independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl; R^5 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, halo, OH, or CN, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl; each R^N is independently H or C_{1-6}alkyl optionally substituted with 1, 2, or 3 R^7; Het is a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N and optionally substituted with 1, 2, or 3 R^6; each R^6 is independently halo, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, COOH, $C(O)NR^NR^N$, C_{1-6}alkylene-$C(O)OR^N$, $P(O)(R^N)(R^N)$, C(O)-5- or 6-membered heterocycloalkyl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, C_{3-10}cycloalkyl, 5- or 6-membered heterocycloalkyl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, C_{6-10}aryl, or 5- or 6-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, wherein the C_{3-10}cycloalkyl, 5- or 6-membered heterocycloalkyl, C_{6-10}aryl, or 5- or 6-membered heteroaryl can optionally be substituted with 1, 2, or 3 R^7 and each C_{1-6}alkyl or C_{1-6}alkylene can be optionally substituted with 1 or 2 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl; and each R^7 is independently OH, halo, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, NH_2, $NH(C_{1-6}alkyl)$, or $N(C_{1-6}alkyl)_2$.

[0007] Also provided are compositions comprising compounds as disclosed herein and a pharmaceutically acceptable excipient. Further provided are methods of modulating RBM39 protein by contacting RBM30 protein with a compound as disclosed herein. Also provided are methods of treating a disease associated with aberrant RBM39 activity (e.g., cancer such as renal cell carcinoma) in a subject by administering a therapeutically effective amount of a compound as disclosed herein to the subject.

[0007a] In an aspect of the present disclosure, there is provided a compound listed in Table A, or a pharmaceutically acceptable salt thereof.

[0007b] In another aspect of the present disclosure, there is provided a use of a compound or salt as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for modulating an RBM39 protein, wherein the compound, salt, or pharmaceutical composition is to be contacted with the RBM39 protein.

[0007c] In a further aspect of the present disclosure, there is provided a use of the compound or salt as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease associated with aberrant RBM39 activity in a subject.

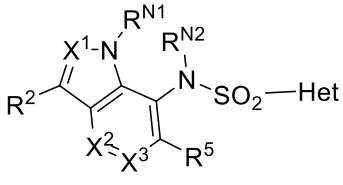
[0007d] In another aspect of the present disclosure, there is provided a compound or salt as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in therapy.

DETAILED DESCRIPTION

[0008] Provided herein are compounds, and their use in treating or preventing diseases and disorders associated with aberrant RBM39 activity, e.g., cancer. Also provided are uses of the compounds described herein, or pharmaceutically acceptable salts thereof, or pharmaceutically acceptable compositions comprising such a compound or a pharmaceutically acceptable salt thereof, for the treatment or prevention of diseases and disorders associated with aberrant RBM39 activity, e.g., cancer.

Compounds

[0009] Provided herein are compounds of Formula (I), and pharmaceutically acceptable salts thereof:



(I),

wherein

R^{N1} is H or C_{1-6}alkyl optionally substituted with 1, 2, or 3 R^7;

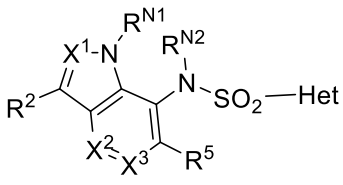
R^{N2} is H or C_{1-6}alkyl optionally substituted with 1, 2, or 3 R^7;

X^1 is CR^1 or N;

X^2 is CR^3 or N;

What is Claimed:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

wherein

R^{N1} is H or C_{1-6}alkyl optionally substituted with 1, 2, or 3 R^7;

R^{N2} is H or C_{1-6}alkyl optionally substituted with 1, 2, or 3 R^7;

X^1 is CR^1 or N;

X^2 is CR^3 or N;

X^3 is CR^4 or N;

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, halo, OH, or CN, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl;

R^2 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, halo, OH, or CN, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl;

R^3 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, halo, OH, or CN, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl;

R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, halo, OH, or CN, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl;

R^5 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, halo, OH, or CN, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl;

each R^N is independently H, C_{1-6}alkyl optionally substituted with 1, 2, or 3 R^7, or C_{3-10}cycloalkyl;

