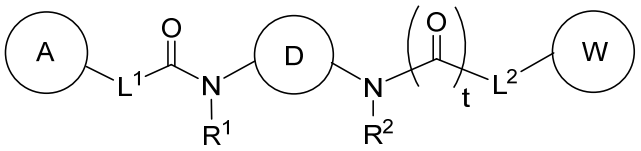
eIF2B4) are also highly homologous to one another and form a "regulatory sub-complex" that provides binding sites for eIF2B's substrate eIF2 (Dev, K. et al, *Mol Cell Biol* (2010) 30:5218-5233). The exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) 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

The present disclosure features compounds, compositions, and methods for the modulation of eIF2B (e.g., activation of eIF2B) and the attenuation of the ISR signaling pathway. In some embodiments, the present disclosure features an eIF2B modulator (e.g., an eIF2B activator) comprising a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In other embodiments, the present disclosure features methods of using a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer 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).

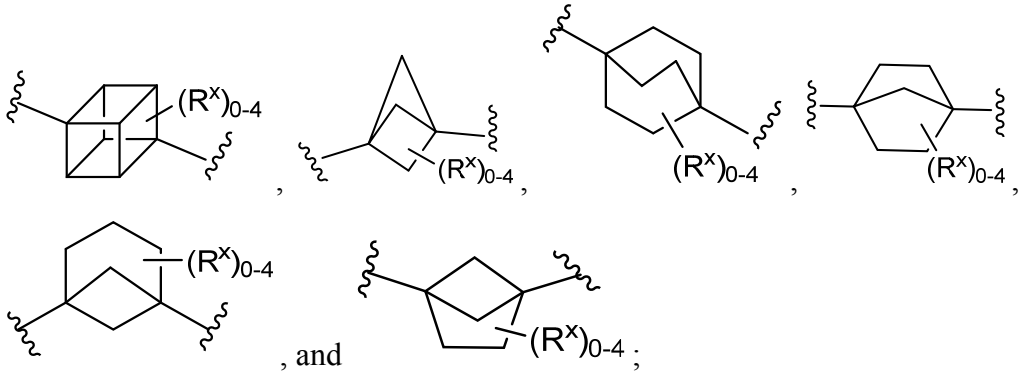
In one aspect, the present disclosure refers to a compound of Formula (I):



Formula (I)

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

D is selected from the group consisting of:



L^1 is selected from CH_2O-* and CH=CH-*, L^2 is selected from CH_2O-*, CH_2CH_2-*, $CH_2CH_2CH_2$-*, CH_2-*, $CH_2C(O)$-*, CH=CH-*, CH_2CH_2O-*, CH_2OCH_2-*, $CH_2OCH_2CH_2$-*, $CH_2CH_2CH_2O$-*, $CH_2CH_2OCH_2$-*, $NHCH_2$-*, CH_2NH-*, $CH_2N(CH_3)$-*, $CH_2N(CH_3)C(O)$-*, $CH_2N(C(O)CH_3)$-*, $CH_2CH(OH)$-*, CH(OH)-*, $CH(OH)CH_2CH_2$-*, $CH_2CH(OH)$-*, $CH_2NHC(O)$-*, $NHC(O)OCH_2$-*, O-*, NH-*, $S(O)_2CH$-*, $S(O)_2CH_2CH_2$-*, $S(O)_2CH_2CH_2O$-*, or $CH_2C(O)$-*, and "-*" indicates the attachment point to A and W, respectively;

R^1 and R^2 are each independently hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, or silyloxy-C_1-C_6 alkyl;

A is phenyl and W is phenyl or 5-6-membered heteroaryl, wherein A and W is optionally substituted with 1-5 R^Y;

each R^X is independently selected from the group consisting of C_1-C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-OS(O)_2R^D$, $-S(O)_2R^D$, $-SR^E$, $NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, –C(O)OH, NR^BR^C, or G^2;

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, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, –C(O)OH, $-C(O)OR^D$, $-S(R^F)_m$,$-S(O)_2R^D$, 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, heterocyclyl, aryl, or heteroaryl ring optionally substituted with 1-5 R^X;

each G^1 and G^2 is independently C_3-C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3-C_6 cycloalkyl, 4-7-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 $–S(O)_2R^D$;

each R^A is independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, 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^D is independently C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl, wherein each C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl is optionally substituted with 1-5 R^G;

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;

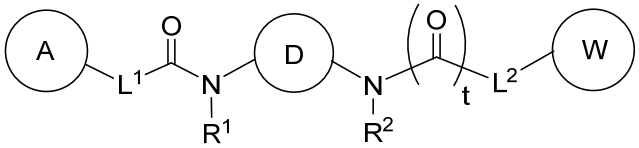
each R^G is independently aryl or 5-6 membered heteroaryl, wherein each aryl or 5-6 membered heteroaryl is optionally substituted with 1-5 R^H;

each R^H is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

m is 1, 3, or 5; and

t is 0 or 1.

In another aspect, the present disclosure refers to a compound represented by Formula (I-b):



Formula (I-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,

wherein:

D is (1,2,3,4,6,7)-cubane, bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, or bicycle[3.1.1]heptane, each of which is optionally substituted with 1-4 R^X groups;

L^1 and L^2 are each independently CH_2O-*, CH_2CH_2-*, $CH_2CH_2CH_2$-*, CH_2-*, $CH_2C(O)$-*, CH=CH-*, CH_2CH_2O-*, CH_2OCH_2-*, $CH_2OCH_2CH_2$-*, $CH_2CH_2CH_2O$-*,

$CH_2CH_2OCH_2$-*, $NHCH_2$-*, CH_2NH-*, $CH_2N(CH_3)$-*, $CH_2N(CH_3)C(O)$-*, $CH_2N(C(O)CH_3)$-*, $CH_2CH(OH)$-*, $CH(OH)$-*, $CH(OH)CH_2CH_2$-*, $CH_2CH(OH)$-*, $CH_2NHC(O)$-*, $NHC(O)OCH_2$-*, O-*, NH-*, $S(O)_2CH$-*, $S(O)_2CH_2CH_2$-*, $S(O)_2CH_2CH_2O$-*, or $CH_2C(O)$-*, and "-*" indicates the attachment point to A and W, respectively.

R^1 and R^2 are each independently hydrogen, CH_3, CH_2CH_2OH, or $CH_2CH_2OSi(CH_3)_2C(CH_3)_3$;

A and W are each independently phenyl, pyridyl, pyrazinyl, pyridazinyl, pyridazinonyl, triazinyl, thiazolyl, triazolyl, oxadiazolyl, or oxadiazolonyl, each of which is optionally substituted with 1-5 R^Y groups;

each R^X is independently selected from CH_3, oxo, fluoro, OH, cyano, OCH_3, NH_2, $N(CH_3)_2$, $NHC(O)CH_3$, $OC(O)CH_3$, $C(O)NH_2$, $OS(O)_2CH_3$, $-S(O)_2CH_3$, $-S(O)_2\ CH_2CH_3$, C(O)OH, $OC(O)R^D$, $-C(O)CH_3$, $-SCH_3$, or G^2;

each R^Y is independently chloro, fluoro, iodo, CF_3, CHF_2, CH_2CF_3, CH_3, CH_2CH_3, $C(CH_3)_2OH$, OCH_3, OCH_2CH_3, OCF_3, $S(O)_2CH_3$, $S(O)_2CH_2CH_2CH_3$, CN, $N(CH_3)_2$, SF_5, SCH_3, NH_2, $C(CH)_3$, $CH(CH_3)_2$, CH_2CN, CH_2NH_2, $CH(OH)CH_3$, $C(OH)(CH_3)CF_3$, $S(O)_2CH_3$, $C(O)CH_3$, $C(O)OCH_3$, C(O)OH, $OCHF_2$ or G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a pyrazolyl, pyrrolyl, isoxazolyl, thiophenyl, furanyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X;

G^1 and G^2 are cyclopropyl, isoxazolyl, phenyl, piperidinyl, oxadiazolyl, or tetrazolyl, or pyrazolyl, each of which is optionally substituted with 1-2 R^Z;

each R^D is CH_2O optionally substituted with 1-5 R^G;

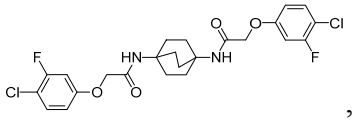
each R^G is independently pyridyl optionally substituted with 1-5 R^H;

each R^H is independently CF_3;

each R^Z is independently CH_3; and

t is 0 or 1.

In a further aspect, the present disclosure refers to a compound selected from the group consisting of:



