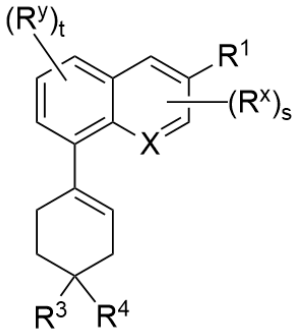
TEAD INHIBITORS AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/322,600, filed March 22, 2022, the contents of which are hereby incorporated by reference in their entirety.

SUMMARY

[0001a] In a first aspect of the present disclosure, there is provided a compound having the chemical formula (I):



(I), or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

R^1 is selected from the group consisting of -C(O)OR^5, -C(O)-NR^6R^2, -$S(O)_2$-$N(R^6)_2$, -$S(O)_m$-(C_{1-6}alkyl), and -S(O)$N(R^6)_2$;

R^2 is selected from the group consisting of -C_1-C_6 alkyl, -(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)$N(R^6)_2$, -(C_0-C_4 alkylene)-phenyl, -(C_1-C_6 alkylene)-$N(R^6)_2$, 5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S, -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), -(C_0-C_4 alkylene)-C_3-C_{10}cycloalkyl, and -(C_0-C_4 alkylene)-(3-10 membered heterocyclyl having one, two, three, or four heteroatoms each independently selected from N, O, and S), wherein any aforementioned phenyl, 5-6 membered heteroaryl, C_3-C_{10}cycloalkyl, and 3-10 membered heterocyclyl are optionally substituted;

m is 1 or 2;

n is 0, 1, or 2;

R^3 is selected from the group consisting of hydrogen, halogen, -C_1-C_6 alkyl, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), and -O-(C_1-C_6 haloalkyl);

R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the carbocyclic ring is optionally substituted with one or more halogens;

each R^5 is independently hydrogen or -C_1-C_6 alkyl;

each R^6 is independently hydrogen or -C_1-C_6 alkyl;

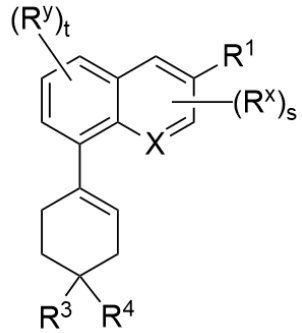
each R^x is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, -CN, and -$N(R^6)_2$;

each R^y is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, -CN, and -$N(R^6)_2$;

s is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0001b] In another aspect of the present disclosure, there is provided a compound having the chemical formula (I'):



(I'), or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

R^1 is selected from the group consisting of -$C(O)OR^5$, -$C(O)$-NR^6R^2, -$S(O)_2$-$N(R^6)_2$, -$S(O)_m$-(C_{1-6}alkyl), and -$S(O)N(R^6)_2$;

R^2 is selected from the group consisting of -C_1-C_6 alkyl, -(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with CN or OR^5)-C(O)N(R^6)$_2$, -(C_0-C_4 alkylene)-phenyl, -(C_1-C_6 alkylene)-N(R^6R^7), -(C_1-C_6 alkylene)-OP(O)(OR^5)$_2$, 5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S, -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), -(C_0-C_4 alkylene)-C_3-C_{10}cycloalkyl, and -(C_0-C_4 alkylene)-(3-10 membered heterocyclyl having one, two, three, or four heteroatoms each independently selected from N, O, and S), wherein any aforementioned phenyl, 5-6 membered heteroaryl, C_3-C_{10}cycloalkyl, and 3-10 membered heterocyclyl are optionally substituted with one or more R^w;

m is 1 or 2;

n is 0, 1, or 2;

R^3 is selected from the group consisting of hydrogen, halogen, -C_1-C_6 alkyl, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), and -O-(C_1-C_6 haloalkyl);

R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the carbocyclic ring is optionally substituted with one or more halogens;

each R^5 is independently hydrogen or -C_1-C_6 alkyl;

each R^6 is independently hydrogen or -C_1-C_6 alkyl;

R^7 is selected from the group consisting of hydrogen, -C_1-C_6 alkyl, -C(O)-(C_{1-6} alkyl), -C(O)N(R^6)$_2$, -$C(O)_2$-(C_{1-6} alkyl), -$S(O)_n$-(C_1-C_6 alkyl), and -$S(O)_n$NR^6-(C_1-C_6 alkyl);

each R^w is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -N(R^6)$_2$, and oxo, wherein the -C_1-C_6 alkyl is optionally substituted with -OH;

