TEAD INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 62/855,082, filed May 31, 2019; U.S. Provisional Patent Application No. 62/928,931, filed October 31, 2019; U.S. Provisional Patent Application No. 62/944,567, filed December 6, 2019; and U.S. Provisional Patent Application No. 63/025,336, filed May 15, 2020, the contents of each of which are herein incorporated by reference in their entireties.

TECHNICAL FIELD OF THE INVENTION

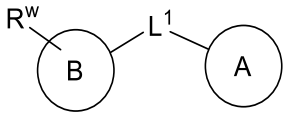
[0002] The present invention relates to compounds and methods useful for inhibition of Transcriptional Enhancer Associate Domain (TEAD). The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various diseases, disorders, and conditions as described herein.

BACKGROUND OF THE INVENTION

[0003] Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with TEAD transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers.

SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a compound of Formula **I'**:

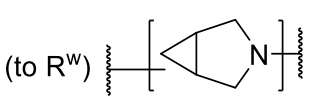


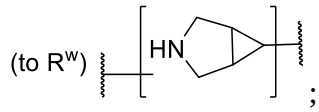
I'

or a pharmaceutically acceptable salt thereof, wherein:

L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

Ring A is optionally substituted phenyl;

Ring B is optionally substituted 

or 

;

R^w is –L-Y;

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, NO_2, 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 1-4 R^e groups;

each R^e is independently selected from -Q-Z, oxo, NO_2, halogen, CN, or a C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN;

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 —N(R)—, —S—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —SO—, or —SO_2—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, or —SO_2N(R)—;

Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; and

each R is independently -H or optionally substituted -C_{1-6} aliphatic.

[0003b] In another aspect of the present disclosure, there is provided a harmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0003c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of the medicament for treating cancer in a patient.

[0003d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the progress of cancer in a patient.

[0003e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with increased TEAD expression.

[0003f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with increased TEAD activity.

[0003g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of the medicament for treating a disease or disorder in which inhibition of TEAD activity is beneficial.

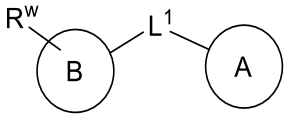
[0003h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder in which Hippo pathway inhibition is beneficial.

[0003i] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0004] The Hippo signaling cascade is an important pathway for cancer biogenesis and tumor maintenance. The Hippo pathway is heavily mutated across many cancer indications through loss of function mutations in genes such as NF2. These pro-tumor mutations lead to the constitutive activation of the downstream transcriptional coactivators YAP and TAZ that drive the expression of many pro-survival and proliferation genes through the essential interaction with a TEAD protein

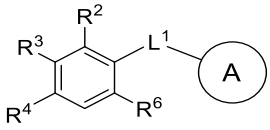
family member. In addition, this unrestrained transcriptional program drives enhanced immune suppression in the tumor microenvironment. As described herein, to target this oncogenic pathway novel small molecule inhibitors were identified that selectively bind to TEAD and disrupt their interaction with YAP and TAZ, thereby downregulating YAP- and TAZ-dependent transcription. As demonstrated herein, these TEAD inhibitors prevent TEAD palmitoylation, which is critical for the interaction between YAP and TEAD. Furthermore, the TEAD inhibitors described herein inhibit *in vitro* proliferation of YAP-dependent (*i.e.*, Hippo pathway-deficient cancer cell lines), but not Hippo pathway wild type cancer cell lines. Importantly, as shown herein, the TEAD inhibitor compounds of the present disclosure did not affect survival of a differentiated mouse podocyte cell line or compromise mouse kidney histology. Subsequent experiments *in vivo* demonstrate the TEAD inhibitors described herein downregulate YAP-dependent genes in human tumor xenografts after oral dosing. In addition, the TEAD inhibitors described herein exhibit single agent tumor growth inhibition of human tumor xenografts in mice at well tolerated oral doses. The data described herein demonstrate the ability of the small molecule TEAD inhibitors provided herein for targeting the Hippo pathway in cancers.