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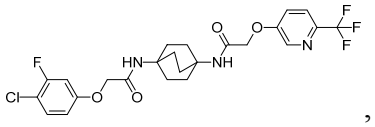
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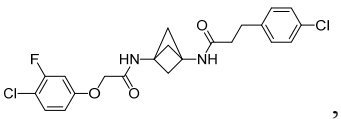
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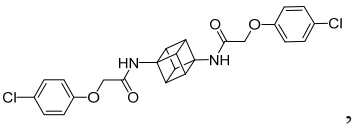
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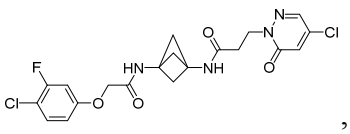
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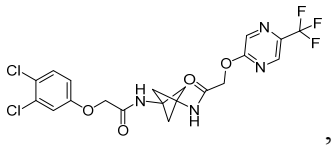
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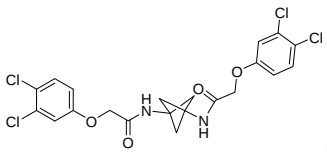
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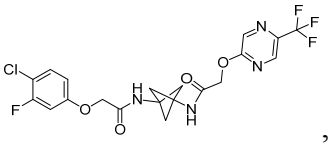
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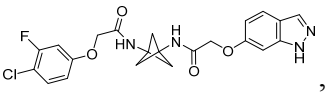
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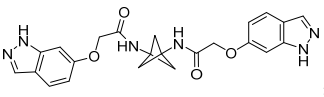
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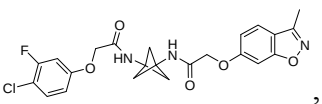
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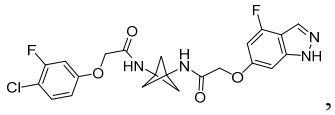
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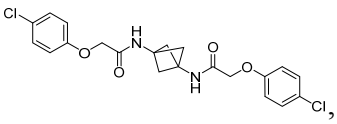
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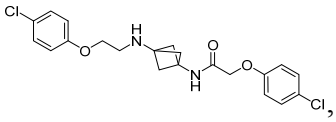
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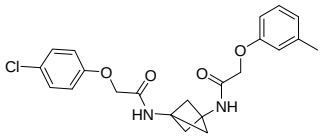
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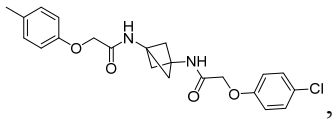
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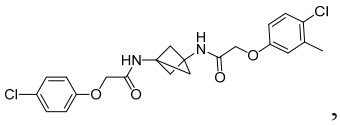
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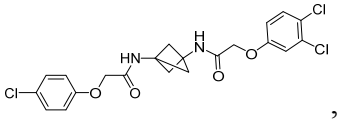
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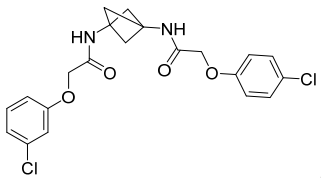
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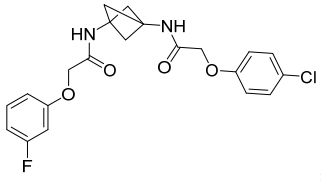
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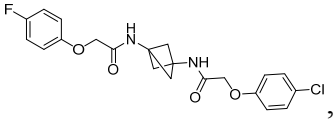
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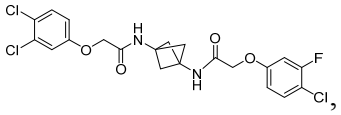
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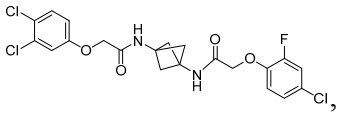
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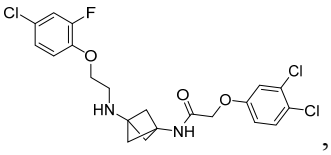
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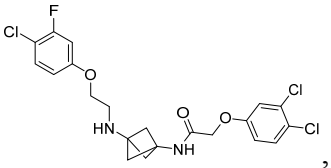
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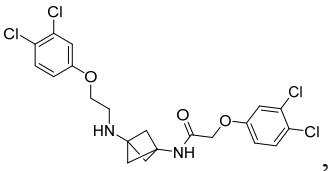
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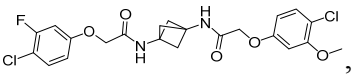
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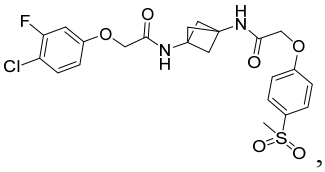
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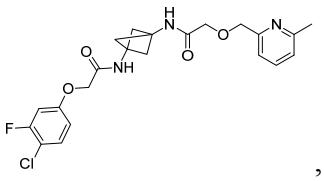
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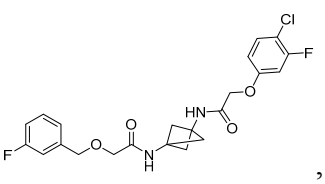
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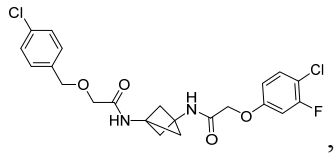
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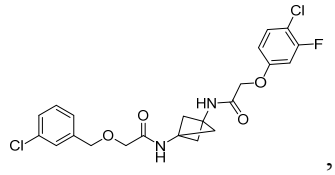
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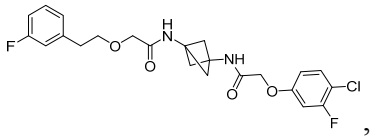
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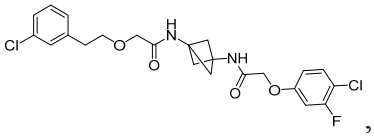
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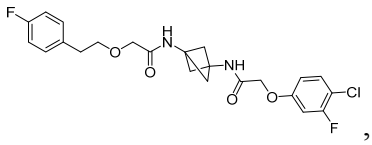
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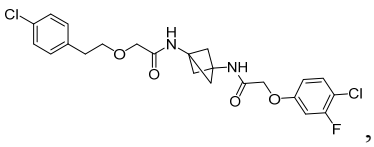
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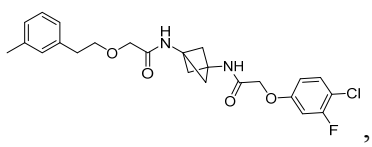
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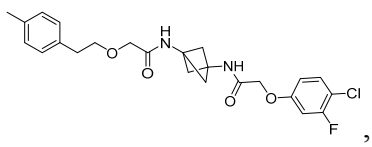
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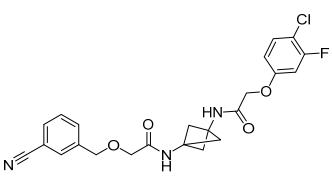
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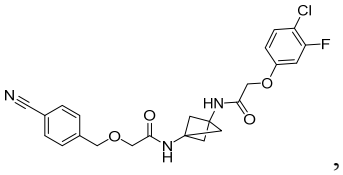
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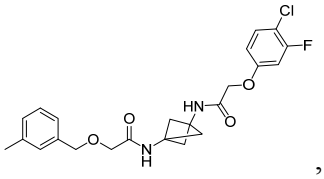
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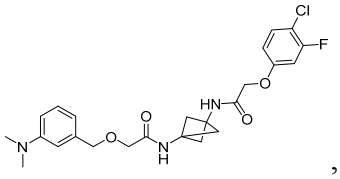
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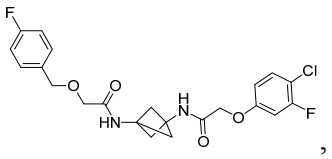
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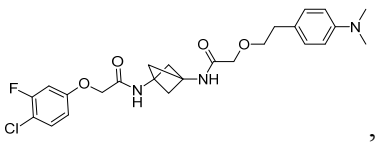
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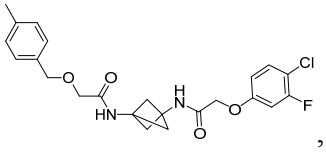
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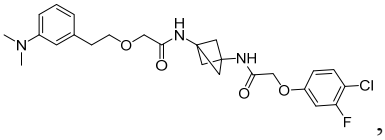
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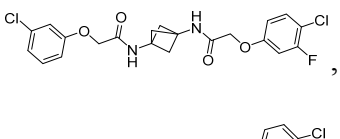
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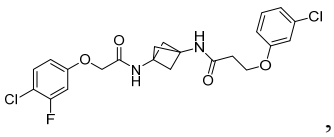
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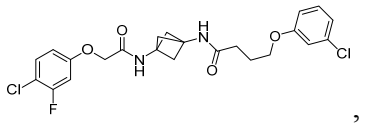
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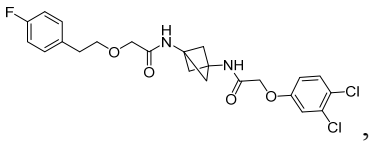
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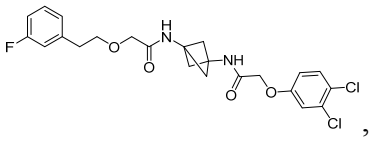
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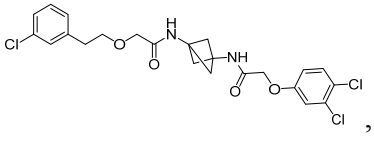
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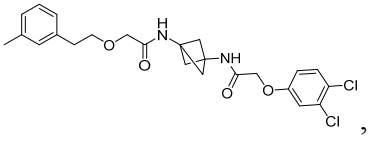
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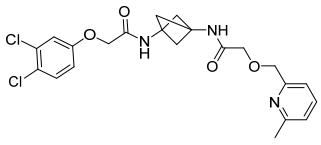
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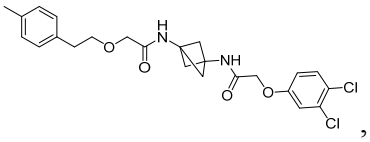
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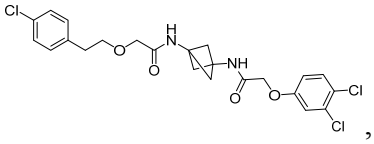
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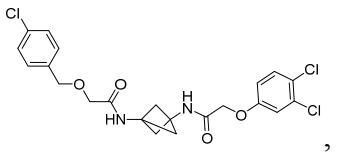
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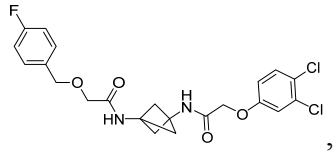
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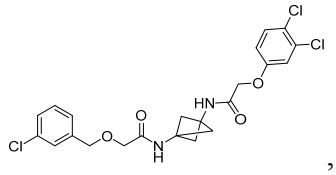
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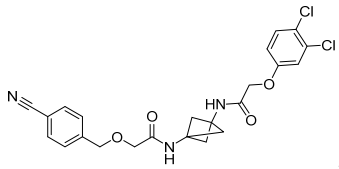
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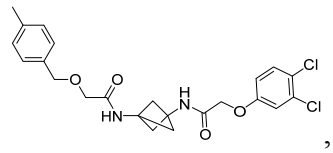
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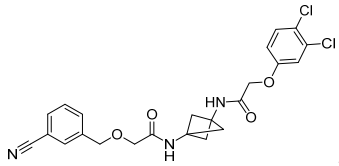
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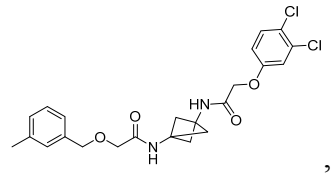
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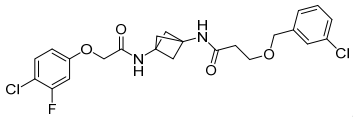
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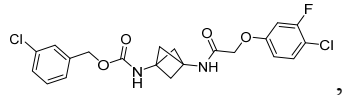
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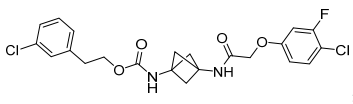
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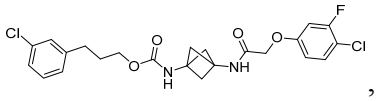
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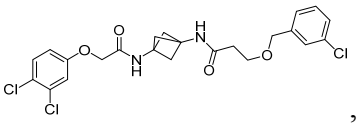
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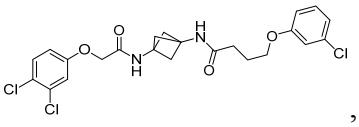
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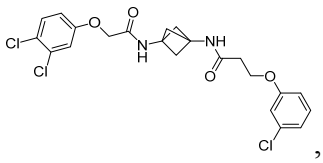
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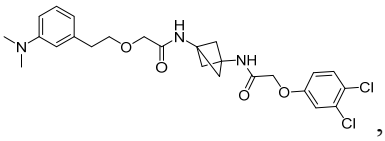
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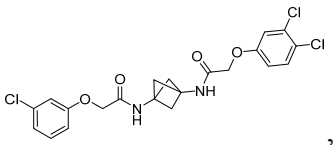
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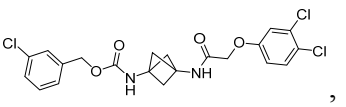
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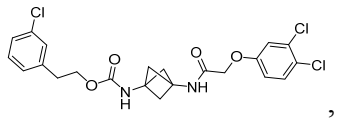
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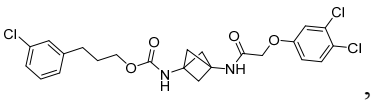
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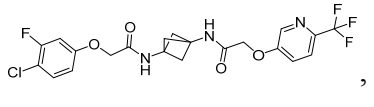
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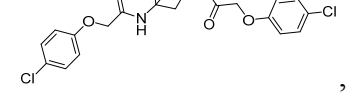
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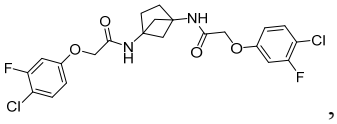
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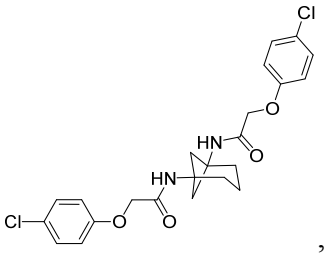
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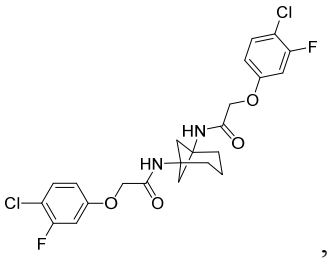
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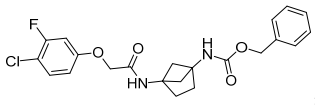
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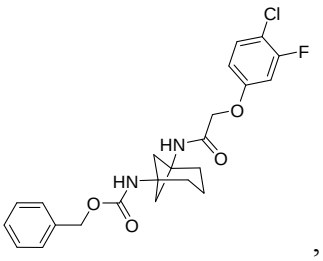
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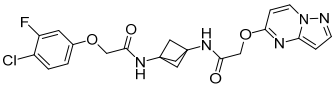
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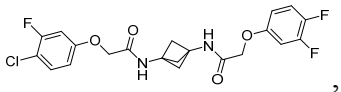
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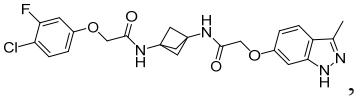
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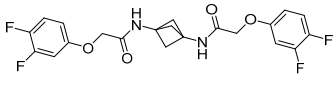
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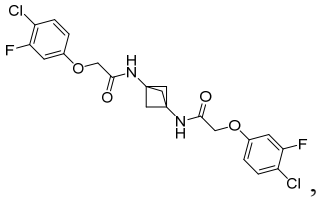
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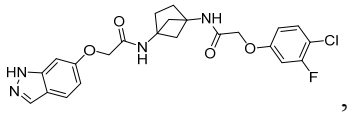
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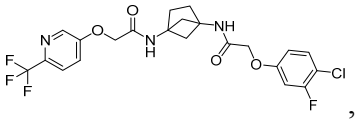
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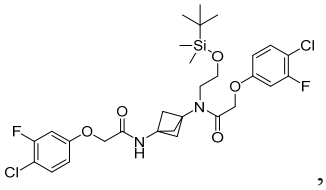
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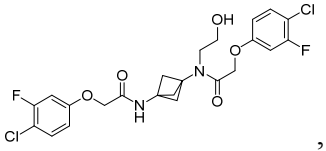
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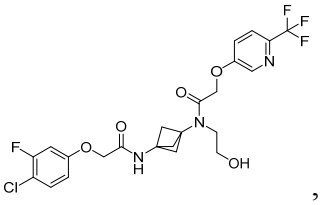
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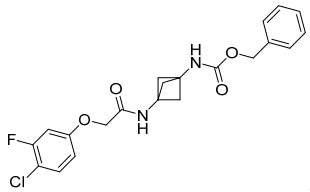
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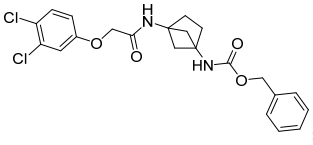
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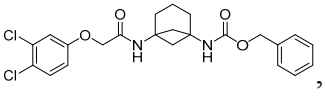
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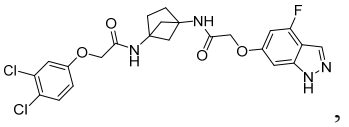
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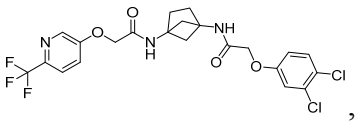
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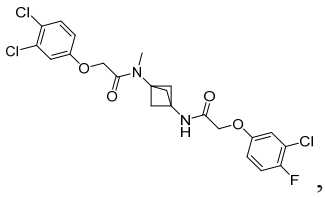
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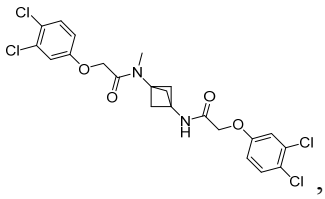
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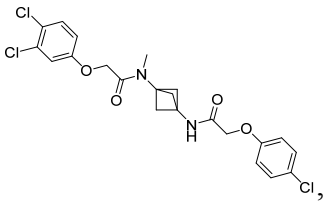
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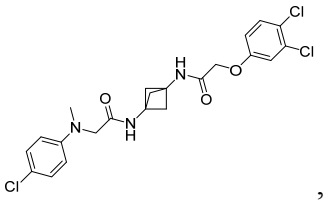
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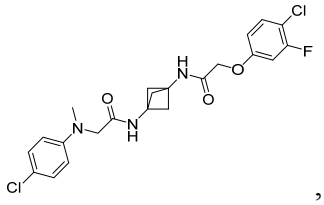
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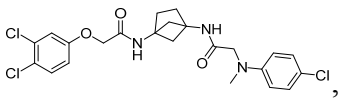
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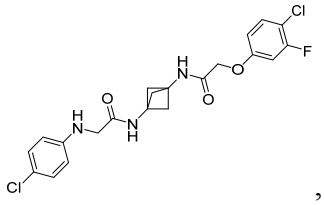
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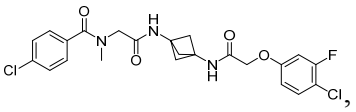
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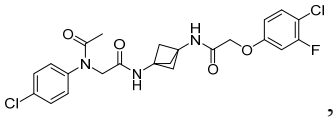
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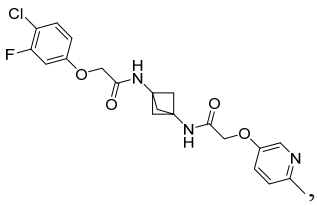
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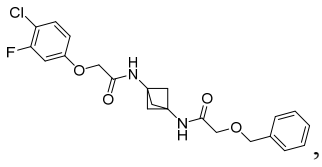
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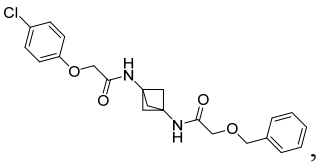
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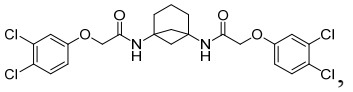
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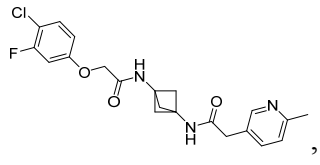
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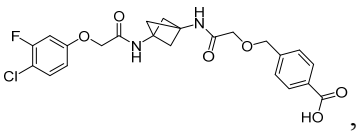
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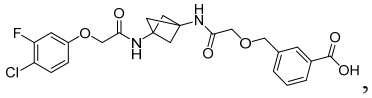
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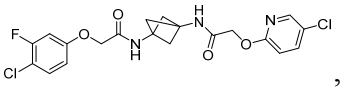
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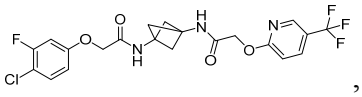
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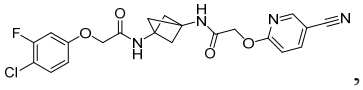
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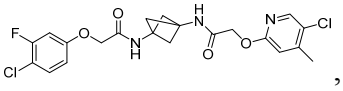
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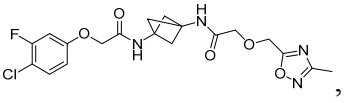
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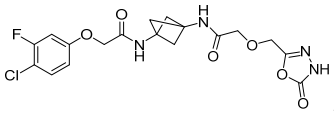
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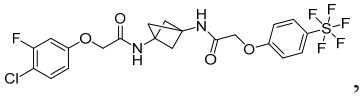
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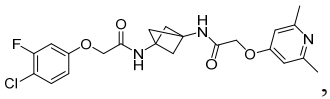
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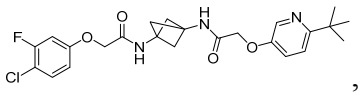
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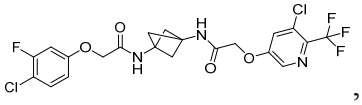
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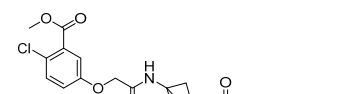
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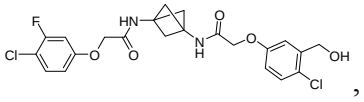
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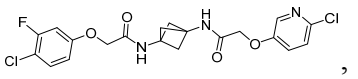
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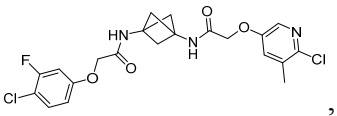
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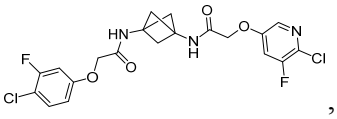
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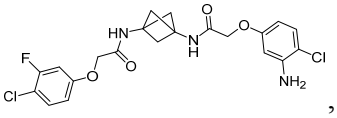
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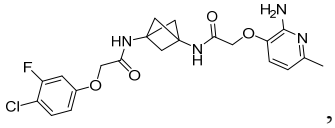
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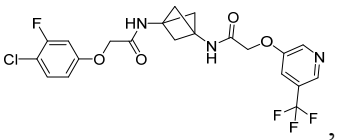
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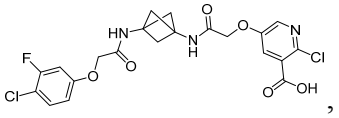
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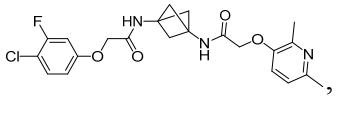
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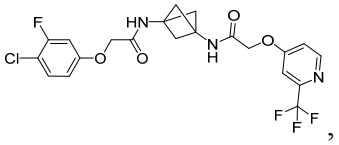
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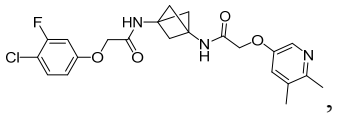
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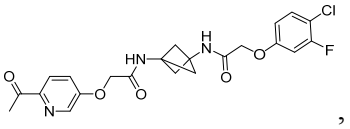
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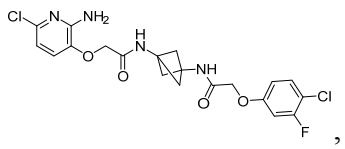
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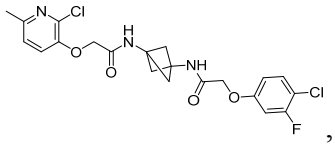
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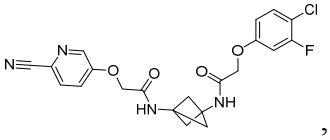
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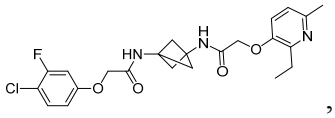
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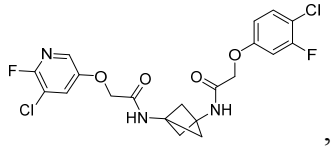
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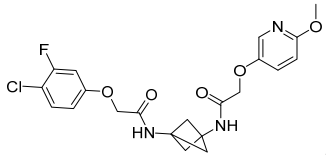
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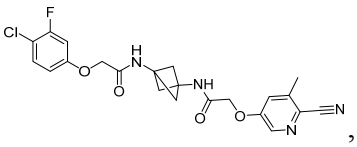
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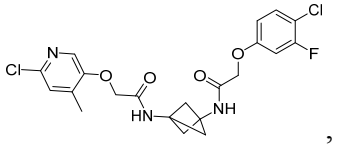
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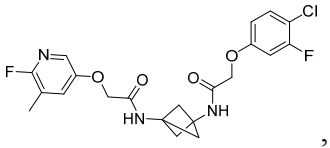
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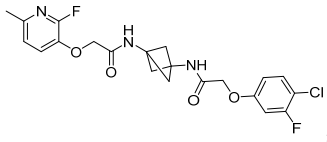
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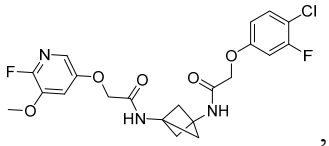
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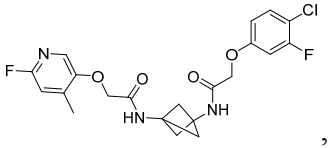
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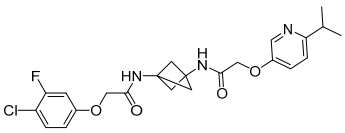
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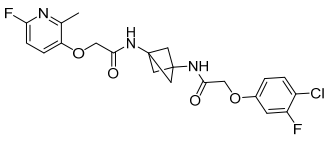
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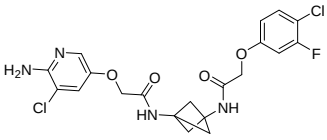
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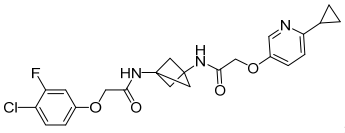
