one or two heteroatoms selected from N, O and/or S; preferred heteroatoms are N or O; preferred (3-7C) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (3-7C)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; even more preferred are piperidine and pyrrolodine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(3-7C)cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

(6-10C)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred (6-10C)aryl group is phenyl;

(1-5C)heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S, wherein the (1-5C)heteroaryl may optionally be substituted.; preferred (1-5C)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, and the more preferred (1-5C)heteroaryl is pyrimidyl;

[(1-4C)alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; the preferred [(1-4C)alkyl]amino group is methylamino;

di[(1-4C)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; the preferred di[(1-4C)alkyl]amino group is dimethylamino;

halogen means means fluorine, chlorine, bromine or iodine;

(1-3C)alkyl-C(O)-S-(1-3C)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

(3-7C)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred (3-7C)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; and cyclohexenyl groups are most preferred;

(2-6C)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; the preferred (2-6C)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl groups.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

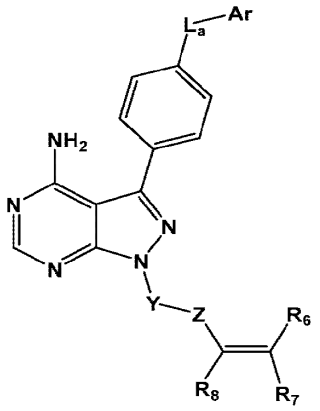
A circle in a ring of Formula (XIX) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

The term "substituted" means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. "Stable compound" or "stable structure" is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties. In one aspect the invention relates to a compound according to formula I wherein B_1 is $C(R_7)$; B_2 is $C(R_8)$; B_3 is $C(R_9)$ and B_4 is $C(R_{10})$.

[00191] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XX):



Formula (XX)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

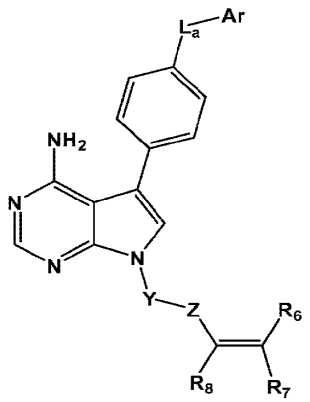
R^7 and R^8 are each independently H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

R is H or C_1-C_6alkyl.

[00192] In an exemplary embodiment, the BTK inhibitor is ibrutinib or a pharmaceutically-acceptable salt thereof.

[00193] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXI):



Formula (XXI)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

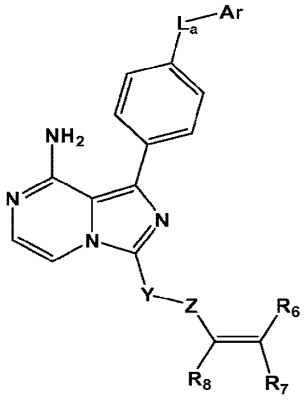
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

R is H or C_1-C_6alkyl.

[00194] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXII):



Formula (XXII)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

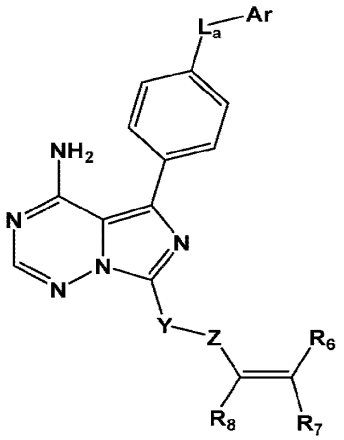
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

R is H or C_1-C_6alkyl.

[00195] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXIII):



Formula (XXIII)

or a pharmaceutically acceptable salt thereof,

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

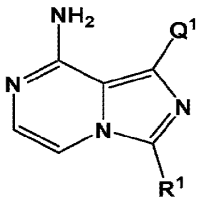
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

R is H or C_1-C_6alkyl.

[00196] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXIV):



Formula (XXIV)

or a pharmaceutically acceptable salt thereof,

wherein:

Q^1 is aryl[1], heteroaryl[1], cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one to five independent G^1 substituents;

R^1 is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, or heterobicycloalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

G^1 and G^{41} are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, -CN, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C{=}O)R^3$, $NR^2(C{=}O)OR^3$, $NR^2(C{=}O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C{=}S)OR^2$, $-(C{=}O)SR^2$, $-NR^2(C{=}NR^3)NR^{2a}R^{3a}$, $-NR^2(C{=}NR^3)OR^{2a}$, $-NR^2(C{=}NR^3)SR^{3a}$, $-O(C{=}O)OR^2$, $-O(C{=}O)NR^2R^3$, $-O(C{=}O)SR^2$, $-S(C{=}O)OR^2$, $-S(C{=}O)NR^2R^3$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333}a)_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333a}$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents; or $-(X^1)_n-(Y^1)_m-R^4$; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333a}$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}$, $R^{333}(R^{333a})_{j3a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j3a}R^{222}$, $-SO_2NR^{222}R^{333}$,

