BICYCLIC COMPOUNDS

CROSS-REFERENCE

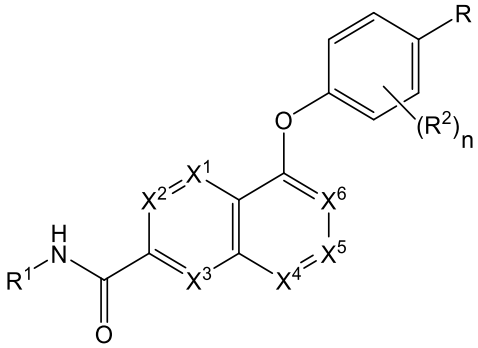
[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/834,671 filed on April 16, 2019, which incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] YAP and TAZ are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with transcriptional enhancer associate domain (TEAD) transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers. Described herein are inhibitors associated with one or more members of the Hippo pathway network, such as inhibitors of YAP/TAZ or inhibitors that modulate the interaction between YAP/TAZ and TEAD.

SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

each X^1, X^4, and X^5, is independently N or CR^X; X^6 is CR^X;

each X^2 and X^3 is independently N or CR^Y;

each R^X is independently hydrogen, halogen, nitro, $-OR^3$, $-SR^3$, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or

unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^Y is independently hydrogen, halogen, nitro, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R is halogen, nitro, -CN, $-OR^3$, $-SR^3$, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

R^1 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, or $-S(=O)_2R^4$;

each R^2 is independently halogen, nitro, $-N_3$, -CN, $-OR^3$, $-SR^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-C(=O)OR^3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^3 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or if two R^3 are on the same nitrogen atom, then two R^3 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_3-C_7 heterocycloalkyl;

R^4 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or $-NH_2$; and

n is 0, 1, 2, 3, or 4.

[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt or solvate disclosed herein, and a pharmaceutically acceptable excipient.

[0002c] In a further aspect of the present disclosure, there is provided a use of the compound or pharmaceutically acceptable salt or solvate disclosed herein, in the manufacture of a medicament for inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway.

[0002d] In another aspect of the present disclosure, there is provided a use of the compound or pharmaceutically acceptable salt or solvate disclosed herein, in the manufacture of a medicament for inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP).

[0002e] In a further aspect of the present disclosure, there is provided a use of the compound or pharmaceutically acceptable salt or solvate disclosed herein, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0002f] In another aspect of the present disclosure, there is provided a use of the compound or pharmaceutically acceptable salt or solvate disclosed herein, in the manufacture of a medicament for treating polycystic kidney disease or liver fibrosis in a subject in need thereof.

[0002g] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or the pharmaceutically acceptable salt or solvate thereof,

for use in inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway, or

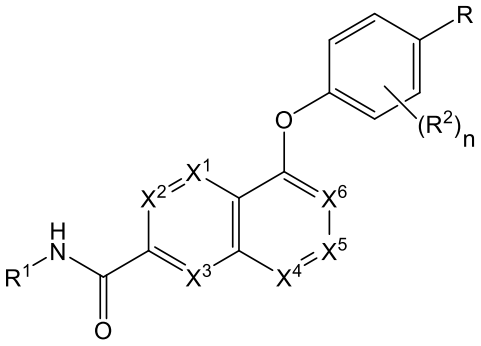
for use in inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP), or

for use in treating cancer in a subject in need thereof, or

for use in treating polycystic kidney disease or liver fibrosis in a subject in need thereof.

[0003] Provided herein are bicyclic compounds and pharmaceutical compositions comprising said compounds. In some examples, the subject compounds are useful for the treatment of cancer.

[0004] In one example, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof



Formula (I)

wherein,

each X^1, X^4, X^5,and X^6, is independently N or CR^X;

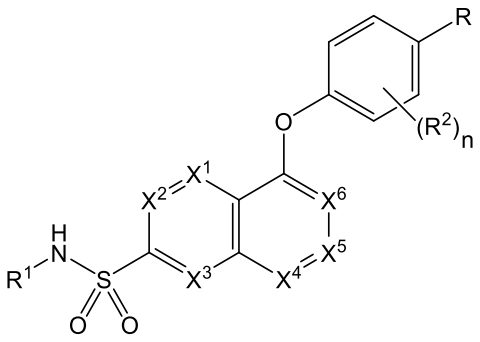
each X^2 and X^3 is independently N or CR^Y;

each R^X is independently hydrogen, halogen, nitro, $-OR^3$, $-SR^3$, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted C_1-C_6 alkyl, substituted or

R^4 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or -NH_2; and

n is 0, 1, 2, 3, or 4.

[0005] In another example, the present disclosure provides a compound of Formula (II), or a pharmaceutically acceptable salt thereof:



Formula (II)

wherein,

each X^1, X^2, X^3, X^4, X^5, and X^6 is independently N or CR^X;

each R^X is independently hydrogen, halogen, nitro, -OR^3, -SR^3, -CN, -$C(=O)R^3$, -$C(=O)N(R^3)_2$, -$C(=O)OR^3$, -$S(=O)R^3$, -$S(=O)_2R^3$, -$N(R^3)_2$, -$NR^3S(=O)_2R^3$, -$NR^3C(=O)R^3$, -$NR^3C(=O)OR^3$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R is halogen, nitro, -CN, -OR^3, -SR^3, -$C(=O)R^3$, -$C(=O)N(R^3)_2$, -$C(=O)OR^3$, -$S(=O)R^3$, -$S(=O)_2R^3$, -$N(R^3)_2$, -$NR^3S(=O)_2R^3$, -$NR^3C(=O)R^3$, -$NR^3C(=O)OR^3$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

R^1 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, or -$S(=O)_2R^4$;

each R^2 is independently halogen, nitro, -N_3, -CN, -OR^3, -SR^3, -$S(=O)_2R^3$, -$N(R^3)_2$, -$C(=O)OR^3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl,

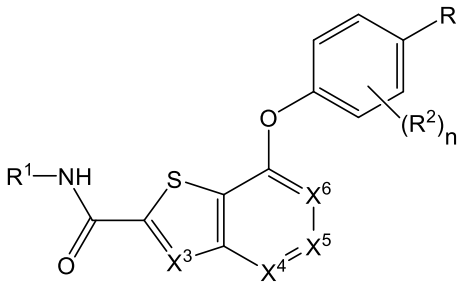
substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^3 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or if two R^3 are on the same nitrogen atom, then two R^3 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_3-C_7 heterocycloalkyl;

R^4 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or $-NH_2$; and

n is 0, 1, 2, 3, or 4.

[0006] In another example, the present disclosure provides a compound of Formula (III), or a pharmaceutically acceptable salt thereof:



Formula (III)

wherein,

each X^3, X^5, and X^6 is independently N or CR^X;

X^4 is CR^X;

each R^X is independently hydrogen, halogen, nitro, $-OR^3$, $-SR^3$, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R is halogen, nitro, -CN, $-OR^3$, $-SR^3$, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

R^1 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, or $-S(=O)_2R^4$;

each R^2 is independently halogen, nitro, $-N_3$, -CN, $-OR^3$, $-SR^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-C(=O)OR^3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^3 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or if two R^3 are on the same nitrogen atom, then two R^3 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_3-C_7 heterocycloalkyl;

R^4 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or $-NH_2$; and

n is 0, 1, 2, 3, or 4.

[0007] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0008] In another example, the present disclosure provides a compound or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1, or a pharmaceutically acceptable salt thereof.

[0009] In some examples, the compounds disclosed herein exhibits an IC_{50} of no more than 10 μM.

[0010] In some examples, the compounds disclosed herein exhibits an IC_{50} of no more than 3 μM.

[0011] In another example, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound disclosed herein or a pharmaceutically acceptable salt thereof.

[0012] In another example, the present disclosure provides a method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof.

INCORPORATION BY REFERENCE

[0013] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0015] **FIG. 1** illustrates a schematic representation of the Hippo signaling network. Hippo pathway components shaded in dark gray indicate components that inhibit YAP/TAZ activity. Hippo pathway components shaded in light gray indicate components that promote YAP/TAZ activity. Pointed and blunt arrowheads indicate activating and inhibitory interactions, respectively. Abbreviations: α-CAT (α-Catenin), AJUB (Ajuba), AMOT (Angiomotin), β-TRCP (β-transducing repeat containing protein), CK1 (Casein Kinase 1), CRB (Crumbs), E-CAD (E-cadherin), EX (Expanded), GPCR (G-protein coupled receptor), HIPK (Homeodomain interacting protein kinase), KIBRA (Kidney brain), LATS (Large tumor suppressor), LGL (Lethal giant larvae), MASK (Multiple ankyrin single KH), MER (Merlin), MOB (Mps one binder), MST (Mammalian sterile 20 like), PALS (Protein Associated with Lin-7), PATJ (Pals1-associated tight junction protein), PP2A (Protein phosphatase 2A), PTPN14 (Protein tyrosine phosphatase non-receptor type 14), RASSF (Ras associated factor), SAV (Salvador), SCRIB (Scribble), SIK (Salt inducible kinase), TAO (Thousand and one amino acid protein), TAZ (transcriptional coactivator with PDZ-binding motif), TEAD (TEA domain protein), VGL4 (Vestigial-like 4), WBP2 (WW domain binding protein 2), YAP (Yes associated protein), ZO (Zonula occludens), ZYX (Zyxin).

[0016] **FIG. 2** illustrates a schematic representation of the Hippo signaling pathway regulated by G alpha proteins.