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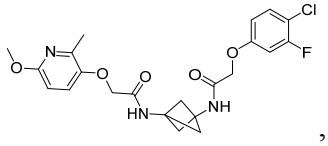
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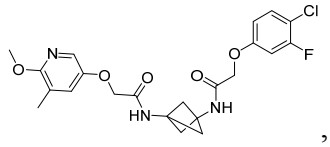
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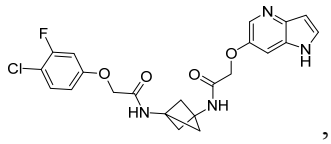
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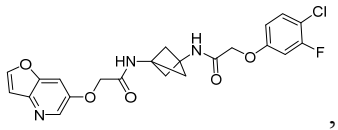
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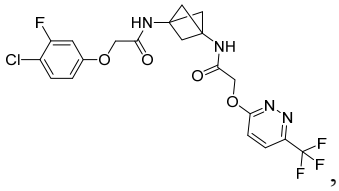
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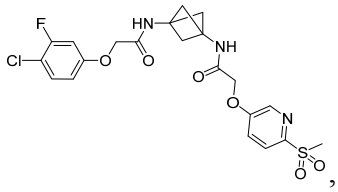
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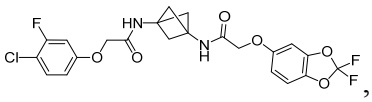
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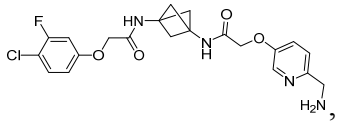
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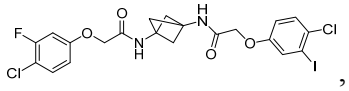
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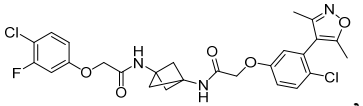
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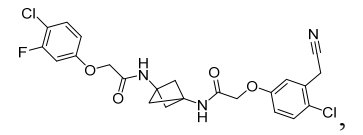
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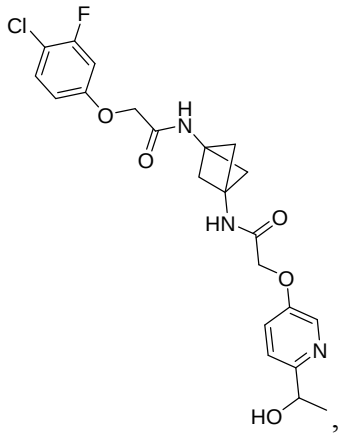
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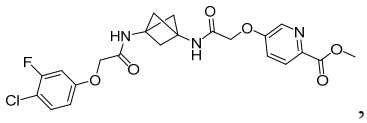
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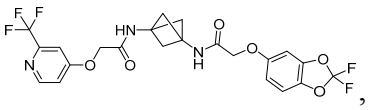
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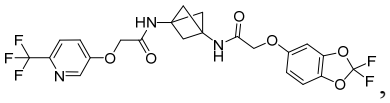
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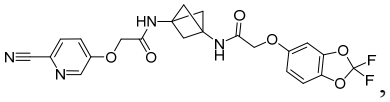
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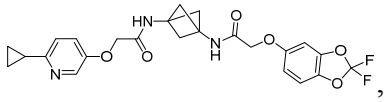
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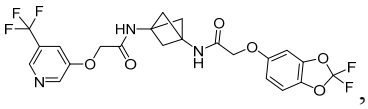
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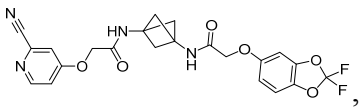
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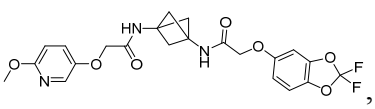
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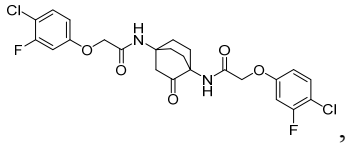
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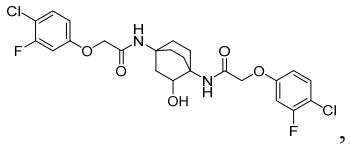
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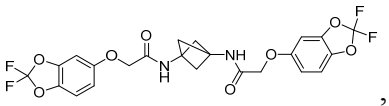
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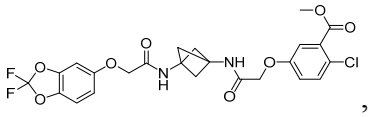
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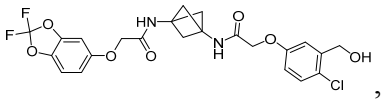
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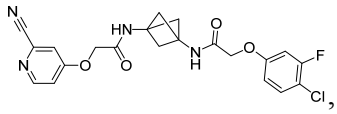
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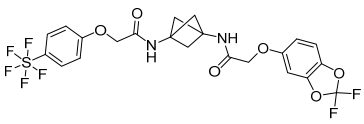
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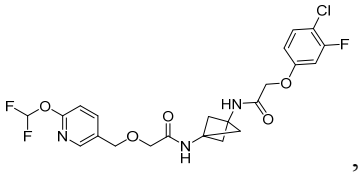
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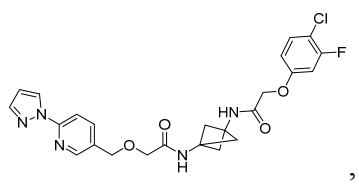
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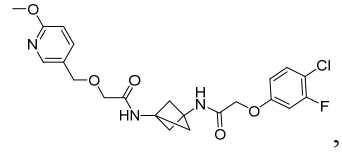
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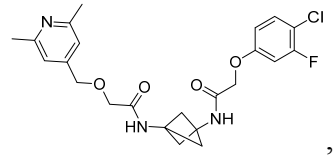
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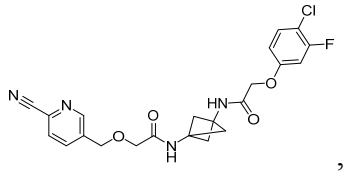
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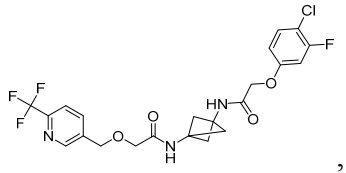
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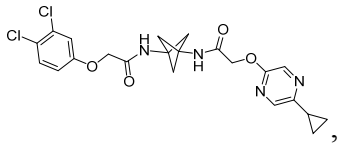
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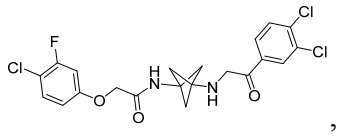
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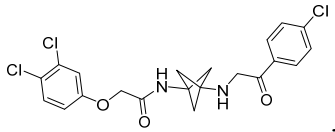
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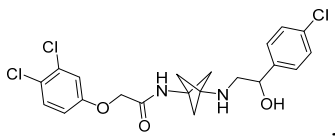
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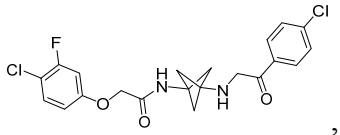
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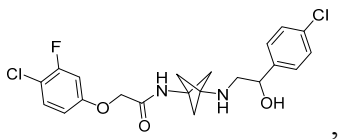
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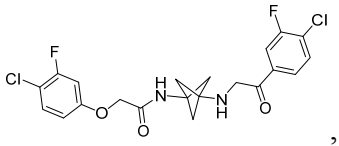
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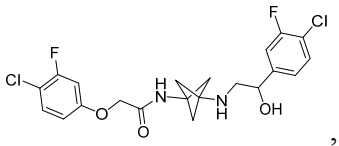
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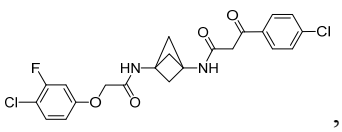
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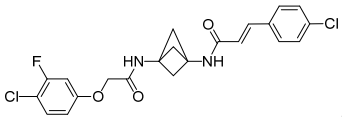
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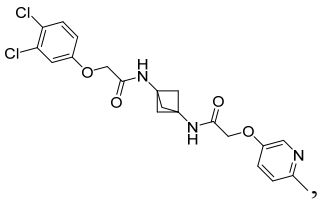
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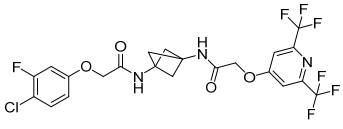
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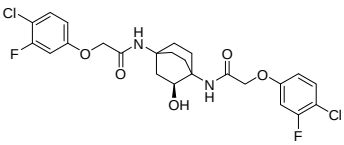
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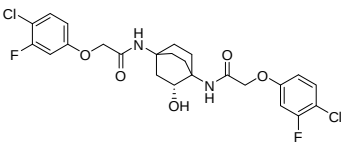
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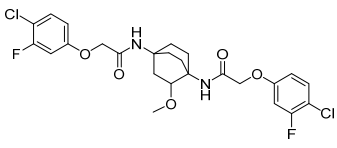
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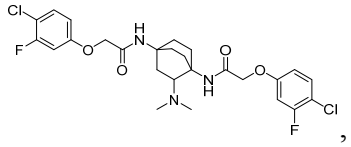
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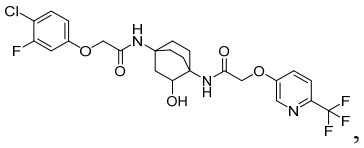
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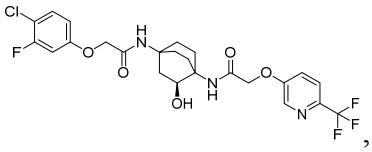
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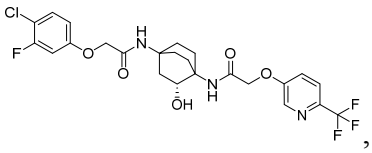
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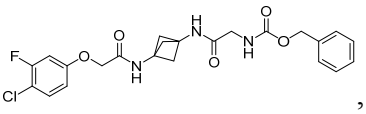
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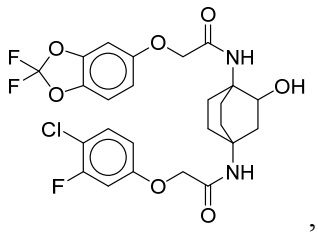
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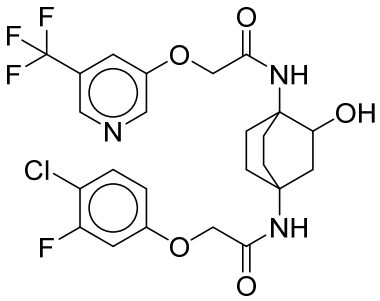
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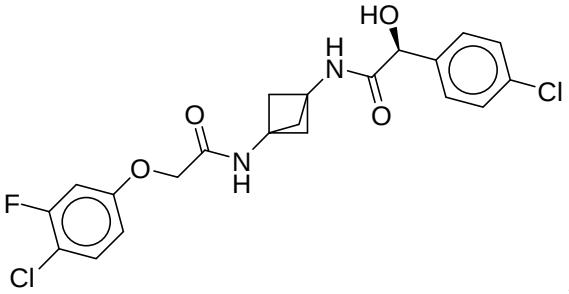
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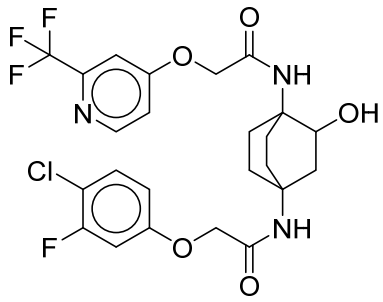
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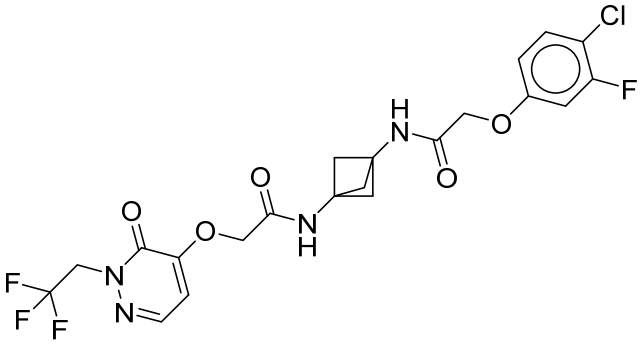
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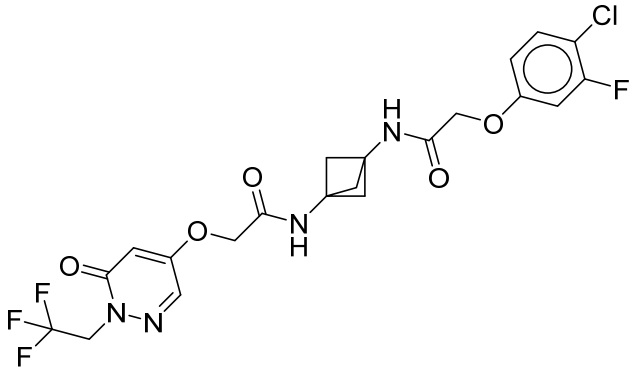
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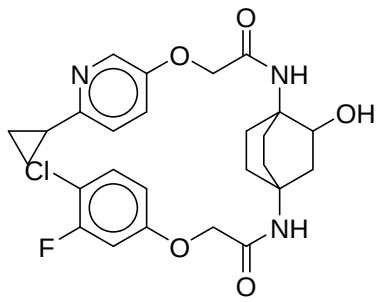
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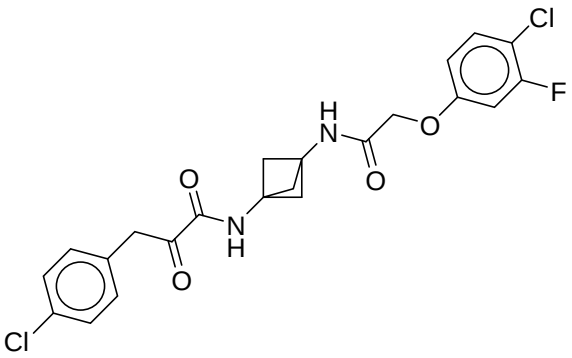
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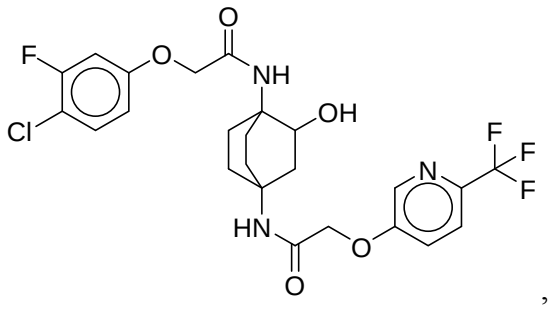
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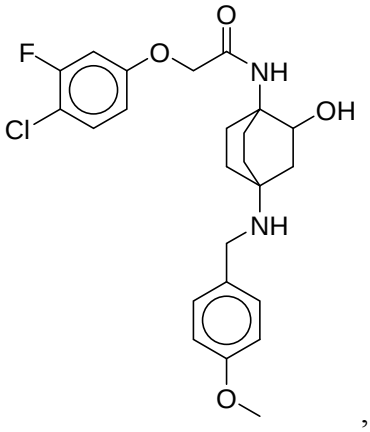
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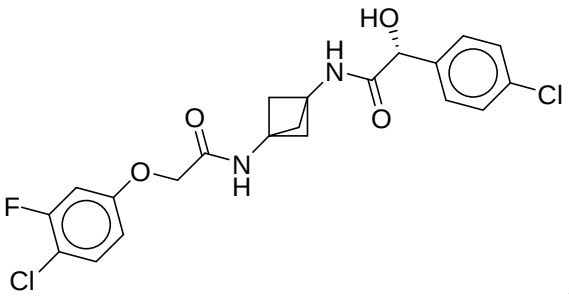
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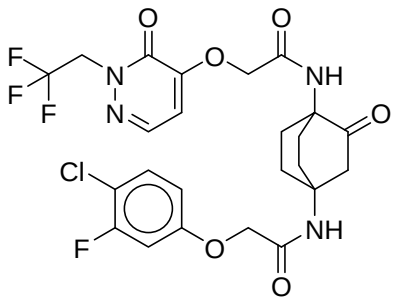
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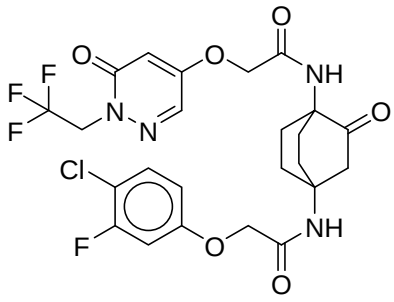
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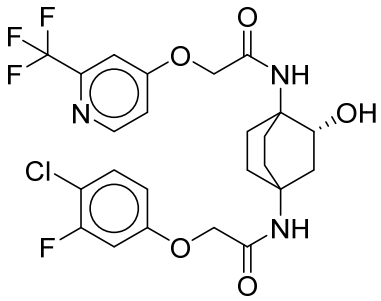
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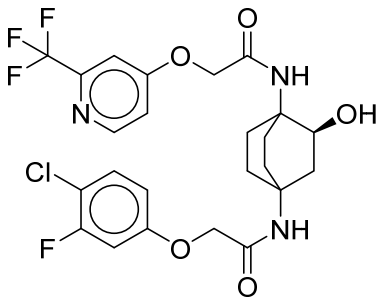
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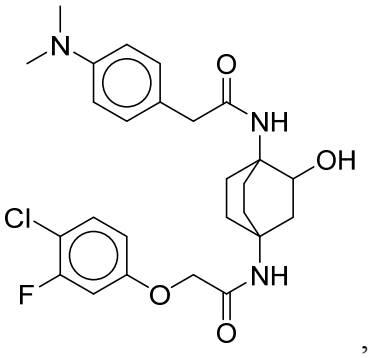
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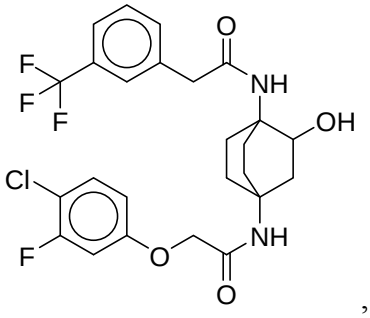
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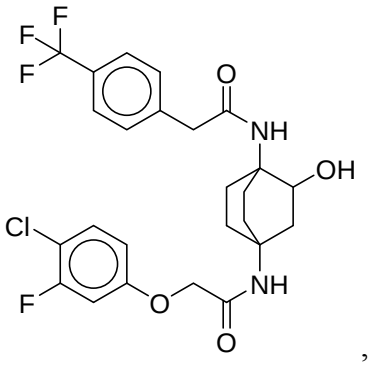
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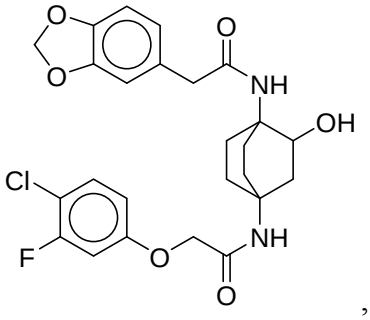
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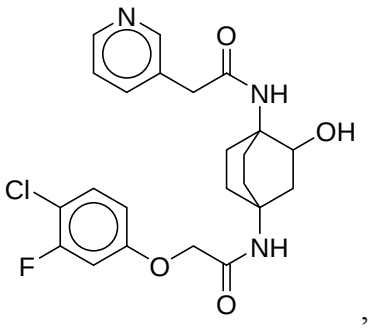
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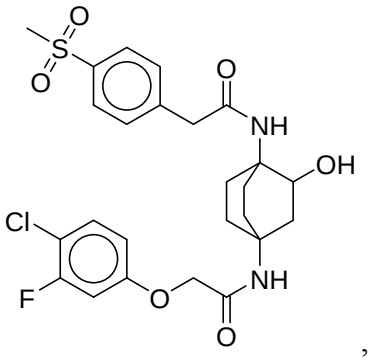
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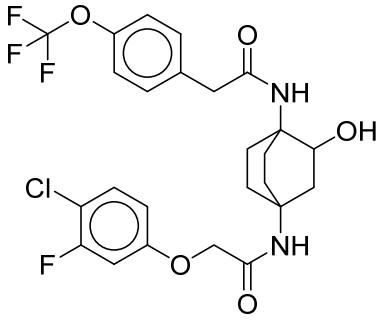
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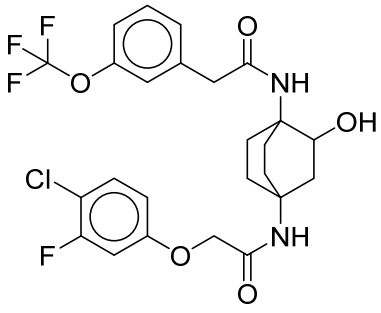
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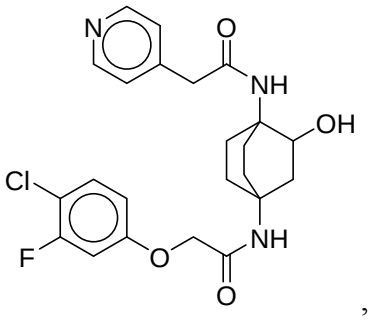
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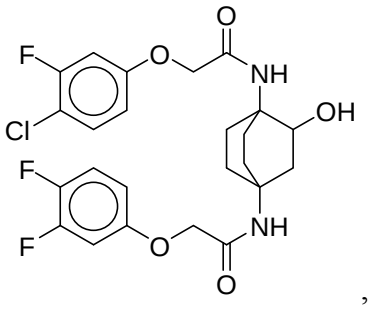
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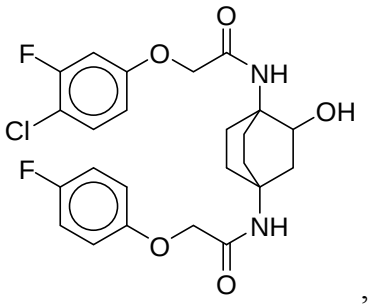
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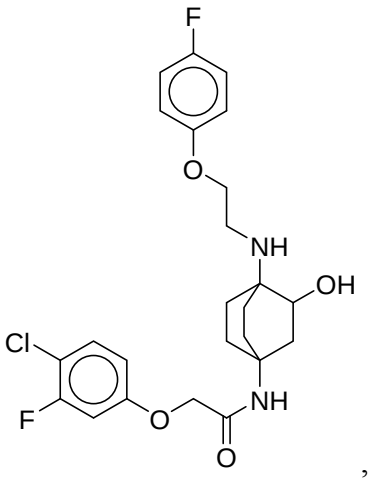
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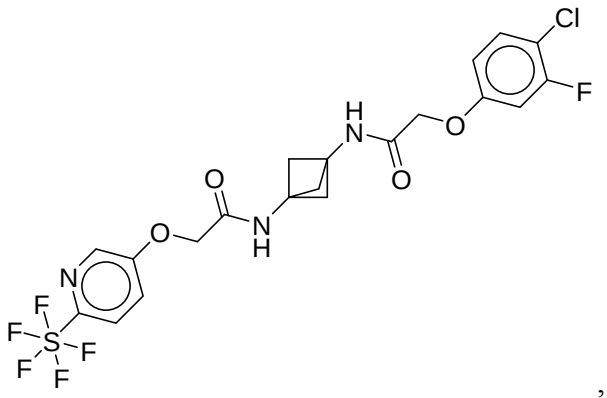
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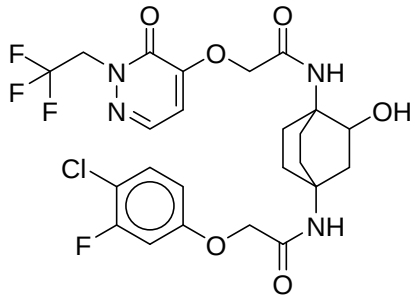
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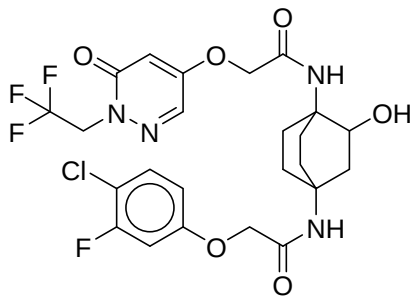
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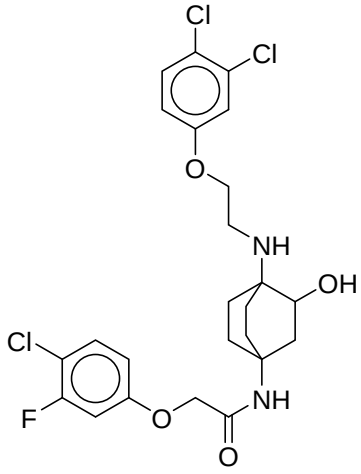
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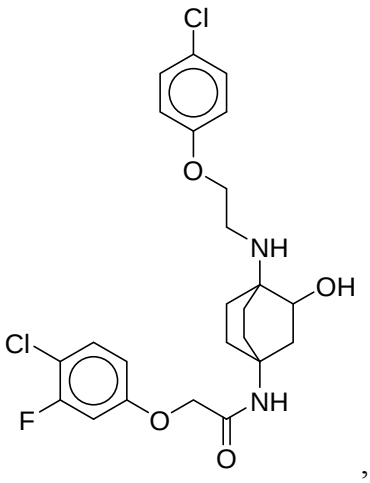
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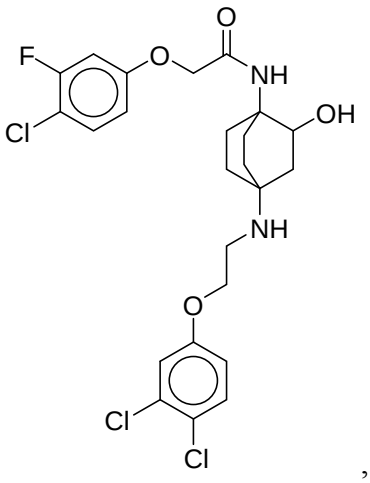
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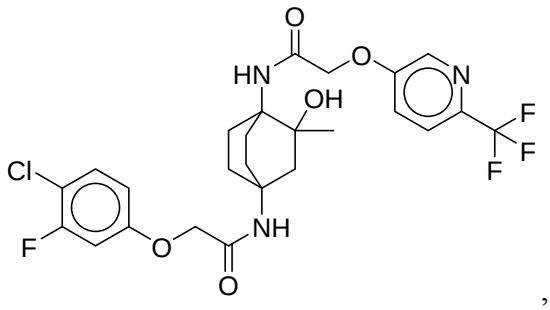
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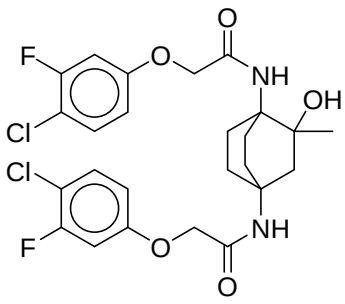
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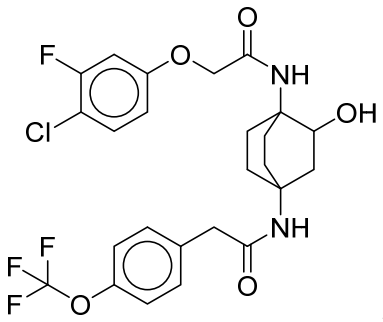
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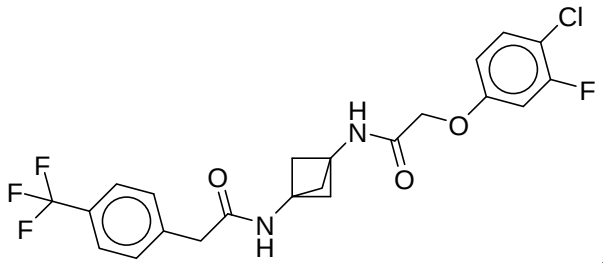
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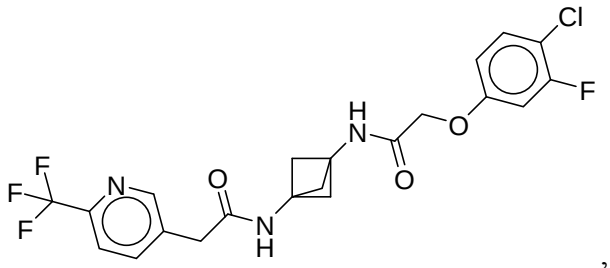
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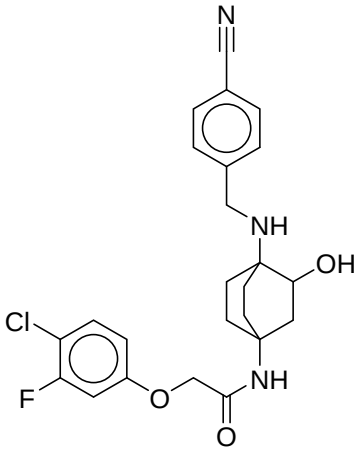
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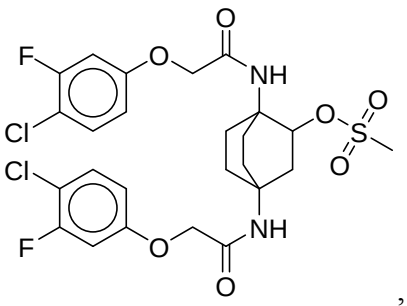
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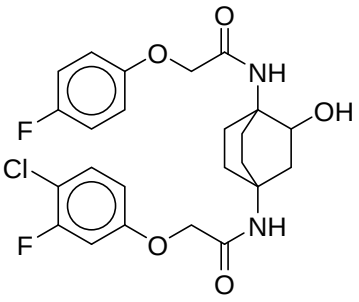
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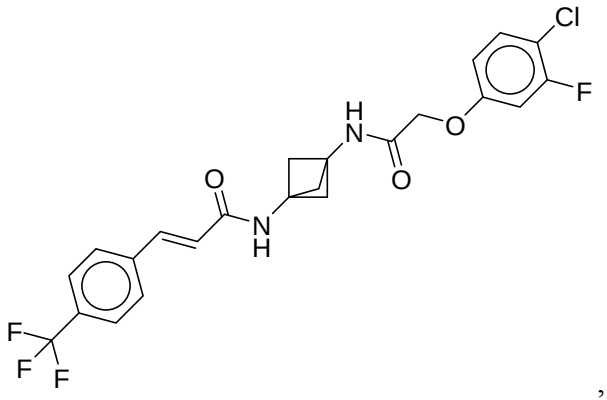
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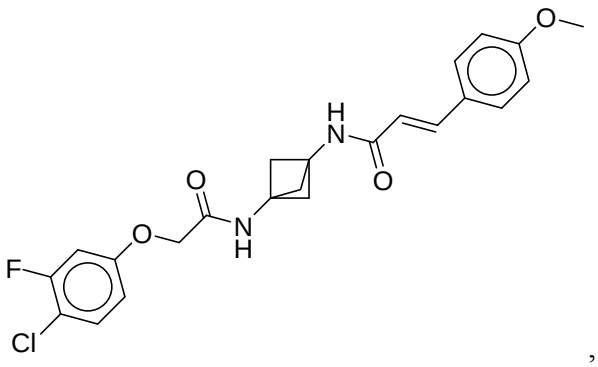
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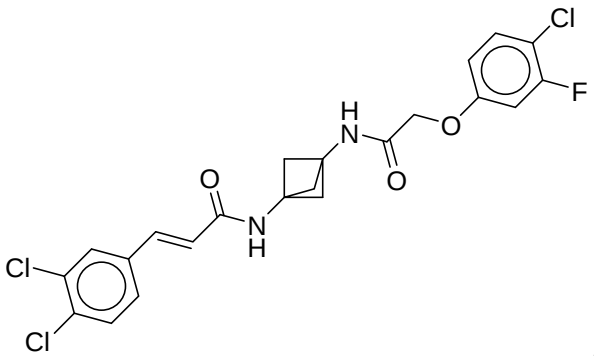
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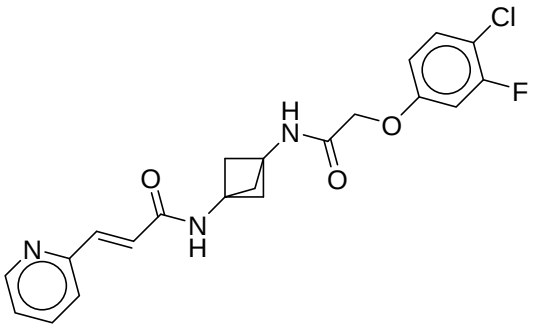
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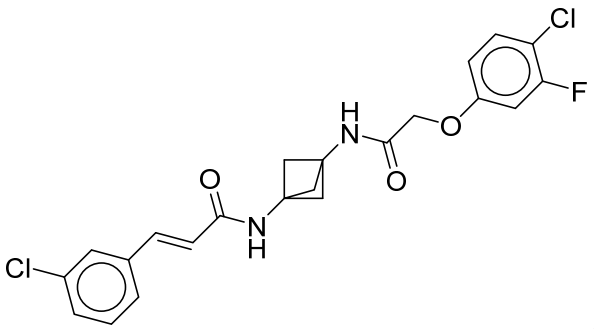
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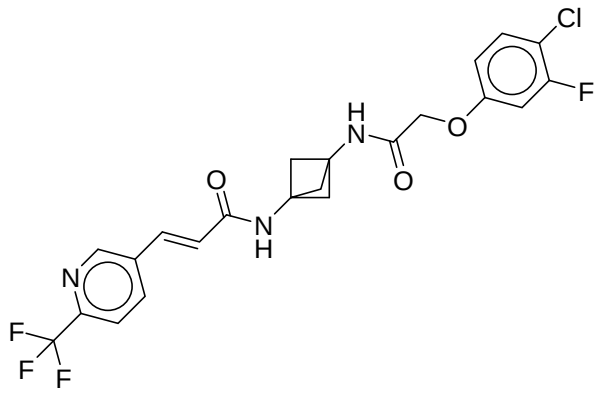
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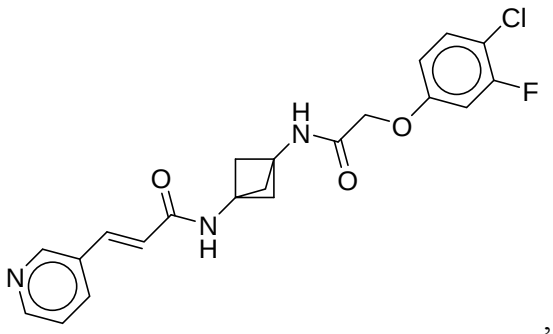
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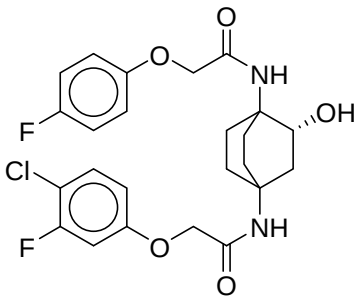
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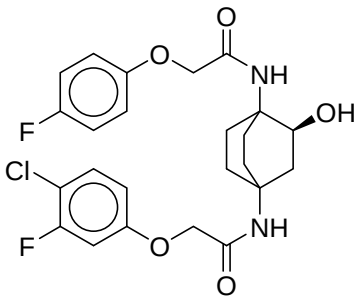
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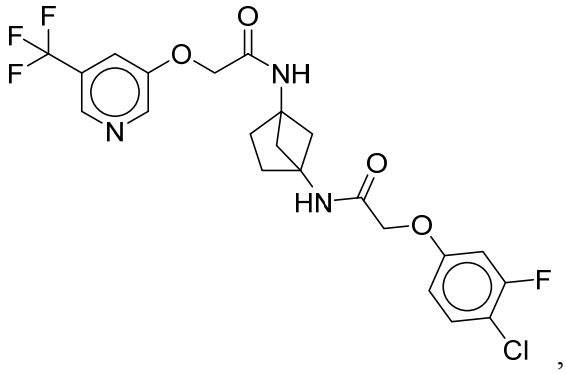
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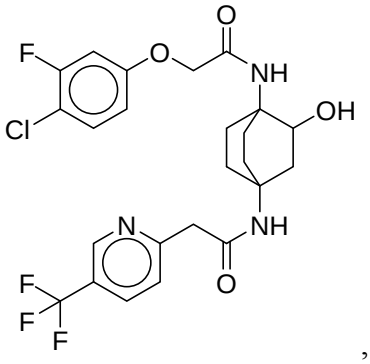
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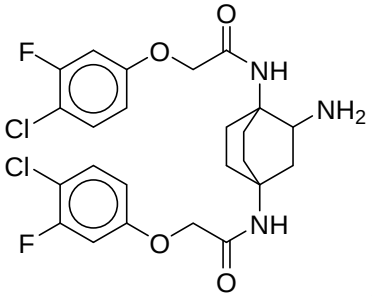
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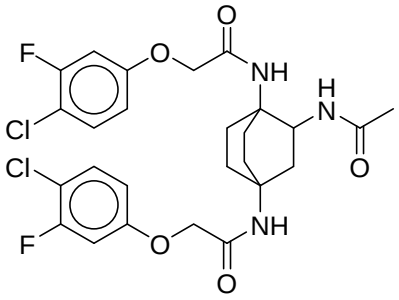
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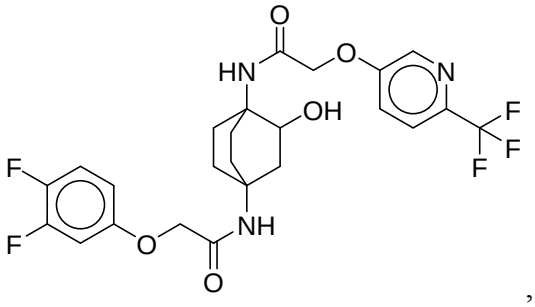
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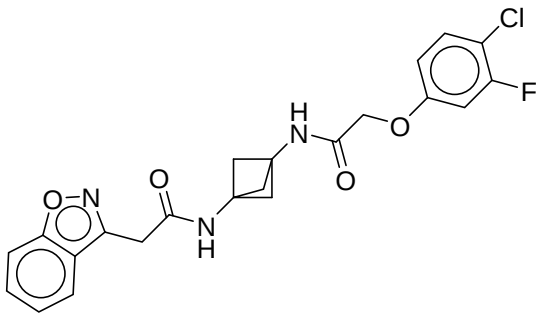
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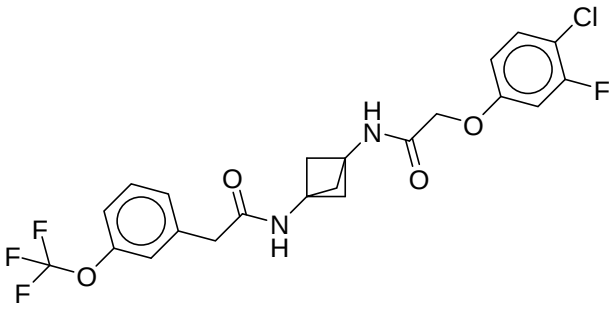
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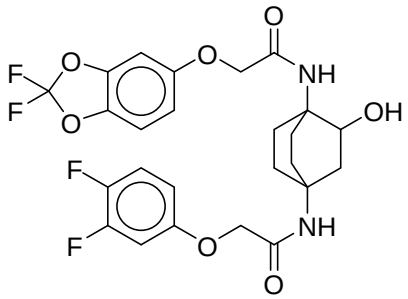
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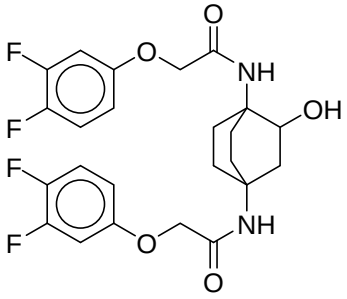
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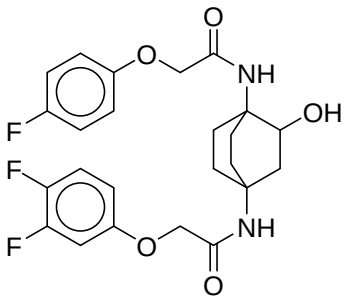
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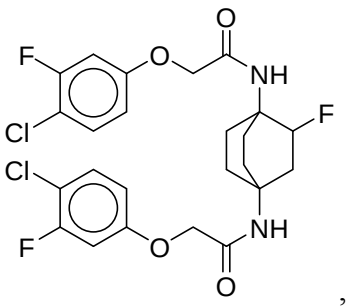
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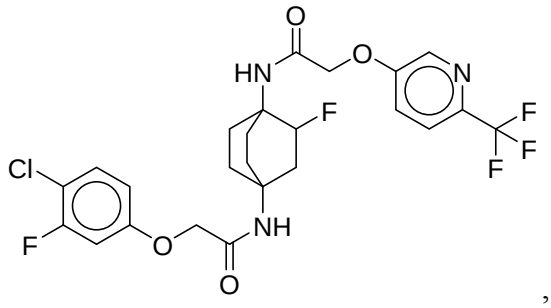
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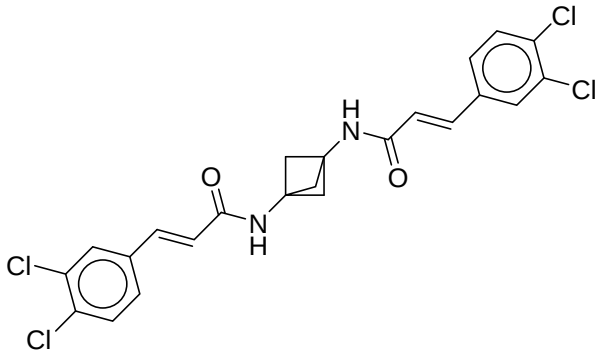
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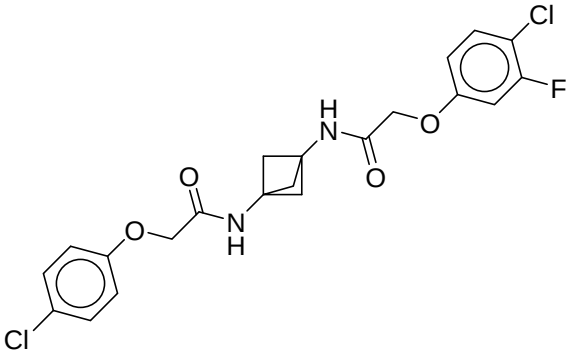
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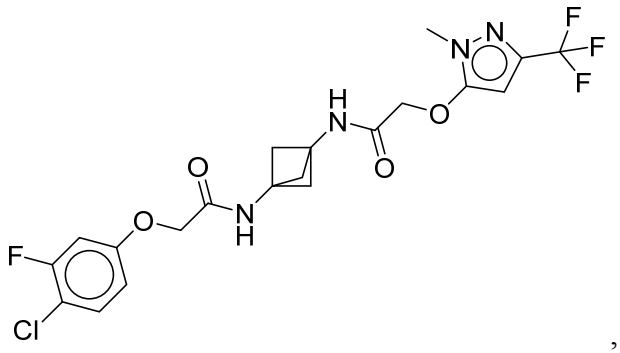
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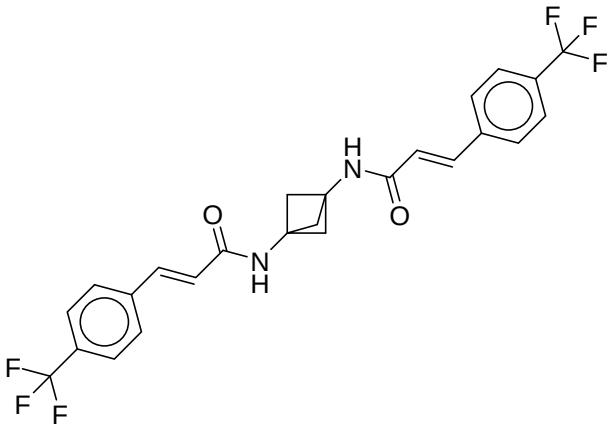
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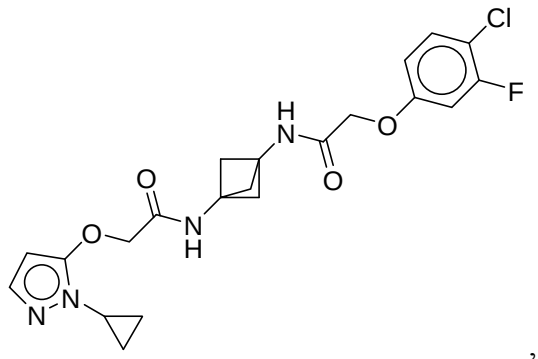
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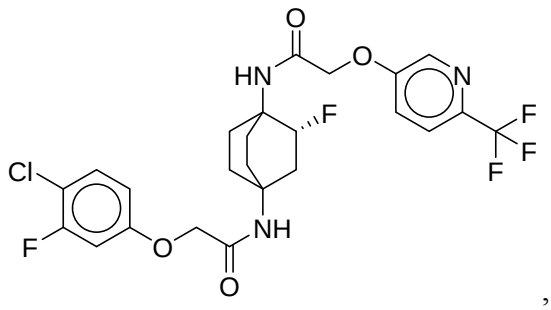
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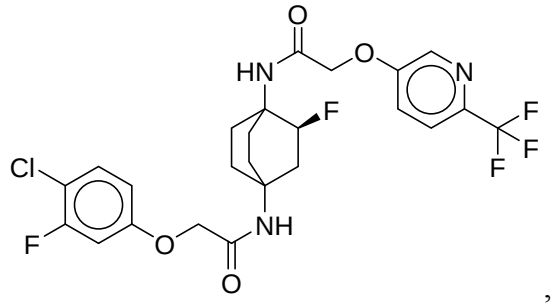
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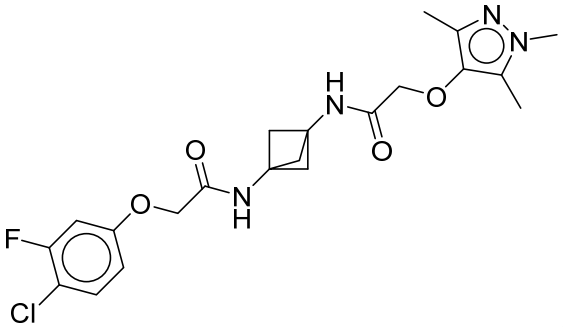
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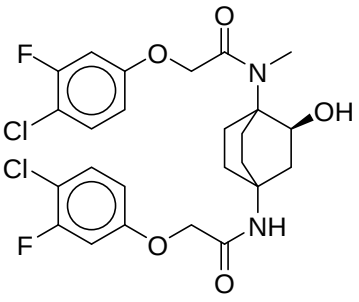
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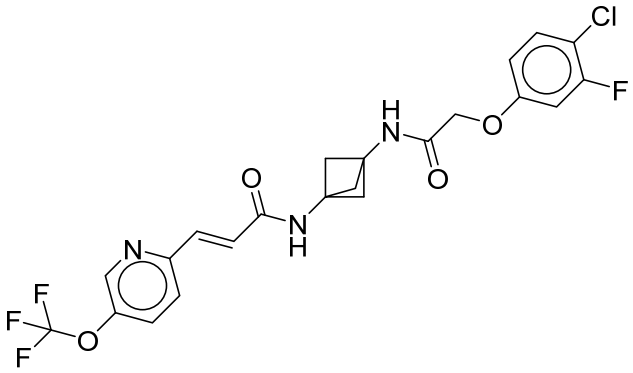
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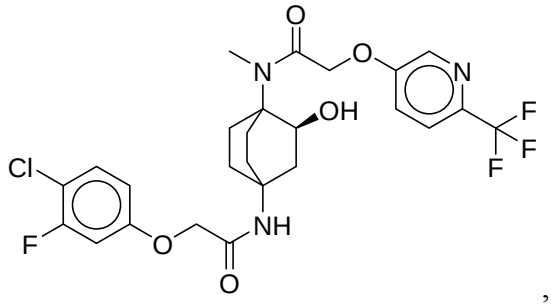
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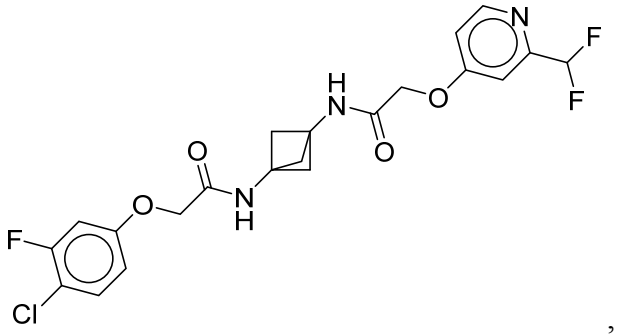
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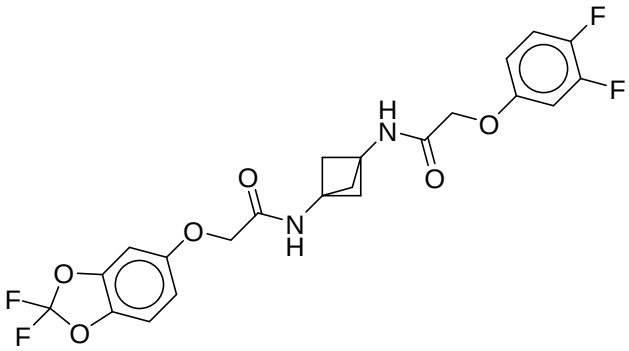
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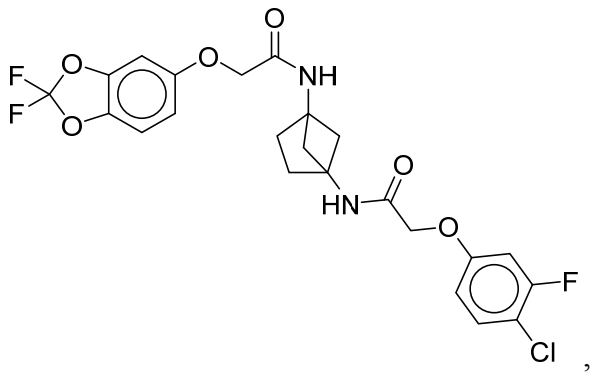
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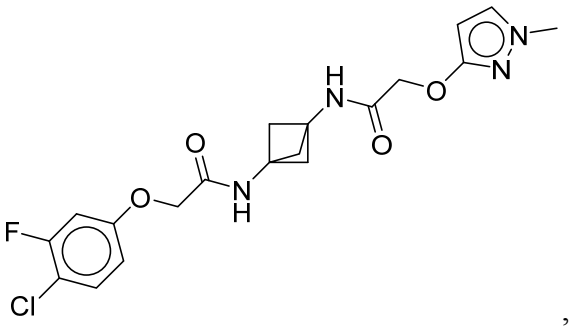
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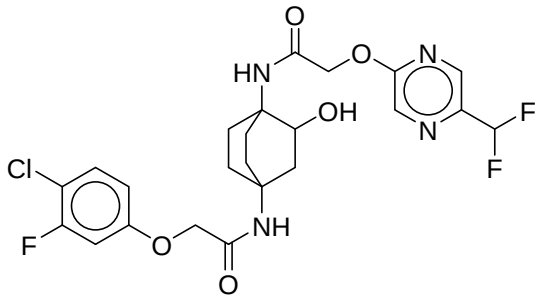
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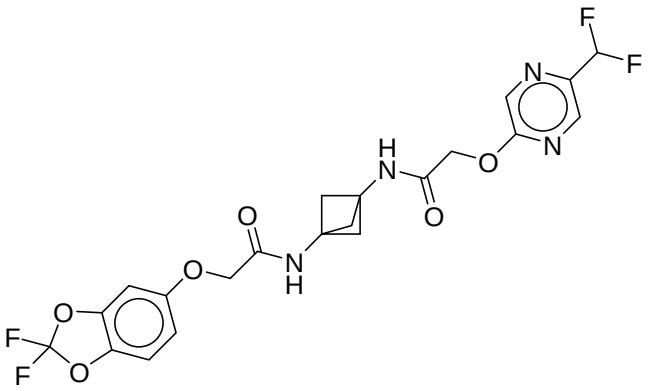
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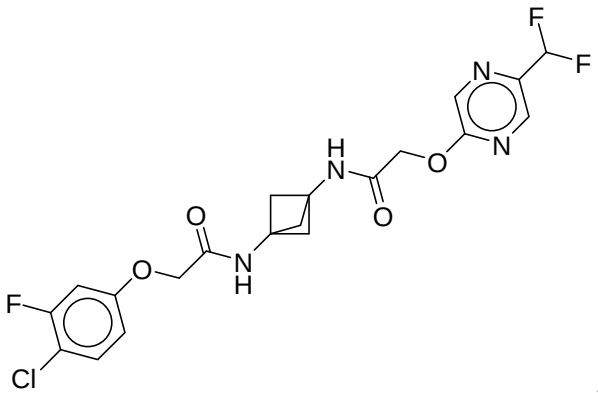
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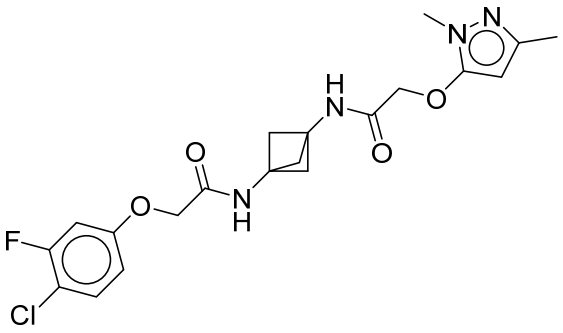
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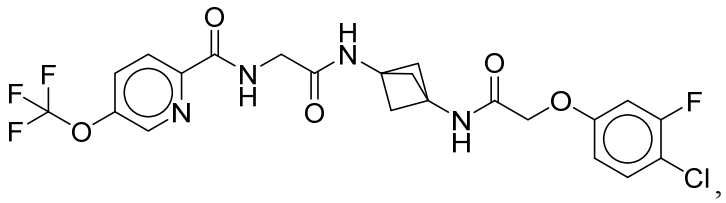
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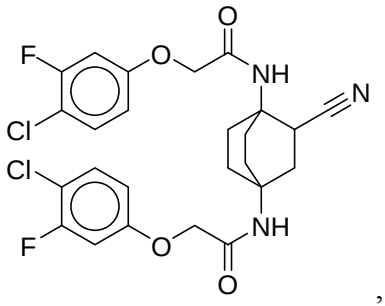
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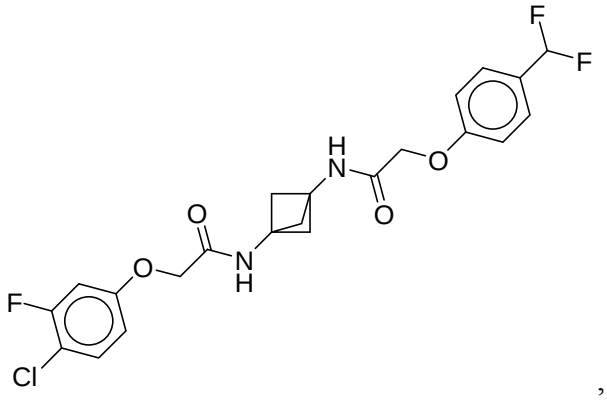
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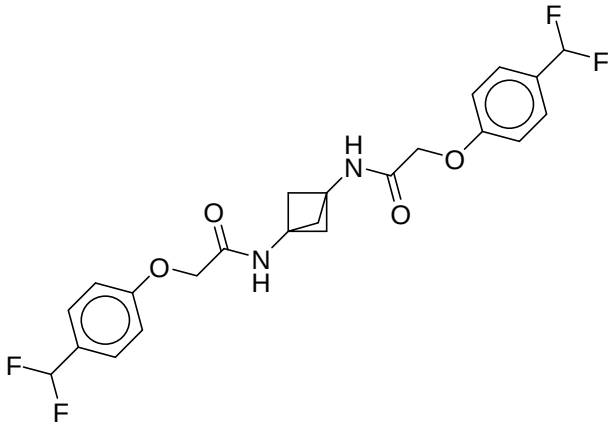
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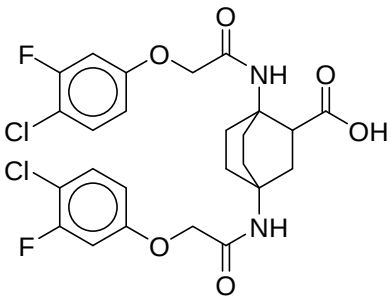
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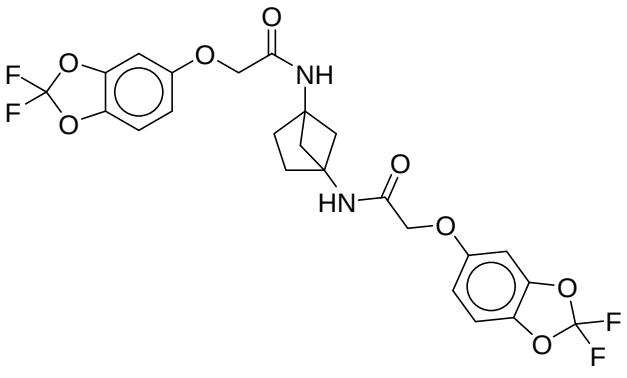
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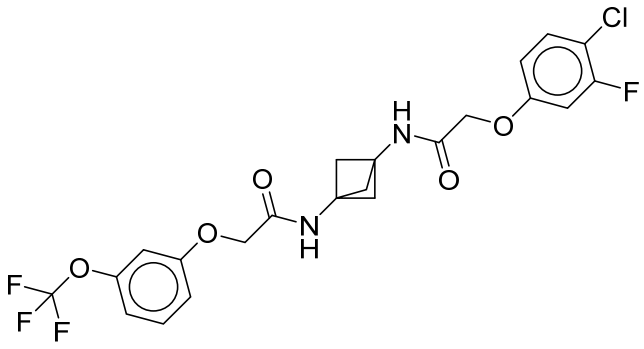
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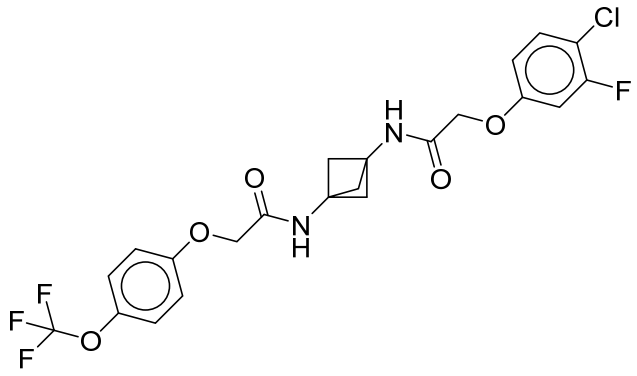
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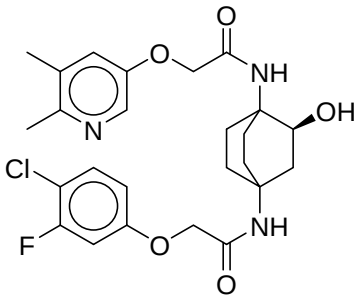
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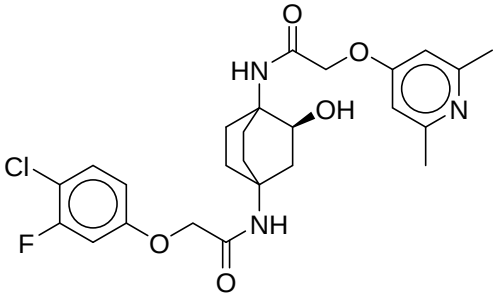
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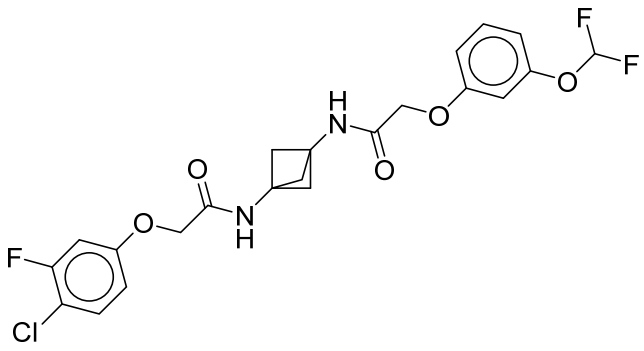
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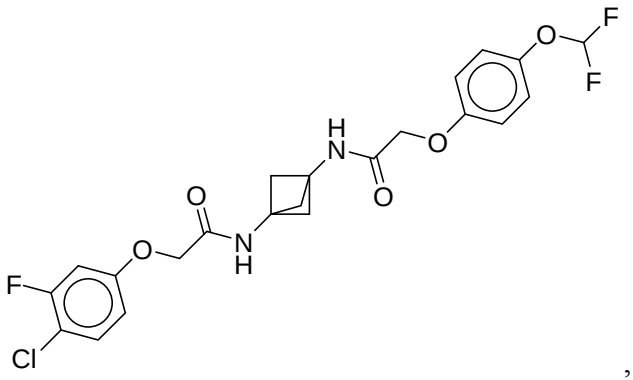
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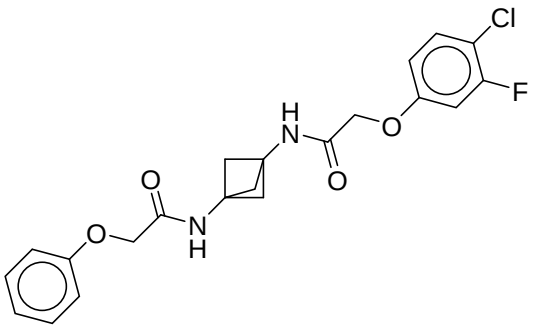
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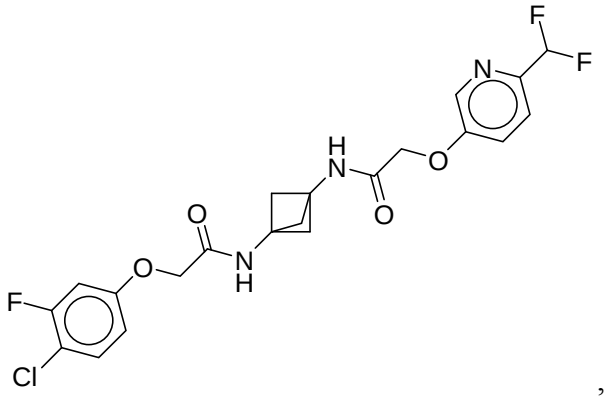
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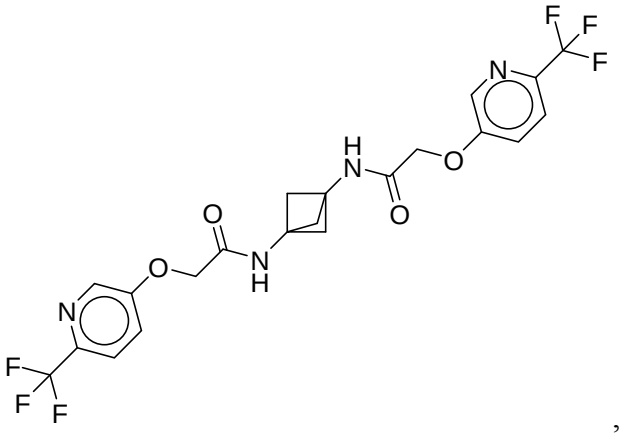
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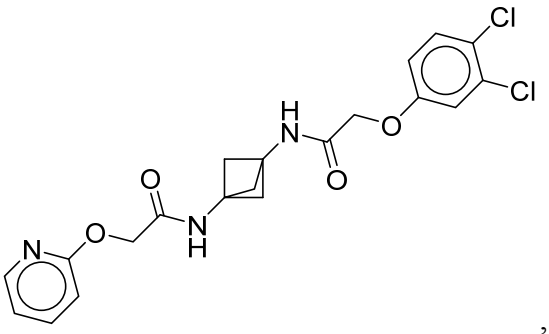

