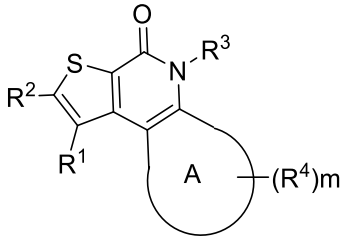
pp. 2030–2050 (2017); Cheng, et al., Cancer Lett., 337, 218–225 (2013).

SUMMARY

[0005] It has now been found that certain fused compounds are inhibitors of CDC7 kinase, and are useful for treating diseases such as proliferative diseases such as cancers.

[0005a] In an aspect, there is provided a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is hydrogen or halogen;

R^2 is a 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen and C1-C6 alkyl; or a 5-6 membered heterocyclyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen and C1-C6 alkyl;

R^3 is hydrogen or C1-C6 alkyl;

Ring A is a C6-C10 cycloalkyl or a 6-10 membered heterocyclyl;

each R^4 is independently selected from the group consisting of halogen, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 hydroxyalkyl, C1-C6 haloalkyl, C1-C6 alkoxy(C1-C6 alkyl)-, -C(=O)C1-C6 alkyl, C2-C6 alkynyl, C3-C6 cycloalkyl, $-NR^AR^B$, and 4-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected halogen;

each R^A and R^B is independently hydrogen or C1-C6 alkyl; and

m is 0, 1, 2, 3, or 4.

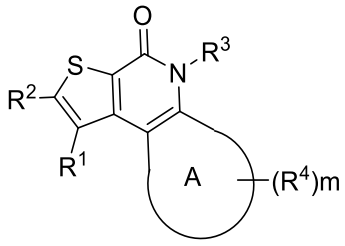
[0005b] In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[0005c] In another aspect, there is provided the use of a compound as defined above or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined above in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0005d] In another aspect, there is provided a method for inhibiting mammalian cell proliferation, comprising contacting the mammalian cell with a compound as defined above or a pharmaceutically acceptable salt thereof.

[0005e] In another aspect, there is provided a method for inhibiting CDC7 kinase activity in a mammalian cell, comprising contacting the mammalian cell with a compound as defined above or a pharmaceutically acceptable salt thereof.

[0006] Accordingly, provided herein is a compound of the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, Ring A and m are as defined herein.

[0007] Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[0008] Also provided herein is a method of inhibiting cell proliferation, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

[0009] Also provided herein is a method of inhibiting CDC7 kinase activity, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

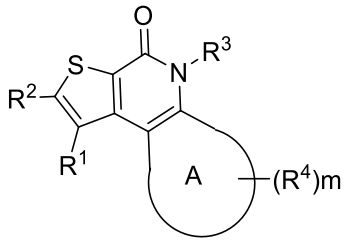
[0010] Also provided herein is a method of treating cancer in a subject in need of such treatment, comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

[0011] Also provided herein is a method of treating a CDC7-associated disease or disorder in a subject in need of such treatment, comprising administering to the subject an effective amount

of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is hydrogen or halogen;

R^2 is a 5-6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen and C1-C6 alkyl; or a 5-6 membered heterocyclyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen and C1-C6 alkyl;

R^3 is hydrogen or C1-C6 alkyl;

Ring A is a C6-C10 cycloalkyl or a 6-10 membered heterocyclyl;

each R^4 is independently selected from the group consisting of halogen, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 hydroxyalkyl, C1-C6 haloalkyl, C1-C6 alkoxy(C1-C6 alkyl)-, -C(=O)C1-C6 alkyl, C2-C6 alkynyl, C3-C6 cycloalkyl, $-NR^AR^B$, and 4-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected halogen;

each R^A and R^B is independently hydrogen or C1-C6 alkyl; and

m is 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein m is 1, 2, 3, or 4.

3. The compound of claim 1, wherein R^2 is a 5 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen and C1-C6 alkyl.

4. The compound of claim 3, wherein the 5 membered heteroaryl of R^2 is pyrazolyl or isothiazolyl.

5. The compound of claim 3, wherein the 5 membered heteroaryl of R^2 is 4-pyrazolyl, 5-pyrazolyl, or 5-isothiazolyl.

6. The compound of claim 1, wherein R^2 is a 6 membered heteroaryl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen and C1-C6 alkyl.

7. The compound of claim 6, wherein the 6 membered heteroaryl of R^2 is pyridyl, pyrimidinyl, or pyridazinyl.

8. The compound of claim 6, wherein the 6 membered heteroaryl of R^2 is 4-pyridyl, pyrimidinyl or 4-pyridazinyl.

9. The compound of claim 1, wherein the heteroaryl of R^2 is substituted with one substituent selected from halogen and C1-C6 alkyl.

