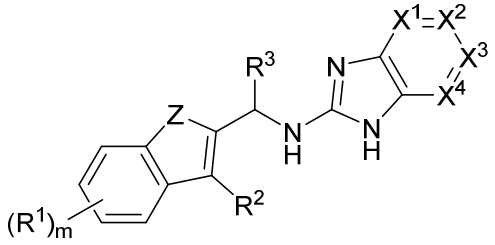
WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or NR^x;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R^1 is an independently selected halogen;

m is 0, 1, 2, or 3;

R^2 is halogen, C1-C6 alkyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

X^1, X^2, X^3, and X^4 are each independently N, CH, or CR^4, wherein no more than two of X^1, X^2, X^3, and X^4 can be N;

each R^4 is independently selected from the group consisting of: halogen, C1-C6 alkyl optionally substituted with $-NR^AR^B$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^AR^B$, $-C(=O)NR^CR^D$, $-SO_2(NR^ER^F)$, $-SO_2$(C1-C6 alkyl), -S(=O)(=NH)(C1-C6 alkyl), -C(=O)(C1-C6 alkyl), $-CO_2$(C1-C6 alkyl), phenyl, 5-6 membered heteroaryl, and a 3-6 membered heterocyclyl or a 3-6 cycloalkyl each optionally substituted with 1 or 2 independently selected R^G;

each R^A, R^{A1}, R^B, R^{B1}, R^C, R^{C1}, R^D, R^{D1}, R^E, and R^F is independently hydrogen, C1-C6 alkyl optionally substituted with R^G, C1-C6 haloalkyl, -C(=O)(C1-C6 alkyl), or $-SO_2$(C1-C6 alkyl); or

R^C and R^D, together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl; and

each R^G is independently selected from the group consisting of: fluoro, hydroxyl, cyano, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, and $-CO_2H$.

2. The compound of claim 1, wherein m is 1 or 2.

3. The compound of claim 1 or 2, wherein each R^1 is independently selected from fluoro and chloro.

4. The compound of any one of claims 1-3, wherein each R^1 is fluoro.

5. The compound of any one of claims 1-4, wherein one of X^1, X^2, X^3, and X^4 is CR^4 and the other three X^1, X^2, X^3, and X^4 are N or CH; or

wherein two of X^1, X^2, X^3, and X^4 are independently selected CR^4 and the other two X^1, X^2, X^3, and X^4 are N or CH; or

wherein one of X^1, X^2, X^3, and X^4 is CR^4 and the other three X^1, X^2, X^3, and X^4 are CH; or

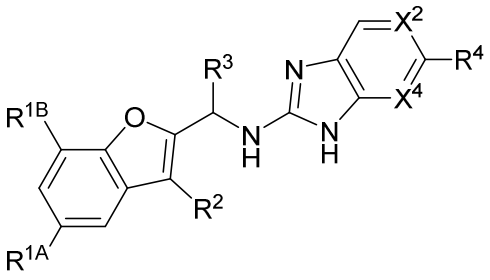
wherein two of X^1, X^2, X^3, and X^4 are independently selected CR^4 and the other two X^1, X^2, X^3, and X^4 are CH; or

wherein one of X^1, X^2, X^3, and X^4 is CR^4 and the other three X^1, X^2, X^3, and X^4 are N; or

wherein two of X^1, X^2, X^3, and X^4 are independently selected CR^4 and the other two X^1, X^2, X^3, and X^4 are N; or

wherein X^1, X^2, X^3, and X^4, together with the carbon atoms adjacent to X^1 and X^4, form a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl ring.

6. The compound of claim 1, having the structure of formula (I-a):



(I-a),

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is halogen;

R^{1B} is halogen or absent;

X^2 and X^4 are each independently N or CH;

7. The compound of claim 6, wherein R^{1A} and R^{1B} are each independently selected halogen.

8. The compound of claim 6, wherein R^{1A} and R^{1B} are each fluoro; or
wherein R^{1A} is fluoro and R^{1B} is absent; or
wherein R^{1A} is fluoro and R^{1B} is chloro.

9. The compound of any one of claims 1-8, wherein R^2 is a C1-C6 alkyl.

10. The compound of any one of claims 1-9, wherein R^2 is methyl.

11. The compound of any one of claims 1-8, wherein R^2 is a C1-C6 haloalkyl.

12. The compound of any one of claims 1-11, wherein R^3 is a C1-C6 haloalkyl.

13. The compound of any one of claims 1-12, wherein R^3 is a trifluoromethyl.

14. The compound of any one of claims 1-11, wherein R^3 is a C1-C6 alkyl.

15. The compound of any one of claims 1-14, wherein R^4 is halogen, hydroxyl, cyano, $-CO_2H$, C1-C6 alkoxy, C1-C6 haloalkyl, $-C(=O)NR^CR^D$, $-SO_2(NR^ER^F)$, $-SO_2$(C1-C6 alkyl), -S(=O)(=NH)(C1-C6 alkyl), -C(=O)(C1-C6 alkyl), $-CO_2$(C1-C6 alkyl), or C1-C6 alkyl optionally substituted with $-NR^AR^B$.

16. The compound of any one of claims 1-14, wherein R^4 is $-NR^AR^B$.

17. The compound of any one of claims 1-16, wherein each R^A and R^B are independently hydrogen or C1-C6 alkyl.

18. The compound of any one of claims 1-17, wherein each R^A and R^B are hydrogen.

19. The compound of any one of claims 1-14, wherein R^4 is phenyl, 5-6 membered heteroaryl, 3-6 membered heterocyclyl, or 3-6 cycloalkyl, each optionally substituted with 1 or 2 independently selected R^G.

20. The compound of any one of claims 1-19, wherein Z is O.

21. The compound of any one of claims 1-19, wherein Z is NR^x.

22. The compound of claim 1, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is selected from a compound in Table A, Table B, or Table C, or a pharmaceutically acceptable salt of any of the foregoing.

23. A pharmaceutical composition comprising a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable diluent or carrier.

24. Use of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 23, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer has one or more mutations in PI3Kα.

25. The use of claim 24, wherein the cancer is a solid tumor.

26. The use of claim 25, wherein the cancer is breast cancer.

27. The use of any one of claims 24-26, wherein the one or more mutations in PI3Kα are selected from the group consisting of: E542A, E542G, E542K, E542Q, E542V, E545A, E545D, E545G, E545K, E545Q, M1043I, M1043L, M1043T, M1043V, H1047L, H1047Q, H1047R, H1047Y, and G1049R, and combinations thereof.