Het is a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N and optionally substituted with 1, 2, or 3 R^6;

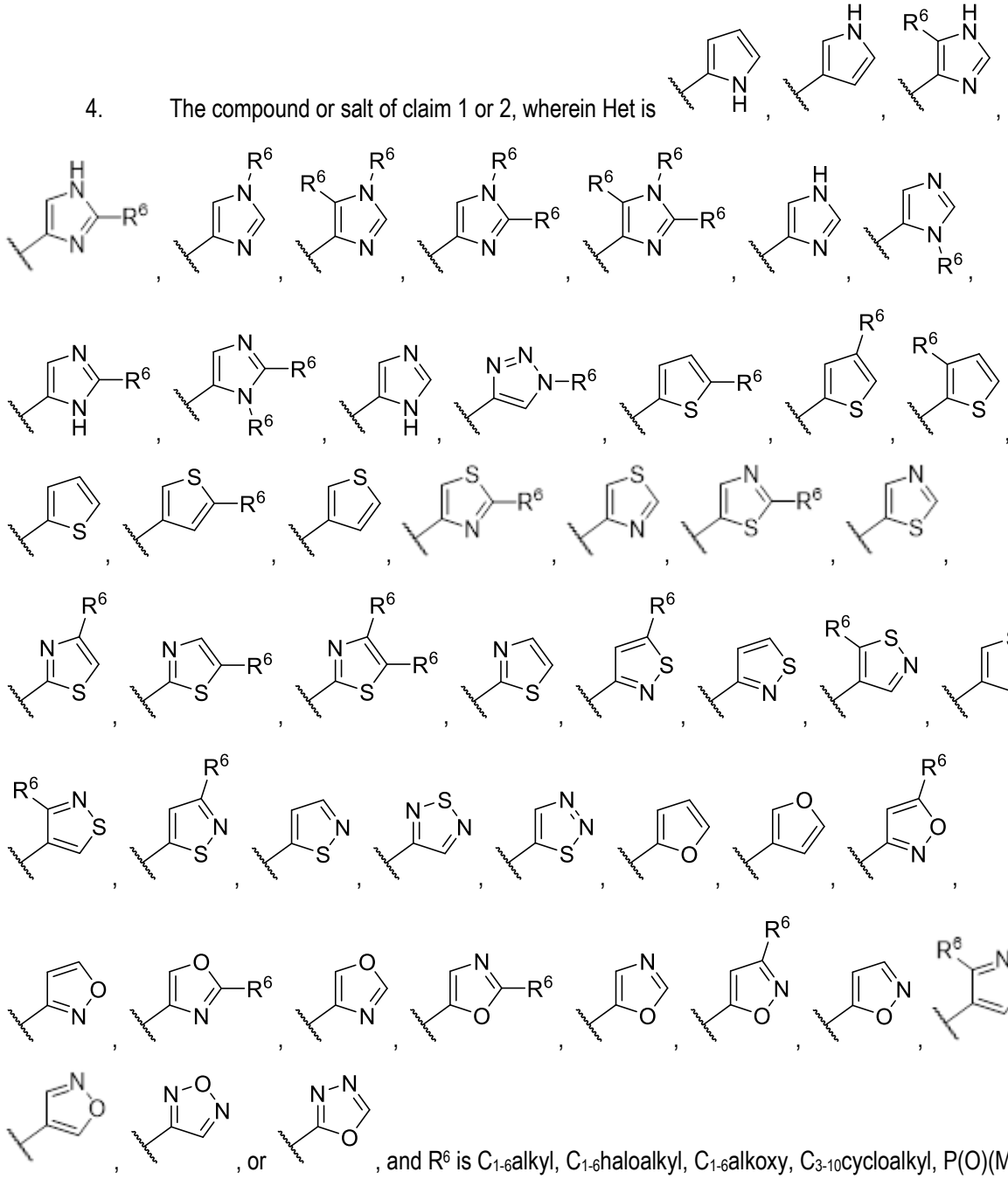
each R^6 is independently halo, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, NR^NR^N, COOH, $C(O)NR^NR^N$, C_{1-6}alkylene-$C(O)OR^N$, C_{1-6}alkylene-$C(O)NR^NR^N$, $SO_2NR^NR^N$, $P(O)(R^N)(R^N)$, C(O)-5- or 6-membered heterocycloalkyl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, C_{1-6}alkylene-C_{3-10}cycloalkyl, C_{3-10}cycloalkyl, 4-6-membered heterocycloalkyl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, C_{6-10}aryl, or 5- or 6-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, wherein the C_{3-10}cycloalkyl, 4-6-membered heterocycloalkyl, C_{6-10}aryl, or 5- or 6-membered heteroaryl can optionally be substituted with 1, 2, or 3 R^7 and each C_{1-6}alkyl, C_{1-6}alkylene, or C_{1-6}alkoxy can be optionally substituted with 1 or 2 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-}

