Lats1/2 proteins are also activated by phosphorylation by the STE20 family protein kinases Mst1 and Mst2, which are homologous to Drosophila Hippo. Lats1/2 kinases phosphorylate the downstream effectors YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif; WWTR1), which are homologous to Drosophila Yorkie. The phosphorylation of YAP and TAZ by Lats1/2 are crucial events within the Hippo signaling pathway. Lats1/2 phosphorylates YAP at multiple sites, but phosphorylation of Ser127 is critical for YAP inhibition. Phosphorylation of YAP generates a protein-binding motif for the 14-3-3 family of proteins, which upon binding of a 14-3-3 protein, leads to retention and/or sequestration of YAP in the cell cytoplasm. Likewise, Lats1/2 phosphorylates TAZ at multiple sites, but phosphorylation of Ser89 is critical for TAZ inhibition. Phosphorylation of TAZ leads to retention and/or sequestration of TAZ in the cell cytoplasm. In addition, phosphorylation of YAP and TAZ is believed to destabilize these proteins by activating phosphorylation-dependent degradation catalyzed by YAP or TAZ ubiquitination. Thus, when the Hippo pathway is "on", YAP and/or TAZ is phosphorylated, inactive, and generally sequestered in the cytoplasm; in contrast, when the Hippo pathway is "off", YAP and/or TAZ is non-phosphorylated, active, and generally found in the nucleus.

[0008] Non-phosphorylated, activated YAP is translocated into the cell nucleus where its major target transcription factors are the four proteins of the TEAD-domain-containing family (TEAD1-TEAD4, collectively "TEAD"). YAP together with TEAD (or other transcription factors such as Smad1, RUNX, ErbB4 and p73) has been shown to induce the expression of a variety of genes, including connective tissue growth factor (CTGF), Gli2, Birc5, Birc2, fibroblast growth factor 1 (FGF1), and amphiregulin (AREG). Like YAP, non-phosphorylated TAZ is translocated into the cell nucleus where it interacts with multiple DNA-binding transcription factors, such as peroxisome proliferator-activated receptor γ (PPARγ), thyroid transcription factor-1 (TTF-1), Pax3, TBX5, RUNX, TEAD1 and Smad2/3/4. Many of the genes activated by YAP/TAZ-transcription factor complexes mediate cell survival and proliferation. Therefore, under some conditions YAP and/or TAZ acts as an oncogene and the Hippo pathway acts as a tumor suppressor.

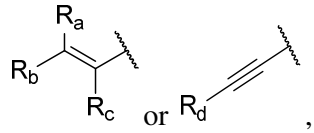
[0009] Hence, pharmacological targeting of the Hippo cascade through inhibition of TEAD would be valuable approach for the treatment of cancers that harbor functional alterations of this pathway.

SUMMARY OF THE DISCLOSURE

[0010] In some examples, a compound, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, of the following formula (B-1) is provided:

molecule, and

(iii) when R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl, and

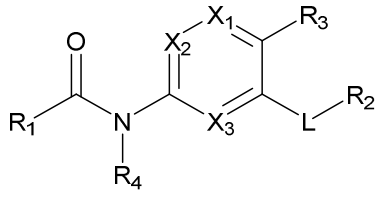
R_1 is  ,

then R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$;

R_4 is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl; and

R^e and R^f are, independently of each other and independently at each occurrence, selected from the group consisting of H, cyano, hydroxyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl of R^e and R^f are each independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, oxo, cyano, halo, NO_2, and hydroxyl.

[0010a] In one aspect, the present disclosure provides a compound of formula (B-1):



(B-1),

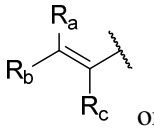
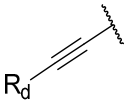
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

X_1 is N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, $C(O)NH_2$, $N(R^e)(R^f)$, C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or $N(R^e)(R^f)$, or

the R_5 of X_1 is taken together with R_3, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl, provided that X_3 is CH;

X_2 is N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, $C(O)NH_2$, $N(R^e)(R^f)$, C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or $N(R^e)(R^f)$;

X_3 is N or C-H,

provided that, when X_3 is N, and R_1 is  or , then at least one of X_1 and X_2 is N;

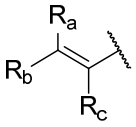
R_1 is:

(i) oxiranyl or oxetanyl, wherein the oxiranyl or oxetanyl is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more $-C(O)NH_2$, and

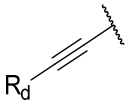
L is absent or is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

(ii) $N(R^e)(CN)$, and

L is absent or is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

(iii) , wherein R_a, R_b, and R_c are each independently selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, provided that at least two of R^a, R^b, and R^c are H, and

L is absent or is selected from the group consisting of *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

(iv) , wherein R_d is selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, and

L is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule;

R_2 is C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl of R_2 is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, $O(R^e)$, and SF_5,

provided that, when R_2 is C_{1-12}alkyl, wherein the C_{1-12}alkyl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$, then L is -CH=CH- or -C≡C-;

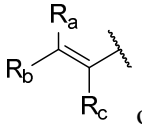
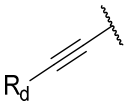
R_3 is cyano, C_{1-6}alkyl, C_{1-4}alkoxy, or C_{2-4}alkenyl, wherein the C_{2-4}alkenyl is optionally substituted with $N(R^e)(R^f)$, or

R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl, provided that X_3 is CH, or

R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl,

provided that:

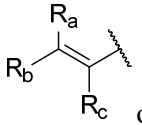
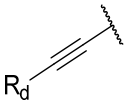
(i) when R_3 is cyano, C_{1-6}alkyl, C_{1-4}alkoxy, or C_{2-4}alkenyl, wherein the C_{2-4}alkenyl is optionally substituted with $N(R^e)(R^f)$, and

R_1 is  or , and

R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$,

then L is *-CH_2-O-**, -CH=CH-, or -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, and

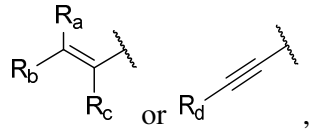
(ii) when R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, provided that X_3 is CH, and

R_1 is  or , and

R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$,

then L is absent or is *-CH_2-O-**, -CH=CH-, or -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, and

(iii) when R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl, and

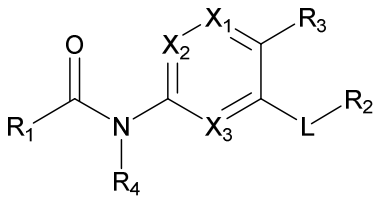
R_1 is  ,

then R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$;

R_4 is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl; and

R^e and R^f are, independently of each other and independently at each occurrence, selected from the group consisting of H, cyano, hydroxyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl of R^e and R^f are each independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, oxo, cyano, halo, NO_2, and hydroxyl.

[0011] In some examples, a compound, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, of the following formula (B) is provided:



(B),

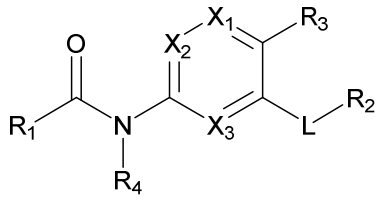
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

X_1 is N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, $C(O)NH_2$, $N(R^e)(R^f)$, C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or $N(R^e)(R^f)$, or

R_4 is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl; and

R^e and R^f are, independently of each other and independently at each occurrence, selected from the group consisting of H, cyano, hydroxyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl of R^e and R^f are each independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, oxo, cyano, halo, NO_2, and hydroxyl.

[0012] In some examples of the present disclosure, the compounds, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, are of the following formula (I):

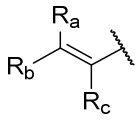


(I),

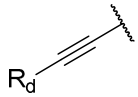
wherein:

X_1 and X_2 are each independently N or C-R_5, wherein R_5 is selected from the group consisting of hydrogen, cyano, halo, C(O)NH_2, NH(R^e), C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{1-6}alkoxy, and C_{6-20}aryl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl;

X_3 is N or CH, provided that, when X_3 is N, at least one of X_1 and X_2 is N;

R_1 is 

, wherein R_a, R_b, and R_c are each independently selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, provided that at least two of R^a, R^b, and R^c are H, and L is absent or is selected from the group consisting of *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

R_1 is 

, wherein wherein R_d is selected from the group consisting of H, halo, cyano,

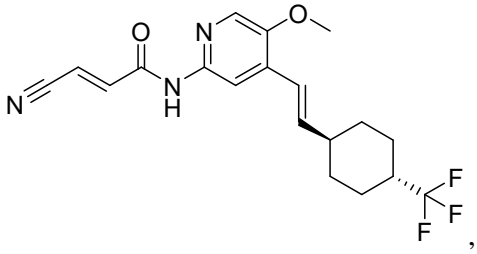
then L is *-CH_2-O-**, -CH=CH-, or -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

(ii) when R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, provided that X_3 is CH, and R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$, then L is absent or is *-CH_2-O-**, -CH=CH-, or -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

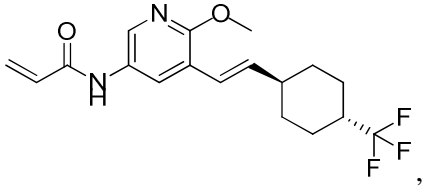
(iii) when R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl, and R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$, then L is *-CH_2-O-**, -CH=CH-, or -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule; and

R_4 is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl.

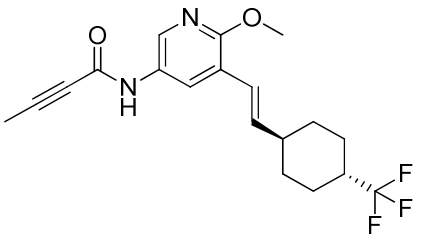
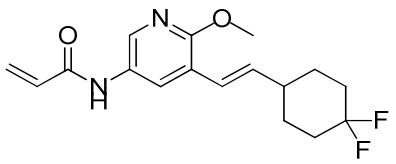
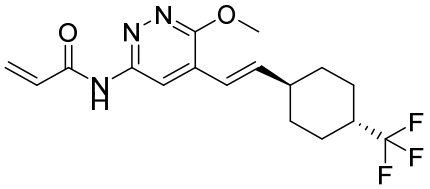
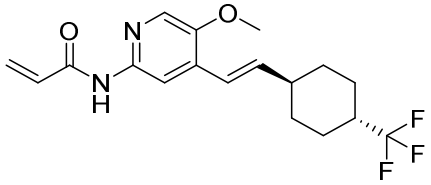
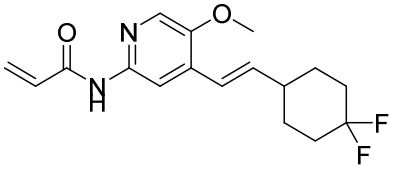
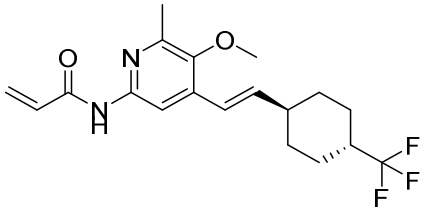
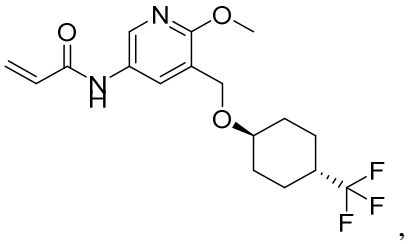
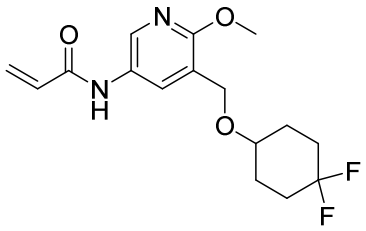
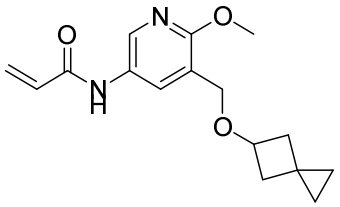
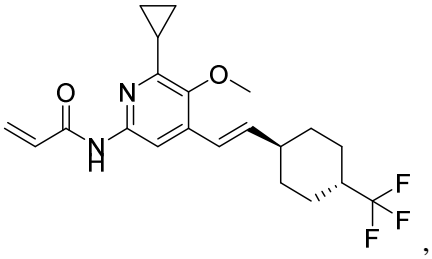
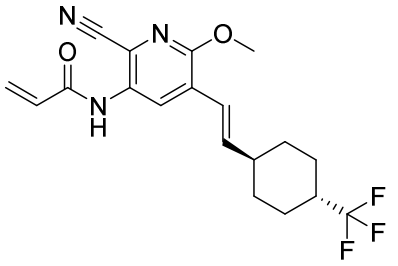
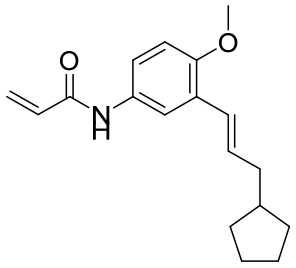
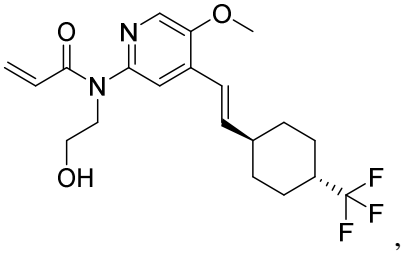
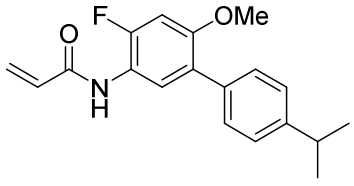
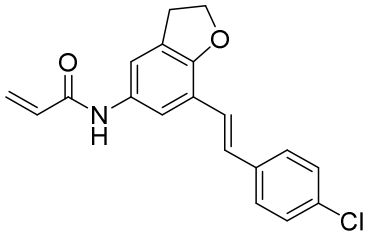
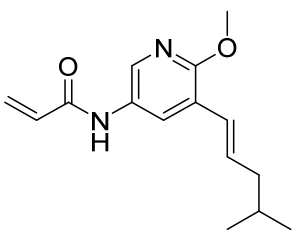
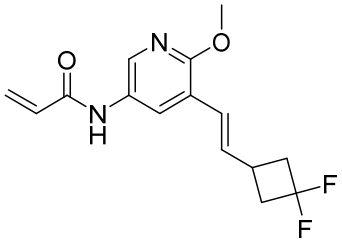
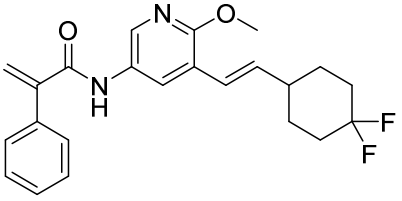
[0012a] In one aspect, the present disclosure provides a compound, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, selected from the group consisting of:

