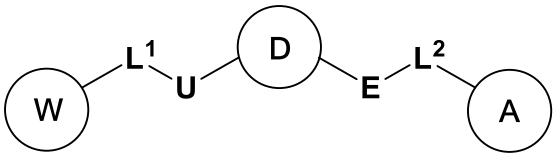
provides binding sites for eIF2B's substrate eIF2 (Dev, K. et al, *Mol Cell Biol* (2010) 30:5218-5233). The exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) eIF2B. eIF2B exists as a decamer ($B1_2\,B2_2\,B3_2\,B4_2\,B5_2$) or dimer of two pentamers in cells (Gordiyenko, Y. et al, Nat Commun (2014) 5:3902; Wortham, N.C. et al, *FASEB J* (2014) 28:2225-2237). Molecules such as ISRIB interact with and stabilize the eIF2B dimer conformation, thereby enhancing intrinsic GEF activity and making cells less sensitive to the cellular effects of phosphorylation of eIF2α (Sidrauski, C. et al, *eLife* (2015) e07314; Sekine, Y. et al, *Science* (2015) 348:1027-1030). As such, small molecule therapeutics that can modulate eIF2B activity may have the potential to attenuate the PERK branch of the UPR and the overall ISR, and therefore may be used in the prevention and/or treatment of various diseases, such as a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, or a metabolic disease.

SUMMARY ~~OF THE INVENTION~~

In one aspect of the present disclosure, there is provided a compound of Formula (I):



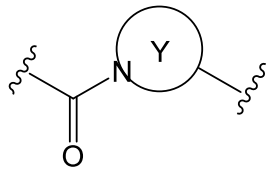
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is a bridged bicyclic cycloalkyl, a bridged bicyclic heterocyclyl, a 4-6-membered monocyclic cycloalkyl, a 4-6-membered monocyclic heterocyclyl, or cubanyl, wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, 4-6-membered monocyclic cycloalkyl, 4-6-membered monocyclic heterocyclyl, or cubanyl is optionally substituted on one or more available carbons with 1-4 R^X; and wherein if the 4-6-membered monocyclic heterocyclyl or bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N1};

U is $–NR^1C(O)–$, $–C(O)NR^1–$ or 5-6-membered heteroaryl;

E is absent or is a bond, $–NR^2C(O)–$, $–C(O)NR^2–$, 5-6-membered heteroaryl or 5-6-membered heterocyclyl; wherein 5-6-membered heteroaryl or 5-6-membered heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^G; and wherein if the 5-6-membered heteroaryl or 5-6-membered heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N2}; or

E is 

; Y is a 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl, wherein the 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^G; and wherein if the 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N2};

L^1 is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, $–NR^{N3}–$, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L1};

L^2 is absent or is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2};

wherein E and L^2 both cannot be either a bond or absent simultaneously;

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl;

W is a 8-10 membered, partially unsaturated, fused bicyclic ring moiety comprising a 5-6 membered heterocyclyl fused to a phenyl or 5-6-membered heteroaryl; wherein the heterocyclyl may be optionally substituted on one or more available carbons with 1-4 R^{W1}; wherein the phenyl or heteroaryl may optionally be substituted on one or more available unsaturated carbons with 1-4 R^{W2}; wherein if the heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may optionally be substituted with R^{N4}; and wherein W is attached to L^2 through an available saturated carbon or nitrogen atom within the heterocyclyl;

A is C_3-C_6 cycloalkyl, phenyl, 4-6-membered heterocyclyl, 5-6-membered heteroaryl, or 8-10-membered bicyclic heteroaryl, wherein C_3-C_6 cycloalkyl, phenyl, 4-6-membered heterocyclyl, 5-6-membered heteroaryl, or 8-10-membered bicyclic heteroaryl is optionally substituted on one or more available carbons or silicons with 1-5 R^Y; and wherein if the 5-6-membered heteroaryl or 8-10-membered bicyclic heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N5};

each R^{L1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^{L2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, thioxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

R^{N1} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N2} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N3} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N4} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, –C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–C_1-C_3 alkyl–O–C_1-C_3 alkyl–O–C_1-C_3 alkyl, –C(O)–phenyl, –C(O)–heteroaryl, –C(O)–heterocyclyl, $–S(O)_2–C_1$-C_6 alkyl, $–S(O)_2–$phenyl, $–S(O)_2–$heteroaryl, $–C(O)NR^BR^C$ and $–C(O)OR^D$; wherein

C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–heterocyclyl, and $–S(O)_2–C_1$-C_6 alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms) and $S(O)_wC_{1\text{-}6}$ alkyl (wherein w is 0, 1 or 2); and

–C(O)–phenyl, –C(O)–heteroaryl, $–S(O)_2–$phenyl and $–S(O)_2–$heteroaryl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms), C_1-C_6 alkoxy (optionally substituted by one, two or three fluorine atoms), and $S(O)_2$-NR^BR^C;

R^{N5} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

each R^{W1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl (optionally substituted by $–CO_2H$), hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6

alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, C=N-OH, halo, cyano, –OR^A, –NR^BR^C, –NR^BR^{CC}, –$NR^BC(O)R^D$, -$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, –SR^E, –$S(O)R^D$, and –$S(O)_2R^D$;

each R^{W2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, -OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, -$S(R^F)_m$, -$S(O)R^D$, and –$S(O)_2R^D$; or

2 R^{W2} groups on adjacent atoms, together with the atoms to which they are attached, form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each R^X is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, -$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, –SR^E, –$S(O)R^D$, and –$S(O)_2R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, oxo, –C_1-C_6 alkylene-OR^A, –OR^A, –NR^BR^C, –NR^BR^{CC}, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, –$S(R^F)_m$, –$S(O)R^D$, –$S(O)_2R^D$, and G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each G^1 is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 R^Z;

each R^Z is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, and –$S(O)_2R^D$;

R^A is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, C_1-C_6 alkoxy-C_1-C_6 alkylene, –$C(O)NR^BR^C$, –$C(O)R^D$, or –$C(O)OR^D$;

each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 R^Z;

each R^{CC} is independently selected from the group consisting of hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, C(O) C_1-C_6 alkyl, $S(O)_2$– C_1-C_6 alkyl and 3-6-membered cycloalkyl and 4-6-membered heterocyclyl; wherein 3-6-membered cycloalkyl and 4-6-membered heterocyclyl may optionally be substituted by one or more substituents each independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, hydroxyl, halo and –C(O)OH;

each R^D is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, or halo-C_1-C_6 alkoxy-C_1-C_6 alkylene;

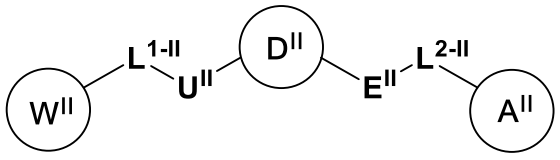
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

each R^F is independently hydrogen, C_1-C_6 alkyl, or halo;

each R^G is independently hydrogen, C_1-C_6 alkyl, halo or oxo; and

m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

In another aspect of the present disclosure, there is provided a compound of Formula (II):



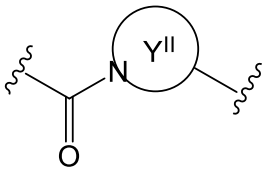
Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

D^{II} is a bridged bicyclic cycloalkyl, a bridged bicyclic heterocyclyl, a 4-6-membered monocyclic cycloalkyl, a 4-6-membered monocyclic heterocyclyl, or cubanyl, wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, 4-6-membered monocyclic cycloalkyl, 4-6-membered monocyclic heterocyclyl, or cubanyl is optionally substituted on one or more available carbons with 1-4 R^{X-II}; and wherein if the 4-6-membered monocyclic heterocyclyl or bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N1-II};

U^{II} is $–NR^{1-II}C(O)–$ or $–C(O)NR^{1-II}–$;

E^{II} is absent or is a bond, $–NR^{2-II}C(O)–$, $–C(O)NR^{2-II}–$, 5-6-membered heteroaryl or 5-6-membered heterocyclyl; wherein 5-6-membered heteroaryl or 5-6-membered heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^{G-II}; and wherein if the 5-6-membered heteroaryl or 5-6-membered heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N2-II}; or

E^{II} is 

; Y^{II} is a 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl, wherein the 4-9 membered monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^{G-II}; and wherein if the 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N2-II};

L^{1-II} is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, $–NR^{N3-II}–$, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L1-II};

L^{2-II} is absent or is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, –C(O)–, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2-II};

wherein E^{II} and L^{2-II} both cannot be either a bond or absent simultaneously;

R^{1-II} is hydrogen or C_1-C_6 alkyl;

R^{2-II} is hydrogen or C_1-C_6 alkyl;

W^{II} is phenyl or 5-6-membered heteroaryl; wherein phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^{W-II}; and wherein if the 5-6-membered heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N4-II};

A^{II} is C_3-C_6 cycloalkyl, 4-6-membered heterocyclyl, phenyl, or 5-6-membered heteroaryl, wherein C_3-C_6 cycloalkyl, phenyl, or 5-6-membered heteroaryl is optionally substituted on one or more available carbons with 1-5 R^{Y-II}; and wherein if the 5-6-membered heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N5-II};

each R^{L1-II} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^{A-II}$, $–NR^{B-II}R^{C-II}$, $–NR^{B-II}C(O)R^{D-II}$, $-C(O)NR^{B-II}R^{C-II}$, $–C(O)R^{D-II}$, –C(O)OH, $–C(O)OR^{D-II}$, $–SR^{E-II}$, $–S(O)R^{D-II}$, and $–S(O)_2R^{D-II}$;

each R^{L2-II} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^{A-II}$, $–NR^{B-II}R^{C-II}$, $–NR^{B-II}C(O)R^{D-II}$, $-C(O)NR^{B-II}R^{C-II}$, $–C(O)R^{D-II}$, –C(O)OH, $–C(O)OR^{D-II}$, $–SR^{E-II}$, $–S(O)R^{D-II}$, and $–S(O)_2R^{D-II}$;

$R^{N1\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^{B\text{-}II}R^{C\text{-}II}$, –$C(O)R^{D\text{-}II}$, –$C(O)OR^{D\text{-}II}$, and –$S(O)_2R^{D\text{-}II}$;

$R^{N2\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^{B\text{-}II}R^{C\text{-}II}$, –$C(O)R^{D\text{-}II}$, –$C(O)OR^{D\text{-}II}$, and –$S(O)_2R^{D\text{-}II}$;

$R^{N3\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^{B\text{-}II}R^{C\text{-}II}$, –$C(O)R^{D\text{-}II}$, –$C(O)OR^{D\text{-}II}$, and –$S(O)_2R^{D\text{-}II}$;

$R^{N4\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, –C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–C_1-C_3 alkyl–O–C_1-C_3 alkyl–O–C_1-C_3 alkyl, –C(O)–phenyl, –C(O)–heteroaryl, –C(O)–heterocyclyl, –$S(O)_2$–C_1-C_6 alkyl, –$S(O)_2$–phenyl, –$S(O)_2$–heteroaryl, –$C(O)NR^{B\text{-}II}R^{C\text{-}II}$ and –$C(O)OR^{D\text{-}II}$; wherein

C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–heterocyclyl, and –$S(O)_2$–C_1-C_6 alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms) and $S(O)_{w\text{-}II}C_{1\text{-}6}$ alkyl (wherein w-II is 0, 1 or 2); and

–C(O)–phenyl, –C(O)–heteroaryl, –$S(O)_2$–phenyl and –$S(O)_2$–heteroaryl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms), C_1-C_6 alkoxy (optionally substituted by one, two or three fluorine atoms), and –$S(O_2)NR^{B\text{-}II}R^{C\text{-}II}$;

$R^{N5\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^{B\text{-}II}R^{C\text{-}II}$, –$C(O)R^{D\text{-}II}$, –$C(O)OR^{D\text{-}II}$, and –$S(O)_2R^{D\text{-}II}$;

each $R^{W\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, C=N-OH, halo, cyano, –$OR^{A\text{-}II}$, –$NR^{B\text{-}II}R^{C\text{-}II}$, –$NR^{B\text{-}II}R^{CC\text{-}II}$, –$NR^{B\text{-}II}C(O)R^{D\text{-}II}$, –$C(O)NR^{B\text{-}II}R^{C\text{-}II}$, –$C(O)R^{D\text{-}II}$, –C(O)OH, –$C(O)OR^{D\text{-}II}$, –$SR^{E\text{-}II}$, –$S(O)R^{D\text{-}II}$, and –$S(O)_2R^{D\text{-}II}$; or

2 $R^{W\text{-}II}$ groups on adjacent atoms, together with the atoms to which they are attached, form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 $R^{X\text{-}II}$;

each $R^{X\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, $–SR^{E\text{-}II}$, $–S(O)R^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

each $R^{Y\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, $-S(R^{F\text{-}II})_{m\text{-}II}$, $-S(O)R^{D\text{-}II}$, $–S(O)_2R^{D\text{-}II}$, and $G^{1\text{-}II}$; or

2 $R^{Y\text{-}II}$ groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 $R^{X\text{-}II}$;

each $G^{1\text{-}II}$ is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 $R^{Z\text{-}II}$;

each $R^{Z\text{-}II}$ is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

$R^{A\text{-}II}$ is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, or $–C(O)OR^{D\text{-}II}$;

each of $R^{B\text{-}II}$ and $R^{C\text{-}II}$ is independently hydrogen or C_1-C_6 alkyl; or

$R^{B\text{-}II}$ and $R^{C\text{-}II}$ together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 $R^{Z\text{-}II}$;

each $R^{CC\text{-}II}$ is independently selected from the group consisting of hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, C(O) C_1-C_6 alkyl, $S(O)_2$–C_1-C_6 alkyl and 3-6-membered cycloalkyl and 4-6-membered heterocyclyl; wherein 3-6-membered cycloalkyl and 4-6-membered heterocyclyl may optionally be substituted by one or more substituents each independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, hydroxyl, halo and –C(O)OH;

each $R^{D\text{-}II}$ is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

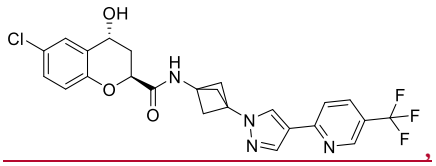
each $R^{E\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

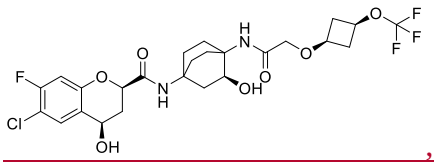
each $R^{F\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, or halo; and

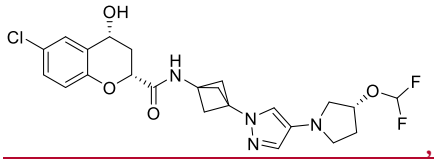
each $R^{G\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, halo or oxo;

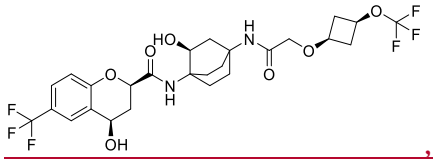
provided that when D^{II} is a bridged bicyclic 5-membered cycloalkyl, E^{II} is $–NR^{2\text{-}II}C(O)–$.

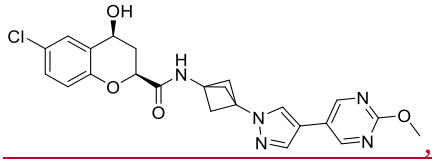
In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