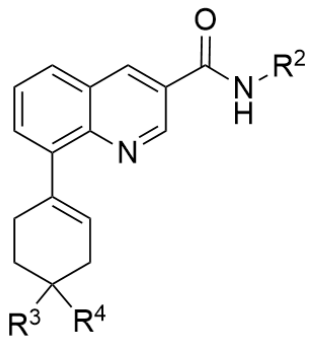
each R^x is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, and -CN;

each R^y is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, and -CN;

s is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0001c] In yet another aspect of the present disclosure, there is provided a compound of formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof, wherein:

R^2 is selected from the group consisting of -C_1-C_6 alkyl,-(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)$N(R^6)_2$, -(C_1-C_6 alkylene)-$N(R^6)_2$, and -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), wherein the 5-6 membered heteroaryl is optionally substituted;

n is 0, 1, or 2;

R^3 is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, and -O-(C_1-C_6 alkyl);

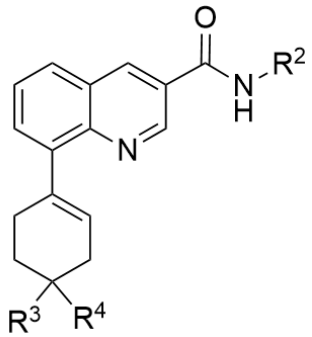
R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the 3-7 membered carbocyclic ring is optionally substituted with one or more halogens;

each R^5 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl; and

each R^6 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl.

[0001d] In a further aspect of the present disclosure, there is provided a compound of formula (Ia'):



(Ia'), or a pharmaceutically acceptable salt thereof, wherein:

R^2 is selected from the group consisting of -C_1-C_6 alkyl,-(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with CN or OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)N(R^6)$_2$, -(C_1-C_6 alkylene)-N(R^6R^7), -(C_1-C_6 alkylene)-OP(O)(OR^5)$_2$, and -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^w;

n is 0, 1, or 2;

R^3 is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, and -O-(C_1-C_6 alkyl);

R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the 3-7 membered carbocyclic ring is optionally substituted with one or more halogens;

each R^5 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl; and

each R^6 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl

R^7 is selected from the group consisting of hydrogen, -C_1-C_6 alkyl, -C(O)-(C_{1-6} alkyl), -C(O)N(R^6)$_2$, -$C(O)_2$-(C_{1-6} alkyl), -$S(O)_n$-(C_1-C_6 alkyl), and -$S(O)_n$NR^6-(C_1-C_6 alkyl);

each R^w is independently selected from the group consisting of -C_1-C_6 alkyl, -N(R^6)$_2$, and oxo, wherein the -C_1-C_6 alkyl is optionally substituted with -OH.

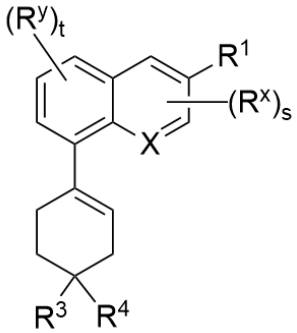
[0001e] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as disclosed herein; and a pharmaceutically acceptable excipient.

[0001f] In yet another aspect of the present disclosure, there is provided a use of a compound or pharmaceutically acceptable salt as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease or condition mediated by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD 4 in a subject in need thereof.

[0001g] In a further aspect of the present disclosure, there is provided a compound or pharmaceutically acceptable salt as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in therapy.

[0002] Disclosed herein, in certain examples, are compounds of formula (I) or formula (I'), e.g., compounds of formula (Ia), formula (Ia'), formula (Ib), formula (Ic), formula (Ib-1), or formula (Ib-2), or pharmaceutically acceptable salts thereof. Additionally, disclosed herein, in certain examples, are compositions comprising a compound of formula (I) or formula (I'), e.g., a compound of formula (Ia), formula (Ia'), formula (Ib), formula (Ic), formula (Ib-1), or formula (Ib-2) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Further disclosed herein, in certain examples, are methods of inhibiting abnormal transcriptional enhanced associate (TEA) domain transcription factor (TEAD) transcriptional complex activity and thus treating certain diseases or disorders such as cancer characterized by abnormal TEAD transcriptional complex activity (e.g., hyperactivation).