$NR^{222}(C{=}O)R^{333}$, $NR^{222}(C{=}O)OR^{333}$, $NR^{222}(C{=}O)NR^{222}R^{333}$, $NR^{222}S(O)_{j3a}R^{333}$, $-(C{=}S)OR^{222}$, $-(C{=}O)SR^{222}$, $-NR^{222}(C{=}NR^{333})NR^{222}aR^{333}a$, $-NR^{222}(C{=}NR^{333})OR^{222a}$, $-NR^{222}(C{=}NR^{333})SR^{333}a$, $-O(C{=}O)OR^{222}$, $-O(C{=}O)NR^{222}R^{333}$, $-O(C{=}O)SR^{222}$, $-S(C{=}O)OR^{222}$, or $-S(C{=}O)NR^{222}R^{333}$ substituents;

G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{3a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-CONR^{21}R^{31}$, $-NO_2$, -CN, $-S(O)_{j4}R^{21}$, $-SO_2NR^{21}R^{31}$, $NR^{21}(C{=}O)R^{31}$, $NR^{21}(C{=}O)OR^{31}$, $NR^{21}(C{=}O)NR^{21}R^{31}$, $NR^{21}S(O)_{j4}R^{31}$, $-(C{=}S)OR^{21}$, $-(C{=}O)SR^{21}$, $-NR^{21}(C{=}NR^{31})NR^{2a1}R^{3a1}$, $-NR^{21}(C{=}NR^{31})OR^{2a1}$, $-NR^{21}(C{=}NR^{31})SR^{3a1}$, $-O(C{=}O)OR^{21}$, $-O(C{=}O)NR^{21}R^{31}$, $-O(C{=}O)SR^{21}$, $-S(C{=}O)OR^{21}$, $-S(C{=}O)NR^{21}R^{31}$, $-P(O)OR^{21}OR^{31}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C{=}O)R^{3331}$, $NR^{2221}(C{=}O)OR^{3331}$, $NR^{2221}(C{=}O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j4a}R^{3331}$, $-(C{=}S)OR^{2221}$, $-(C{=}O)SR^{2221}$, $-NR^{2221}(C{=}NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C{=}NR^{3331})OR^{222a1}$, $-NR^{2221}(C{=}NR^{3331})SR^{333a1}$, $-O(C{=}O)OR^{2221}$, $-O(C{=}O)NR^{2221}R^{3331}$, $-O(C{=}O)SR^{2221}$, $-S(C{=}O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C{=}O)NR^{2221}R^{3331}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C{=}O)R^{3331}$, $NR^{2221}(C{=}O)OR^{3331}$, $NR^{2221}(C{=}O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j5a}R^{3331}$, $-(C{=}S)OR^{2221}$, $-(C{=}O)SR^{2221}$, $-NR^{2221}(C{=}NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C{=}NR^{3331})OR^{222a1}$, $-NR^{2221}(C{=}NR^{3331})SR^{333a1}$, $-O(C{=}O)OR^{2221}$, $-O(C{=}O)NR^{2221}R^{3331}$, $-O(C{=}O)SR^{2221}$, $-S(C{=}O)OR^{2221}$, $-P(O)OR^{2221}R^{3331}$, or $-S(C{=}O)NR^{2221}R^{3331}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j6a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C{=}O)R^{3331}$, $NR^{2221}(C{=}O)OR^{3331}$,

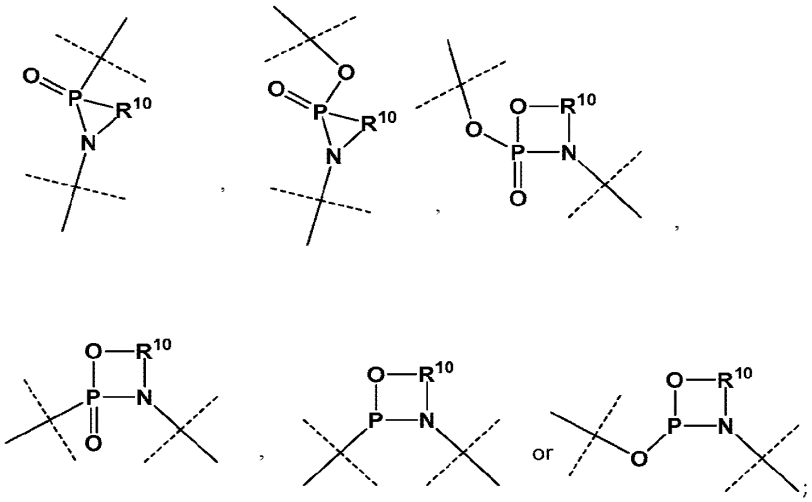
$NR^{2221}(C{=}O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j6a}R^{3331}$, $-(C{=}S)OR^{2221}$, $-(C{=}O)SR^{2221}$, $-NR^{2221}(C{=}NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C{=}NR^{3331})OR^{222a1}$, $-NR^{2221}(C{=}NR^{3331})SR^{333a1}$, $-O(C{=}O)OR^{2221}$, $-O(C{=}O)NR^{2221}R^{3331}$, $-O(C{=}O)SR^{2221}$, $-S(C{=}O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C{=}O)NR^{2221}R^{3331}$ substituents; or G^{11} is taken together with the carbon to which it is attached to form a double bond which is substituted with R^5 and G^{111};