DETAILED DESCRIPTION OF THE DISCLOSURE

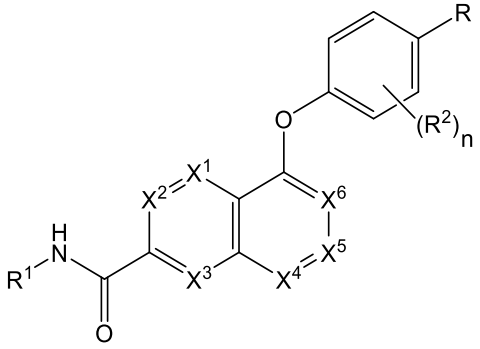
Certain Terminology

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed

CLAIMS

WHAT IS CLAIMED IS:

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



Formula (I)

wherein,

each X^1, X^4, and X^5, is independently N or CR^X; X^6 is CR^X;

each X^2 and X^3 is independently N or CR^Y;

each R^X is independently hydrogen, halogen, nitro, $-OR^3$, $-SR^3$, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^Y is independently hydrogen, halogen, nitro, -CN, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R is halogen, nitro, -CN, $-OR^3$, $-SR^3$, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

R^1 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl,

substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, or -$S(=O)_2R^4$;

each R^2 is independently halogen, nitro, -N_3, -CN, -OR^3, -SR^3, -$S(=O)_2R^3$, -$N(R^3)_2$, -$C(=O)OR^3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^3 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or if two R^3 are on the same nitrogen atom, then two R^3 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_3-C_7 heterocycloalkyl;

R^4 is substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or -NH_2; and

n is 0, 1, 2, 3, or 4.

2. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein: X^1 is CR^X; and each X^2 and X^3 is CR^Y.

3. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1 or 2, wherein:

each X^4, X^5, and X^6 is CR^X.

4. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-3, wherein:

each R^X is independently hydrogen, halogen, -OR^3, -SR^3, -$S(=O)R^3$, -$S(=O)_2R^3$, -$N(R^3)_2$, -$NR^3S(=O)_2R^3$, -$NR^3C(=O)R^3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_2-C_4alkynyl; and

each R^3 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl; or if two R^3 are on the same nitrogen atom, then two R^3 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_3-C_7 heterocycloalkyl.

5. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-3, wherein:

each R^X is independently hydrogen, F, Cl, Br, $-CH_3$, -OH, $-OCH_3$, or $-OCF_3$.

6. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-3, wherein:

each R^X is hydrogen.

7. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-6, wherein:

each R^Y is independently hydrogen, halogen, $-S(=O)R^3$, $-S(=O)_2R^3$, $-N(R^3)_2$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_2-C_4alkynyl; and

each R^3 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl; or if two R^3 are on the same nitrogen atom, then two R^3 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_3-C_7 heterocycloalkyl.

8. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-6, wherein:

each R^Y is independently hydrogen, F, Cl, or $-CH_3$.

9. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-6, wherein:

each R^Y is hydrogen.

10. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-9, wherein:

R^1 is substituted or unsubstituted C_1-C_6alkyl.

11. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-10, wherein:

R^1 is C_1-C_6alkyl substituted with $–OR^3$; and R^3 is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl.

12. The compound or pharmaceutically acceptable salt or solvate thereof of claim 11, wherein:

R^1 is C_1-C_6alkyl substituted with –OH.

13. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-10, wherein:

R^1 is C_1-C_6alkyl substituted with 6-membered heteroaryl ring selected from substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyridazinyl, and substituted or unsubstituted triazinyl.

14. The compound or pharmaceutically acceptable salt or solvate thereof of claim 13, wherein:
R^1 is C_1-C_6alkyl substituted with pyridinyl.

15. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-10, wherein:
R^1 is C_1-C_6alkyl substituted with 1, 2, or 3 substituents each independently selected from -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, and pyridinyl.

16. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-15, wherein:
R is halogen, nitro, -CN, $-OR^3$, $-C(=O)R^3$, $-C(=O)N(R^3)_2$, $-C(=O)OR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NR^3S(=O)_2R^3$, $-NR^3C(=O)R^3$, $-NR^3C(=O)OR^3$, or substituted or unsubstituted C_1-C_6fluoroalkyl; and
each R^3 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted C_2-C_{10}heterocycloalkyl; or if two R^3 are on the same nitrogen atom, then two R^3 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_3-C_7 heterocycloalkyl.

17. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-15, wherein:
R is F, Cl, -CN, $-OCF_3$, $-CHF_2$, or $-CF_3$.

18. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-15, wherein:
R is F, Cl, or $-CF_3$.

19. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-15, wherein:
R is $-CF_3$.

20. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-19, wherein:
each R^2 is independently F, Cl, $-OCF_3$, or $-CF_3$.

21. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-19, wherein:

each R^2 is independently F or Cl.

22. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-21, wherein: n is 0.

23. The compound or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-21, wherein: n is 1 or 2.

24. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein:

each X^4, X^5, and X^6 is CR^X;

or X^4 is N; and each X^5 and X^6 is CR^X;

X^2 and X^3 is CR^Y;

each R^X is independently hydrogen, F, Cl, Br, $-CH_3$, -OH, $-OCH_3$, or $-OCF_3$;

each R^Y is hydrogen.

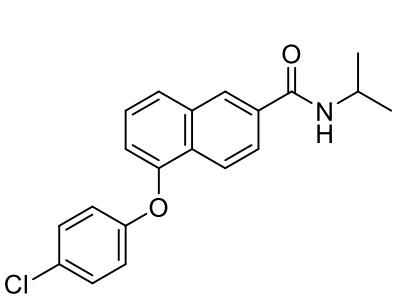
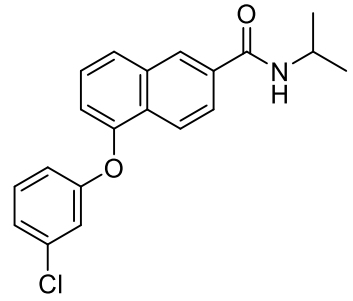
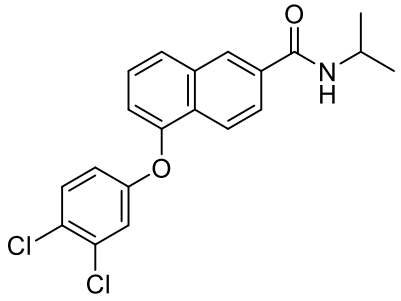
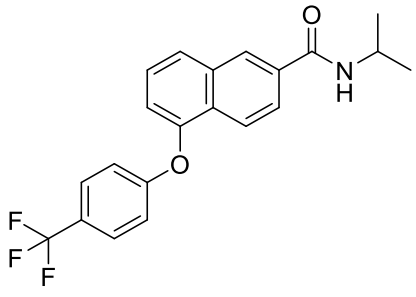
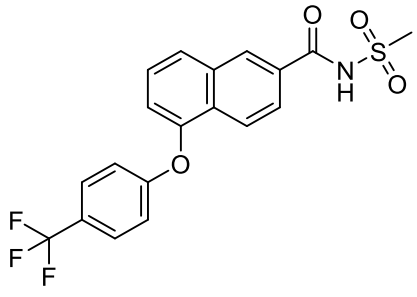
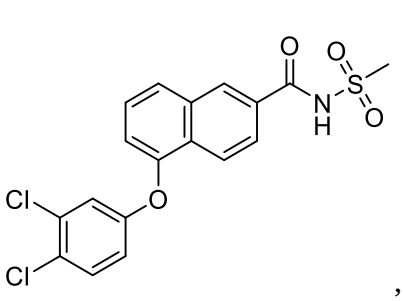
25. The compound or pharmaceutically acceptable salt or solvate thereof of claim 24, wherein:

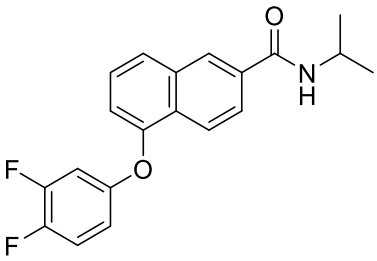
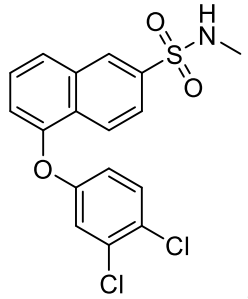
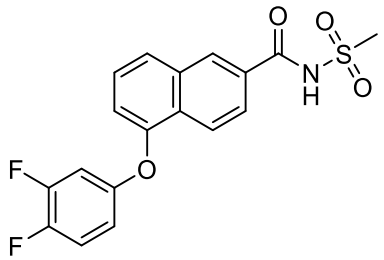
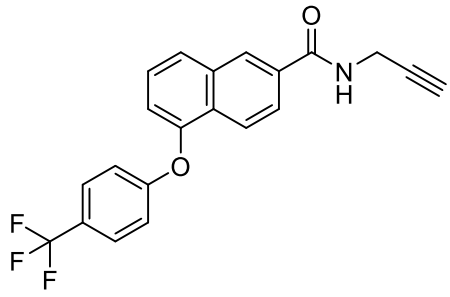
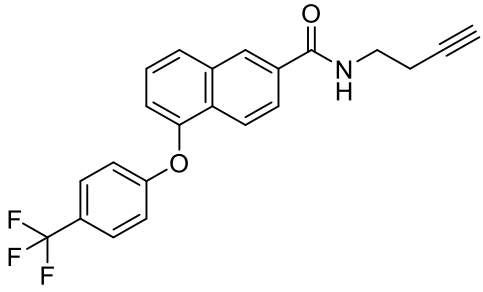
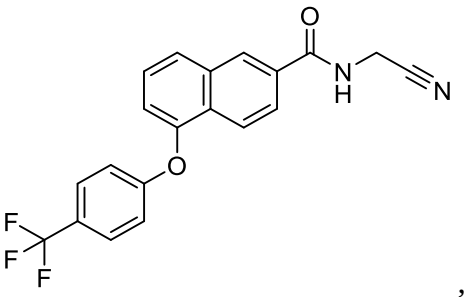
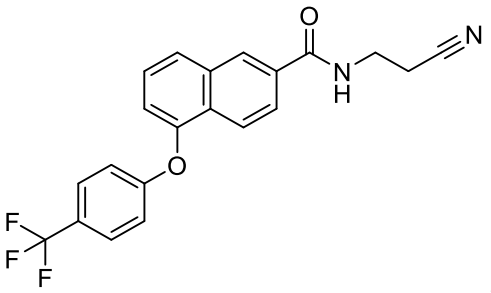
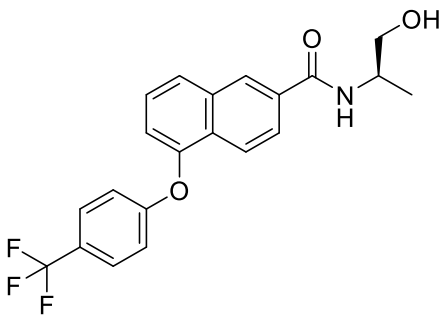
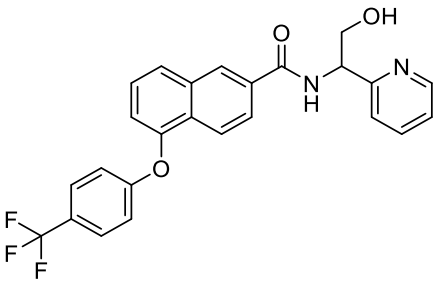
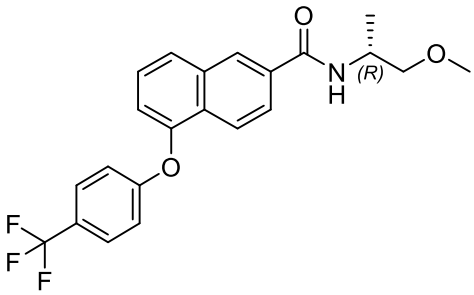
R^1 is C_1-C_6alkyl substituted with $–OR^3$; and R^3 is hydrogen or <u>unsubstituted</u> C_1-C_6alkyl;