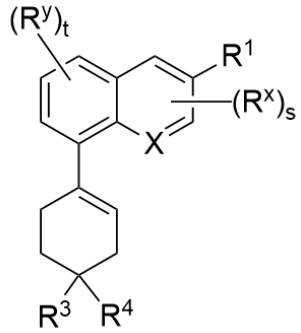
[0003] Disclosed herein, in certain examples, are compounds of formula (I):



(I),

or pharmaceutically acceptable salts thereof, wherein the variables are as defined herein.

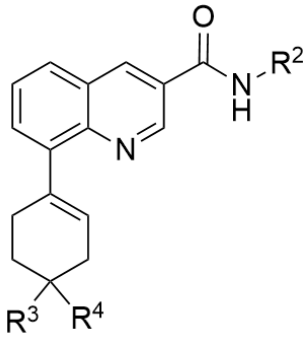
[0004] Also, disclosed herein, in certain examples, are compounds of formula (I'):



(I'),

or pharmaceutically acceptable salts thereof, wherein the variables are as defined herein.

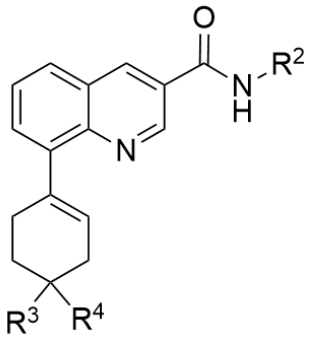
[0005] Also, disclosed herein, in certain examples, are compounds of formula (Ia):



(Ia),

or pharmaceutically acceptable salts thereof, wherein the variables are as defined herein.

[0006] Also, disclosed herein, in certain examples, are compounds of formula (Ia'):



(Ia'),

or pharmaceutically acceptable salts thereof, wherein the variables are as defined herein.

[0007] In some examples, the compounds of formula (I), formula (I'), formula (Ia), formula (Ia'), formula (Ib), formula (Ic), formula (Ib-1), or formula (Ib-2) are selected from Table 1 or a pharmaceutically acceptable salt thereof.

[0008] Also provided herein, in certain examples, are pharmaceutical compositions comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0009] Further disclosed herein, in certain examples, are methods of treating a disease or condition mediated by abnormal TEAD activity (e.g., disregulation) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt described herein or a pharmaceutical composition disclosed herein. In some examples, the disease or condition is a cancer characterized by abnormal TEAD transcriptional complex activity (e.g., hyperactivation).

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The disclosure can be more completely understood with reference to the following drawings.

[0011] FIG. 1 is a diagram showing the domain architecture of human TEAD1, TEAD2, TEAD3, and TEAD4. The percent values represent the identity of the N-terminal DNA binding domain (DNA-BD) and C-terminal YAP/TAZ binding domain (YAP/TAZ-BD) of TEAD2-4 compared to the respective binding domains of TEAD1. Post translation modifications including palmitoylation and phosphorylation as well as the p38 binding D domain of DNA-BD are also shown.

[0012] FIG. 2A is a diagram showing the upstream signaling and downstream transcriptional outputs of TEAD in cancer biology, which regulate critical functions in tumorigenesis, stem cell maintenance, cancer immunology, and metabolism, as well as formation of signaling feedback loops. Oncogenic signal transduction pathways include EGFR signaling, TGFβ signaling, WNt signaling, GPCR signaling, and cancer genes (indicated with *), such as KRAS, BRAF, LKB1, APC, and GNAQ/11.

[0013] FIG. 2B is a diagram showing the role of TEAD in multiple stages of tumorigenesis.

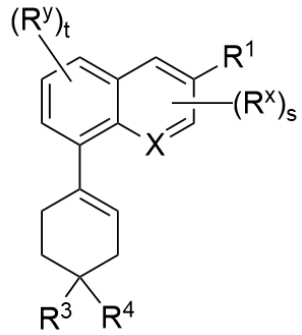
DETAILED DESCRIPTION

[0014] Provided herein, in certain embodiments, are compounds (e.g., compounds of formula (I) or formula (I'), e.g., compounds of formula (Ia), formula (Ia'), formula (Ib), formula (Ic), formula (Ib-1), or formula (Ib-2), or pharmaceutically acceptable salts thereof. Further provided herein, in certain embodiments are compositions comprising a compound of formula (I) or formula (I'), e.g., a compound of formula (Ia), formula (Ia'), formula (Ib), formula (Ic), formula (Ib-1), or formula (Ib-2), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient). Also provided herein, in certain embodiments, are methods of use of compounds and compositions disclosed herein. The contemplated compounds and compositions disclosed herein are inhibitors of transcriptional enhancer factor domain (TEAD) activity and