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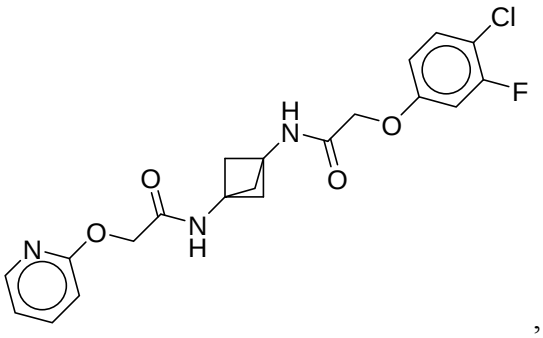

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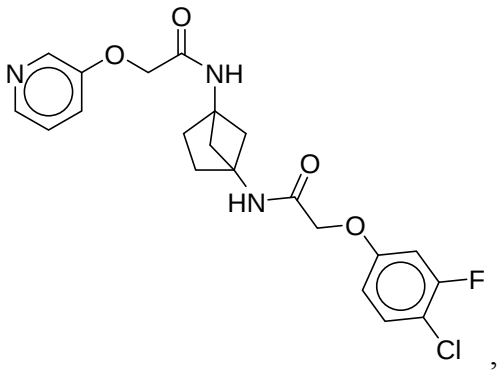

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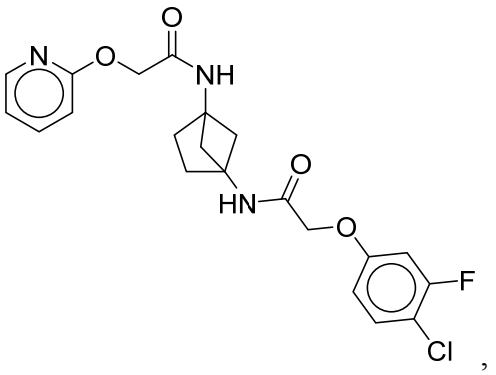