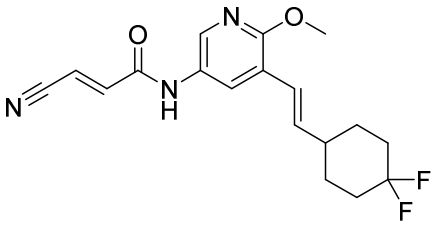
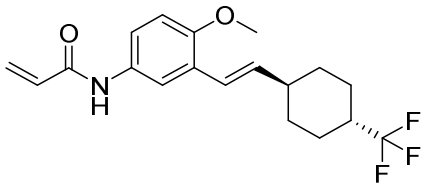
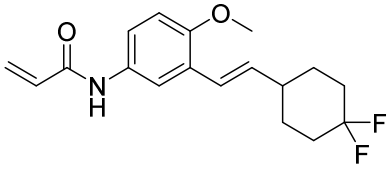
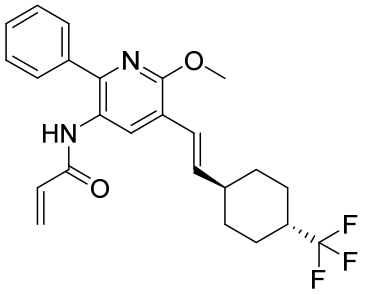
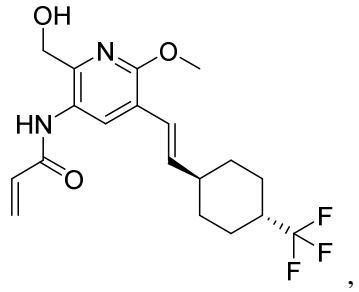
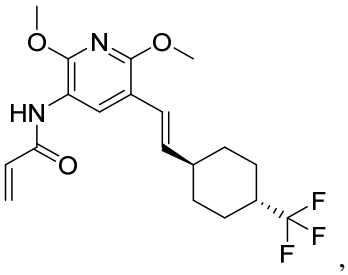
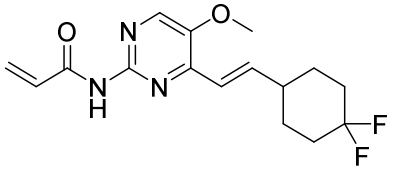
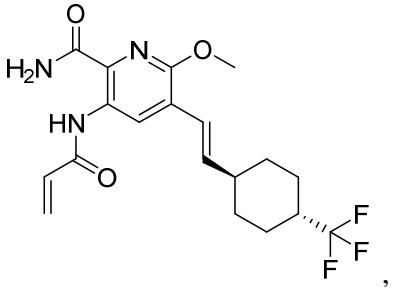
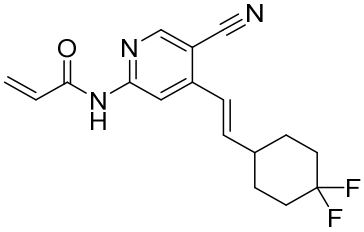
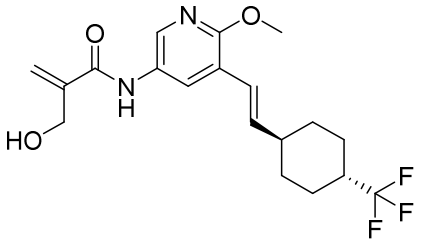
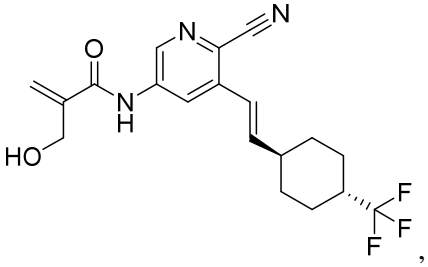
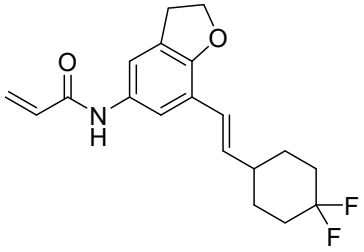
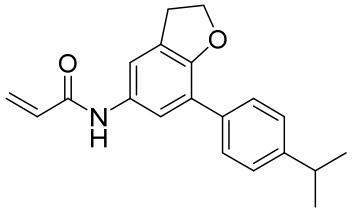
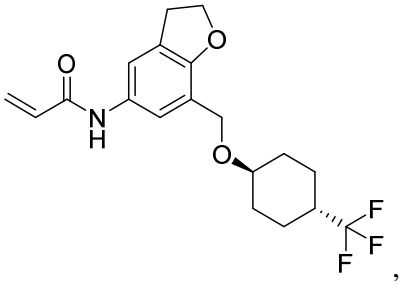
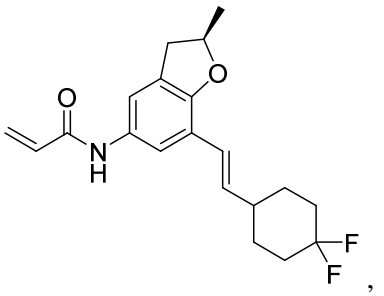
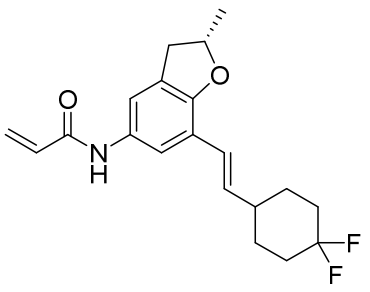


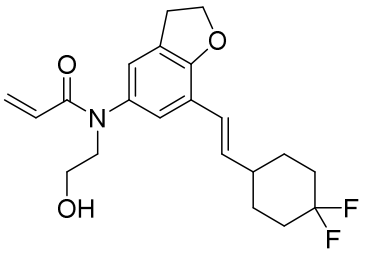
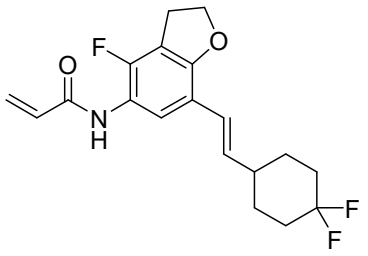
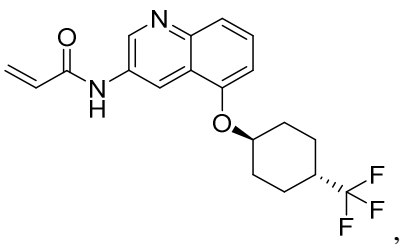
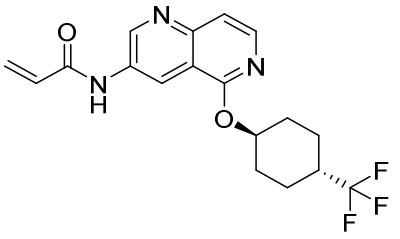
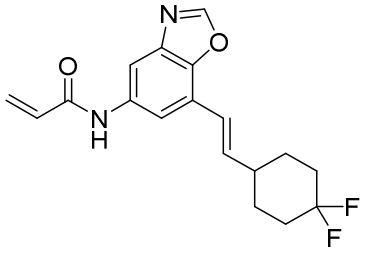
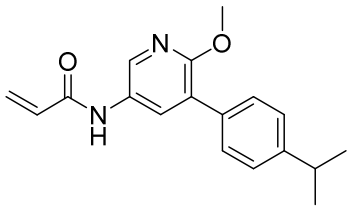
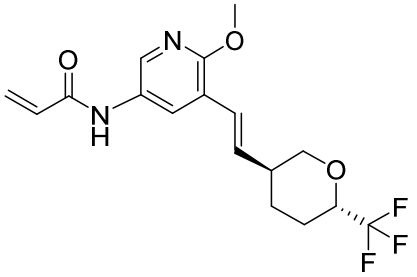
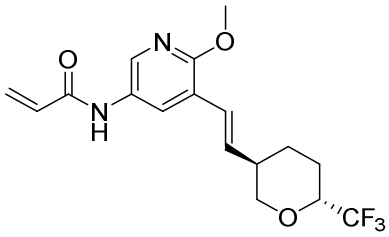
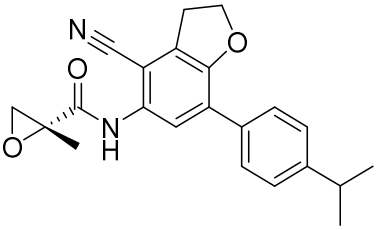
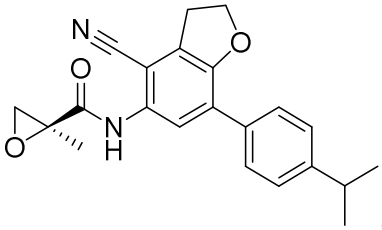
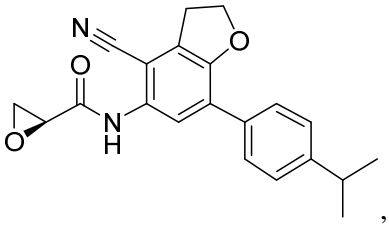
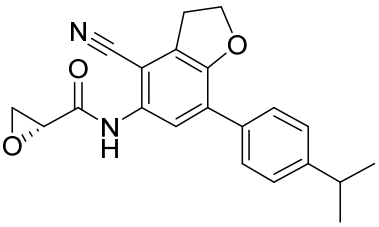
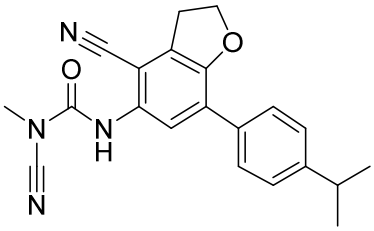
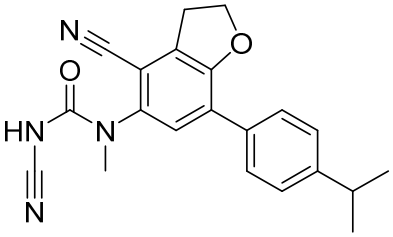
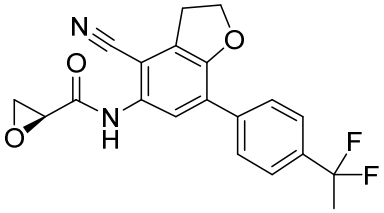
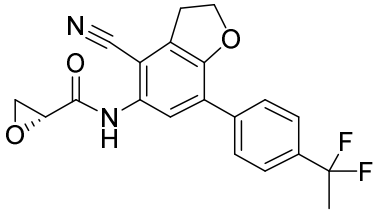
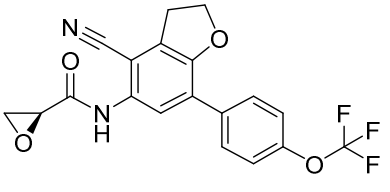
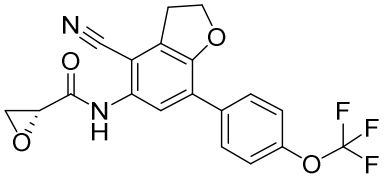
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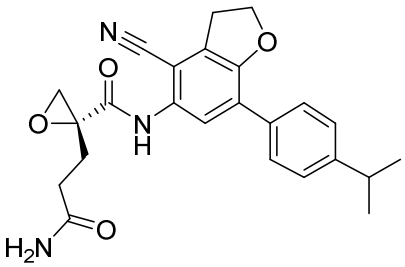
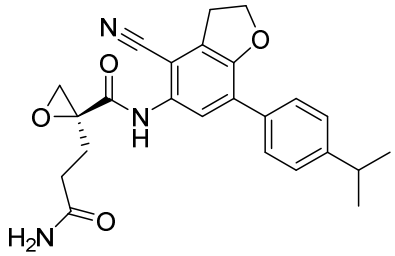
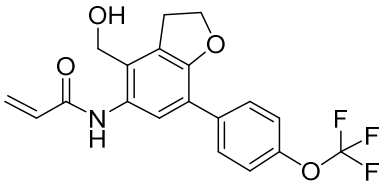
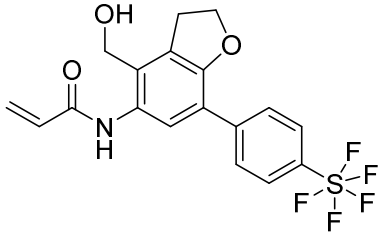
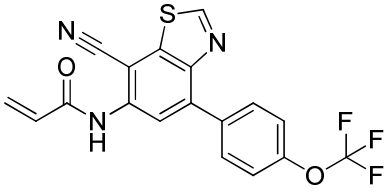


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, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0013] In one aspect, the disclosure provides a pharmaceutical composition, comprising (i) a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and (ii) a pharmaceutically acceptable carrier, diluent, or excipient. In some examples, a pharmaceutical composition comprising a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient, is provided.

[0014] In one aspect, the disclosure provides a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in medical therapy. In some examples, a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, is provided for use in medical therapy.

[0015] In some examples, a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, is provided for the treatment or prophylaxis of cancer, mesothelioma, sarcoma, or leukemia.

[0016] In one aspect, the disclosure provides use of a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of acoustic neuroma, acute leukemia, acute

lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor. In some examples, a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, is provided for the preparation of a medicament for the treatment or prophylaxis of cancer,

mesothelioma, sarcoma, or leukemia.

[0017] In one aspect, the present disclosure provides use of a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a mammal. In some examples, a method for treating cancer, mesothelioma, sarcoma, or leukemia in a mammal is provided, the method comprising, administering a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, to the mammal.

[0018] In some examples, a method for treating cancer, mesothelioma, sarcoma, or leukemia in a mammal is provided, the method comprising, administering a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, to the mammal in combination with a second therapeutic agent.

[0019] In one aspect, the present disclosure provides a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in modulating TEAD activity. In some examples, a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, is provided for modulating TEAD activity.

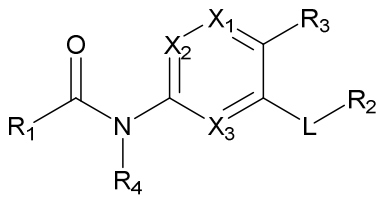
[0020] In one aspect, the present disclosure provides a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in the treatment and/or prophylaxis of a disease or condition mediated by TEAD activity. In some examples, a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, is provided for the treatment or prophylaxis of a disease or condition mediated by TEAD activity.

[0021] In one aspect, the present disclosure provides use of a compound as described herein, or a stereoisomer, automer, or pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment and/or prophylaxis of a disease or condition that is mediated by TEAD activity. In some examples, a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, is provided for use for the preparation of a medicament for the treatment or prophylaxis of a disease or condition that is mediated by TEAD activity.