CLAIMS

What is claimed is:

1. A compound having the chemical formula (I):



(I), or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

R^1 is selected from the group consisting of -C(O)OR^5, -C(O)-NR^6R^2, -$S(O)_2$-$N(R^6)_2$, -$S(O)_m$-(C_{1-6}alkyl), and -S(O)$N(R^6)_2$;

R^2 is selected from the group consisting of -C_1-C_6 alkyl, -(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)$N(R^6)_2$, -(C_0-C_4 alkylene)-phenyl, -(C_1-C_6 alkylene)-$N(R^6)_2$, 5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S, -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), -(C_0-C_4 alkylene)-C_3-C_{10}cycloalkyl, and -(C_0-C_4 alkylene)-(3-10 membered heterocyclyl having one, two, three, or four heteroatoms each independently selected from N, O, and S), wherein any aforementioned phenyl, 5-6 membered heteroaryl, C_3-C_{10}cycloalkyl, and 3-10 membered heterocyclyl are optionally substituted;

m is 1 or 2;

n is 0, 1, or 2;

R^3 is selected from the group consisting of hydrogen, halogen, -C_1-C_6 alkyl, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), and -O-(C_1-C_6 haloalkyl);

R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to

which R^3 and R^4 are attached, wherein the carbocyclic ring is optionally substituted with one or more halogens;

each R^5 is independently hydrogen or -C_1-C_6 alkyl;

each R^6 is independently hydrogen or -C_1-C_6 alkyl;

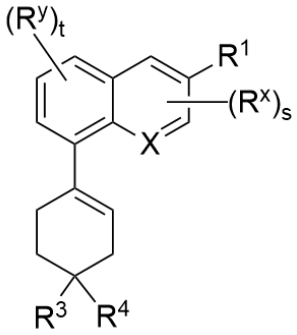
each R^x is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, -CN, and -$N(R^6)_2$;

each R^y is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, -CN, and -$N(R^6)_2$;

s is 0, 1, or 2; and

t is 0, 1, 2, or 3.

2. A compound having the chemical formula (I'):



(I'), or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

R^1 is selected from the group consisting of -$C(O)OR^5$, -$C(O)$-NR^6R^2, -$S(O)_2$-$N(R^6)_2$, -$S(O)_m$-(C_{1-6}alkyl), and -$S(O)N(R^6)_2$;

R^2 is selected from the group consisting of -C_1-C_6 alkyl, -(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-$C(O)OR^5$, -(C_1-C_4 alkylene optionally substituted with CN or OR^5)-$C(O)N(R^6)_2$, -(C_0-C_4 alkylene)-phenyl, -(C_1-C_6 alkylene)-$N(R^6R^7)$, -(C_1-C_6 alkylene)-$OP(O)(OR^5)_2$, 5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S, -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), -

(C_0-C_4 alkylene)-C_3-C_{10}cycloalkyl, and -(C_0-C_4 alkylene)-(3-10 membered heterocyclyl having one, two, three, or four heteroatoms each independently selected from N, O, and S), wherein any aforementioned phenyl, 5-6 membered heteroaryl, C_3-C_{10}cycloalkyl, and 3-10 membered heterocyclyl are optionally substituted with one or more R^w;

m is 1 or 2;

n is 0, 1, or 2;

R^3 is selected from the group consisting of hydrogen, halogen, -C_1-C_6 alkyl, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), and -O-(C_1-C_6 haloalkyl);

R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the carbocyclic ring is optionally substituted with one or more halogens;

each R^5 is independently hydrogen or -C_1-C_6 alkyl;

each R^6 is independently hydrogen or -C_1-C_6 alkyl;

R^7 is selected from the group consisting of hydrogen, -C_1-C_6 alkyl, -C(O)-(C_{1-6} alkyl), -C(O)N(R^6)$_2$, -$C(O)_2$-(C_{1-6} alkyl), -$S(O)_n$-(C_1-C_6 alkyl), and -$S(O)_n$NR^6-(C_1-C_6 alkyl);

each R^w is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -N(R^6)$_2$, and oxo, wherein the -C_1-C_6 alkyl is optionally substituted with -OH;

each R^x is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, and -CN;

each R^y is independently selected from the group consisting of -C_1-C_6 alkyl, halogen, -OR^5, and -CN;

s is 0, 1, or 2; and

t is 0, 1, 2, or 3.

