TEAD INHIBITORS AND METHODS OF USE

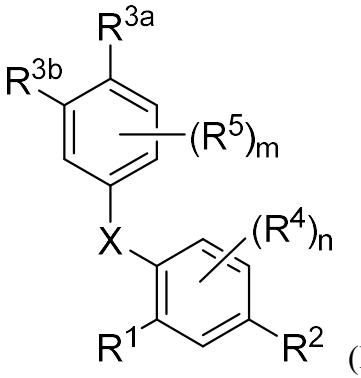
CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/369,036, filed July 21, 2022, the contents of which are hereby incorporated by reference in their entirety.

SUMMARY

[0002] Disclosed herein, in certain examples, are compounds of formula (I), formula (I'), formula (I-1), or formula (I-1'), e.g., compounds of formula (Ia), formula (Ia'), formula (Ib), formula (Ib'), formula (Ic), formula (Ic'), formula (Id), and/or formula (Ie), or pharmaceutically acceptable salts thereof. Additionally, disclosed herein, in certain examples, are compositions comprising a compound of formula (I), formula (I'), formula (I-1), or formula (I-1'), e.g., a compound of formula (Ia), formula (Ia'), formula (Ib), formula (Ib'), formula (Ic), formula (Ic'), formula (Id), and/or formula (Ie), 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).

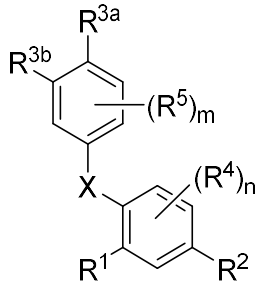
[0003] Disclosed herein, in certain examples, are compounds of formula (I):



(I),

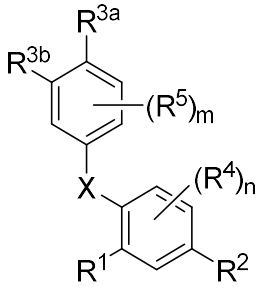
or pharmaceutically acceptable salts thereof, wherein the variables are as defined herein.

[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.

[0004a] In one aspect, the present disclosure refers to a compound having the chemical formula (I'):


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

X is NR^a or S;

R^1 is a 5-10 membered heteroaryl having one, two, three, or four heteroatoms each independently selected from the group consisting of N, O, and S; wherein the 5-10 membered heteroaryl is optionally substituted;

R^2 is 3-10 membered heterocyclyl or -(C_1-C_4alkylene)-(3-10 membered heterocyclyl), wherein the 3-10 membered heterocyclyl contains at least 2 carbon atoms and one, two, three or, four heteroatoms and is optionally substituted, wherein the heteroatoms are nitrogen, and wherein the C_1-C_4alkylene is optionally substituted;

one of R^{3a} and R^{3b} is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl are optionally substituted; and the other one of R^{3a} and R^{3b} is selected from the group consisting of hydrogen, halogen, and -C_1-C_6 alkyl;

each R^4 is independently selected from halogen and -C_1-C_6 alkyl;

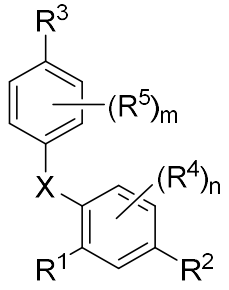
each R^5 is independently selected from halogen and -C_1-C_6 alkyl;

m is selected from the group consisting of 0, 1, 2, and 3;

n is selected from the group consisting of 0, 1, 2, and 3; and

R^a is selected from hydrogen and -C_1-C_6 alkyl.

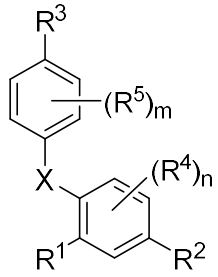
[0005] Also, disclosed herein, in certain examples, are compounds of formula (I-1):


(I-1),

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

[0005a] In one aspect, the present disclosure refers to a compound having the chemical formula

(I-1):



(I-1), or a pharmaceutically acceptable salt thereof, wherein:

X is NR^a or S;

R^1 is a 5-10 membered heteroaryl having one, two, three, or four heteroatoms each independently selected from the group consisting of N, O, and S; wherein the 5-10 membered heteroaryl is optionally substituted;

R^2 is 3-10 membered heterocyclyl or -(C_1-C_4alkylene)-(3-10 membered heterocyclyl); wherein the 3-10 membered heterocyclyl has one, two, three, or four heteroatoms each independently selected from the group consisting of N, O, and S, and is optionally substituted, wherein the C_1-C_4alkylene is optionally substituted;

R^3 is selected from the group consisting of halogen, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl, wherein the C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl are optionally substituted;

each R^4 is independently selected from halogen and -C_1-C_6 alkyl;

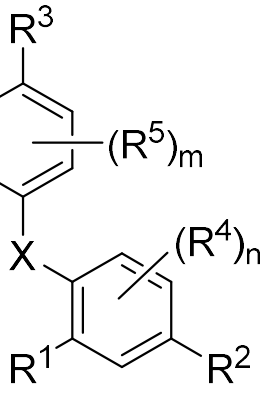
each R^5 is independently selected from halogen and -C_1-C_6 alkyl;

m is selected from the group consisting of 0, 1, 2, 3, and 4;

n is selected from the group consisting of 0, 1, 2, and 3; and

R^a is selected from hydrogen and -C_1-C_6 alkyl.