10. The compound of claim 1, wherein the heteroaryl of R^2 is substituted with one substituent selected from fluoro, chloro, and methyl.

11. The compound of claim 1, wherein the heteroaryl of R^2 is substituted with two substituents independently selected from halogen and C1-C6 alkyl.

12. The compound of claim 1, wherein the heteroaryl of R^2 is substituted with two substituents independently selected from fluoro and methyl.

13. The compound of claim 1, wherein R^2 is an unsubstituted 5-6 membered heteroaryl.

14. The compound of claim 13, wherein R^2 is selected from the group consisting of pyrazolyl, isothiazolyl, pyridyl, and pyridazinyl.

15. The compound of claim 14, wherein R^2 is 4-pyrazolyl, -isothiazolyl, 4-pyridyl, or -pyridazinyl.

16. The compound of claim 1, wherein R^2 is a 5-6 membered heterocyclyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen and C1-C6 alkyl.

17. The compound of claim 1, wherein R^2 is morpholinyl.

18. The compound of claim 1, wherein R^2 is 4-morpholinyl.

19. The compound of claim 1, wherein Ring A is C6-C10 cycloalkyl.

20. The compound of claim 1, wherein Ring A is cyclohexyl or bicyclo[2.2.2]octanyl.

21. The compound of claim 1, wherein Ring A is 6-10 membered heterocyclyl.

22. The compound of claim 1, wherein Ring A is tetrahydropyranyl or piperidinyl.

23. The compound of claim 1, wherein one R^4 is halogen.

24. The compound of claim 1, wherein one R^4 is fluoro.

25. The compound of claim 1, wherein one R^4 is hydroxyl.

26. The compound of claim 1, wherein one R^4 is C1-C6 alkyl.

27. The compound of claim 1, wherein one R^4 is selected from the group consisting of $–CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-C(CH_3)_2CH_2CH_3$, and $–C(CH_3)_3$.

28. The compound of claim 1, wherein one R^4 is C1-C6 alkoxy.

29. The compound of claim 1, wherein one R^4 is methoxy.

30. The compound of claim 1, wherein one R^4 is C1-C6 hydroxyalkyl.

31. The compound of claim 1, wherein one R^4 is $–CH_2OH$ or $-C(CH_3)_2OH$.

32. The compound of claim 1, wherein one R^4 is C1-C6 haloalkyl.

33. The compound of claim 1, wherein one R^4 is $–CF_3$, $–CHF_2$, $–CF_2CH_3$, or $–CH_2CF_2CH_3$.

34. The compound of claim 1, wherein one R^4 is C1-C6 alkoxy(C1-C6 alkyl)-.

35. The compound of claim 1, wherein one R^4 is $–CH_2OCH_3$.

36. The compound of claim 1, wherein one of R^4 is -C(=O)C1-C6 alkyl.

37. The compound of claim 1, wherein one R^4 is $-C(=O)CH_3$.

38. The compound of claim 1, wherein one R^4 is C2-C6 alkynyl.

39. The compound of claim 1, wherein one R^4 is 1-propynyl.

40. The compound of claim 1, wherein one R^4 is C3-C6 cycloalkyl.

41. The compound of claim 1, wherein one R^4 is cyclopentyl.

42. The compound of claim 1, wherein one R^4 is $-NR^AR^B$, wherein: one of R^A and R^B is hydrogen and the other of R^A and R^B is C1-C6 alkyl; R^A and R^B are both C1-C6 alkyl; or R^A and R^B are both H.

43. The compound of claim 1, wherein one R^4 is 4-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected halogen.

44. The compound of claim 1, wherein one R^4 is pyrrolidinyl or azetidinyl, wherein said pyrrolidinyl or azetidinyl is optionally substituted with 1 or 2 independently selected halogen.

45. The compound of any one of claims 1-46 and 74-76, wherein one R^4 is pyrrolidinyl substituted with 1 or 2 independently selected halogen.

46. The compound of any one of claims 1-46 and 74, wherein one R^4 is azetidinyl optionally substituted with 1 or 2 independently selected halogen.

47. The compound of any one of claims 1-46, 74, and 78, wherein one R^4 is azetidinyl substituted with 1 or 2 independently selected halogen.