[0022] In one aspect, the present disclosure provides a method for modulating TEAD activity, comprising contacting TEAD with a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof. In some examples, a method for modulating TEAD activity is provided, the method comprising contacting TEAD with a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0023] In one aspect, the present disclosure provides use of a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition mediated by TEAD activity in a mammal. In another aspect, the present disclosure provides use of a compound as described herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating TEAD activity. In some examples, a method for treating a disease or condition mediated by TEAD activity in a mammal is provided, the method comprising administering a compound as described herein, such as a compound of formula (B-1), formula (B), or formula (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, to the mammal.

[0023a] In one aspect, the present disclosure provides a process for preparing a compound of formula (C-1):



(C-1),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

X_1 is N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, C(O)NH_2, N(R^e)(R^f), C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or N(R^e)(R^f), or

the R_5 of X_1 is taken together with R_3, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl;

X_2 and X_3 are each independently N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, C(O)NH_2, N(R^e)(R^f), C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or N(R^e)(R^f);

X_3 is N or C-H,

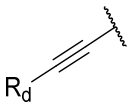
R_1 is:

(i) oxiranyl or oxetanyl, wherein the oxiranyl or oxetanyl is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -C(O)NH_2, or

(ii) N(R^e)(CN), or

(iii) 

, wherein R_a, R_b, and R_c are each independently selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, or

(iv) 

, wherein R_d is selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl;

L is absent or is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule;

R_2 is C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl of R_2 is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, $O(R^e)$, and SF_5;

R_3 is cyano, C_{1-6}alkyl, C_{1-4}alkoxy, or C_{2-4}alkenyl, wherein the C_{2-4}alkenyl is optionally substituted with $N(R^e)(R^f)$, or

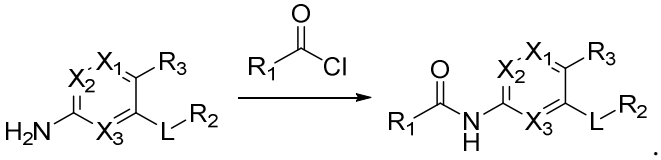
R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl, provided that X_3 is CH, or

R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl;

R_4 is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl; and

R^e and R^f are, independently of each other and independently at each occurrence, selected from the group consisting of H, cyano, hydroxyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl of R^e and R^f are each independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, oxo, cyano, halo, NO_2, and hydroxyl,

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, comprising converting an amino (NH_2) group to an amide ($NHC(O)R_1$) group using an acyl chloride compound



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[0023b] In another aspect, the present dislcosure provides a compound prepared by the process described herein.

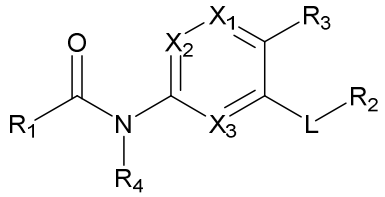
DETAILED DESCRIPTION

DEFINITIONS

[0024] Unless otherwise indicated, the following specific terms and phrases used in the description and claims are defined as follows.

WHAT IS CLAIMED IS:

1. A compound of formula (B-1):



(B-1),

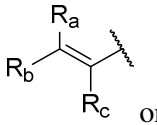
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

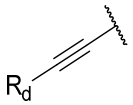
X_1 is N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, C(O)NH_2, N(R^e)(R^f), C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or N(R^e)(R^f), or

the R_5 of X_1 is taken together with R_3, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl, provided that X_3 is CH;

X_2 is N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, C(O)NH_2, N(R^e)(R^f), C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or N(R^e)(R^f);

X_3 is N or C-H,

provided that, when X_3 is N, and R_1 is 

or 

, then at least one of X_1 and X_2 is N;

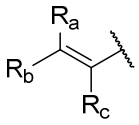
R_1 is:

(i) oxiranyl or oxetanyl, wherein the oxiranyl or oxetanyl is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -C(O)NH_2, and

L is absent or is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

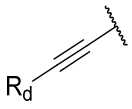
(ii) $N(R^e)(CN)$, and

L is absent or is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

(iii) 

, wherein R_a, R_b, and R_c are each independently selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, provided that at least two of R^a, R^b, and R^c are H, and

L is absent or is selected from the group consisting of *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, or

(iv) 

, wherein R_d is selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, and

L is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule;

R_2 is C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl of R_2 is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, $O(R^e)$, and SF_5,

provided that, when R_2 is C_{1-12}alkyl, wherein the C_{1-12}alkyl is independently optionally

substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$, then L is -CH=CH- or -C≡C-;

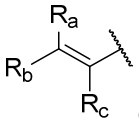
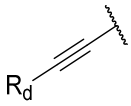
R_3 is cyano, C_{1-6}alkyl, C_{1-4}alkoxy, or C_{2-4}alkenyl, wherein the C_{2-4}alkenyl is optionally substituted with $N(R^e)(R^f)$, or

R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl, provided that X_3 is CH, or

R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl,

provided that:

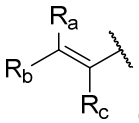
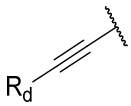
(i) when R_3 is cyano, C_{1-6}alkyl, C_{1-4}alkoxy, or C_{2-4}alkenyl, wherein the C_{2-4}alkenyl is optionally substituted with $N(R^e)(R^f)$, and

R_1 is  or , and

R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$,

then L is *-CH_2-O-**, -CH=CH-, or -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, and

(ii) when R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, provided that X_3 is CH, and

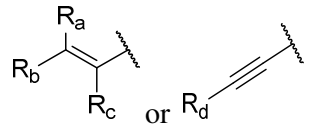
R_1 is  or , and

R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally

substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$,

then L is absent or is *-CH_2-O-**, -CH=CH-, or -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule, and

(iii) when R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl, and

R_1 is  or ,

then R_2 is 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl, wherein the 3-10 membered saturated heterocyclyl or 5-20 membered heteroaryl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$;

R_4 is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl; and

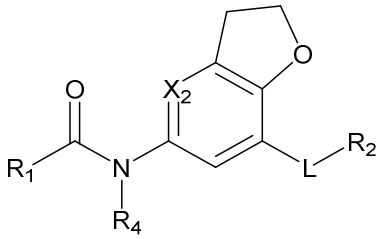
R^e and R^f are, independently of each other and independently at each occurrence, selected from the group consisting of H, cyano, hydroxyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl of R^e and R^f are each independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, oxo, cyano, halo, NO_2, and hydroxyl.

2. The compound of claim 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

X_1 is C-R_5, wherein R_5 is C_{1-6}alkyl, C_{1-6}alkoxy, or $NH(R^e)$, and

R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl, wherein the 5-membered heterocyclyl is optionally substituted with one or more C_{1-6}alkyl, provided that X_3 is CH.

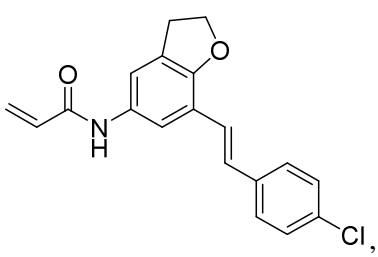
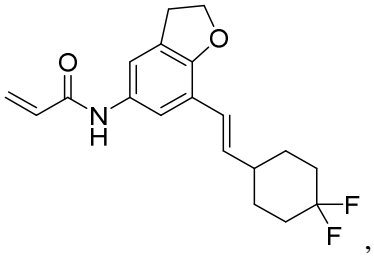
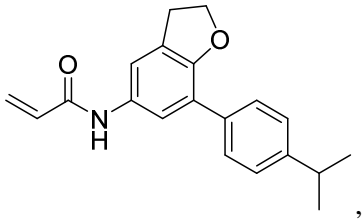
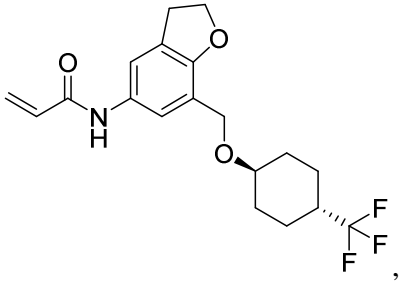
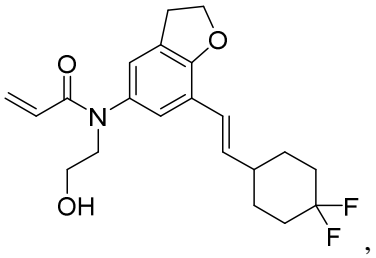
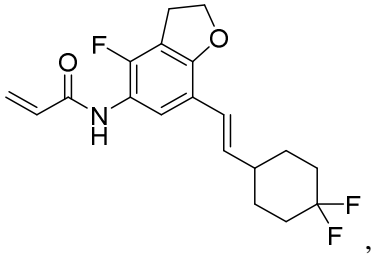
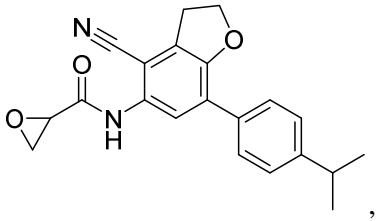
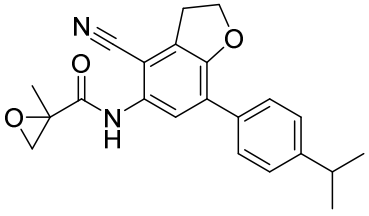
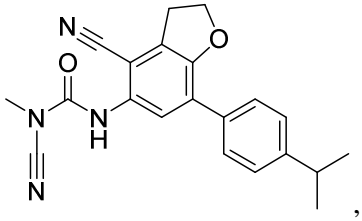
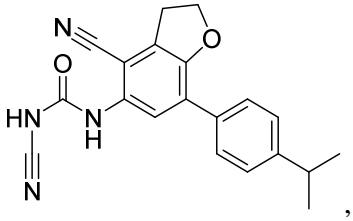
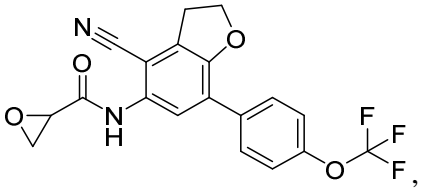
3. The compound of claim 1 or claim 2, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (IA):

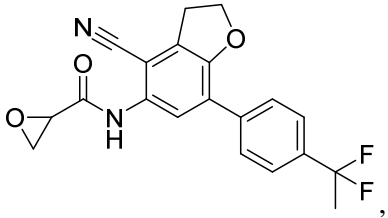
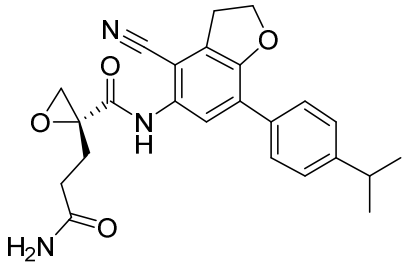
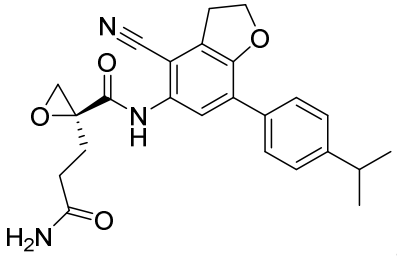
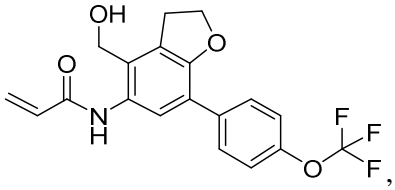
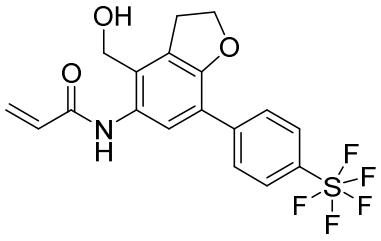


(IA),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

4. The compound of claim 3, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (IA) is a compound selected from the group consisting of:

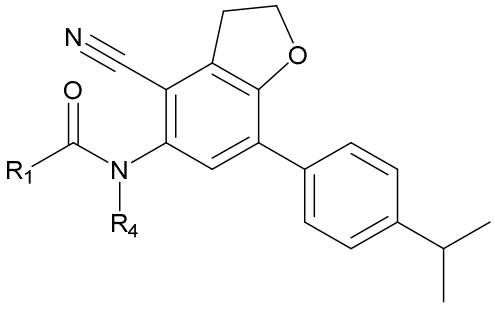

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, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

5. The compound of claim 3, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein L is absent and R_2 is C_{6-20}aryl, wherein the C_{6-20}aryl is optionally substituted with one or more C_{1-6}alkyl.

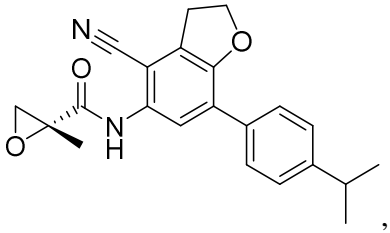
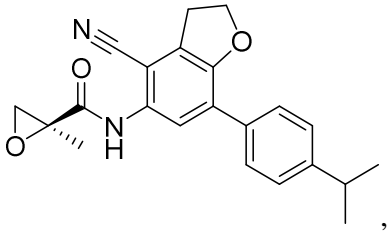
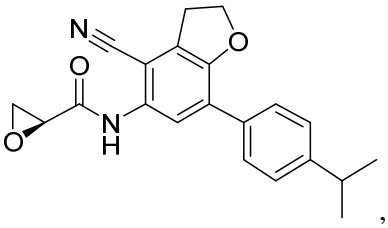
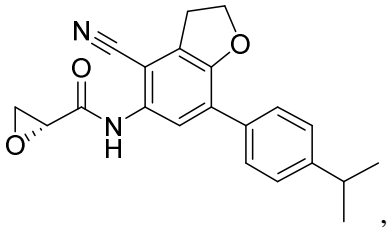
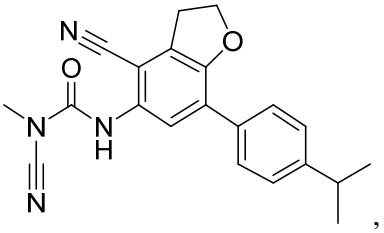
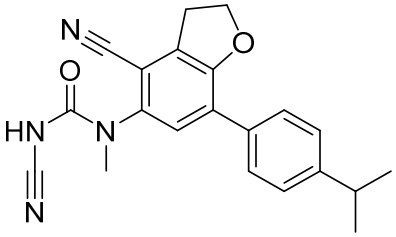
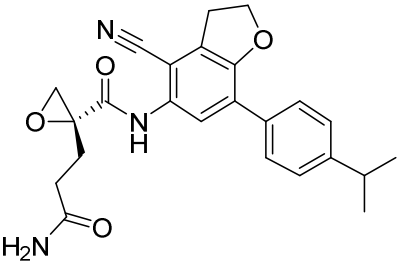
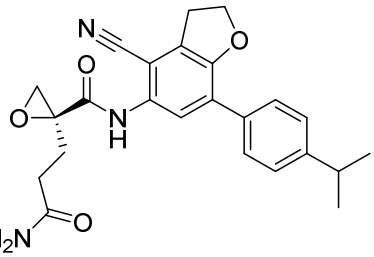
6. The compound of claim 5, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein X_2 is C-R_5, wherein R_5 is cyano.