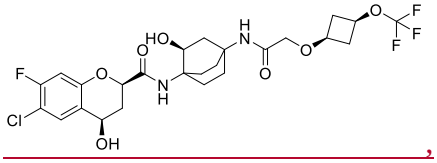


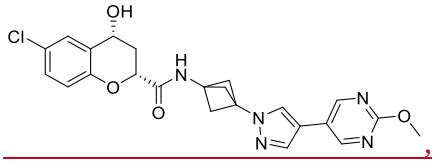


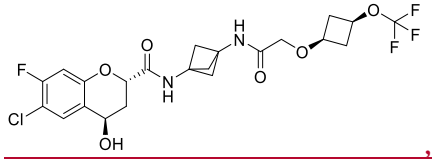


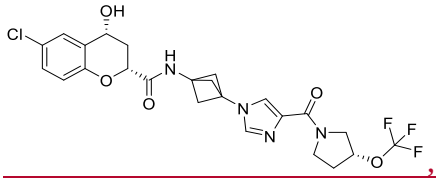


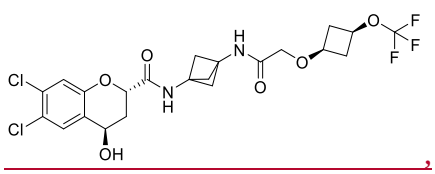


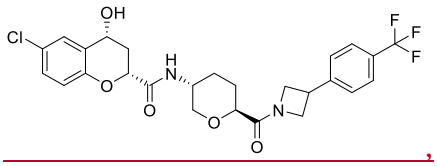


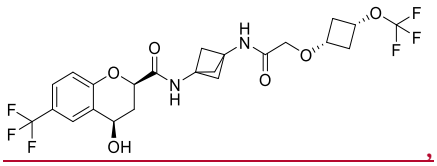


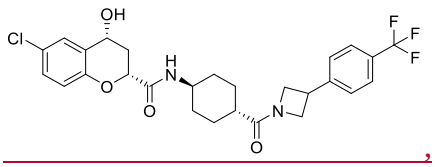


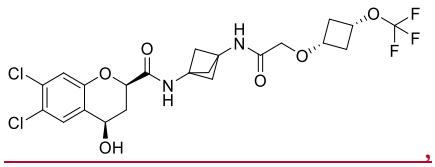


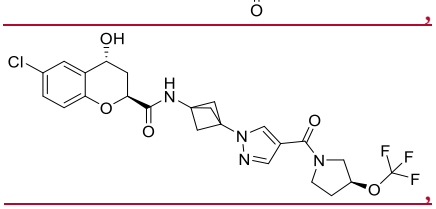


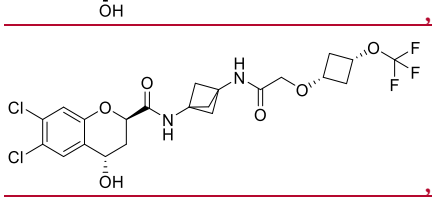


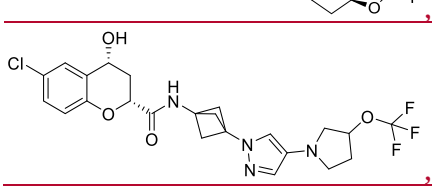


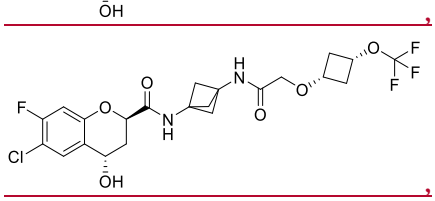


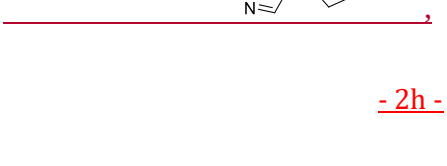




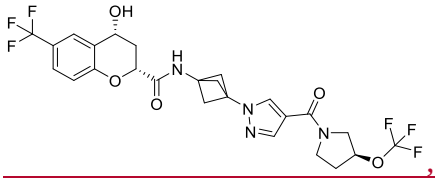


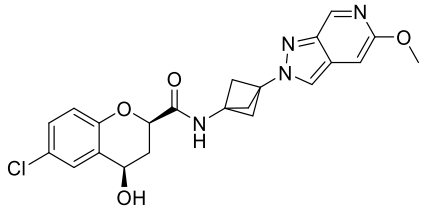


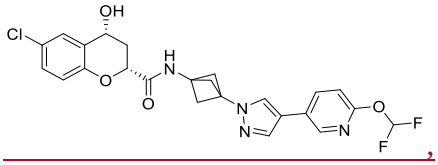


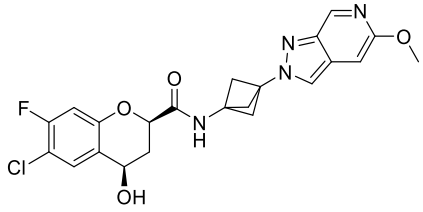


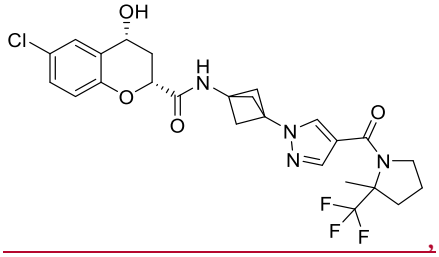


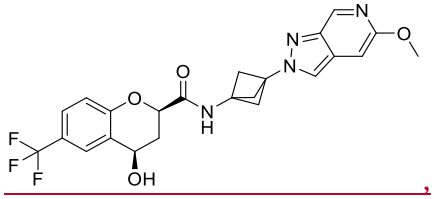


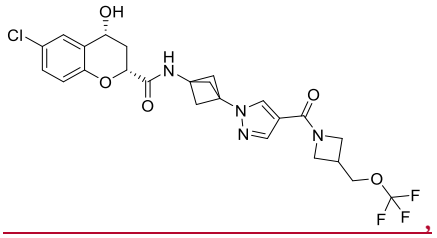


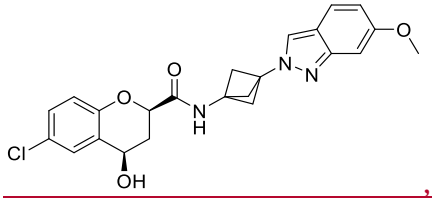


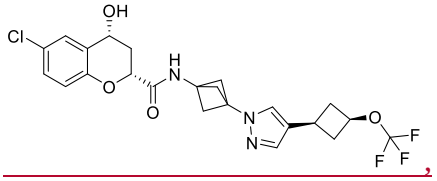


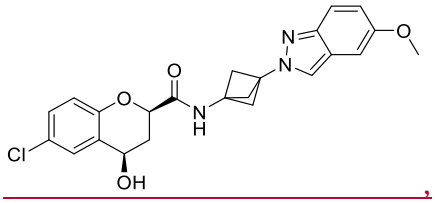


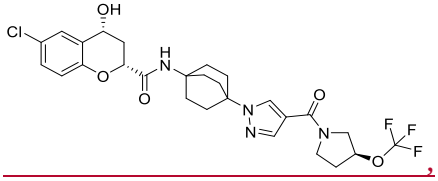


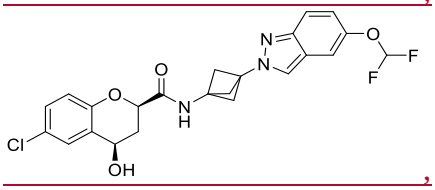


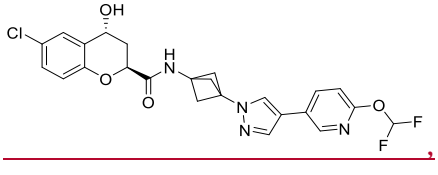


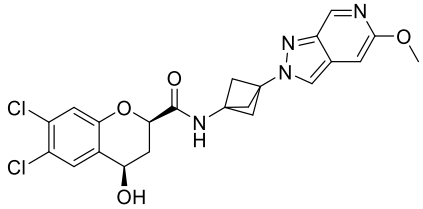


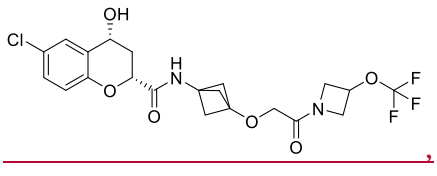


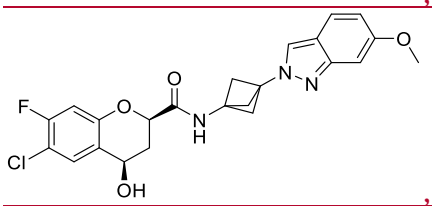




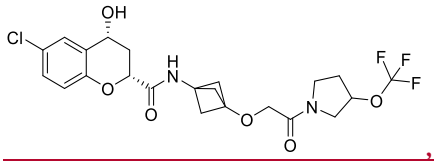


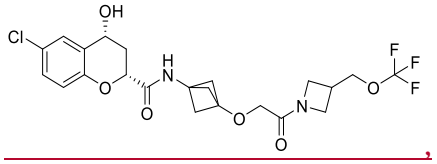


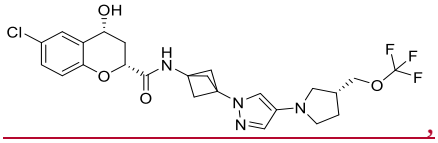


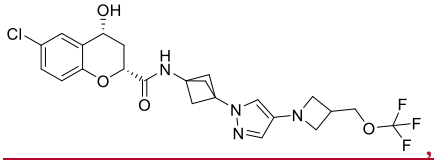


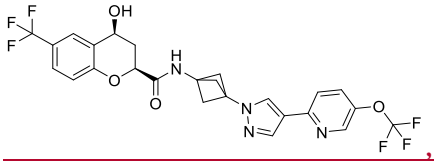


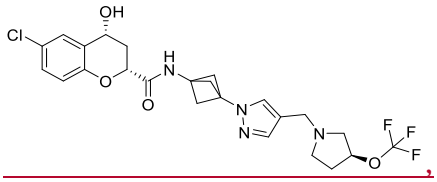


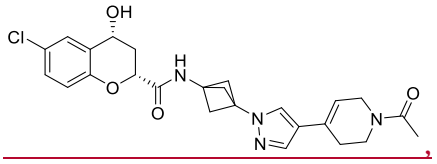


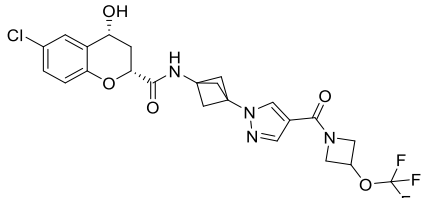


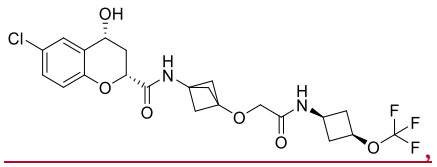


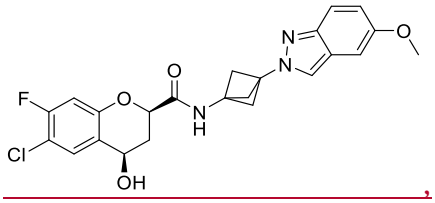


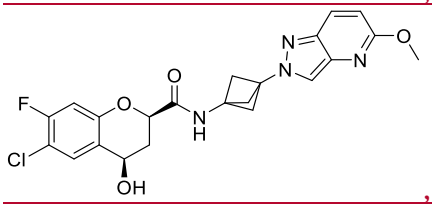


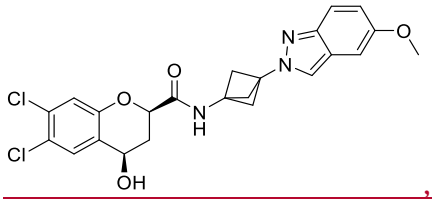


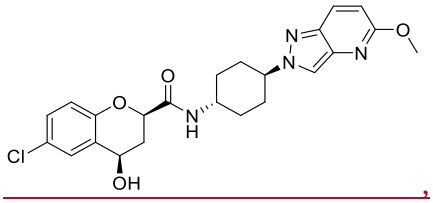


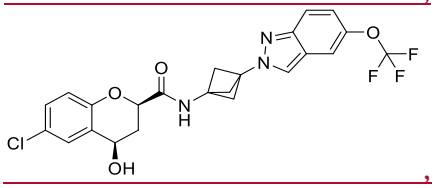


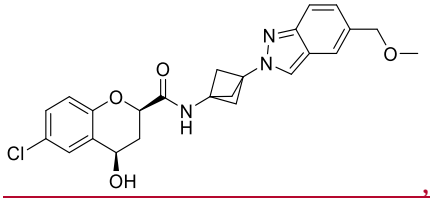


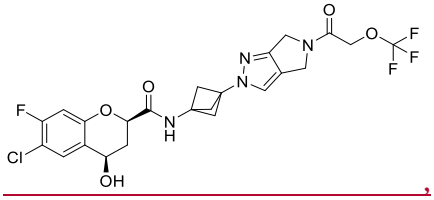


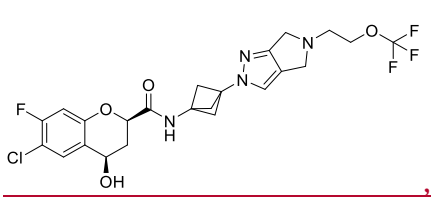


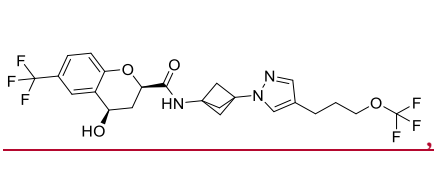


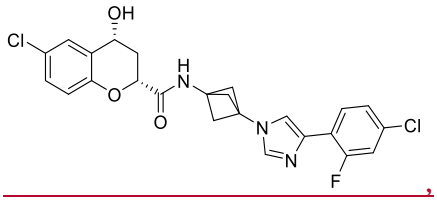


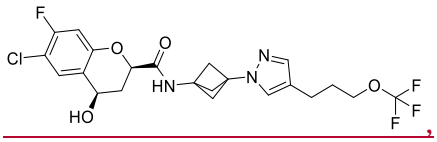


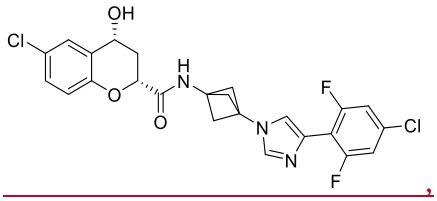


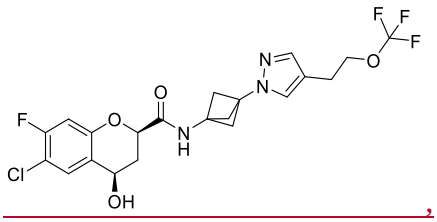


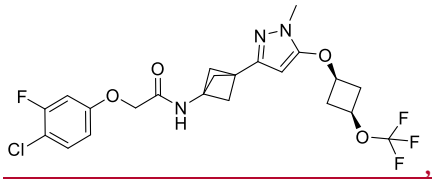


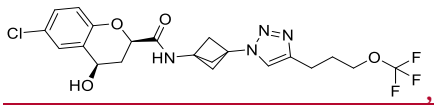


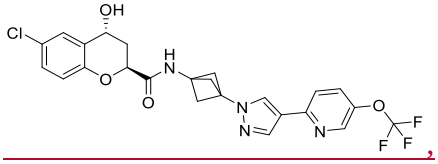


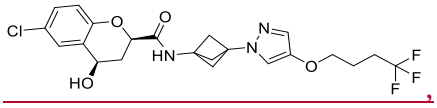


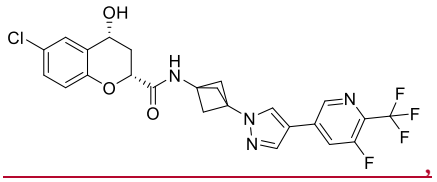


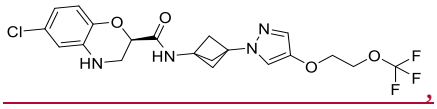


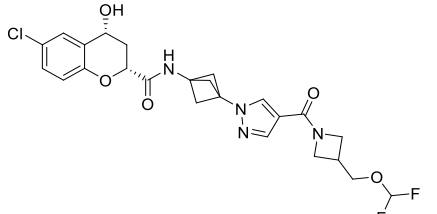


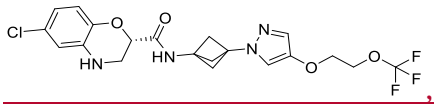


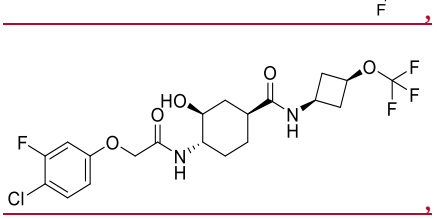


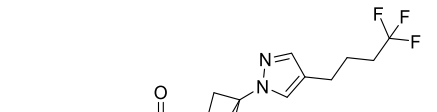


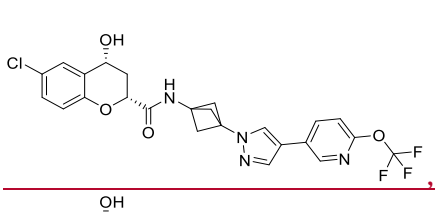


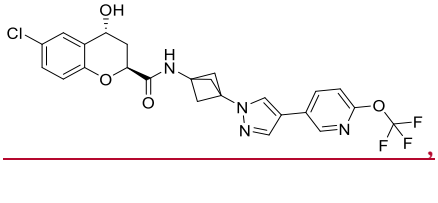


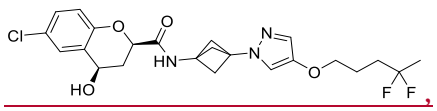




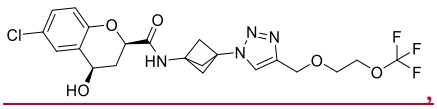


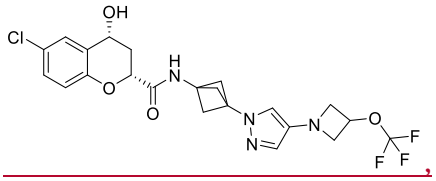


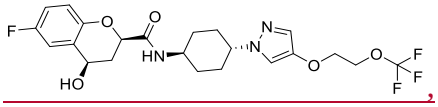


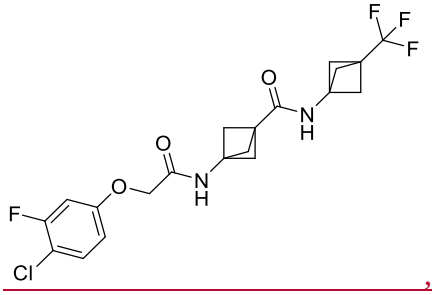


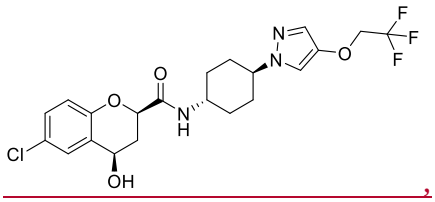


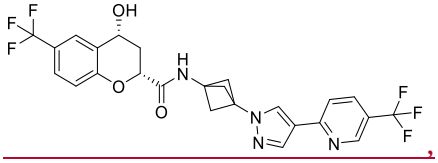


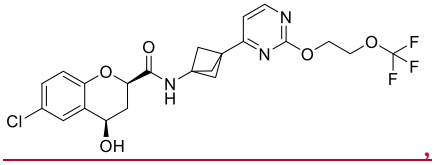


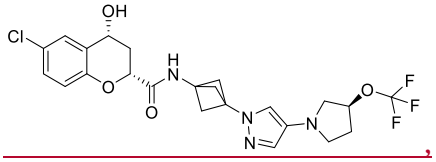


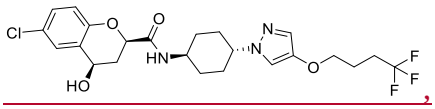


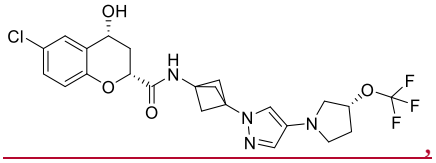


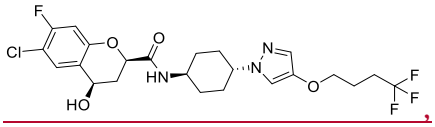


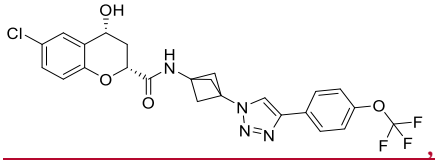


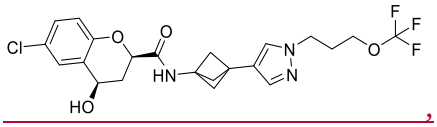


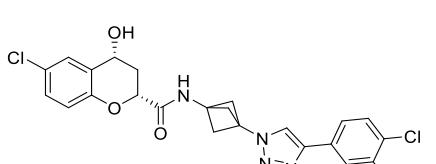


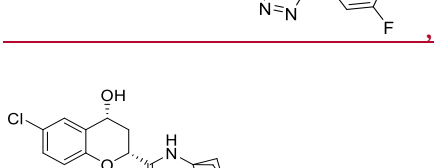


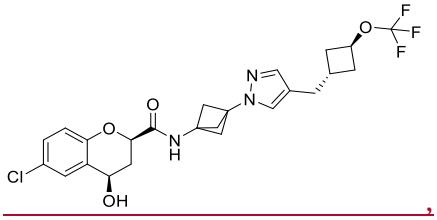


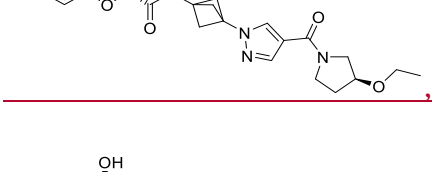


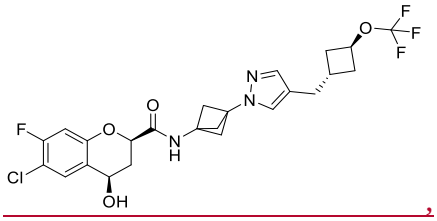


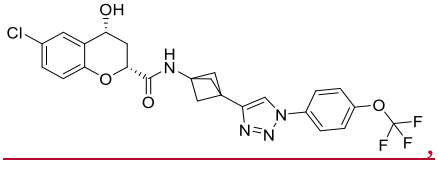


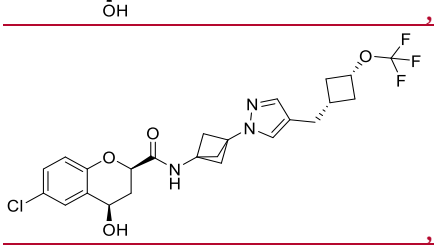




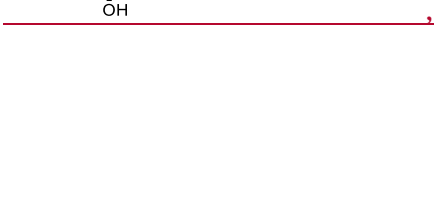


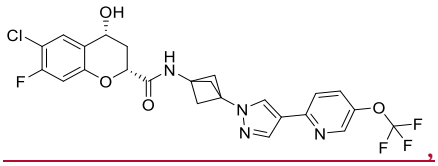


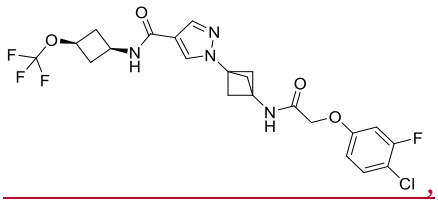


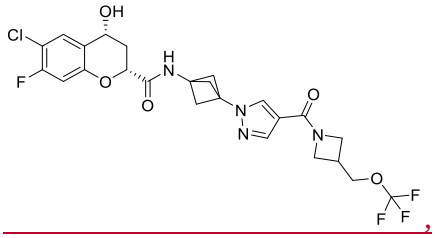


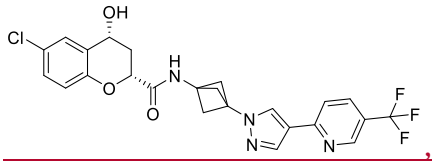


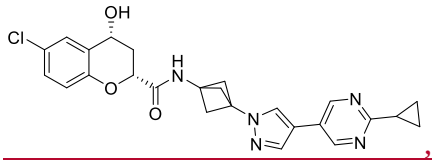


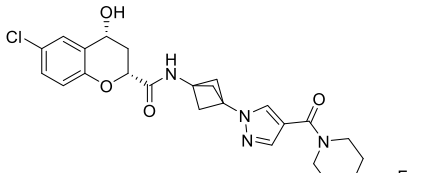




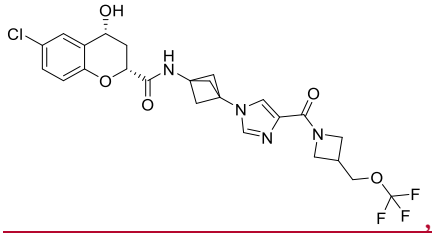


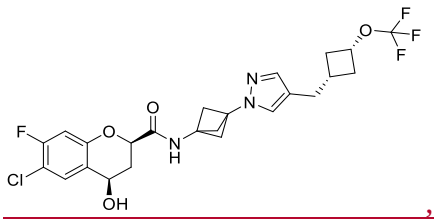


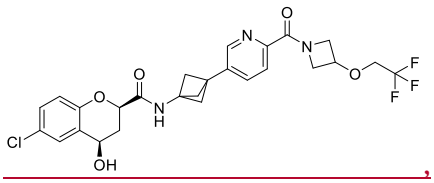


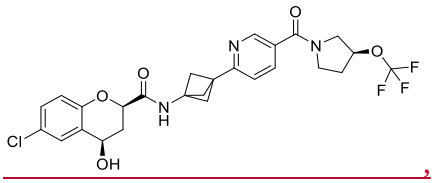


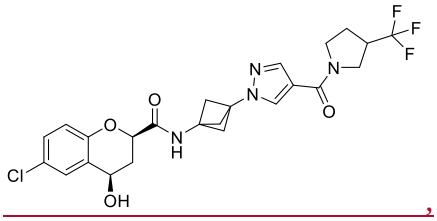


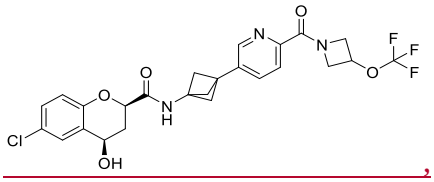


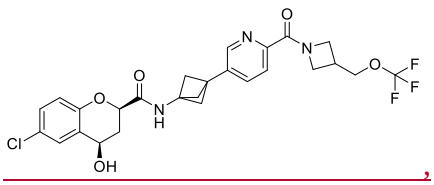


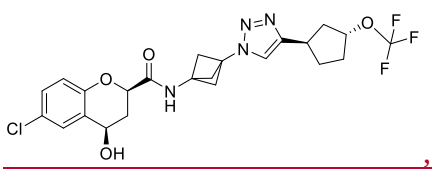


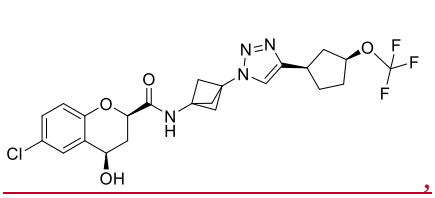


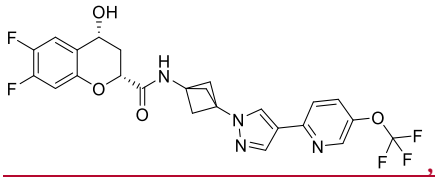


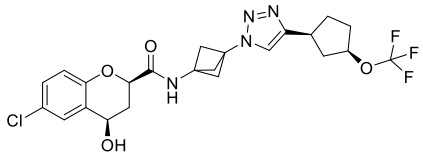


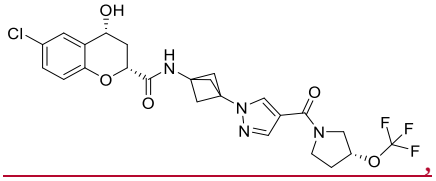


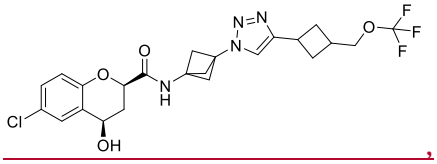


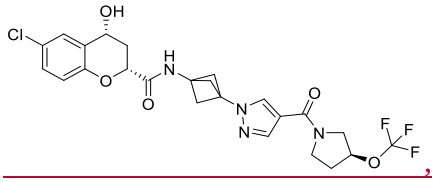


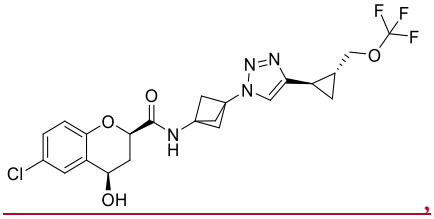


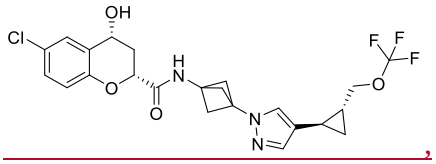


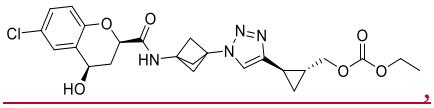


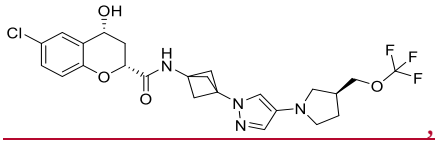


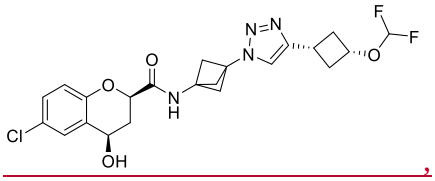


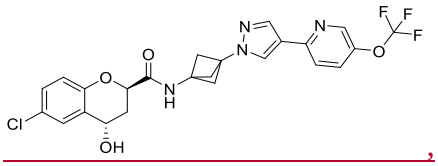


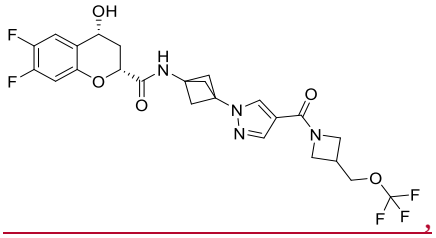


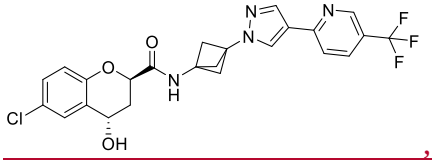


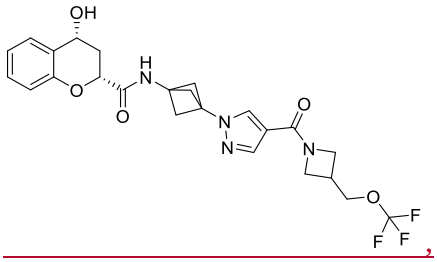


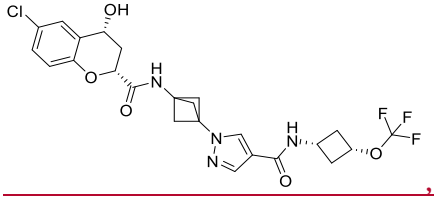


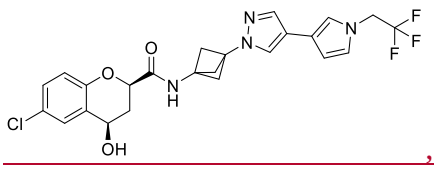


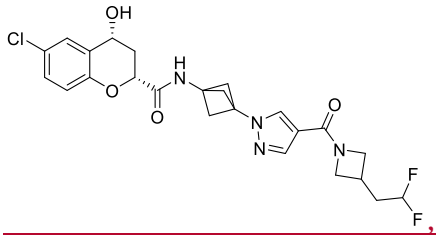


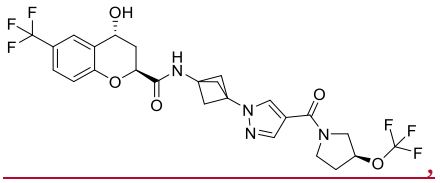


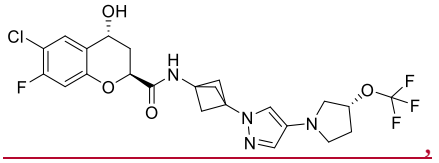


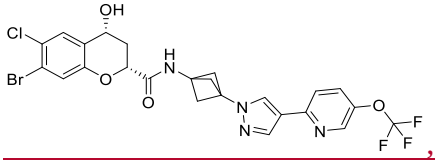


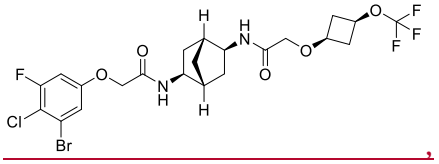


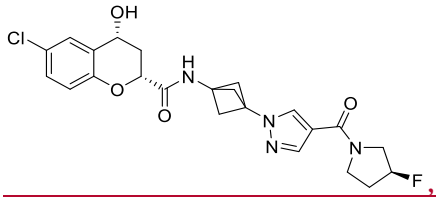


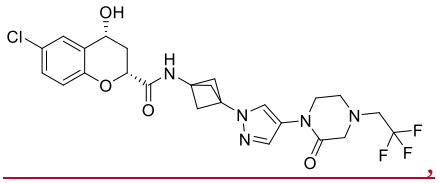


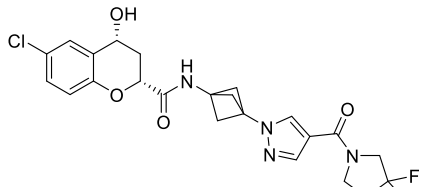


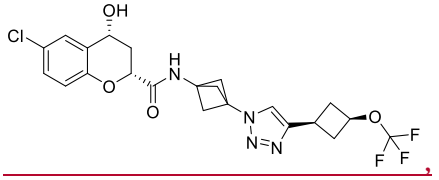


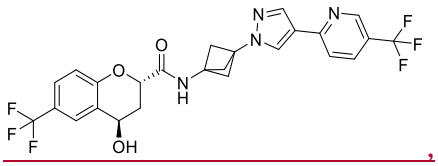


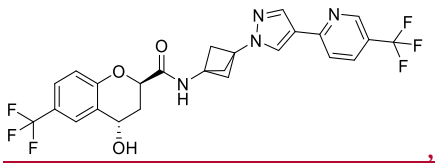


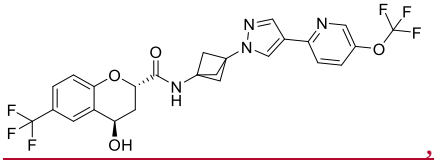


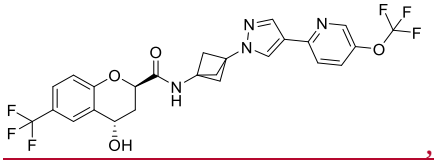


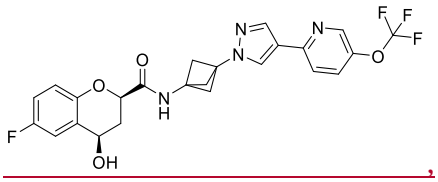


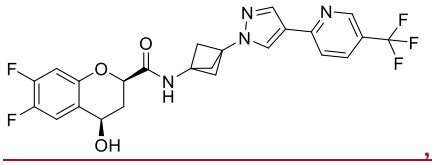


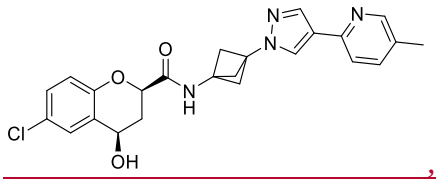


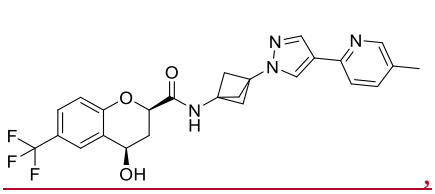


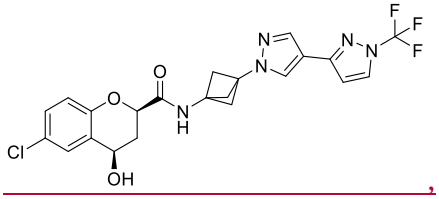


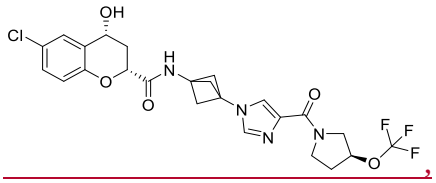


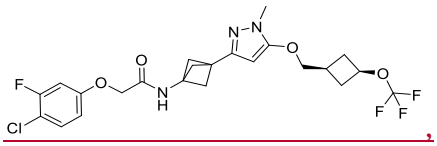


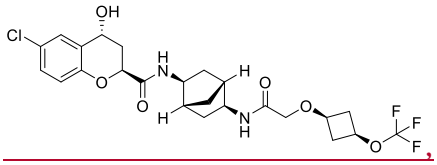


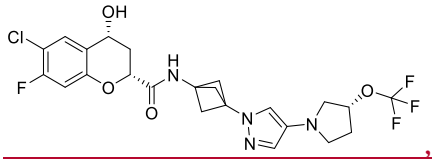


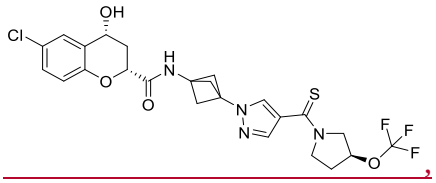


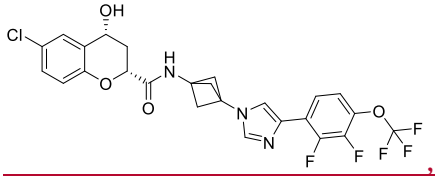


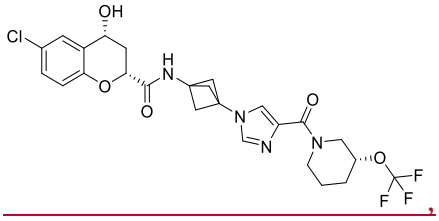


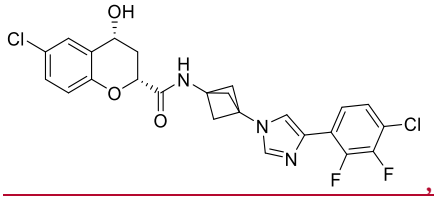


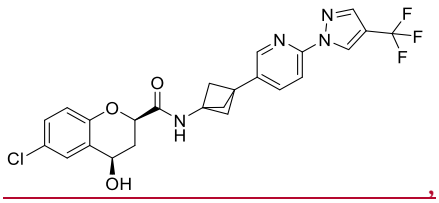


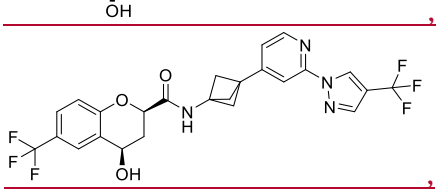


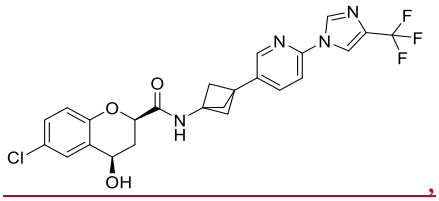


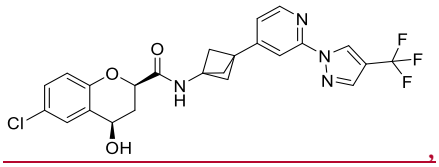


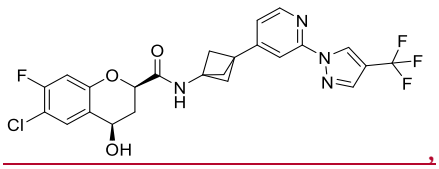


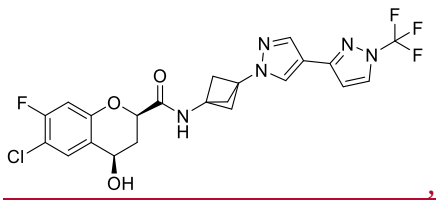


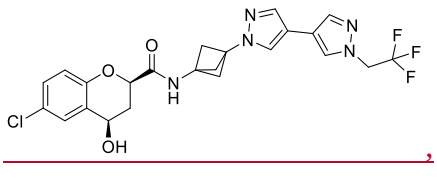


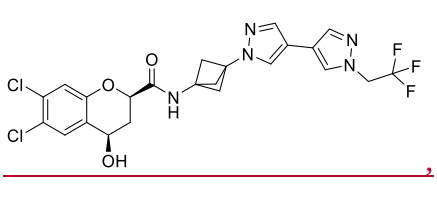


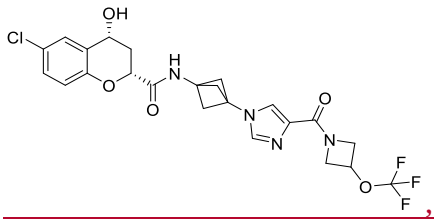


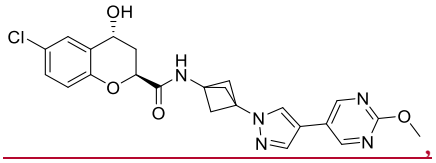


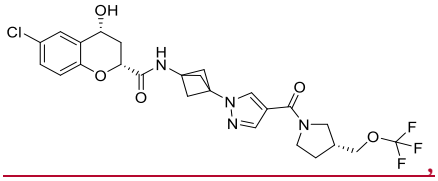


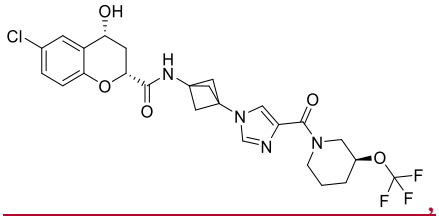


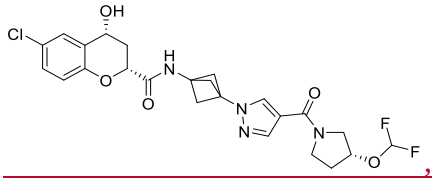


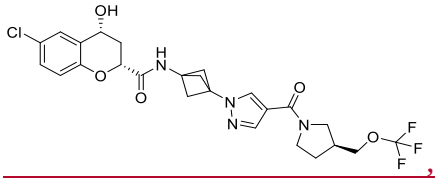


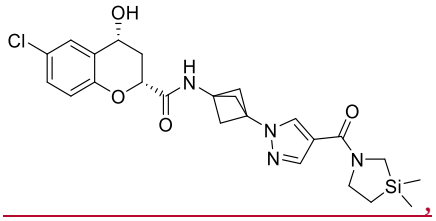


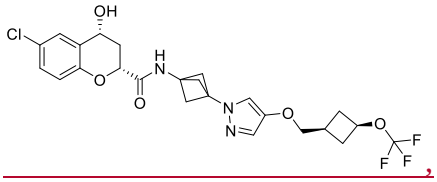


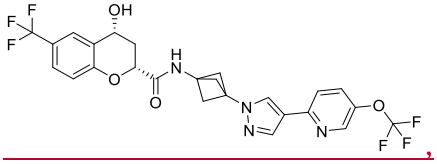


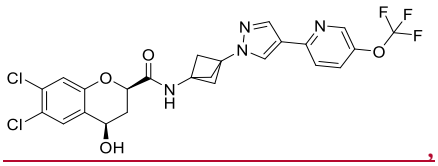


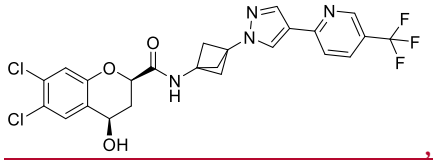


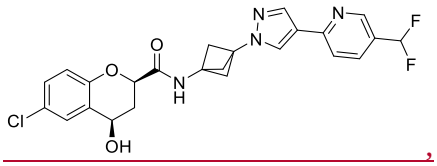


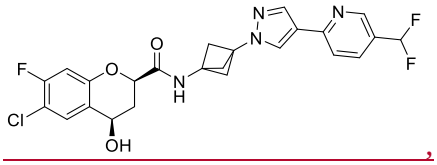


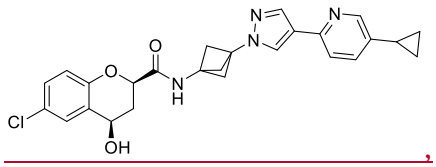


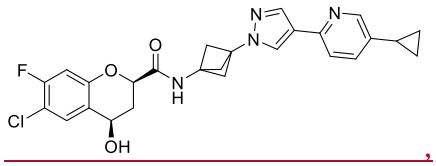


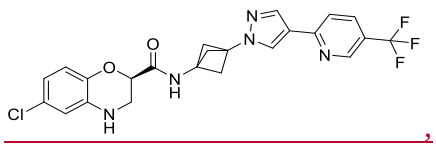


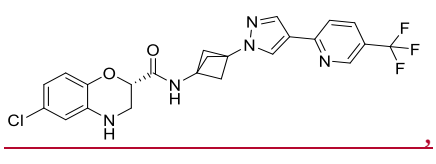


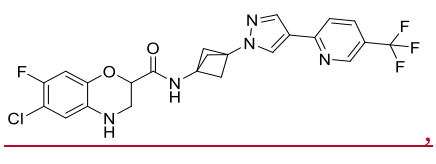


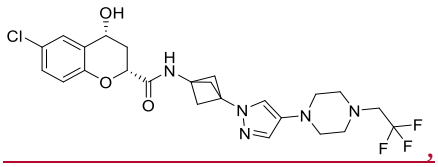


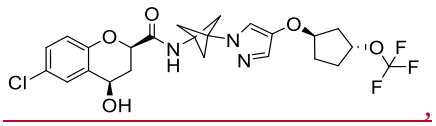


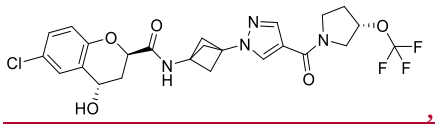


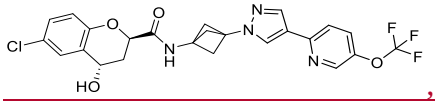


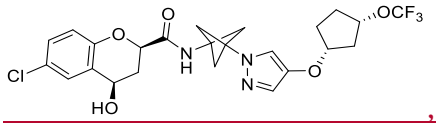


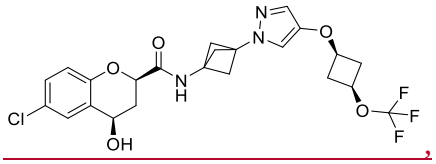


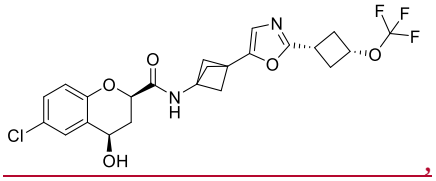


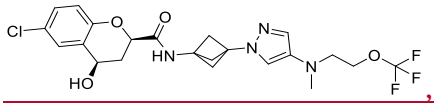


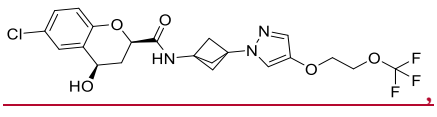


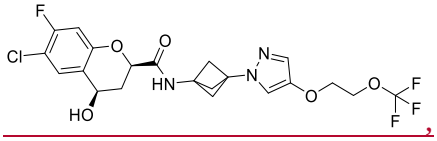


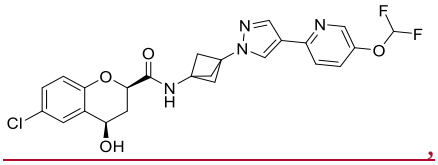


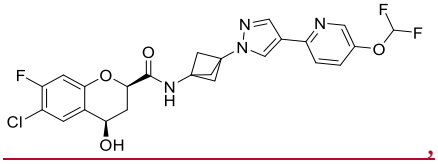


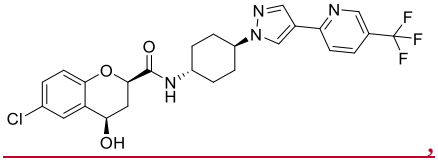


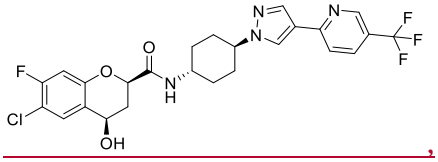


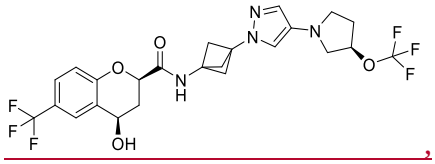


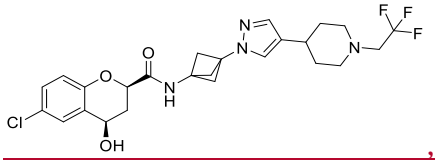


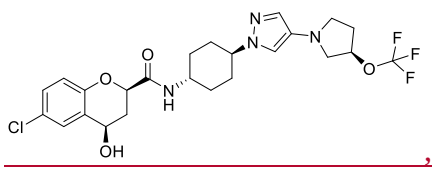


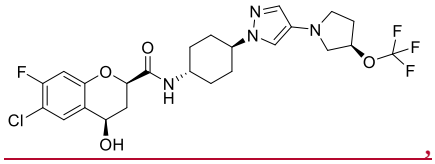


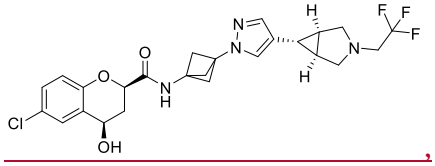


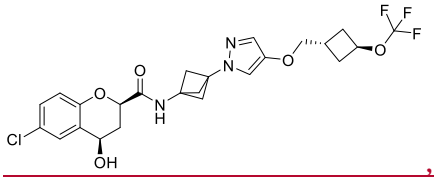


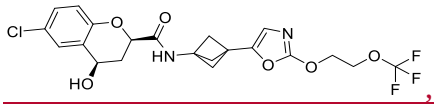


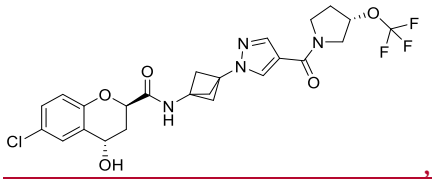


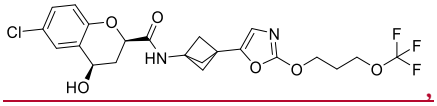


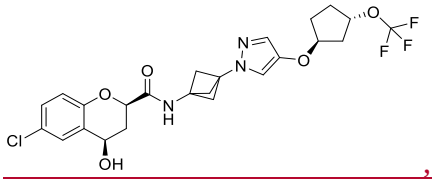


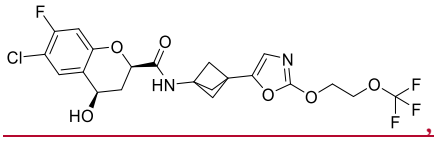


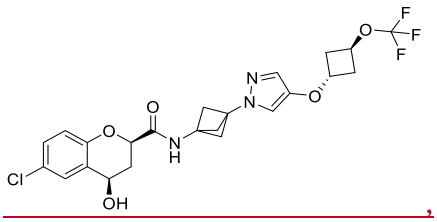


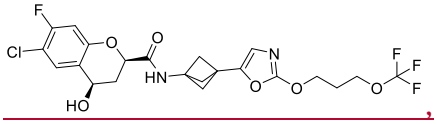


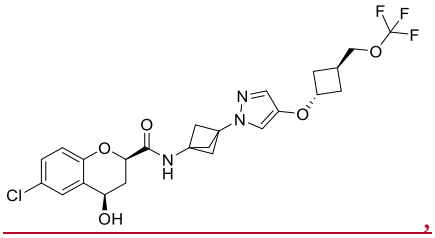


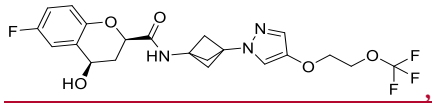


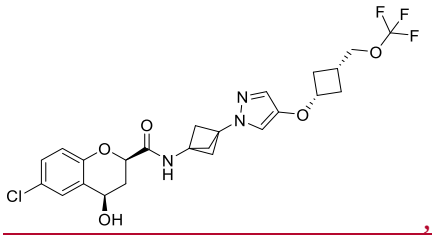


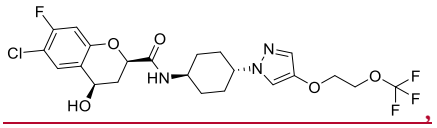


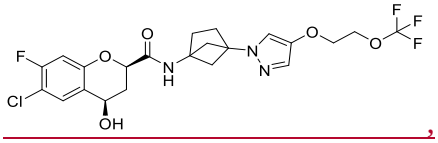


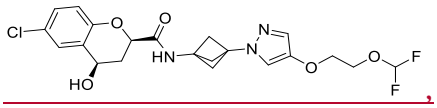


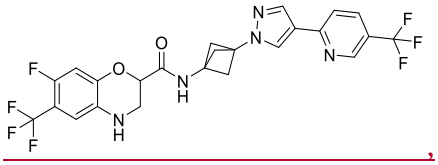


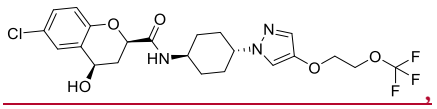


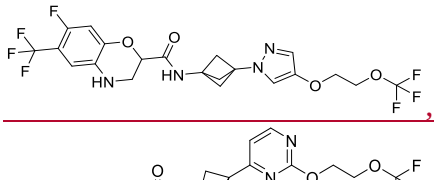


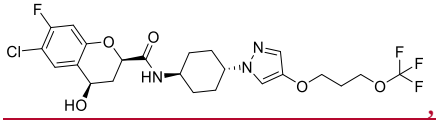


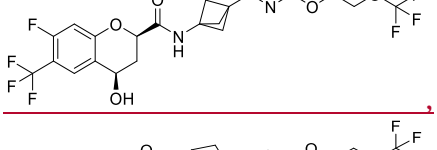


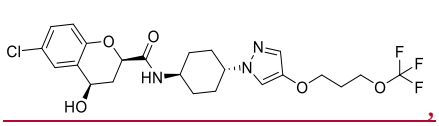


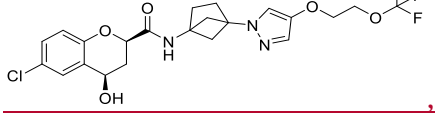


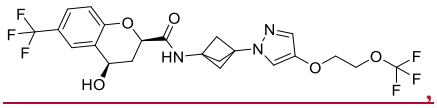


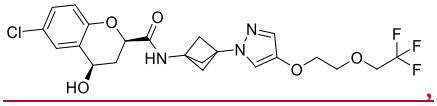


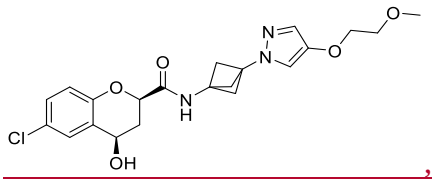


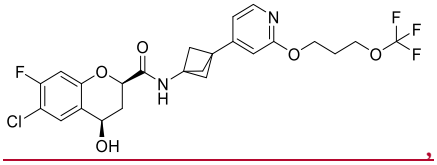


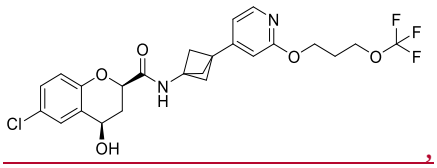


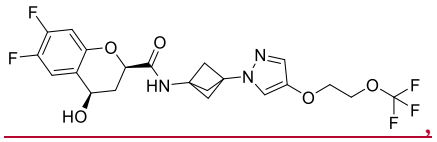


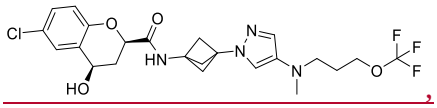


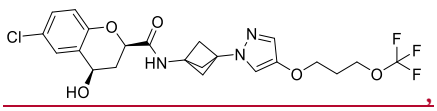


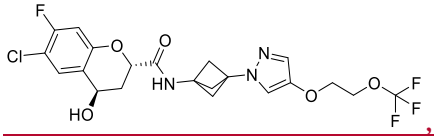


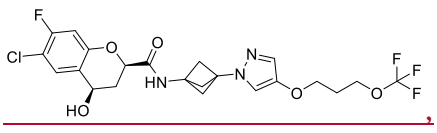


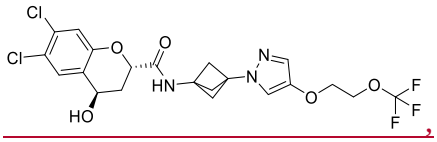


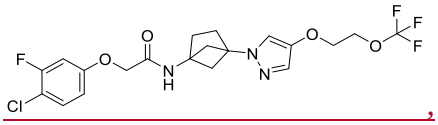


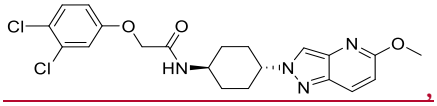


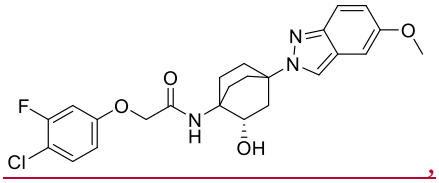


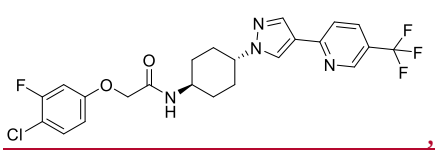


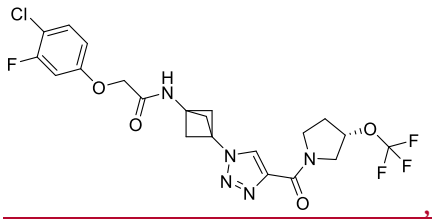


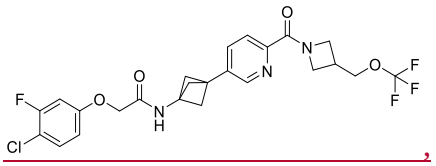


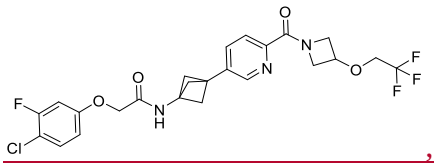


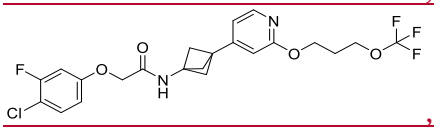


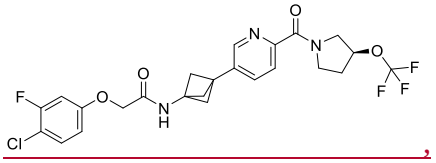


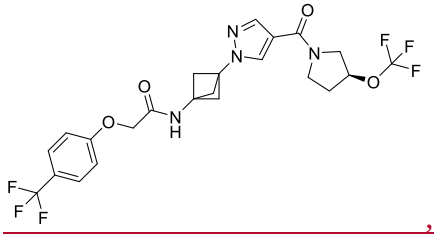


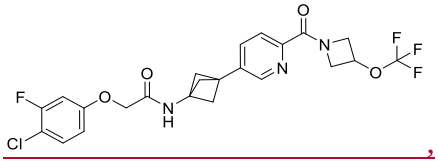


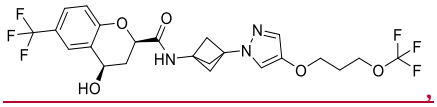


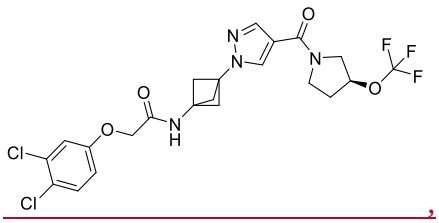


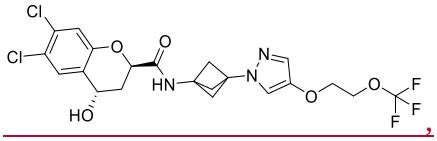


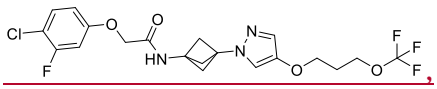


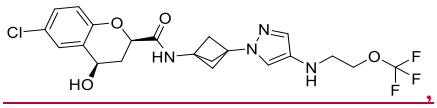


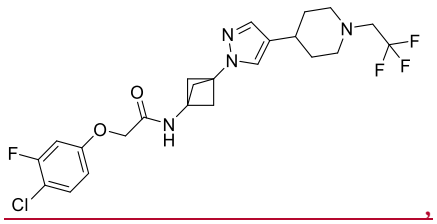


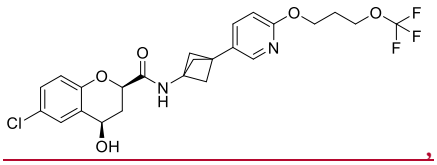


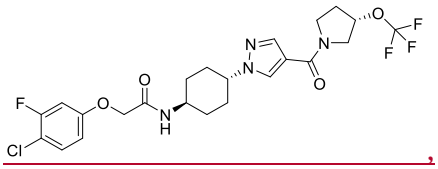


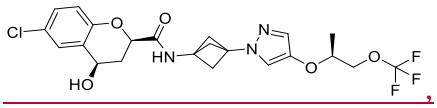


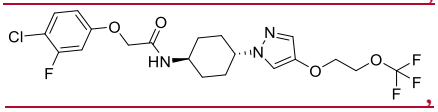


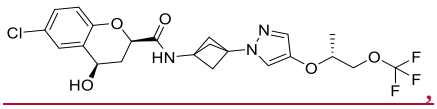


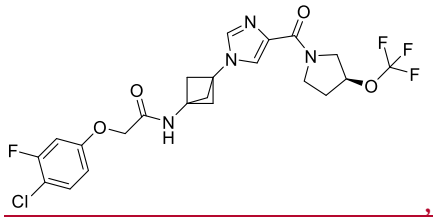


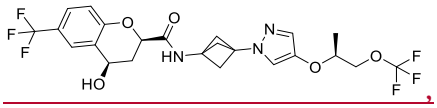


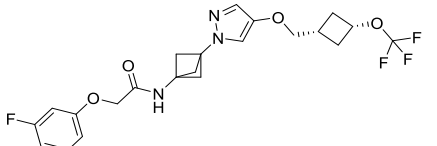


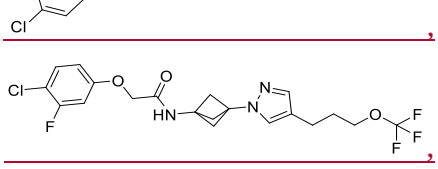