R^2, R^{2a}, R^3, R^{3a}, R^{222}, $R^{222}a$, R^{333}, R^{333a}, R^{21}, R^{2a1}, R^{31}, R^{3a1}, R^{2221}, R^{222a1}, R^{3331}, and R^{333a1} are each independently equal to C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or in the case of $-NR^2R^3(R^{3a})_{j1}$ or $-NR^{222}R^{333}(R^{333}a)_{j1a}$ or $-NR^{222}R^{333}(R^{333}a)_{j2a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j3a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, R^2 and R^3 or R^{222} and $R^{333}3$ or R^{2221} and R^{3331} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted by one or more G^{111} substituents;

X^1 and Y^1 are each independently -O-, $-NR^7-$, $-S(O)_{j7}-$, $-CR^5R^6-$, $-N(C(O)OR^7)-$, $-N(C(O)R^7)-$, $-N(SO_2R^7)-$, $-CH_2O-$, $-CH_2S-$, $-CH_2N(R^7)-$, $-CH(NR^7)-$, $-CH_2N(C(O)R^7)-$, $-CH_2N(C(O)OR^7)-$, $-CH_2N(SO_2R^7)-$, $-CH(NHR^7)-$, $-CH(NHC(O)R^7)-$, $-CH(NHSO_2R^7)-$, $-CH(NHC(O)OR^7)-$, $-CH(OC(O)R^7)-$, $-CH(OC(O)NHR^7)-$, -CH=CH-, -C.ident.C-, $-C(=NOR^7)-$, -C(O)-, $-CH(OR^7)-$, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$ $-OC(O)N(R^7)-$, $-N(R^7)C(O)N(R^7)-$, $-NR^7C(O)O-$, $-S(O)N(R^7)-$, $-S(O)_2N(R^7)-$, $-N(C(O)R^7)S(O)-$, $-N(C(O)R^7)S(O)_2-$, $-N(R^7)S(O)N(R^7)-$, $-N(R^7)S(O)_2N(R^7)-$, $-C(O)N(R^7)C(O)-$, $-S(O)N(R^7)C(O)-$, $-S(O)_2N(R^7)C(O)-$, $-OS(O)N(R^7)-$, $-OS(O)_2N(R^7)-$, $-N(R^7)S(O)O-$, $-N(R^7)S(O)_2O-$, $-N(R^7)S(O)C(O)-$, $-N(R^7)S(O)_2C(O)-$, $-SON(C(O)R^7)-$, $-SO_2N(C(O)R^7)-$, $-N(R^7)SON(R^7)-$, $-N(R^7)SO_2N(R^7)-$, -C(O)O-, $-N(R^7)P(OR^8)O-$, $-N(R^7)P(OR^8)-$, $-N(R^7)P(O)(OR^8)O-$, $-N(R^7)P(O)(OR^8)-$, $-N(C(O)R^7)P(OR^8)O-$, $-N(C(O)R^7)P(OR^8)-$, -

$N(C(O)R^7)P(O)(OR^8)O$-, -$N(C(O)R^7)P(OR^8)$-, -$CH(R^7)S(O)$-, -$CH(R^7)S(O)_2$-, -$CH(R^7)N(C(O)OR^7)$-, -$CH(R^7)N(C(O)R^7)$-, -$CH(R^7)N(SO_2R^7)$-, -$CH(R^7)O$-, -$CH(R^7)S$-, -$CH(R^7)N(R^7)$-, -$CH(R^7)N(C(O)R^7)$-, -$CH(R^7)N(C(O)OR^7)$-, -$CH(R^7)N(SO_2R^7)$-, -$CH(R^7)C(=NOR^7)$-, -$CH(R^7)C(O)$-, -$CH(R^7)CH(OR^7)$-, -$CH(R^7)C(O)N(R^7)$-, -$CH(R^7)N(R^7)C(O)$-, -$CH(R^7)N(R^7)S(O)$-, -$CH(R^7)N(R^7)S(O)_2$-, -$CH(R^7)OC(O)N(R^7)$-, -$CH(R^7)N(R^7)C(O)N(R^7)$-, -$CH(R^7)NR^7C(O)O$-, -$CH(R^7)S(O)N(R^7)$-, -$CH(R^7)S(O)_2N(R^7)$-, -$CH(R^7)N(C(O)R^7)S(O)$-, -$CH(R^7)N(C(O)R^7)S(O)$-, -$CH(R^7)N(R^7)S(O)N(R^7)$-, -$CH(R^7)N(R^7)S(O)_2N(R^7)$-, -$CH(R^7)C(O)N(R^7)C(O)$-, -$CH(R^7)S(O)N(R^7)C(O)$-, -$CH(R^7)S(O)_2N(R^7)C(O)$-, -$CH(R^7)OS(O)N(R^7)$-, -$CH(R^7)OS(O)_2N(R^7)$-, -$CH(R^7)N(R^7)S(O)O$-, -$CH(R^7)N(R^7)S(O)_2O$-, -$CH(R^7)N(R^7)S(O)C(O)$-, -$CH(R^7)N(R^7)S(O)_2C(O)$-, -$CH(R^7)SON(C(O)R^7)$-, -$CH(R^7)SO_2N(C(O)R^7)$-, -$CH(R^7)N(R^7)SON(R^7)$-, -$CH(R^7)N(R^7)SO_2N(R^7)$-, -$CH(R^7)C(O)O$-, -$CH(R^7)N(R^7)P(OR^8)O$-, -$CH(R^7)N(R^7)P(OR^8)$-, -$CH(R^7)N(R^7)P(O)(OR^8)O$-, -$CH(R^7)N(R^7)P(O)(OR^8)$-, -$CH(R^7)N(C(O)R^7)P(OR^8)O$-, -$CH(R^7)N(C(O)R^7)P(OR^8)$-, -$CH(R^7)N(C(O)R^7)P(O)(OR^8)O$-, or -$CH(R^7)N(C(O)R^7)P(OR^8)$-;