R is $-CF_3$; and

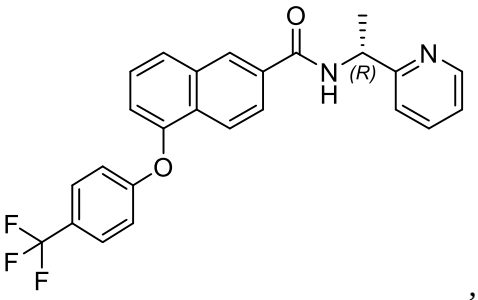
n is 0.

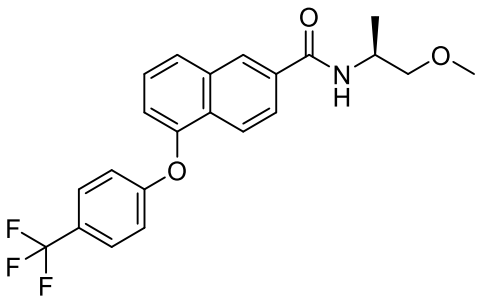
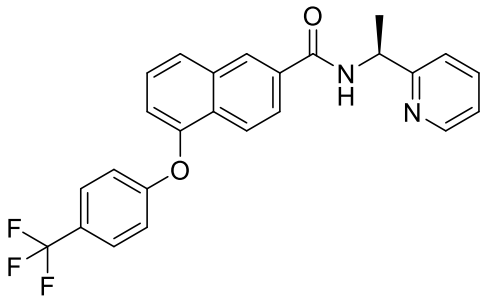
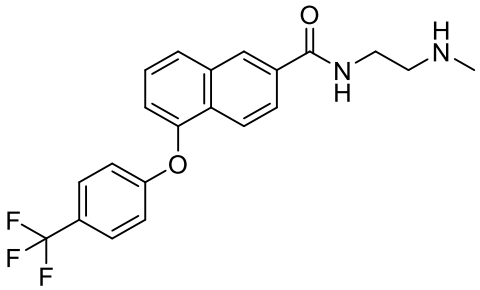
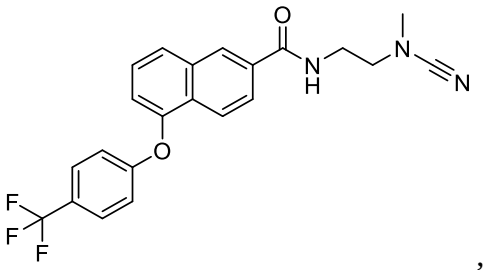
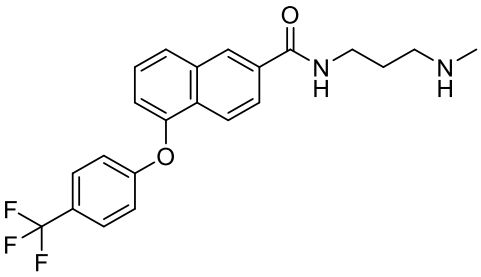
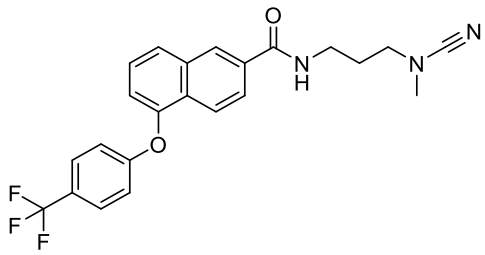
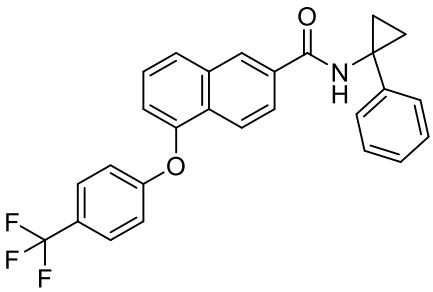
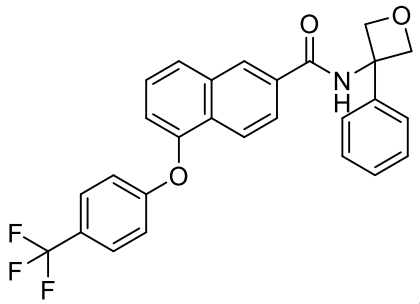
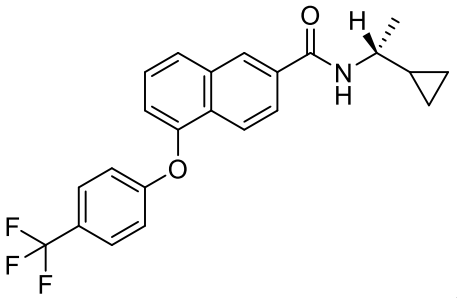
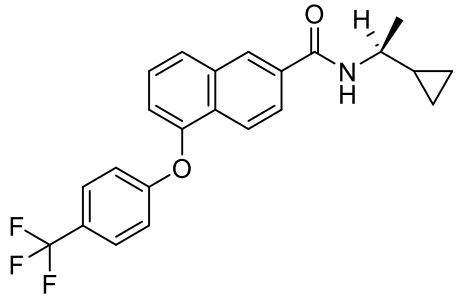
26. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the compound is selected from the group consisting of:

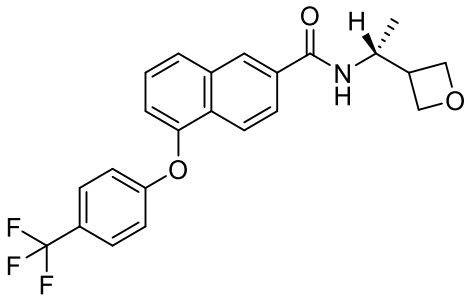
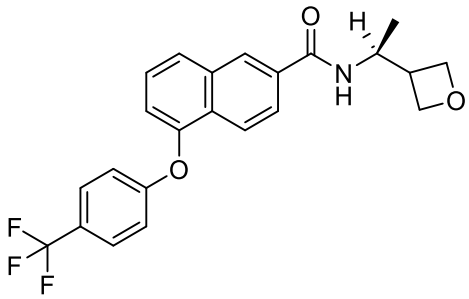
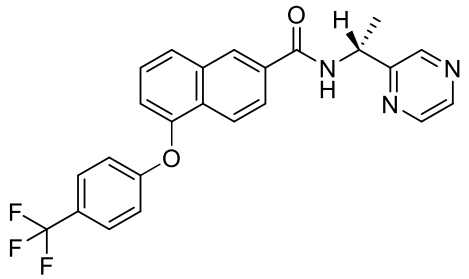
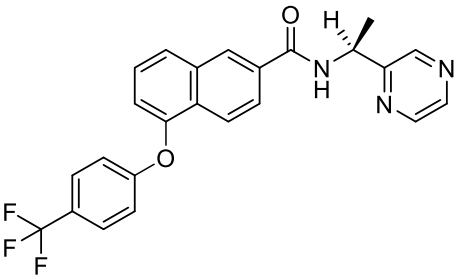
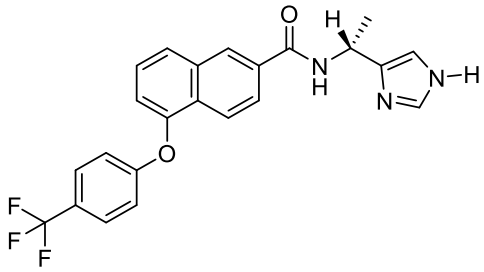
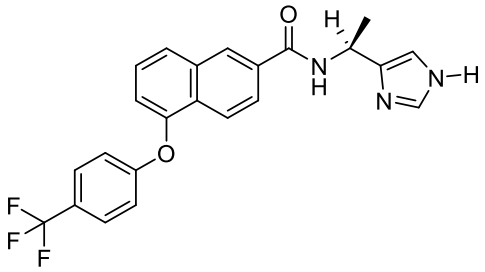
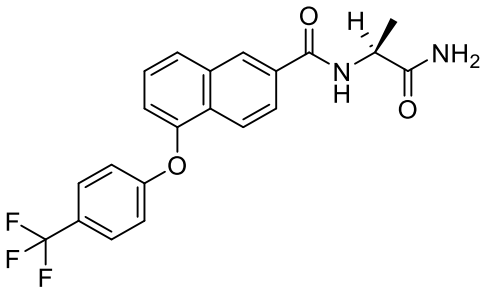
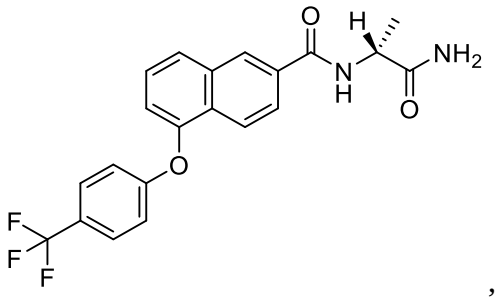
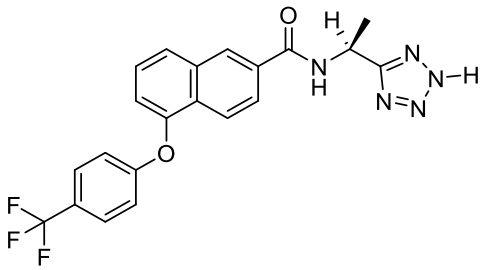
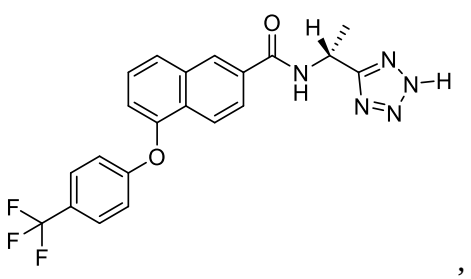
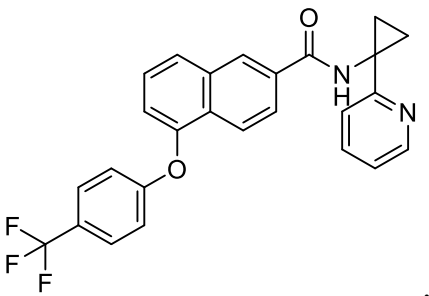

