PLK4 MODULATORS

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application Number 63/546,320, filed October 30, 2023, which is incorporated by reference herein in its entirety.

BACKGROUND

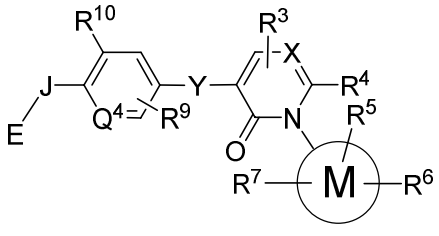
[0002] Polo-like kinases (PLKs) are a family of Ser/Thr kinases involved in multiple functions of cell division. There are five family members of PLKs, of which PLK4 has been identified as a critical component in regulating centriole duplication. Deregulation of PLK4 causes centrosome number abnormalities, mitotic defects, chromosomal instability, and tumorigenesis. Over expression of PLK4 has also been reported in many human cancers. See e.g., Zhang et al., Front Oncol. 2021; 11: 587554 and Zhao et al., Journal of Cancer Research and Clinical Oncology (2019) 145:2413–2422. Although small molecules targeting PLK4 have been shown to provide significant anticancer response, the medical field currently lacks sufficient PLK4 therapeutics needed to combat the ever growing battle with cancer.

INCORPORATION BY REFERENCE

[0003] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY

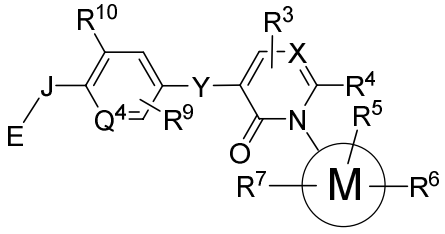
[0004] Provided herein are compounds having the Formula **A**.



(**A**);

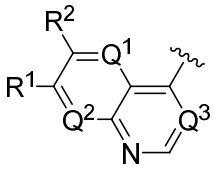
and pharmaceutically acceptable salts thereof, wherein E, J, Y, X, R^4, R^5, R^6, R^7, R^9, R^{10}, and Q^4 are as defined herein. The compounds of Formula **A** modulate PLK4 (e.g., PLK4 inhibitors) and are useful in treating conditions responsive to the inhibition of PLK4 (e.g., cancer).

[0004a] In one aspect, there is provided a compound of the Formula **A**:



(**A**);

or a pharmaceutically acceptable salt thereof, wherein

E is  or a bicyclic heterocyclic ring system comprising a 5-membered ring ortho-fused to a 6-membered ring, wherein the bicyclic heterocyclic ring system is optionally substituted by 1 to 3 groups independently selected from halo, oxo, and (C_1-C_4)alkyl;

R^1 and R^2 are each independently -OR^a or -NR^bR^c; or R^1 and R^2, together with the carbon atoms to which R^1 and R^2 are bound, form a 5- to 7-membered heterocyclyl;

R^a is selected from (C_1-C_4)alkyl, 4- to 6-membered heterocyclyl, (C_3-C_6)cycloalkyl, -(C_1-C_4)alkyl(C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, -(C_1-C_4)alkyl(COOH), and -(C_1-C_4)alkyl[4- to 6-membered heterocyclyl], wherein said (C_3-C_6)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 2 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, and -(C_1-C_4)alkyl(C_1-C_4)alkoxy;

R^b and R^c are each independently selected from hydrogen and (C_1-C_4)alkyl, or R^b and R^c taken together with the nitrogen atom to which R^b and R^c are attached form a 4- to 6-membered heterocyclyl;

R^3 is hydrogen or (C_1-C_4)alkoxy;

R^4 is (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy, (C_3-C_6)cycloalkyl, -(C_1-C_4)alkyl(C_3-C_6)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C_3-C_6)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups independently selected from halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, cyano, and -NH(C_1-C_4)alkyl;

Ring M is a 6-membered aryl or 6-membered heteroaryl;