or X^1 and Y^1 are each independently represented by one of the following structural formulas:



R^{10}, taken together with the phosphinamide or phosphonamide, is a 5-, 6-, or 7-membered aryl, heteroaryl or heterocyclyl ring system;

R^5, R^6, and G^{111} are each independently a C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}R^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C{=}S)OR^{77}$, $-(C{=}O)SR^{77}$, $-NR^{77}(C{=}NR^{87})NR^{78}R^{88}$, $-NR^{77}(C{=}NR^{87})OR^{78}$, $-NR^{77}(C{=}NR^{87})SR^{78}$, $-O(C{=}O)OR^{77}$, $-O(C{=}O)NR^{77}R^{87}$, $-O(C{=}O)SR^{77}$, $-S(C{=}O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C{=}O)NR^{77}R^{87}$ substituents; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R^{69}; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R^{69};

R^7 and R^8 are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G^{111} substituents;

R^4 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G^{41} substituents;

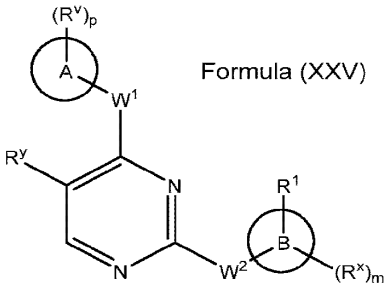
R^{69} is equal to halo, $-OR^{78}$, -SH, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-CONR^{78}R^{88}$, $-NO_2$, -CN, $-S(O)_{j8}R^{78}$, $-SO_2NR^{78}R^{88}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, or heterocyclyl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or -N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, $-CONR^{778}R^{888}$ $SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

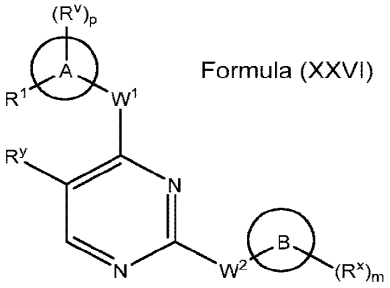
R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl,

cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl-C_{0-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, C_{1-10}alkylcarbonyl, C_{2-10}alkenylcarbonyl, C_{2-10}alkynylcarbonyl, C_{1-10}alkoxycarbonyl, C_{1-10}alkoxycarbonylC_{1-10}alkyl, monoC_{1-6}alkylaminocarbonyl, diC_{1-6}alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C_{1-10}alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, -$SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or -$N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; or aryl-C_{0-10}alkyl, aryl-C_{2-10}alkenyl, or aryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$O(C_{0-4}alkyl)$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, -$CON(C_{0-4}alkyl)(C_{0-10}alkyl)$, -$SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or -$N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; or hetaryl-C_{0-10}alkyl, hetaryl-C_{2-10}alkenyl, or hetaryl-C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$O(C_{0-4}alkyl)$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, -$CON(C_{0-4}alkyl)(C_{0-4}alkyl)$, -$SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or -$N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; or mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or -N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$O(C_{0-4}alkyl)$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, -COOH, C_{1-4}alkoxycarbonyl, -$CON(C_{0-4}alkyl)(C_{0-4}alkyl)$, -$SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or -$N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents; and

n, m, j1, j1a, j2a, j3a, j4, j4a, j5a, j6a, j7, and j8 are each independently equal to 0, 1, or 2.