,

,

,

,

,

,

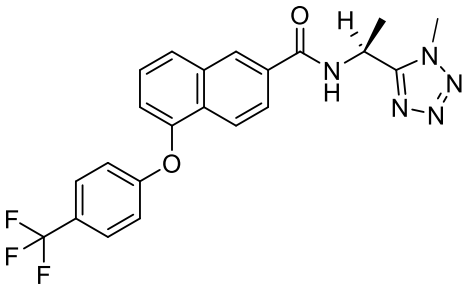
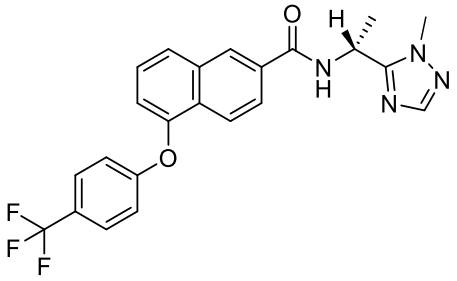
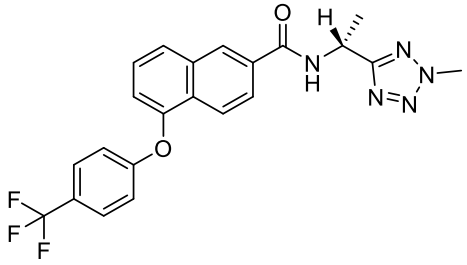
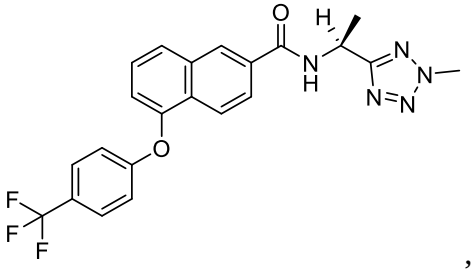
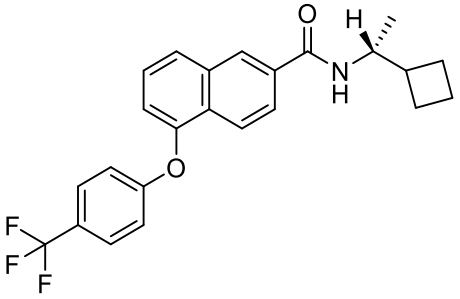
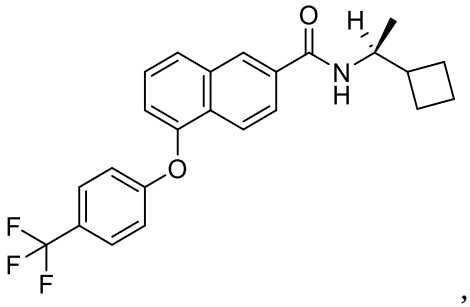
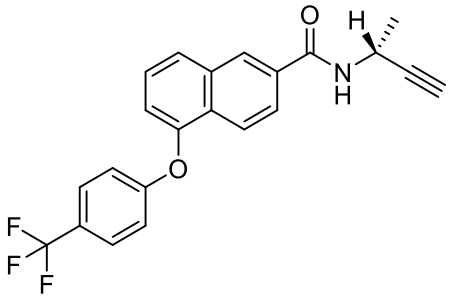
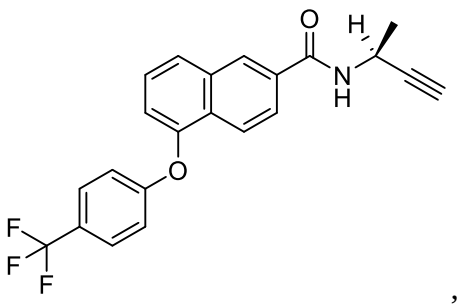
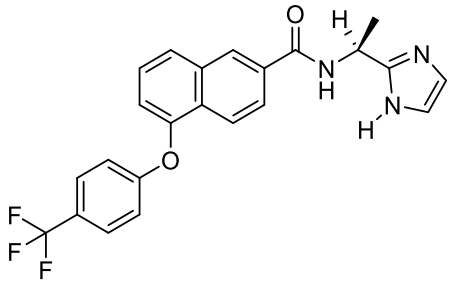
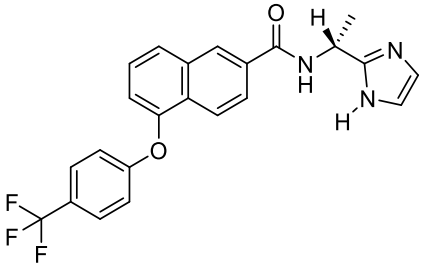
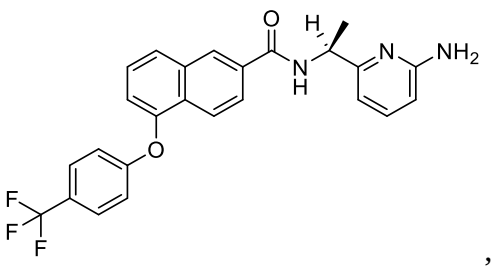

,

,

,

,

,

,

,

,

,

,

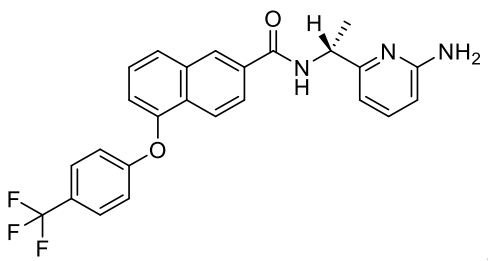
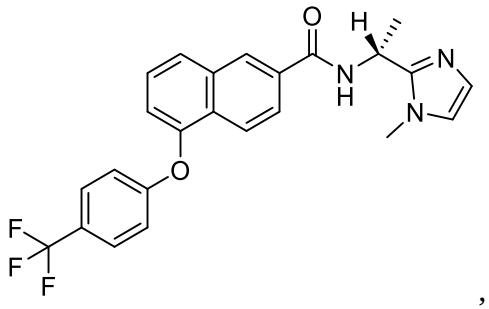
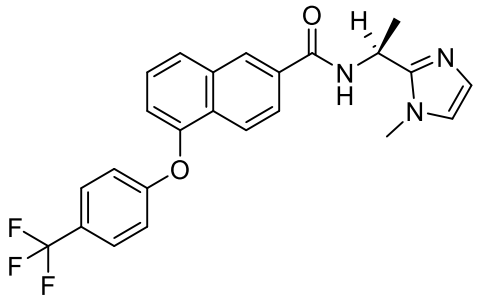
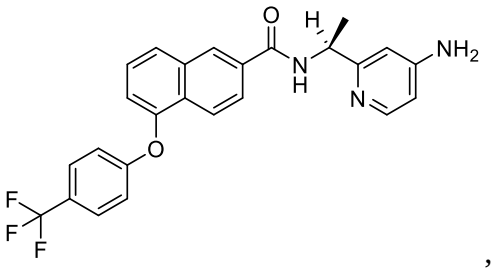
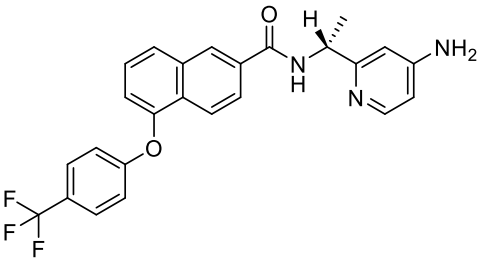
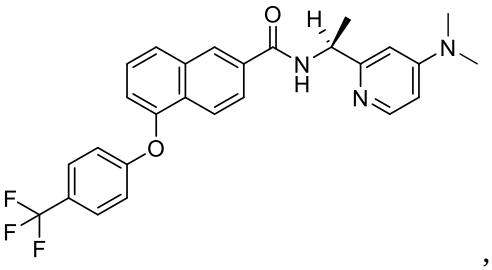
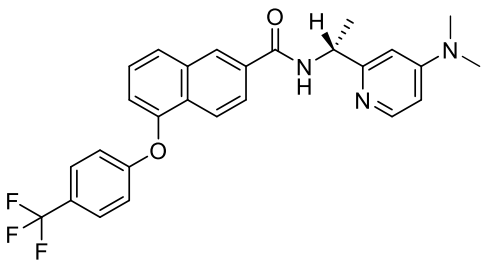
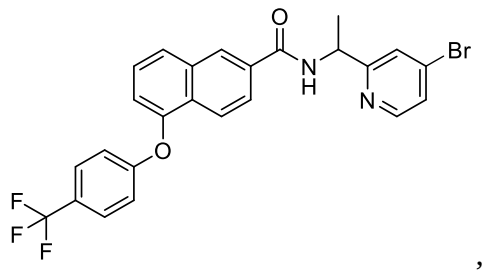
,