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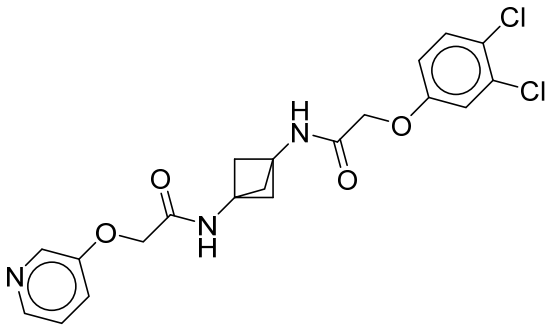
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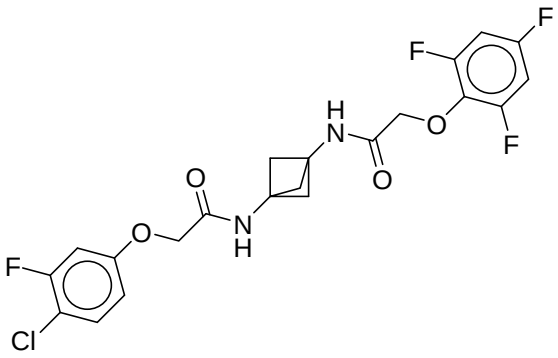
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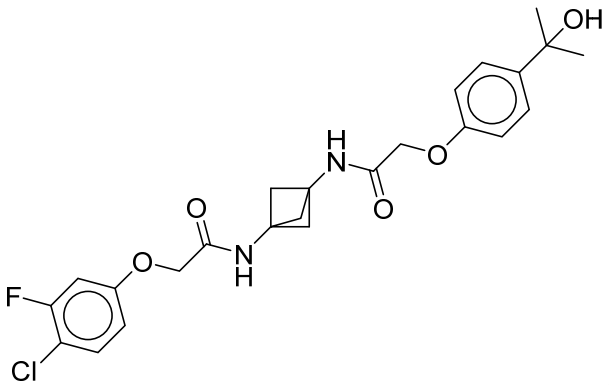
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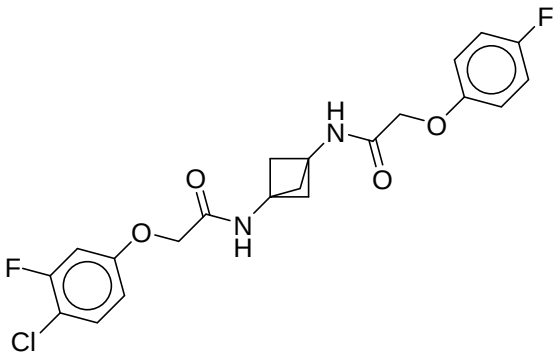
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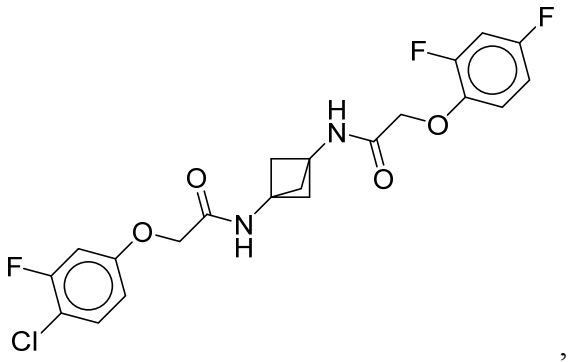
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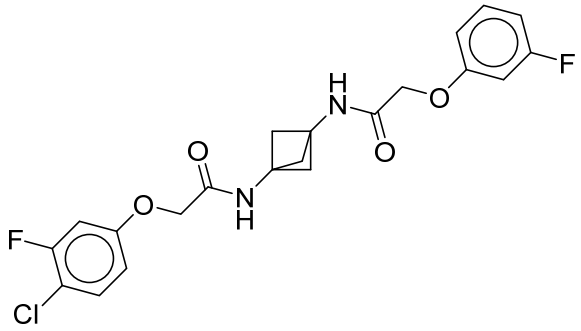
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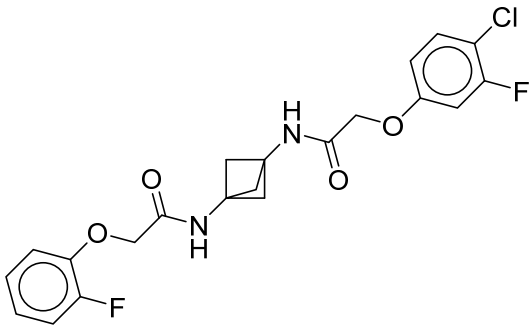
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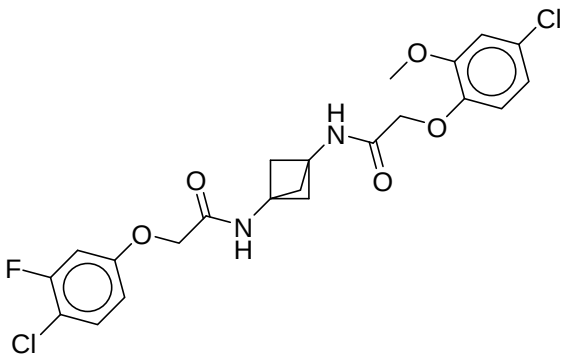
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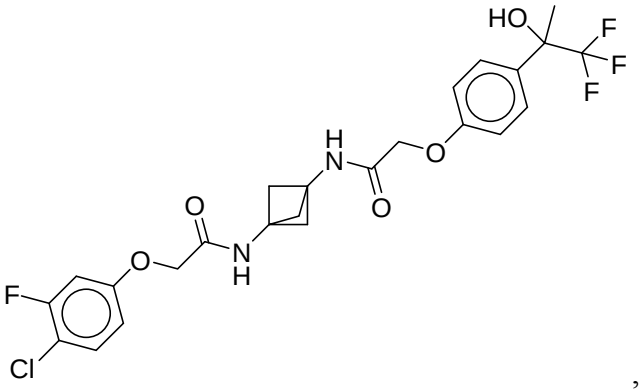
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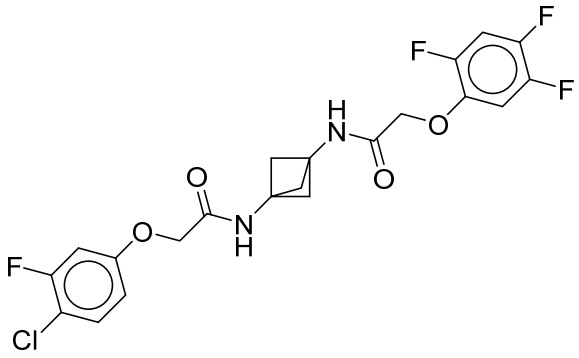
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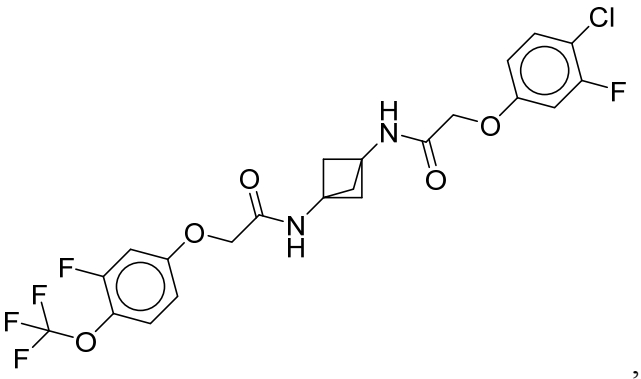
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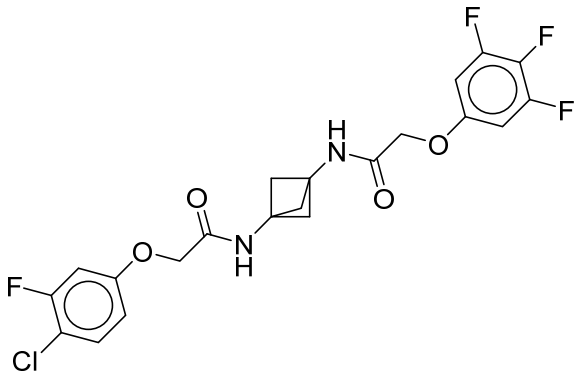
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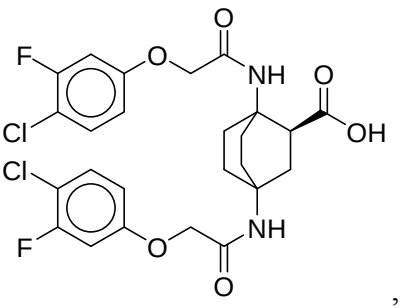
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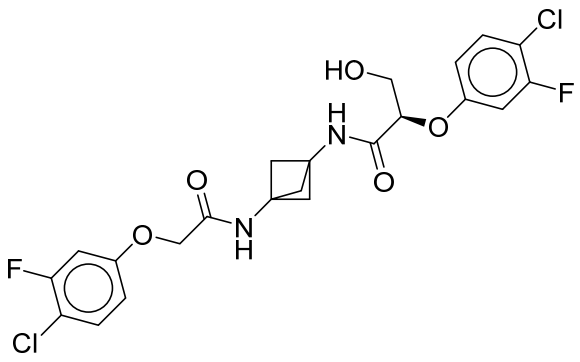
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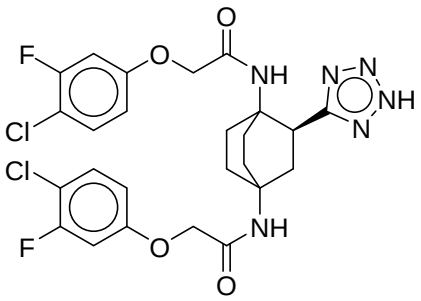
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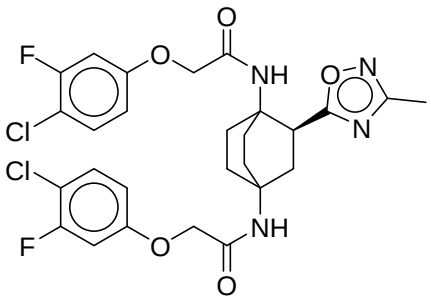
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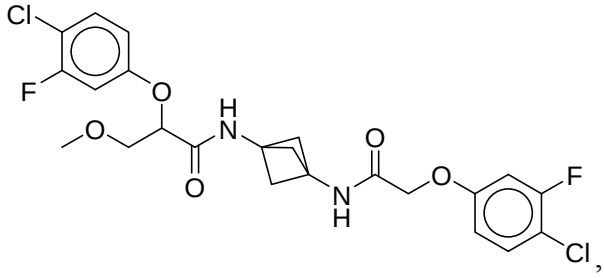
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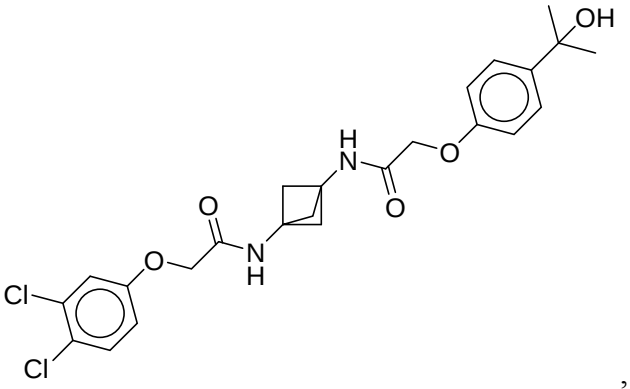
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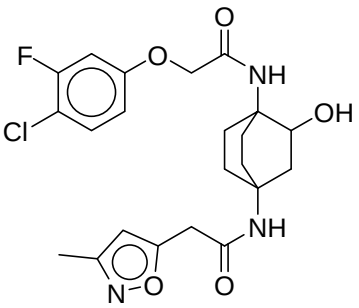
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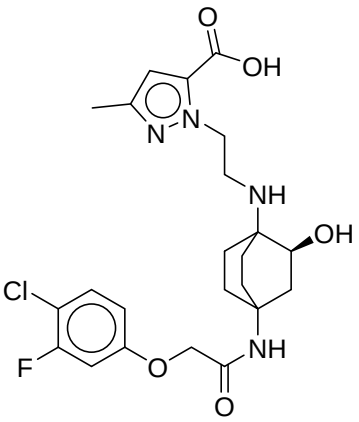
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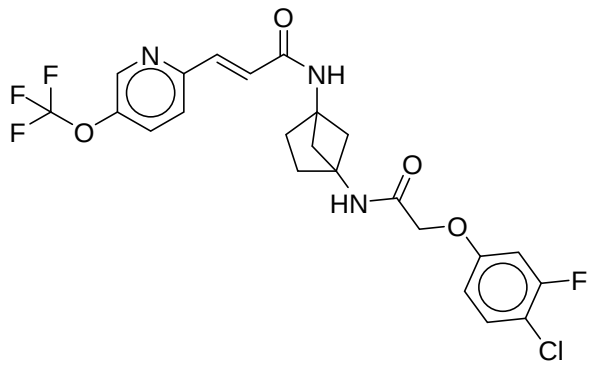
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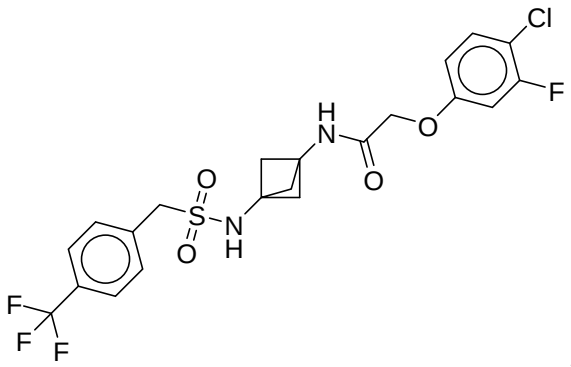
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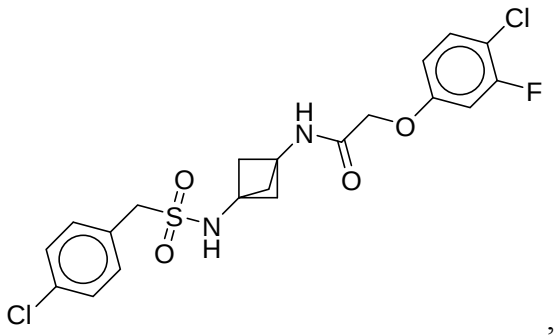
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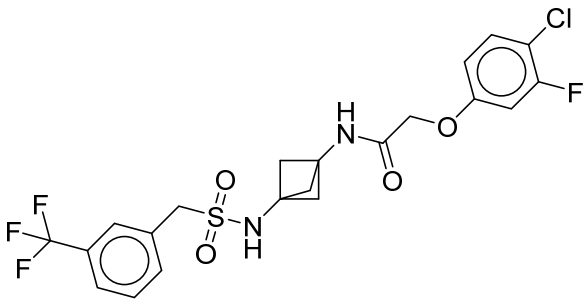
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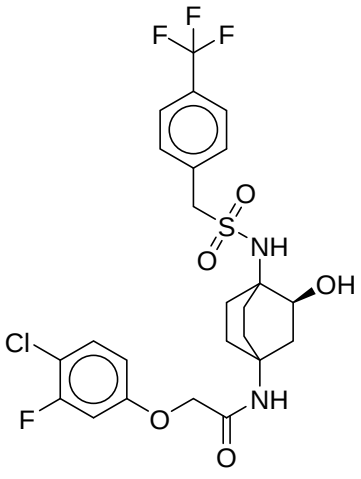
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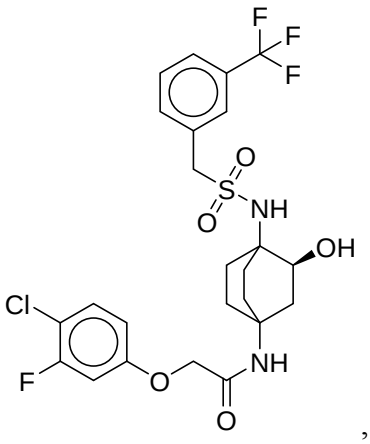
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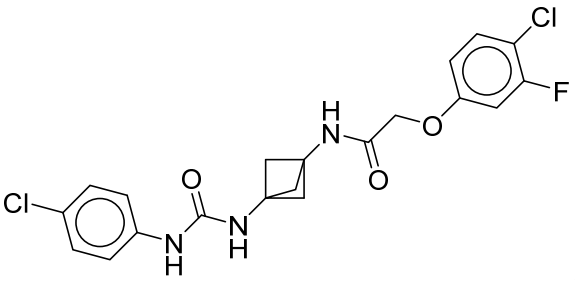
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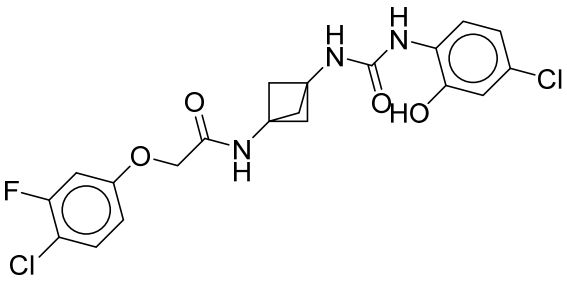
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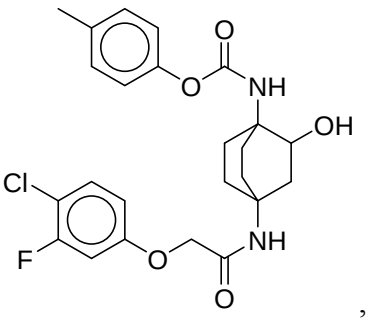
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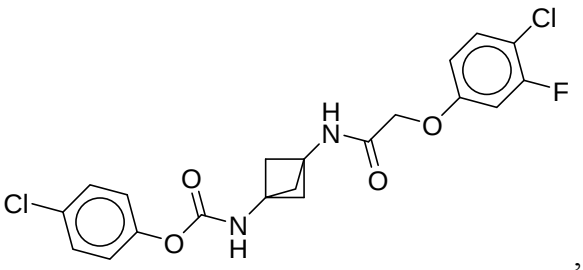
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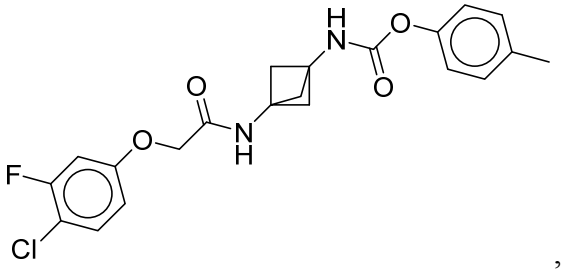
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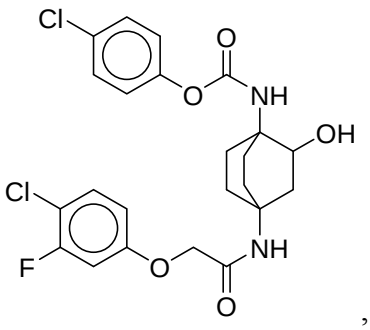
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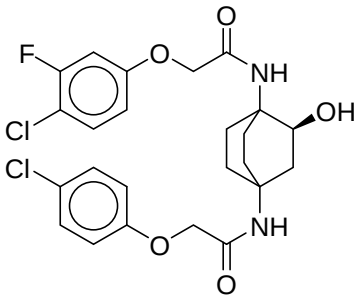
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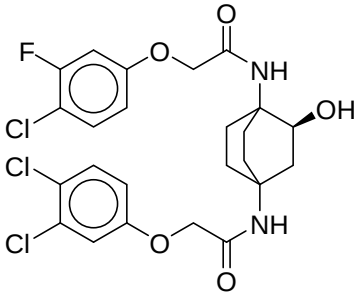
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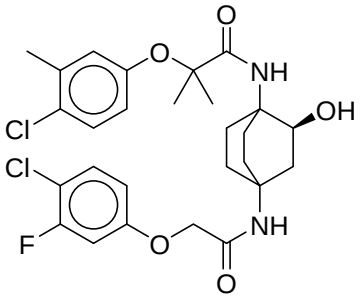
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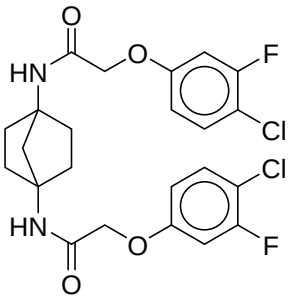
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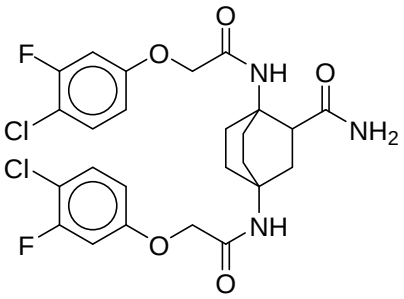
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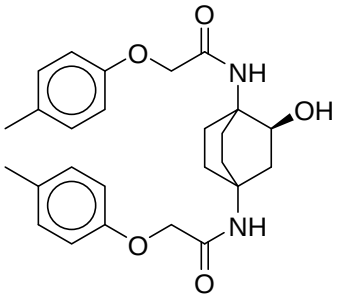
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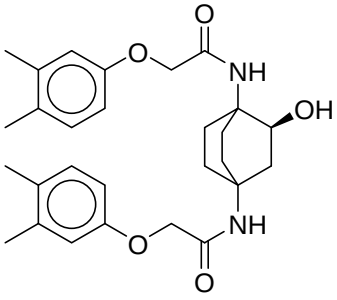
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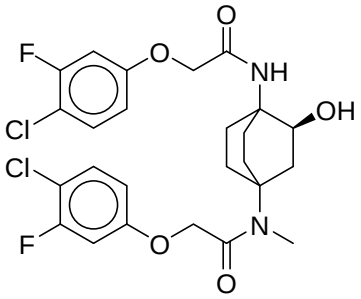
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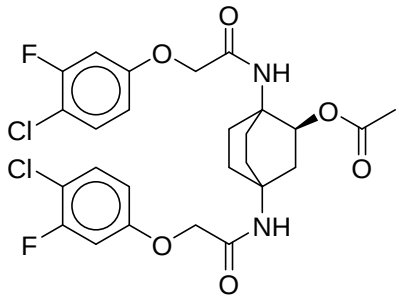
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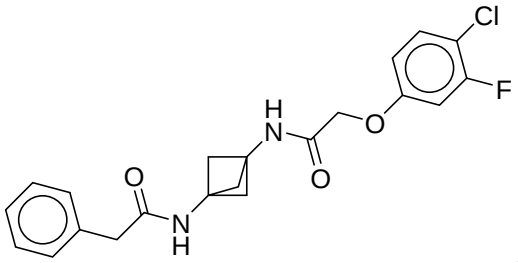
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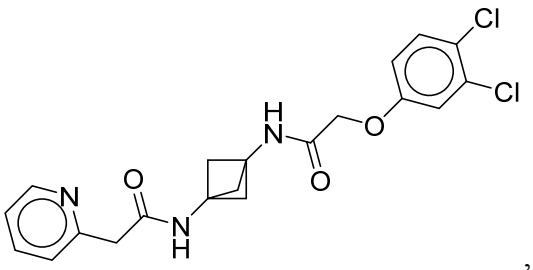
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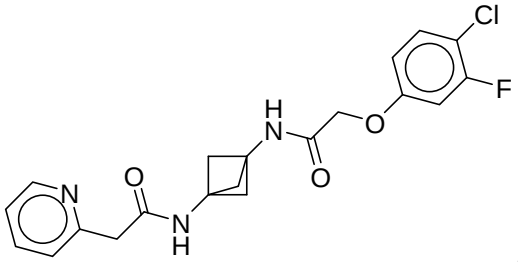
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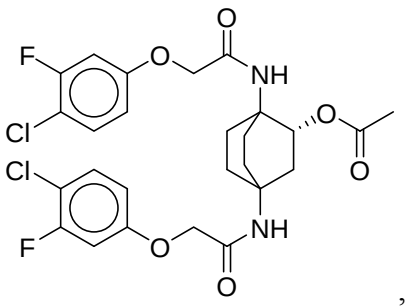
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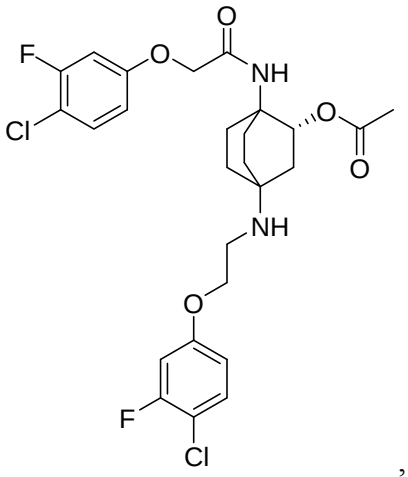
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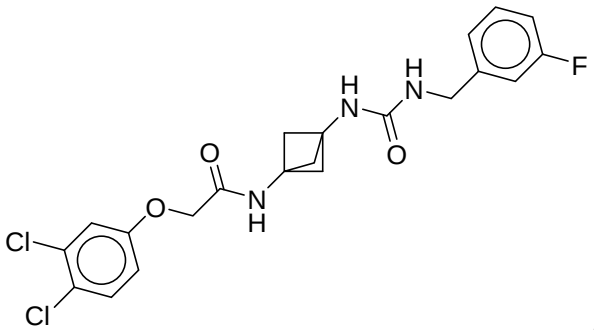
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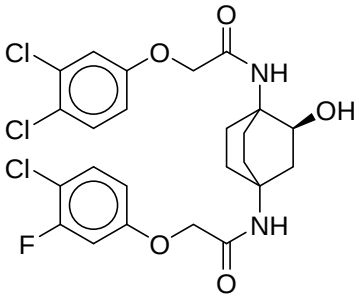
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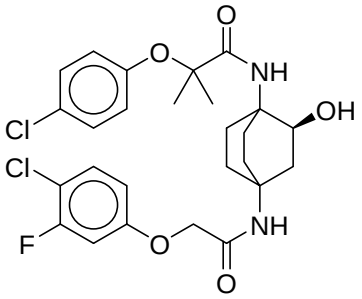
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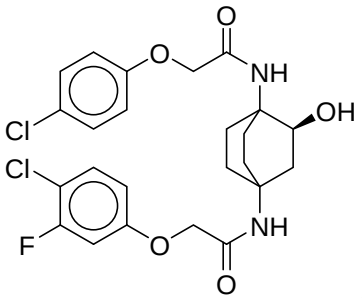
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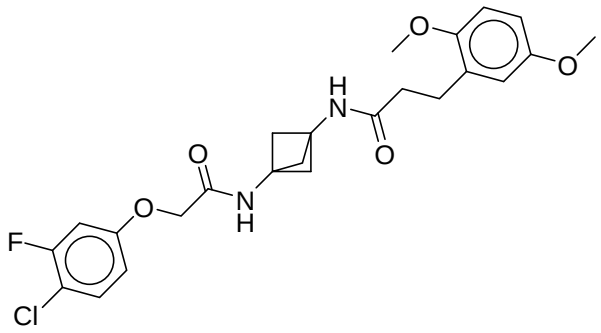
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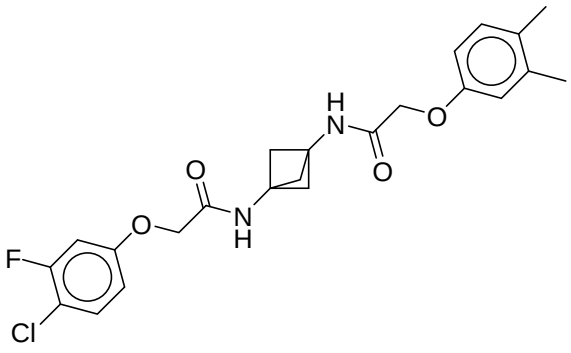
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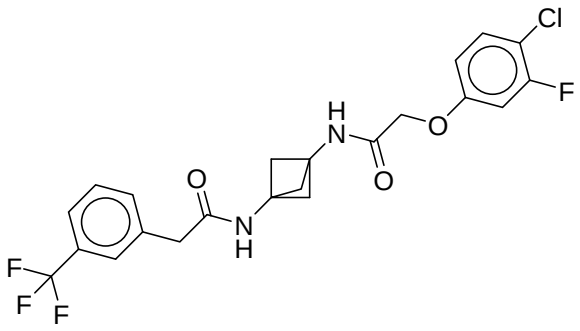
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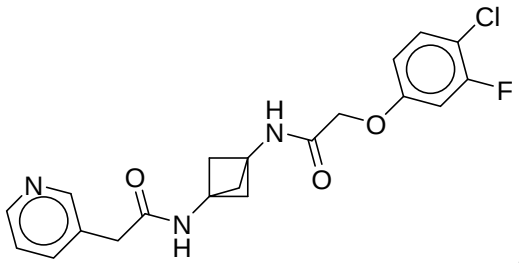
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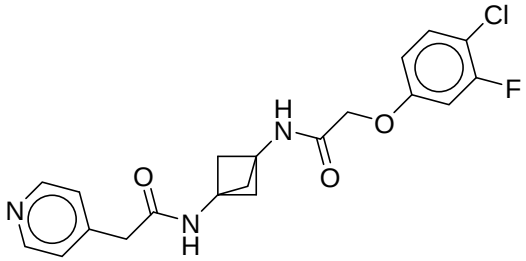
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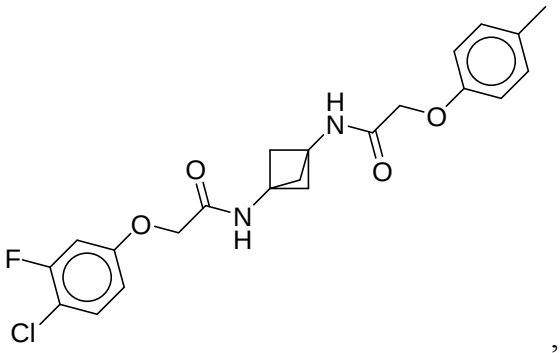
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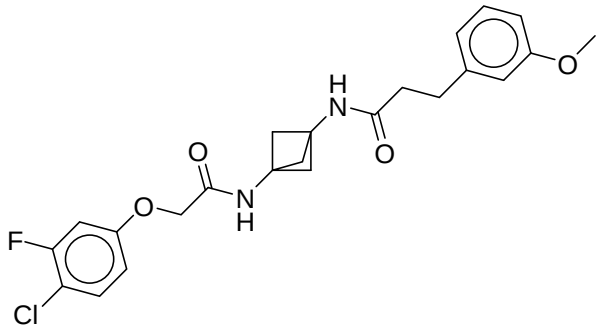
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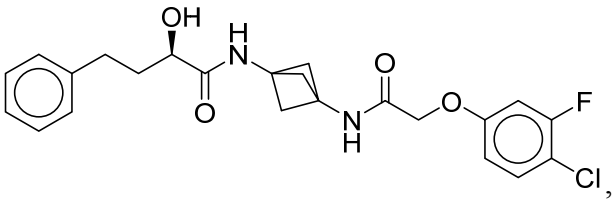
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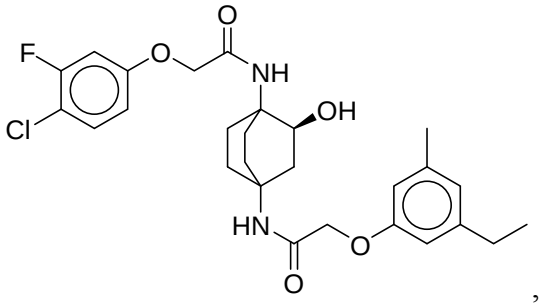
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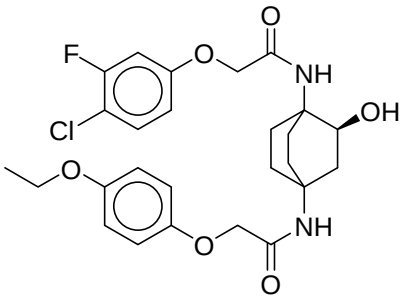
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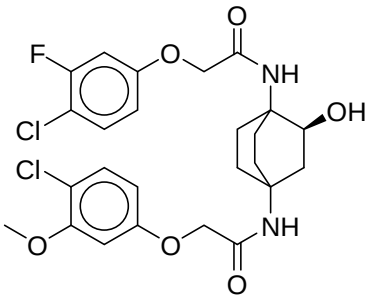
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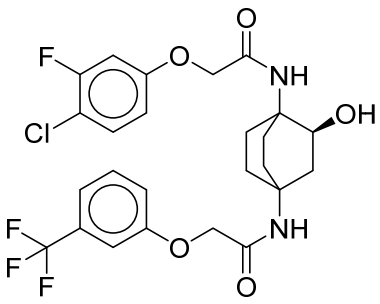
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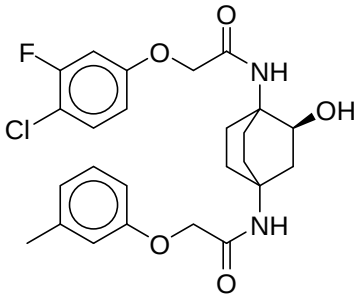
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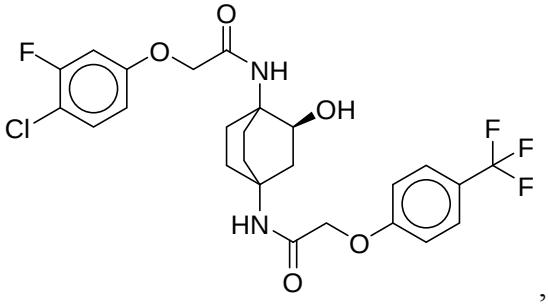
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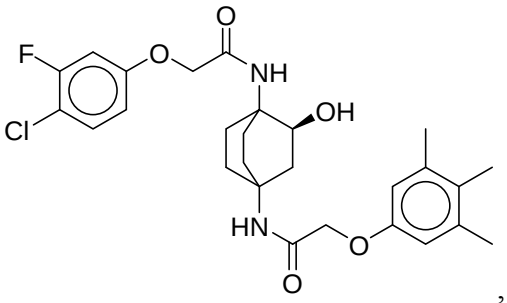
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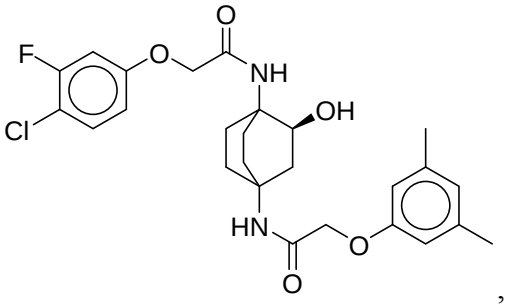
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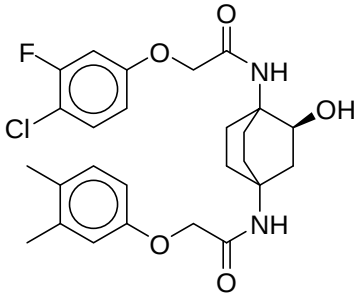
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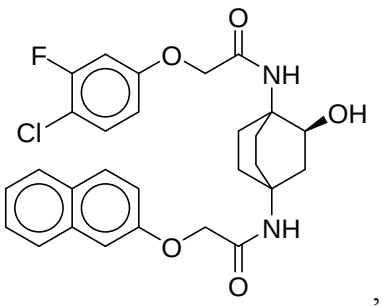
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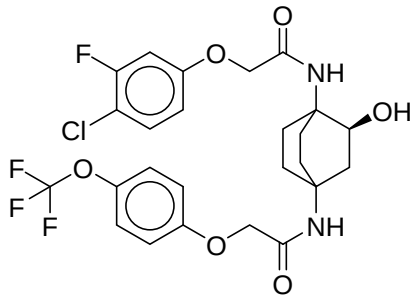
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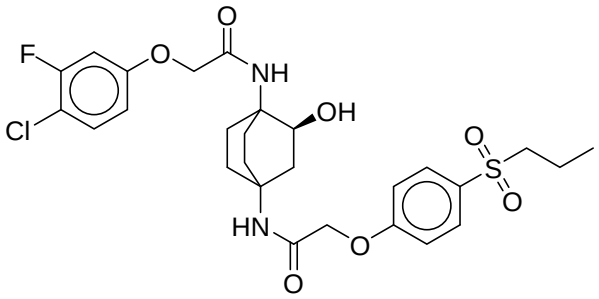
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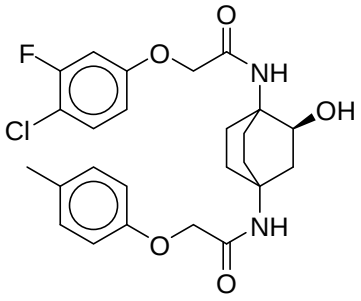
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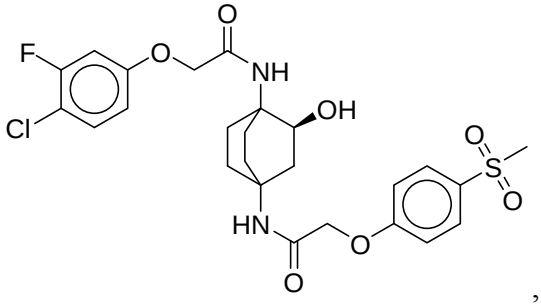
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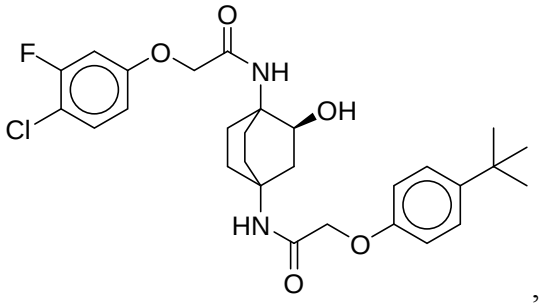
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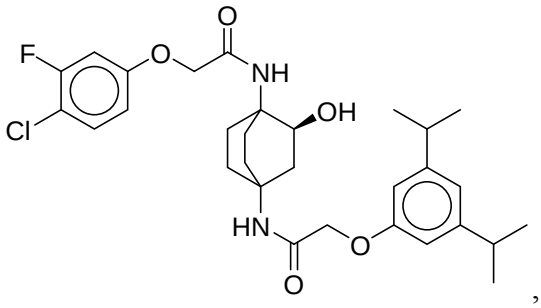
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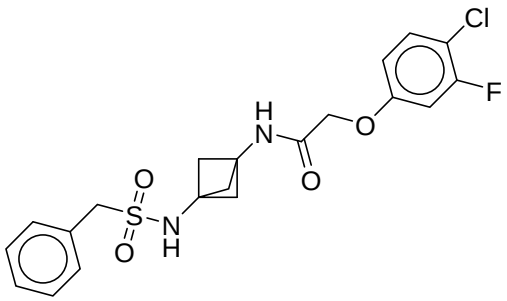
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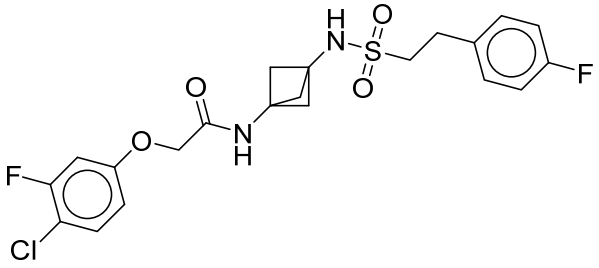
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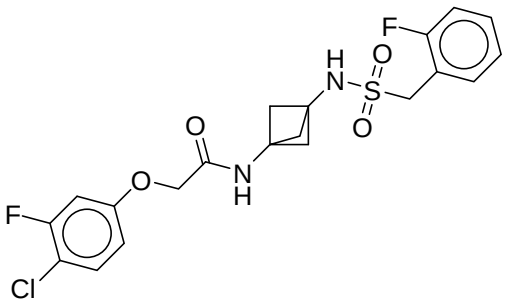
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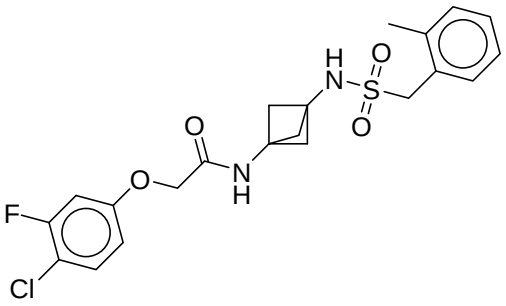
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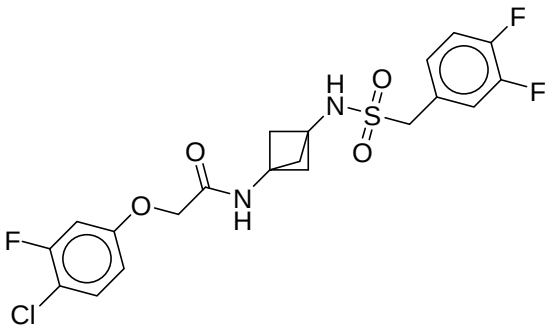
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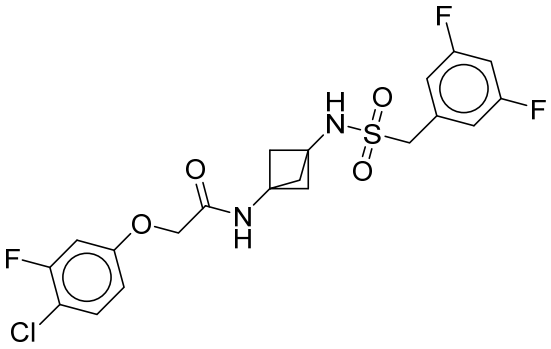
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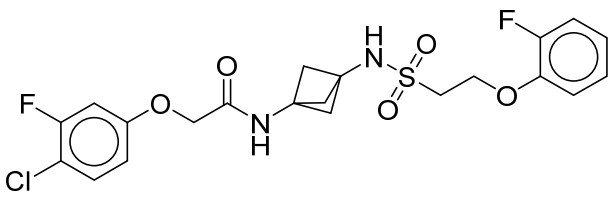
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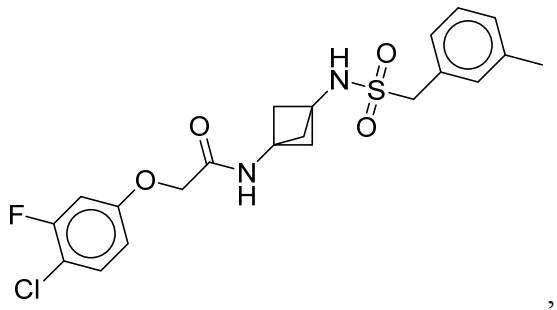
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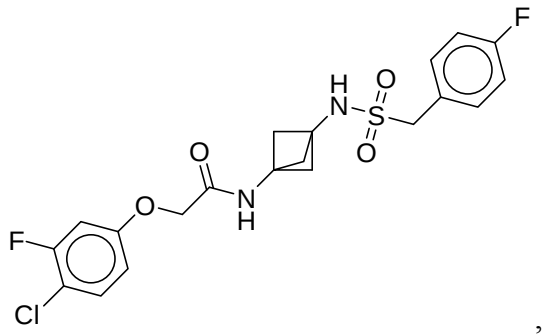
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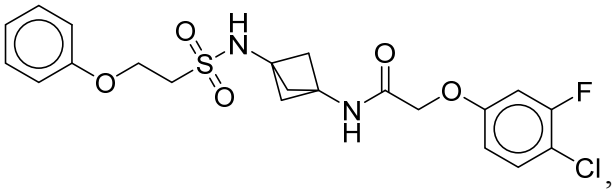
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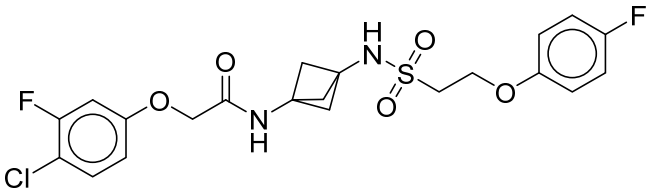
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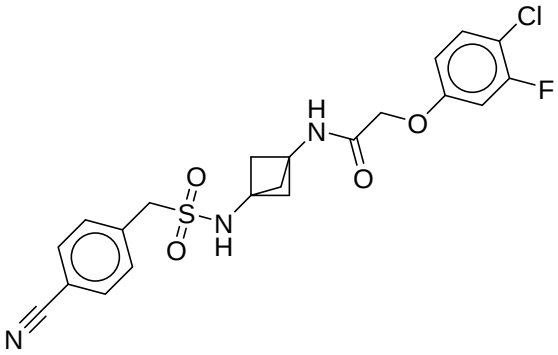
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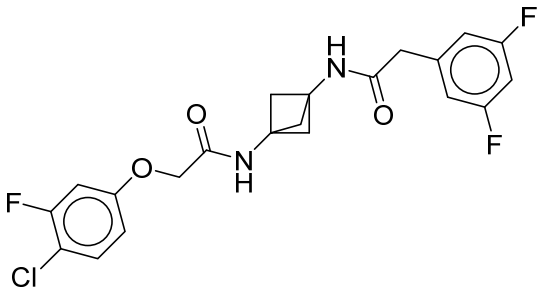
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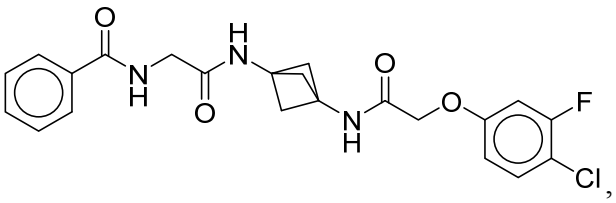
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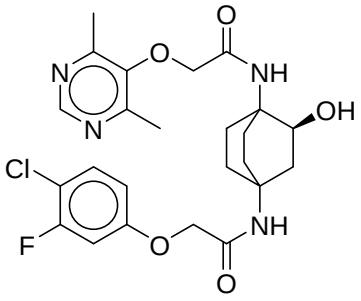
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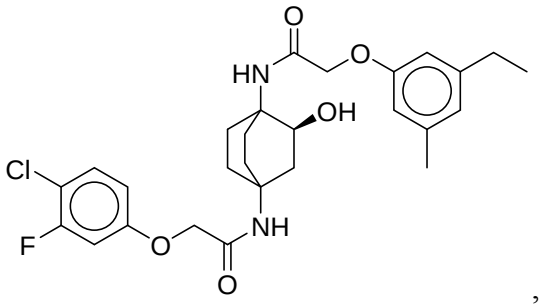
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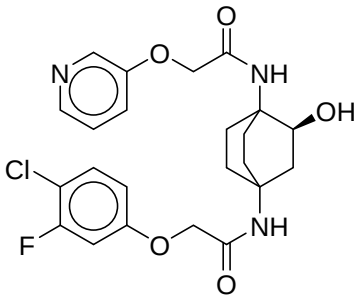
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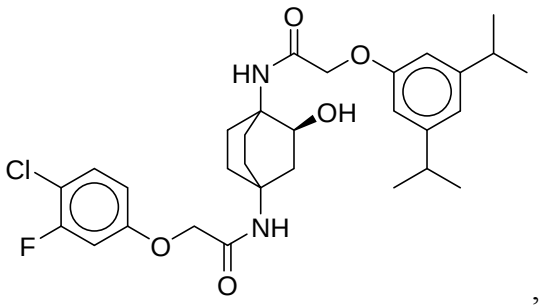
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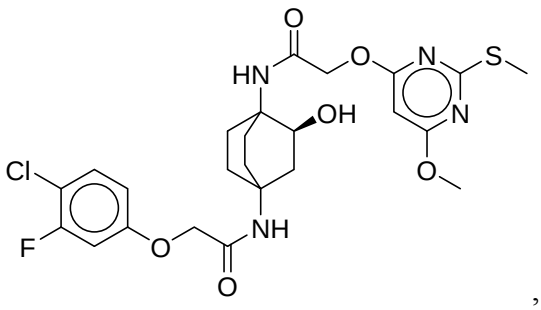
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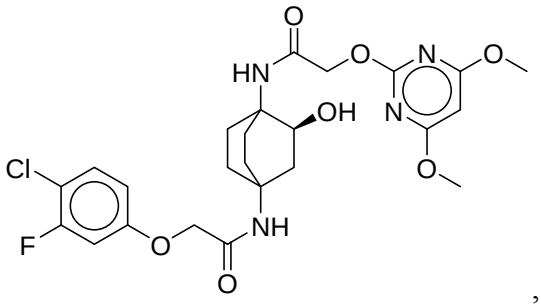
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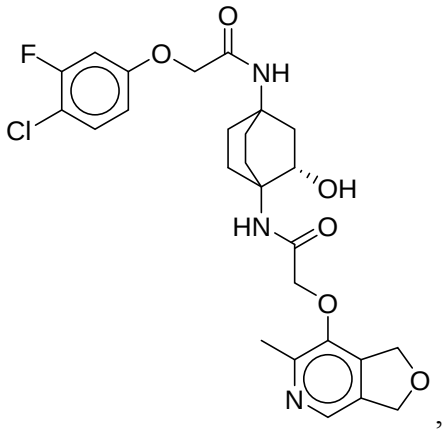
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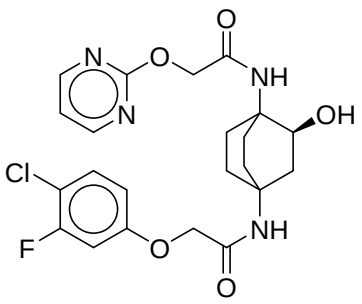
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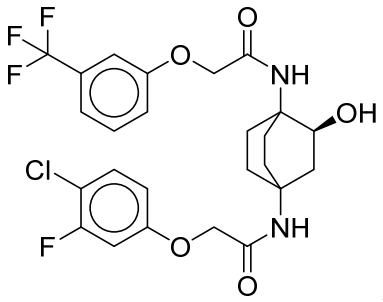
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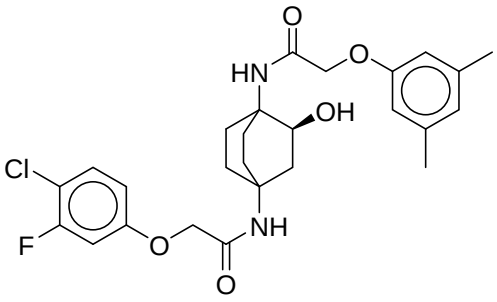
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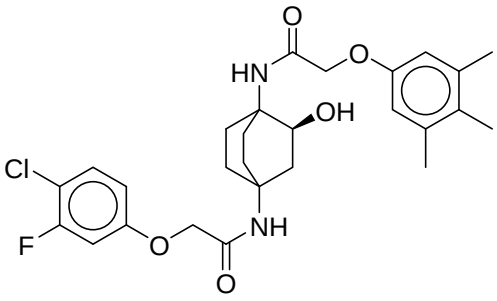
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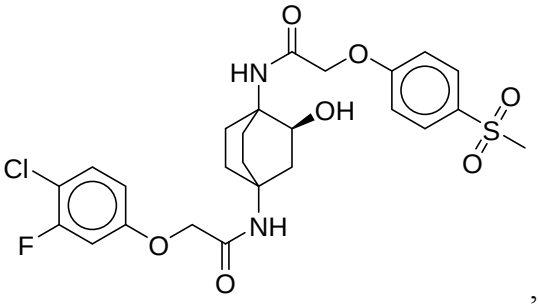
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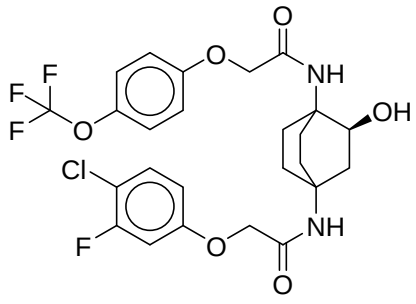
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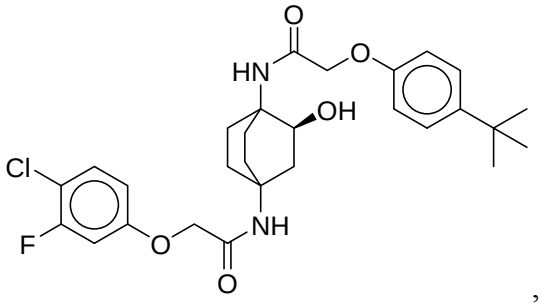
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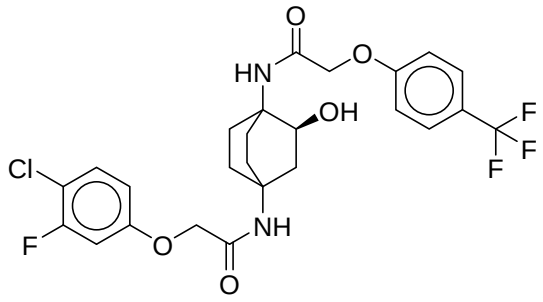
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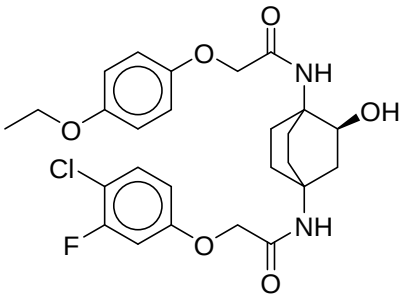
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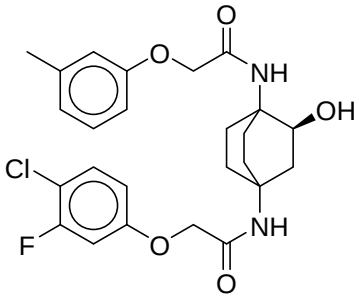
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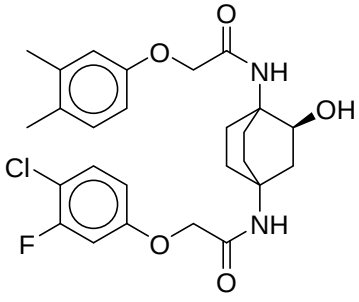
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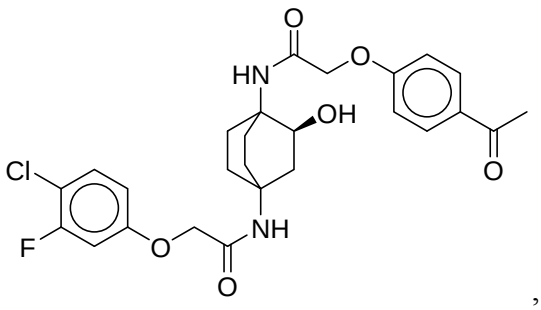
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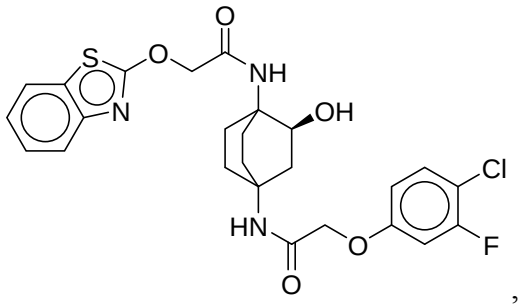
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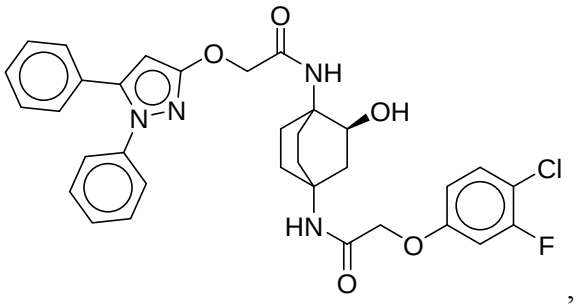
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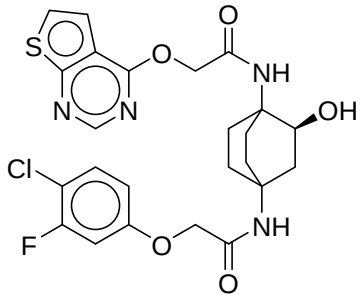
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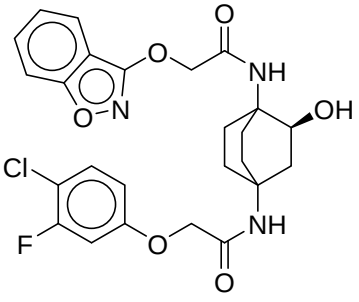
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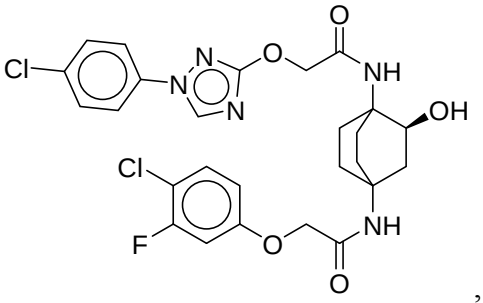
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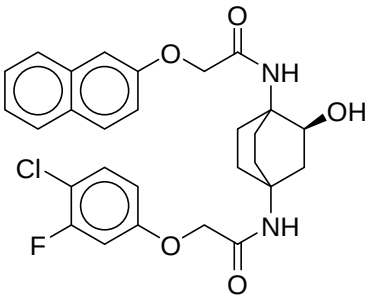
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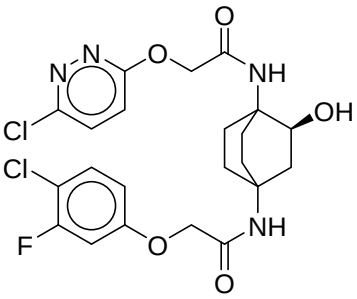
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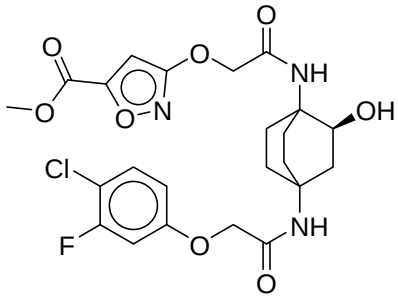
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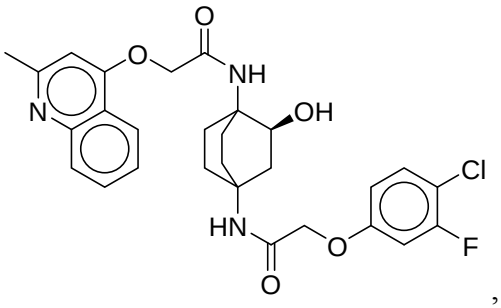
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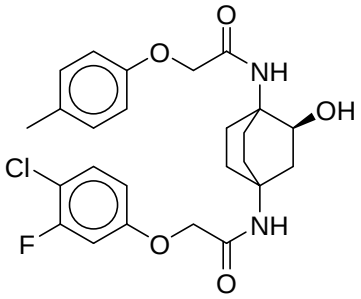
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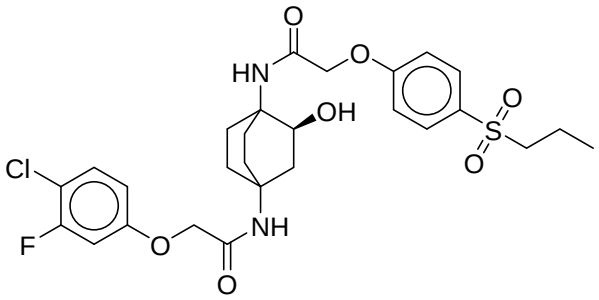
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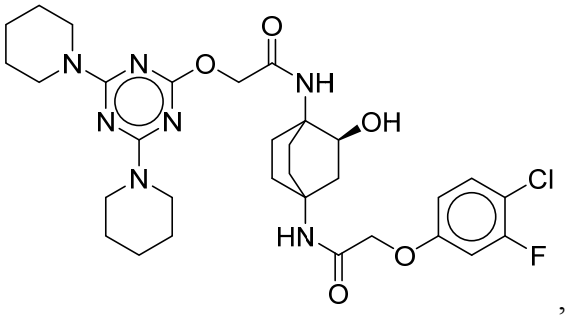
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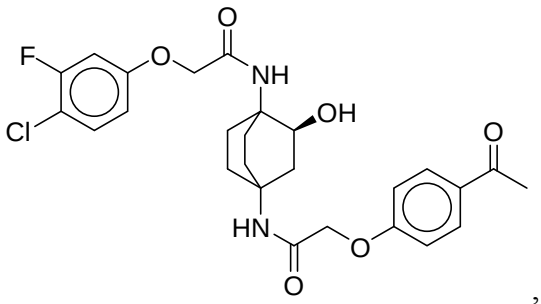
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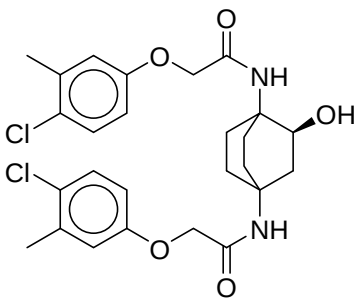
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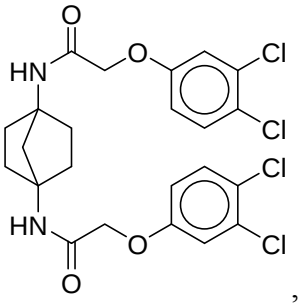
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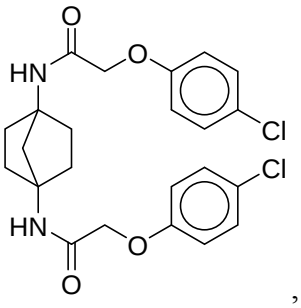
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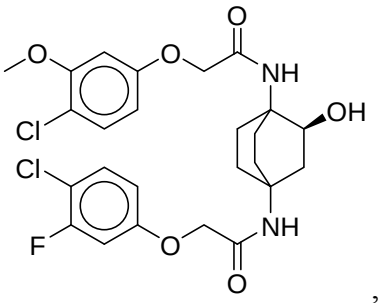
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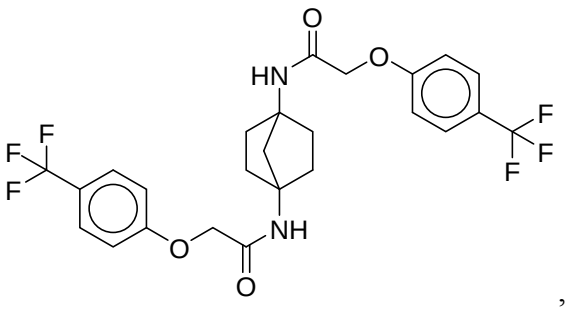
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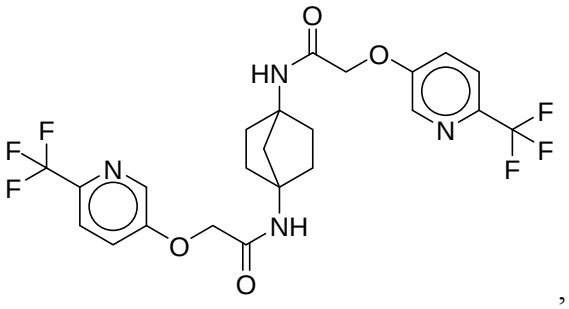
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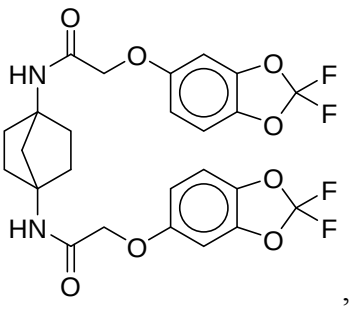
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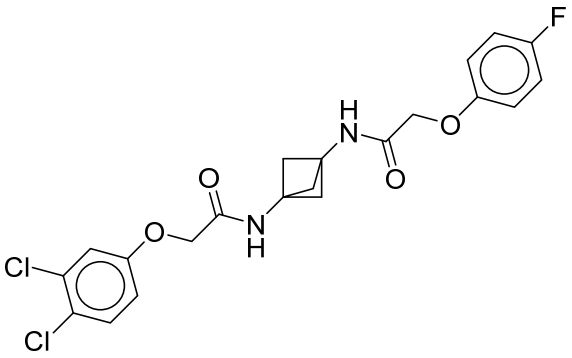
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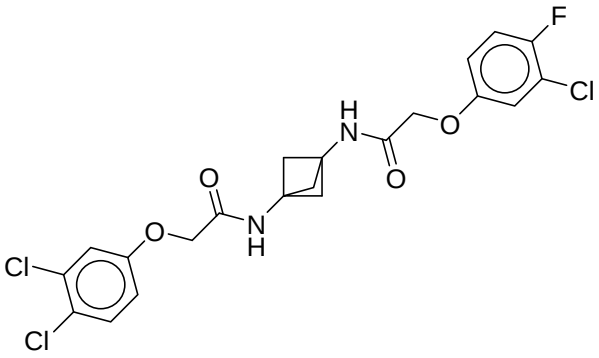
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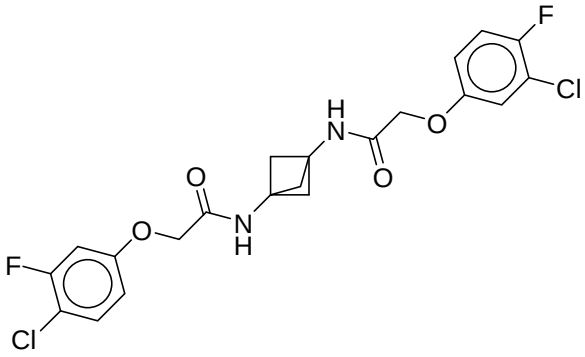
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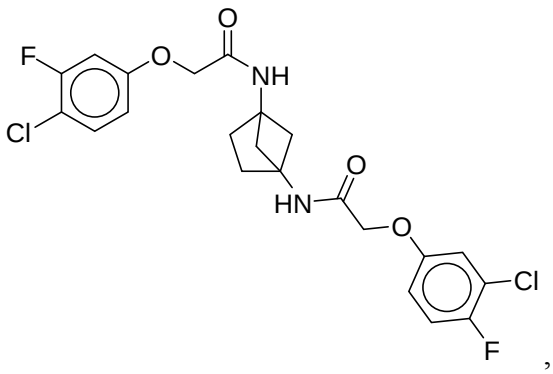
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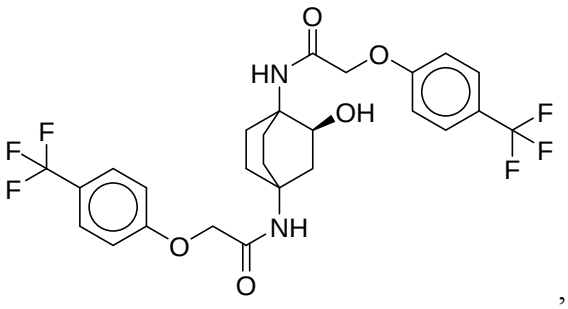
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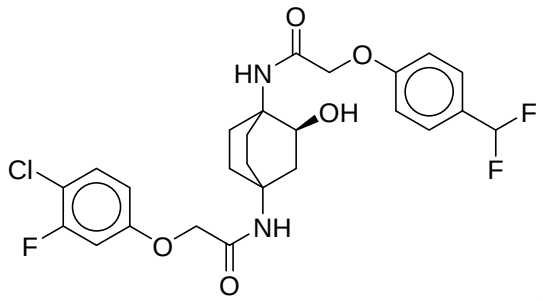
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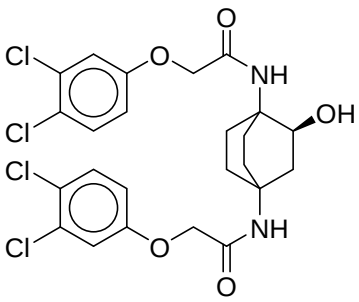
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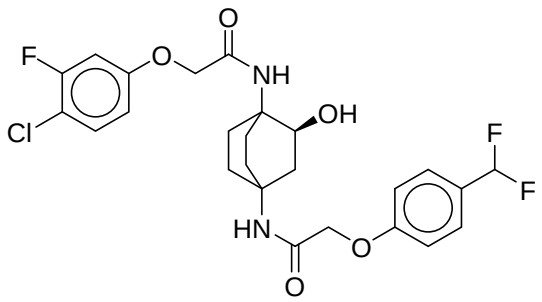
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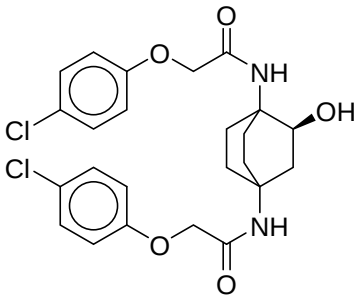
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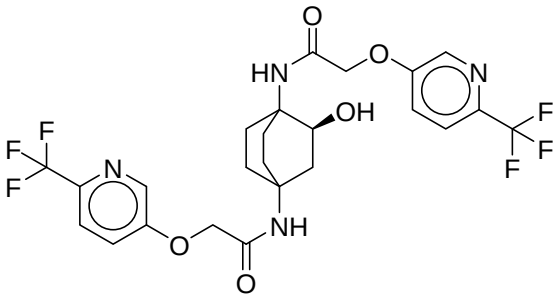
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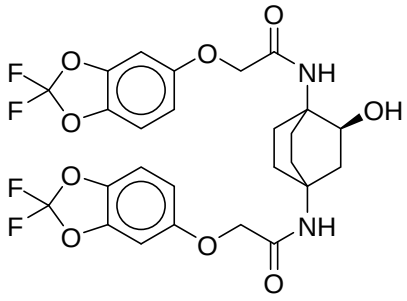
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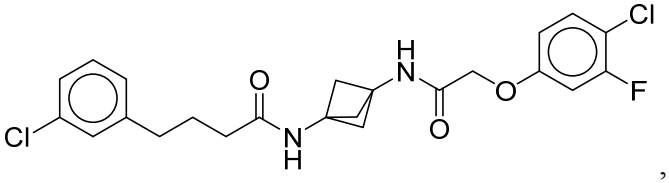
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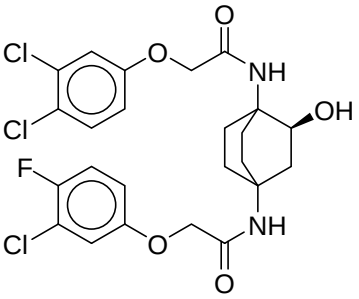
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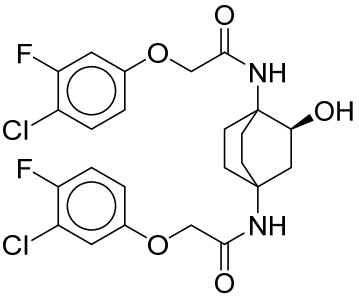
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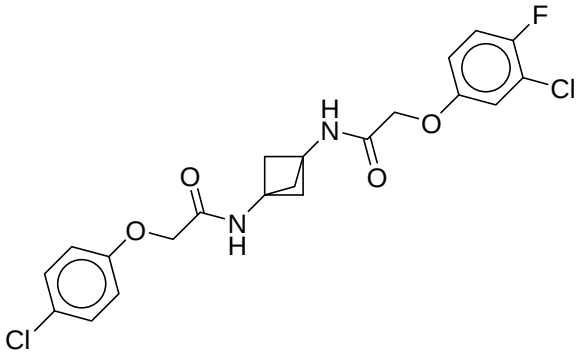
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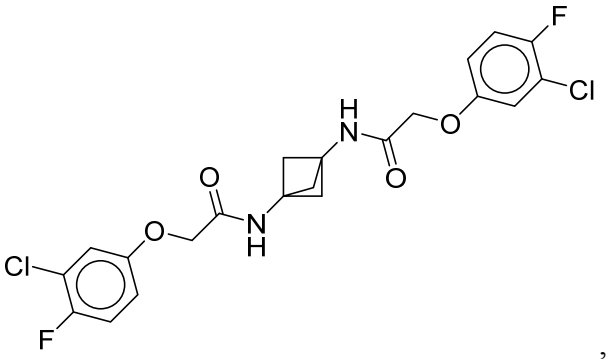
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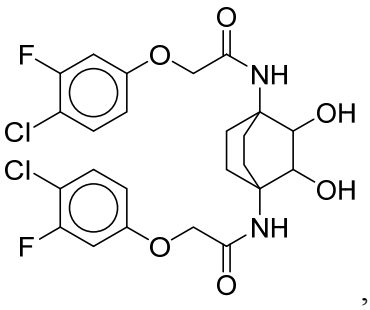