[00197] In an exemplary embodiment, the BTK inhibitor is a compound selected from the structures dislosed in U.S. Patent Nos. 8,450,335 and 8,609,679, and U.S. Patent Application Publication Nos. 2010/0029610 A1, 2012/0077832 A1, 2013/0065879 A1, 2013/0072469 A1, and 2013/0165462 A1, the disclosures of which are incorporated by reference herein. In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI):





or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated

heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is a warhead group;

R^y is hydrogen, halogen, —CN, —CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —C(O)N$(R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by —NR^2—, —N(R^2)C(O)—, —C(O)N(R^2)—, —N(R^2)SO_2—, —SO_2N(R^2)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or —C(O)R, or:

R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring, or:

R^2 and R^y are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^v are independently selected from —R, halogen, —OR, —O$(CH_2)_q$OR, —CN, —NO_2, —SO_2R, —SO_2N$(R)_2$, —SOR, —C(O)R, —CO_2R, —C(O)N$(R)_2$, —NRC(O)R, —NRC(O)NR_2, —NRSO_2R, or —N$(R)_2$, wherein q is 1-4; or:

R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic; or

R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with

a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic.

[00198] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI), wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is -L-Y, wherein:

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, —SO_2N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR)—, —N=N—, or —C(=N_2)—;

Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -Q-Z, oxo, NO_2, halogen, CN, or C_{1-6} aliphatic, wherein:

Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —S—, —O—, —C(O)—, —SO—, or —SO_2—; and

Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN;

R^y is hydrogen, halogen, —CN, —CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —C(O)N$(R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by —NR^2—, —N(R^2)C(O)—, —C(O)N(R^2)—, —N(R^2)SO_2—, —SO_2N(R^2)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or —C(O)R, or:

R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or

R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^v are independently selected from —R, halogen, —OR, —$O(CH_2)_qOR$, —CN, —NO_2, —SO_2R, —$SO_2N(R)_2$, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)NR_2$, —$NRSO_2R$, or —$N(R)_2$, or:

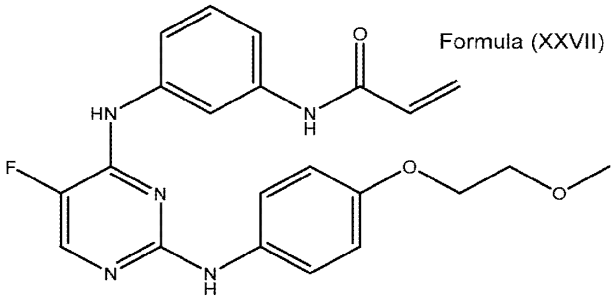
R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic; or

R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic.

As defined generally above, Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is an optionally substituted phenyl group. In some embodiments, Ring A is an optionally substituted naphthyl ring or a bicyclic 8-10 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain other embodiments, Ring A is an optionally substituted 3-7 membered carbocyclic ring. In yet other embodiments, Ring A is an optionally substituted 4-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

In certain embodiments, Ring A is substituted as defined herein. In some embodiments, Ring A is substituted with one, two, or three groups independently selected from halogen, R^o, or —$(CH_2)_{0-4}OR^o$, or —$O(CH_2)_{0-4}R^o$, wherein each R^o is as defined herein. Exemplary substituents on Ring A include Br, I, Cl, methyl, —CF_3, —C≡CH, —OCH_2phenyl, —OCH_2(fluorophenyl), or —OCH_2pyridyl.

[00199] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVII):



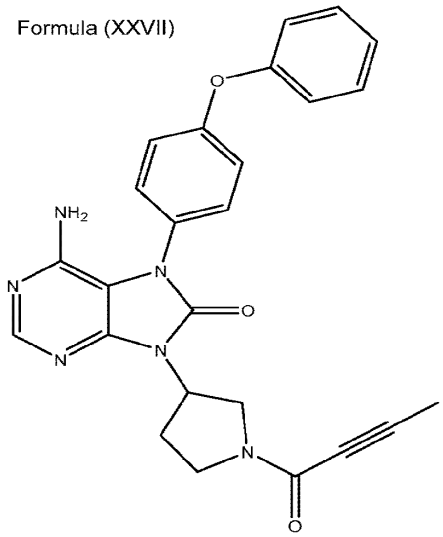
or a pharmaceutically acceptable salt thereof, or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of the besylate salt of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00200] In an exemplary embodiment, the BTK inhibitor is *N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00201] In an exemplary embodiment, the BTK inhibitor is (N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide), or a pharmaceutically acceptable salt thereof, or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20. The preparation of its besylate salt is described in U.S. Patent Application Publication No. 2012/0077832 A1.

[00202] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (XXVIII):

Formula (XXVII)



6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one

or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00203] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00204] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4- phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00205] In an exemplary embodiment, the BTK inhibitor is 6-amino-9-[(3S)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4- phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt thereof, or a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1.

[00206] BTK inhibitors suitable for use in the described combination with a PI3K inhibitor, a PI3K-γ inhibitor, and/or a PI3K-δ inhibitor also include, but are not limited to, those described in, for example, International Patent Application Publication Nos. WO 2013/010868; WO 2012/158843; WO 2012/135944; WO 2012/135937; U.S. Patent Application Publication No. 2011/0177011; and U.S. Patent Nos. 8,501,751; 8,476,284; 8,008,309; 7,960,396; 7,825,118; 7,732,454; 7,514,444; 7,459,554; 7,405,295; and 7,393,848, the disclosures of each of which are incorporated herein by reference.