3. The compound of claim 1 or 2, wherein X is N.

4. The compound of any one of claims 1-3, wherein R^1 is -C(O)-NHR^2.

5. The compound of any one of claims 1-3, wherein R^1 is -C(O)OH.

6. The compound of any one of claims 1-3, wherein R^1 is $-S(O)CH_3$.

7. The compound of any one of claims 1-3, wherein R^1 is $-S(O)_2CH_3$.

8. The compound of any one of claims 1-3, wherein R^1 is $-S(O)_2NHCH_3$.

9. The compound of any one of claims 1-8, wherein R^2 is selected from the group consisting of -C_1-C_6 alkyl, -(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)$N(R^6)_2$, -(C_1-C_6 alkylene)-$N(R^6)_2$, and -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S).

10. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_4 alkylene)-5-6 membered heteroaryl.

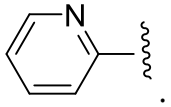
11. The compound of any one of claims 1-10, wherein R^2 is $-CH(CH_3)$-5-6 membered heteroaryl.

12. The compound of any one of claims 1-10, wherein R^2 is $-CH_2$-5-6 membered heteroaryl.

13. The compound of any one of claims 1-12, wherein the 5-6 membered heteroaryl is optionally substituted with C_1-C_6alkyl or $N(R^a)_2$, wherein each R^a is independently hydrogen or C_1-C_6alkyl.

14. The compound of any one of claims 1-13, wherein the 5-6 membered heteroaryl is pyridyl.

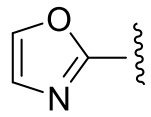
15. The compound of any one of claims 1-14, wherein the 5-6 membered heteroaryl is



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16. The compound of any one of claims 1-13, wherein the 5-6 membered heteroaryl is oxazolyl.

17. The compound of any one of claims 1-13 and 16, wherein the 5-6 membered heteroaryl is



18. The compound of any one of claims 1-9, wherein R^2 is -C_1-C_6 alkyl.

19. The compound of any one of claims 1-9 and 18, wherein R^2 is isopropyl.

20. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_6 alkyl substituted with one or two -OR^5).

21. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_6 alkyl substituted with -OR^5).

22. The compound of any one of claims 1-9, 20, and 21, wherein R^2 is -(C_1-C_6 alkyl substituted with -OH).

23. The compound of any one of claims 1-9 and 20, wherein R^2 is -(C_1-C_6 alkyl substituted with -OH and -OCH_3).

24. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl).

25. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_6 alkylene)-CN.

26. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5.

27. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)N(R^6)$_2$.

28. The compound of any one of claims 1-9, wherein R^2 is -(C_1-C_6 alkylene)-N(R^6)$_2$,

29. The compound of any one of claims 1-28, wherein R^3 is -(C_1-C_6 haloalkyl).

30. The compound of any one of claims 1-29, wherein R^3 is trifluoromethyl.

31. The compound of any one of claims 1-28, wherein R^3 is halogen (e.g., -F).

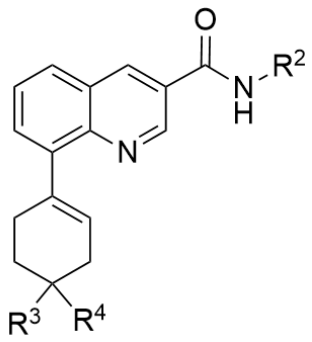
32. The compound of any one of claims 1-31, wherein R^4 is hydrogen.

33. The compound of any one of claims 1-31, wherein R^4 is halogen (e.g., -F).

34. The compound of any one of claims 1-28, wherein R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the carbocyclic ring is optionally substituted with one or more halogens (e.g., -F).