R^5 and R^7 are each independently hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, halo, hydroxy, cyano, -(C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, -O(C_3-C_6)cycloalkyl, deuterated(C_1-C_4)alkoxy, or -(C_1-C_4)alkoxy[hydroxy(C_1-C_4)alkyl];

R^6 is halo, hydroxy, cyano, (C_2-C_4)acyl, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, (C_3-C_6)cycloalkyl, -O(C_3-C_6)cycloalkyl, or deuterated (C_1-C_4)alkoxy;

R^8 and R^9 are each independently hydrogen or halo;

J is O, NR^{11}, S, or CH_2;

R^{10} is halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, or deuterated(C_1-C_4)alkyl, and R^{11} is hydrogen; or R^{10} and R^{11}, together with the atoms to which R^{10} and R^{11} are bound, form a 5-membered heterocyclyl;

each of Q^1 and Q^2 is independently CH or N;

Q^3 is CR^8 or N;

Q^4 is N, CH, or a carbon atom attached to R^9;

X is N, CH, or a carbon atom attached to R^3; and

Y is –NHC(O)- or –C(O)NH-;

provided that: (i) if R^4 is CH_3, then: (a) R^5 is not hydrogen or (b) Q^3 is CR^8 wherein R^8 is halo; and (ii) if Q^1 is N, Q^2 is CH, Q^3 is CR^8, and R^4 is CH_3 or CH_2OH, then R^8 is halo.

[0005] Pharmaceutical compositions comprising the compounds and pharmaceutically acceptable salts of the described compounds of Formula **A**, as well as methods for their preparation are also included.

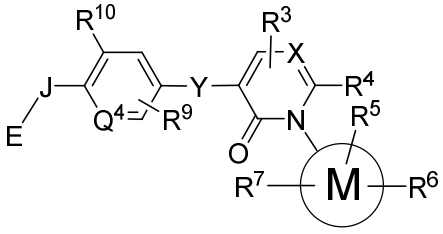
[0005a] In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0005b] In another aspect, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition as described herein for use in therapy.

CLAIMS

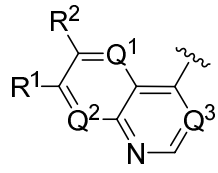
What is claimed is:

1. A compound of the Formula **A**:



(**A**);

or a pharmaceutically acceptable salt thereof, wherein

E is  or a bicyclic heterocyclic ring system comprising a 5-membered ring ortho-fused to a 6-membered ring, wherein the bicyclic heterocyclic ring system is optionally substituted by 1 to 3 groups independently selected from halo, oxo, and (C_1-C_4)alkyl;

R^1 and R^2 are each independently -OR^a or -NR^bR^c; or R^1 and R^2, together with the carbon atoms to which R^1 and R^2 are bound, form a 5- to 7-membered heterocyclyl;

R^a is selected from (C_1-C_4)alkyl, 4- to 6-membered heterocyclyl, (C_3-C_6)cycloalkyl, -(C_1-C_4)alkyl(C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, -(C_1-C_4)alkyl(COOH), and -(C_1-C_4)alkyl[4- to 6-membered heterocyclyl], wherein said (C_3-C_6)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 2 groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, and -(C_1-C_4)alkyl(C_1-C_4)alkoxy;

R^b and R^c are each independently selected from hydrogen and (C_1-C_4)alkyl, or R^b and R^c taken together with the nitrogen atom to which R^b and R^c are attached form a 4- to 6-membered heterocyclyl;

R^3 is hydrogen or (C_1-C_4)alkoxy;

R^4 is (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy, (C_3-C_6)cycloalkyl, -(C_1-C_4)alkyl(C_3-C_6)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C_3-C_6)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups independently selected from halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, cyano, and -NH(C_1-C_4)alkyl;

Ring M is a 6-membered aryl or 6-membered heteroaryl;

R^5 and R^7 are each independently hydrogen, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, halo, hydroxy, cyano, -(C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, -O(C_3-C_6)cycloalkyl, deuterated(C_1-C_4)alkoxy, or -(C_1-C_4)alkoxy[hydroxy(C_1-C_4)alkyl];