Pharmaceutical Compositions

[00207] In selected embodiments, the invention provides pharmaceutical compositions for treating solid tumor cancers, lymphomas and leukemia.

[00208] In selected embodiments, the invention provides pharmaceutical compositions of a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, and a BTK inhibitor for the treatment of disorders such as hyperproliferative disorder including but not limited to cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (*e.g.*, lymphoma and Kaposi's sarcoma) or viral-induced cancer. In some embodiments, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate (*e.g.*, benign prostatic hypertrophy (BPH)).

[00209] The invention further provides a composition for the prevention of blastocyte implantation in a mammal.

[00210] The invention also relates to a composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which can manifest as tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy,

retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00211] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, and BTK inhibitor as the active ingredients, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[00212] The pharmaceutical compositions are administered as a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, and a BTK inhibitor. Where desired, other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations for use in combination separately or at the same time.

[00213] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v.

[00214] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%,

2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v.

[00215] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors of the invention is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v. v/v.

[00216] In selected embodiments, the concentration of each of the PI3K and BTK inhibitors of the invention is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[00217] In selected embodiments, the amount of each of the PI3K and BTK inhibitors of the invention is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g,

0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g.

[00218] In selected embodiments, the amount of each of the PI3K and BTK inhibitors of the invention is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g or 10 g.

[00219] Each of the PI3K and BTK inhibitors according to the invention is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently range from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[00220] Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing the indicated diseases or disorders can be tested using various animal models known in the art. Efficacy in treating, preventing and/or managing asthma can be assessed using the ova induced asthma model described, for example, in Lee *et al.*, J. Allergy Clin. Immunol. 118(2):403-9 (2006). Efficacy in treating, preventing and/or managing arthritis (*e.g.*, rheumatoid or psoriatic arthritis) can be assessed using the autoimmune animal models described in, for example, Williams *et al.*, Chem Biol, 17(2):123-34 (2010), WO 2009/088986, WO 2009/088880, and WO 2011/008302. Efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immuno-deficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke *et al.*, Clinics in Dermatology, 25: 596-605 (2007). Efficacy in treating, preventing and/or managing fibrosis or

fibrotic conditions can be assessed using the unilateral ureteral obstruction model of renal fibrosis, which is described, for example, in Chevalier *et al.*, Kidney International 75:1145-1152 (2009); the bleomycin induced model of pulmonary fibrosis described in, for example, Moore *et al.*, Am. J. Physiol. Lung. Cell. Mol. Physiol. 294:L152-L160 (2008); a variety of liver/biliary fibrosis models described in, for example, Chuang *et al.*, Clin. Liver Dis.12:333-347 (2008) and Omenetti *et al.*, Laboratory Investigation 87:499-514 (2007) (biliary duct-ligated model); or any of a number of myelofibrosis mouse models such as described in Varicchio *et al.*, Expert Rev. Hematol. 2(3):315-334 (2009). Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto *et al.*, J. Invest. Dermatol. 112: 456-462 (1999). Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi *et al.*, Arthritis & Rheumatism, 60(10): 3118-3127 (2009). Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi *et al.*, Lupus, 19: 1029-1035 (2009); Ohl *et al.*, Journal of Biomedicine and Biotechnology, Article ID 432595 (2011); Xia *et al.*, Rheumatology, 50:2187-2196 (2011); Pau *et al.*, PLoS ONE, 7(5):e36761 (2012); Mustafa *et al.*, Toxicology, 290:156-168 (2011); Ichikawa *et al.*, Arthritis and Rheumatism, 62(2): 493-503 (2012); Ouyang *et al.*, J. Mol. Med. (2012); Rankin *et al.*, Journal of Immunology,188:1656-1667 (2012). Efficacy in treating, preventing and/or managing Sjogren's syndrome can be assessed using various mouse models described, for example, in Chiorini *et al.*, J. Autoimmunity, 33: 190-196 (2009).

[00221] To explore the role of PI3K signaling in diffuse large B-cell lymphoma ("DLBCL"), several DLBCL cell lines of varying molecular profiles may be utilized. In an exemplary embodiment, a cellular growth inhibition assay used five cell lines, including four GCB (SU-DHL-4, SU-DHL-6, OCI-LY-8 and WSU-DLCL-2) and one ABC (Ri-1) subtype. In an exemplary embodiment, a cellular growth inhibition assay used five cell lines that were OCI-LY-3, OCI-LY-7, Pfeiffer, Toledo and U2932. In an exemplary embodiment, evidence of PI3K pathway inhibition is measured by reduction in phospho (p)-AKT. In an exemplary embodiment, the kinetics of pathway modulation was characterized by examination of phosphorylation of AKT, PRAS40 and S6 following a time-course of treatment by a PI3K-

inhibitor in selected cell lines. In one embodiment, upon B-cell receptor stimulation via antibody-induced crosslinking, some cell lines exhibited enhanced AKT phosphorylation.