[0005] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as TEAD inhibitors. In one example, the present disclosure provides a compound of Formula **I'**:



I'

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein. In one example, the present disclosure provides a compound of Formula **I**:



I

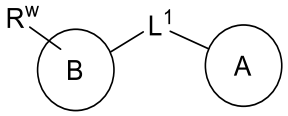
or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0006] Compounds of the present disclosure, and pharmaceutically acceptable salts and compositions thereof, are useful for treating a variety of diseases, disorders or conditions

CLAIMS

What is claimed is:

1. A compound of Formula **I'**:

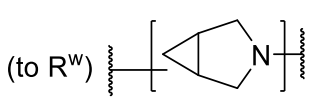


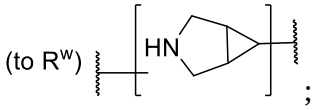
I'

or a pharmaceutically acceptable salt thereof, wherein:

L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, or -(R)NC(S)N(R)-;

Ring A is optionally substituted phenyl;

Ring B is optionally substituted 

or 

;

R^w is –L-Y;

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, NO_2, 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 1-4 R^e groups;

each R^e is independently selected from -Q-Z, oxo, NO_2, halogen, CN, or a C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN;

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

—N(R)—, —S—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —SO—, or —SO_2—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, or —SO_2N(R)—;

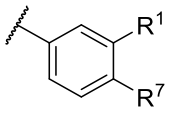
Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; and

each R is independently -H or optionally substituted -C_{1-6} aliphatic.

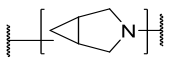
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently replaced with -O-, -CH(OR)-, –CH($N(R)_2$)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, or -N(R)C(O)N(R)-.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein L^1 is –CH_2-.

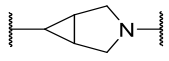
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is phenyl, optionally substituted 1-2 times by halogen, -CN, –NO_2, or -C_{1-6} aliphatic substituted 0-6 times by halogen, -CN, or –NO_2.

5. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein Ring A is 

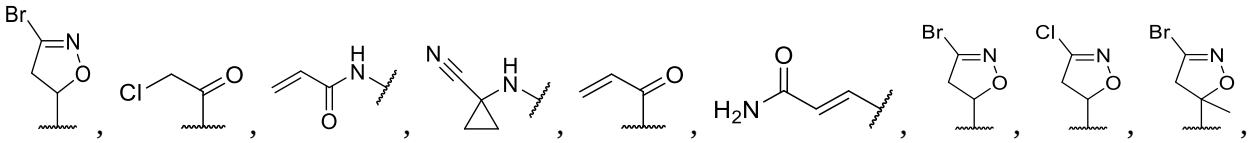
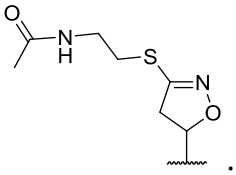
, R^1 is hydrogen, and R^7 is -C_{1-6} aliphatic substituted 0-6 times by halogen.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring B is 

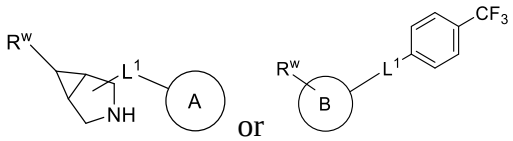
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7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein Ring B is 

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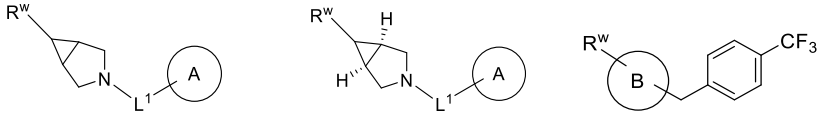
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^w is a  or .

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(IX)** or **(X)**:



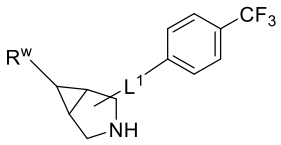
IX **X.**

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(IXa)**, **(IXb), or (Xa)**:



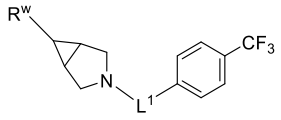
IXa **IXb** **Xa.**

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(XII)**:



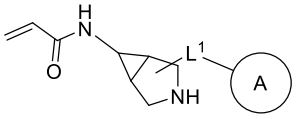
XII.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(XIIa)**:



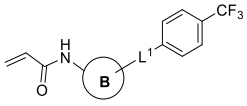
XIIa.