R^6 is halo, hydroxy, cyano, (C_2-C_4)acyl, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, (C_3-C_6)cycloalkyl, -O(C_3-C_6)cycloalkyl, or deuterated (C_1-C_4)alkoxy;

R^8 and R^9 are each independently hydrogen or halo;

J is O, NR^{11}, S, or CH_2;

R^{10} is halo, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, or deuterated(C_1-C_4)alkyl, and R^{11} is hydrogen; or R^{10} and R^{11}, together with the atoms to which R^{10} and R^{11} are bound, form a 5-membered heterocyclyl;

each of Q^1 and Q^2 is independently CH or N;

Q^3 is CR^8 or N;

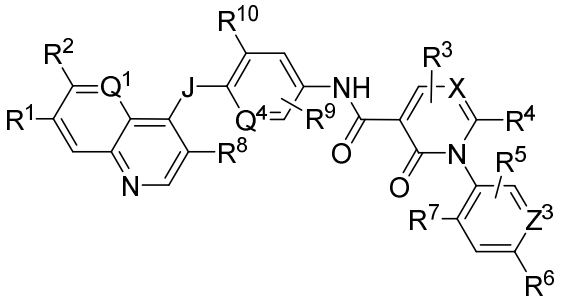
Q^4 is N, CH, or a carbon atom attached to R^9;

X is N, CH, or a carbon atom attached to R^3; and

Y is –NHC(O)- or –C(O)NH-;

provided that: (i) if R^4 is CH_3, then: (a) R^5 is not hydrogen or (b) Q^3 is CR^8 wherein R^8 is halo; and (ii) if Q^1 is N, Q^2 is CH, Q^3 is CR^8, and R^4 is CH_3 or CH_2OH, then R^8 is halo.

2. The compound of Claim 1, wherein the compound is of the Formula **A-VI**:



(**A-VI**);

or a pharmaceutically acceptable salt thereof, wherein Z^3 is N.

3. The compound of Claim 1 or Claim 2, or a pharmaceutically acceptable salt thereof, wherein J is O.

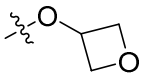
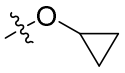
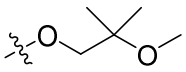
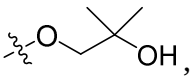
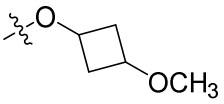
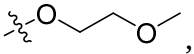
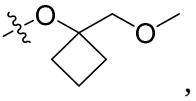
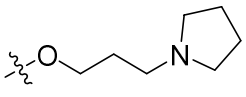
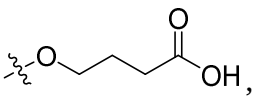
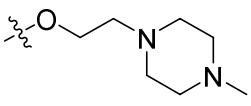
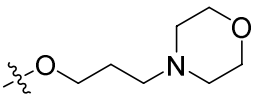
4. The compound of any one of Claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^{10} is halo.

5. The compound of any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein Q^1 is N.

6. The compound of any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein Q^4 is a carbon atom bound to R^9.

7. The compound of any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, cyano, hydroxy, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, or halo.

8. The compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein X is CH.

9. The compound of any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected from OCH_3, , , , , , , , , , , , and .

10. The compound of any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^4 is $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, hydroxy$(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkoxy, $(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_4)$alkyl$(C_3$-$C_6)$cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said $(C_3$-$C_6)$cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH$(C_1$-$C_4)$alkyl, and halo$(C_1$-$C_4)$alkyl.

11. The compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^7 is $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, cyano, hydroxy, or halo.

12. The compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^6 is halo, hydroxy, cyano, $(C_2$-$C_4)$acyl, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo$(C_1$-$C_4)$alkoxy, -O$(C_3$-$C_6)$cycloalkyl, or deuterated $(C_1$-$C_4)$alkoxy.

13. The compound of Claim 1, wherein the compound is selected from any of those in Table 1, or Table 2; or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of any one of Claims 1 to 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. A compound of any one of Claims 1 to 13, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition of Claim 14 for use in therapy.