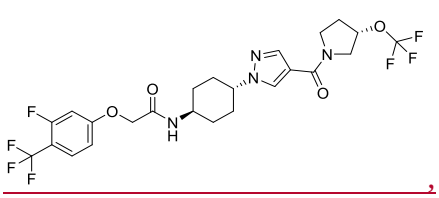


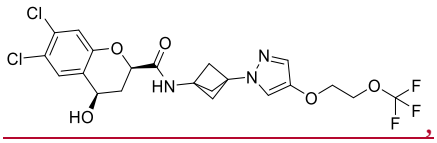


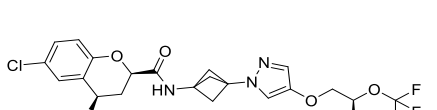


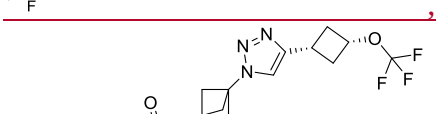


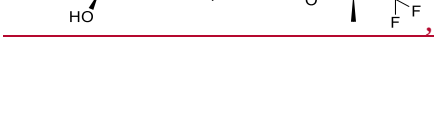


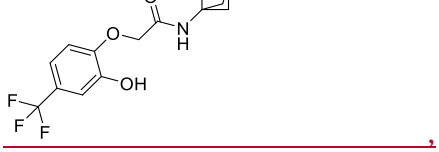


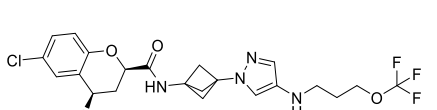


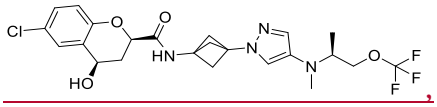


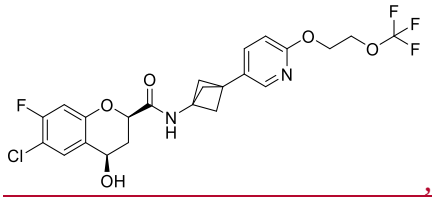


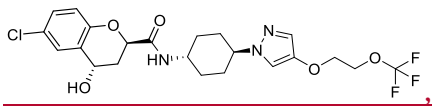


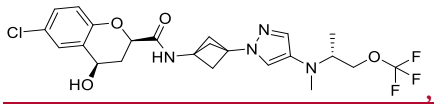


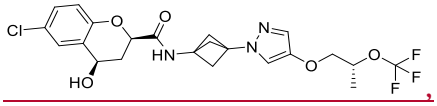


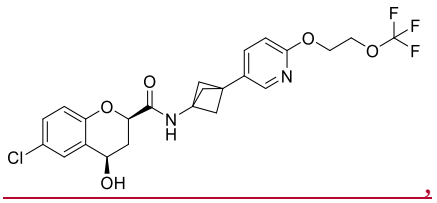


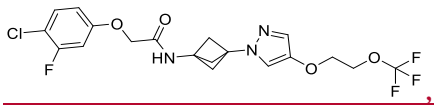


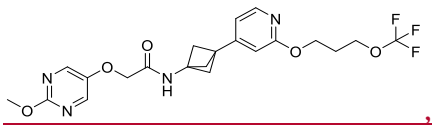


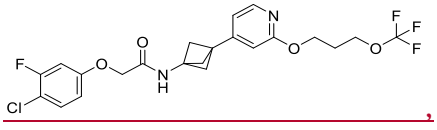


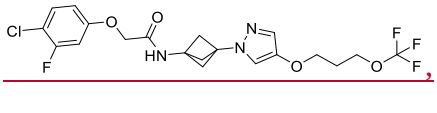


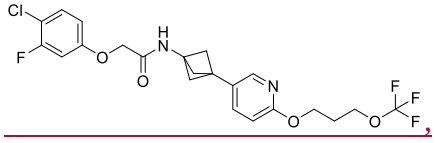


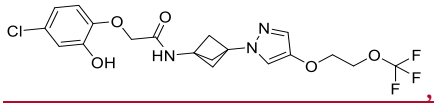


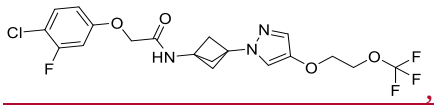


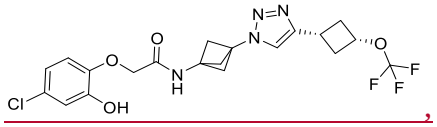


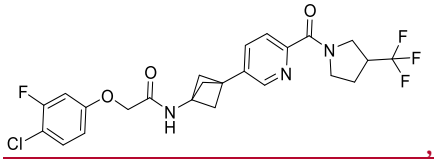


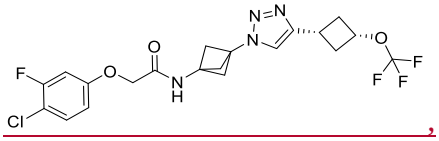


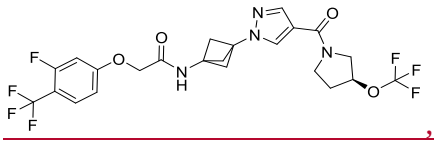


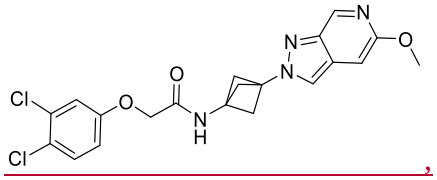


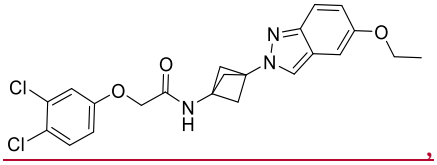


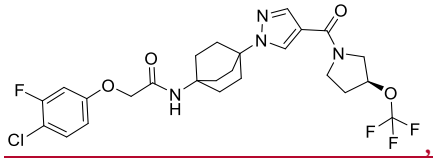


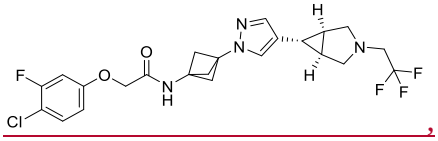


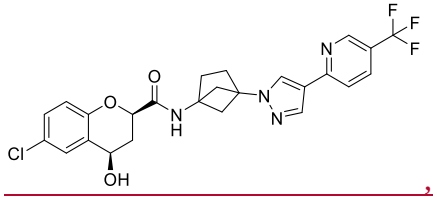


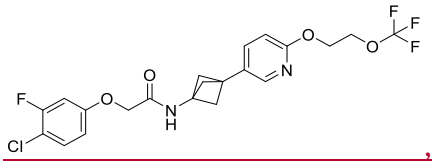


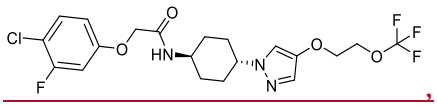


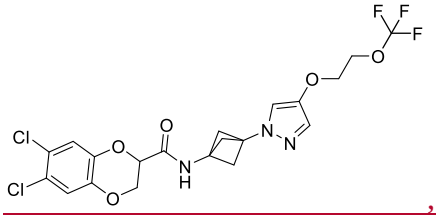


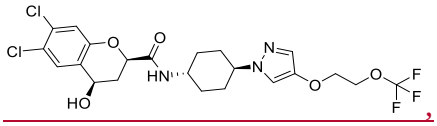


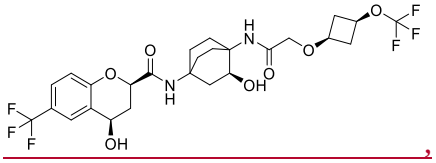


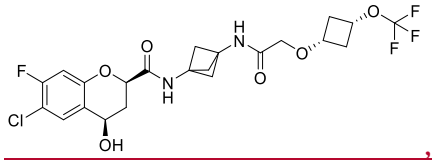


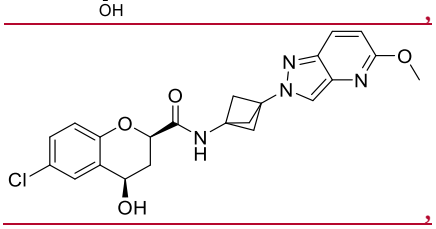


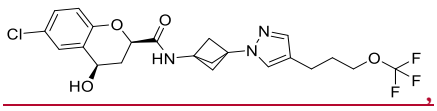


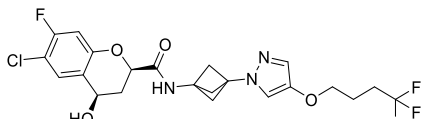


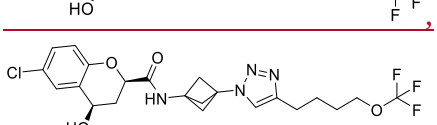


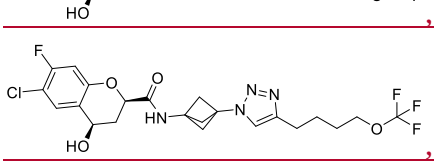


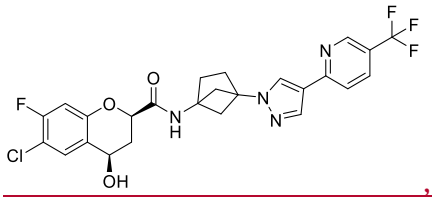


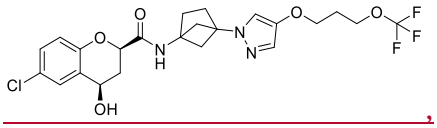


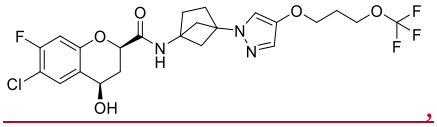


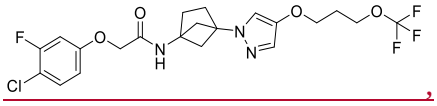


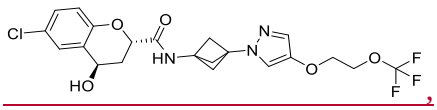


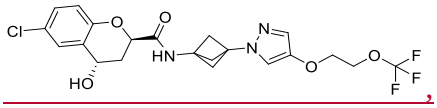


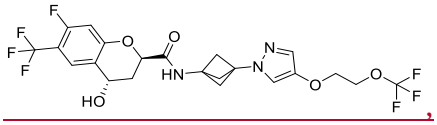


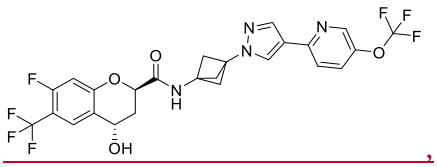


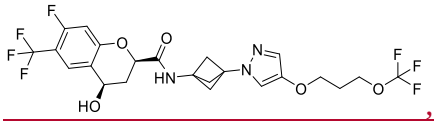


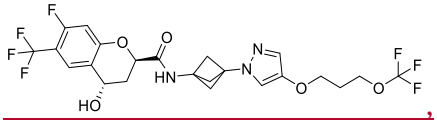


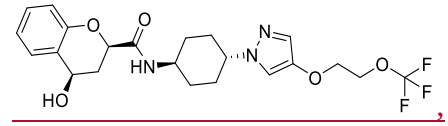


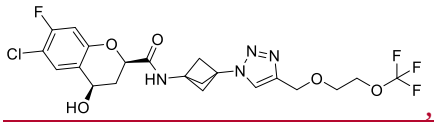


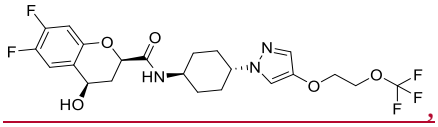


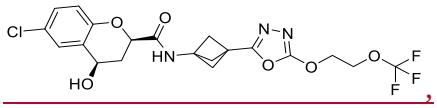


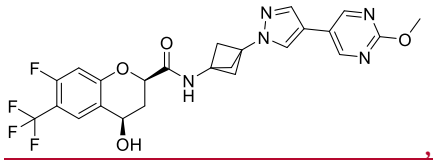


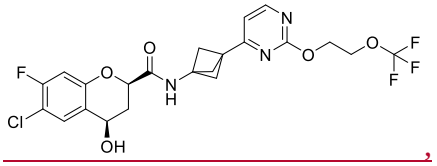


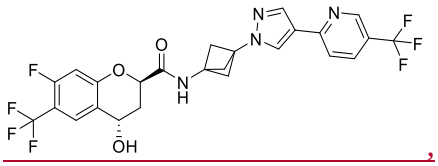


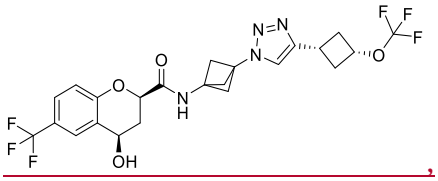


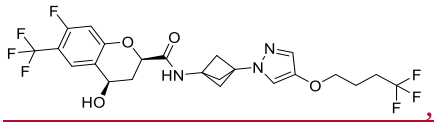


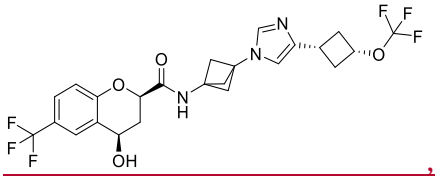


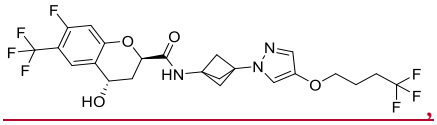


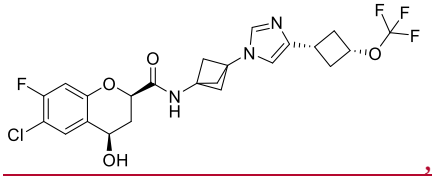


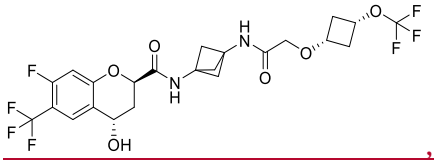


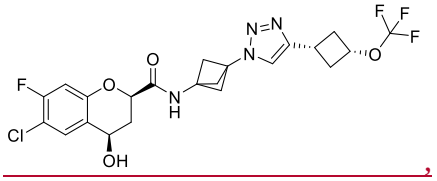


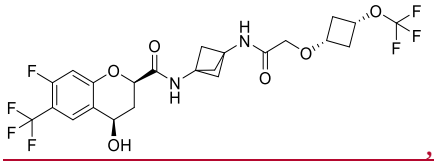


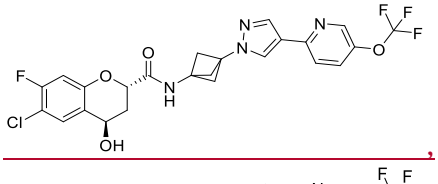


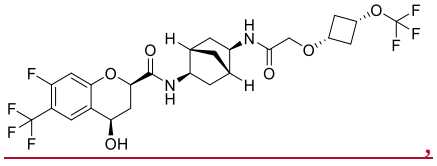


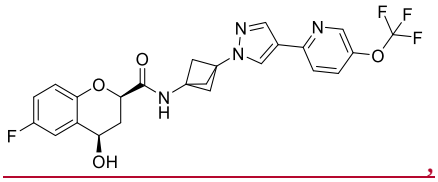


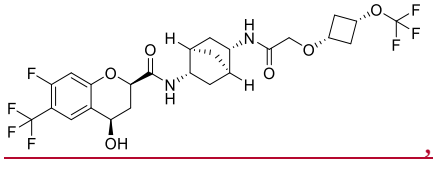


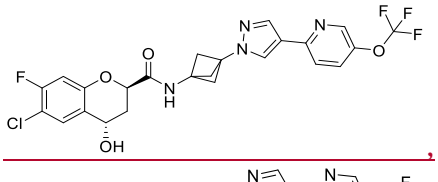


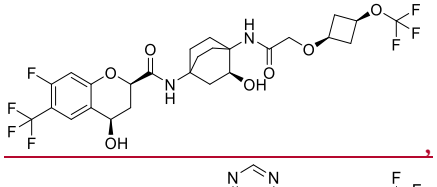


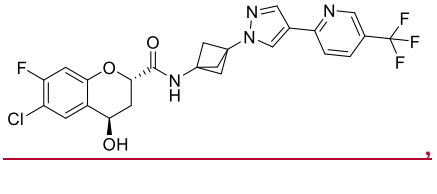


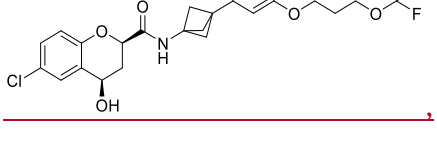




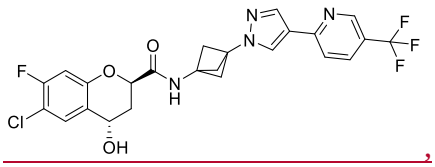








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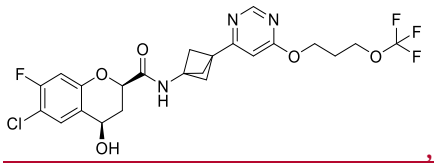
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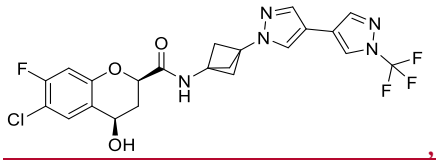
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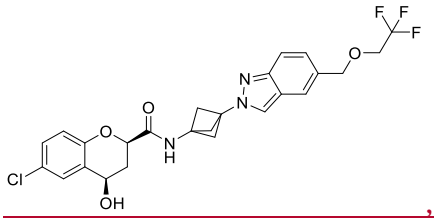
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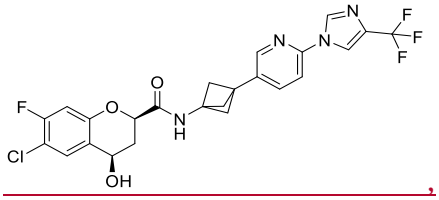
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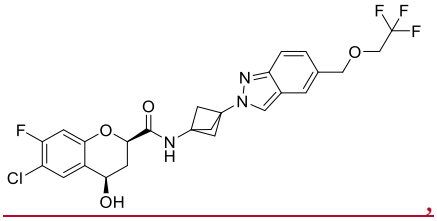
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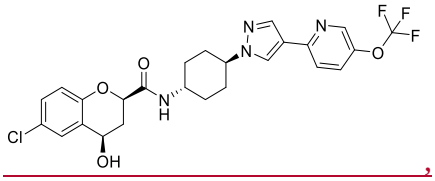
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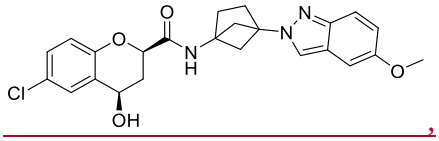
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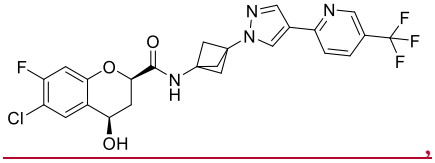
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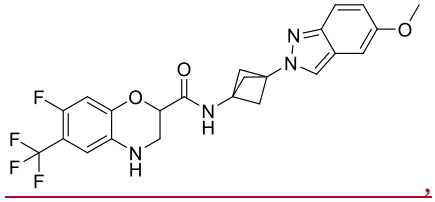
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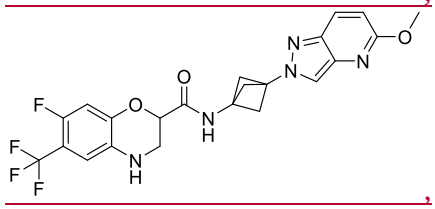
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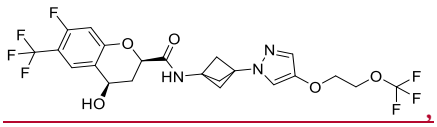
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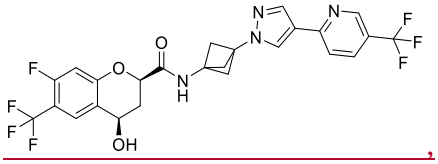
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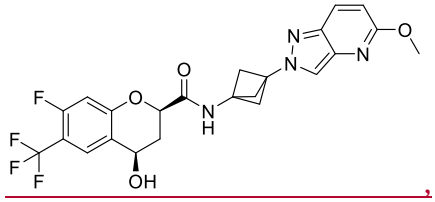
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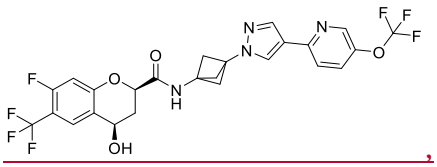
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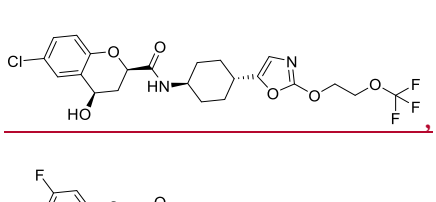
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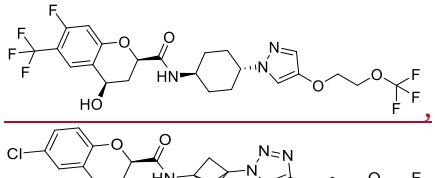
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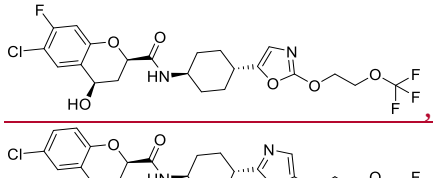
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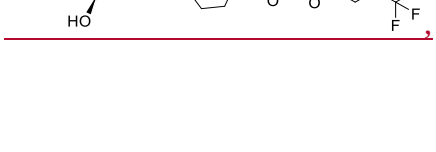
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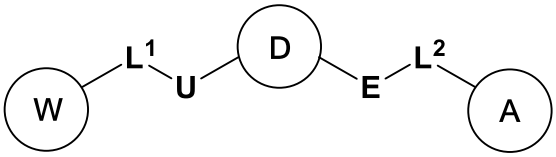
and a pharmaceutically acceptable salt thereof.

The present disclosure is directed, at least in part, to compounds, compositions, and methods for the modulation of eIF2B (*e.g.*, activation of eIF2B) and the attenuation of the ISR signaling pathway. In some ~~embodiment~~example<u>s</u>, disclosed herein is an eIF2B modulator (*e.g.*, an eIF2B activator) comprising a compound of Formula (I), Formula (II), Formula (III-a) or Formula (III-b), or a pharmaceutically acceptable salt thereof. In other ~~embodiment~~example<u>s</u>, disclosed herein are methods of using a compound of Formula (I), Formula (II), Formula (III-a) or Formula (III-b), or a pharmaceutically acceptable salt thereof for the treatment of a disease or disorder, *e.g.*, a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B or components in the ISR pathway (*e.g.*, eIF2 pathway).

For example, disclosed herein is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is a bridged bicyclic cycloalkyl, a bridged bicyclic heterocyclyl, a 4-6-membered monocyclic cycloalkyl, a 4-6-membered monocyclic heterocyclyl, or cubanyl, wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, 4-6-membered monocyclic cycloalkyl, 4-6-membered monocyclic heterocyclyl, or cubanyl is optionally substituted on one

each $R^{CC\text{-}II}$ is independently selected from the group consisting of hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, C(O) C_1-C_6 alkyl, $S(O)_2$–C_1-C_6 alkyl and 3-6-membered cycloalkyl and 4-6-membered heterocyclyl; wherein 3-6-membered cycloalkyl and 4-6-membered heterocyclyl may optionally be substituted by one or more substituents each independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, hydroxyl, halo and –C(O)OH;

each $R^{D\text{-}II}$ is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

each $R^{E\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

each $R^{F\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, or halo; and

each $R^{G\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, halo or oxo;

provided that when D^{II} is a bridged bicyclic 5-membered cycloalkyl, E^{II} is $–NR^{2\text{-}II}C(O)–$.

In some ~~embodiment~~example, a compound disclosed herein is selected from a compound set forth in Table 1 or Table 2, or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~example, a compound disclosed herein is selected from a compound set forth in Table 1, or a pharmaceutically acceptable salt thereof.

In some ~~embodiment~~example, a compound disclosed herein, or a pharmaceutically acceptable salt thereof is formulated as a pharmaceutically acceptable composition comprising a disclosed compound and a pharmaceutically acceptable carrier.

In another ~~aspect~~example, the present ~~invention~~disclosure features a method of treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease or a disease or disorder associated with impaired function of eIF2B or components in the ISR pathway (*e.g.*, eIF2 pathway) in a subject, wherein the method comprises administering a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, or a composition thereof, to a subject.

In another ~~aspect~~example, the present ~~invention~~disclosure features a method of treating a disease or disorder related to modulation (*e.g.*, a decrease) in eIF2B activity or level, modulation (*e.g.*, a decrease) of eIF2α activity or level, modulation (*e.g.*, an increase) in eIF2α phosphorylation, modulation (*e.g.*, an increase) of phosphorylated eIF2α pathway activity, or modulation (*e.g.*, an increase) of ISR activity in a subject, wherein the method comprises administering a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, or a composition thereof, to a subject. In some ~~embodiment~~examples, the disease may be caused by a mutation to a gene or protein

sequence related to a member of the eIF2 pathway (*e.g.*, the eIF2α signaling pathway or ISR pathway).

In another ~~aspect~~example, the present ~~invention~~disclosure features a method of treating cancer in a subject, the method comprising administering to the subject a compound of Formula (I) or Formula (II) in combination with an immunotherapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features compounds, compositions, and methods comprising a compound of Formula (I), Formula (II), Formula (III-a) or Formula (III-b), or a pharmaceutically acceptable salt thereof for use, *e.g.*, in the modulation (*e.g.*, activation) of eIF2B and the attenuation of the ISR signaling pathway.

Definitions

Chemical Definitions

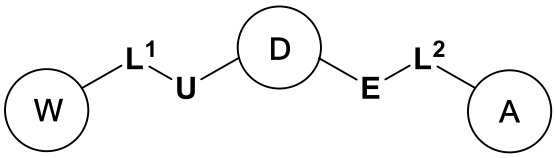
Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred

CLAIMS

1. A compound of Formula (I):



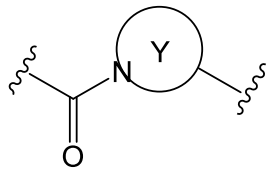
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is a bridged bicyclic cycloalkyl, a bridged bicyclic heterocyclyl, a 4-6-membered monocyclic cycloalkyl, a 4-6-membered monocyclic heterocyclyl, or cubanyl, wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, 4-6-membered monocyclic cycloalkyl, 4-6-membered monocyclic heterocyclyl, or cubanyl is optionally substituted on one or more available carbons with 1-4 R^X; and wherein if the 4-6-membered monocyclic heterocyclyl or bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N1};

U is $–NR^1C(O)–$, $–C(O)NR^1–$ or 5-6-membered heteroaryl;

E is absent or is a bond, $–NR^2C(O)–$, $–C(O)NR^2–$, 5-6-membered heteroaryl or 5-6-membered heterocyclyl; wherein 5-6-membered heteroaryl or 5-6-membered heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^G; and wherein if the 5-6-membered heteroaryl or 5-6-membered heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N2}; or