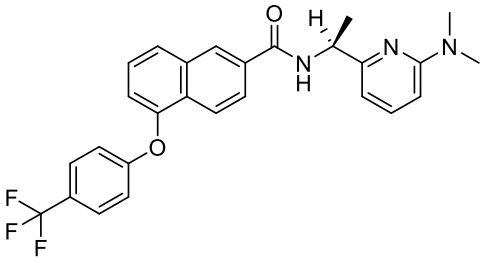
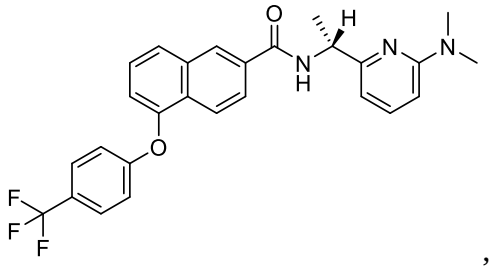
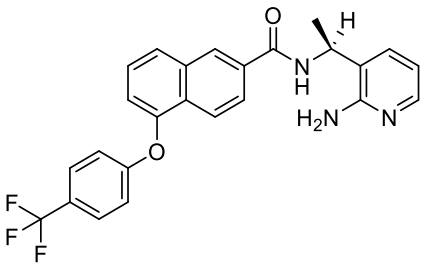
,

,

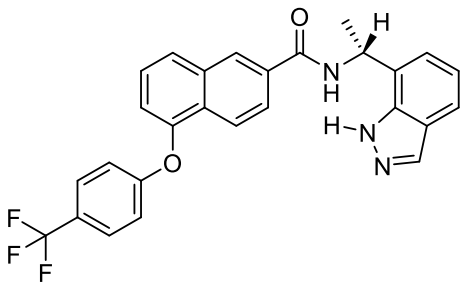
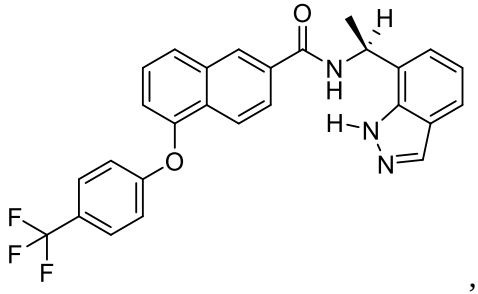
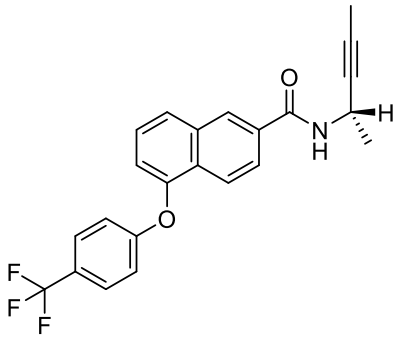
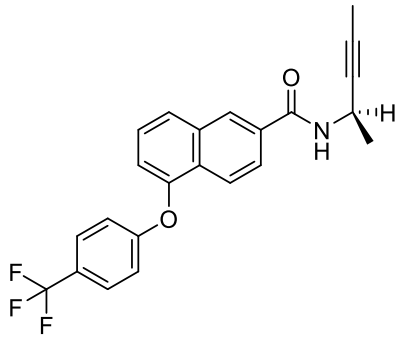
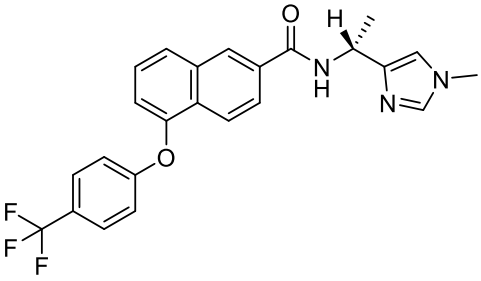
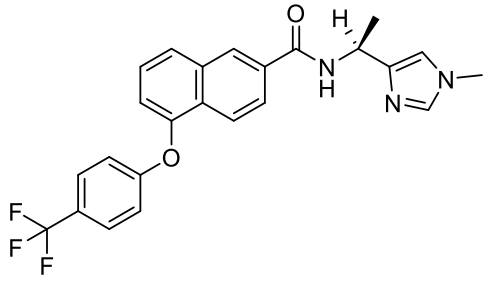
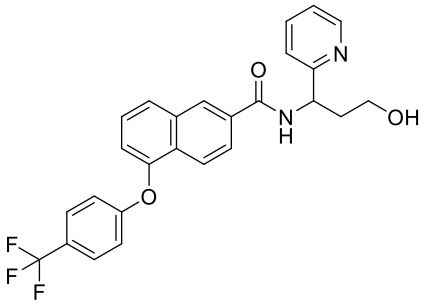
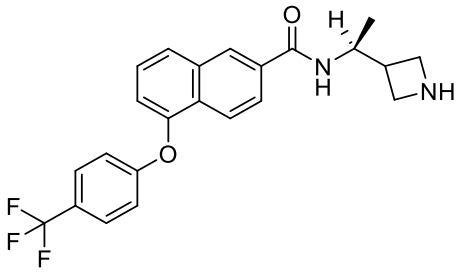
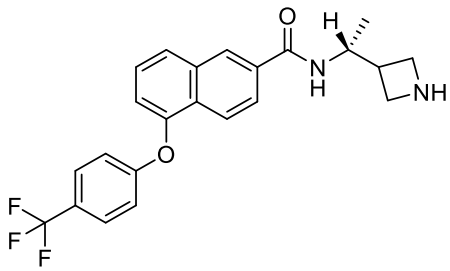
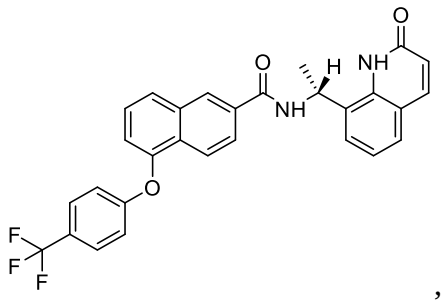

,

,

,

,

,

,

,

,

,

.

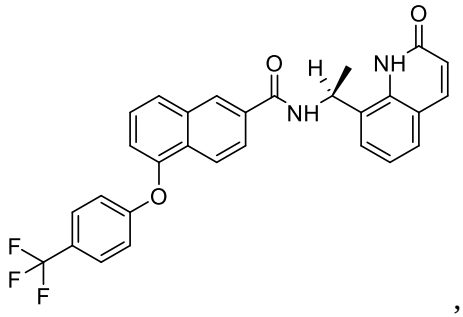
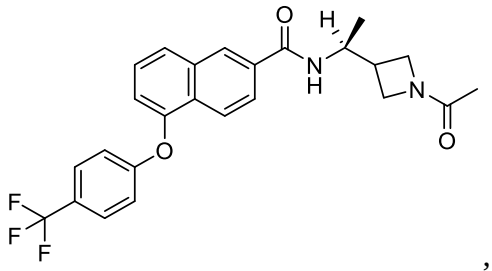
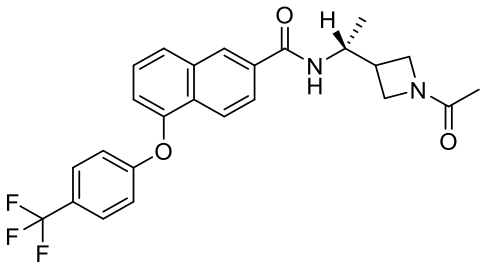
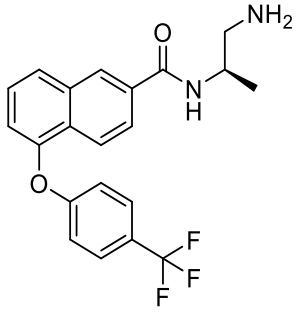
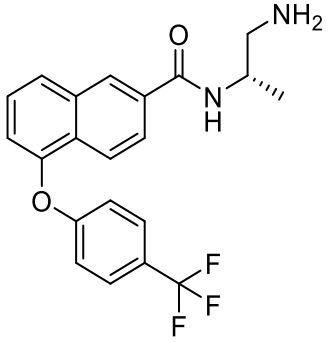
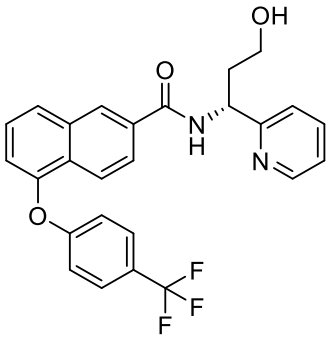
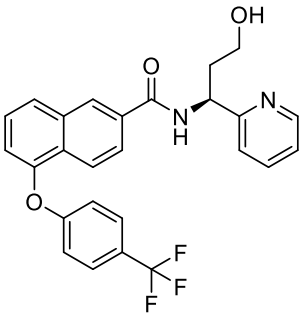
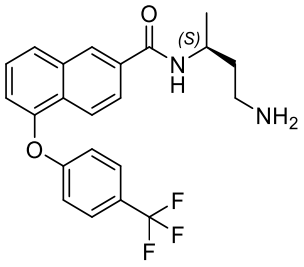
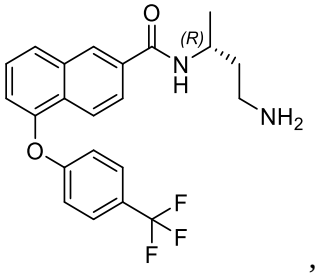
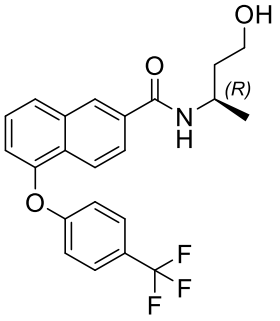
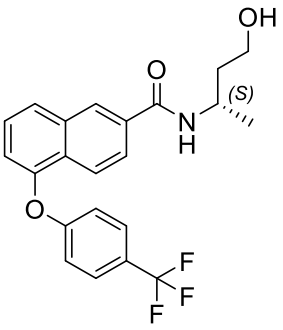