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(XIII)** or **(XIV)**:



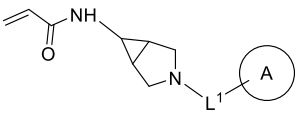
XIII

or

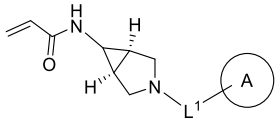


XIV.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(XIIIa) or (XIIIb)**:

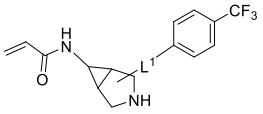


XIIIa



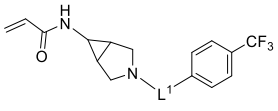
XIIIb.

15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(XV)**:

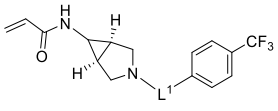


XV.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula **(XVa) or (XVb)**:

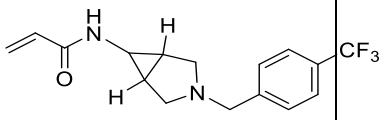
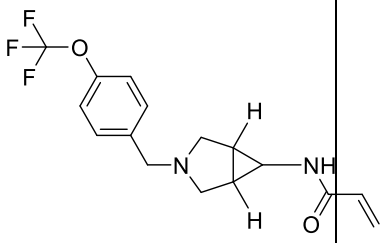
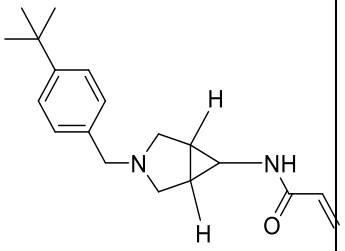
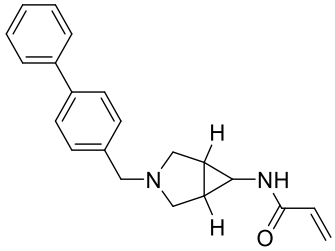
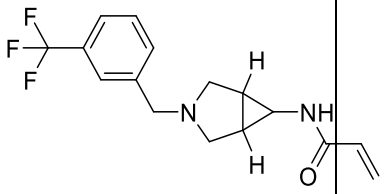
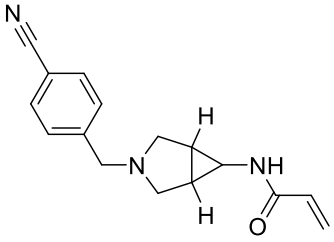
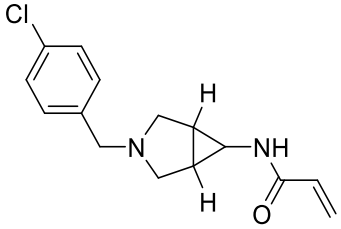
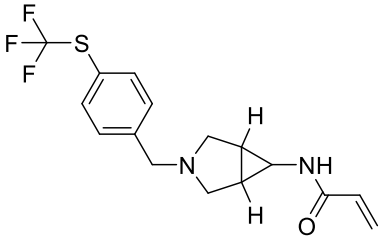
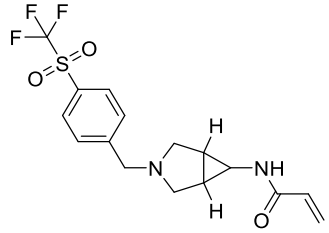
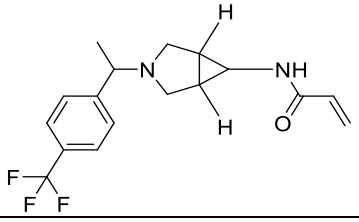
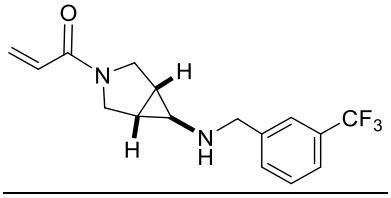
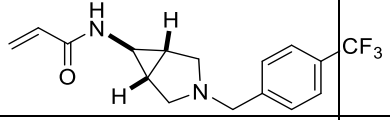
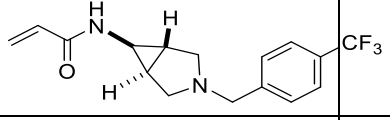
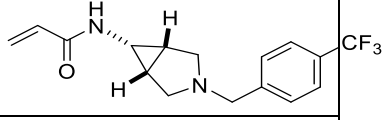