E is 

; Y is a 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl, wherein the 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^G; and wherein if the 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N2};

L^1 is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, $–NR^{N3}–$, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L1};

L^2 is absent or is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2};

wherein E and L^2 both cannot be either a bond or absent simultaneously;

R^1 is hydrogen or C_1-C_6 alkyl;

R^2 is hydrogen or C_1-C_6 alkyl;

W is a 8-10 membered, partially unsaturated, fused bicyclic ring moiety comprising a 5-6 membered heterocyclyl fused to a phenyl or 5-6-membered heteroaryl; wherein the heterocyclyl may be optionally substituted on one or more available carbons with 1-4 R^{W1}; wherein the phenyl or heteroaryl may optionally be substituted on one or more available unsaturated carbons with 1-4 R^{W2}; wherein if the heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may optionally be substituted with R^{N4}; and wherein W is attached to L^2 through an available saturated carbon or nitrogen atom within the heterocyclyl;

A is C_3-C_6 cycloalkyl, phenyl, 4-6-membered heterocyclyl, 5-6-membered heteroaryl, or 8-10-membered bicyclic heteroaryl, wherein C_3-C_6 cycloalkyl, phenyl, 4-6-membered heterocyclyl, 5-6-membered heteroaryl, or 8-10-membered bicyclic heteroaryl is optionally substituted on one or more available carbons or silicons with 1-5 R^Y; and wherein if the 5-6-membered heteroaryl or 8-10-membered bicyclic heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N5};

each R^{L1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^{L2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, thioxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

R^{N1} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N2} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^{N3} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, and –$S(O)_2R^D$;

R^{N4} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, –C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–C_1-C_3 alkyl–O–C_1-C_3 alkyl–O–C_1-C_3 alkyl, –C(O)–phenyl, –C(O)–heteroaryl, –C(O)–heterocyclyl, –$S(O)_2$–C_1-C_6 alkyl, –$S(O)_2$–phenyl, –$S(O)_2$–heteroaryl, –$C(O)NR^BR^C$ and –$C(O)OR^D$; wherein

C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–heterocyclyl, and –$S(O)_2$–C_1-C_6 alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms) and $S(O)_wC_{1\text{-}6}$ alkyl (wherein w is 0, 1 or 2); and

–C(O)–phenyl, –C(O)–heteroaryl, –$S(O)_2$–phenyl and –$S(O)_2$–heteroaryl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, hydroxyl, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms), C_1-C_6 alkoxy (optionally substituted by one, two or three fluorine atoms), and $S(O)_2$-NR^BR^C;

R^{N5} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, -$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, and –$S(O)_2R^D$;

each R^{W1} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl (optionally substituted by –CO_2H), hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, C=N-OH, halo, cyano, –OR^A, –NR^BR^C, –NR^BR^{CC}, –$NR^BC(O)R^D$, -$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, –SR^E, –$S(O)R^D$, and –$S(O)_2R^D$;

each R^{W2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, -OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, –C(O)OH, –$C(O)OR^D$, -$S(R^F)_m$, -$S(O)R^D$, and –$S(O)_2R^D$; or

2 R^{W2} groups on adjacent atoms, together with the atoms to which they are attached, form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each R^X is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, oxo, $–C_1$-C_6 alkylene-OR^A, $–OR^A$, $–NR^BR^C$, $–NR^BR^{CC}$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–S(R^F)_m$, $–S(O)R^D$, $–S(O)_2R^D$, and G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 R^X;

each G^1 is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 R^Z;

each R^Z is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^A is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, C_1-C_6 alkoxy-C_1-C_6 alkylene, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 R^Z;

each R^{CC} is independently selected from the group consisting of hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, C(O) C_1-C_6 alkyl, $S(O)_2$– C_1-C_6 alkyl and 3-6-membered cycloalkyl and 4-6-membered heterocyclyl; wherein 3-6-membered cycloalkyl and 4-6-membered heterocyclyl may optionally be substituted by one or more substituents each independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, hydroxyl, halo and –C(O)OH;

each R^D is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, or halo-C_1-C_6 alkoxy-C_1-C_6 alkylene;

each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

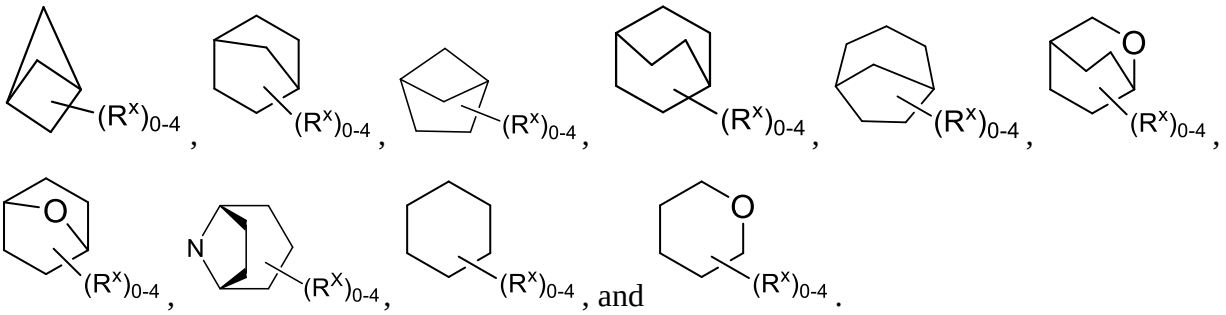
each R^F is independently hydrogen, C_1-C_6 alkyl, or halo;

each R^G is independently hydrogen, C_1-C_6 alkyl, halo or oxo; and

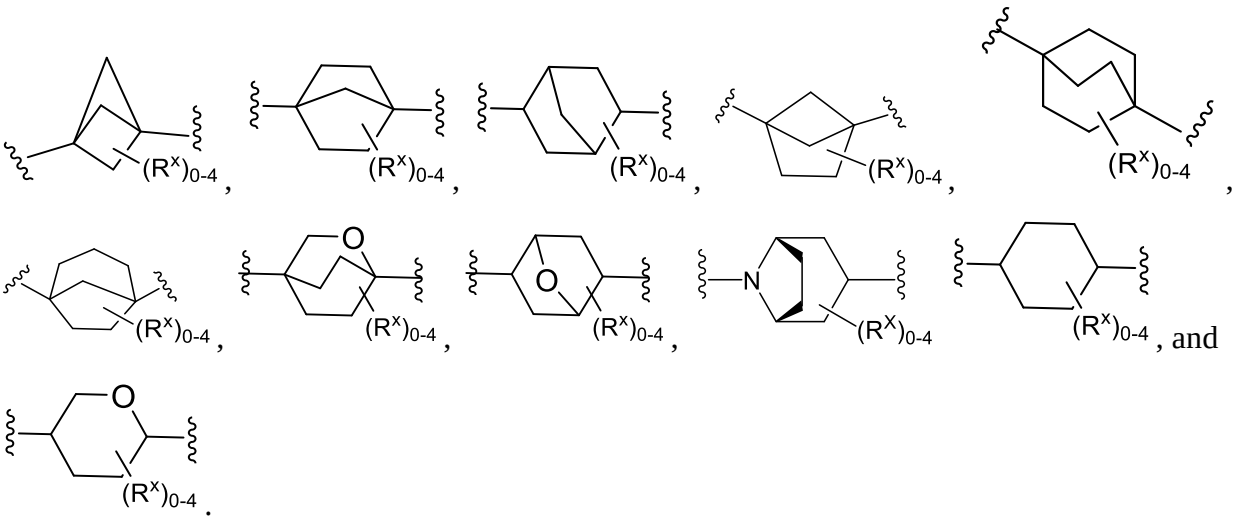
m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

2. The compound of claim 1, wherein D is bicyclo[1.1.1]pentane, bicyclo[2.2.1]heptane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, 2-oxabicyclo[2.2.2]octane, 7-oxabicyclo[2.2.1]heptane, 8-azabicyclo[3.2.1]octane, cyclohexyl or tetrahydro-2H-pyranyl, each of which is optionally substituted with 1-4 R^X groups.

3. The compound of claim 1 or 2, wherein D is selected from the group consisting of

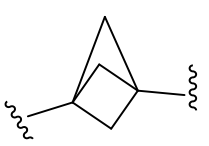
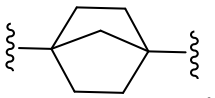
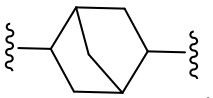
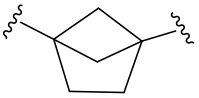
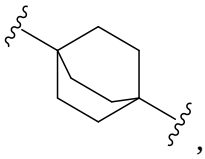
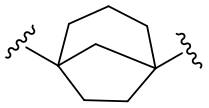
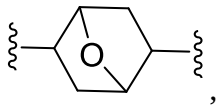
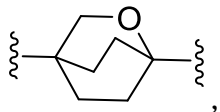
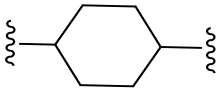
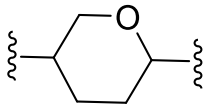


4. The compound of any one of claims 1-3, wherein D is selected from the group consisting of

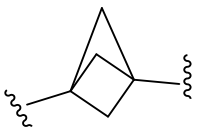
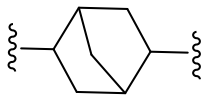
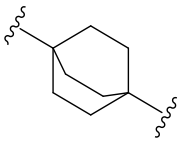
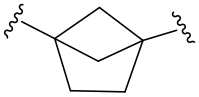
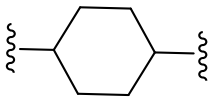
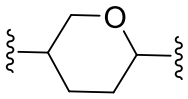


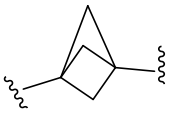
5. The compound of any one of claims 1-4, wherein D is substituted with 0 R^X.

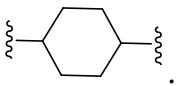
6. The compound of any one of claims 1-5, wherein D is selected from the group consisting of

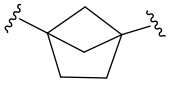
 ,  ,  ,  ,  ,
 ,  ,  ,  ,  , and
 .

7. The compound of any one of claims 1-6, wherein D is selected from the group consisting of

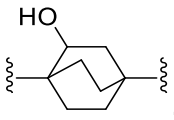
 ,  ,  ,  ,  , or
 .

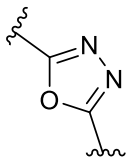
8. The compound of any one of claims 1-7, wherein D is  .

9. The compound of any one of claims 1-7, wherein D is  .

10. The compound of any one of claims 1-7, wherein D is  .

11. The compound of any one of claims 1-4, wherein D is substituted with 1 R^X.

12. The compound of any one of claims 1-4 and 11, wherein D is  .

13. The compound of any one of claims 1-12, wherein U is selected from the group consisting of *–NHC(O)–, *–C(O)NH–, and  , wherein "*" indicates the attachment point to D.

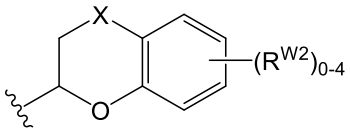
14. The compound of any one of claims 1-13, wherein U is *–NHC(O)–, wherein "*" indicates the attachment point to D.

15. The compound of any one of claims 1-14, wherein L^1 is a bond or C_1-C_6 alkylene, wherein C_1-C_6 alkylene is optionally substituted with 1-5 R^{L1}.

16. The compound of any one of claims 1-14, wherein L^1 is a bond or C_1-C_6 alkylene, wherein C_1-C_6 alkylene is substituted with 0 R^{L1}.

17. The compound of any one of claims 1-16, wherein L^1 is a bond.

18. The compound of any one of claims 1-17, wherein W is represented by Formula (W-a):



Formula (W-a)

wherein:

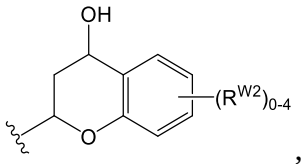
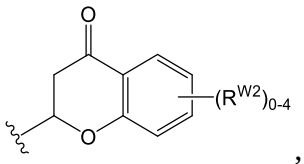
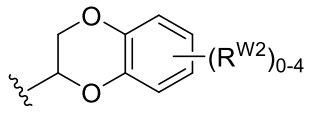
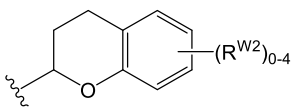
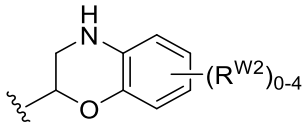
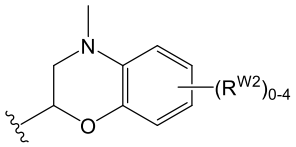
X is O, NR^{N4}, or $C(R^{X1})(R^{X2})$;

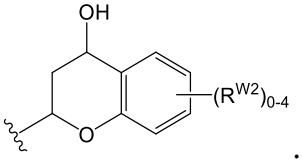
R^{N4} is hydrogen or C_1-C_6 alkyl;

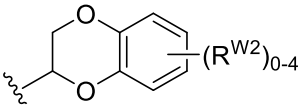
R^{X1} is hydrogen or hydroxyl;

R^{X2} is hydrogen or hydroxyl; or

R^{X1} and R^{X2} taken together to form an oxo moiety.

19. The compound of any one of claims 1-18, wherein W is selected from the group consisting of  ,  ,  ,  ,  , and  .

20. The compound of any one of claims 1-19, wherein W is  .

21. The compound of any one of claims 1-19, wherein W is  .

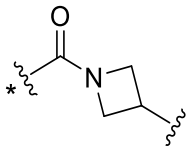
22. The compound of any one of claims 1-21, wherein W is substituted with 0 R^{W2}.

23. The compound of any one of claims 1-21, wherein W is substituted with 1 R^{W2}.

24. The compound of claim 23, wherein R^{W2} is chloro or $–CF_3$.

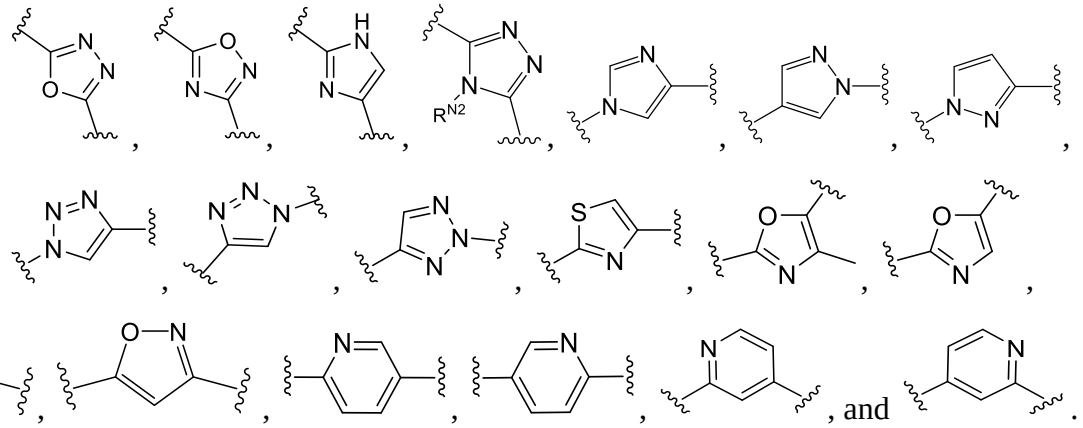
25. The compound of any one of claims 1-21, wherein W is substituted with 2 R^{W2}.

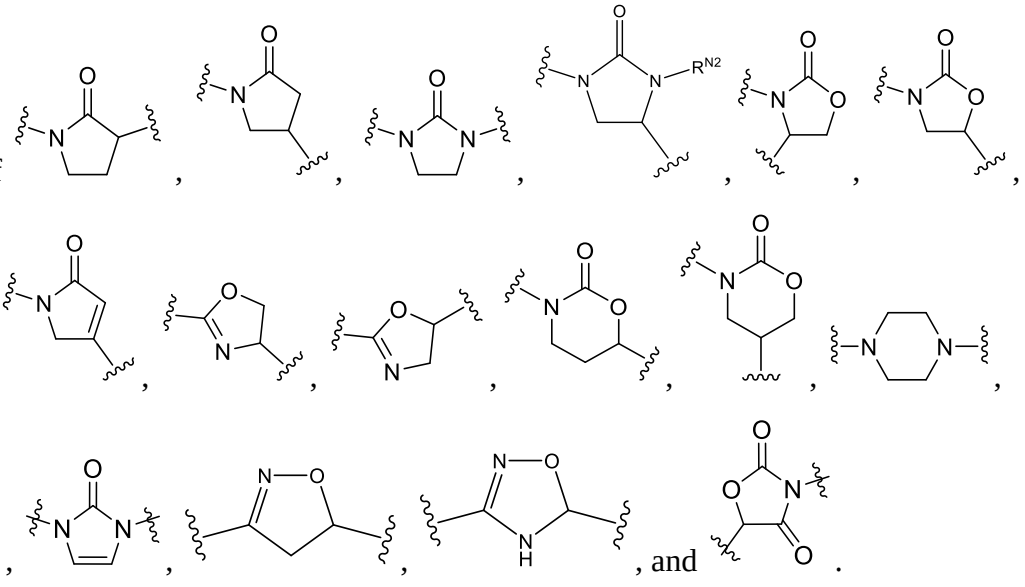
26. The compound of claim 25, wherein each R^{W2} is independently bromo, chloro, fluoro, or $–CF_3$.

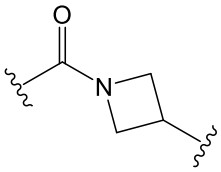
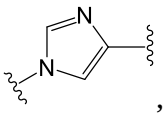
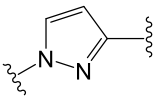
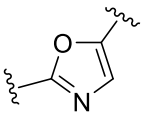
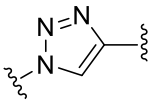
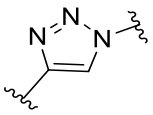
27. The compound of any one of claims 1-26, wherein E is selected from the group consisting of a bond, *–$NR^2C(O)$–, *–$C(O)NR^2$–, and  , wherein "*" indicates the attachment point to D.

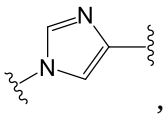
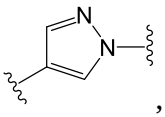
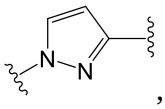
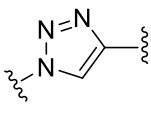
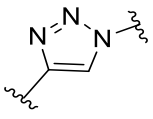
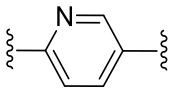
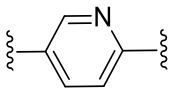
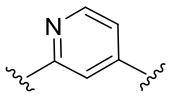
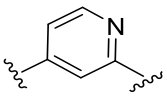
28. The compound of any one of claims 1-27, wherein E is *–NHC(O)–, wherein "*" indicates the attachment point to D.

29. The compound of any one of claims 1-26, wherein E is absent.

30. The compound of any one of claims 1-26, wherein E is selected from the group consisting of  , and .

31. The compound of any one of claims 1-26, wherein E is selected from the group consisting of  , and .

32. The compound of any one of claims 1-26, wherein E is selected from the group consisting of a bond, –NR^{2}C(O)–,  ,  ,  ,  ,  , and  .