,

,

,

,

,

,

,

,

,

,

,

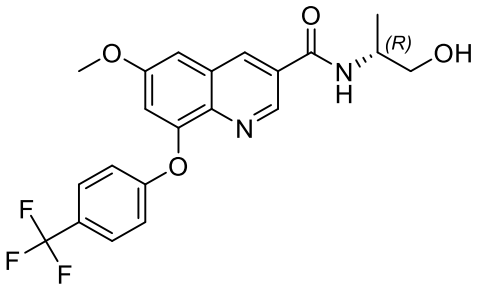
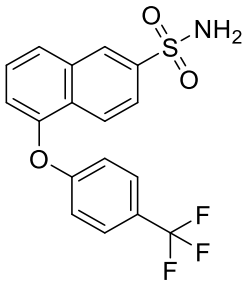

,

,

,

,

,

,

,

,

,

,

,

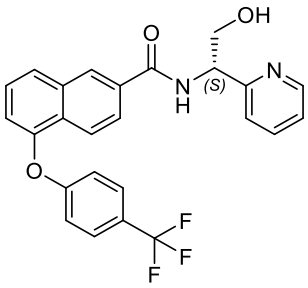
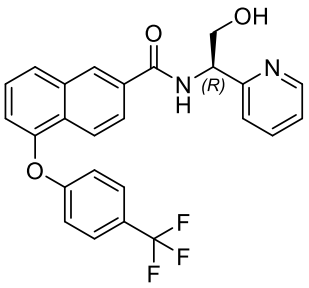
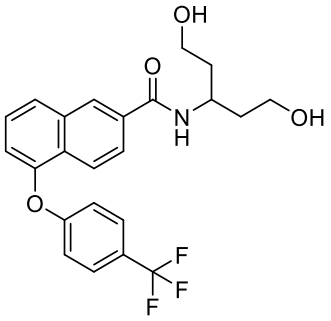

,

,

,

,

,

,

,

,

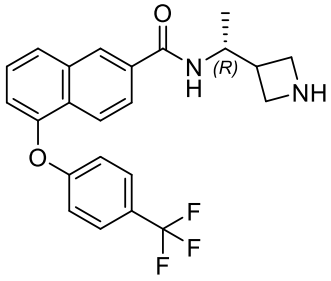
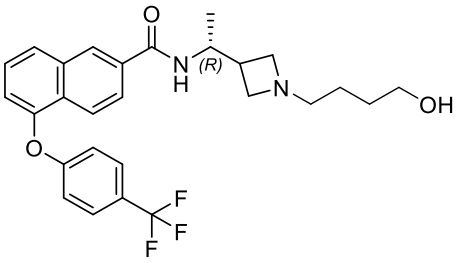

,

,

,

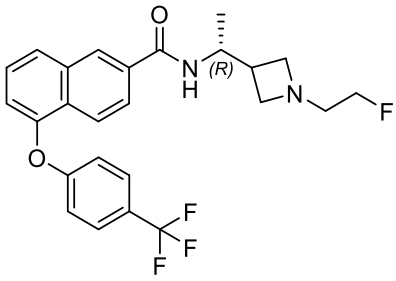
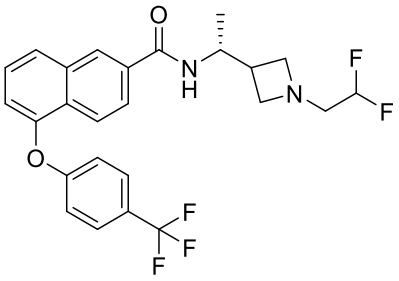

,

,

,

,

,

,

,

,

,

,

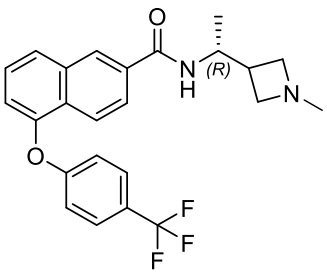
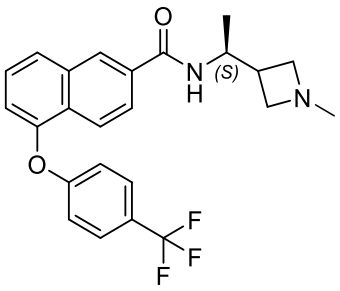
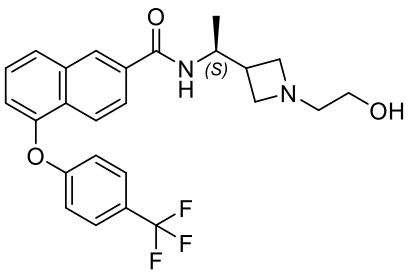

,

,

,

,

,

,

,

,

,

,

,

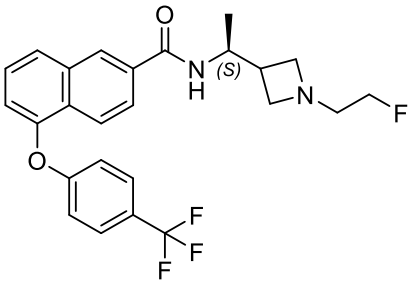
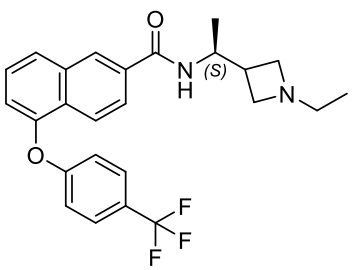
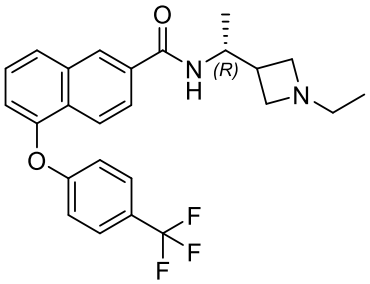



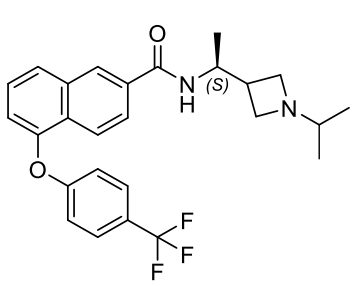
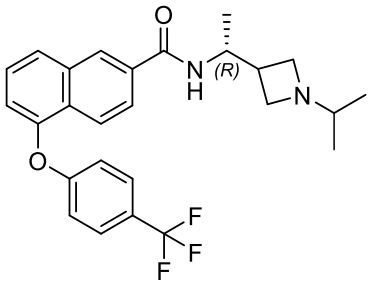
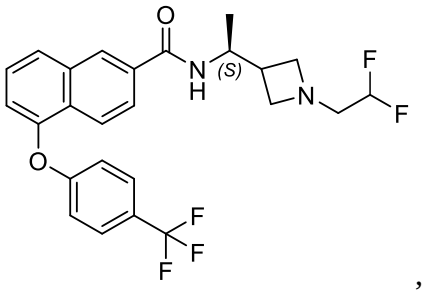
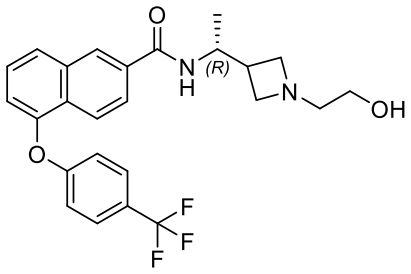
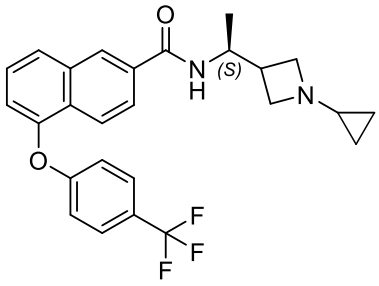
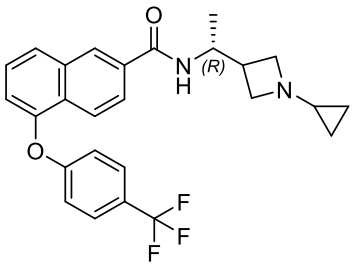
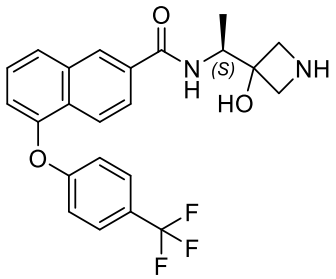
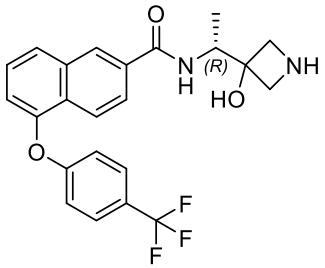
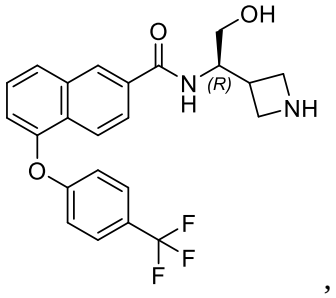
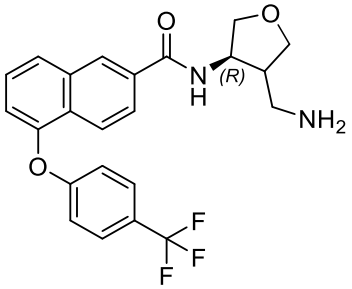
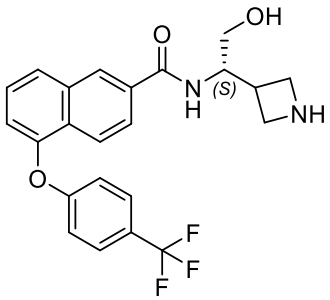
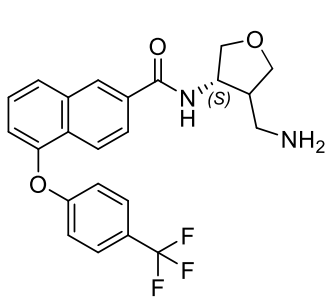
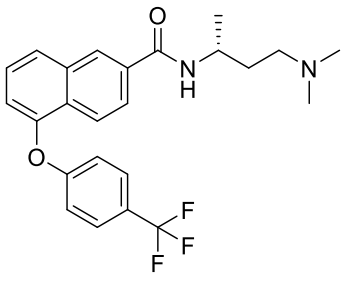
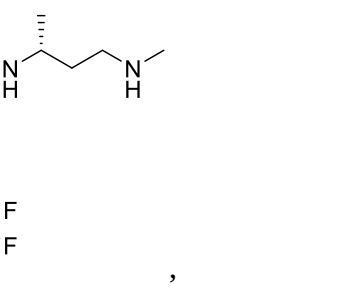