$_{6}$alkyl; and

each R^7 is independently OH, halo, CN, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkoxy, NH_2, $NH(C_{1\text{-}6}alkyl)$, or $N(C_{1\text{-}6}alkyl)_2$.

2. The compound or salt of claim 1, wherein Het is a 5-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N and optionally substituted with 1, 2, or 3 R^6.

3. The compound or salt of claim 2, wherein Het is thiazolyl optionally substituted with 1, 2, or 3 R^6.

4. The compound or salt of claim 1 or 2, wherein Het is , and R^6 is $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}10}$cycloalkyl, $P(O)(Me)_2$, or C(O)-morpholinyl.

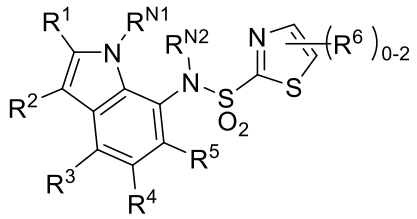
5. The compound or salt of any one of claims 1 to 4, wherein X^1 is CR^1, X^2 is CR^3, and X^3 is CR^4.

6. The compound or salt of any one of claims 1 to 4, wherein one of X^1, X^2, and X^3 is N.

7. The compound or salt of claim 6, wherein X^1 is N.

8. The compound or salt of claim 6, wherein X^3 is N.

9. The compound or salt of claim 1, having the structure of Formula (Ia):



(Ia).

10. The compound or salt of any one of claims 1 to 9, wherein R^{N1} is H.

11. The compound or salt of any one of claims 1 to 10, wherein R^{N2} is H.

12. The compound or salt of any one of claims 1 to 6 and 8 to 11, wherein R^1 is H or C_{1-6}alkyl, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

13. The compound or salt of claim 12, wherein R^1 is H.

14. The compound or salt of any one of claims 1 to 13, wherein R^2 is H, C_{1-6}alkyl, halo, or CN, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

15. The compound or salt of claim 14, wherein R^2 is H, halo, or CN.

16. The compound or salt of claim 15, wherein R^2 is Cl.

17. The compound or salt of claim 16, wherein R^2 is CN.

18. The compound or salt of any one of claims 1 to 17, wherein R^3 is H, C_{1-6}alkyl, or halo, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

19. The compound or salt of claim 18, wherein R^3 is H.

20. The compound or salt of claim 18, wherein R^3 is C_{1-6}alkyl, and the C_{1-6}alkyl can optionally be substituted with 1, 2, or 3 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

21. The compound or salt of claim 20, wherein R^3 is methyl.

22. The compound or salt of claim 18, wherein R^3 is halo.

23. The compound or salt of claim 22, wherein R^3 is fluoro.

24. The compound or salt of any one of claims 1 to 7 and 9 to 23, wherein R^4 is H.

25. The compound or salt of any one of claims 1 to 24, wherein R^5 is H.

26. The compound or salt of claim 1, wherein X^1 is CH, R^2 is H or CN, X^2 is CH or CMe, X^3 is CH, R^5 is H, and Het is thiazolyl, imidazolyl, isooxazolyl, 1,2,4-triazolyl, or oxazolyl, and Het is unsubstituted, or substituted with 1 or 2 R^6.