7. The compound of claim 6, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (IA) is a compound of formula (IJ):


(IJ),

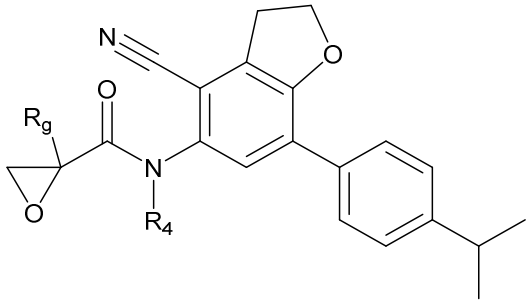
or a stereosiomer, tautomer, or pharmaceutically acceptable salt thereof.

8. The compound of claim 7, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (IJ) is selected from the group consisting of


,

,

,

,

,

,

, and

, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

9. The compound of claim 7, or a stereoisomer, tautomer, or pharamceutically acceptable salt thereof, wherein R_1 is oxiranyl or oxetanyl, wherein the oxiranyl or oxetanyl is optionally substituted with one or more $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl is optionally substituted with one or more -$C(O)NH_2$.

10. The compound of claim 9, or a stereoisomer, tautomer, or pharamceutically acceptable salt thereof, wherein the compound of formula (IJ) is a compound of formula (IK):

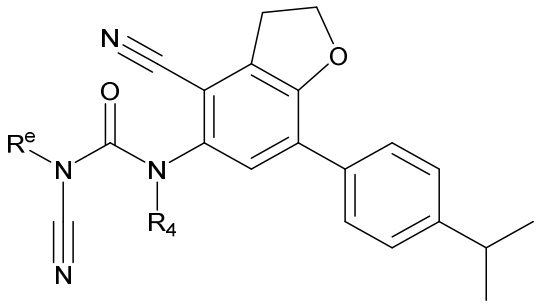


(IK),

wherein R_g is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -$C(O)NH_2$, or a stereosiomer, tautomer, or pharmaceutically acceptable salt thereof.

11. The compound of claim 7, or a stereoisomer, tautomer, or pharamceutically acceptable salt thereof, wherein R_1 is $N(R^e)(CN)$.

12. The compound of claim 11, or a stereoisomer, tautomer, or pharamceutically acceptable salt thereof, wherein the compound of formula (IJ) is a compound of formula (IL):

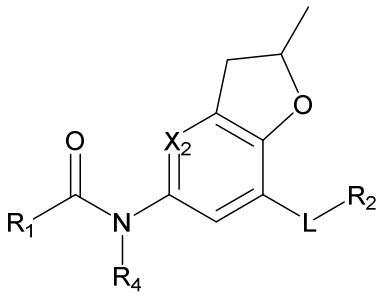


(IL),

or a stereosiomer, tautomer, or pharmaceutically acceptable salt thereof.

13. The compound of claim 12, or a stereoisomer, tautomer, or pharamceutically acceptable salt thereof, wherein R^e is H or C_{1-6}alkyl.

14. The compound of claim 2, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (IB):



(IB),

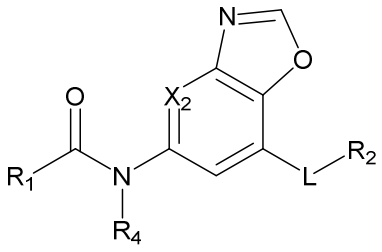
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

15. The compound of claim 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

X_1 is C-R_5, wherein R_5 is $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, or NH(R^e), and

R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heteroaryl, wherein the 5-membered heteroaryl is optionally substituted with one or more $C_{1\text{-}6}$alkyl, provided that X_3 is CH.

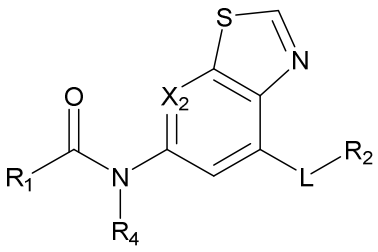
16. The compound of claim 15, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (IC):



(IC),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

17. The compound of claim 15, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (IC-1):



(IC-1),

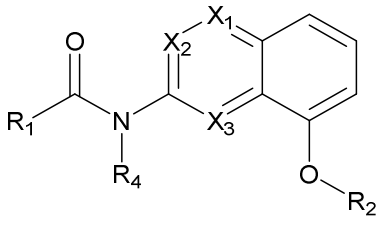
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

18. The compound of claim 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

L is *-CH_2-O-**, and

R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl.

19. The compound of claim 18, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (ID):



(ID),

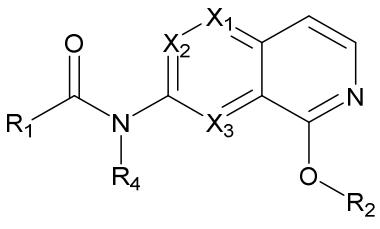
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

20. The compound of claim 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

L is *-CH_2-O-**, and

R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a 6-membered heteroaryl.

21. The compound of claim 20, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (IE):


(IE),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

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

X_3 is CH,

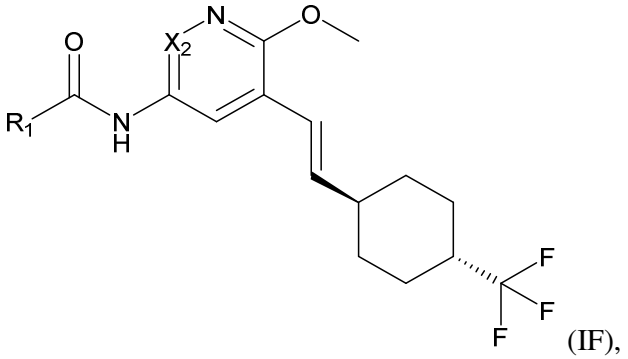
L is -CH=CH-,

R_2 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$,

R_3 is C_{1-4}alkoxy, and

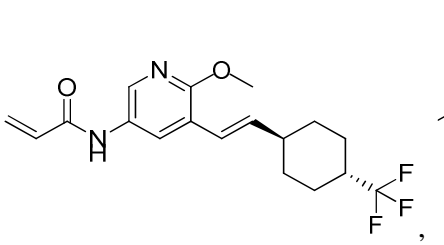
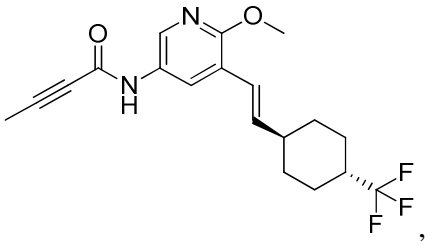
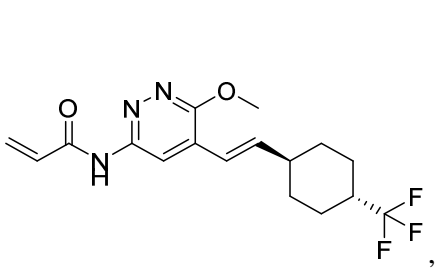
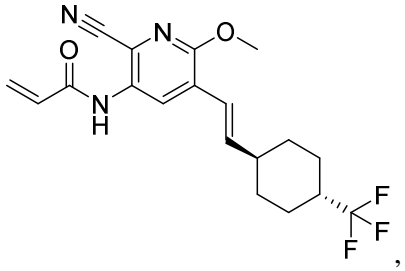
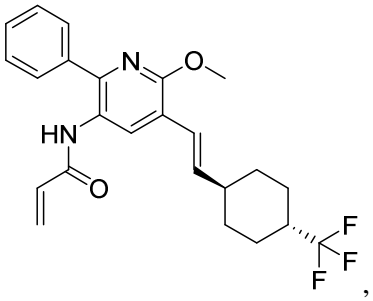
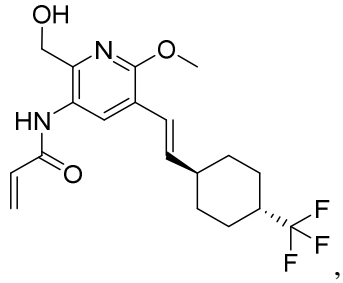
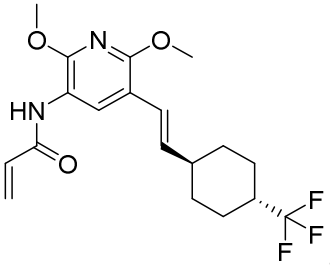
R_4 is H.

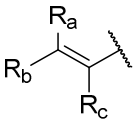
23. The compound of claim 22, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of the formula (IF):


(IF),

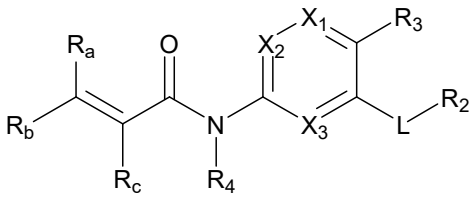
or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

24. The compound of claim 23, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (IF) is a compound selected from the group

consisting of , , , , , , and , or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

25. The compound of any one of claims 1-3, 5-7, and 14-23, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R_1 is , wherein R_a, R_b, and R_c are each independently selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, provided that at least two of R^a, R^b, and R^c are H, and L is absent or is selected from the group consisting of *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule.

26. The compound of claim 25, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (IG):

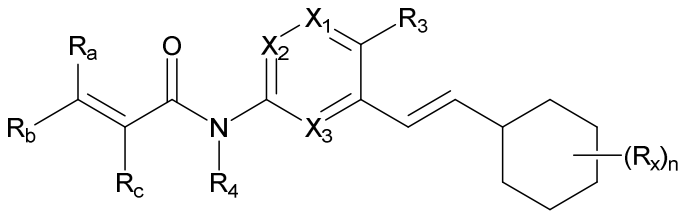


(IG),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

27. The compound of claim 26, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein L is -CH=CH- and R_2 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$.

28. The compound of claim 27, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (B-1) is a compound of formula (IH):



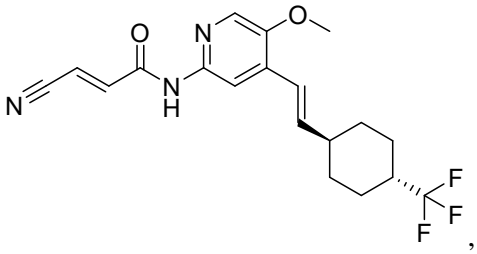
(IH),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

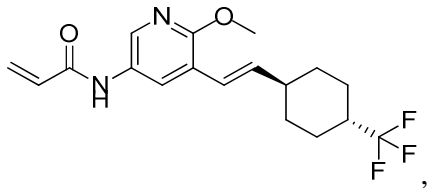
n is 0, 1, or 2, and

each R_x, if present, is independently selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$.

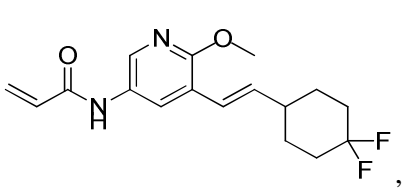
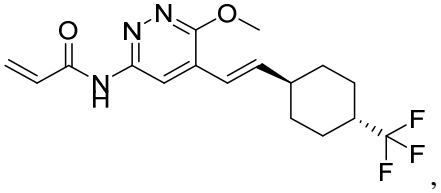
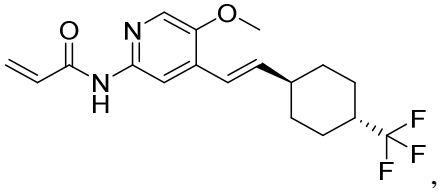
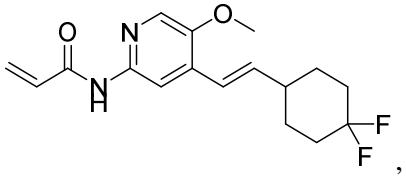
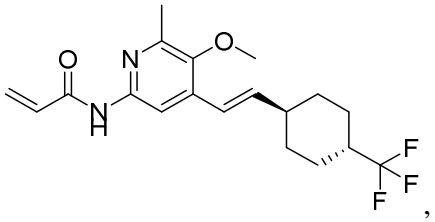
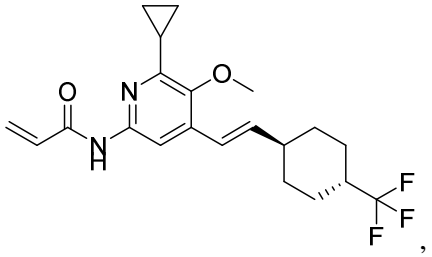
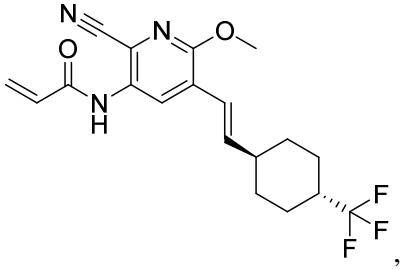
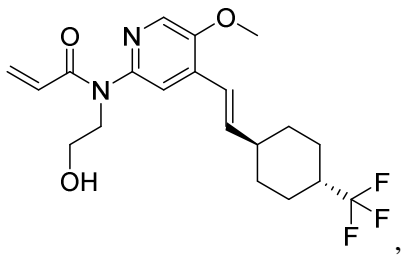
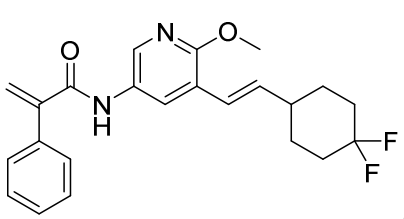
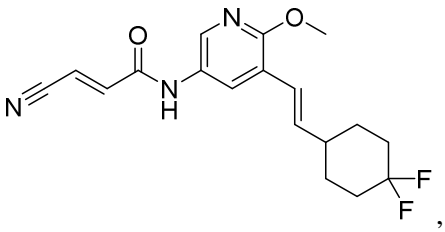
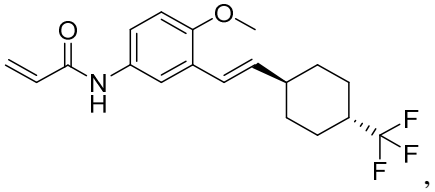
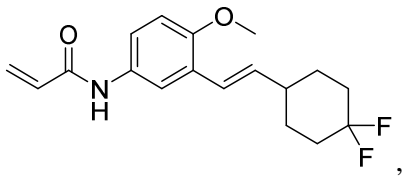
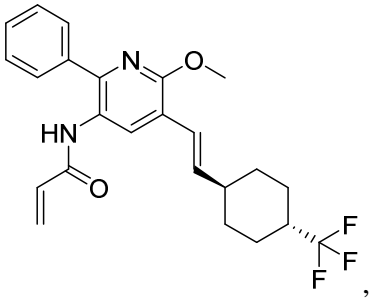
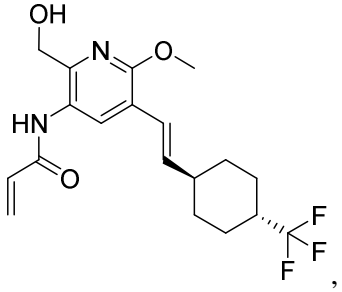
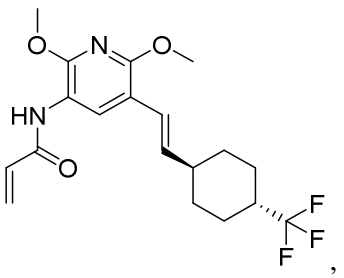
29. The compound of claim 28, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound of formula (IH) is selected from the group consisting of:

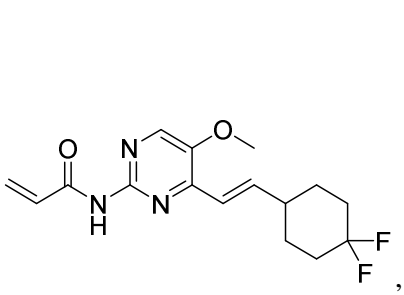
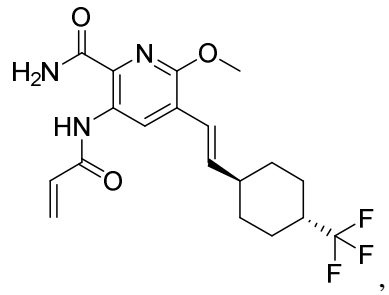
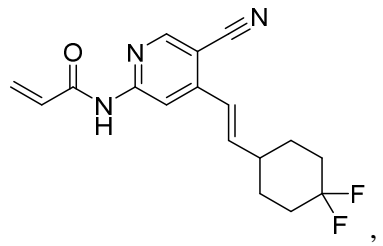
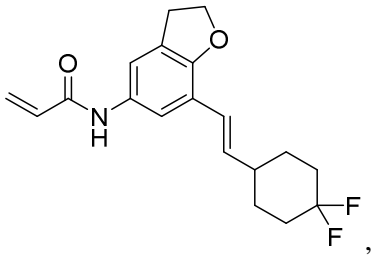
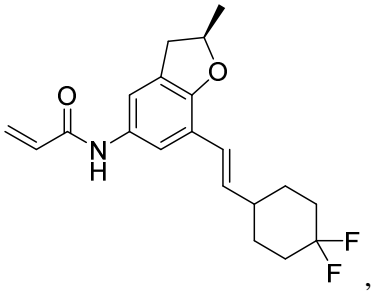
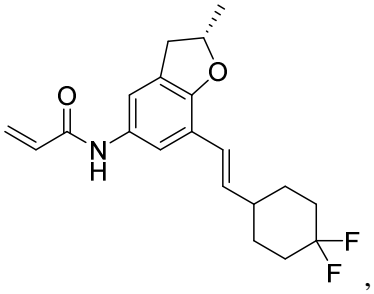
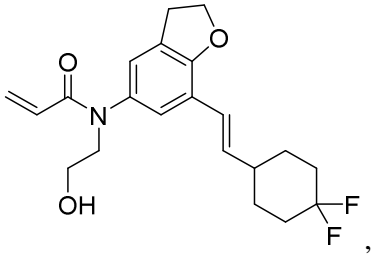
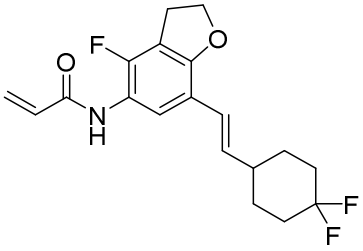
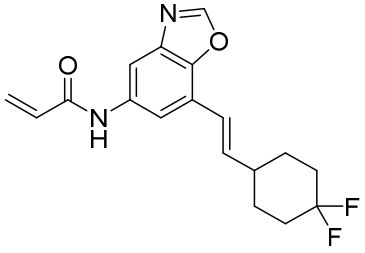


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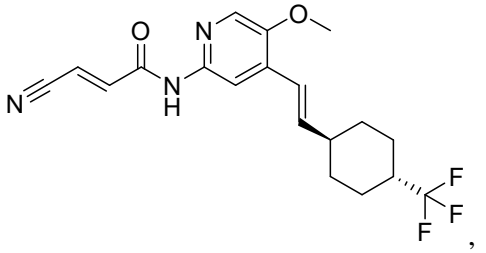
, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

30. The compound of claim 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R_2 is C_{1-12}alkyl, wherein the C_{1-12}alkyl is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, and $O(R^e)$, and L is -CH=CH- or -C≡C-.

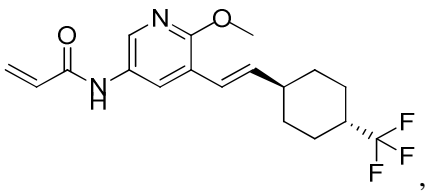
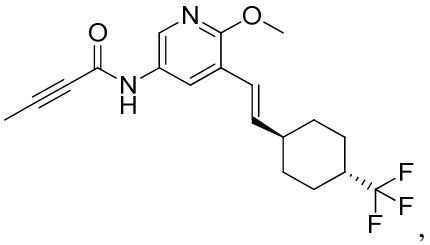
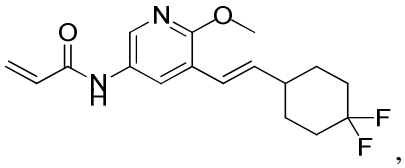
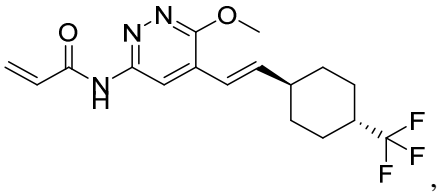
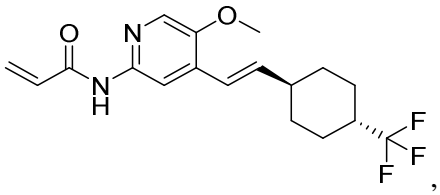
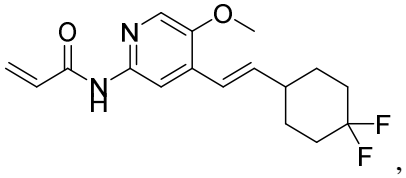
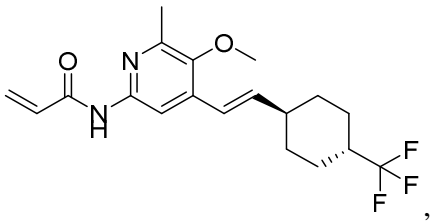
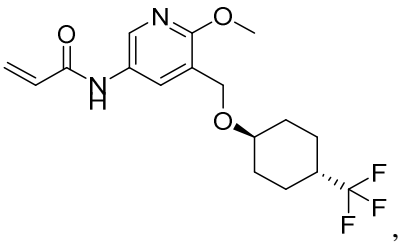
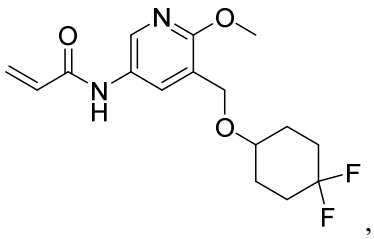
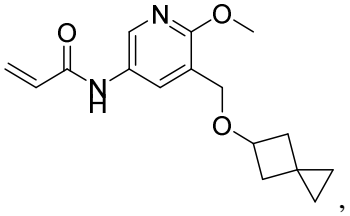
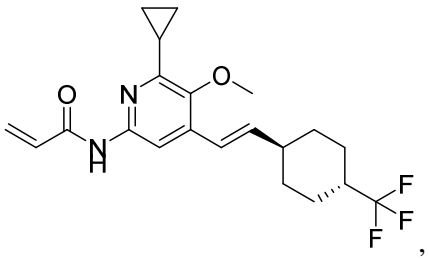
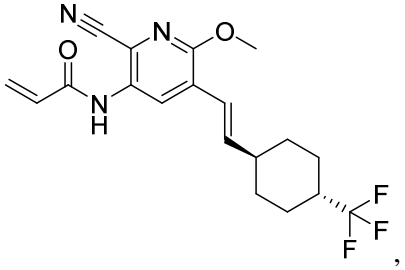
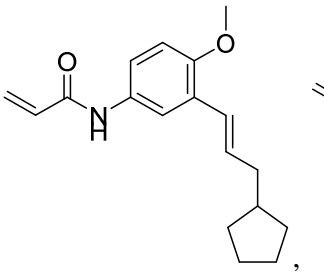
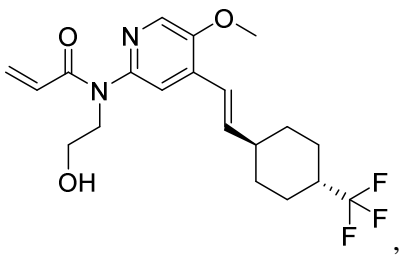
31. The compound of claim 30, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein L is -CH=CH-.

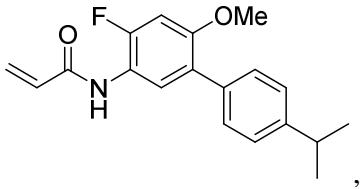
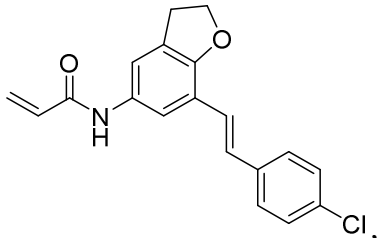
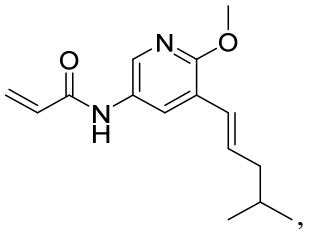
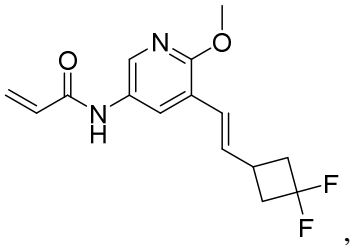
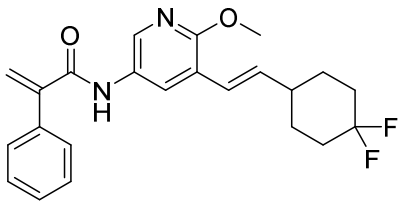
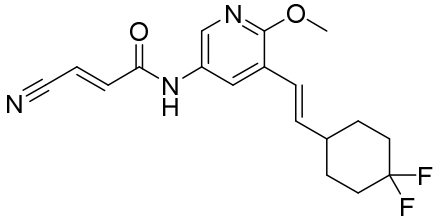
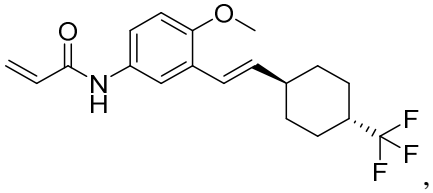
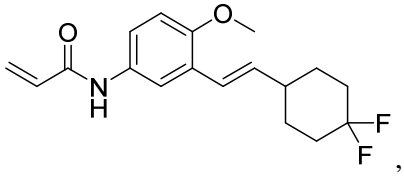
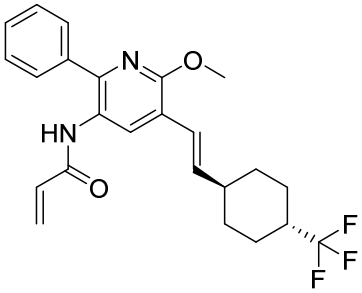
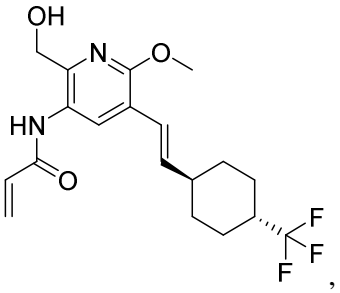
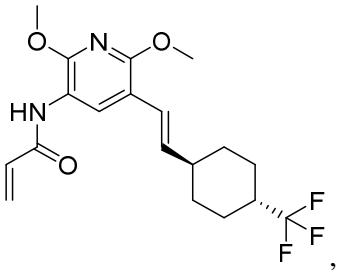
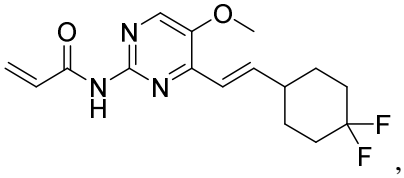
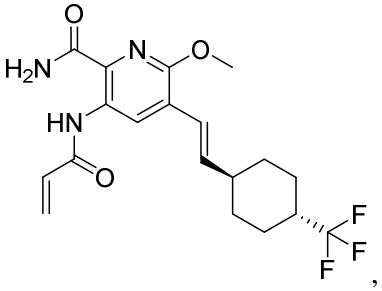
32. The compound of claim 31, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein L is -C≡C-.