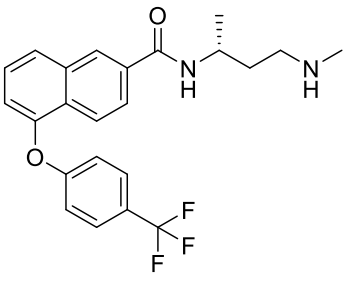
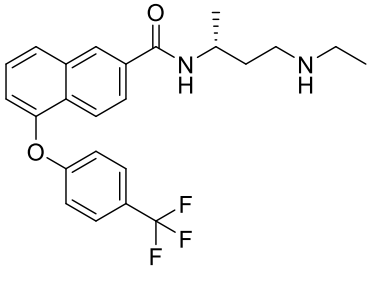
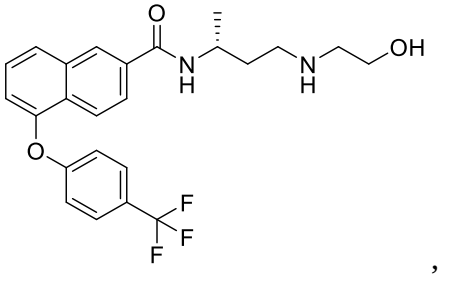



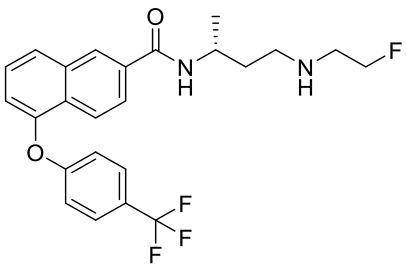
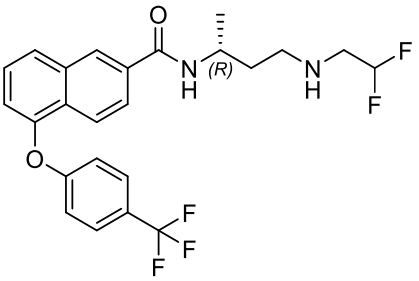
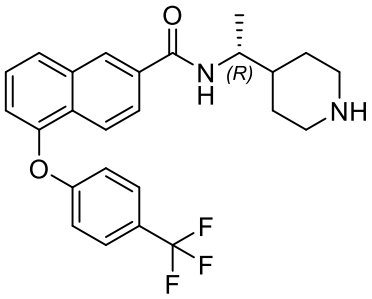
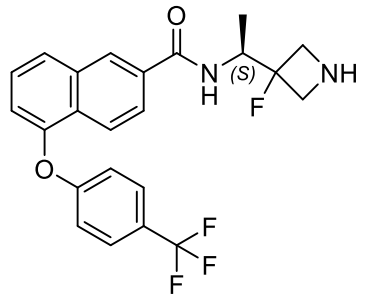
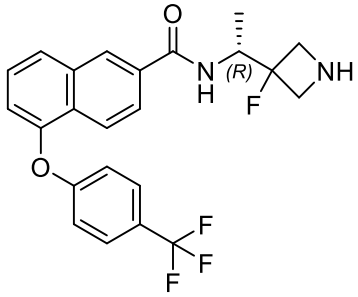
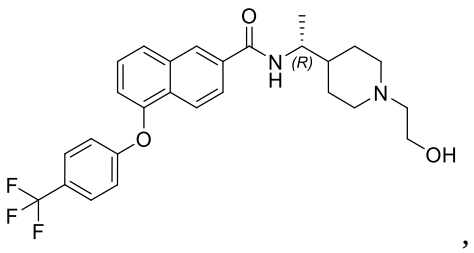
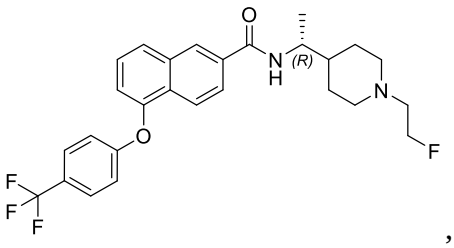
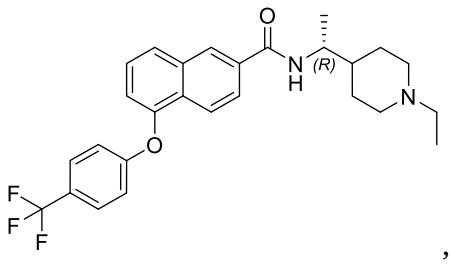
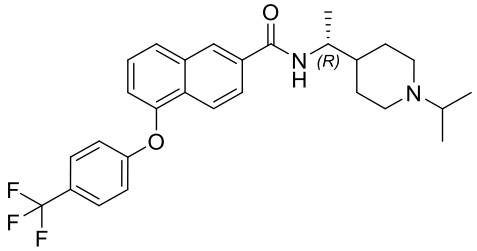
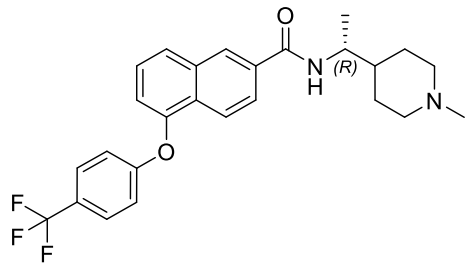
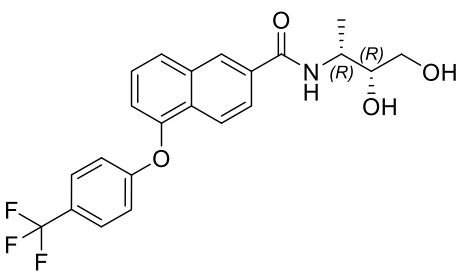
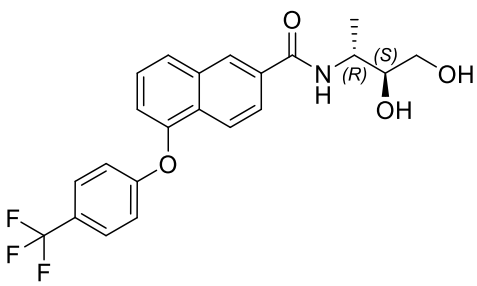



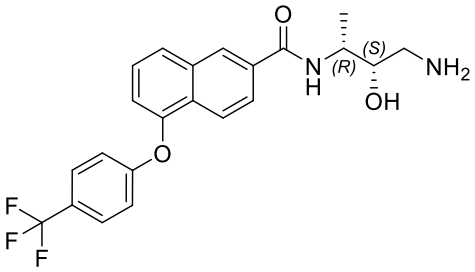
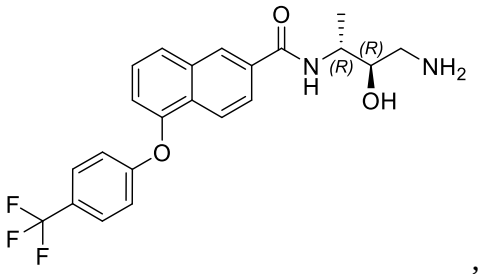
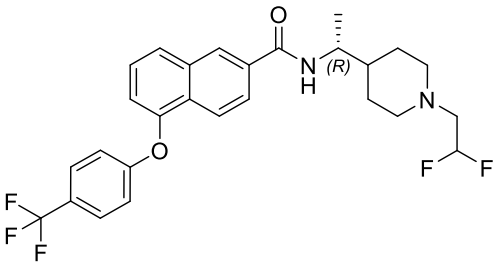
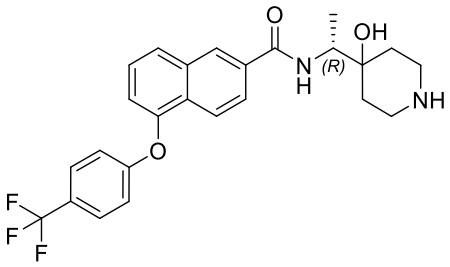