35. The compound of any one of claims 1-34, wherein s and t are both 0.

36. A compound of formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof, wherein:

R^2 is selected from the group consisting of -C_1-C_6 alkyl,-(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)N(R^6)$_2$, -(C_1-C_6 alkylene)-N(R^6)$_2$, and -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), wherein the 5-6 membered heteroaryl is optionally substituted;

n is 0, 1, or 2;

R^3 is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, and -O-(C_1-C_6 alkyl);

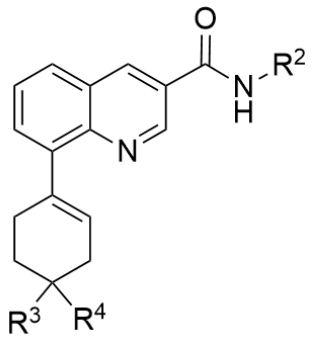
R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the 3-7 membered carbocyclic ring is optionally substituted with one or more halogens;

each R^5 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl; and

each R^6 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl.

37. A compound of formula (Ia'):



(Ia'), or a pharmaceutically acceptable salt thereof, wherein:

R^2 is selected from the group consisting of -C_1-C_6 alkyl,-(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-CN, -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with CN or OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)N(R^6)$_2$, -(C_1-C_6 alkylene)-N(R^6R^7), -(C_1-C_6 alkylene)-OP(O)(OR^5)$_2$, and -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^w;

n is 0, 1, or 2;

R^3 is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, and -O-(C_1-C_6 alkyl);

R^4 is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl; or

R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the 3-7 membered carbocyclic ring is optionally substituted with one or more halogens;

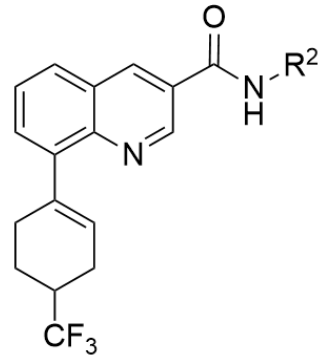
each R^5 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl; and

each R^6 is independently for each occurrence, hydrogen or -C_1-C_6 alkyl

R^7 is selected from the group consisting of hydrogen, -C_1-C_6 alkyl, -C(O)-(C_{1-6} alkyl), -C(O)N(R^6)$_2$, -$C(O)_2$-(C_{1-6} alkyl), -$S(O)_n$-(C_1-C_6 alkyl), and -$S(O)_nNR^6$-(C_1-C_6 alkyl);

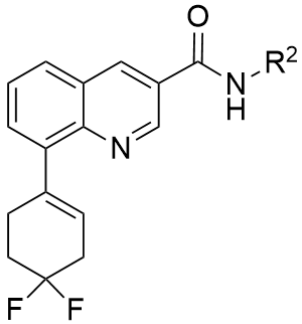
each R^w is independently selected from the group consisting of -C_1-C_6 alkyl, -N(R^6)$_2$, and oxo, wherein the -C_1-C_6 alkyl is optionally substituted with -OH.

38. The compound of claim 36 or 37, wherein the compound is a compound of formula (Ib):



(Ib), or a pharmaceutically acceptable salt thereof.

39. The compound of claim 36 or 37, wherein the compound is a compound of formula (Ic):



(Ic), or a pharmaceutically acceptable salt thereof.

40. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_4 alkylene)-5-6 membered heteroaryl.

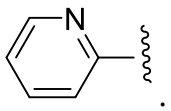
41. The compound of any one of claims 36-39, wherein R^2 is -$CH(CH_3)$-5-6 membered heteroaryl.

42. The compound of any one of claims 36-39, wherein R^2 is -CH_2-5-6 membered heteroaryl.

43. The compound of any one of claims 36-42, wherein the 5-6 membered heteroaryl is optionally substituted with -C_1-C_6alkyl or -$N(R^a)_2$, wherein each R^a is independently hydrogen or C_1-C_6alkyl.

44. The compound of any one of claims 36-43, wherein the 5-6 membered heteroaryl is pyridyl.

45. The compound of any one of claims 36-44, wherein the 5-6 membered heteroaryl is

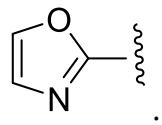


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46. The compound of any one of claims 36-43, wherein the 5-6 membered heteroaryl is

oxazolyl.

47. The compound of any one of claims 36-43 and 46, wherein the 5-6 membered heteroaryl is



.