33. A compound, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof,



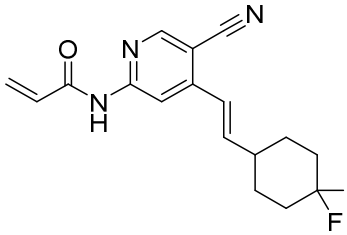
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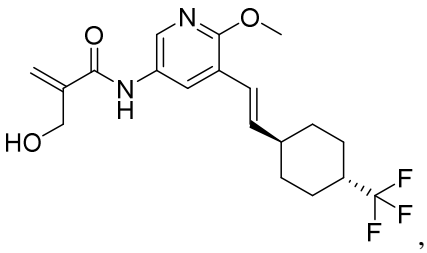
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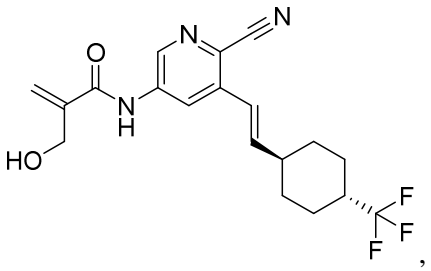
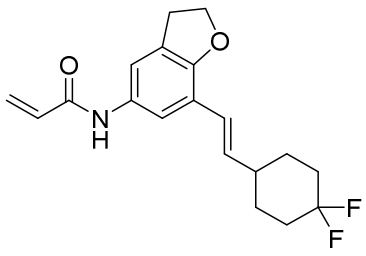
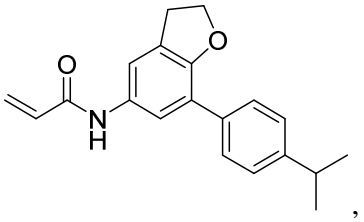
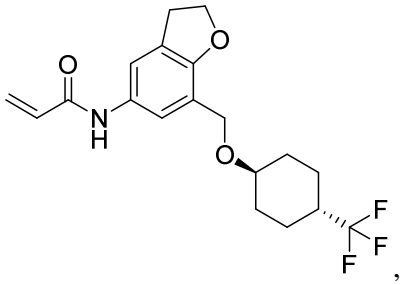
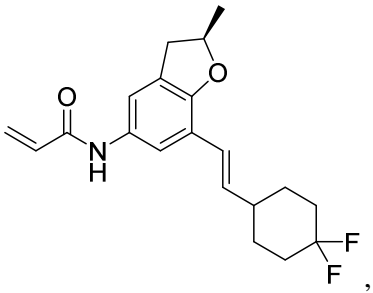
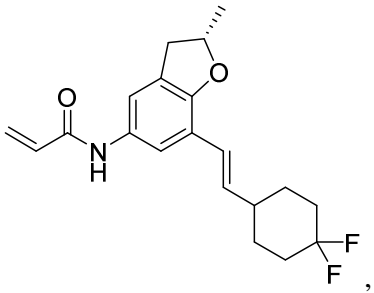
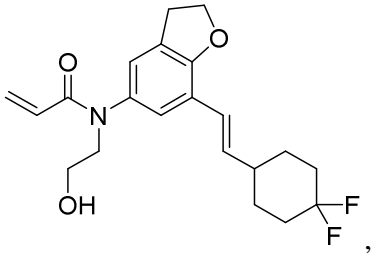
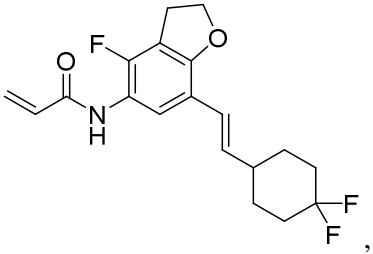
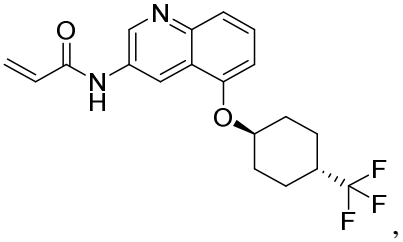
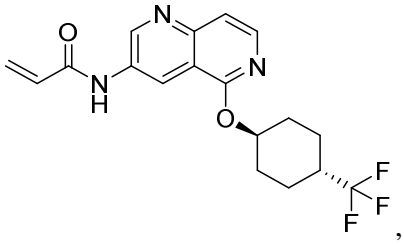
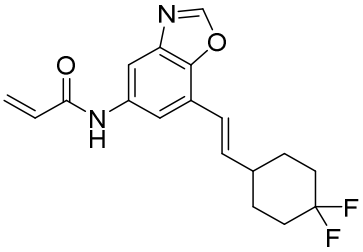
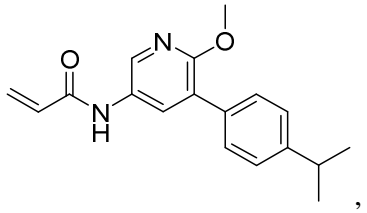
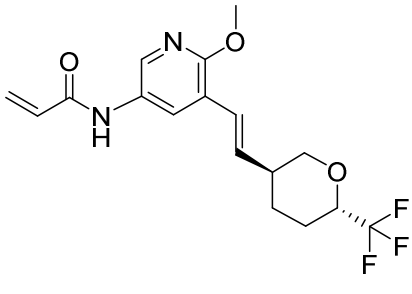
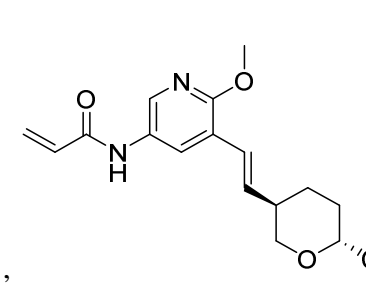
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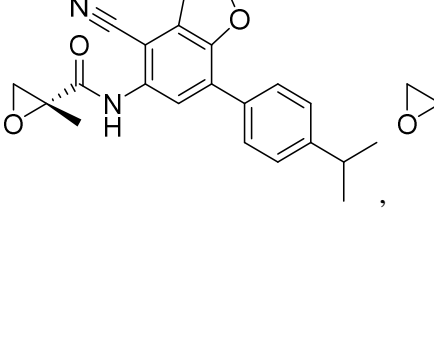
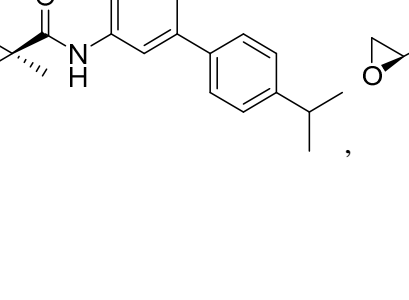
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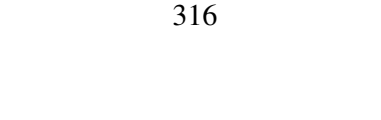
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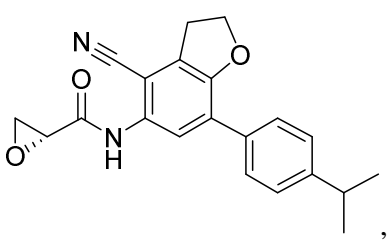
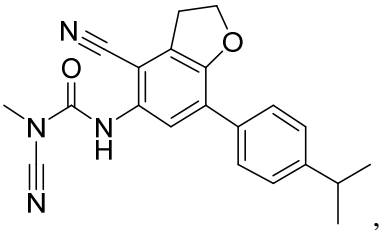
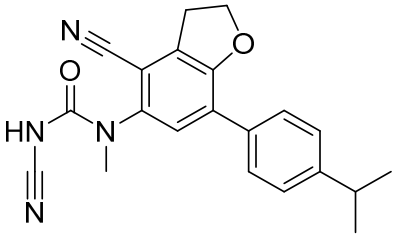
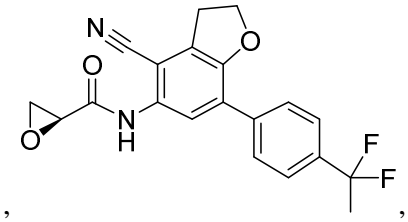
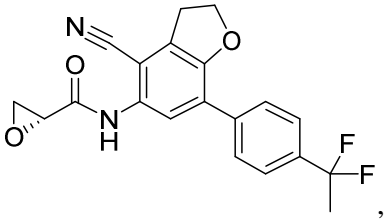
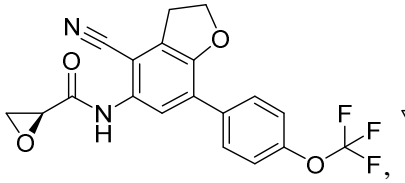
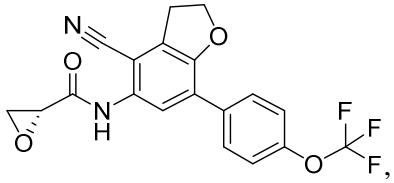
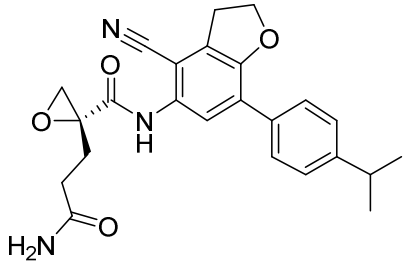
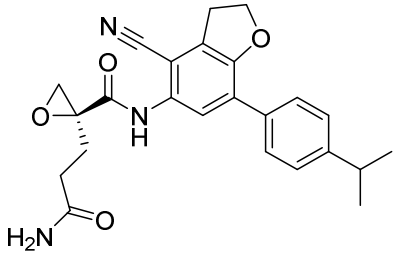
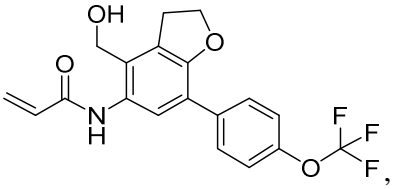
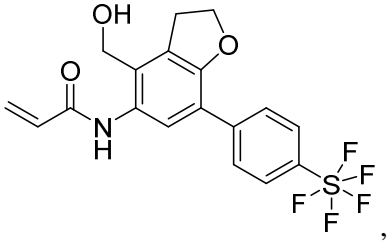
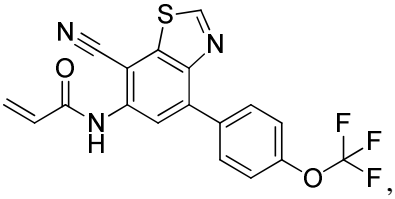
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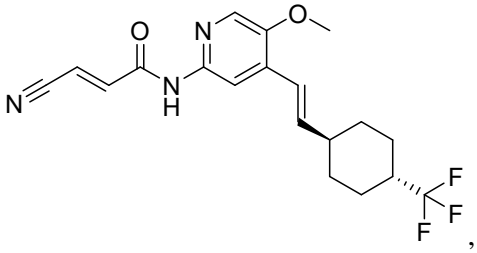
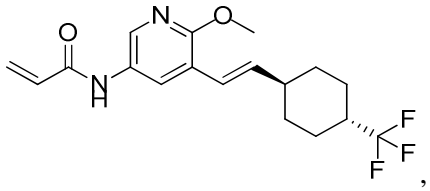
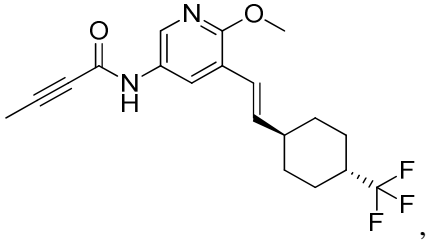
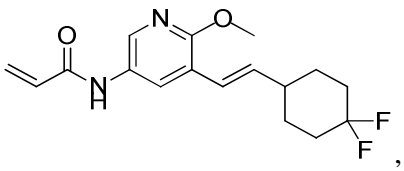
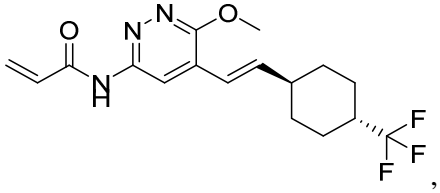
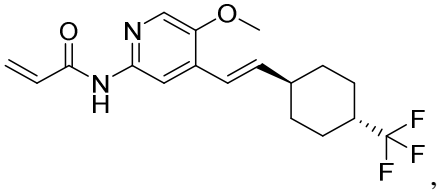
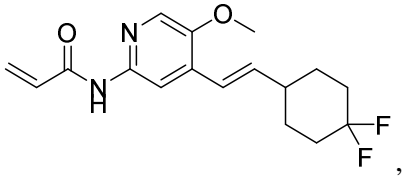
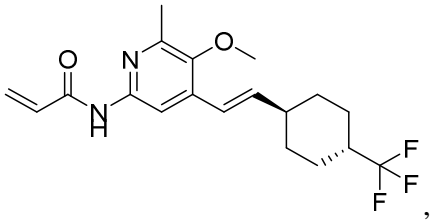
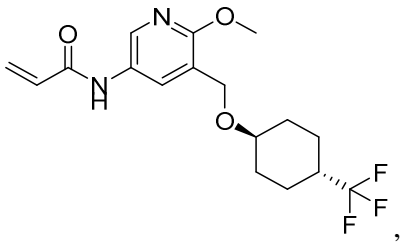
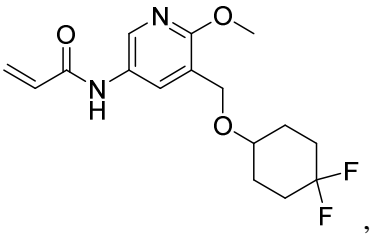
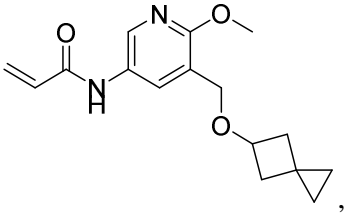
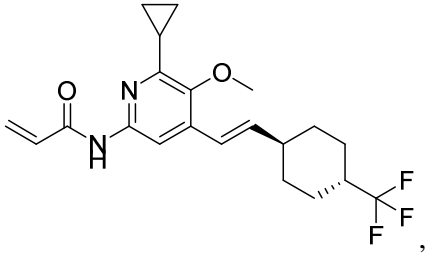
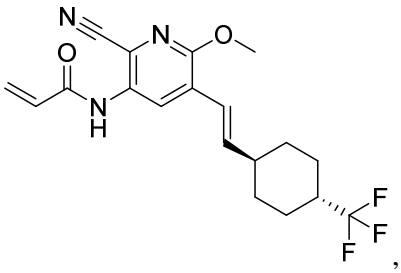
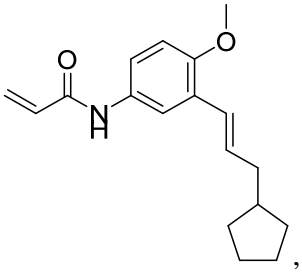
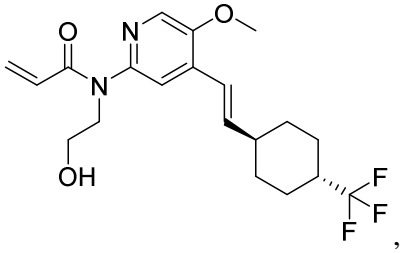
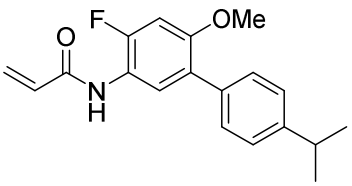
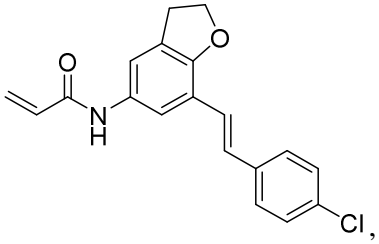
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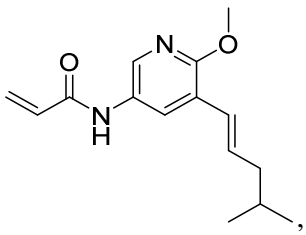
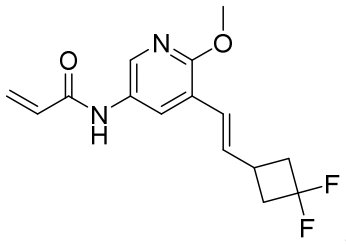
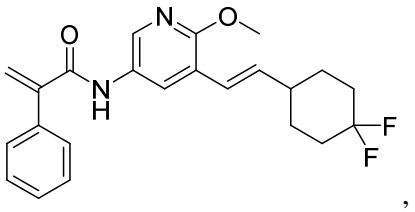
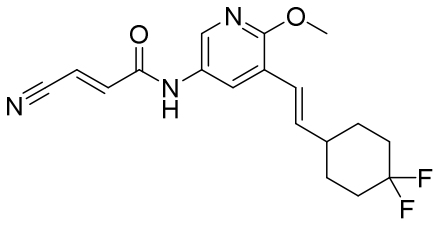
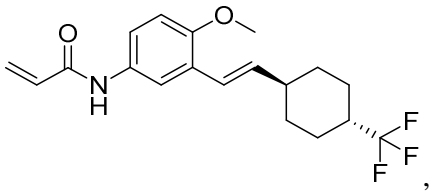
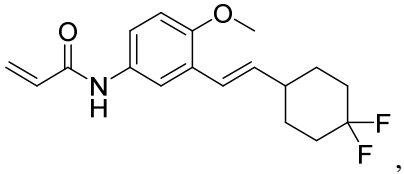
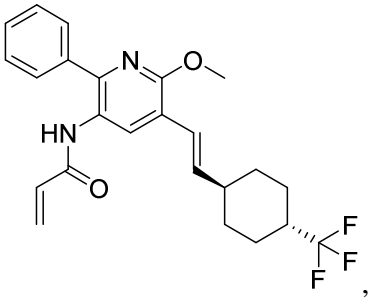
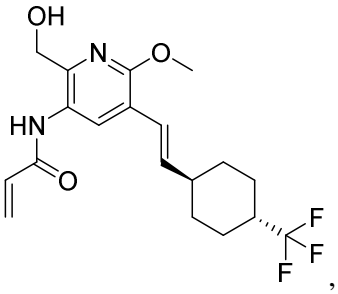
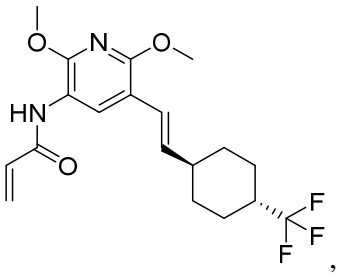
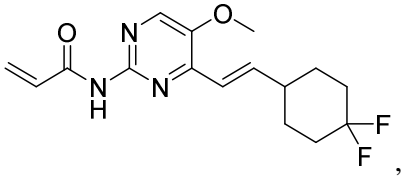
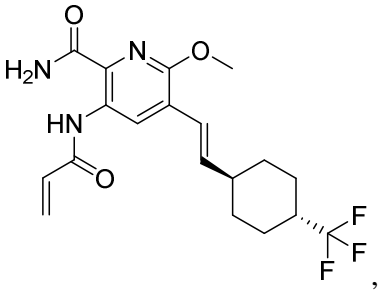
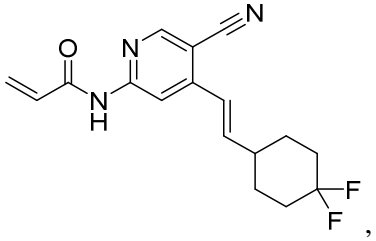
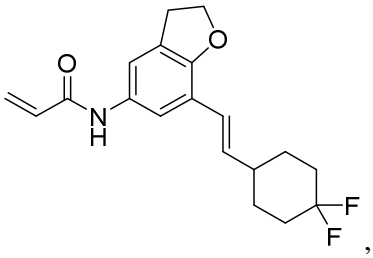
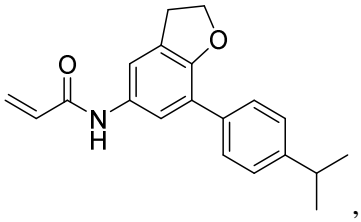
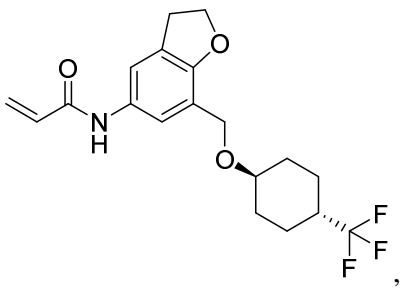
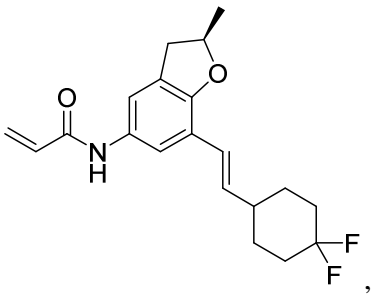
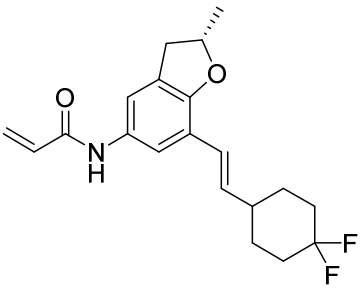
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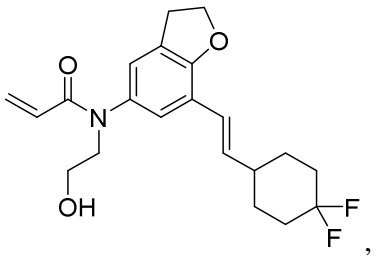
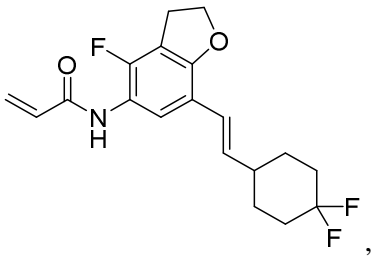
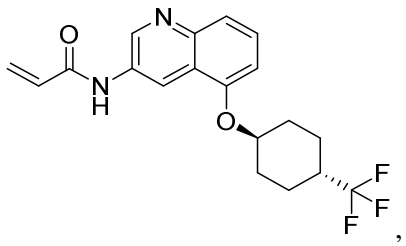
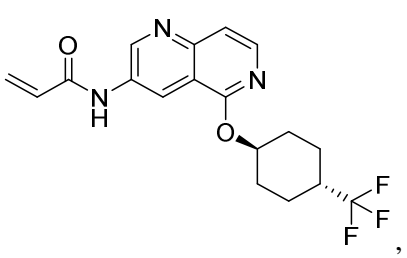
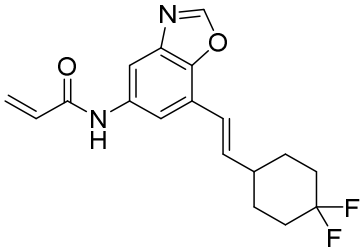
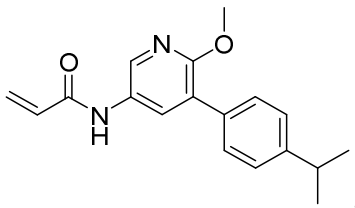
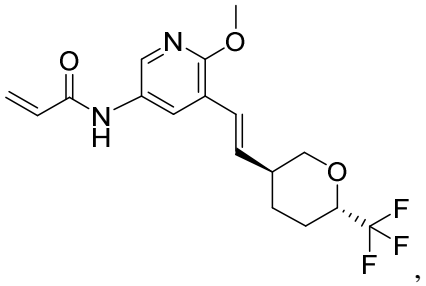
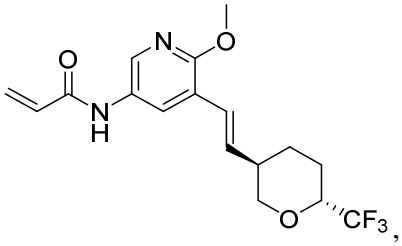
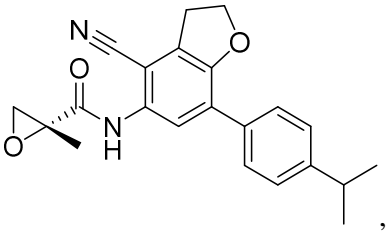
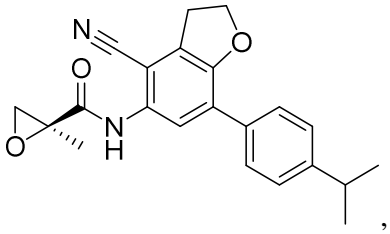
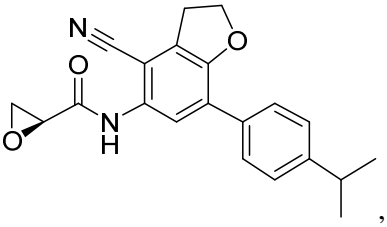
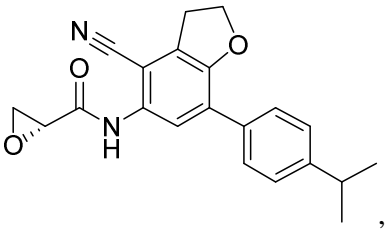
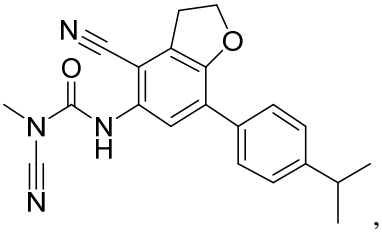
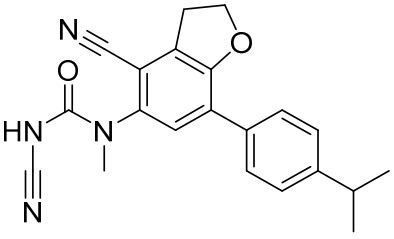
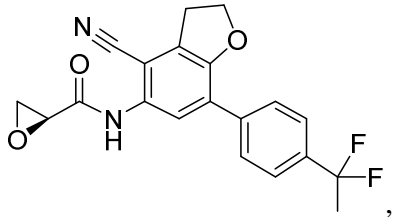
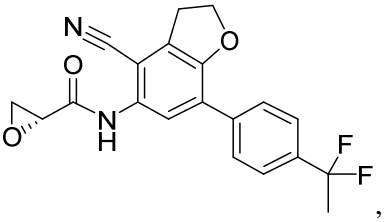
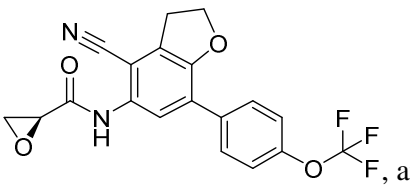
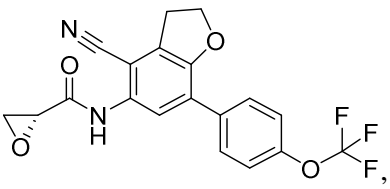
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, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