33. The compound of any one of claims 1-26, wherein E is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  .

34. The compound of any one of claims 1-33, wherein R^2 is hydrogen.

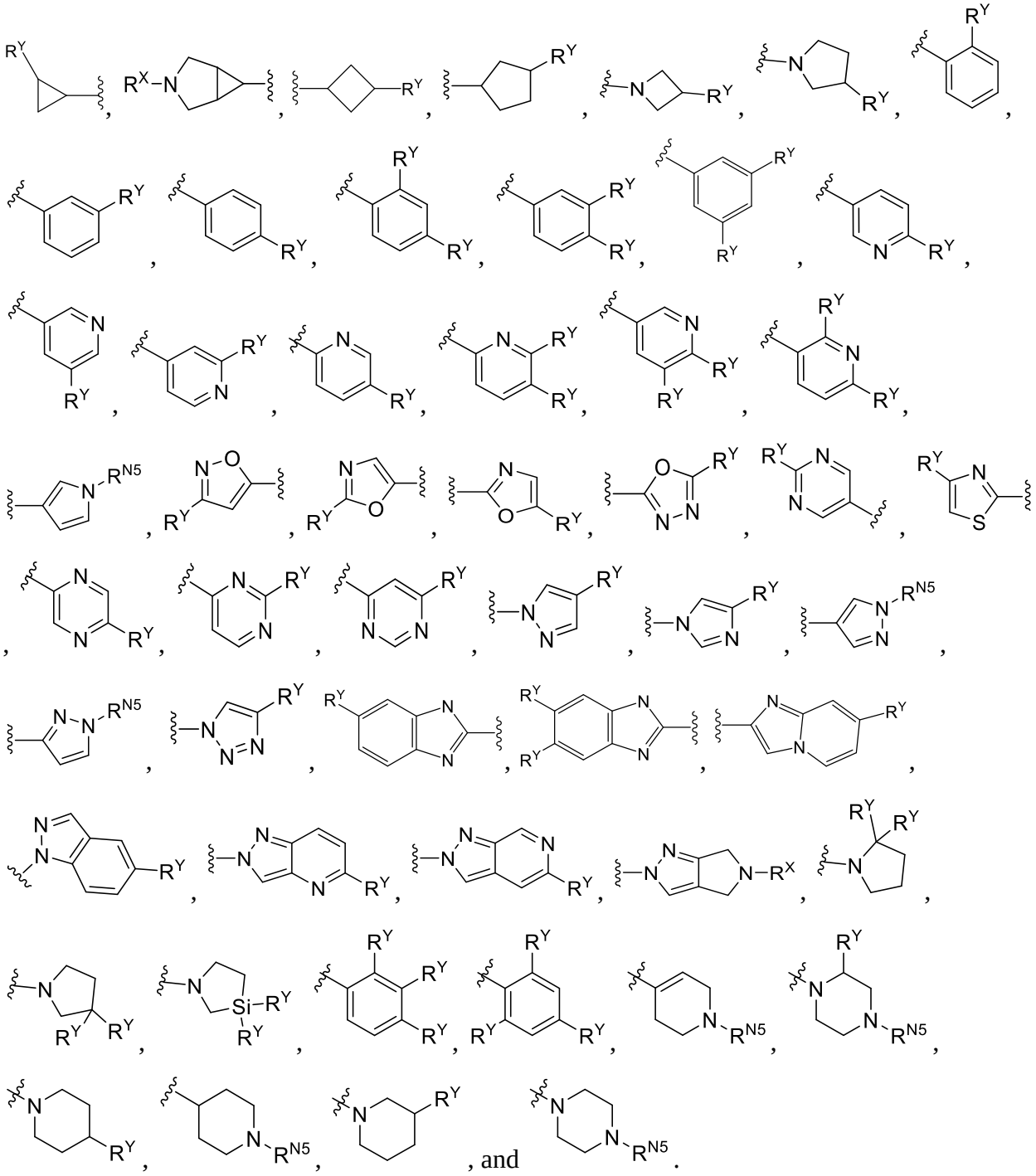
35. The compound of any one of claims 1-34, wherein L^2 is a bond, –O–, C_1-C_6 alkylene, or 2-7 membered heteroalkylene, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2}, wherein each R^{L2} is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, oxo, thioxo, halo, –OR^A.

36. The compound of any one of claims 1-35, wherein L^2 is a bond, –CH_2–, –CH_2O–*, –C(O)–, –C(S)–, –OCH_2C(O)–*, –C(O)NH–*, –OCH_2–*, –OCH_2C(O)NH–*, or –O–, wherein "*" indicates the attachment point to A.

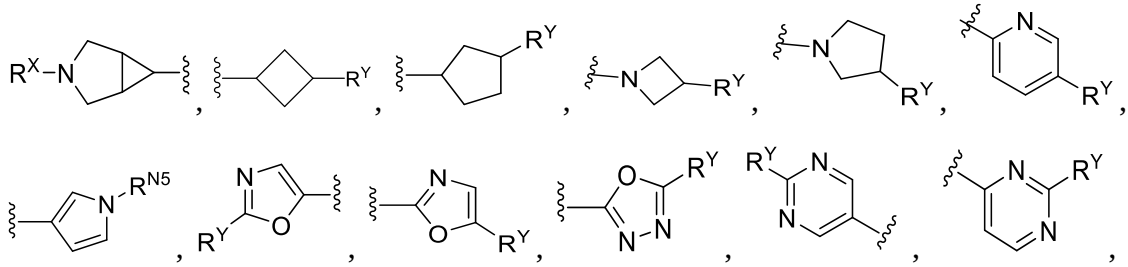
37. The compound of any one of claims 1-36, wherein L^2 is a bond, –CH_2–, –CH_2O–*, –C(O)–, –OCH_2–*, or –O–, wherein "*" indicates the attachment point to A.

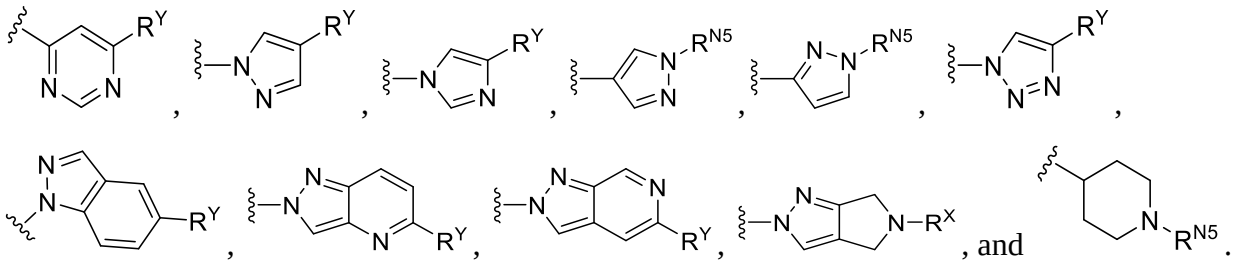
38~~36~~. The compound of any one of claims 1-34, wherein L^2 is absent.

39~~37~~. The compound of any one of claims 1-~~36~~38, wherein A is selected from the group consisting of



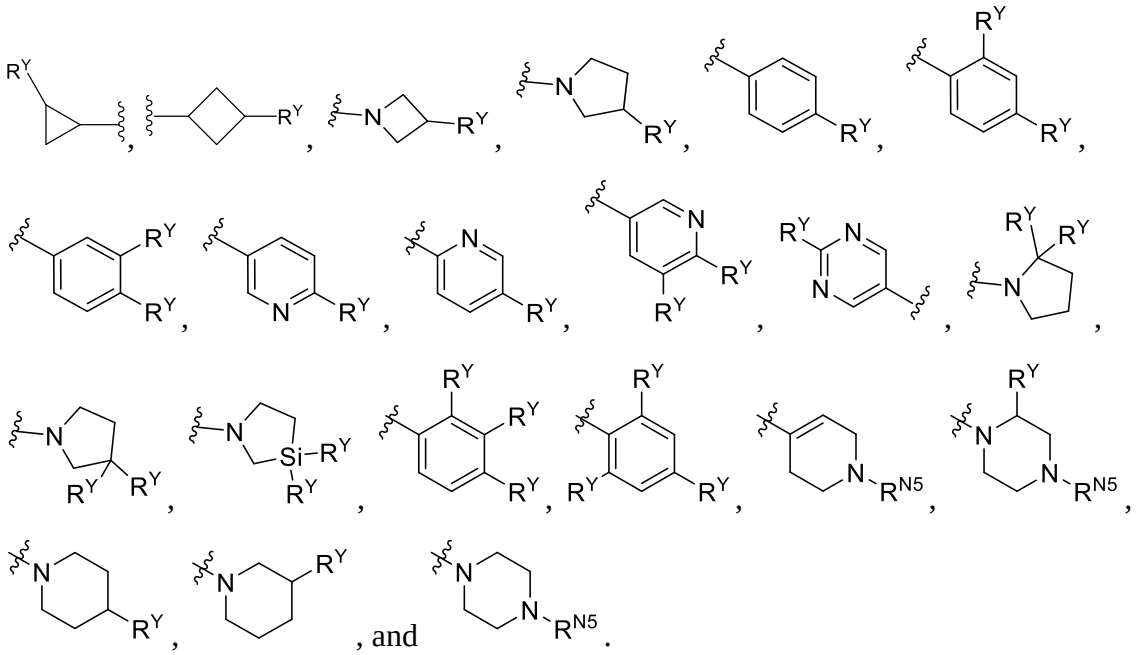
3840. The compound of any one of claims 1-3739, wherein A is selected from the group consisting of



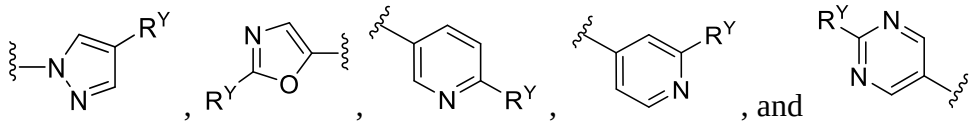


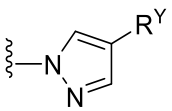
~~39~~41. The compound of claim ~~37~~39 or ~~38~~40, wherein R^X is $–CH_2CH_2OCF_3$.

~~40~~42. The compound of any one of claims 1-~~37~~39, wherein A is selected from the group consisting of



~~41~~43. The compound of any one of claims 1-~~37~~39, wherein A is selected from the group consisting of



~~42~~44. The compound of any one of claims 1-~~37~~39, wherein A is  .

~~43~~45. The compound of any one of claims 1-~~42~~44, wherein each R^Y is independently selected from the group consisting of hydrogen, chloro, fluoro, hydroxyl, phenyl, oxo, $–CHF_2$, $–CF_3$, –

CH_3, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–OCH_2CF_3$, $–OCH(CH_3)_2$, $–CH_2OCF_3$, $–CH_2OCH_2CF_3$, $–CH_2OCH_3$, $–CH_2CH_2CH_2OCF_3$, $–CH_2CH_2CH_2CH_2OCF_3$, –CN, $–OCH_2CH_3$, $–OCH_2CH_2CH_2CF_3$, $–OCH_2CH_2CH_2C(CH_3)F_2$, $–CH_2CHF_2$,$–CH_2CF_3$, $–CH_2CH_2CH_2CF_3$, $–NHCH_2CH_2OCF_3$, $–NHCH_2CH_2CH_2OCF_3$, $–N(CH_3)CH_2CH_2OCF_3$, $–N(CH_3)CH_2CH_2CH_2OCF_3$, $–N(CH_3)CH(CH_3)CH_2OCF_3$, $–OCH_2CH_2OCF_3$, $–OCH_2CH_2OCHF_2$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2CH_2OCF_3$, $–OCH_2CH_2OCH_2CF_3$, $–OCH(CH_3)CH_2OCF_3$, $–OCH_2CH(CH_3)OCF_3$, $–CH_2OCH_2CH_2OCF_3$, $–C(O)CH_2OCF_3$, $–CH_2OC(O)OCH_2CH_3$, and cyclopropyl.

~~44~~46. The compound of any one of claims 1-~~43~~45, wherein each R^Y is independently selected from the group consisting of $–CHF_2$, $–CF_3$, $–CH_3$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–OCH_2CF_3$, $–CH_2OCF_3$, $–CH_2OCH_2CF_3$, $–CH_2OCH_3$, $–CH_2CH_2CH_2OCF_3$, $–CH_2CH_2CH_2CH_2OCF_3$, $–OCH_2CH_2CH_2CF_3$, $–OCH_2CH_2CH_2C(CH_3)F_2$, $–CH_2CF_3$, $–CH_2CH_2CH_2CF_3$,$–OCH_2CH_2OCF_3$ $–OCH_2CH_2CH_2OCF_3$, $–CH_2OCH_2CH_2OCF_3$, $–C(O)CH_2OCF_3$, $–CH_2OC(O)OCH_2CH_3$, and cyclopropyl.

~~45~~47. The compound of any one of claims 1-~~43~~45, wherein each R^Y is independently selected from the group consisting of fluoro, chloro, oxo, $–CF_3$, $–CH_3$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–CH_2OCF_3$, $–OCH_2CH_3$, $–CH_2CF_3$, $–CH_2CHF_2$, and cyclopropyl.

~~46~~48. The compound of any one of claims 1-~~42~~44, wherein A is substituted with 1 R^Y.

~~47~~49. The compound of claim ~~46~~48, wherein R^Y is $–C_1$-C_6 alkylene$–OR^A$, $–OR^A$, or $–NR^BR^{CC}$.

~~48~~50. The compound of claim ~~46~~48 or ~~47~~49, wherein R^Y is $–C_1$-C_6 alkylene$–O–C(O)–C_1$-C_6 alkyl, $–O–C_1$-C_6 alkylene$–C_1$-C_6 alkoxy, $–N(H)–C_1$-C_6 alkylene$–C_1$-C_6 alkoxy, or $–N(C_1$-C_6 alkyl$)–C_1$-C_6 alkylene$–C_1$-C_6 alkoxy, wherein $–O–C_1$-C_6 alkylene$–C_1$-C_6 alkoxy, $–N(H)–C_1$-C_6 alkylene$–C_1$-C_6 alkoxy, or $–N(C_1$-C_6 alkyl$)–C_1$-C_6 alkylene$–C_1$-C_6 alkoxy is optionally substituted with 1-6 halogen.

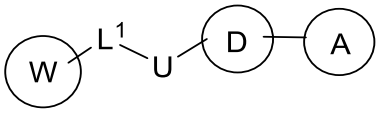
~~49~~51. The compound of any one of claims ~~46~~48-~~48~~50, wherein R^Y is $–O–C_1$-C_6 alkylene$–C_1$-C_6 alkoxy optionally substituted with 1-6 halogen.

~~50~~52. The compound of any one of claims ~~46~~48-~~49~~51, wherein R^Y is selected from the group consisting of $–NHCH_2CH_2OCF_3$, $–NHCH_2CH_2CH_2OCF_3$, $–N(CH_3)CH_2CH_2OCF_3$, –

$N(CH_3)CH_2CH_2CH_2OCF_3$, $–N(CH_3)CH(CH_3)CH_2OCF_3$, $–OCH_2CH_2OCF_3$, $–OCH_2CH_2CH_2OCF_3$, $–OCH_2CH_2OCHF_2$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2OCH_2CF_3$, $–OCH(CH_3)CH_2OCF_3$, and $–OCH_2CH(CH_3)OCF_3$.

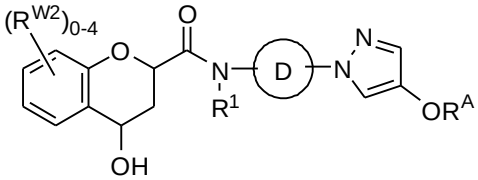
~~51~~53. The compound of any one of claims 1-~~49~~51, wherein each R^{N5} is independently $–C(O)CH_3$, $–CF_3$, or $–CH_2CF_3$.

~~52~~54. The compound of any one of claims 1-~~51~~53, wherein the compound is represented by Formula (I-a):



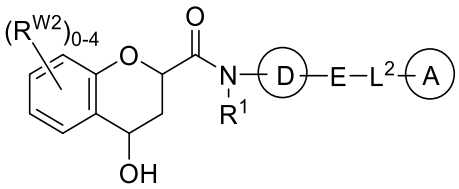
Formula (I-a).

~~53~~55. The compound of any one of claims 1-~~52~~54, wherein the compound is represented by Formula (I-b):



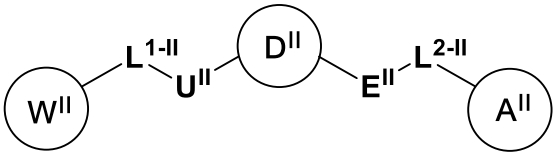
Formula (I-b).

~~54~~56. The compound of any one of claims 1-~~51~~53, wherein the compound is represented by Formula (I-c):



Formula (I-c).

~~55~~57. A compound of Formula (II):



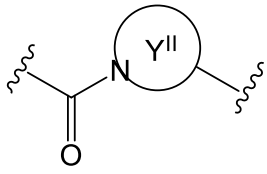
Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

D^{II} is a bridged bicyclic cycloalkyl, a bridged bicyclic heterocyclyl, a 4-6-membered monocyclic cycloalkyl, a 4-6-membered monocyclic heterocyclyl, or cubanyl, wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, 4-6-membered monocyclic cycloalkyl, 4-6-membered monocyclic heterocyclyl, or cubanyl is optionally substituted on one or more available carbons with 1-4 $R^{X\text{-}II}$; and wherein if the 4-6-membered monocyclic heterocyclyl or bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by $R^{N1\text{-}II}$;

U^{II} is $–NR^{1\text{-}II}C(O)–$ or $–C(O)NR^{1\text{-}II}–$;

E^{II} is absent or is a bond, $–NR^{2\text{-}II}C(O)–$, $–C(O)NR^{2\text{-}II}–$, 5-6-membered heteroaryl or 5-6-membered heterocyclyl; wherein 5-6-membered heteroaryl or 5-6-membered heterocyclyl is optionally substituted on one or more available carbons with 1-5 $R^{G\text{-}II}$; and wherein if the 5-6-membered heteroaryl or 5-6-membered heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by $R^{N2\text{-}II}$; or

E^{II} is 

; Y^{II} is a 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl, wherein the 4-9 membered monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl is optionally substituted on one or more available carbons with 1-5 $R^{G\text{-}II}$; and wherein if the 4-9-membered nitrogen-containing monocyclic, bridged bicyclic, fused bicyclic or spirocyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by $R^{N2\text{-}II}$;

$L^{1\text{-}II}$ is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, $–NR^{N3\text{-}II}–$, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 $R^{L1\text{-}II}$;

$L^{2\text{-}II}$ is absent or is a bond, C_1-C_6 alkylene, 2-7 membered heteroalkylene, –C(O)–, or –O–, wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 $R^{L2\text{-}II}$;

wherein E^{II} and $L^{2\text{-}II}$ both cannot be either a bond or absent simultaneously;

$R^{1\text{-}II}$ is hydrogen or C_1-C_6 alkyl;

$R^{2\text{-}II}$ is hydrogen or C_1-C_6 alkyl;

W^{II} is phenyl or 5-6-membered heteroaryl; wherein phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 $R^{W\text{-}II}$; and wherein if the 5-6-membered heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by $R^{N4\text{-}II}$;

A^{II} is C_3-C_6 cycloalkyl, 4-6-membered heterocyclyl, phenyl, or 5-6-membered heteroaryl, wherein C_3-C_6 cycloalkyl, phenyl, or 5-6-membered heteroaryl is optionally substituted on one or more available carbons with 1-5 $R^{Y\text{-}II}$; and wherein if the 5-6-membered heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by $R^{N5\text{-}II}$;

each $R^{L1\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, $–SR^{E\text{-}II}$, $–S(O)R^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

each $R^{L2\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, $–SR^{E\text{-}II}$, $–S(O)R^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

$R^{N1\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, $–C(O)OR^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

$R^{N2\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, $–C(O)OR^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

$R^{N3\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, $–C(O)OR^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

$R^{N4\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, –C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–C_1-C_3 alkyl–O–C_1-C_3 alkyl–O–C_1-C_3 alkyl, –C(O)–phenyl, –C(O)–heteroaryl, –C(O)–heterocyclyl, $–S(O)_2–C_1$-C_6 alkyl, $–S(O)_2$–phenyl, $–S(O)_2$–heteroaryl, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$ and $–C(O)OR^{D\text{-}II}$; wherein

C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, C_1-C_6 alkyl–C_1-C_6 cycloalkyl, C_1-C_6 alkenyl, C(O)–C_1-C_6 alkyl, –C(O)–C_1-C_6 cycloalkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, –C(O)–heterocyclyl, and $–S(O)_2–C_1$-C_6 alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of fluoro, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms) and $S(O)_{w\text{-}II}C_{1\text{-}6}$ alkyl (wherein w-II is 0, 1 or 2); and

–C(O)–phenyl, –C(O)–heteroaryl, $–S(O)_2$–phenyl and $–S(O)_2$–heteroaryl may optionally be substituted by one or more substituents each independently selected from

the group consisting of halogen, hydroxyl, C_1-C_6 alkyl (optionally substituted by one, two or three fluorine atoms), C_1-C_6 alkoxy (optionally substituted by one, two or three fluorine atoms), and $–S(O_2)NR^{B\text{-}II}R^{C\text{-}II}$;

$R^{N5\text{-}II}$ is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, $–C(O)OR^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

each $R^{W\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl–O–, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, C=N-OH, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}R^{CC\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, $–SR^{E\text{-}II}$, $–S(O)R^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$; or

2 $R^{W\text{-}II}$ groups on adjacent atoms, together with the atoms to which they are attached, form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 $R^{X\text{-}II}$;

each $R^{X\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $-C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, $–SR^{E\text{-}II}$, $–S(O)R^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

each $R^{Y\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, $-S(R^{F\text{-}II})_{m\text{-}II}$, $-S(O)R^{D\text{-}II}$, $–S(O)_2R^{D\text{-}II}$, and $G^{1\text{-}II}$; or

2 $R^{Y\text{-}II}$ groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl, each of which is optionally substituted with 1-5 $R^{X\text{-}II}$;

each $G^{1\text{-}II}$ is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 $R^{Z\text{-}II}$;

each $R^{Z\text{-}II}$ is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^{A\text{-}II}$, $–NR^{B\text{-}II}R^{C\text{-}II}$, $–NR^{B\text{-}II}C(O)R^{D\text{-}II}$, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, –C(O)OH, $–C(O)OR^{D\text{-}II}$, and $–S(O)_2R^{D\text{-}II}$;

$R^{A\text{-}II}$ is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy-C_1-C_6 alkylene, $–C(O)NR^{B\text{-}II}R^{C\text{-}II}$, $–C(O)R^{D\text{-}II}$, or $–C(O)OR^{D\text{-}II}$;

each of $R^{B\text{-}II}$ and $R^{C\text{-}II}$ is independently hydrogen or C_1-C_6 alkyl; or $R^{B\text{-}II}$ and $R^{C\text{-}II}$ together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 $R^{Z\text{-}II}$;

each $R^{CC\text{-}II}$ is independently selected from the group consisting of hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_1-C_6 alkyl–CO_2H, C_1-C_6 alkyl–CO_2–C_1-C_6 alkyl, C(O) C_1-C_6 alkyl, $S(O)_2$–C_1-C_6 alkyl and 3-6-membered cycloalkyl and 4-6-membered heterocyclyl; wherein 3-6-membered cycloalkyl and 4-6-membered heterocyclyl may optionally be substituted by one or more substituents each independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, hydroxyl, halo and –C(O)OH;

each $R^{D\text{-}II}$ is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

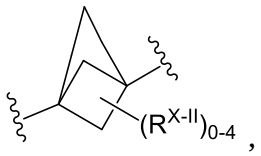
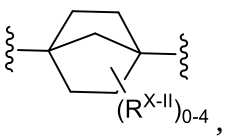
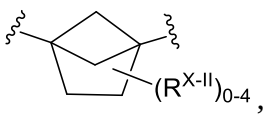
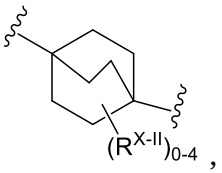
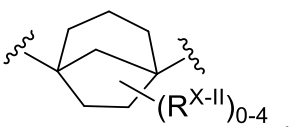
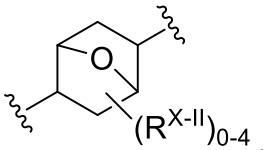
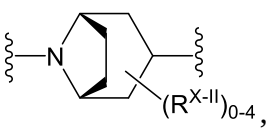
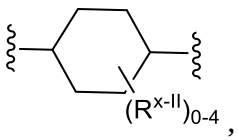
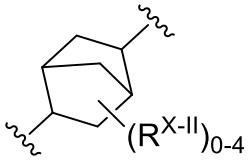
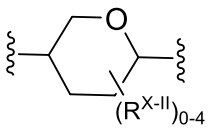
each $R^{E\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

each $R^{F\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, or halo; and

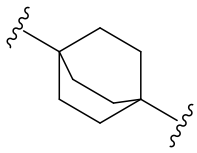
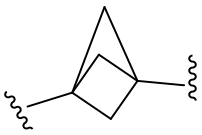
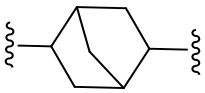
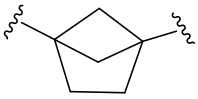
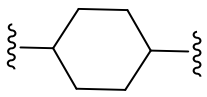
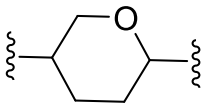
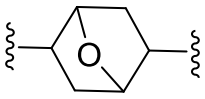
each $R^{G\text{-}II}$ is independently hydrogen, C_1-C_6 alkyl, halo or oxo;

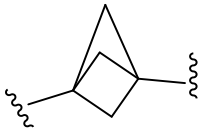
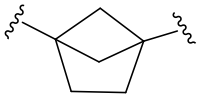
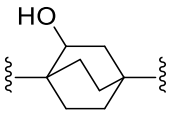
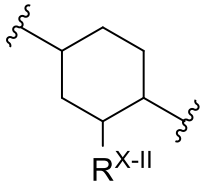
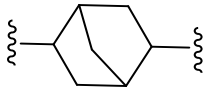
provided that when D^{II} is a bridged bicyclic 5-membered cycloalkyl, E^{II} is $–NR^{2\text{-}II}C(O)–$.

~~56~~58. The compound of claim ~~55~~57, wherein D^{II} is bicyclo[1.1.1]pentane, bicyclo[2.2.1]heptane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, 7-oxabicyclo[2.2.1]heptane, 8-azabicyclo[3.2.1]octane, cyclohexyl or tetrahydro-2H-pyranyl, each of which is optionally substituted with 1-4 $R^{X\text{-}II}$ groups.

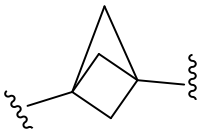
~~57~~59. The compound of claim ~~55~~57 or ~~56~~58, wherein D^{II} is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

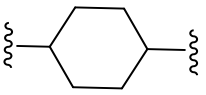
~~58~~60. The compound of any one of claims ~~55~~57-~~57~~59, wherein D^{II} is substituted with 0 $R^{X\text{-}II}$.

~~59~~61. The compound of any one of claims ~~55~~57-~~58~~60, wherein D^{II} is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

~~60~~62. The compound of any one of claims ~~55~~57-~~57~~59, wherein D^{II} is selected from the group consisting of  ,  ,  ,  , and  .

~~61~~63. The compound of any one of claims ~~55~~57-~~57~~59 and ~~60~~62, wherein R^{X-II} is –OH.

~~62~~64. The compound of any one of claims ~~55~~57-~~60~~62, wherein D^{II} is  .

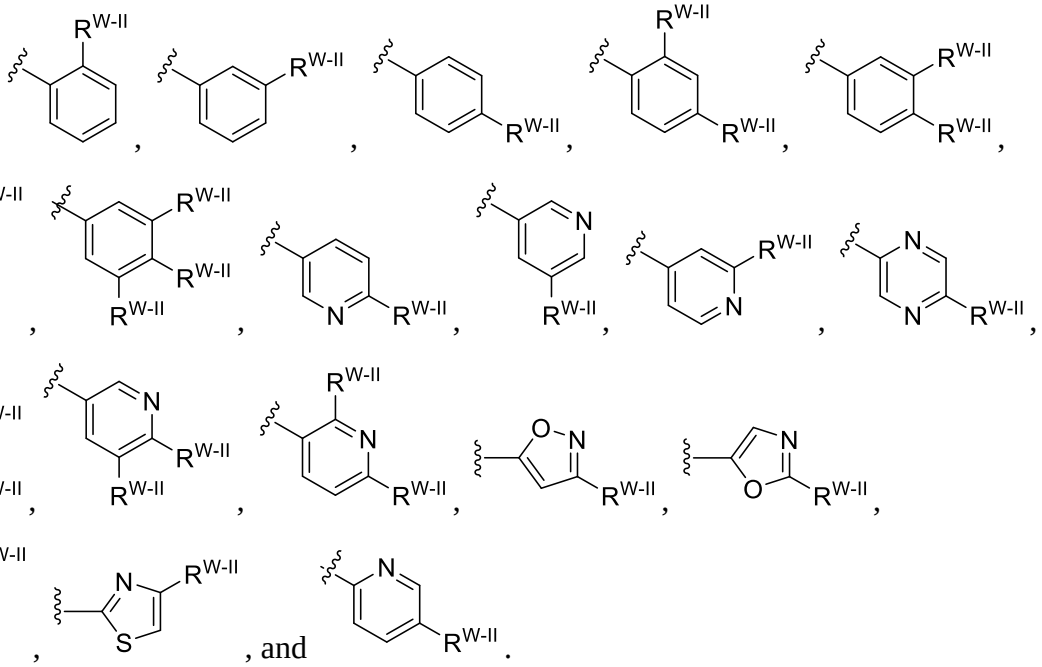
~~63~~65. The compound of any one of claims ~~55~~57-~~60~~62, wherein D^{II} is  .

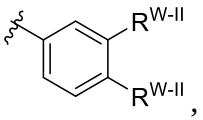
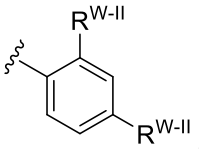
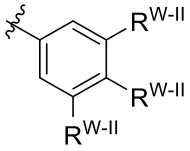
~~64~~66. The compound of any one of claims ~~55~~57-~~63~~65, wherein L^{1-II} is a C_1-C_6 alkylene or a 2-7 membered heteroalkylene.

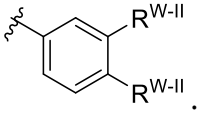
~~65~~67. The compound of any one of claims ~~55~~57-~~64~~66, wherein L^{1-II} is CH_2O–*, wherein "*" indicates the attachment point to W^{II}.

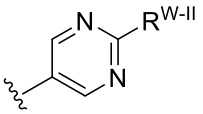
~~66~~68. The compound of any one of claims ~~55~~57-~~65~~67, wherein R^{1-II} is hydrogen.

~~67~~69. The compound of any one of claims ~~55~~57-~~66~~68, wherein U^{II} is –NHC(O)–.

~~68~~70. The compound of any one of claims ~~55~~57-~~67~~69, wherein W^{II} is selected from the group consisting of  .

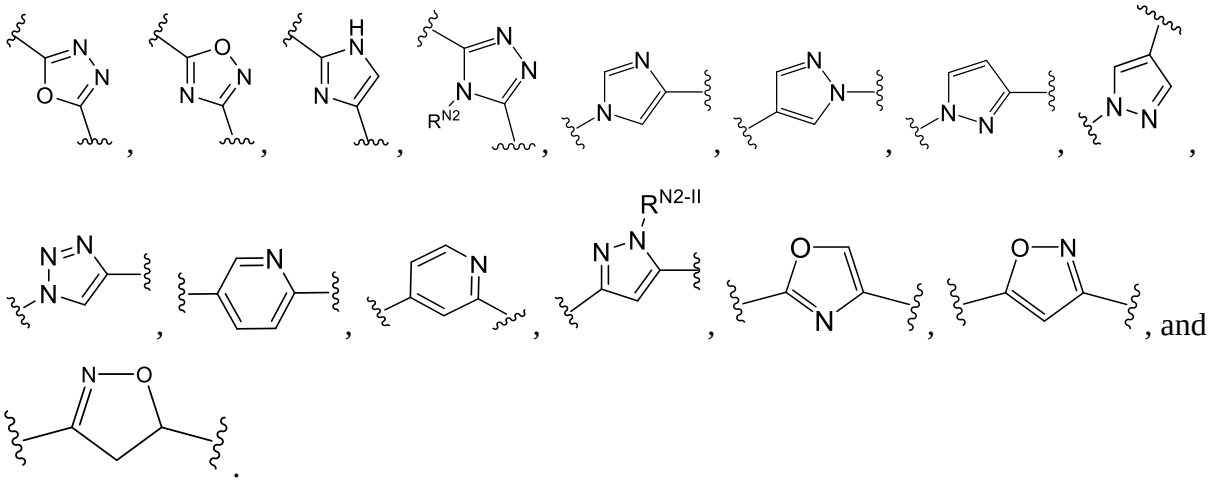
~~69~~71. The compound of any one of claims ~~55~~57-~~68~~70, wherein W^{II} is  ,  , or  .