48. The compound of any one of claims 37-39, wherein R^2 is selected from the group consisting of -(C_1-C_6 alkyl substituted with one or two -OR^5), -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl), -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)OR^5, -(C_1-C_4 alkylene optionally substituted with OR^5)-C(O)N(R^6)$_2$, -(C_1-C_6 alkylene)-N(R^6R^7)$_2$, -(C_1-C_6 alkylene)-OP(O)(OR^5)$_2$, -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), and -(C_0-C_4 alkylene)-(3-10 membered heterocyclyl having one, two, three, or four heteroatoms each independently selected from N, O, and S), wherein any aforementioned 5-6 membered heteroaryl and 3-10 membered heterocyclyl are optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of methyl, -NH_2, and oxo.

49. The compound of any one of claims 37-39, wherein R^2 is selected from the group consisting of -(C_1-C_6 alkyl substituted with one or two-OR^5), -(C_1-C_6 alkylene)-N(R^6R^7)$_2$, and -(C_1-C_4 alkylene optionally substituted with OR^5)-(5-6 membered heteroaryl having one, two, or three heteroatoms each independently selected from N, O, and S), wherein any aforementioned 5-6 membered heteroaryl and 3-10 membered heterocyclyl are optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of methyl, -NH_2, and oxo.

50. The compound of any one of claims 36-39, wherein R^2 is -C_1-C_6 alkyl.

51. The compound of any one of claims 36-39 and 50, wherein R^2 is isopropyl.

52. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_6 alkyl substituted with one or two-OR^5).

53. The compound of any one of claims 36-39 and 52, wherein R^2 is -(C_1-C_6 alkyl substituted with -OR^5).

54. The compound of any one of claims 36-39, 52, and 53, wherein R^2 is -(C_1-C_6 alkyl

substituted with -OH).

55. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_6 alkyl substituted with -OH and -OCH_3).

56. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_6 alkylene)-$S(O)_n$-(C_1-C_6 alkyl).

57. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_6 alkylene)-CN.

58. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_4 alkylene optionally substituted with OR^5)-$C(O)OR^5$.

59. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_4 alkylene optionally substituted with OR^5)-$C(O)N(R^6)_2$.

60. The compound of any one of claims 36-39, wherein R^2 is -(C_1-C_6 alkylene)-$N(R^6)_2$,

61. The compound of any one of claims 36, 37, and 40-60, wherein R^3 is -C_1-C_6 haloalkyl.

62. The compound of any one of claims 36, 37, and 40-61, wherein R^3 is trifluoromethyl.

63. The compound of any one of claims 36, 37, and 40-60, wherein R^3 is halogen.

64. The compound of any one of claims 36, 37, 40-60, and 63, wherein R^3 is -F.

65. The compound of any one of claims 36, 37, and 40-64, wherein R^4 is hydrogen.

66. The compound of any one of claims 36, 37 and 40-64, wherein R^4 is halogen.

67. The compound of any one of claims 36, 37, 40-64, and 66, wherein R^4 is -F.

68. The compound of any one of claims 36, 37 and 40-60, wherein R^3 and R^4 are taken together to form a 3-7 membered carbocyclic ring with the carbon to which R^3 and R^4 are attached, wherein the carbocyclic ring is optionally substituted with one or more halogens (e.g., -F).

69. The compound of claim any one of claims 1-68, wherein the compound is selected from Table 1.

70. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-69; and a pharmaceutically acceptable excipient.

71. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-69, or a pharmaceutical composition of claim 70, in the manufacture of a medicament for treating a disease or condition mediated by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD 4 in a subject in need thereof.

72. The use of claim 71, wherein the disease or condition is a cancer characterized by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD4.

73. The use of claim 72, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, gastric cancer, colorectal cancer, pancreatic cancer including pancreatic adenocarcinoma, mesothelioma including malignant mesothelioma, hepatocellular cancer, prostate cancer, head and neck cancer, renal cell carcinoma, and medulloblastoma.

74. The use of claim 72 or 73, wherein the cancer is selected from the group consisting of hepatocellular cancer, breast cancer, pancreatic adenocarcinoma, and malignant mesothelioma.

75. The use of any one of claims 72-74, wherein the cancer is malignant mesothelioma.

76. The use of any one of claims 72-75, wherein the cancer is metastatic.

77. A compound or pharmaceutically acceptable salt of any one of claims 1-69, or a pharmaceutical composition of claim 70, for use in therapy.