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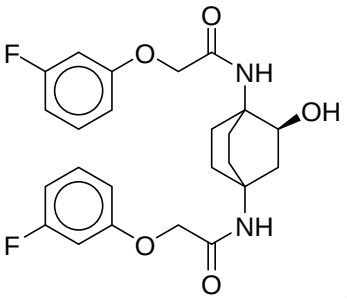

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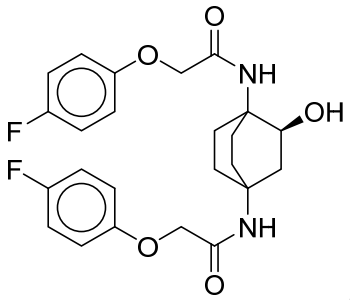

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and a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

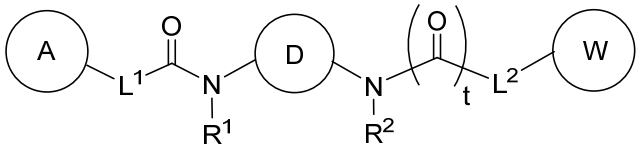
In another aspect, the present disclosure refers to a pharmaceutically acceptable composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

In a further aspect, the present disclosure refers to a use of a composition comprising a compound disclosed herein or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in the manufacture of a medicament for treating a disease associated with impaired function of eIF2B or a component of integrated stress response (ISR) pathway in a subject, wherein the disease is a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, or a metabolic disease.

In another aspect, the present disclosure refers to a composition for use in treating a disease associated with impaired function of eIF2B or a component of ISR pathway in a subject, wherein the disease is a neurodegenerative disease, a leukodystrophy, cancer, an

inflammatory disease, a musculoskeletal disease, or a metabolic disease, and wherein the composition comprises a compound disclosed herein or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

The present disclosure features a compound of Formula (I):



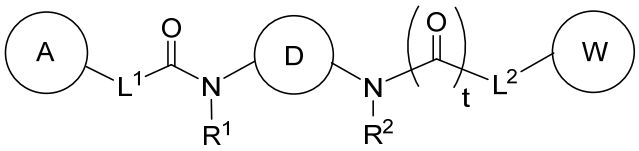
Formula (I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein D is a bridged monocyclic cycloalkyl, bridged monocyclic heterocyclyl, or cubanyl,

CLAIMS

We claim:

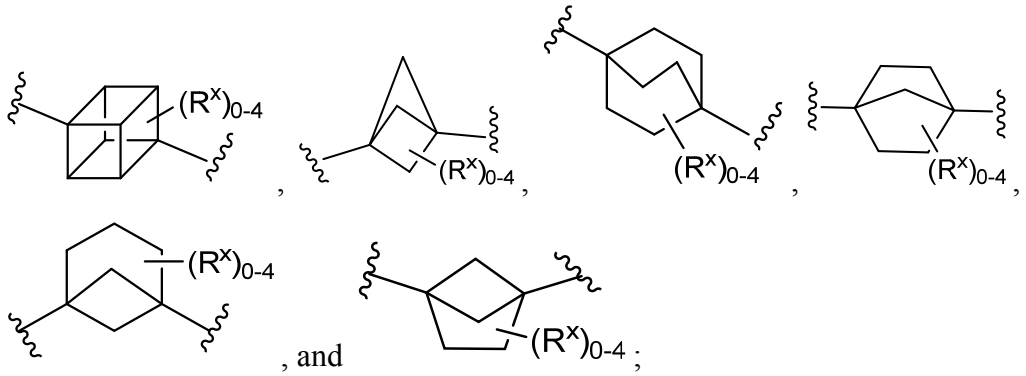
1. A compound of Formula (I):



Formula (I)

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

D is selected from the group consisting of:



L^1 is selected from CH_2O-* and CH=CH-*, L^2 is selected from CH_2O-*, CH_2CH_2-*, $CH_2CH_2CH_2$-*, CH_2-*, $CH_2C(O)$-*, CH=CH-*, CH_2CH_2O-*, CH_2OCH_2-*, $CH_2OCH_2CH_2$-*, $CH_2CH_2CH_2O$-*, $CH_2CH_2OCH_2$-*, $NHCH_2$-*, CH_2NH-*, $CH_2N(CH_3)$-*, $CH_2N(CH_3)C(O)$-*, $CH_2N(C(O)CH_3)$-*, $CH_2CH(OH)$-*, CH(OH)-*, $CH(OH)CH_2CH_2$-*, $CH_2CH(OH)$-*, $CH_2NHC(O)$-*, $NHC(O)OCH_2$-*, O-*, NH-*, $S(O)_2CH$-*, $S(O)_2CH_2CH_2$-*, $S(O)_2CH_2CH_2O$-*, or $CH_2C(O)$-*, and "-*" indicates the attachment point to A and W, respectively;

R^1 and R^2 are each independently hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, or silyloxy-C_1-C_6 alkyl;

A is phenyl and W is phenyl or 5-6-membered heteroaryl, wherein A and W is optionally substituted with 1-5 R^Y;

each R^X is independently selected from the group consisting of C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–OS(O)_2R^D$, $–S(O)_2R^D$, $–SR^E$, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, NR^BR^C, or G^2;

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, amino-C_1-C_6 alkyl, cyano-C_1-C_6

alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–S(R^F)_m$,$–S(O)_2R^D$, 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, heterocyclyl, aryl, or heteroaryl ring optionally substituted with 1-5 R^X;

each G^1 and G^2 is independently C_3-C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3-C_6 cycloalkyl, 4-7-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 $–S(O)_2R^D$;

each R^A is independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, 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^D is independently C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl, wherein each C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl is optionally substituted with 1-5 R^G;

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 aryl or 5-6 membered heteroaryl, wherein each aryl or 5-6 membered heteroaryl is optionally substituted with 1-5 R^H;

each R^H is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

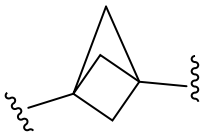
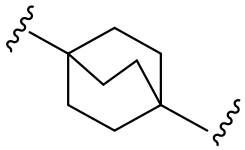
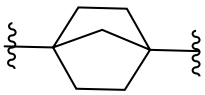
m is 1, 3, or 5; and

t is 0 or 1.

2. The compound of claim 1, wherein D is substituted with 1 R^X.

3. The compound of claim 1 or 2, wherein R^X is selected from the group consisting of CH_3, oxo, fluoro, OH, cyano, OCH_3, NH_2, $N(CH_3)_2$, $NHC(O)CH_3$, $OC(O)CH_3$, $C(O)NH_2$, $OS(O)_2CH_3$, $-S(O)_2CH_3$, $-S(O)_2$ CH_2CH_3, C(O)OH, $OC(O)R^D$, $-C(O)CH_3$, $-SCH_3$, oxadiazolyl, and tetrazolyl.

4. The compound of any one of claims 1-3, wherein D is substituted with 0 R^X.

5. The compound of any one of claims 1-4, wherein D is , , or .

6. The compound of any one of claims 1-5, wherein t is 1.

7. The compound of any one of claims 1-5, wherein t is 0.

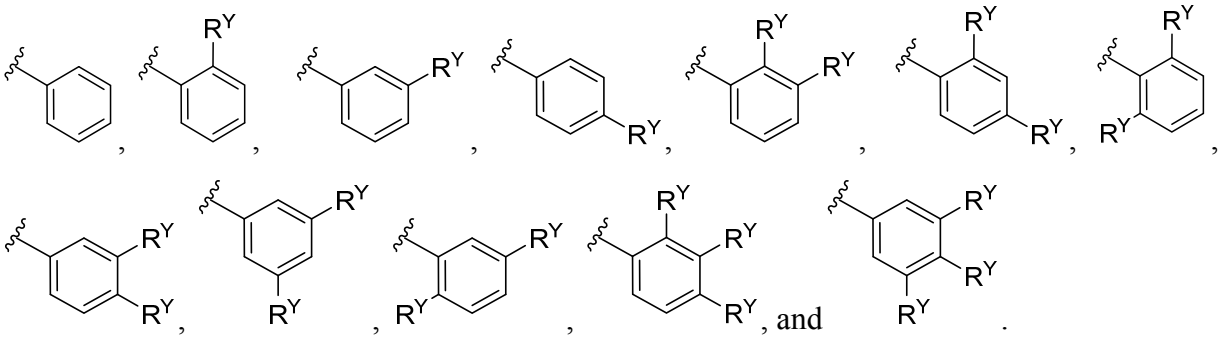
8. The compound of any one of claims 1-7, wherein R^1 and R^2 are each independently hydrogen, *-CH_3, *-CH_2CH_2OH, or *-$CH_2CH_2OSi(CH_3)_2C(CH_3)_3$, and "*-" indicates the attachment point to the nitrogen atom.

9. The compound of any one of claims 1-8, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is hydrogen, *-CH_3, *-CH_2CH_2OH, or *-$CH_2CH_2OSi(CH_3)_2C(CH_3)_3$, and "*-" indicates the attachment point to the nitrogen atom.

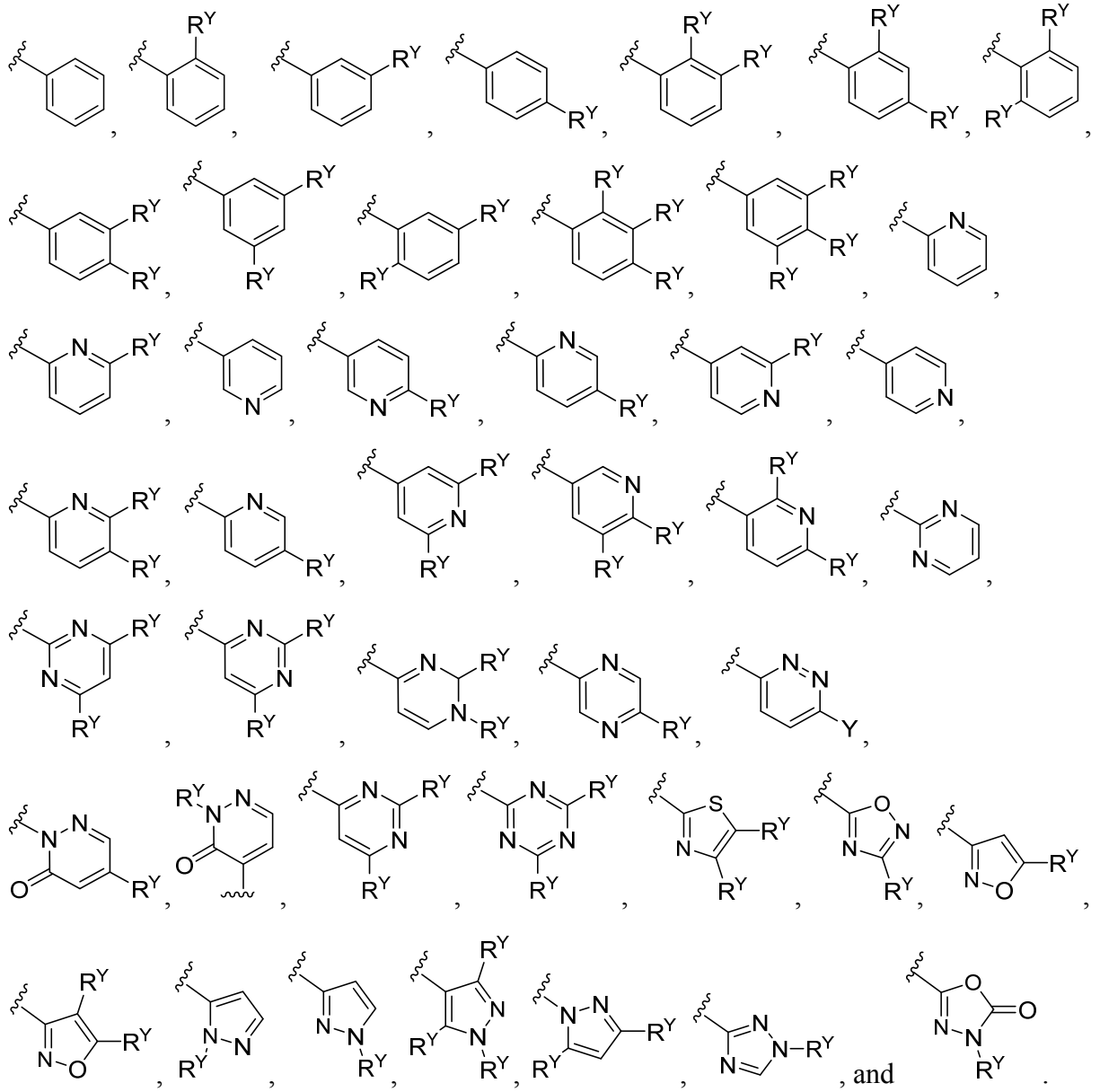
10. The compound of any one of claims 1-9, wherein R^1 and R^2 are each hydrogen.

11. The compound of any one of claims 1-10, wherein A is phenyl and W is phenyl, pyridyl, pyrazinyl, pyridazinyl, pyridazinonyl, triazinyl, thiazolyl, triazolyl, oxadiazolyl, or oxadiazolonyl, each of which is optionally substituted with 1-5 R^Y.

12. The compound of any one of claims 1-11, wherein A is selected from:



13. The compound of any one of claims 1-12, wherein W is selected from:



14. The compound of any one of claims 1-13, wherein each R^Y is independently selected from the group consisting of chloro, fluoro, iodo, CF_3, CHF_2, CH_2CF_3, CH_3, CH_2CH_3, $C(CH_3)_2OH$, OCH_3, OCH_2CH_3, OCF_3, $S(O)_2CH_3$, $S(O)_2CH_2CH_2CH_3$, CN, $N(CH_3)_2$, SF_5, SCH_3, NH_2, $C(CH)_3$, $CH(CH_3)_2$, CH_2CN, CH_2NH_2, $CH(OH)CH_3$, $C(OH)(CH_3)CF_3$, $S(O)_2CH_3$, $C(O)CH_3$, $C(O)OCH_3$, C(O)OH, $OCHF_2$ 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 ring optionally substituted with 1-5 R^X.

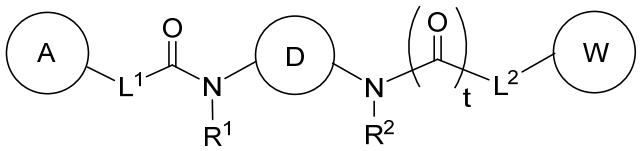
15. The compound of claim 14, wherein the 2 R^Y together with the atoms to which they are attached form a pyrazolyl, pyrrolyl, isoxazolyl, thiophenyl, furanyl, or dioxolanyl ring, each of which is optionally substituted with 1-5 R^X.

16. The compound of claim 14 or 15, wherein each R^X is independently C_1-C_6 alkyl or halo.

17. The compound of any one of claims 1-14, wherein G^1 is cyclopropyl, isoxazolyl, piperidinyl, phenyl, or pyrazolyl, each of which is optionally substituted with 1-5 R^Z.

18. The compound of claim 17, wherein each R^Z is independently C_1-C_6 alkyl or halo.

19. A compound represented by Formula (I-b):



Formula (I-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,

wherein:

D is (1,2,3,4,6,7)-cubane, bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, or bicycle[3.1.1]heptane, each of which is optionally substituted with 1-4 R^X groups;

L^1 and L^2 are each independently CH_2O-*, CH_2CH_2-*, $CH_2CH_2CH_2$-*, CH_2-*, $CH_2C(O)$-*, CH=CH-*, CH_2CH_2O-*, CH_2OCH_2-*, $CH_2OCH_2CH_2$-*, $CH_2CH_2CH_2O$-*, $CH_2CH_2OCH_2$-*, $NHCH_2$-*, CH_2NH-*, $CH_2N(CH_3)$-*, $CH_2N(CH_3)C(O)$-*, $CH_2N(C(O)CH_3)$-*, $CH_2CH(OH)$-*, CH(OH)-*, $CH(OH)CH_2CH_2$-*, $CH_2CH(OH)$-*, $CH_2NHC(O)$-*, $NHC(O)OCH_2$-*, O-*, NH-*, $S(O)_2CH$-*, $S(O)_2CH_2CH_2$-*, $S(O)_2CH_2CH_2O$-*, or $CH_2C(O)$-*, and "-*" indicates the attachment point to A and W, respectively.

R^1 and R^2 are each independently hydrogen, CH_3, CH_2CH_2OH, or $CH_2CH_2OSi(CH_3)_2C(CH_3)_3$;

A and W are each independently phenyl, pyridyl, pyrazinyl, pyridazinyl, pyridazinonyl, triazinyl, thiazolyl, triazolyl, oxadiazolyl, or oxadiazolonyl, each of which is optionally substituted with 1-5 R^Y groups;

each R^X is independently selected from CH_3, oxo, fluoro, OH, cyano, OCH_3, NH_2, $N(CH_3)_2$, $NHC(O)CH_3$, $OC(O)CH_3$, $C(O)NH_2$, $OS(O)_2CH_3$, $-S(O)_2CH_3$, $-S(O)_2 CH_2CH_3$, C(O)OH, $OC(O)R^D$, $-C(O)CH_3$, $-SCH_3$, or G^2;

each R^Y is independently chloro, fluoro, iodo, CF_3, CHF_2, CH_2CF_3, CH_3, CH_2CH_3, $C(CH_3)_2OH$, OCH_3, OCH_2CH_3, OCF_3, $S(O)_2CH_3$, $S(O)_2CH_2CH_2CH_3$, CN, $N(CH_3)_2$, SF_5, SCH_3, NH_2, $C(CH)_3$, $CH(CH_3)_2$, CH_2CN, CH_2NH_2, $CH(OH)CH_3$, $C(OH)(CH_3)CF_3$, $S(O)_2CH_3$, $C(O)CH_3$, $C(O)OCH_3$, C(O)OH, $OCHF_2$ or G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a pyrazolyl, pyrrolyl, isoxazolyl, thiophenyl, furanyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X;

G^1 and G^2 are cyclopropyl, isoxazolyl, phenyl, piperidinyl, oxadiazolyl, or tetrazolyl, or pyrazolyl, each of which is optionally substituted with 1-2 R^Z;

each R^D is CH_2O optionally substituted with 1-5 R^G;

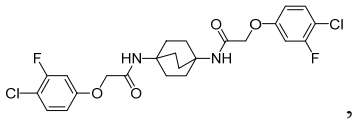
each R^G is independently pyridyl optionally substituted with 1-5 R^H;

each R^H is independently CF_3;

each R^Z is independently CH_3; and

t is 0 or 1.

20. A compound selected from the group consisting of: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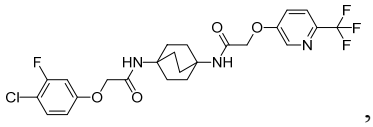
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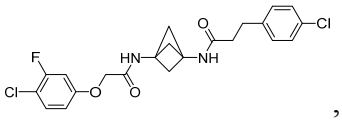
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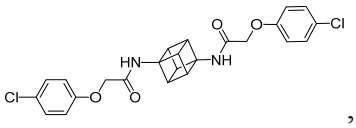
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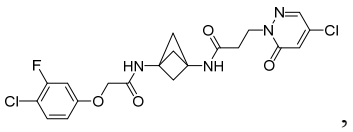
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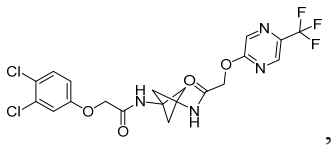
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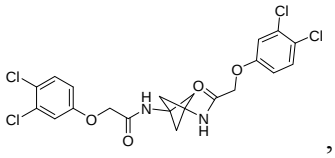
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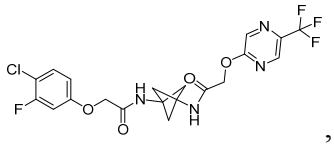
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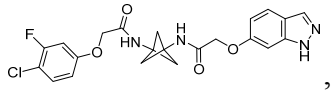
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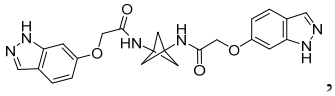
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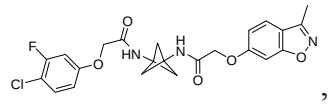
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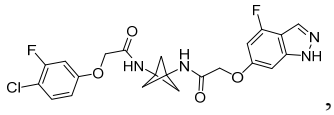
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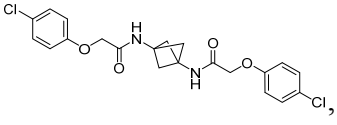
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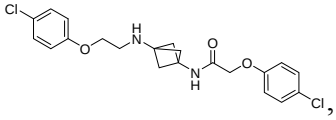
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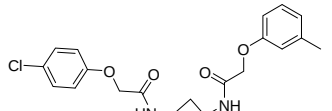
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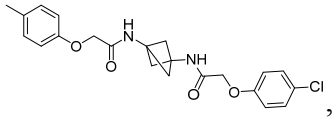
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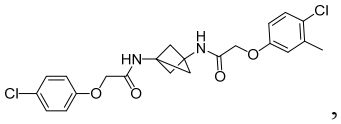
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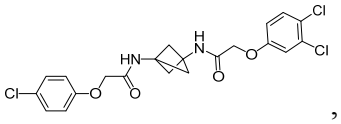
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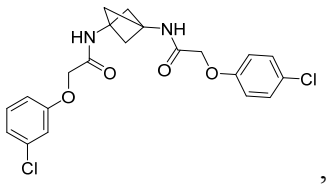
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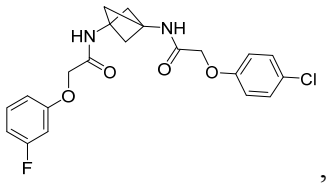
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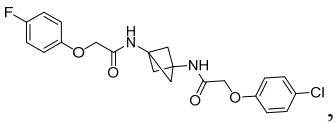
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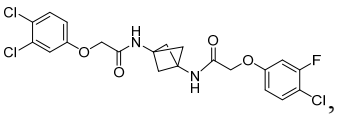
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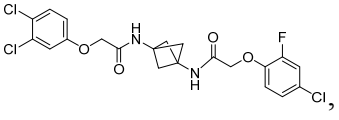
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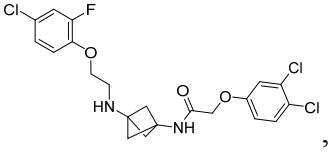
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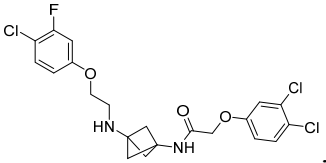
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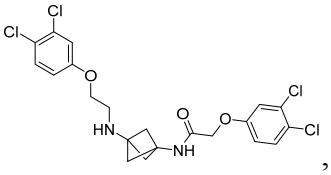
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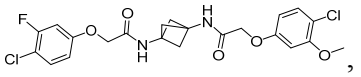
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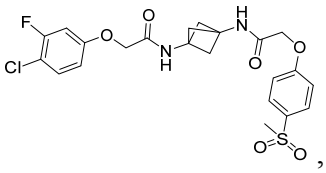
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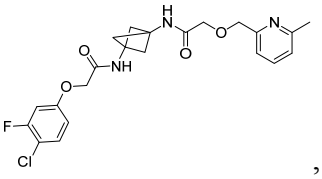
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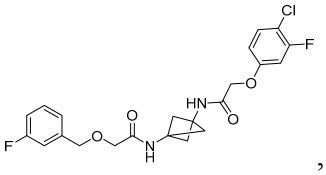
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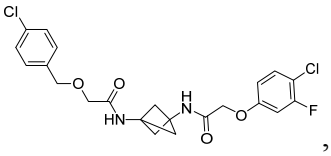
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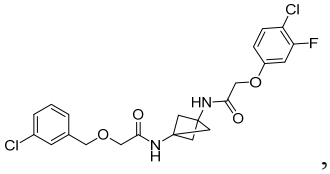
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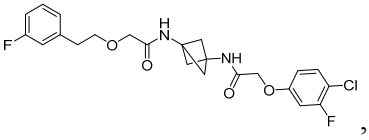
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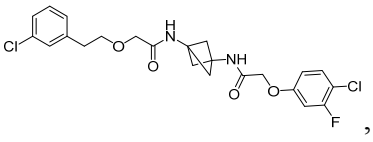
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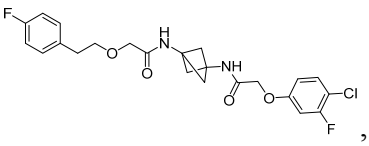
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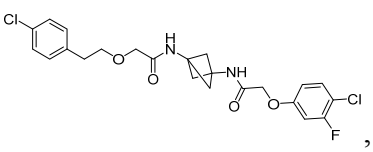
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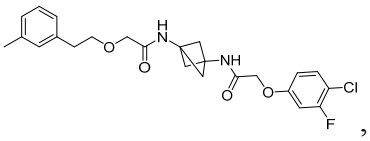

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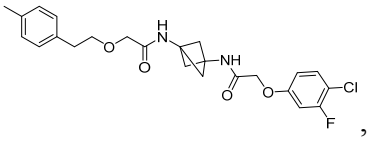

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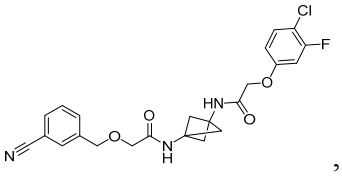

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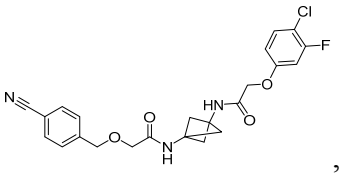