27. The compound or salt of claim 26, wherein Het is substituted with 1 R^6.

28. The compound or salt of claim 26, wherein Het is substituted with 2 R^6.

29. The compound or salt of any one of claims 1 to 28, wherein each R^6 is independently halo, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, COOH, $C(O)NR^NR^N$, C_{1-6}alkylene-$C(O)OR^N$, $P(O)(R^N)(R^N)$, C(O)-5- or 6-

membered heterocycloalkyl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, C_{3-5}cycloalkyl, 5- or 6-membered heterocycloalkyl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, C_{6-10}aryl, or 5- or 6-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, wherein the C_{3-5}cycloalkyl, 5- or 6-membered heterocycloalkyl, C_{6-10}aryl, or 5- or 6-membered heteroaryl can optionally be substituted with 1, 2, or 3 R^7 and each C_{1-6}alkyl or C_{1-6}alkylene can be optionally substituted with 1 or 2 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

30. The compound or salt of claim 29, wherein each R^6 is independently halo, CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}alkylene-C(O)O-C_{1-6}alkyl, 5- or 6-membered heterocycloalkyl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, C_{6-10}aryl, or 5- or 6-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, wherein the 5- or 6-membered heterocycloalkyl, C_{6-10}aryl, or 5- or 6-membered heteroaryl can optionally be substituted with 1, 2, or 3 R^7 and each C_{1-6}alkyl or C_{1-6}alkylene can be optionally substituted with 1 or 2 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

31. The compound or salt of claim 30, wherein each R^6 is independently halo, C_{1-6}alkyl, or 5- or 6-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, wherein the 5- or 6-membered heteroaryl can optionally be substituted with 1, 2, or 3 R^7 and each C_{1-6}alkyl can be optionally substituted with 1 or 2 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

32. The compound or salt of claim 30, wherein at least one R^6 is halo.

33. The compound or salt of claim 32, wherein at least one R^6 is chloro or bromo.

34. The compound or salt of claim 30, wherein at least one R^6 is C_{1-6}alkyl, and each C_{1-6}alkyl can be optionally substituted with 1 or 2 substituents independently selected from C_{1-6}alkoxy, OH, CN, CO_2H, NR^NR^N, and CO_2C_{1-6}alkyl.

35. The compound or salt of claim 34, wherein at least one R^6 is methyl, ethyl, or isopropyl.

36. The compound or salt of claim 30, wherein each R^6 is independently 5- or 6-membered heteroaryl comprising 1, 2, or 3 ring heteroatoms selected from O, S, and N, wherein the 5- or 6-membered heteroaryl can optionally be substituted with 1, 2, or 3 R^7.

37. The compound or salt of claim 36, wherein at least one R^6 is pyrazolyl, pyridinyl, pyridazinyl, or pyrimidinyl, each of which can optionally be substituted with 1, 2, or 3 R^7.

38. The compound or salt of any one of claims 1 to 37, wherein each R^7 is independently halo, C_{1-6}alkyl, or C_{1-6}haloalkyl.

39. The compound or salt of claim 38, wherein at least one R^7 is C_{1-6}alkyl.

40. The compound or salt of claim 39, wherein at least one R^7 is methyl.

41. A compound listed in Table A, or a pharmaceutically acceptable salt thereof.

42. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 41 and a pharmaceutically acceptable excipient.

43. Use of a compound or salt of any one of claims 1 to 41, or the pharmaceutical composition of claim 42, in the manufacture of a medicament for modulating an RBM39 protein, wherein the compound, salt, or pharmaceutical composition is to be contacted with the RBM39 protein.

44. The use of claim 43, wherein modulating an RBM39 protein comprises degrading the RBM39 protein.

45. The use of claim 43 or 44, wherein the compound, salt, or pharmaceutical composition is to be administered to a subject.

46. The use of claim 45, wherein the subject is human.

47. Use of the compound or salt of any one of claims 1 to 41, or the pharmaceutical composition of claim 42, in the manufacture of a medicament for treating a disease associated with aberrant RBM39 activity in a subject.

48. The use of claim 47, wherein the disease is cancer.

49. The use of claim 48, wherein the cancer is renal cell carcinoma.

50. A compound or salt of any one of claims 1 to 41, or a pharmaceutical composition of claim 42, for use in therapy.