34. The compound of claim 33, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of

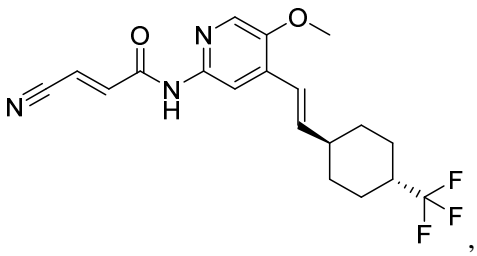
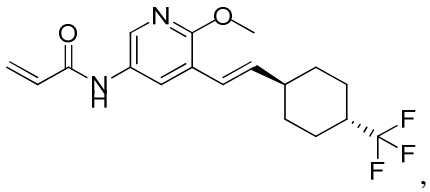
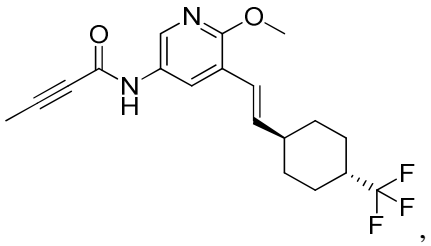
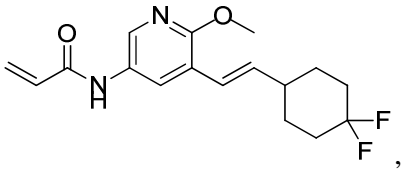
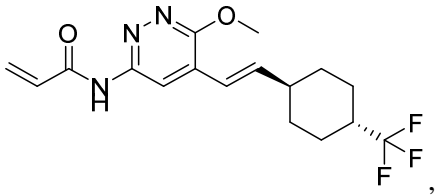
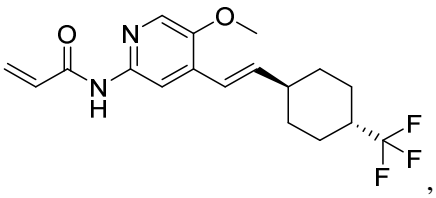
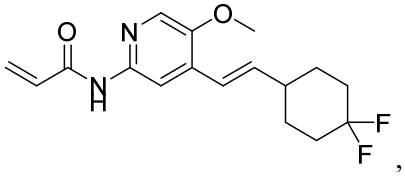
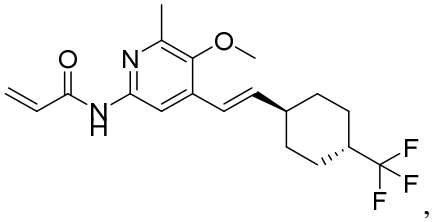
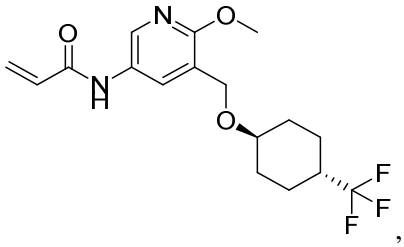
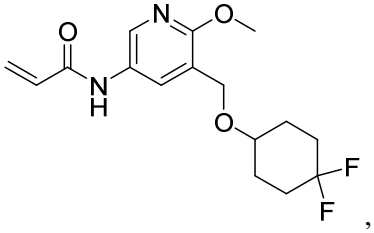
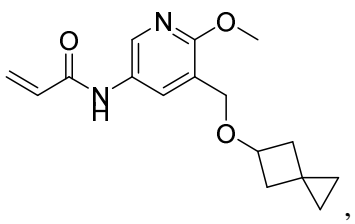
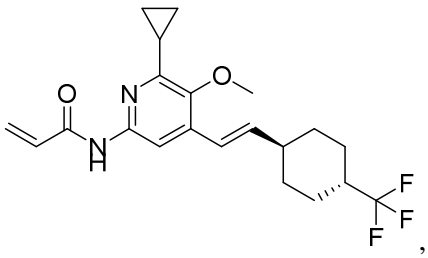
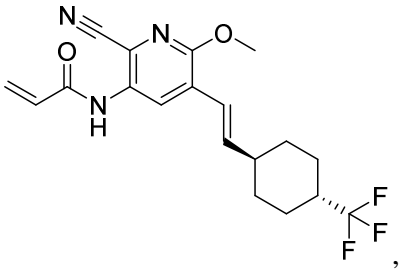
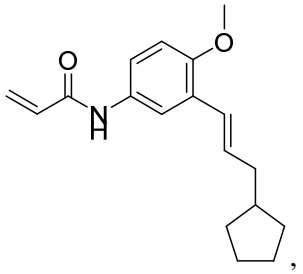