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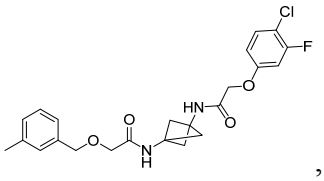

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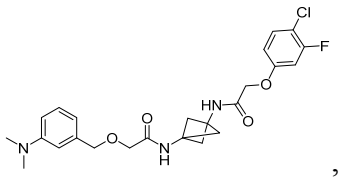

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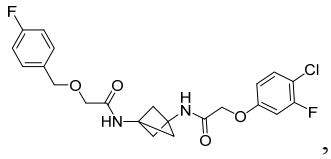

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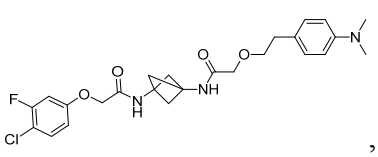

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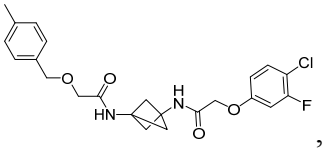

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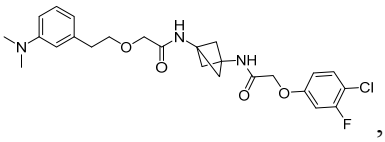
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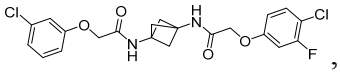
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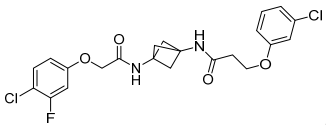
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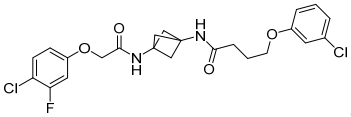
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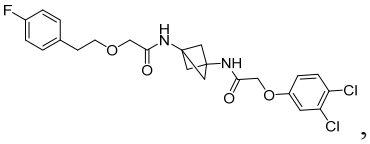
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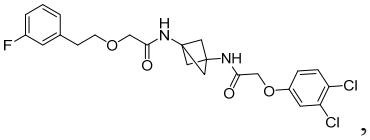
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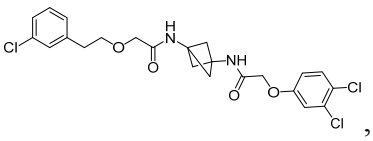
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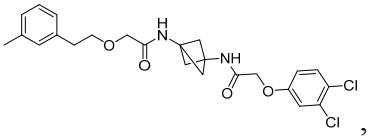
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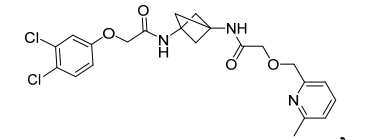
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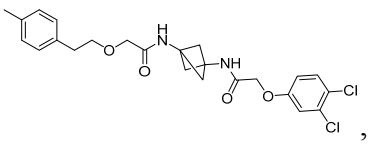
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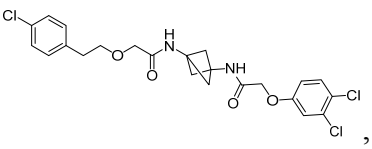
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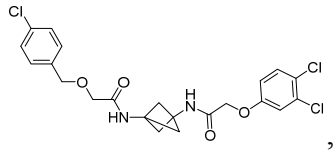
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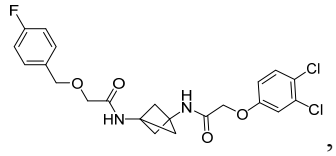
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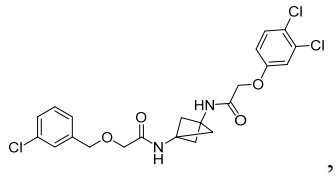
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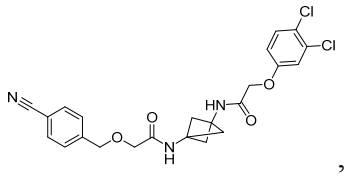
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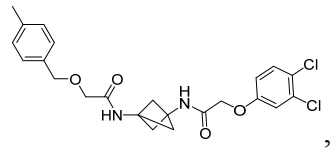
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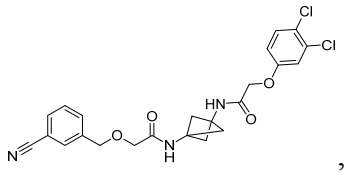
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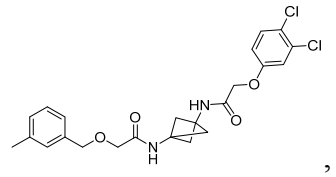
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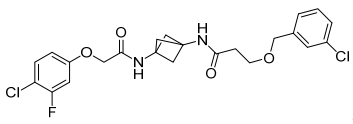
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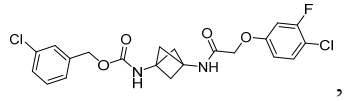
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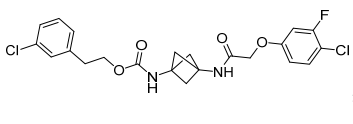
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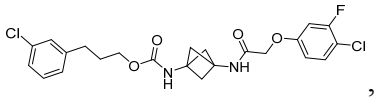
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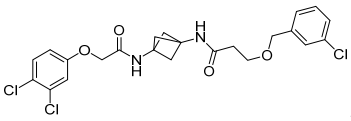
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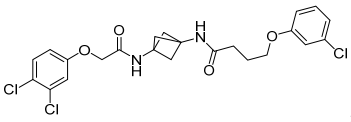
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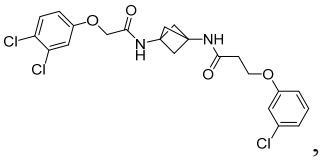
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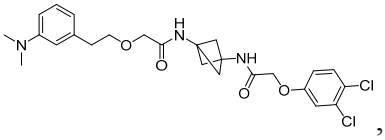
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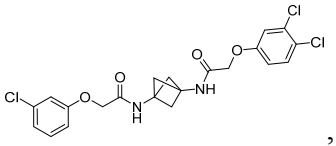
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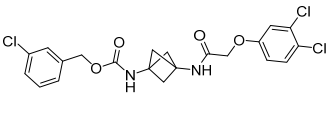
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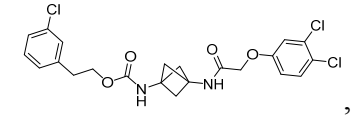
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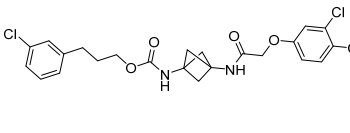
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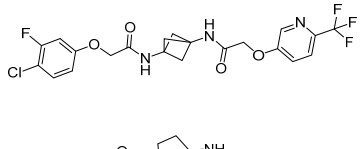
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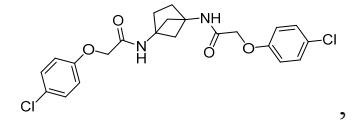
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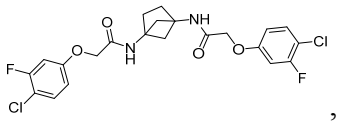
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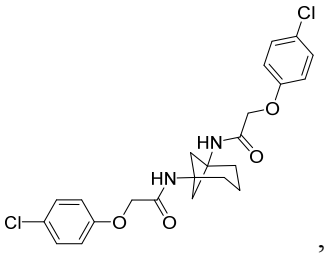
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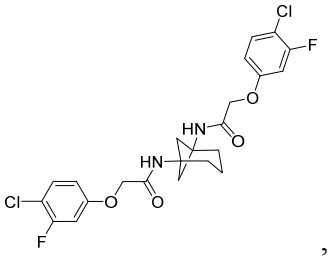
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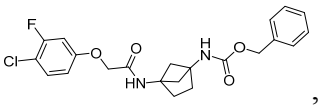
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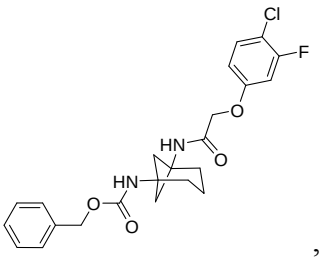
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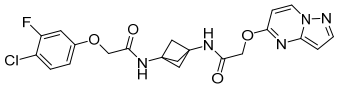
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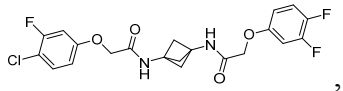
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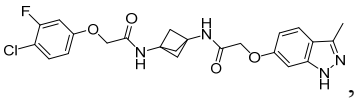
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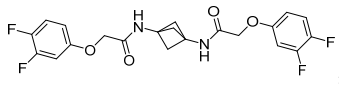
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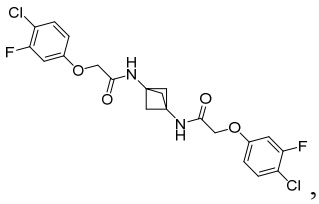
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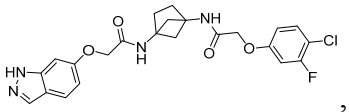
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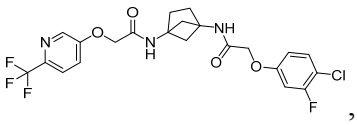
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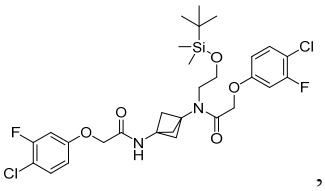
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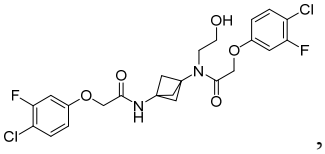
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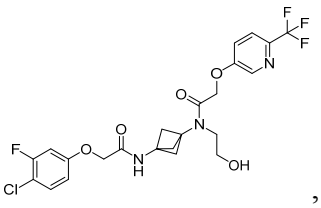
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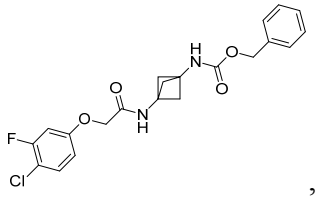
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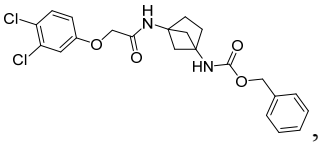
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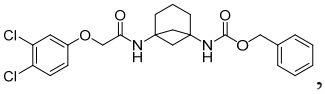
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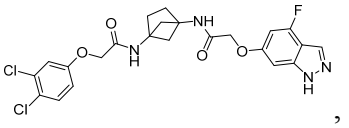

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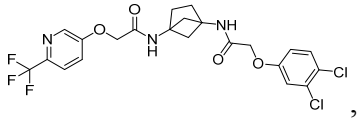

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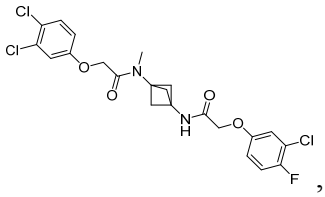

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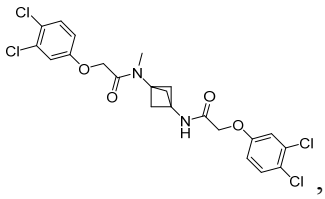

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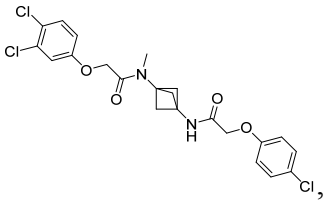

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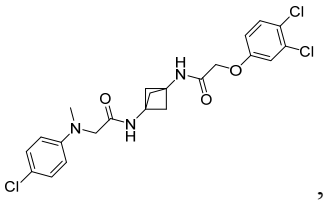

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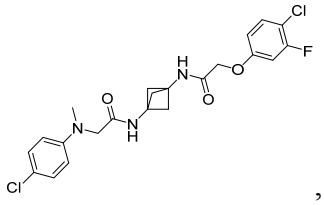

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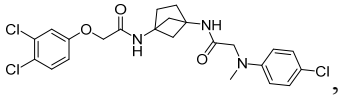

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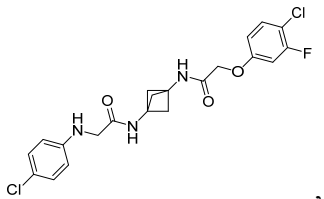

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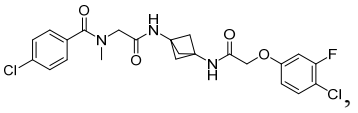

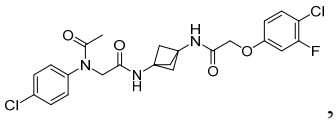

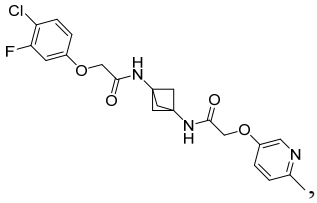

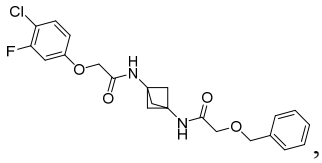

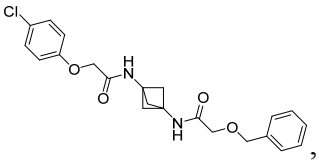

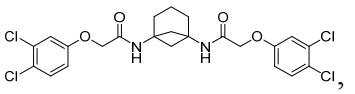

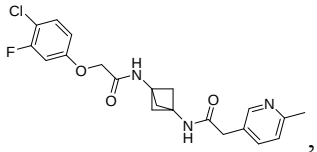

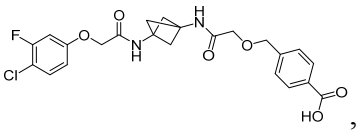

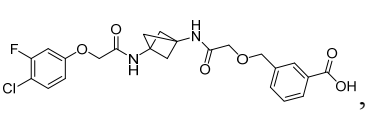

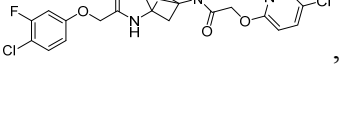

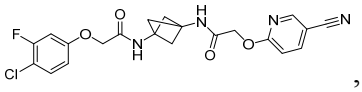

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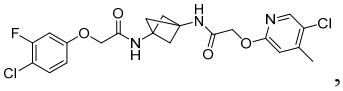

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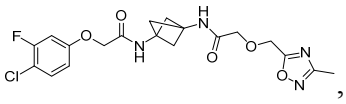

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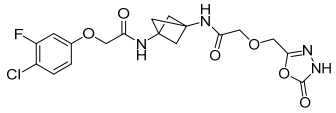

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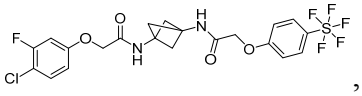

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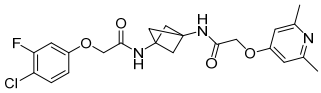

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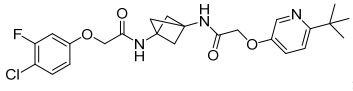

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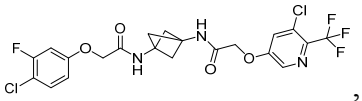

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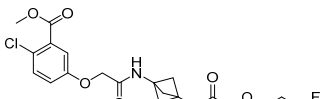

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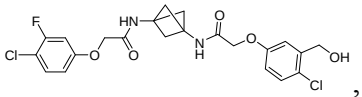

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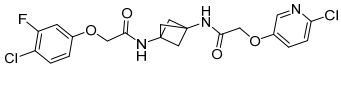

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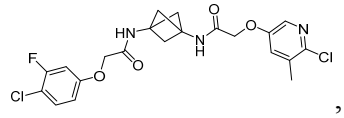

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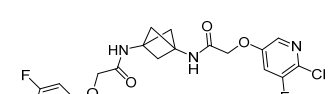

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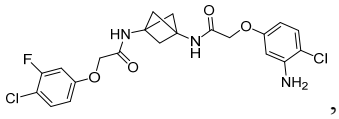
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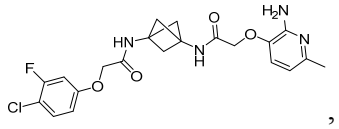
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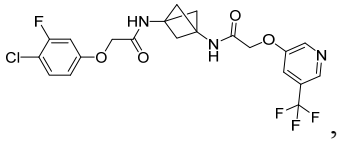
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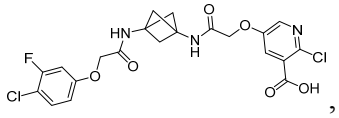
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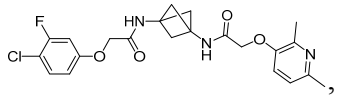
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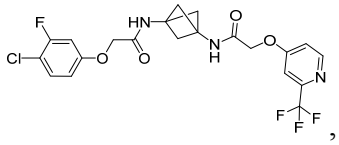
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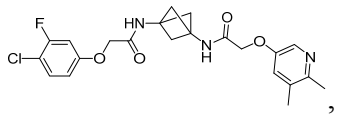
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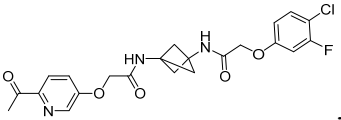
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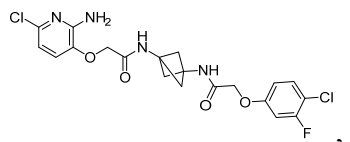
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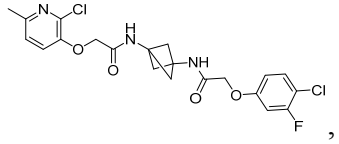
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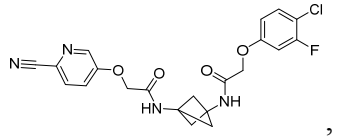
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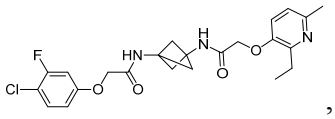
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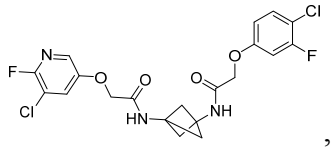
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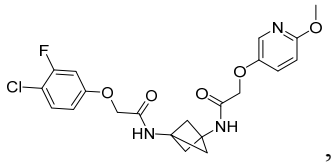
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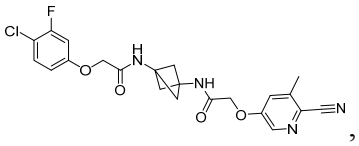
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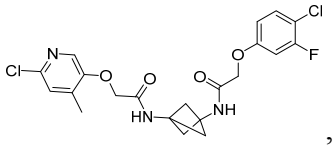
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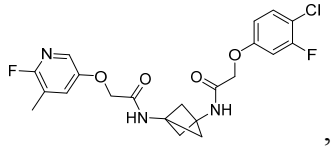
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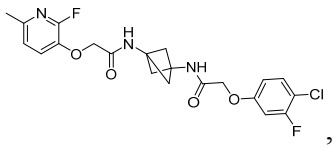
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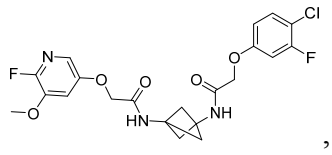
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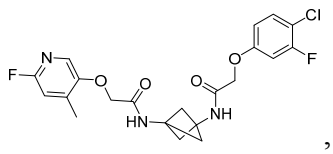
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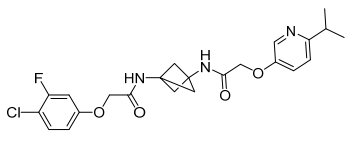
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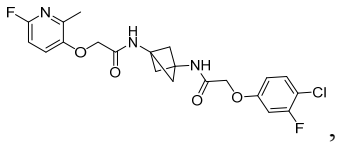
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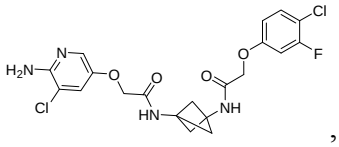
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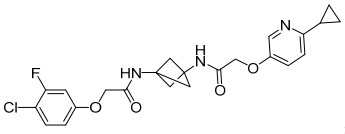
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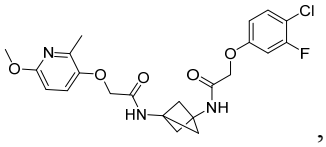
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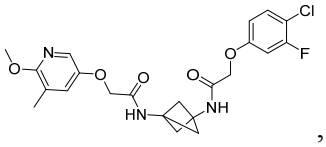
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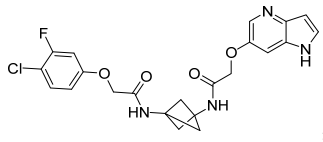
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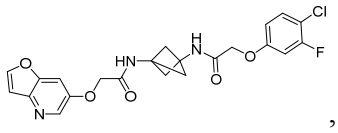
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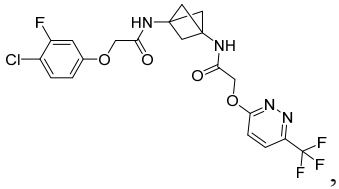
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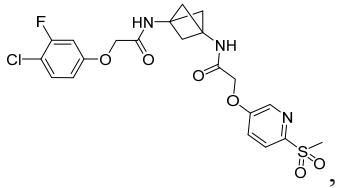
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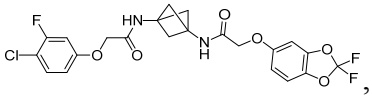
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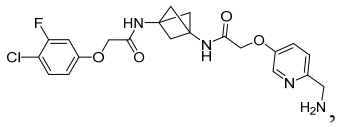
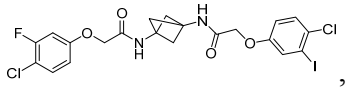
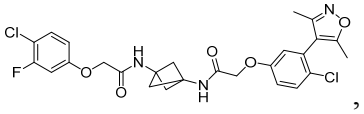
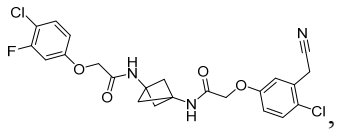
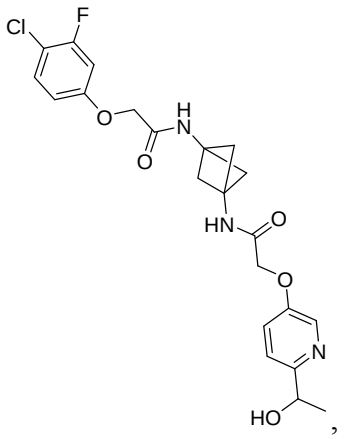
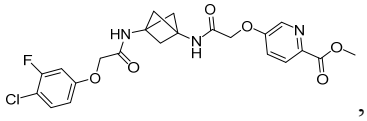


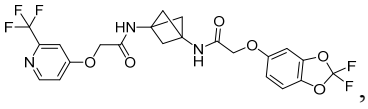


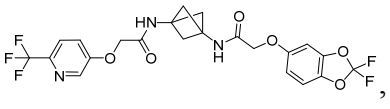


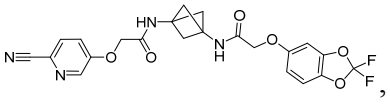


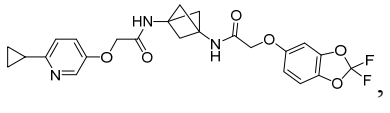


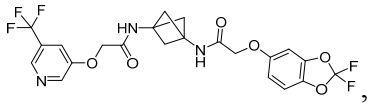


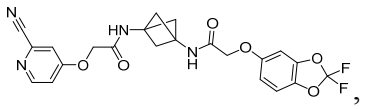


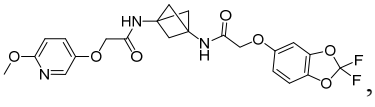


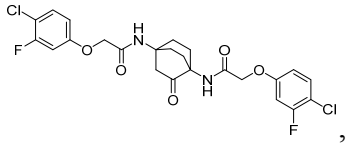


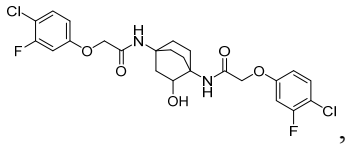


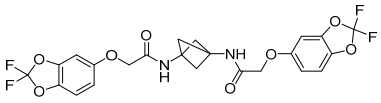
,

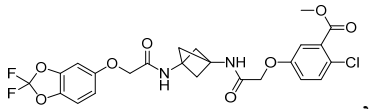
,

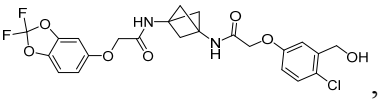
,

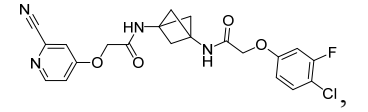
,

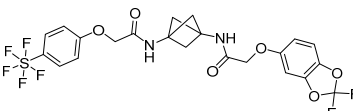
,

,

,

,

,

,

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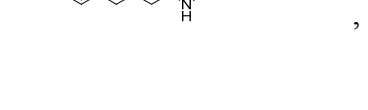,

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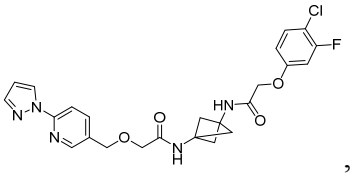
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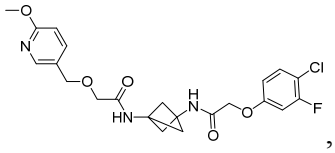
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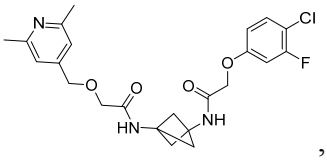
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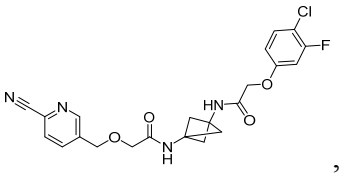
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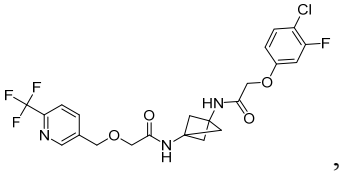
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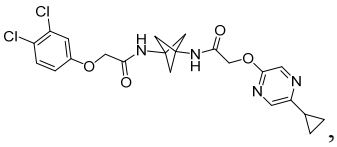
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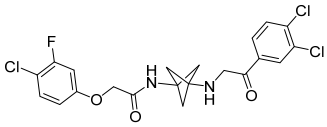
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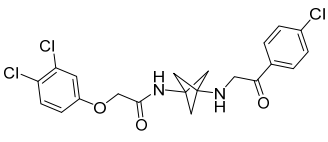
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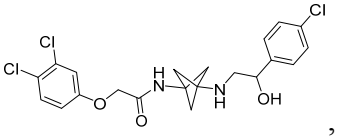
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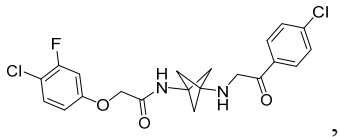
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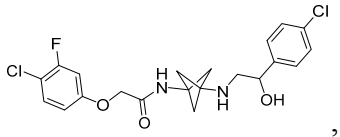
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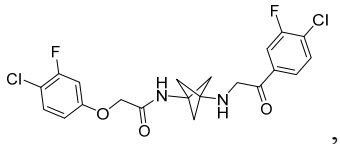
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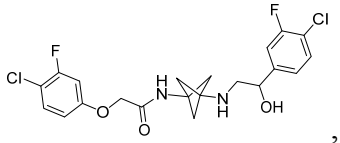
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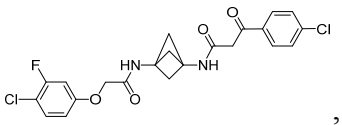
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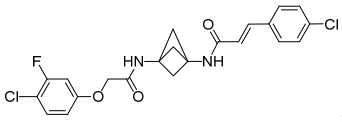
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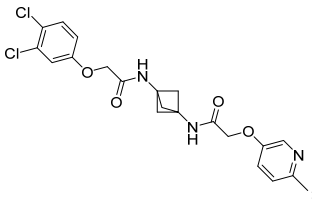
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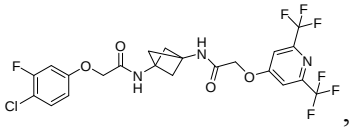
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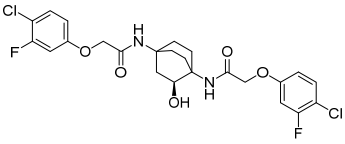
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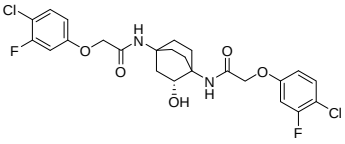
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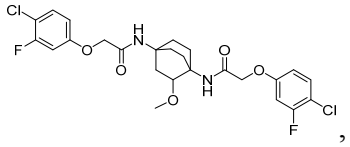

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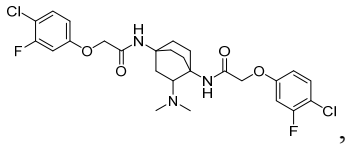

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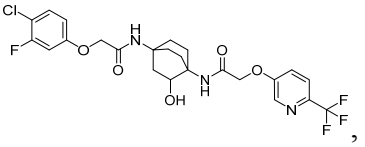

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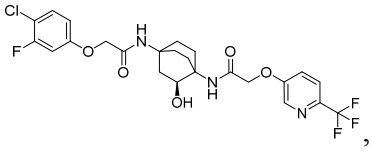

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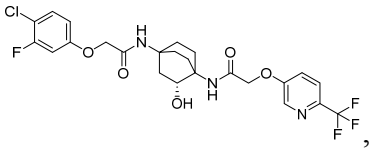

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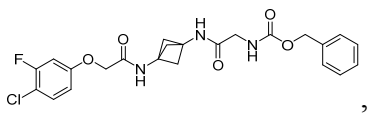

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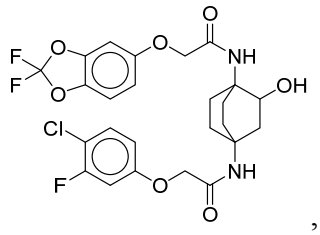

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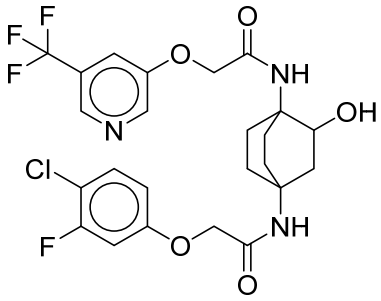

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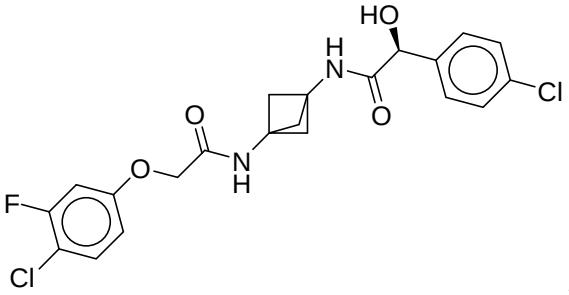

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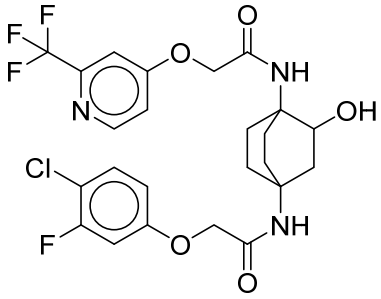

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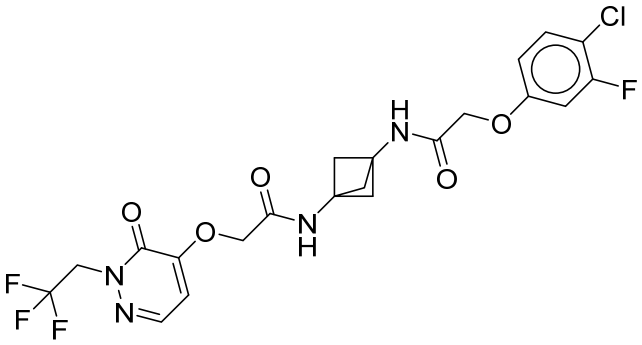

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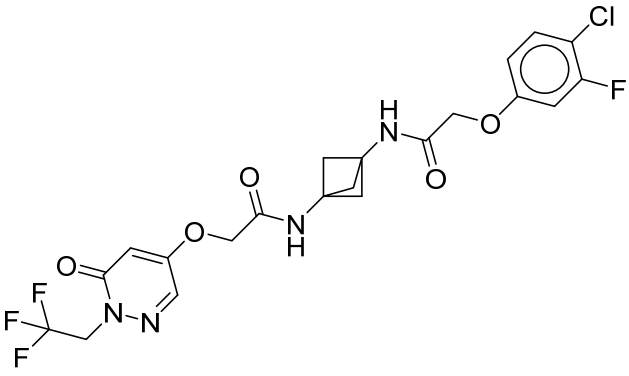

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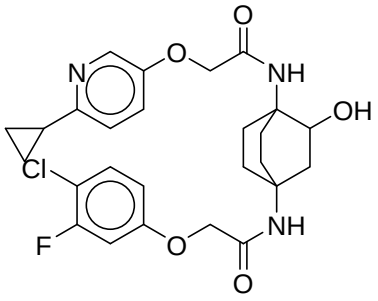