~~70~~72. The compound of any one of claims ~~55~~57-~~69~~71, wherein W^{II} is  .

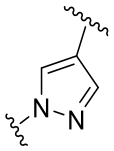
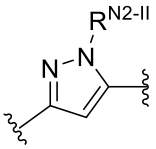
~~71~~73. The compound of any one of claims ~~55~~57-~~68~~70, wherein W^{II} is  .

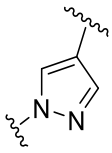
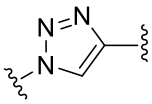
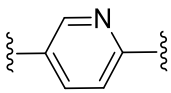
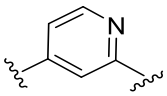
~~72~~74. The compound of any one of claims ~~55~~57-~~71~~73, wherein each $R^{W\text{-}II}$ is independently chloro, bromo, fluoro, hydroxyl, $–OCH_3$, or $–CF_3$.

~~73~~75. The compound of any one of claims ~~55~~57-~~72~~74, wherein E^{II} is selected from the group consisting of



.

~~74~~76. The compound of any one of claims ~~55~~57-~~73~~75, wherein E^{II} is selected from the group consisting of –$NR^{2\text{-}II}C(O)$–, –$C(O)NR^{2\text{-}II}$–,  , and  .

~~75~~77. The compound of any one of claims ~~55~~57-~~73~~75, wherein E^{II} is selected from the group consisting of  ,  ,  , and  .

~~76~~78. The compound of any one of claims ~~55~~57-~~72~~74, wherein E^{II} is absent.

~~77~~79. The compound of any one of claims ~~55~~57-~~76~~78, wherein $R^{2\text{-}II}$ is hydrogen.

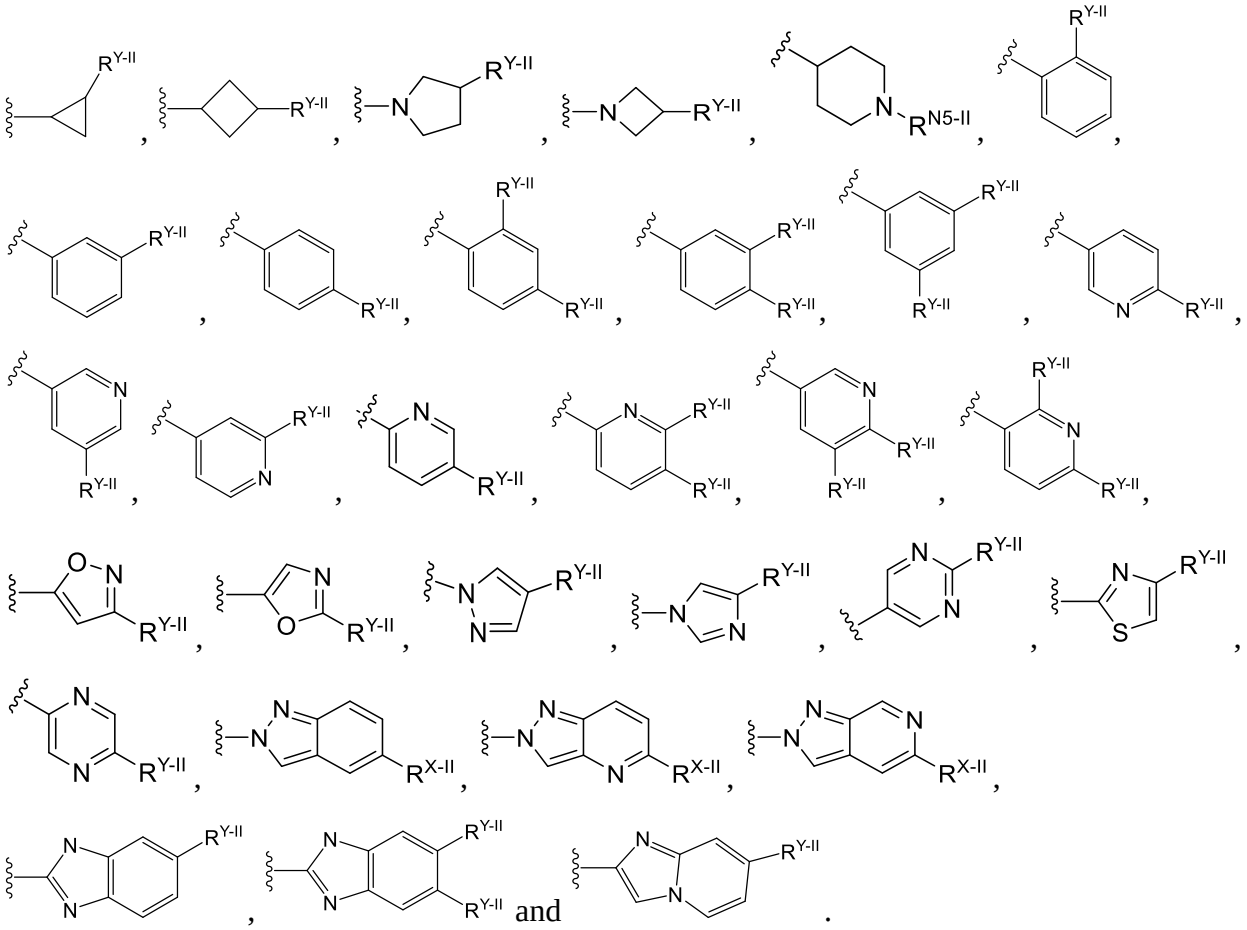
~~78~~80. The compound of any one of claims ~~55~~57-~~77~~79, wherein $L^{2\text{-}II}$ is a bond, –C(O)–, –O–, or 2-7 membered heteroalkylene, wherein 2-7 membered heteroalkylene is optionally substituted with 1-5 $R^{L2\text{-}II}$, wherein each $R^{L2\text{-}II}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, oxo, halo, and –$OR^{A\text{-}II}$.

~~79~~81. The compound of any one of claims ~~55~~57-~~78~~80, wherein $L^{2\text{-}II}$ is a bond, –C(O)–,–CH_2O–*, – $(CH_2)_2O$–*, –$(CH_2)_3O$–*, –C(O)NH–*, –OCH_2–*, or –O–, wherein "–*" indicates the attachment point to A^{II}.

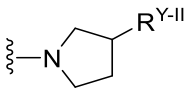
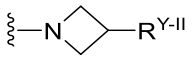
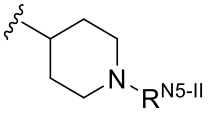
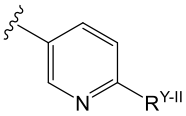
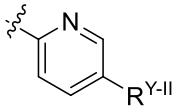
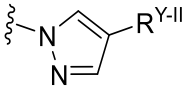
~~80~~82. The compound of any one of claims ~~55~~57-~~79~~81, wherein $L^{2\text{-}II}$ is a bond, –C(O)–, –CH_2O–*, –C(O)NH–*, –OCH_2–*, or –O–, wherein "–*" indicates the attachment point to A^{II}.

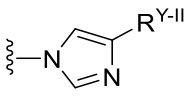
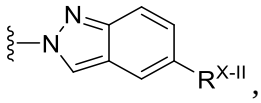
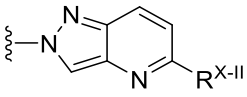
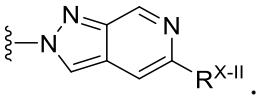
~~81~~83. The compound of any one of claims ~~55~~57-~~77~~79, wherein $L^{2\text{-}II}$ is absent.

~~82~~84. The compound of any one of claims ~~55~~57-~~81~~83, wherein A^{II} is selected from the group consisting of:

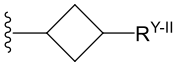
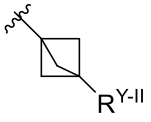


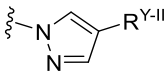
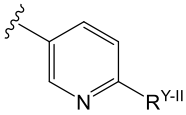
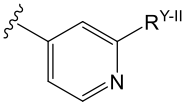
~~83~~85. The compound of any one of claims ~~55~~57-~~82~~84, wherein A^{II} is selected from the group consisting of:

 ,  ,  ,  ,  ,  ,

 ,  ,  , and  .

~~84~~86. The compound of claim ~~82~~84 or ~~83~~85, wherein $R^{X\text{-}II}$ is $–OCH_3$.

~~85~~87. The compound of any one of claims ~~55~~57-~~81~~83, wherein A^{II} is  or  .

~~86~~88. The compound of any one of claims ~~55~~57-~~81~~83, wherein A^{II} is  ,  , or  .

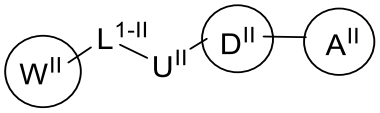
~~87~~89. The compound of any one of claims ~~55~~57-~~86~~88, wherein each $R^{Y\text{-}II}$ is independently chloro, $–CF_3$, $–CH_2CF_3$, $–CH_2OCF_3$, $–CH_2CH_2CH_2OCF_3$,$–OCF_3$, $–OCH_2CH_2OCF_3$, or $–OCH_2CH_2CH_2OCF_3$.

~~88~~90. The compound of any one of claims ~~55~~57-~~86~~88, wherein $R^{Y\text{-}II}$ is halo–C_1-C_6 alkoxy–C_1-C_6 alkylene–O–.

~~89~~91. The compound of any one of claims ~~55~~57-~~87~~89, wherein each $R^{Y\text{-}II}$ is independently chloro, $–CF_3$, or $–OCF_3$.

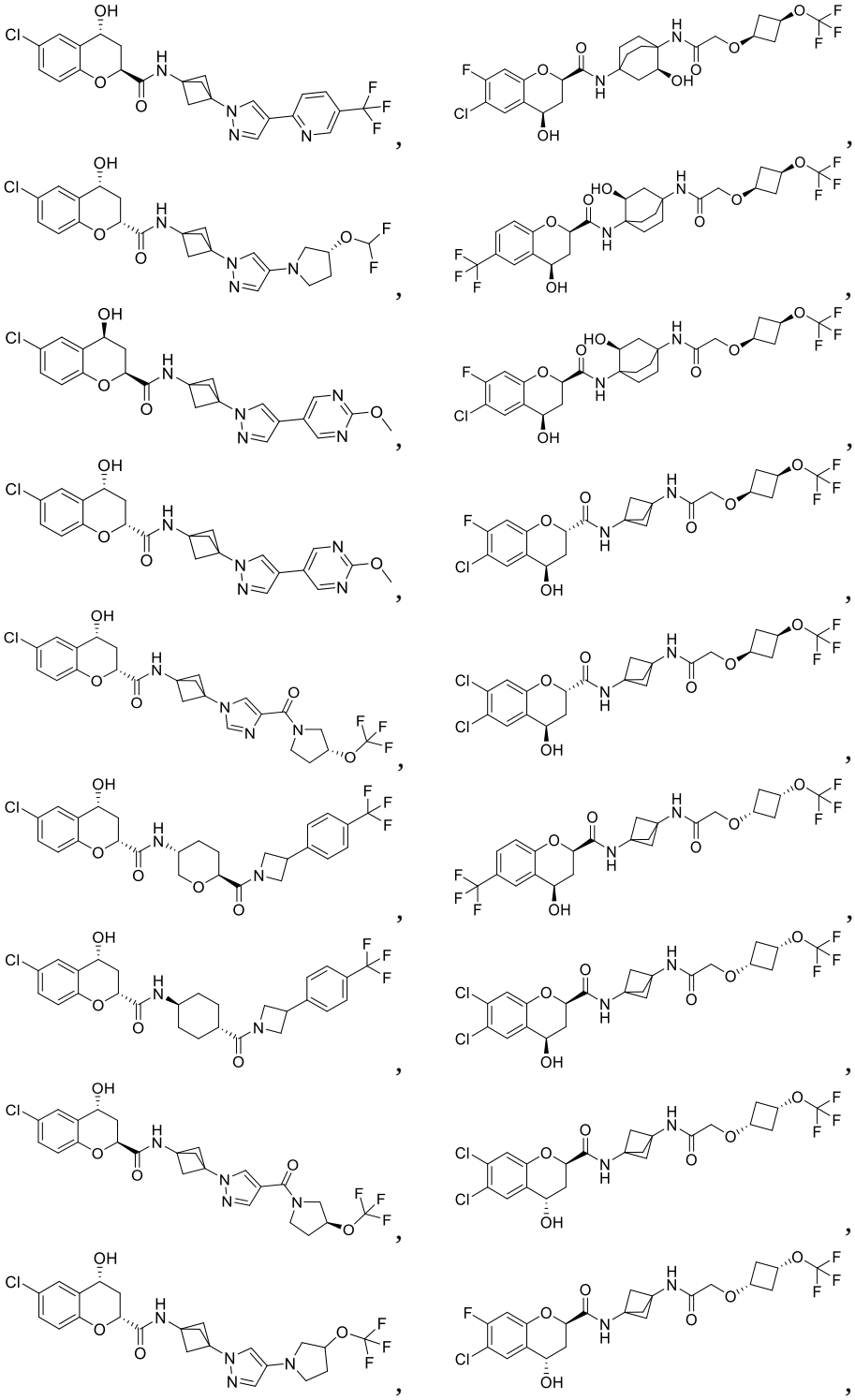
~~90~~92. The compound of any one of claims ~~55~~57-~~88~~90, wherein each $R^{Y\text{-}II}$ is independently $–OCH_2CH_2OCF_3$ or $–OCH_2CH_2CH_2OCF_3$.

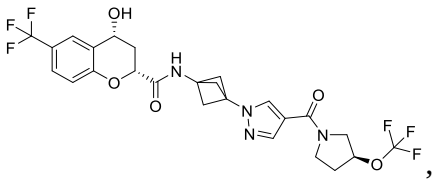
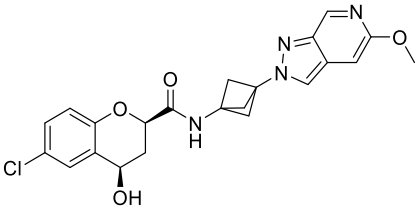
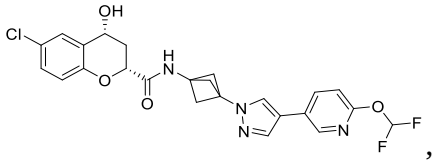
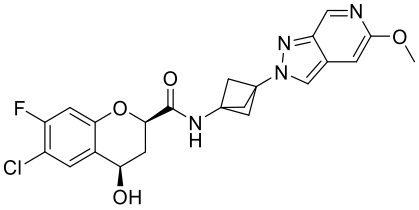
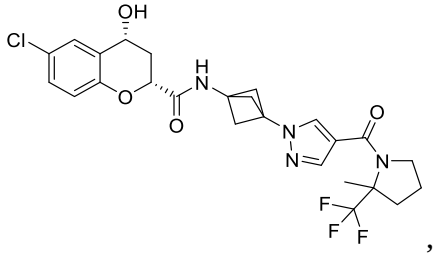
~~91~~93. The compound of any one of claims ~~55~~57-~~90~~92, wherein the compound is represented by Formula (II-a):



Formula (II-a).

~~92~~94. A compound selected from the group consisting of:




,

,

,

,

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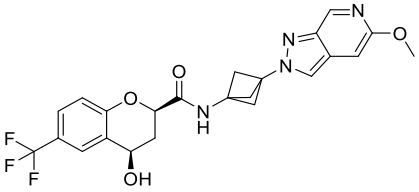
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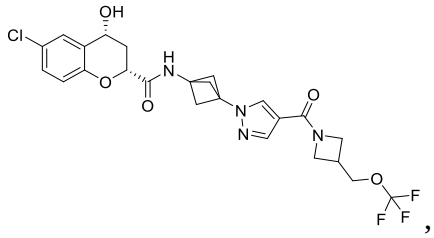
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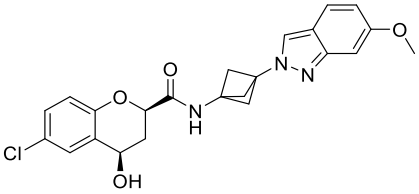
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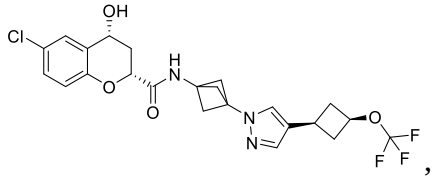
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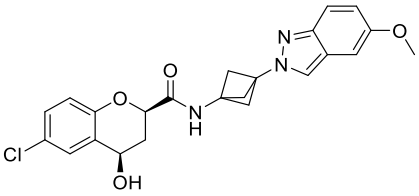
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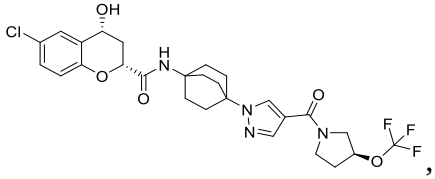
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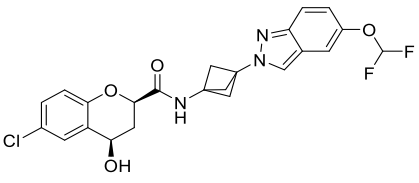
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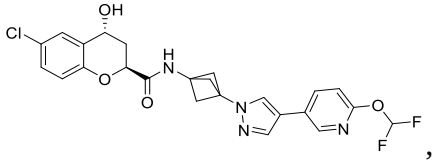
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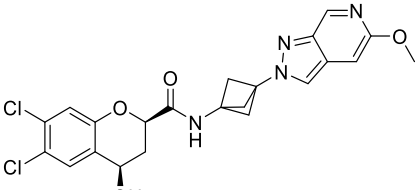
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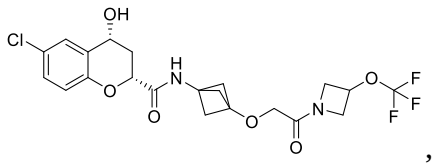
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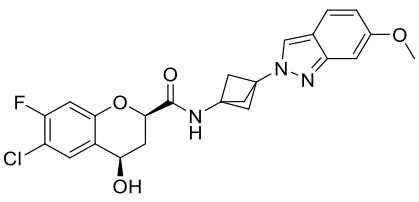
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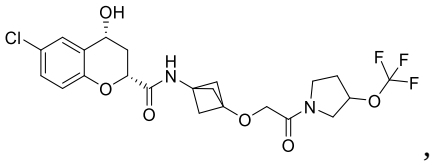
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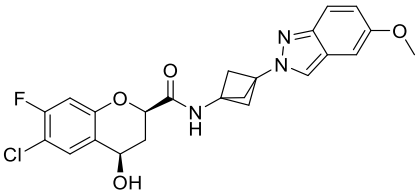
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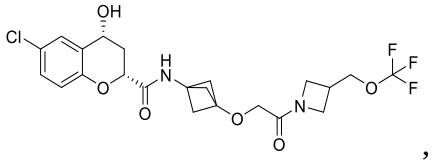
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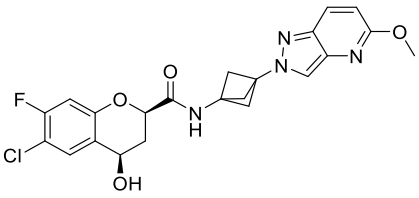
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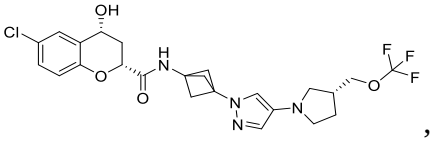
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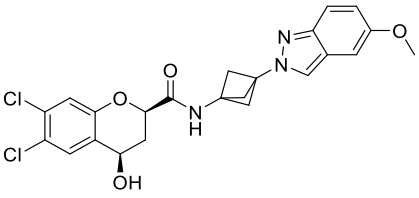
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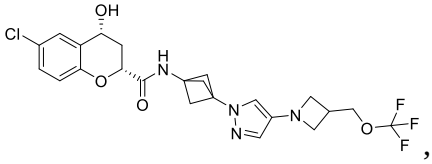
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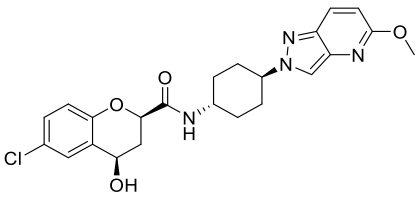
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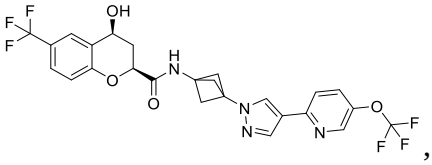
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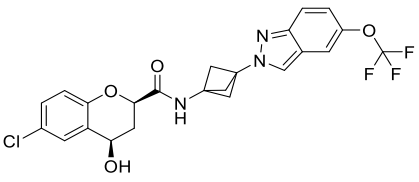
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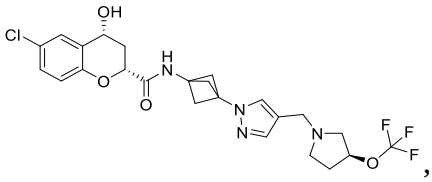
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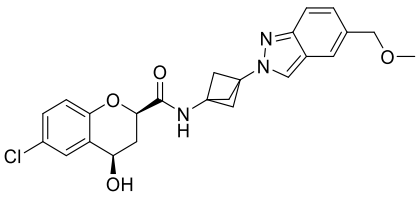
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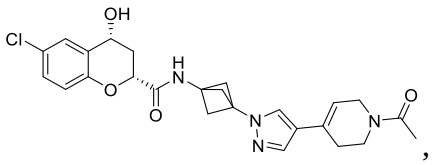
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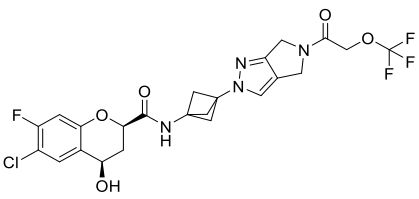
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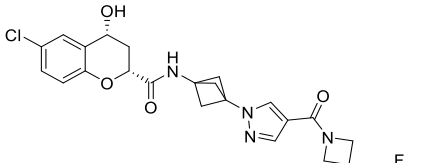
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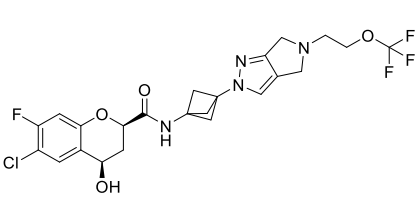
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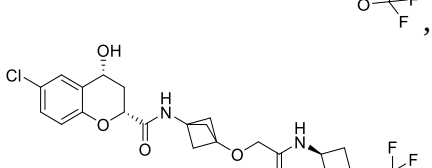
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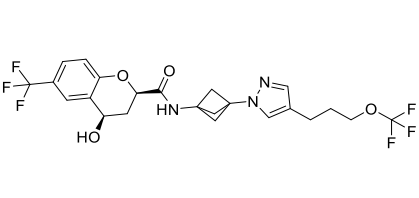
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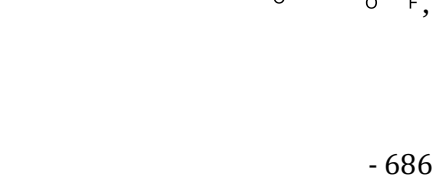
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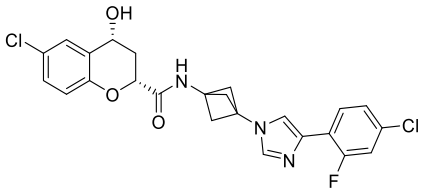
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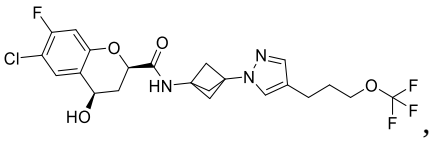
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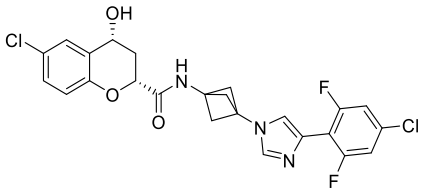
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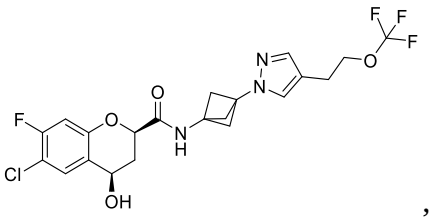
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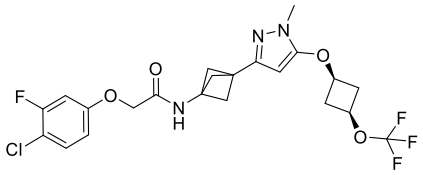
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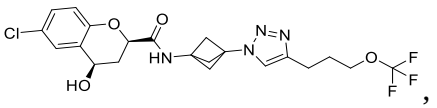
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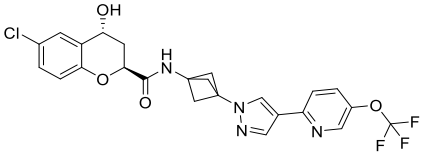
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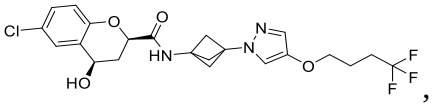
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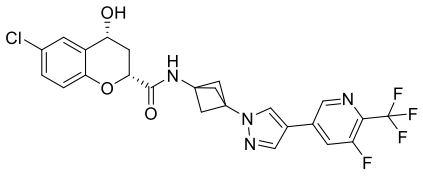
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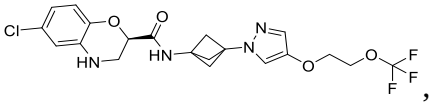
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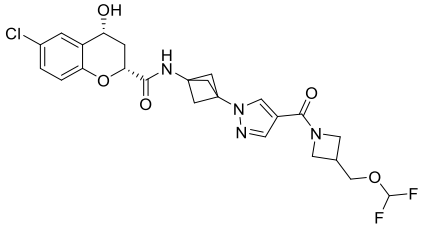
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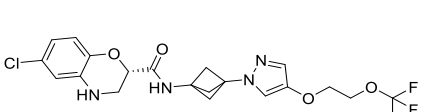
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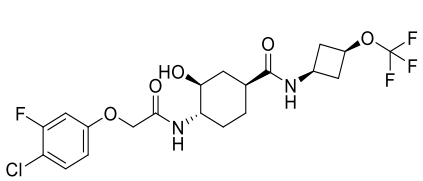
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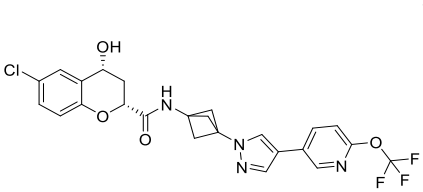
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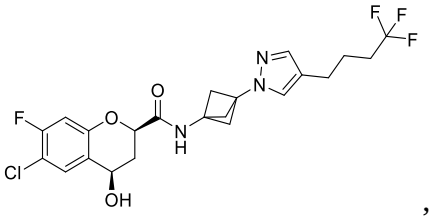
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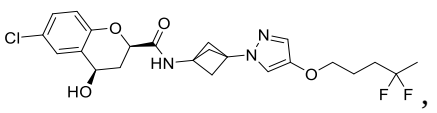
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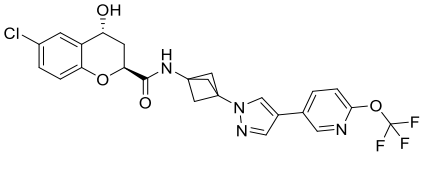
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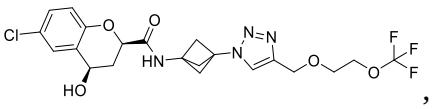
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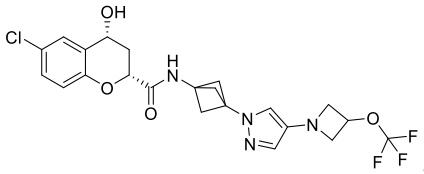
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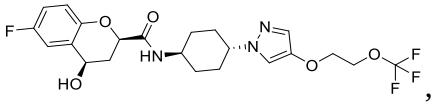
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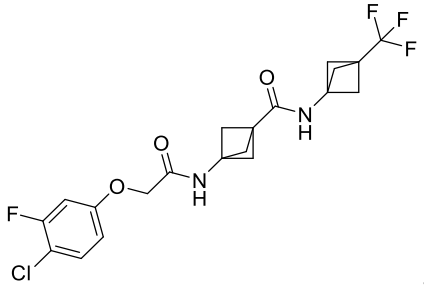
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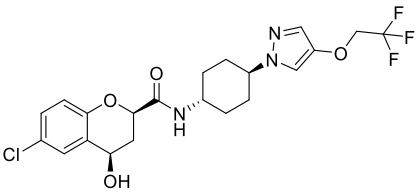
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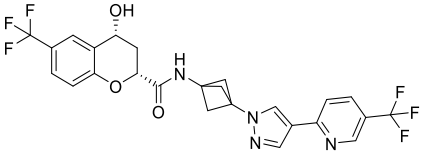
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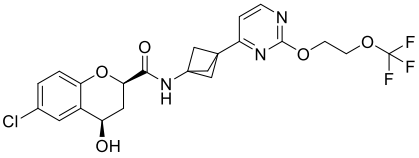
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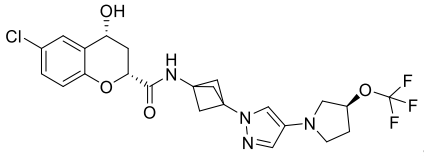
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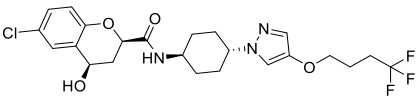
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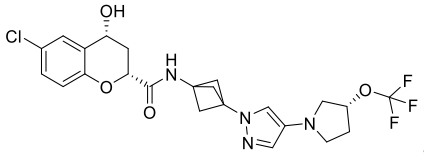
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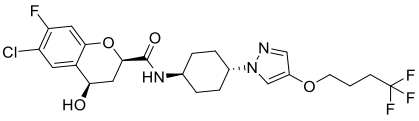
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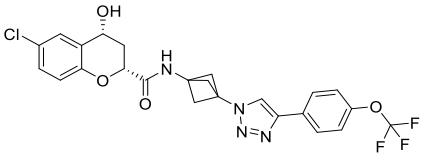
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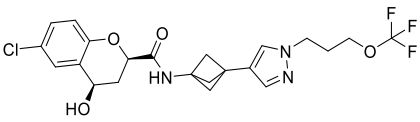
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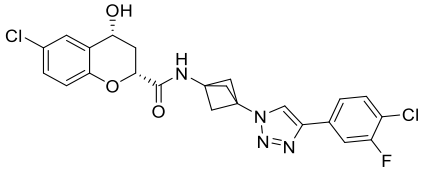
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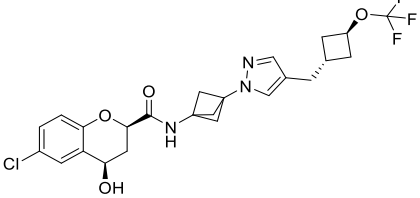
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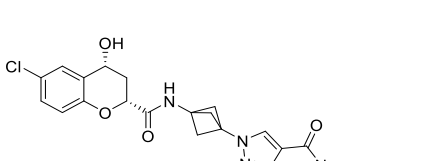
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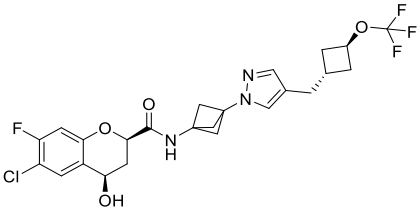
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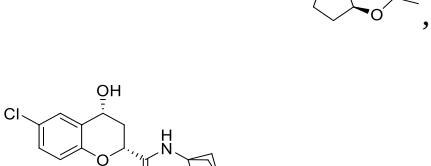
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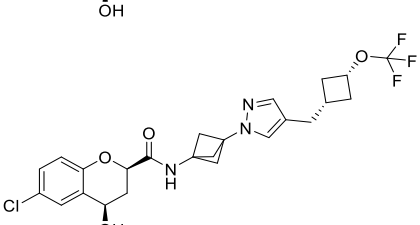
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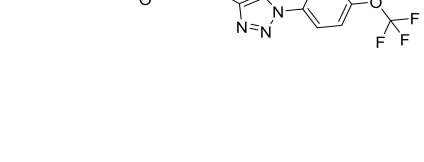
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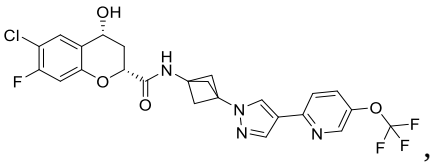
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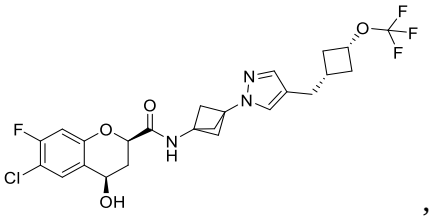
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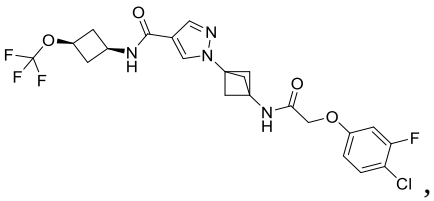
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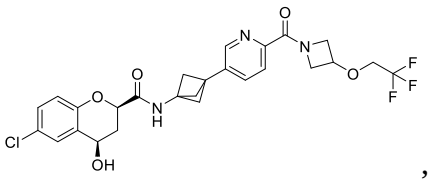
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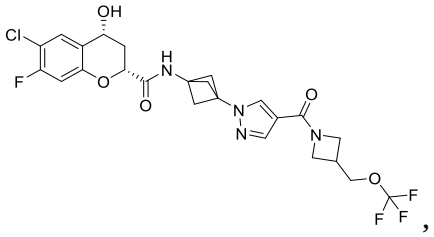
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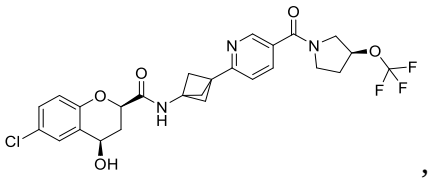
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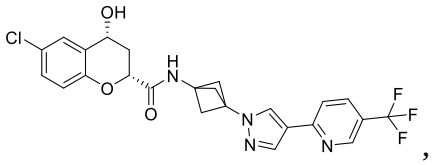
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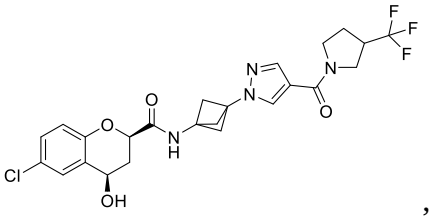
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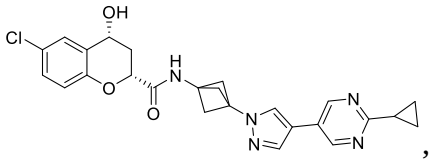
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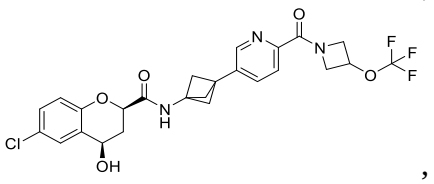
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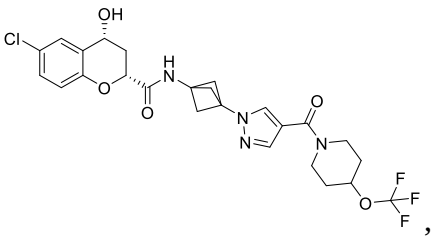
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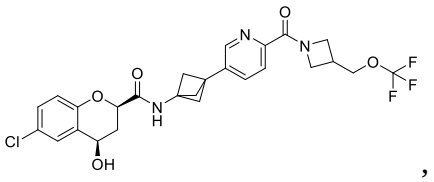
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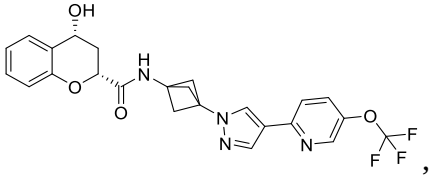
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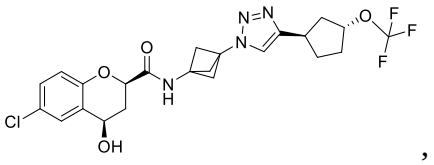
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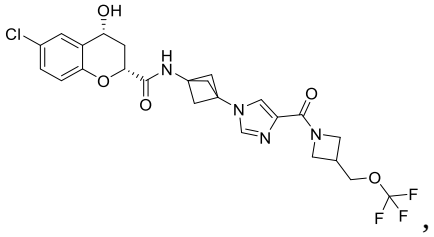
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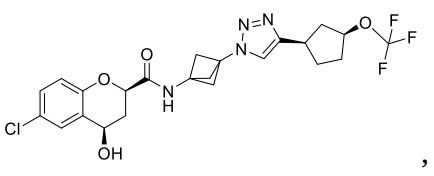
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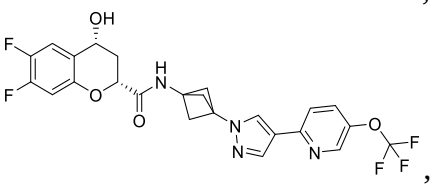
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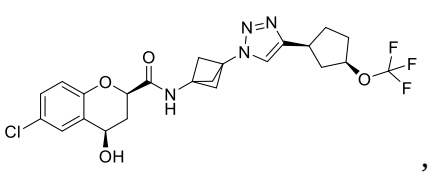
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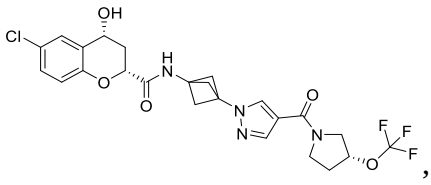
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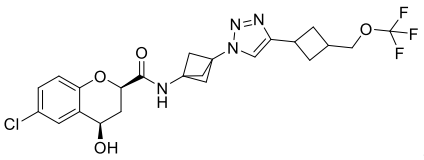
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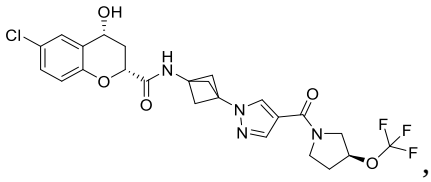
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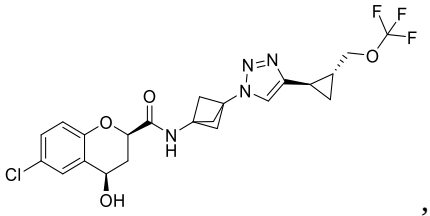
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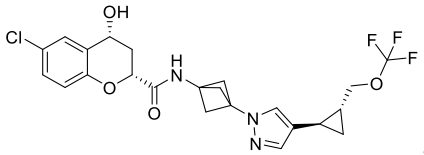
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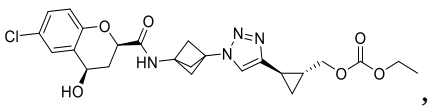
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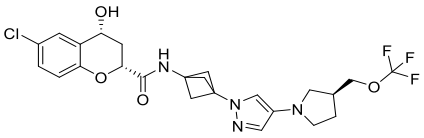
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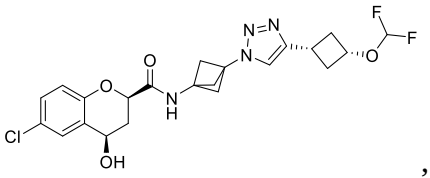
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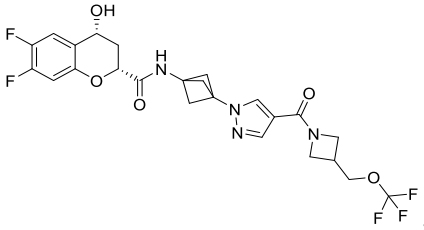
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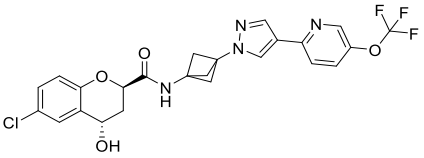
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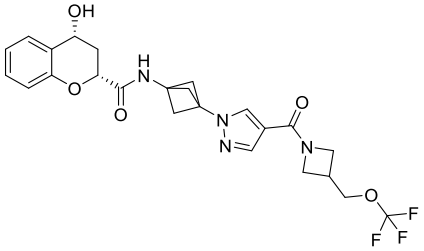
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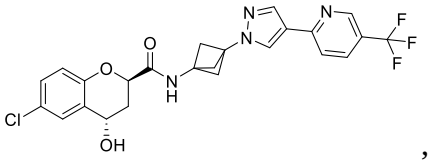
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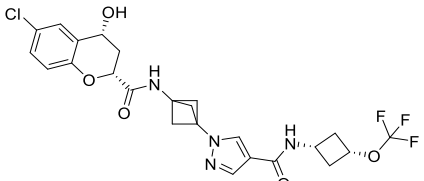
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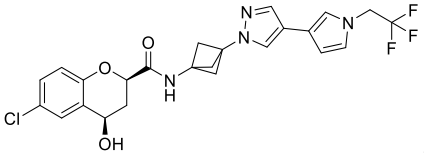
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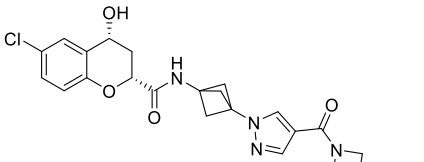
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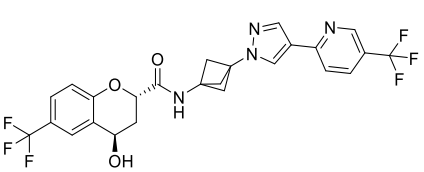
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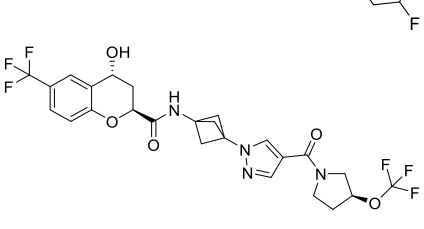
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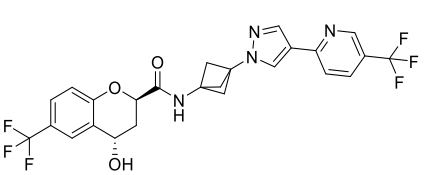
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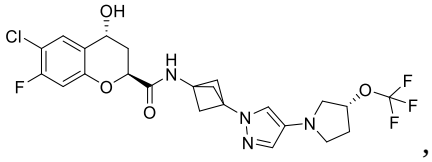
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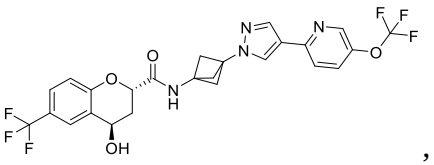
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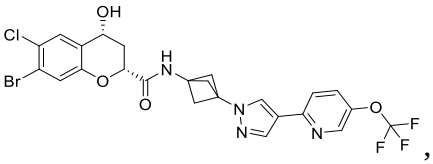
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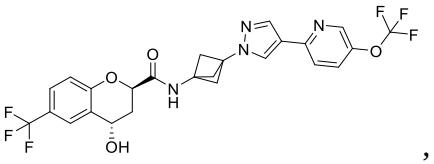
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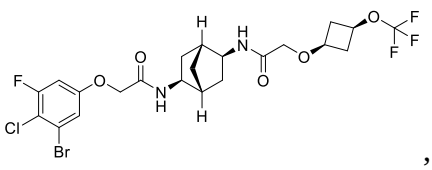
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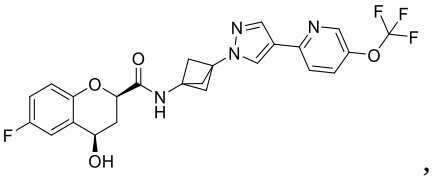
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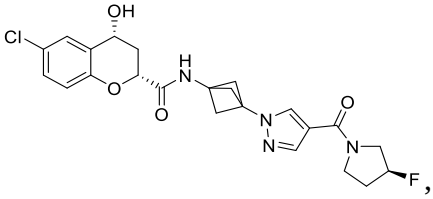
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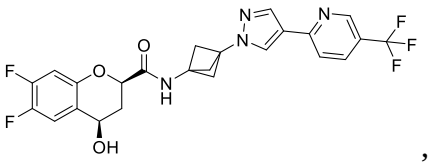
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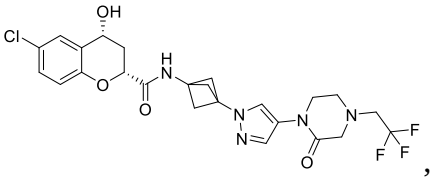
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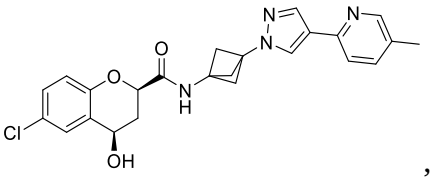
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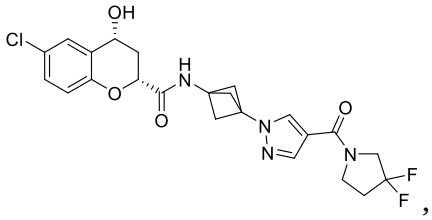
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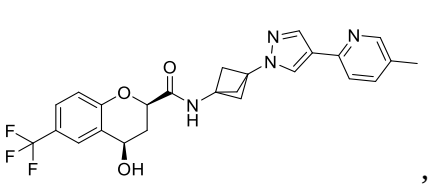
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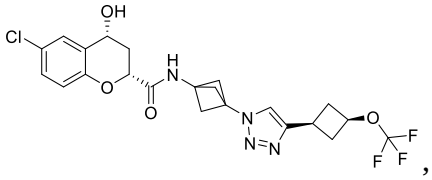
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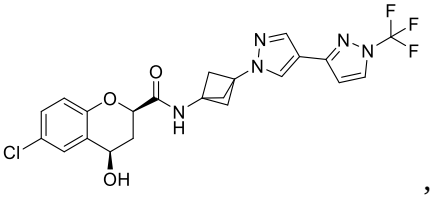
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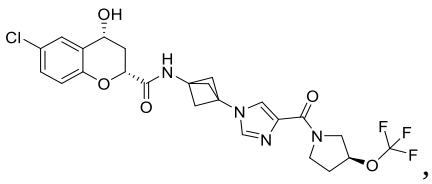
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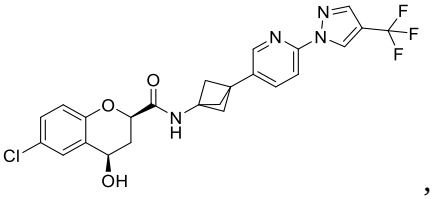
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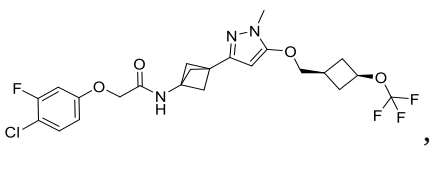
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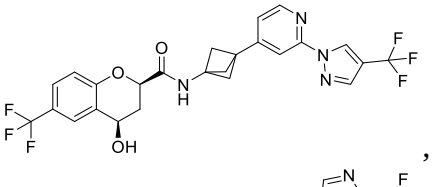
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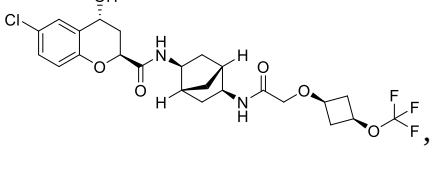
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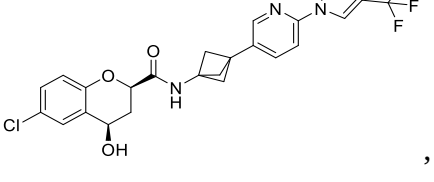
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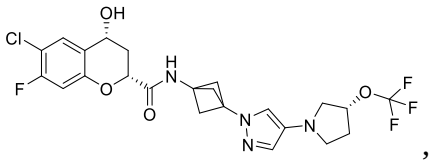
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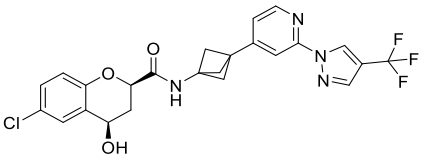
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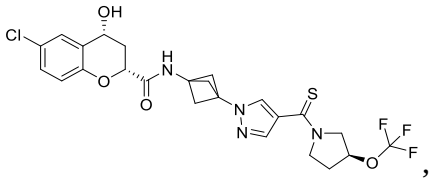
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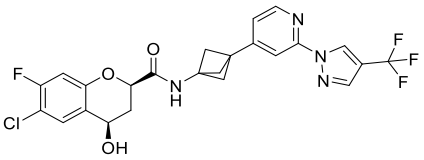
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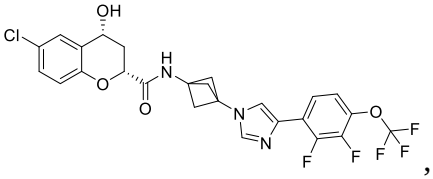
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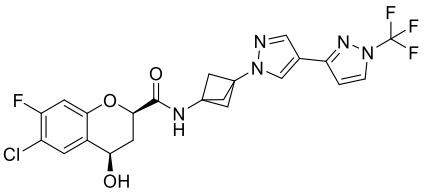
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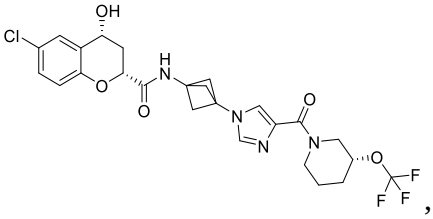
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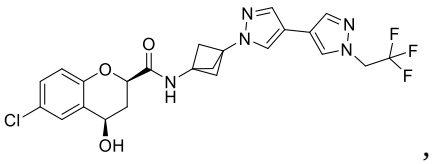
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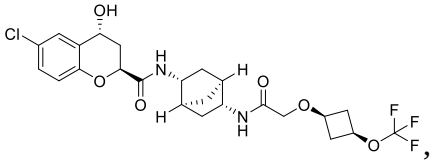
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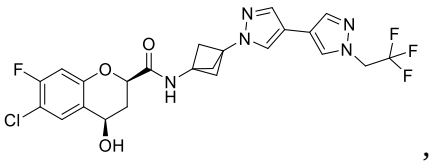
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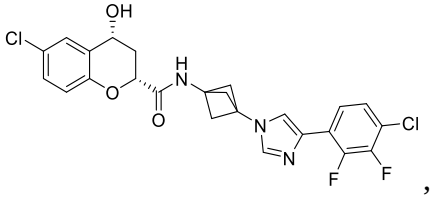
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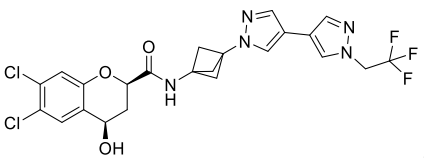
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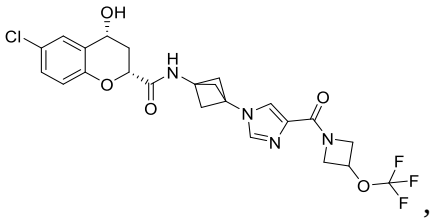
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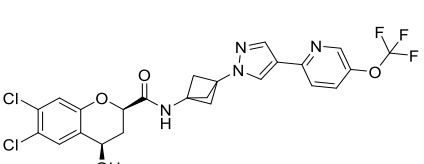
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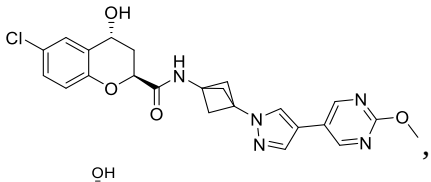
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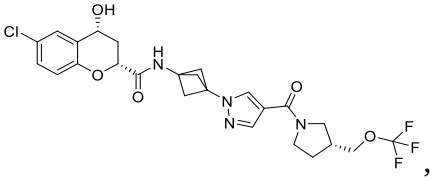
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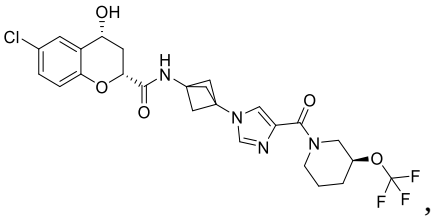
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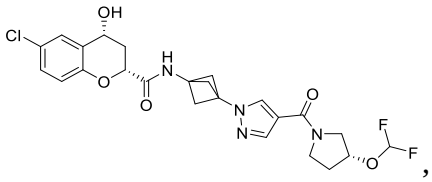
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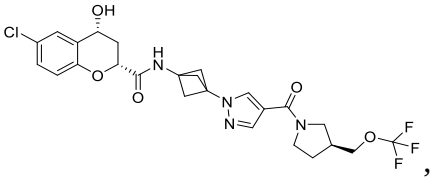
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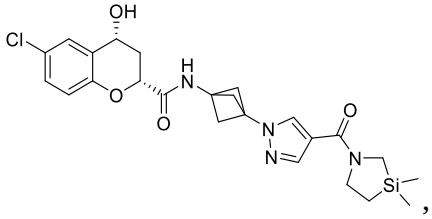
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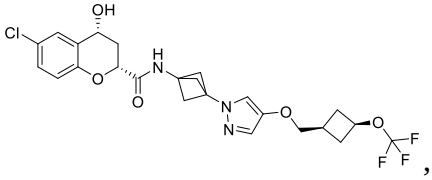
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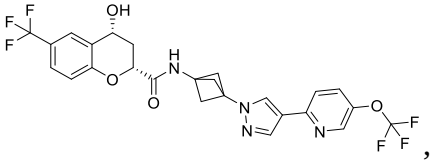
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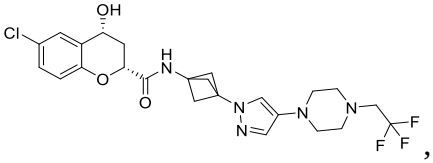
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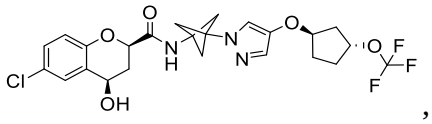
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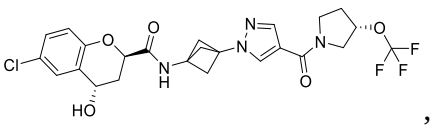
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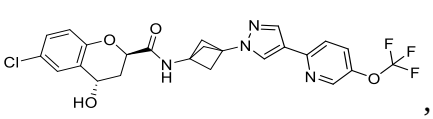
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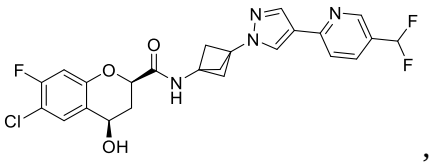
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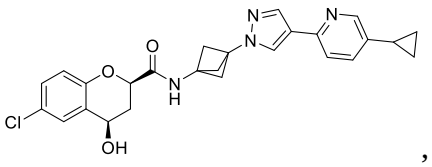
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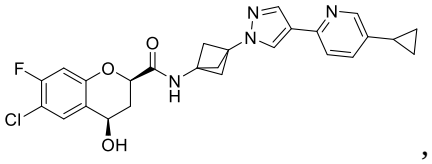
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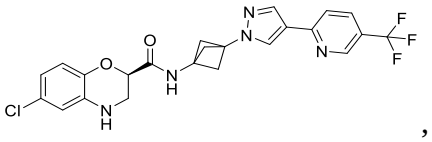
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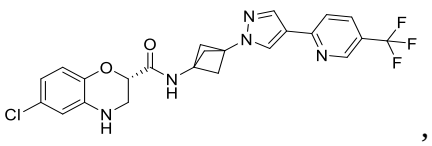
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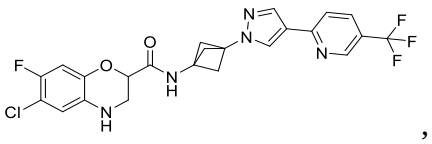
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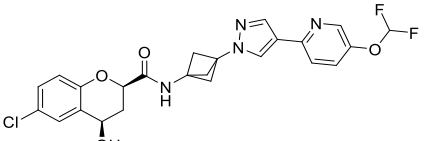
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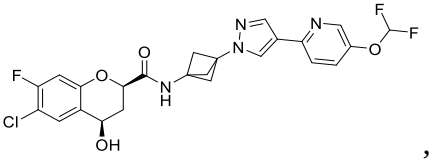
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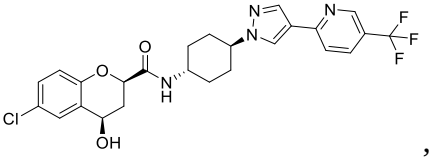
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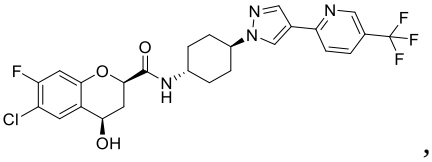
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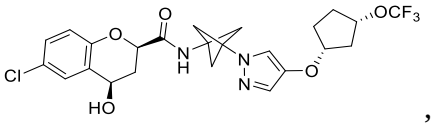
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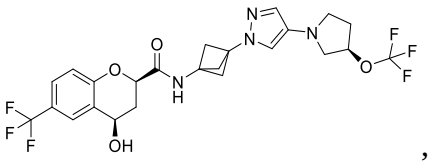
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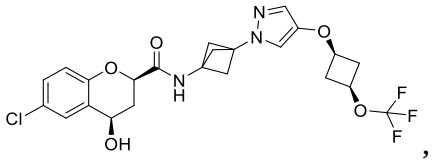