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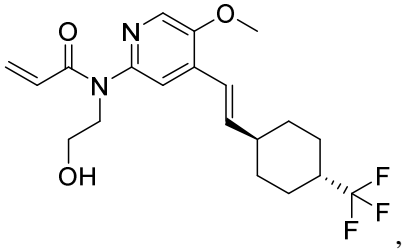
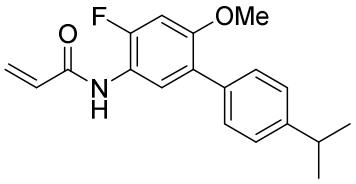
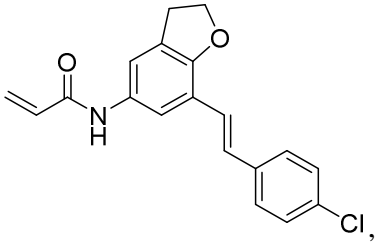
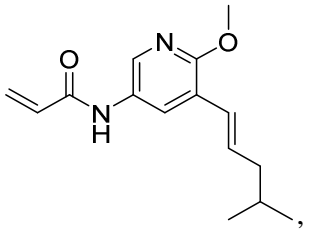
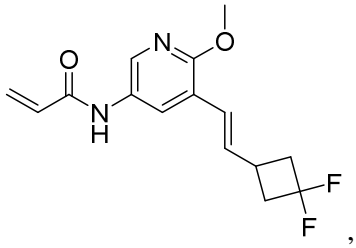
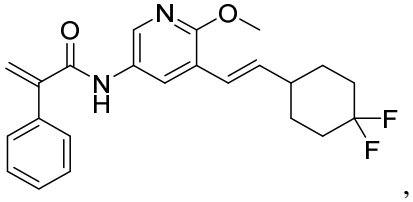
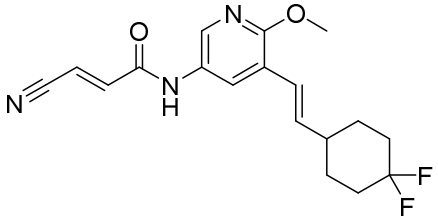
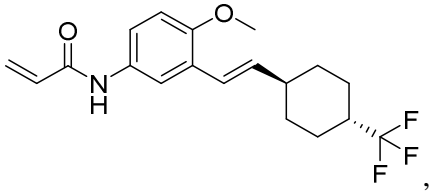
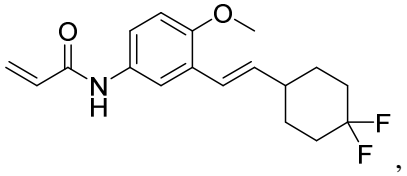
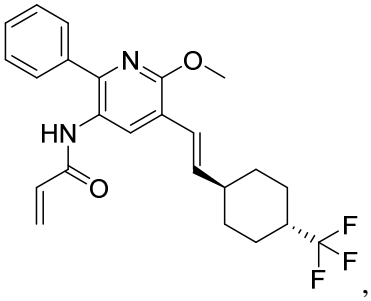
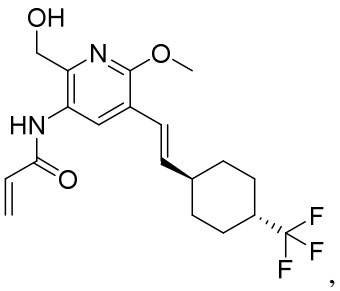
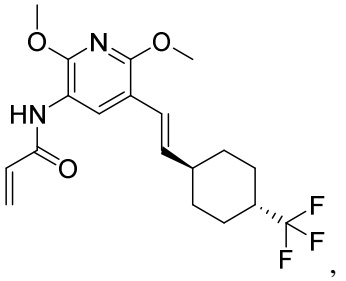
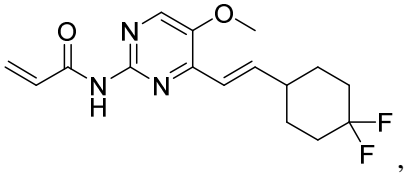
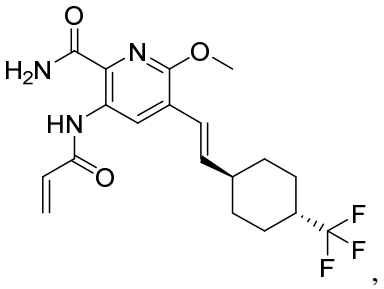
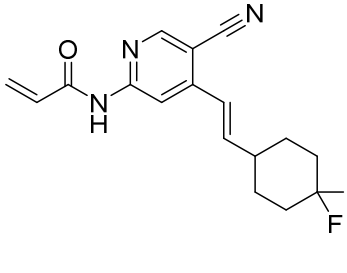
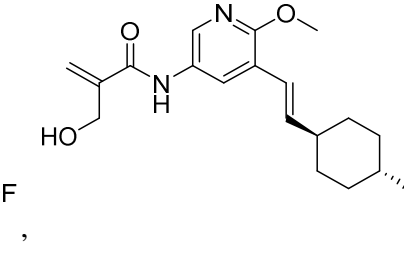

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tautomer, or pharmaceutically acceptable salt thereof.

35. The compound of claim 33, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of

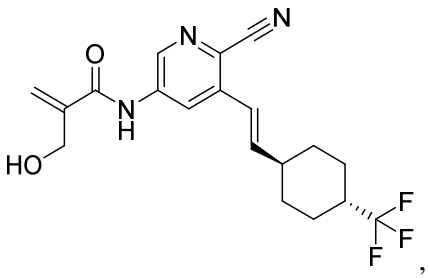
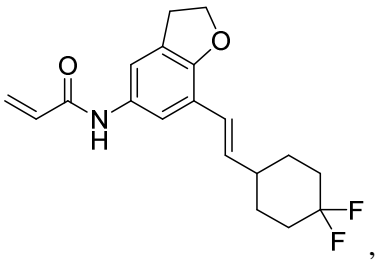
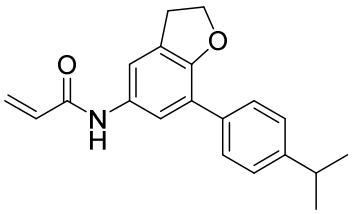
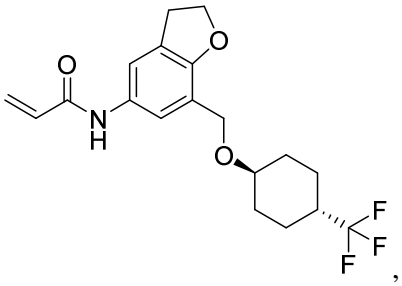
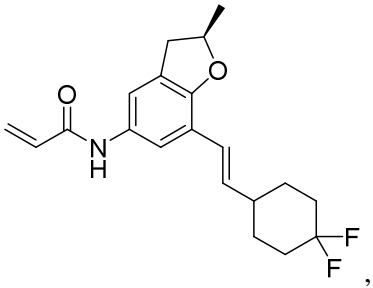
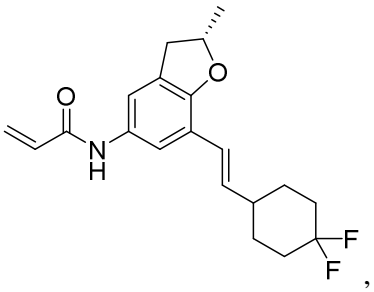
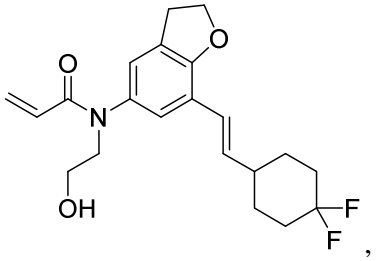
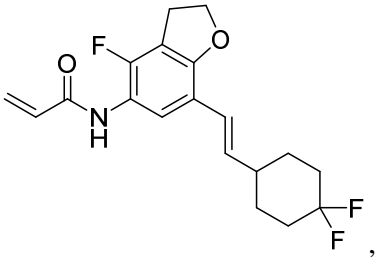
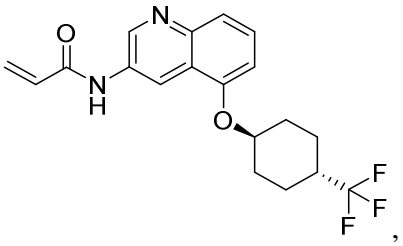
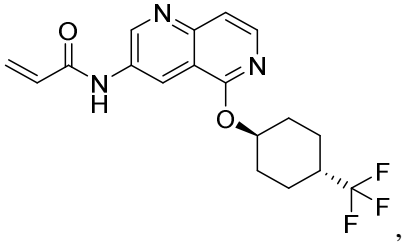
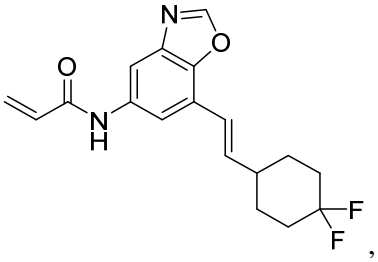
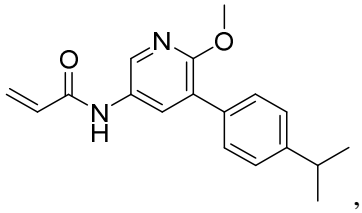
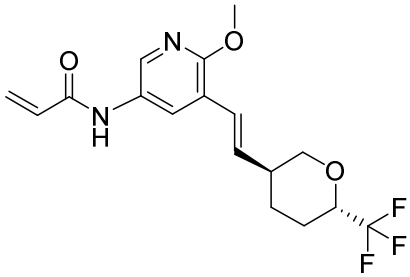
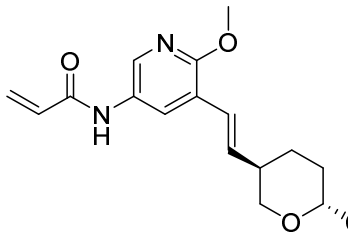
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, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition, comprising (i) a compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and (ii) a pharmaceutically acceptable carrier, diluent, or excipient.

37. A compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in medical therapy.

38. Use of a compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

39. Use of a compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a mammal.

40. A compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in modulating TEAD activity.

41. A compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in the treatment and/or prophylaxis of a disease or condition mediated by TEAD activity.

42. The compound for the use of claim 41, wherein the disease or condition is acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

43. Use of a compound as described in any one of claims 1-35, or a stereoisomer, automer, or pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment and/or prophylaxis of a disease or condition that is mediated by TEAD activity.

44. The use of claim 43, wherein the disease or condition is acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

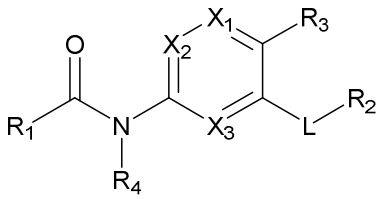
45. A method for modulating TEAD activity, comprising contacting TEAD with a compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

46. Use of a compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition mediated by TEAD activity in a mammal.

47. The use of claim 46, wherein the disease or condition is acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

48. Use of a compound as described in any one of claims 1-35, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating TEAD activity.

49. A process for preparing a compound of formula (C-1):



(C-1),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

X_1 is N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, C(O)NH_2, N(R^e)(R^f), C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or N(R^e)(R^f), or

the R_5 of X_1 is taken together with R_3, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl;

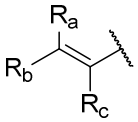
X_2 and X_3 are each independently N or C-R_5, wherein each R_5 is independently selected from the group consisting of H, cyano, halo, C(O)NH_2, N(R^e)(R^f), C_{3-10}cycloalkyl, C_{1-6}alkoxy, C_{6-20}aryl, and C_{1-6}alkyl, wherein the C_{1-6}alkyl of R_5 is optionally substituted with hydroxyl or N(R^e)(R^f);

X_3 is N or C-H,

R_1 is:

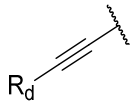
(i) oxiranyl or oxetanyl, wherein the oxiranyl or oxetanyl is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -C(O)NH_2, or

(ii) N(R^e)(CN), or

(iii) 

, wherein R_a, R_b, and R_c are each independently selected from the group

consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl, or

(iv) 

, wherein R_d is selected from the group consisting of H, halo, cyano, hydroxyl, C_{1-6}alkyl, C_{6-20}aryl, 3-10 membered heterocyclyl, and 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is further optionally substituted with hydroxyl;

L is absent or is selected from the group consisting of -O-, *-CH_2-O-**, *-O-CH_2-**, -CH=CH-, and -C≡C-, wherein ** indicates the attachment point to the R_2 moiety and * indicates the attachment point to the remainder of the molecule;

R_2 is C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-12}alkyl, C_{3-10}cycloalkyl, 3-10 membered saturated heterocyclyl, C_{6-20}aryl, C_{5-13}spirocyclyl, or 5-20 membered heteroaryl of R_2 is independently optionally substituted with one or two substituents selected from the group consisting of cyano, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, NO_2, $N(R^e)(R^f)$, $O(R^e)$, and SF_5;

R_3 is cyano, C_{1-6}alkyl, C_{1-4}alkoxy, or C_{2-4}alkenyl, wherein the C_{2-4}alkenyl is optionally substituted with $N(R^e)(R^f)$, or

R_3 is taken together with R_5 of X_1, and the atoms to which they are attached, to form a 5-membered heterocyclyl or a 5-membered heteroaryl, wherein the 5-membered heterocyclyl or 5-membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl, provided that X_3 is CH, or

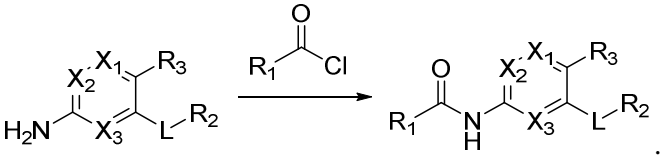
R_3 is taken together with the carbon atom of *-CH_2-O-** of L, and the atoms to which they are attached, to form a C_6aryl or a 6-membered heteroaryl;

R_4 is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with hydroxyl; and

R^e and R^f are, independently of each other and independently at each occurrence, selected from the group consisting of H, cyano, hydroxyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl,

C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{1-6}alkyl-C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-20}aryl, and 3-20 membered heteroaryl of R^e and R^f are each independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, oxo, cyano, halo, NO_2, and hydroxyl,

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, comprising converting an amino (NH_2) group to an amide ($NHC(O)R_1$) group using an acyl chloride compound



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50. A compound prepared by the process of claim 49.