[00222] In an exemplary embodiment, the combination effect of a PI3K inhibitor with a BTK inhibitor was observed in a cellular growth inhibition assay in the SU-DHL-4 cell line and in the OCI-LY-8 cell line with BCR crosslinking.

[00223] In one embodiment, provided herein is a method of treating, preventing and/or managing asthma. As used herein, "asthma" encompasses airway constriction regardless of the cause. Common triggers of asthma include, but are not limited to, exposure to an environmental stimulants (e.g., allergens), cold air, warm air, perfume, moist air, exercise or exertion, and emotional stress. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with asthma. Examples of the symptoms include, but are not limited to, severe coughing, airway constriction and mucus production.

[00224] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Oral Administration

[00225] In selected embodiments, the invention provides a pharmaceutical composition for oral administration containing the combination of a PI3K and BTK inhibitor, and a pharmaceutical excipient suitable for oral administration.

[00226] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of each of a PI3K and BTK inhibitor in combination and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of a fourth compound.

[00227] In selected embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount

of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00228] The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (*e.g.*, 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00229] Each of the PI3K and BTK inhibitors active ingredients can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation

desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00230] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00231] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00232] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to

form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[00233] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00234] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00235] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00236] Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00237] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00238] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00239] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00240] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-

phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00241] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00242] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8

caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00243] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00244] In an exemplary embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use - *e.g.*, compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00245] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to

about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, Ɛ-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, .epsilon.-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00246] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00247] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00248] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents,

viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00249] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00250] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

[00251] In selected embodiments, the invention provides a pharmaceutical composition for injection containing the combination of the PI3K and BTK inhibitors and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00252] The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00253] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

[00254] Sterile injectable solutions are prepared by incorporating the combination of the PI3K and BTK inhibitors in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical Compositions for Topical Delivery

[00255] In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the combination of the PI3K and BTK inhibitors and a pharmaceutical excipient suitable for transdermal delivery.

[00256] Compositions of the present invention can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

[00257] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*, menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00258] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the combination of the PI3K and BTK inhibitors in controlled amounts, either with or without another agent.

[00259] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, *e.g.*, U.S. Patent Nos. 5,023,252; 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Pharmaceutical Compositions for Inhalation

[00260] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Other Pharmaceutical Compositions

[00261] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

[00262] Administration of the combination of the PI3K and BTK inhibitors or pharmaceutical composition of these compounds can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (*e.g.*, transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

[**00263**] The compositions of the invention may also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration may, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds of the invention may slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound of the invention may be administered, for example, by local delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound of the invention is admixed with a matrix. Such a matrix may be a polymeric matrix, and may serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for example, lactone-based polyesters or copolyesters such as polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly(ether-ester) copolymers (e.g. PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (*e.g.*, polyhydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices may be nondegrading or may degrade with time, releasing the compound or compounds. The combination of the PI3K and BTK inhibitors may be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds may be applied in a solvent and the solvent may be allowed to evaporate, thus forming a layer of compound onto the stent. Alternatively, the compound may be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the compound diffuses out of the body of the stent to contact the arterial wall. Such stents may be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound of the invention in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent may be removed via an additional brief solvent wash. In yet other embodiments, compounds of the invention may be covalently linked to a stent or graft. A covalent linker may be used which degrades *in vivo*, leading to the release of the compound of the invention. Any bio-labile linkage may be used for such a purpose, such as ester, amide or anhydride linkages. The combination of the PI3K and BTK inhibitors may additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the combination of the PI3K and BTK inhibitors via the pericard or via

advential application of formulations of the invention may also be performed to decrease restenosis.

[00264] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00265] The invention also provides kits. The kits include each of the PI3K and BTK inhibitors, either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. The kit may further contain another agent. In selected embodiments, the PI3K and BTK inhibitors and the agent are provided as separate compositions in separate containers within the kit. In selected embodiments, the PI3K and BTK inhibitors and the agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer.

Dosages and Dosing Regimens

[00266] The amounts of the combination of the PI3K and BTK inhibitors administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human,

this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

[00267] In selected embodiments, the combination of the PI3K and BTK inhibitors is administered in a single dose. Typically, such administration will be by injection - *e.g.*, intravenous injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of the combination of the PI3K and BTK inhibitors may also be used for treatment of an acute condition.

[00268] In selected embodiments, the combination of the PI3K and BTK inhibitors is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In other embodiments, the combination of the PI3K and BTK inhibitors is administered about once per day to about 6 times per day. In another embodiment the administration of the combination of the PI3K and BTK inhibitors continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00269] Administration of the agents of the invention may continue as long as necessary. In selected embodiments, the combination of the PI3K and BTK inhibitors is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the combination of the PI3K and BTK inhibitors is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In selected embodiments, the combination of the PI3K and BTK inhibitors is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects.