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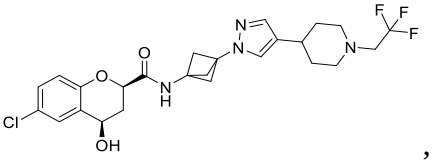
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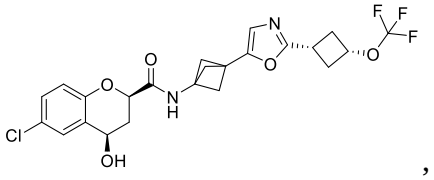
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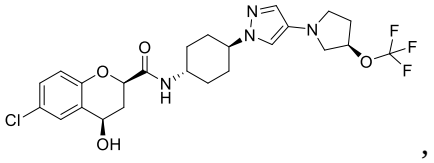
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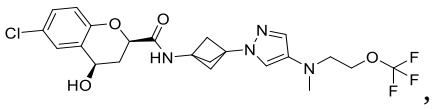
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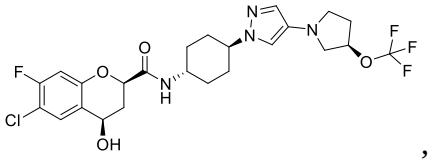
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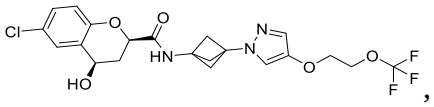
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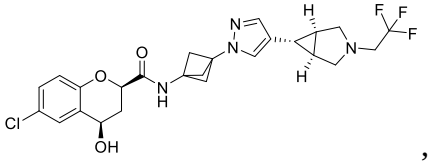
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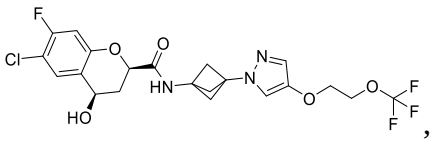
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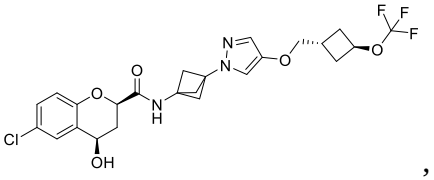
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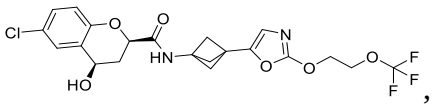
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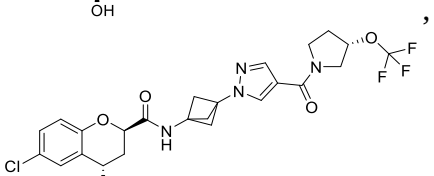
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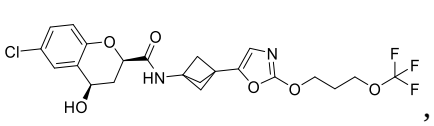
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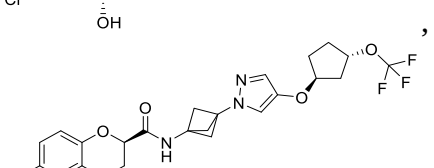
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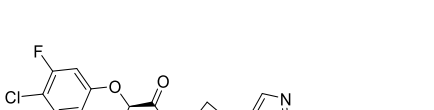
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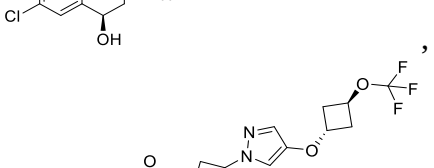
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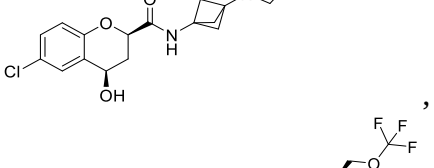
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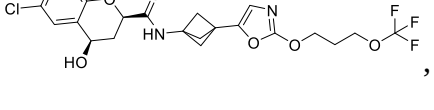
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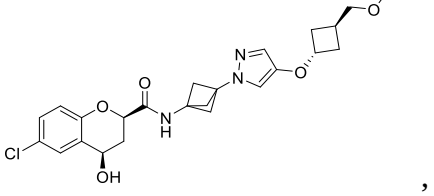
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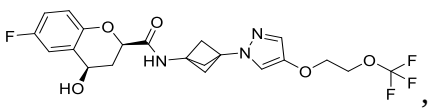
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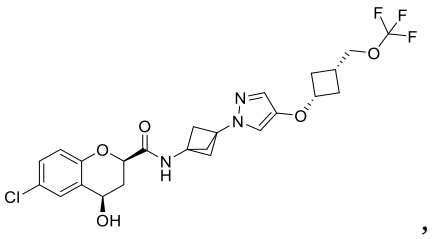
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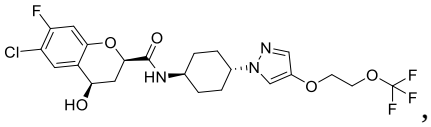
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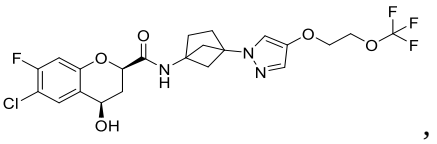
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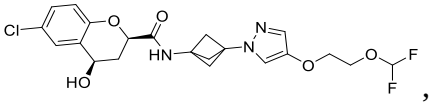
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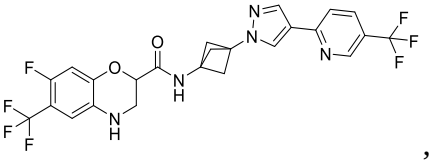
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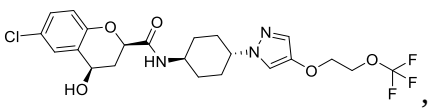
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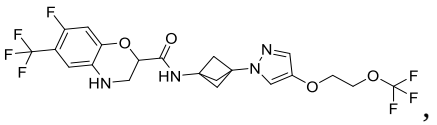
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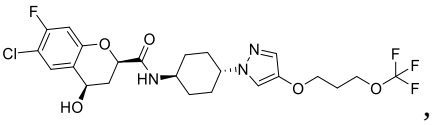
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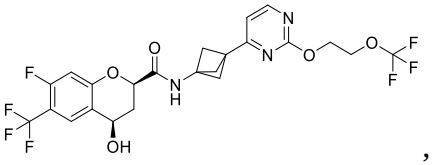
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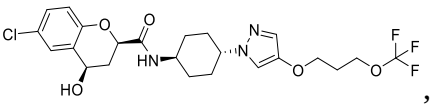
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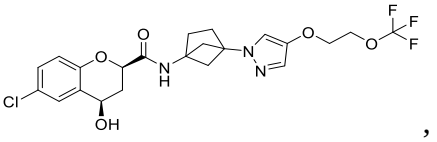
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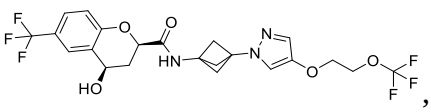
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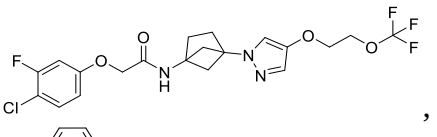
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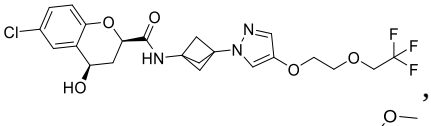
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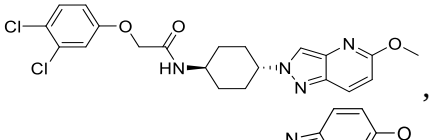
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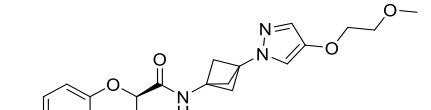
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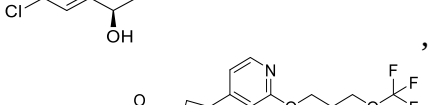
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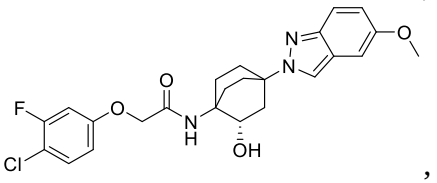
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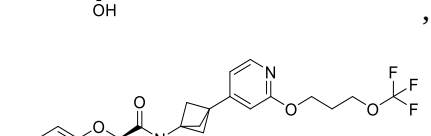
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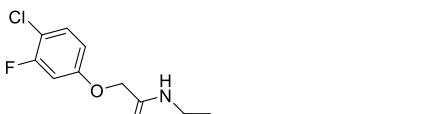
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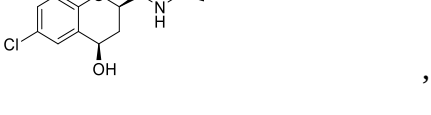
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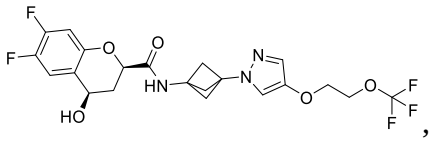
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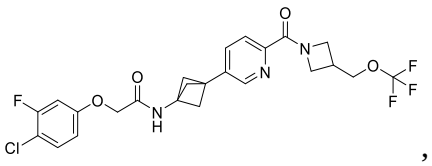
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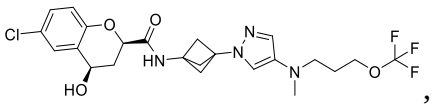
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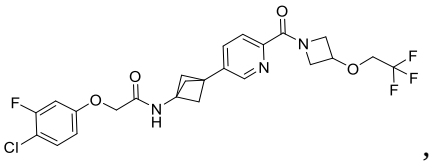
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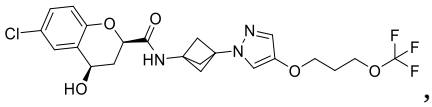
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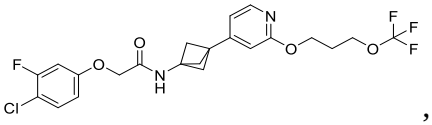
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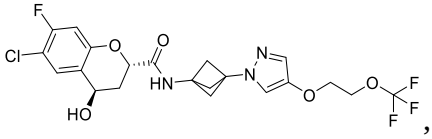
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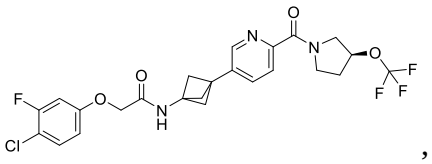
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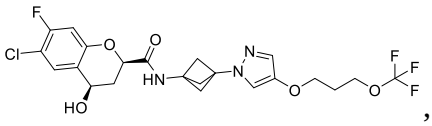
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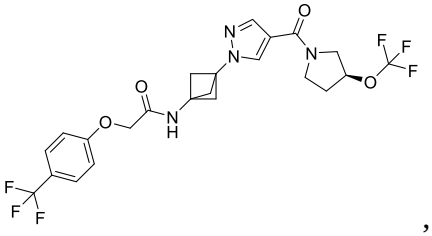
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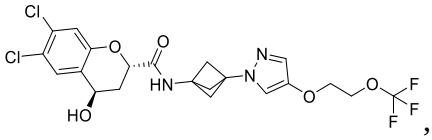
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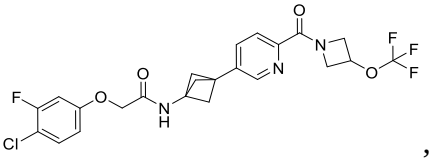
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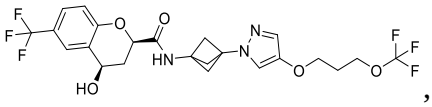
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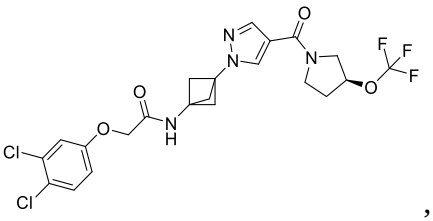
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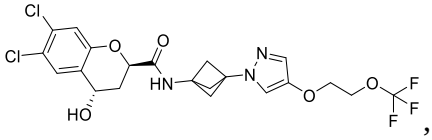
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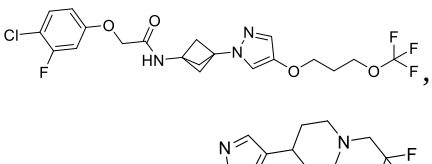
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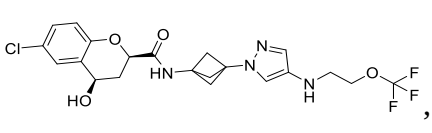
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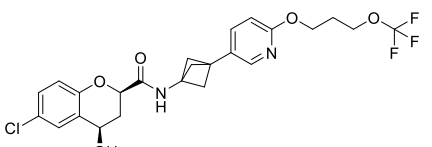
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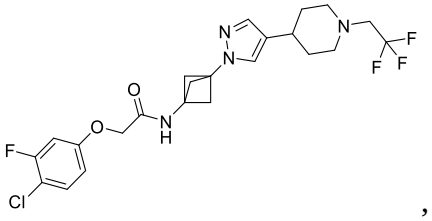
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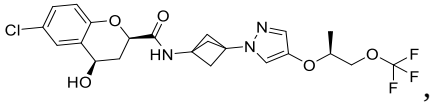
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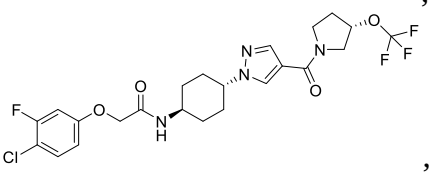
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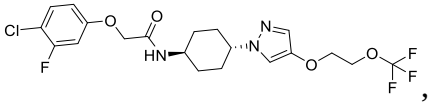
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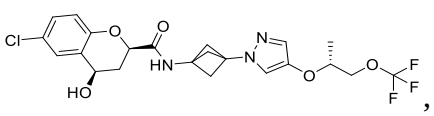
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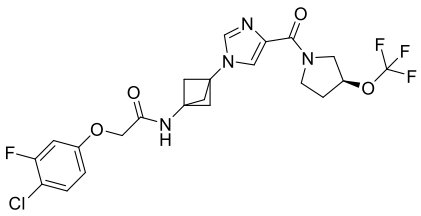
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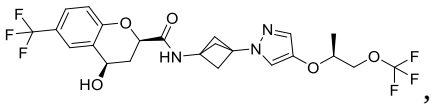
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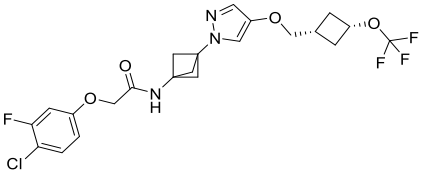
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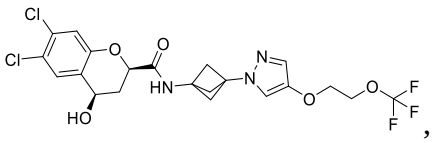
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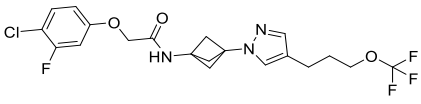
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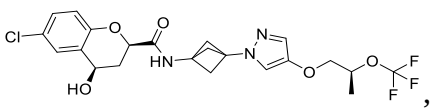
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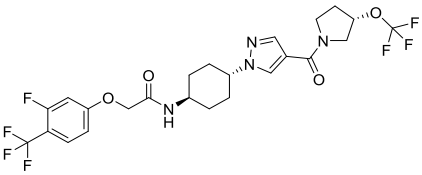
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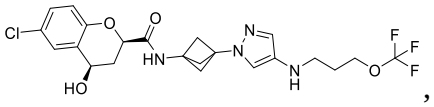
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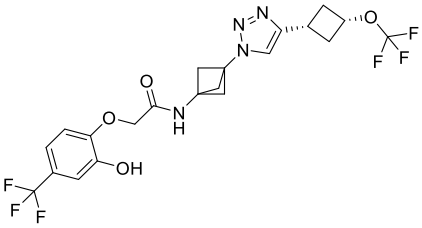
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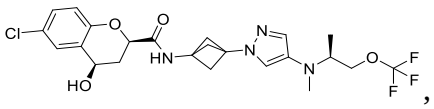
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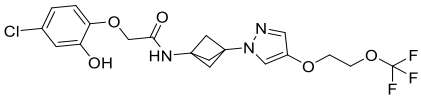
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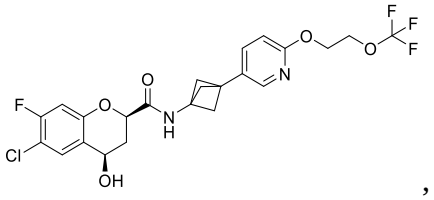
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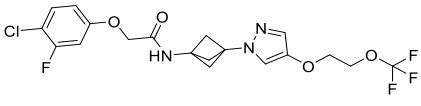
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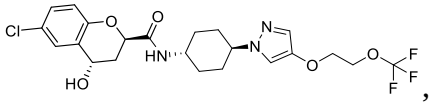
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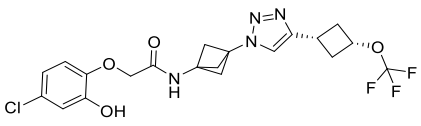
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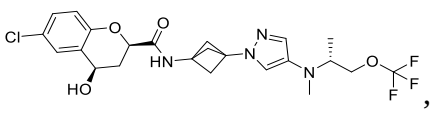
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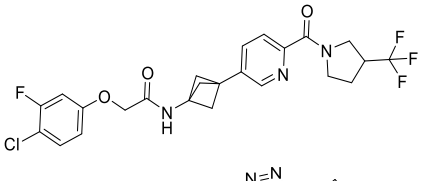
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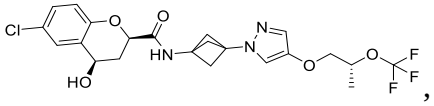
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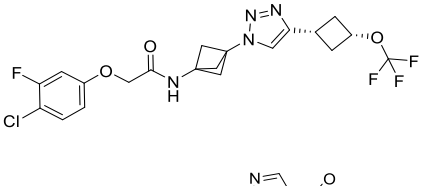
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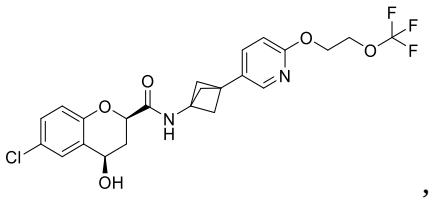
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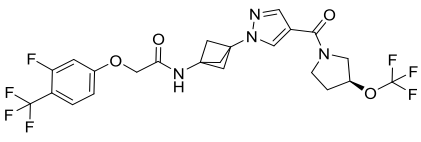
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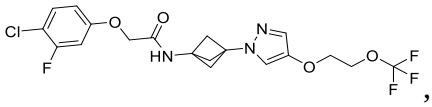
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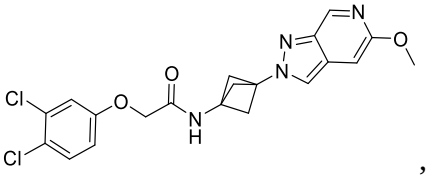
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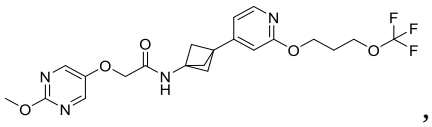
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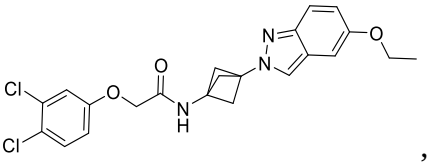
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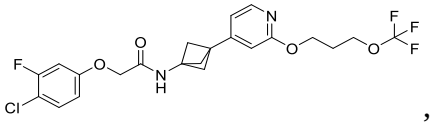
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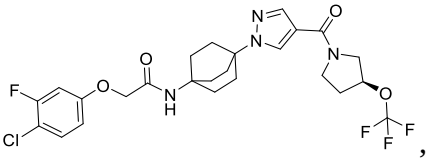
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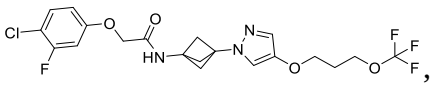
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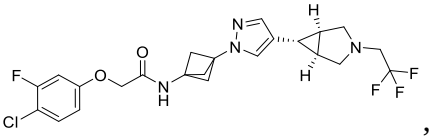
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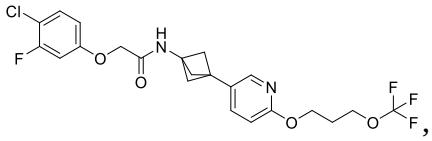
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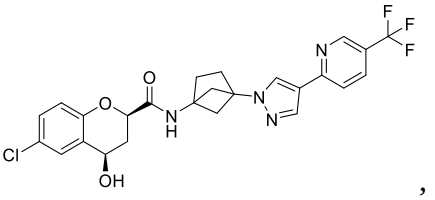
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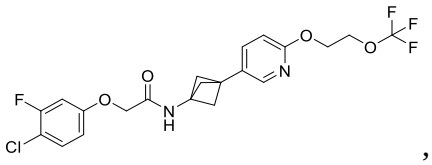
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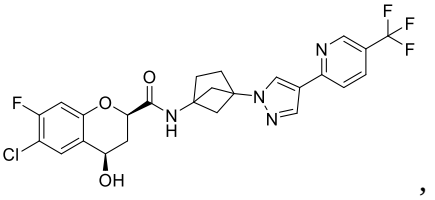
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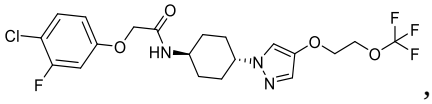
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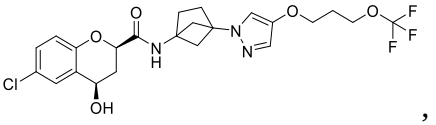
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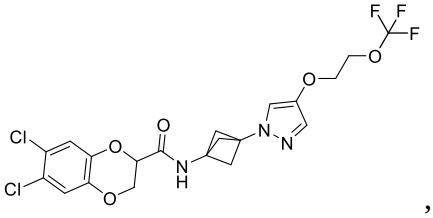
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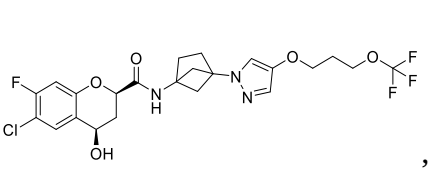
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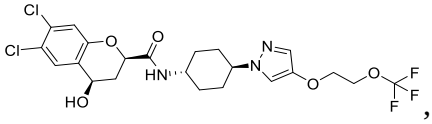
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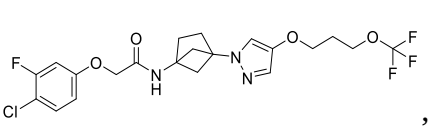
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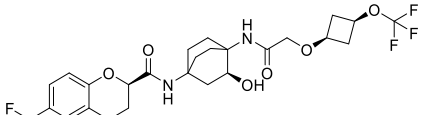
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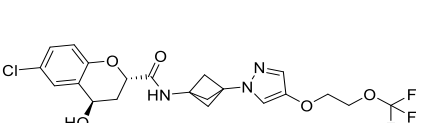
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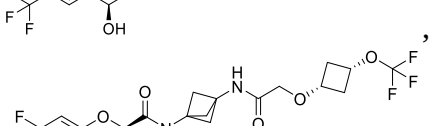
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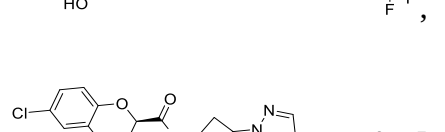
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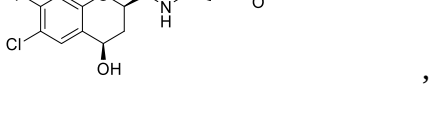
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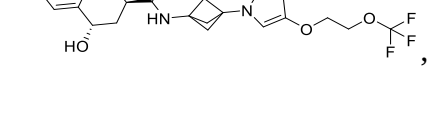
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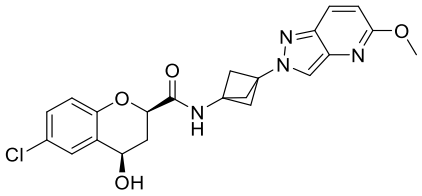
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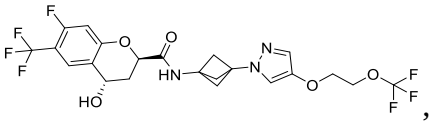
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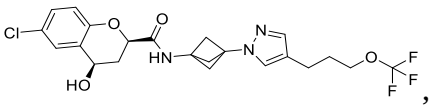
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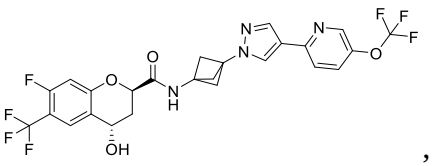
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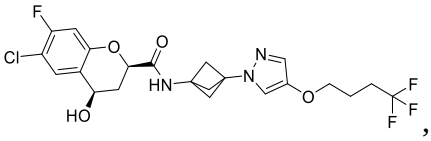
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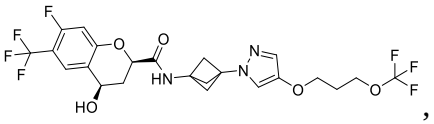
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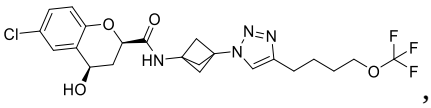
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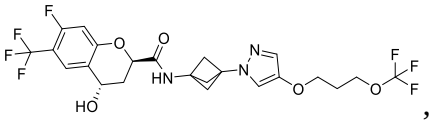
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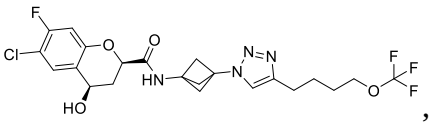
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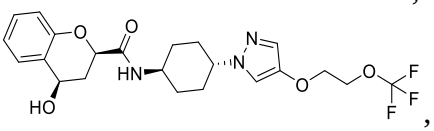
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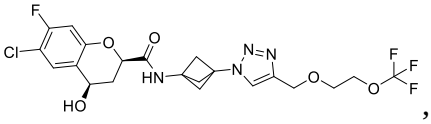
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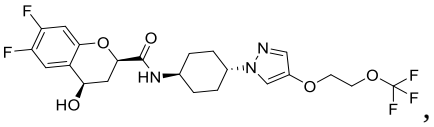
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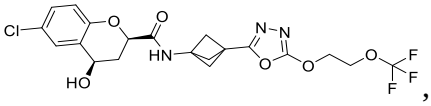
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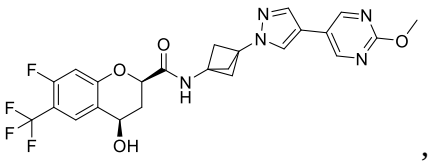
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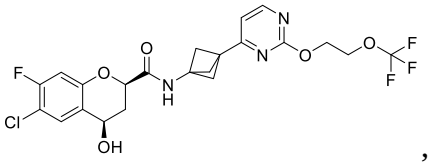
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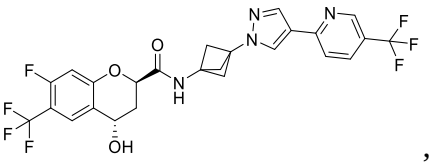
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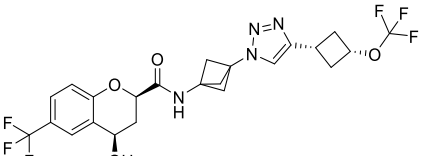
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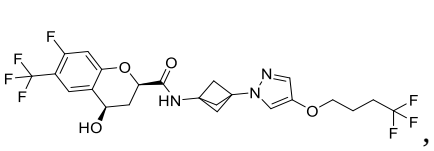
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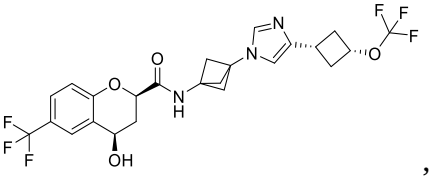
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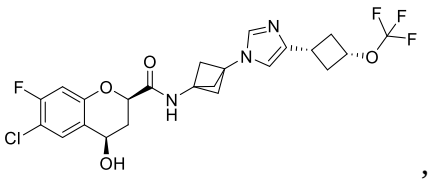
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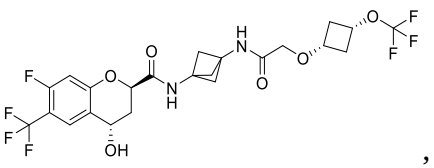
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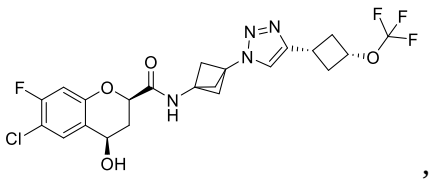
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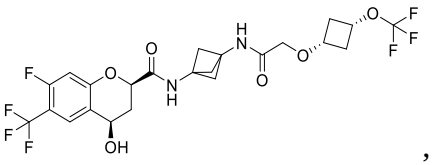
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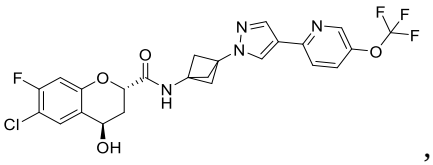
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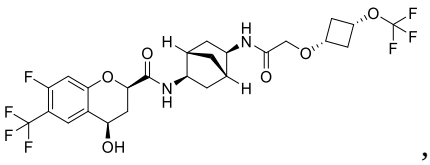
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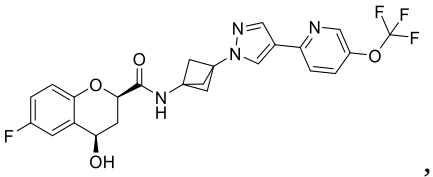
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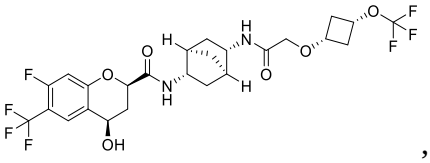
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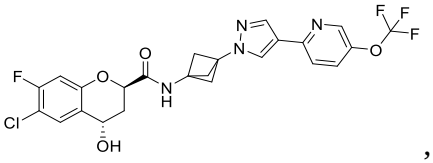
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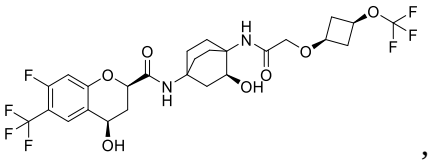
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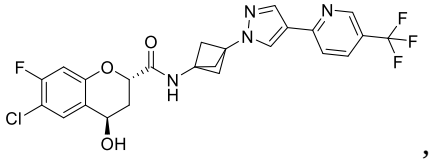
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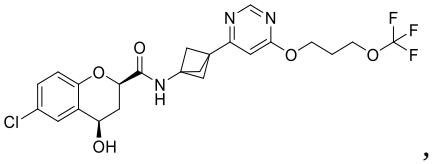
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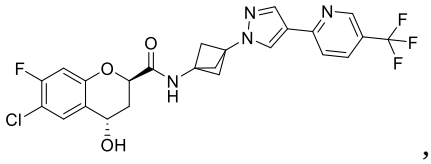
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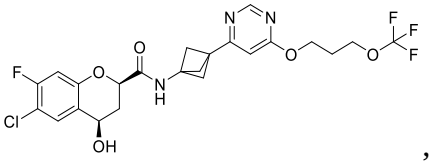
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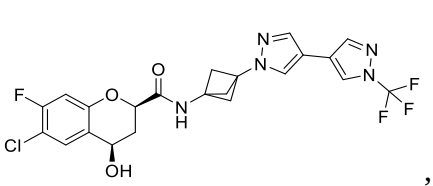
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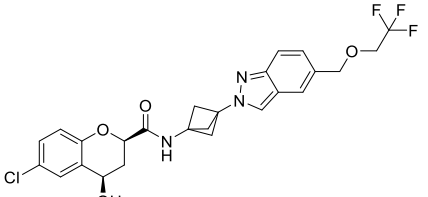
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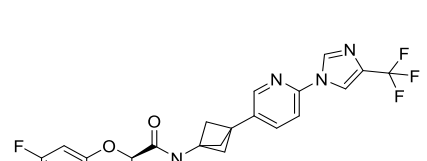
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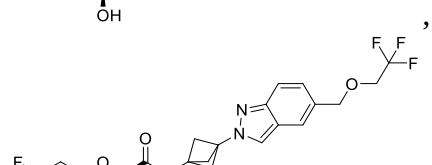
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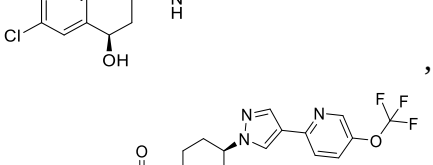
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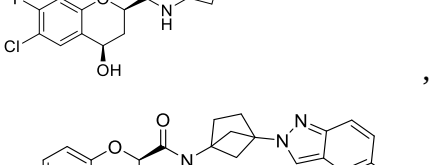
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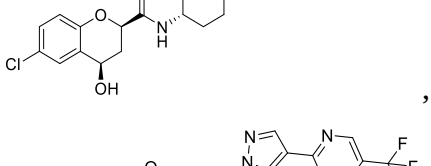
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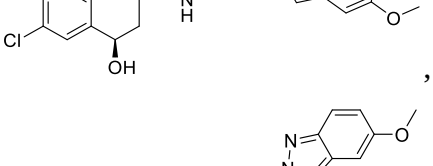
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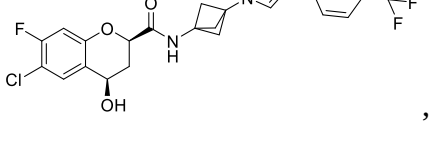
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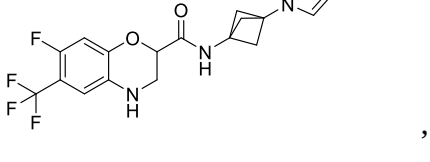
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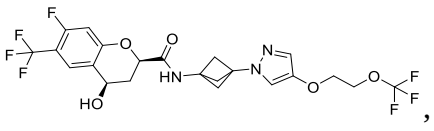
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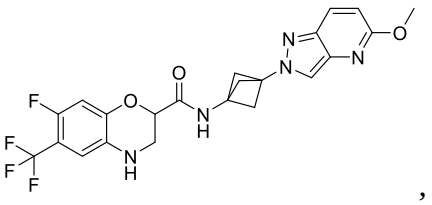
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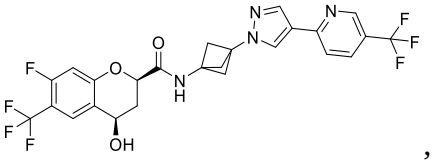
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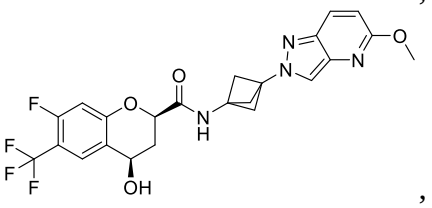
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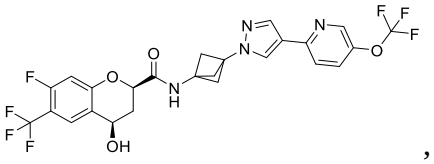
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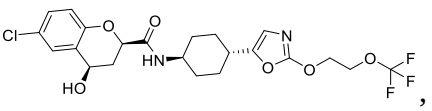
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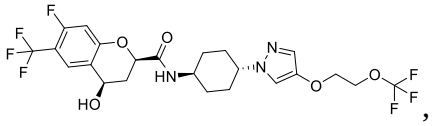
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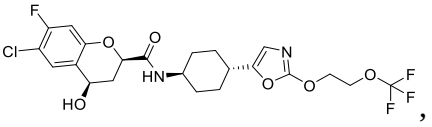
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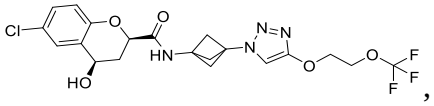
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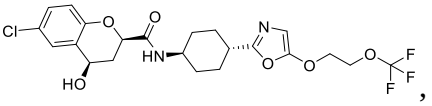
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and a pharmaceutically acceptable salt thereof.