48. The compound of any one of claims 1-46 and 74, wherein one R^4 is an unsubstituted 4-6 membered heterocyclyl.

49. The compound of any one of claims 1-46, 74, and 80, wherein one R^4 is an unsubstituted pyrrolidinyl.

50. The compound of claim 1, wherein one R^4 is 1-pyrrolidinyl or 1-azetidinyl.

51. The compound of claim 1, wherein m is 2, 3, or 4; and wherein two R^4 groups are geminal.

47. The compound of claim 1, wherein m is 2; and wherein the two R^4 groups are geminal; wherein:

one R^4 is hydroxyl; and the other R^4 is C1-C6 alkyl;
each R^4 is fluoro;
one R^4 is hydroxyl; and the other R^4 is C1-C6 haloalkyl;
one R^4 is hydroxyl; and the other R^4 is C2-C6 alkynyl;
one R^4 is hydroxyl; and the other R^4 is C3-C6 cycloalkyl;
one R^4 is hydroxyl; and the other R^4 is C1-C6 alkoxy(C1-C6 alkyl)-;
each R^4 is independently selected C1-C6 alkyl;
one R^4 is C1-C6 alkyl; and the other R^4 is C1-C6 hydroxyalkyl;
one R^4 is C1-C6 alkyl; and the other R^4 is C1-C6 alkoxy;
one R^4 is C1-C6 alkyl; and the other R^4 is $-NR^AR^B$; or
one R^4 is C1-C6 alkyl; and the other R^4 is 4-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected halogen.

48. The compound of claim 1, wherein m is 4; and wherein the two R^4 groups are geminal; wherein:
two R^4 are fluoro; one R^4 is C1-C6 alkoxy; and one R^4 is C1-C6 alkyl
two R^4 are fluoro; one R^4 is C1-C6 hydroxyalkyl; and one R^4 is C1-C6 alkyl;
two R^4 are fluoro; one R^4 is hydroxyl; and one R^4 is C1-C6 alkyl; or
two R^4 are fluoro; one R^4 is hydroxyl; and one R^4 is C1-C6 alkoxy(C1-C6 alkyl)-.

49. The compound of claim 1, wherein m is 0.

50. The compound of claim 1, wherein R^1 is halogen.

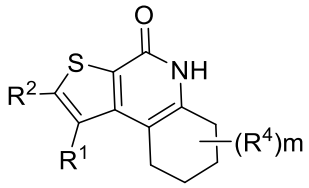
51. The compound of claim 1, wherein R^1 is fluoro.

52. The compound of claim 1, wherein R^1 is hydrogen.

53. The compound of claim 1, wherein R^3 is hydrogen.

54. The compound of claim 1, wherein R^3 is C1-C6 alkyl.

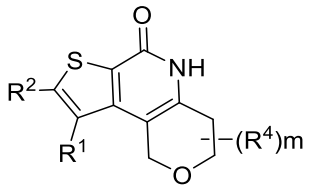
55. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (I-A):



Formula (I-A)

or a pharmaceutically acceptable salt thereof.

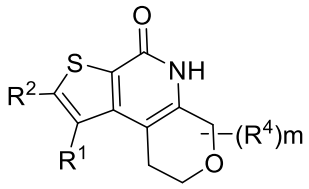
56. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (I-B):



Formula (I-B)

or a pharmaceutically acceptable salt thereof.

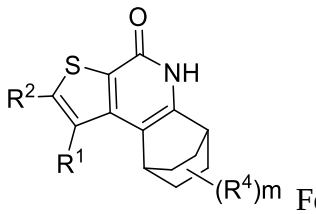
57. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (I-C):



Formula (I-C)

or a pharmaceutically acceptable salt thereof.

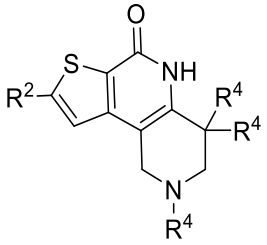
58. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (I-D):



Formula (I-D)

or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (I-P):



Formula (I-P)

or a pharmaceutically acceptable salt thereof.

60. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds in Table 1, and pharmaceutically acceptable salts thereof.

61. A pharmaceutical composition comprising a compound of any one of claims 1-60, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

62. Use of a compound of any one of claims 1-60 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 61 in the manufacture of a medicament for treating cancer in a subject in need thereof.

63. A method for inhibiting mammalian cell proliferation, comprising contacting the mammalian cell with a compound of any one of claims 1-60 or a pharmaceutically acceptable salt thereof.

64. A method for inhibiting CDC7 kinase activity in a mammalian cell, comprising contacting the mammalian cell with a compound of any one of claims 1-60 or a pharmaceutically acceptable salt thereof.

65. Use of a compound of any one of claims 1-60, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 61 in the manufacture of a medicament for inhibiting metastasis in a subject having a particular cancer.