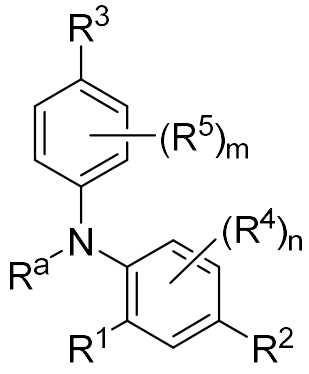
[0006] Also, disclosed herein, in certain examples, are compounds of formula (I-1'):



(I-1'),

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

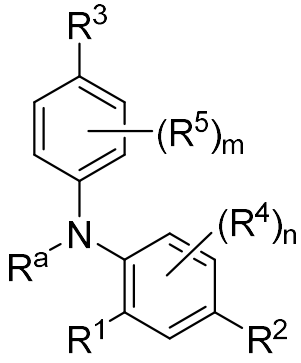
[0007] Also, disclosed herein, in certain examples, are compounds of formula (Ia)p:



(Ia),

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

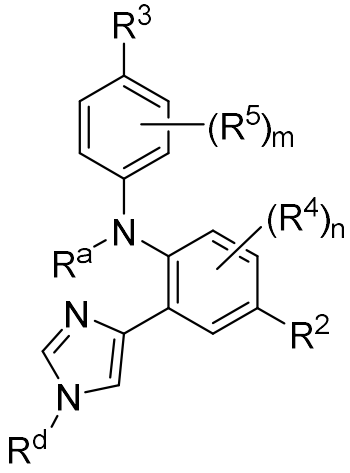
[0008] Also, disclosed herein, in certain examples, are compounds of formula (Ia'):



(Ia'),

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

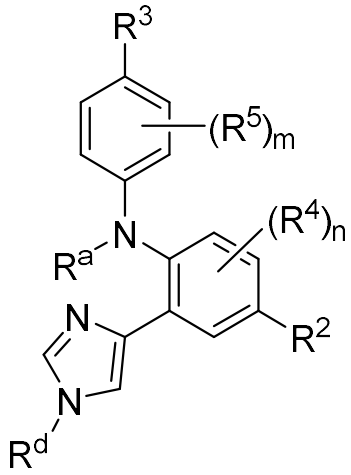
[0009] Also, disclosed herein, in certain examples, are compounds of formula (Ib):



(Ib),

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

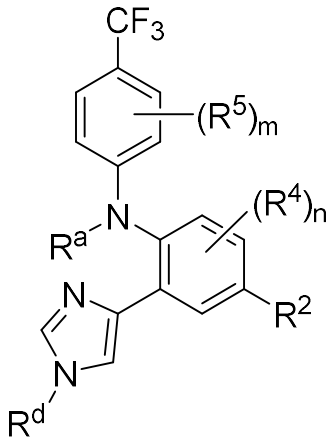
[0010] Also, disclosed herein, in certain examples, are compounds of formula (Ib'):



(Ib'),

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

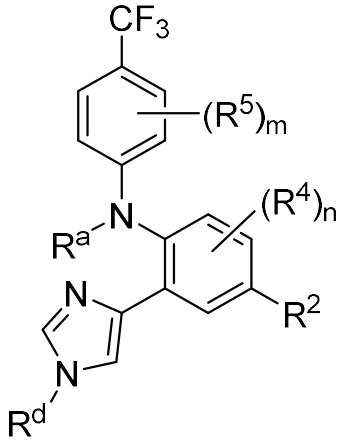
[0011] Also, disclosed herein, in certain examples, are compounds of formula (Ic):



(Ic),

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

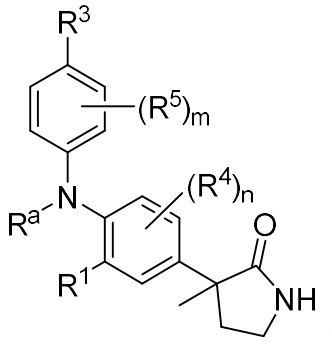
[0012] Also, disclosed herein, in certain examples, are compounds of formula (Ic'):



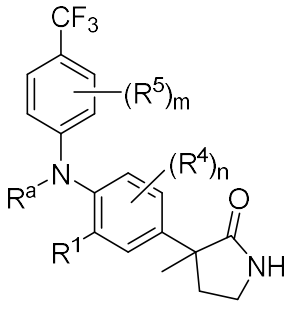
(Ic'),

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

[0013] Also, disclosed herein, in certain examples, are compounds of formula (Id):


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

[0014] Also, disclosed herein, in certain examples, are compounds of formula (Ie):


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

[0015] In some examples, the compounds of formula (I), formula (I'), formula (I-1), formula (I-1'), formula (Ia), formula (Ia'), formula (Ib), formula (Ib'), formula (Ic), formula (Ic'), formula (Id), or formula (Ie) are selected from the compounds of Table 1 or a pharmaceutically acceptable salt thereof.

[0016] 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.

[0016a] In one aspect, the present disclosure refers to a pharmaceutical composition, comprising: (a) a compound or a pharmaceutically acceptable salt thereof disclosed herein; and (b) a pharmaceutically acceptable excipient.

[0017] Further disclosed herein, in certain examples, are methods of treating a disease or condition mediated by 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).

[0017a] In one aspect, the present disclosure refers to use of a compound or pharmaceutically acceptable salt disclosed herein, or a pharmaceutical composition 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 TEAD4 in a subject in need thereof.

[0017b] In one aspect, the present disclosure refers to a compound or pharmaceutically acceptable salt disclosed herein, or the pharmaceutical composition disclosed herein, for use in treating a disease or condition mediated by hyperactivation of a TEAD isoform selected from TEAD1 and TEAD4 in a subject in need thereof.