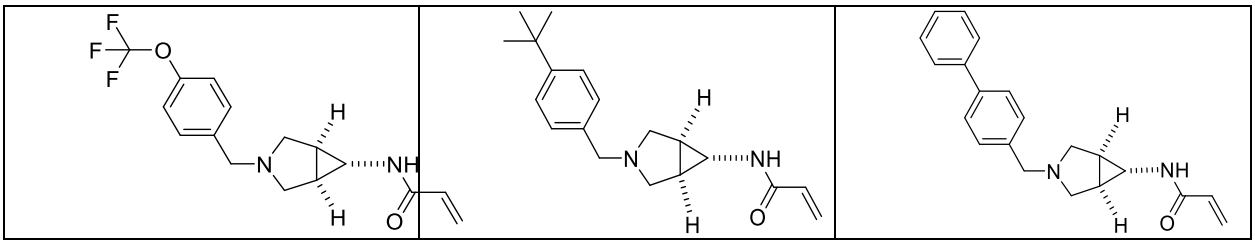
XVa



XVb.

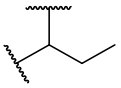
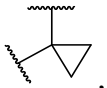
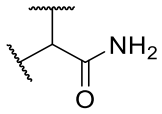
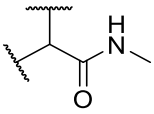
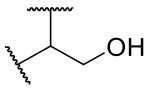
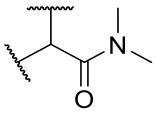
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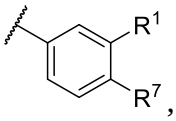
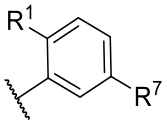
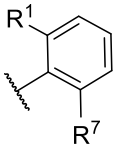
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I-323 	**I-324** 	**I-325** 
I-329 	**I-331** 	**I-340** 
I-375 	**<u>I-72</u>** 	
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I-212	**I-220**	**I-221**

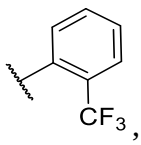
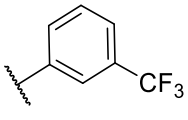
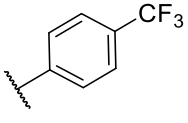
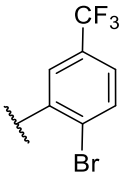
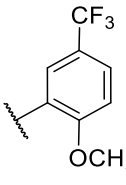
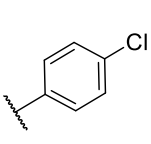
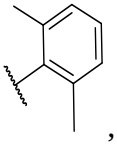


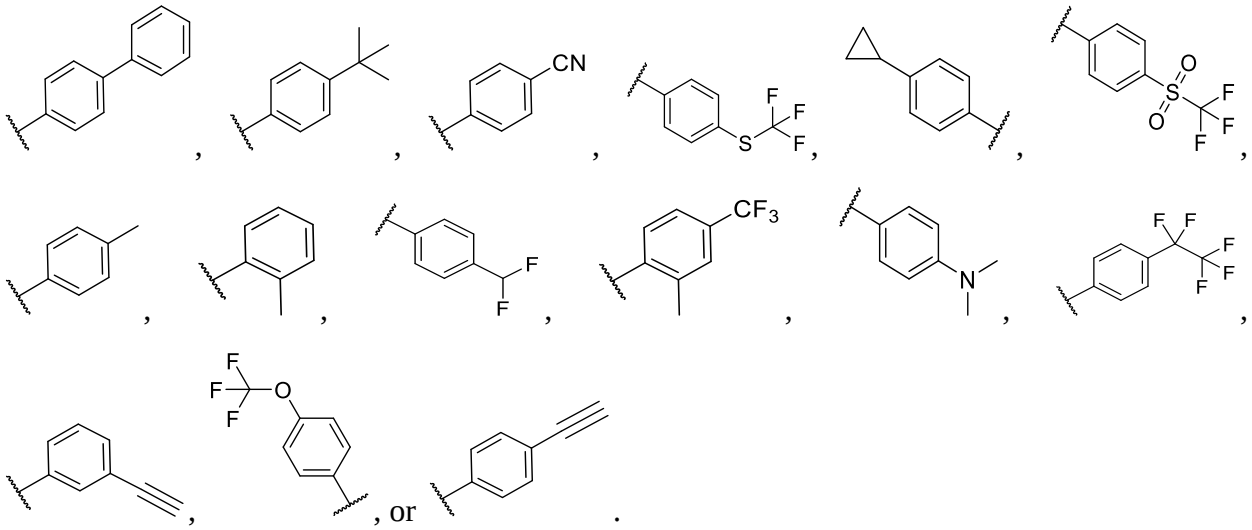
, or a pharmaceutically acceptable salt thereof.

18. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein L^1 is C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently replaced with -N(R)-.

19. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1 is $-CH_2-$, $-CH(CH_3)-$, $-NH-CH_2-$, $-NH-CH(CH_3)-$, $-C(O)-NH-$, or $-N(CH_3)-$, , , , , , or .

20. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is , , or , wherein each of R^1 and R^7 is independently -H, -halogen, -CN, $-NO_2$, $-C_{1-6}$ aliphatic, or $-O-C_{1-6}$ aliphatic, wherein each of $-C_{1-6}$ aliphatic and $-O-C_{1-6}$ aliphatic is independently substituted 0, 1, 2, 3, 4, 5, or 6 times by -halogen, -CN, or $-NO_2$.

21. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is , , , , , , ,



22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

L is —NRC(O)CH═CH—, —NRC(O)CH═CHCH$_2$N(CH$_3$)—, —NRC(O)CH═CHCH$_2$O—, —CH$_2$NRC(O)CH═CH—, —NRSO$_2$CH═CH—, —NRSO$_2$CH═CHCH$_2$—, —NRC(O)(C═N$_2$)—, —NRC(O)(C═N$_2$)C(O)—, —NRC(O)CH═CHCH$_2$N(CH$_3$)—, —NRSO$_2$CH═CH—, —NRSO$_2$CH═CHCH$_2$—, —NRC(O)CH═CHCH$_2$O—, —NRC(O)C(═CH$_2$)CH$_2$—, —CH$_2$NRC(O)—, —CH$_2$NRC(O)CH═CH—, —CH$_2$CH$_2$NRC(O)—, or —CH$_2$NRC(O)cyclopropylene-; and

Y is hydrogen or C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN.

23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

L is a covalent bond;

Y is a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; and

each R^e is independently selected from oxo, NO$_2$, halogen, and CN.

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

25. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, in the manufacture of the medicament for treating cancer in a patient.

26. The use of claim 25, wherein the cancer is associated with increased TEAD expression.

27. The use of claim 25, wherein the cancer is associated with increased TEAD activity.

28. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the progress of cancer in a patient.

29. The use of claim 28, wherein the cancer is associated with increased TEAD expression.

30. The use of claim 28, wherein the cancer is associated with increased TEAD activity.

31. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with increased TEAD expression.

32. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder associated with increased TEAD activity.

33. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, in the manufacture of the medicament for treating a disease or disorder in which inhibition of TEAD activity is beneficial.

34. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder in which Hippo pathway inhibition is beneficial.

35. The use of any one of claims 31-34, wherein the disease or disorder is a cellular proliferative disorder.

36. The use of claim 35, wherein the cellular proliferative disorder is cancer.

37. The use of any one of claims 25-30 and 36, wherein the cancer is a cancer in which YAP is localized in the nucleus of cells of the cancer.

38. The use of any one of claims 26, 27, and 29-33, wherein the increased TEAD expression or increased TEAD activity is increased TEAD1 expression or increased TEAD1 activity.

39. The use of any one of claims 26, 27, and 29-33, wherein the increased TEAD expression or increased TEAD activity is increased TEAD2 expression or increased TEAD2 activity.

40. The use of any one of claims 26, 27, and 29-33, wherein the increased TEAD expression or increased TEAD activity is increased TEAD3 expression or increased TEAD3 activity.

41. The use of any one of claims 26, 27, and 29-33, wherein the increased TEAD expression or increased TEAD activity is increased TEAD4 expression or increased TEAD4 activity.

42. The use of any one of claims 26, 27, and 29-33, wherein the increased TEAD expression or increased TEAD activity is increased TEAD1 expression or increased TEAD1 activity; increased TEAD2 expression or increased TEAD2 activity; increased TEAD3 expression or increased TEAD3 activity; increased TEAD4 expression or increased TEAD4 activity; or any combination thereof.

43. A compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, for use in therapy.