[00270] An effective amount of the combination of the PI3K and BTK inhibitors may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Methods of Treatment

[00271] In selected embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) and BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both the PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or the BTK inhibitor. In selected embodiments, the method relates to the treatment of cancer such as non-Hodgkin's lymphomas (such as diffuse large B-cell lymphoma), acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, bone (*e.g.*, metastatic bone), esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (e.g. lymphoma and Kaposi's sarcoma), viral-induced cancers, B cell acute lymphoblastic leukemia, Burkitt's leukemia, juvenile myelomonocytic leukemia, hairy cell leukemia, Hogkin's disease, multiple myeloma, mast cell leukemia, or mastocytosis. In selected embodiments, the method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate conditions (*e.g.*, benign prostatic hypertrophy (BPH)).

[00272] In selected embodiments, the invention relates to a method of treating an inflammatory, immune, or autoimmune disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) and BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both the PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or the BTK inhibitor. In selected embodiments, the invention also relates to a method of treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma and melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcets disease,

polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spoldylitis, Crohn's Disease, lupus, and lupus nephritis.

EXAMPLES

[00273] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

[00274] Ficoll purified mantle cell lymphoma (MCL) cells (2×10^5) isolated from bone marrow or peripheral blood were treated with each drug alone and with six equimolar concentrations of a BTK inhibitor (Formula XVIII) and a PI3K-δ inhibitor (Formula IX) ranging from 0.01 nM to 10 μM on 96-well plates in triplicate. Plated cells were then cultured in HS-5 conditioned media at 37°C with 5% CO_2. After 72 hours of culture, cell viability was determined using an (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The potential synergy of the combination of the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX at a given equimolar concentration was determined using the median effect model as described in Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul.* 1984; 22: 27-55. The statistical modeling was run in R using a script that utilizes the median effect model as described in Lee JJ, Kong M, Ayers GD, Lotan R, Interaction index and different methods for determining drug interaction in combination therapy. *J Biopharm Stat.* 2007; 17(3): 461-80. A value of 1, less than 1, and greater than 1 using R defines an additive interaction, synergistic and antagonistic, respectively. The Lee et al. method calculates a 95% confidence interval for each data point. For each viability curve, to be considered synergistic, a data point must have an interaction index below 1 and the upper confidence interval must also be below 1. In order to summarize and demonstrate collective synergy results, an interaction dot blot was generated for the primary patient samples.

[00275] A similar approach was utilized to study diffuse large B cell lymphoma (DLBCL) (TMD8) and MCL (MINO) cell lines. Cells were treated with each drug alone and with six equimolar concentrations of the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX ranging from 0.003 nM to 1.0 μM (for TMD8) or 0.03 nM to 10 μM (for MINO) on 96-well plates in triplicate. Plated cells were then cultured in standard conditioned media plus FBS at 37°C with 5% CO_2. After 72 hours of culture, viability was determined using an MTS assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The results of the experiments described in this example are shown in FIGS 1, 2, 3, and 4.

[00276] The following numbered paragraphs 1-24 describe further embodiments of the invention, which are provided by way of example only and are not intended to otherwise limit the scope of the invention.

1. A method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor and a Bruton's tyrosine kinase (BTK) inhibitor.

2. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K-γ inhibitor.

3. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K-δ inhibitor.

4. The method of paragraph 1, wherein the PI3K inhibitor is a PI3K-γ,δ inhibitor.

5. The method of paragraph 1, wherein the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers.

6. The method of paragraph 1, wherein the combination of the PI3K inhibitor with the BTK inhibitor is administered by intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

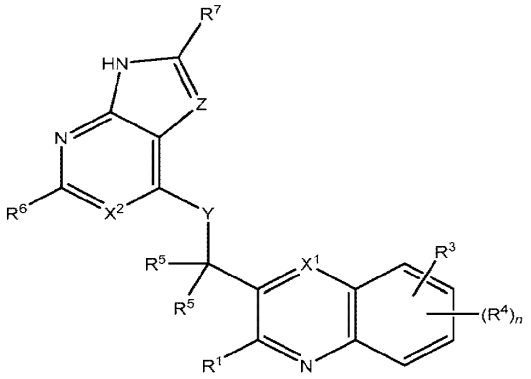
7. The method of paragraph 1, wherein the PI3K inhibitor or BTK inhibitor is in the form of a pharmaceutically acceptable salt.

8. The method of paragraph 1, wherein the PI3K inhibitor is administered to the subject before administration of the BTK inhibitor.

9. The method of paragraph 1, wherein the PI3K inhibitor is administered concurrently with the administration of the BTK inhibitor.

10. The method of paragraph 1, wherein the PI3K inhibitor is administered to the subject after administration of the BTK inhibitor.

11. The method of paragraph 1, wherein the PI3K inhibitor is:



or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R_{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is CR^8 or N;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one 0 or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;