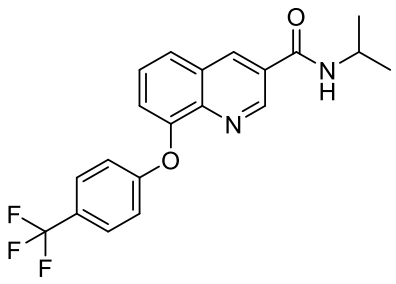
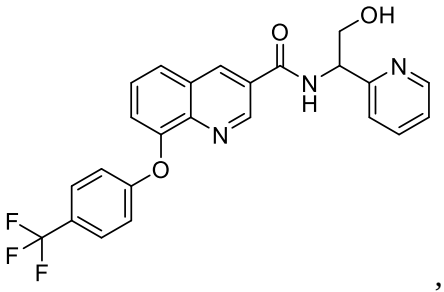
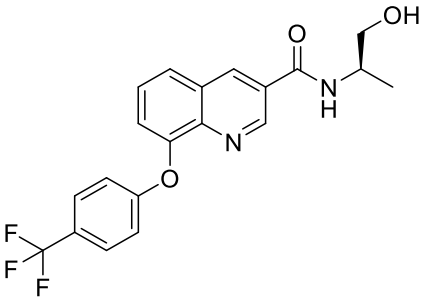
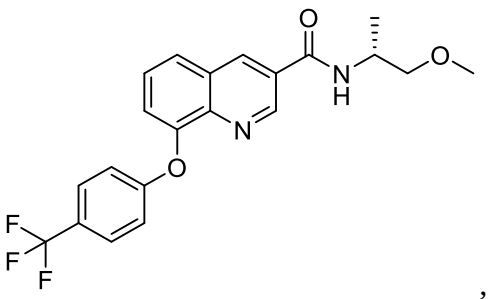
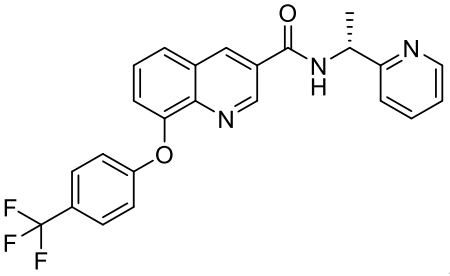
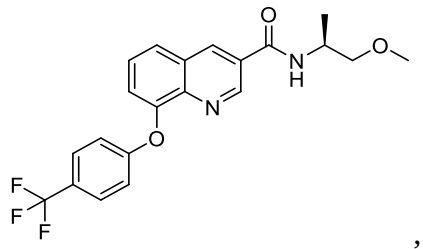

,

,

,

,

,

,

,

,

,

,

,

,

,

,

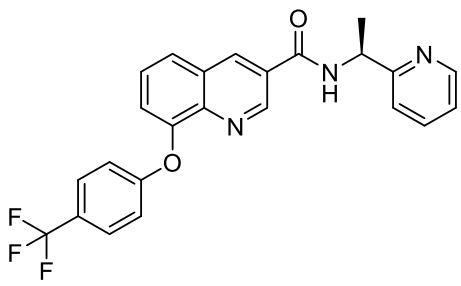
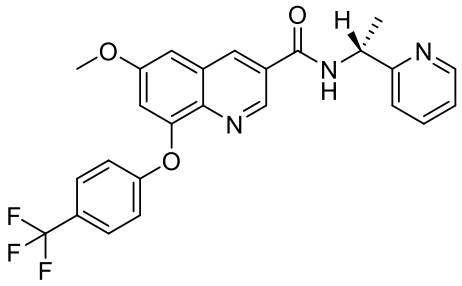
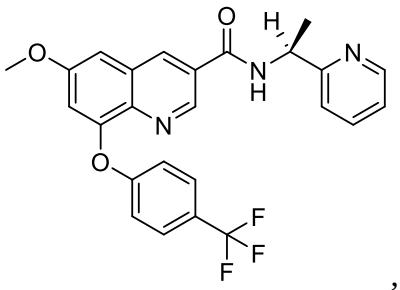
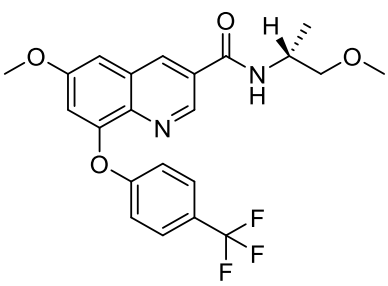
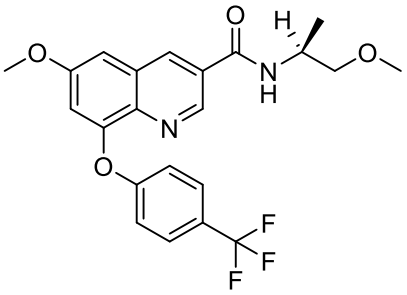
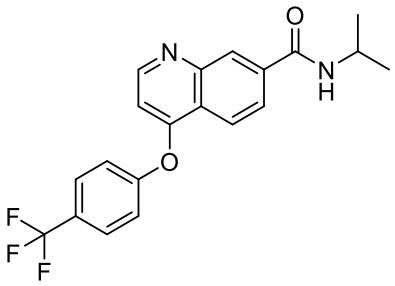
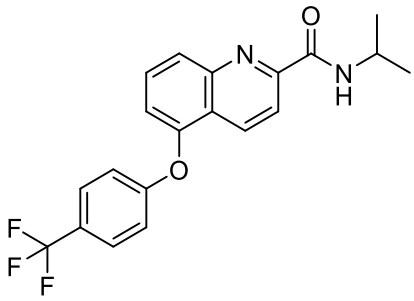
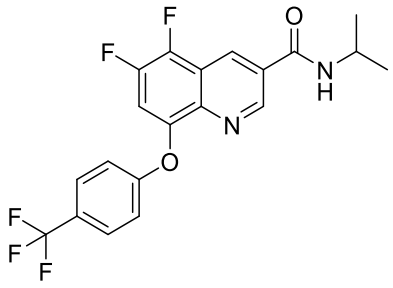
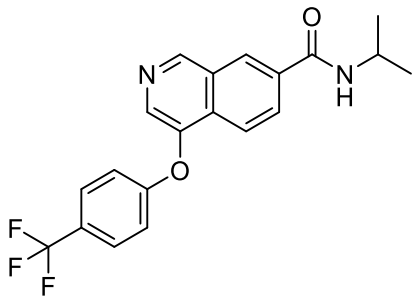
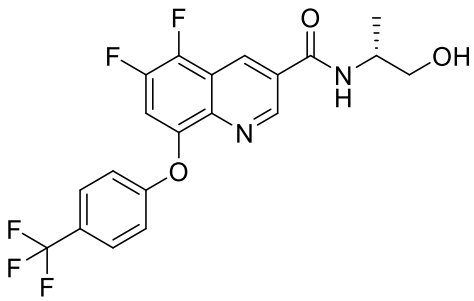
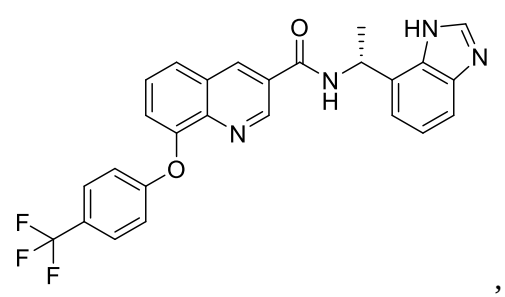
,

,

,

,

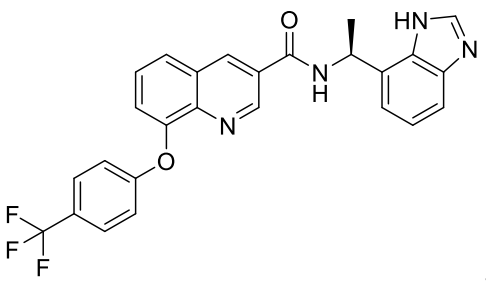
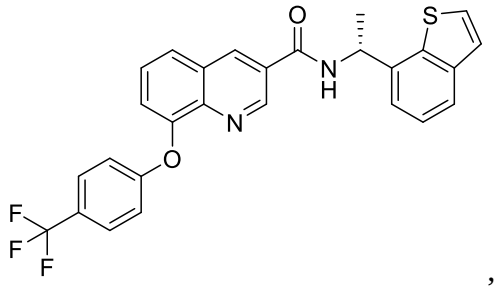
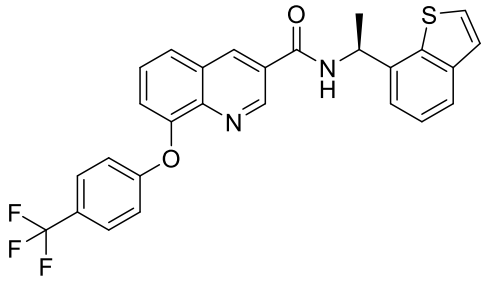
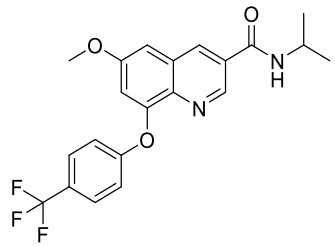
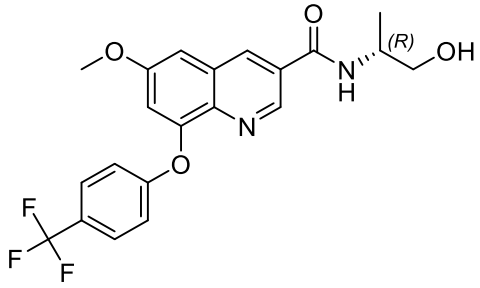
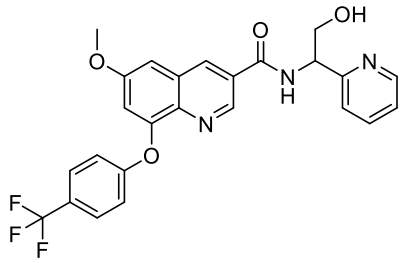

,

,

,

,

,

,

,

,

,

,

,

,

27. The compound or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the compound is selected from the group consisting of:


,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

, and

.

28. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-27, and a pharmaceutically acceptable excipient.

29. Use of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-27, in the manufacture of a medicament for inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway.

30. Use of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-27, in the manufacture of a medicament for inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP).

31. Use of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-27, in the manufacture of a medicament for treating cancer in a subject in need thereof.

32. The use of claim 31, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

33. Use of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-27, in the manufacture of a medicament for treating polycystic kidney disease or liver fibrosis in a subject in need thereof.

34. A compound of any one of claims 1-27, or the pharmaceutically acceptable salt or solvate thereof,

for use in inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway, or

for use in inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP), or

for use in treating cancer in a subject in need thereof, or

for use in treating polycystic kidney disease or liver fibrosis in a subject in need thereof.