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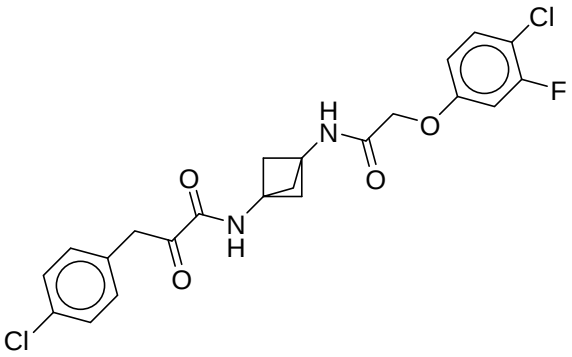
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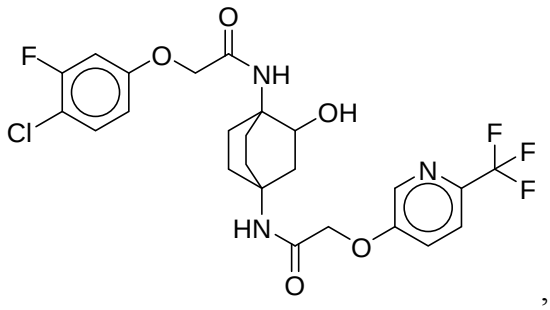
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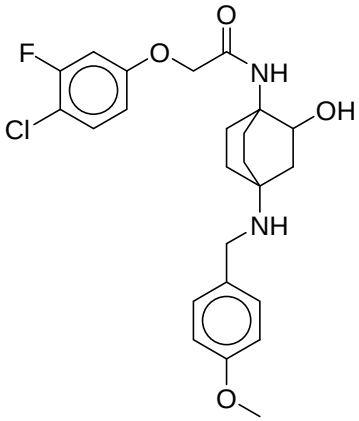
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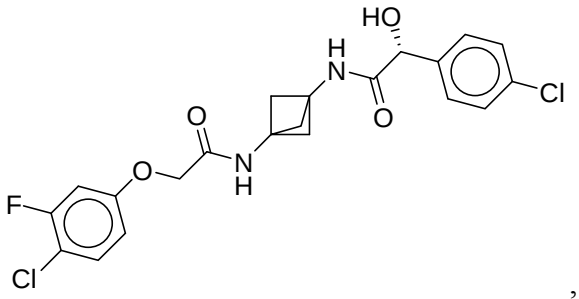
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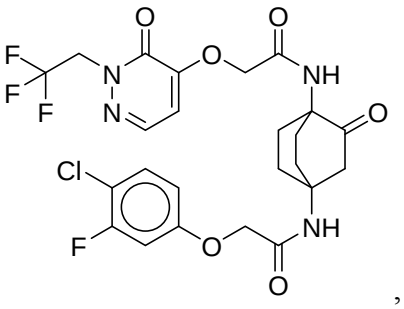

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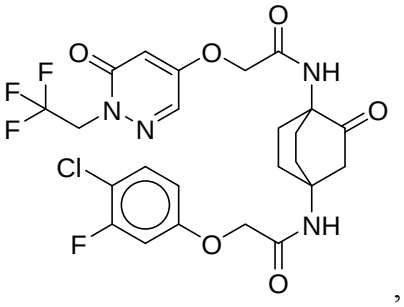

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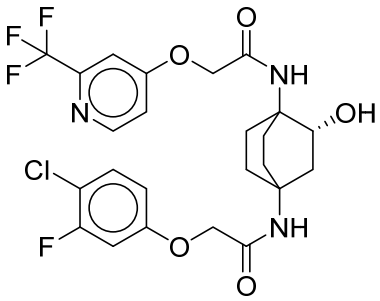

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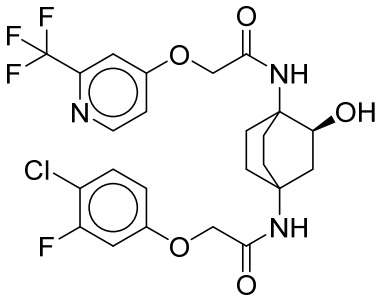

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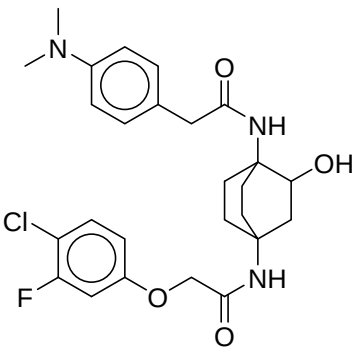

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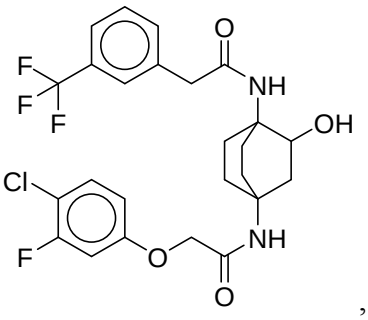

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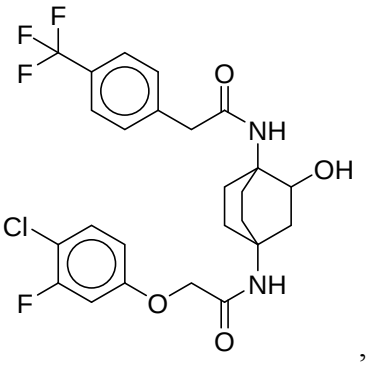

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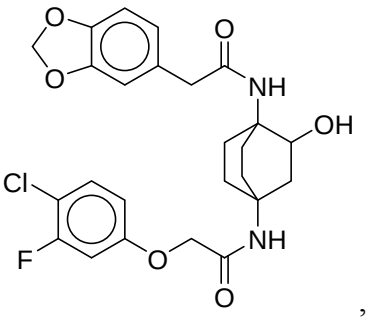

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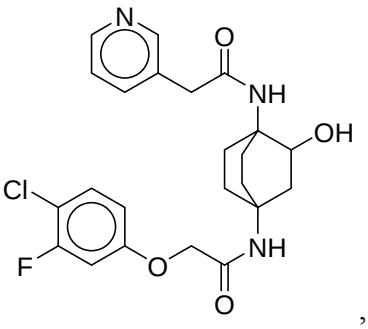

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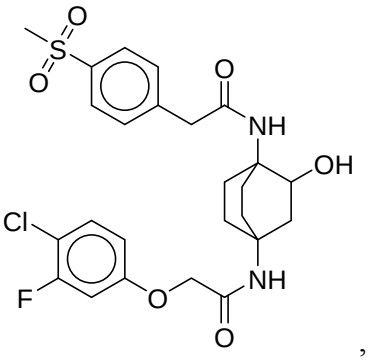

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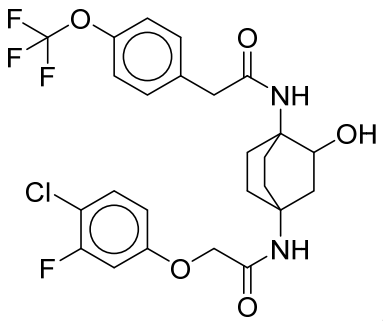

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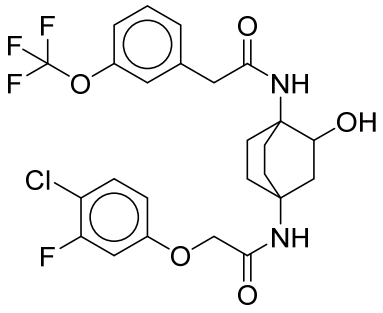

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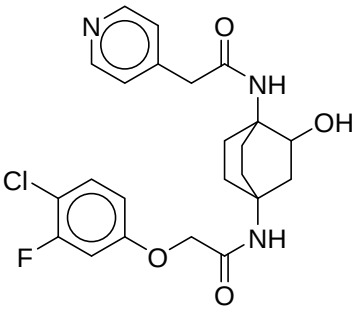

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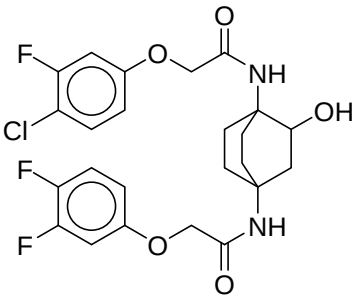

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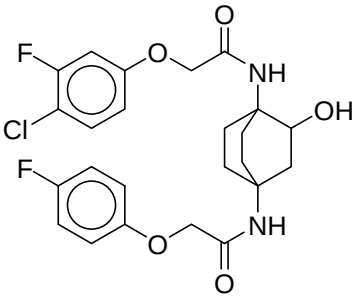

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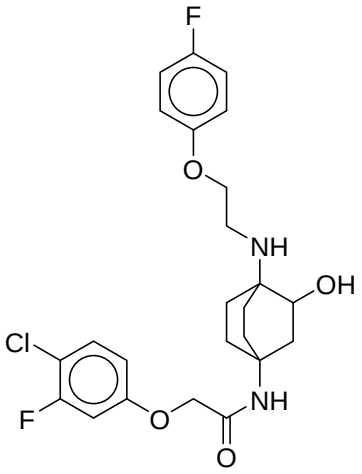

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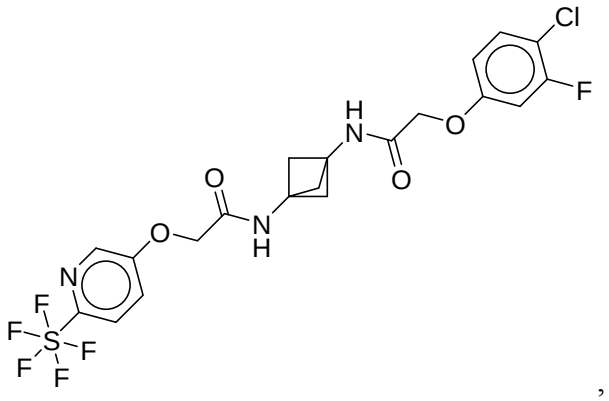

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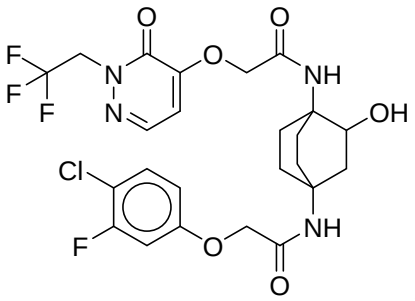

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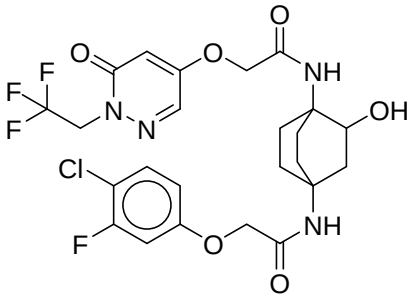

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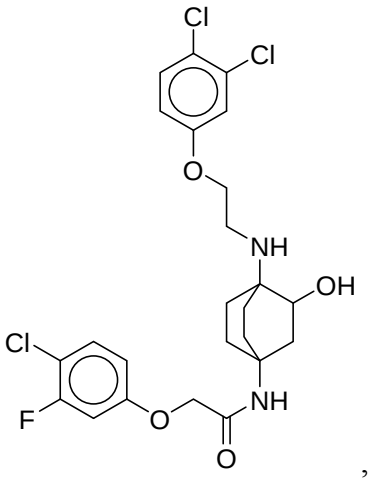
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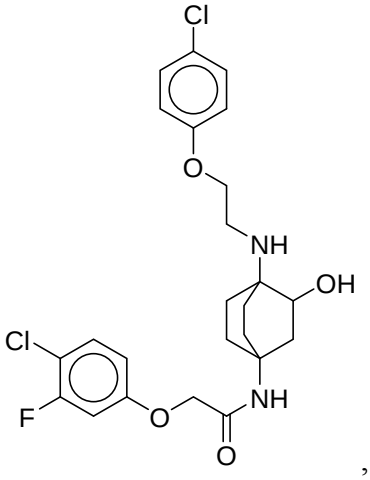
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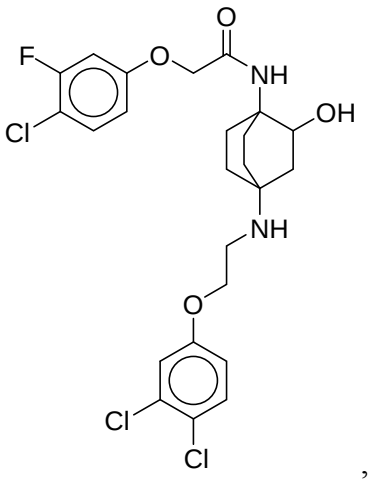
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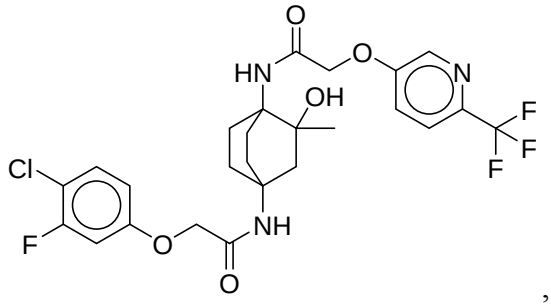

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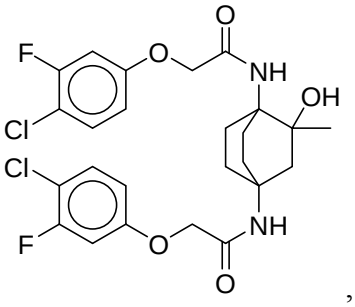

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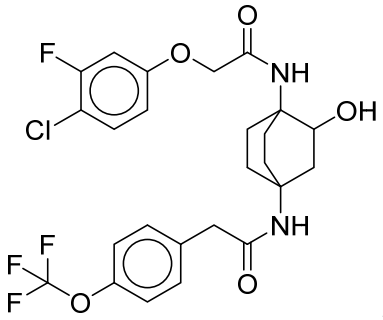

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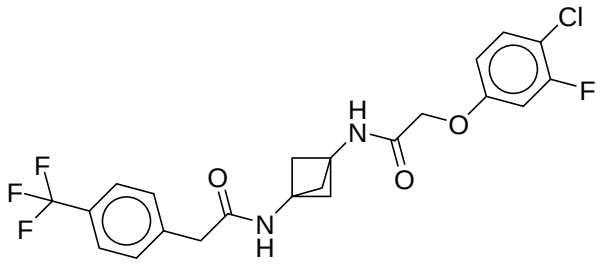

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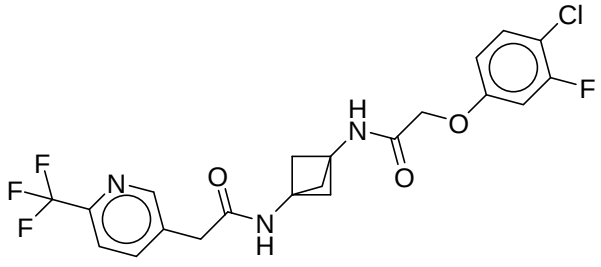

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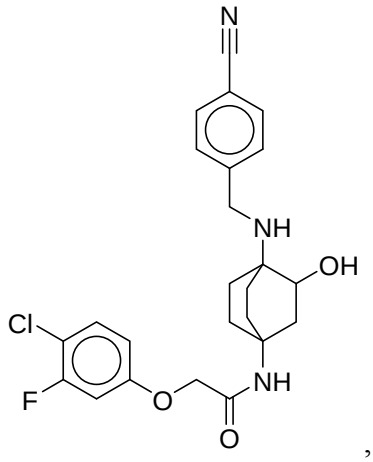
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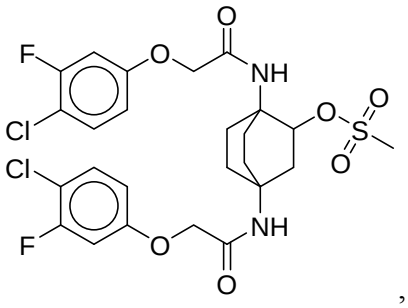
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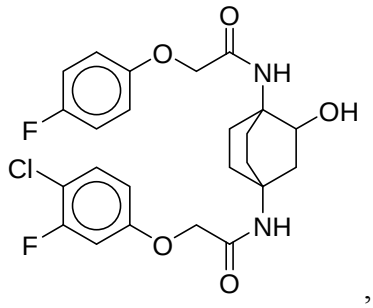
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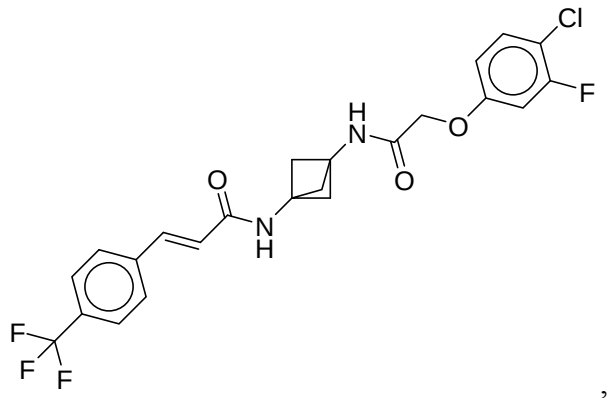
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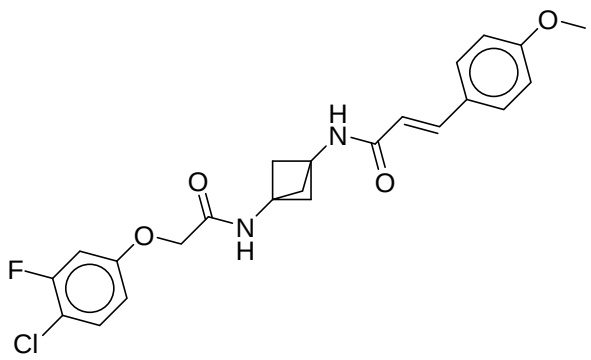

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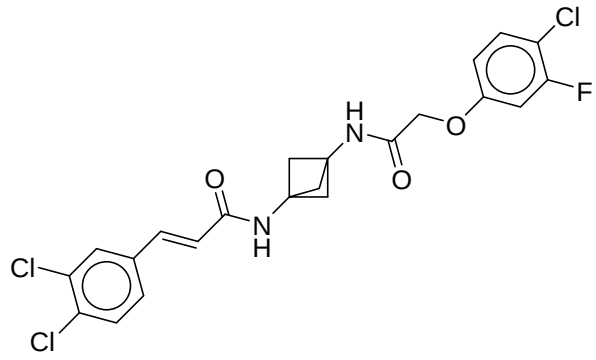

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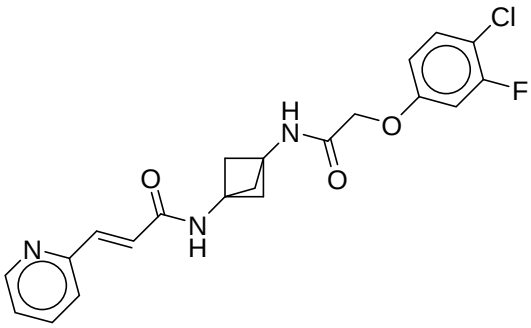

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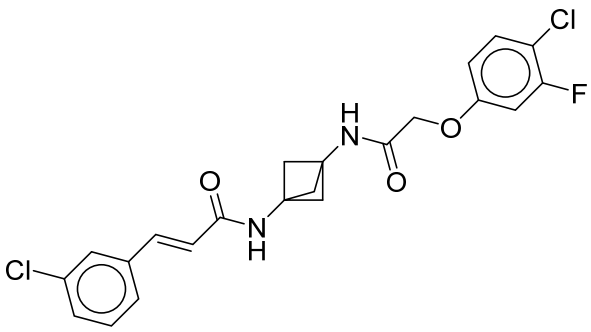

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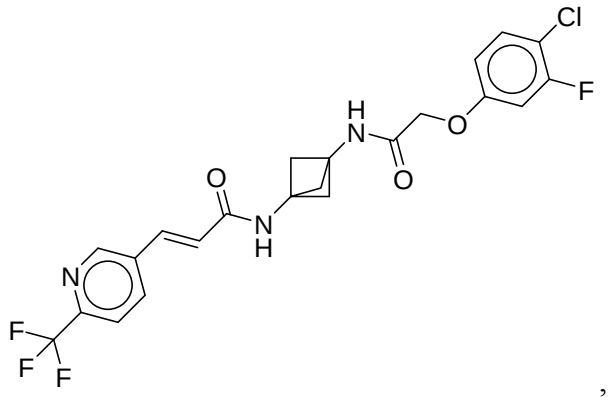
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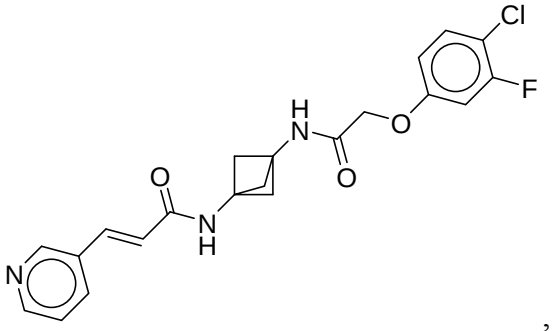
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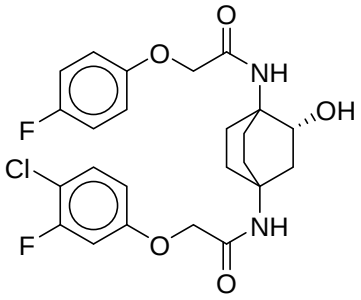
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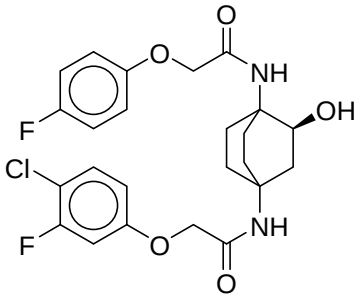
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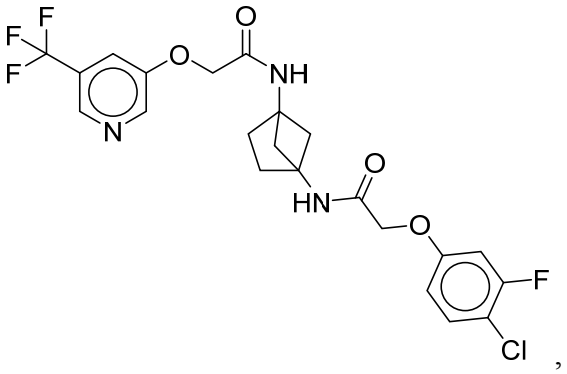

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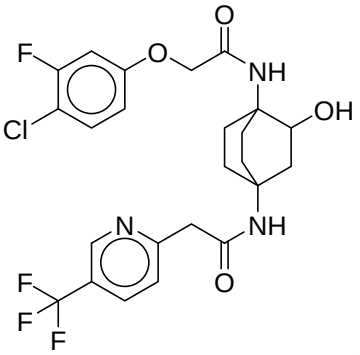

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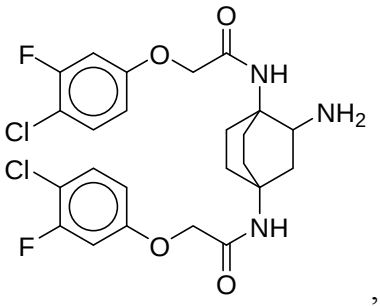

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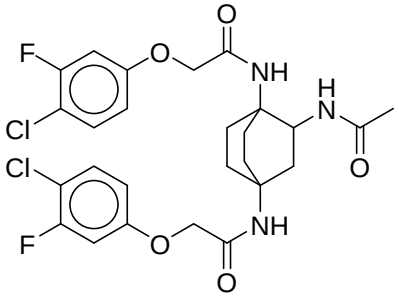

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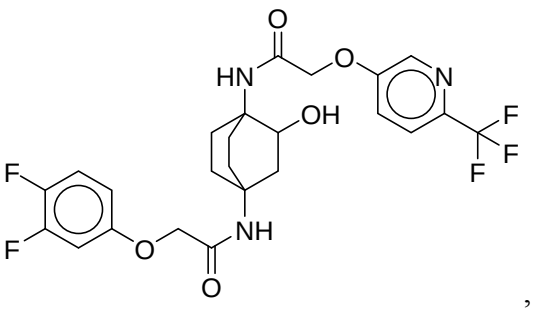

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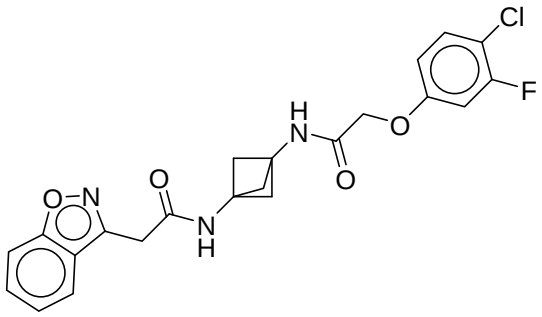

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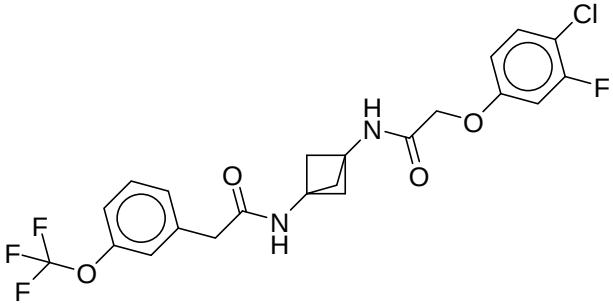

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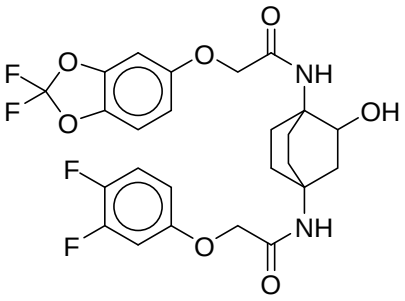

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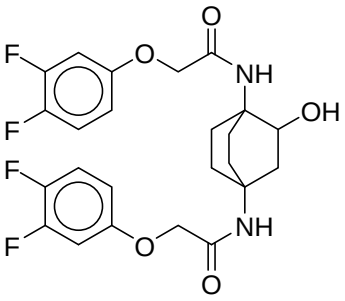

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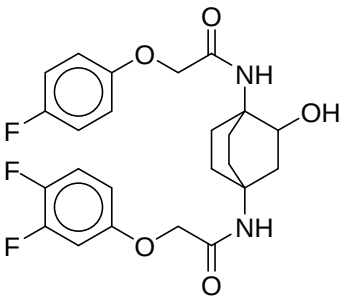

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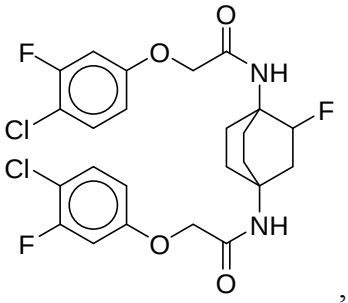

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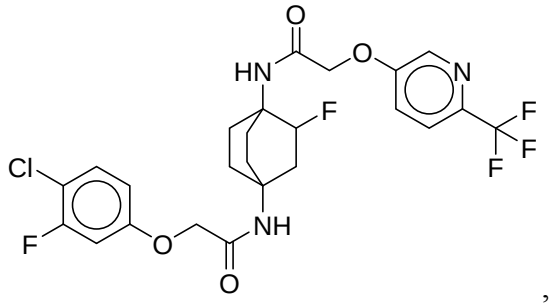

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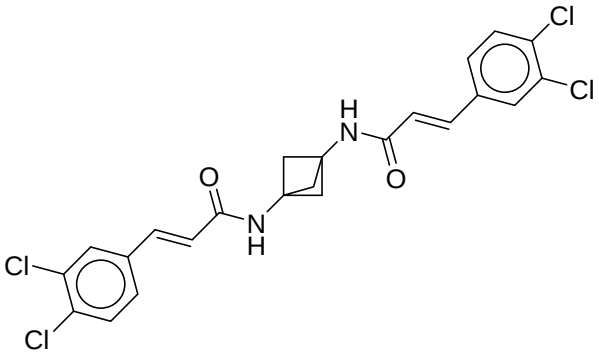

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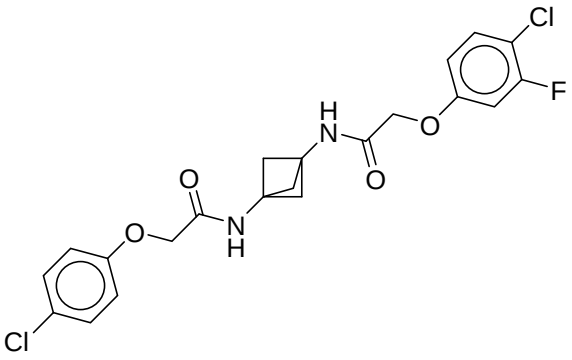

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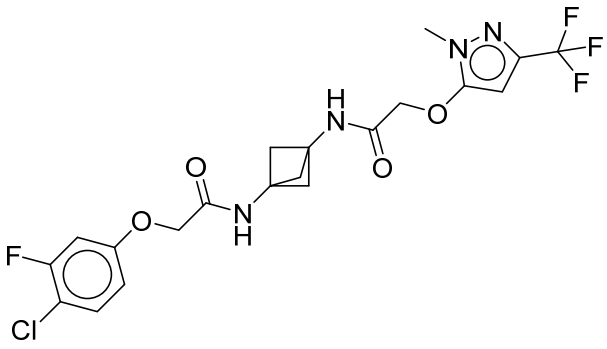

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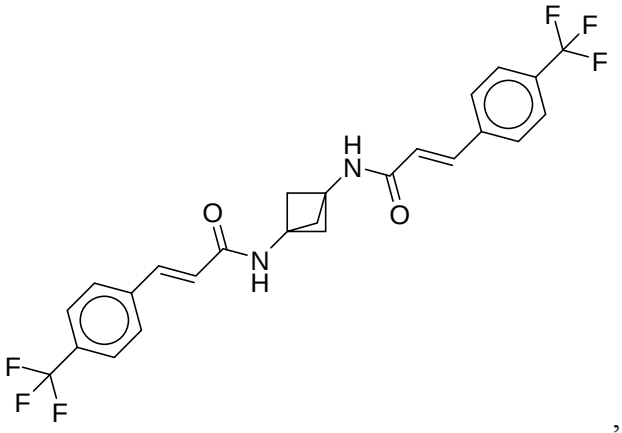

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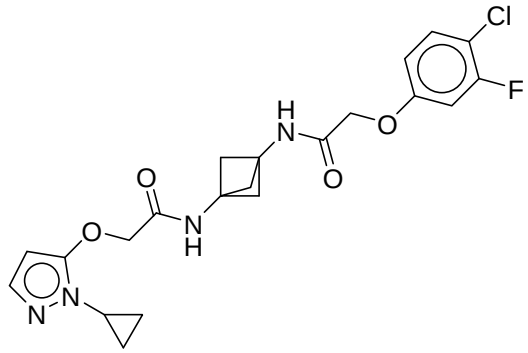

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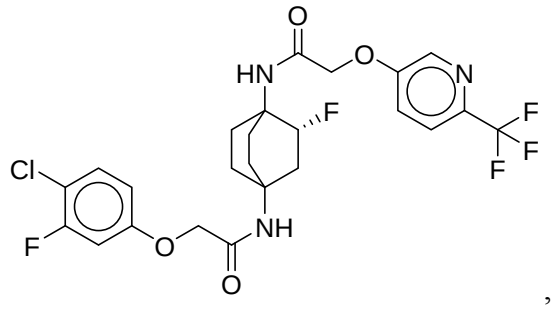

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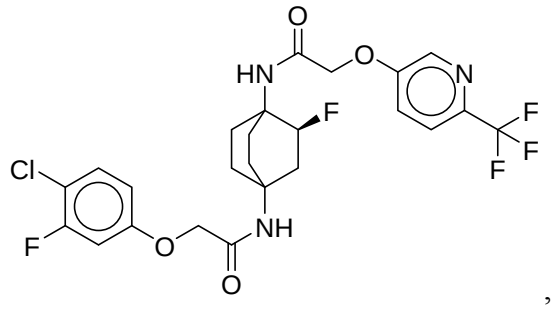

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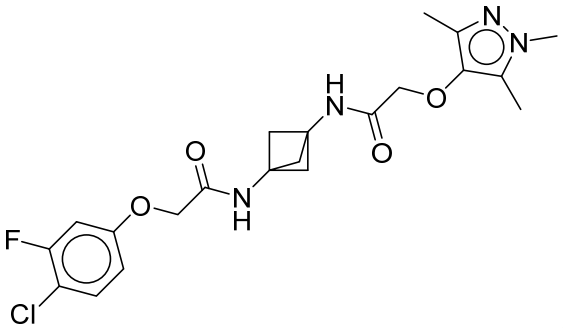

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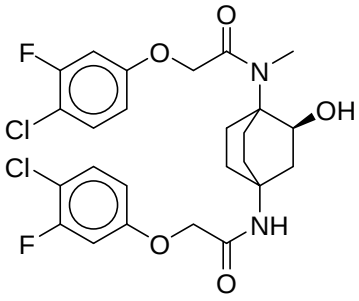

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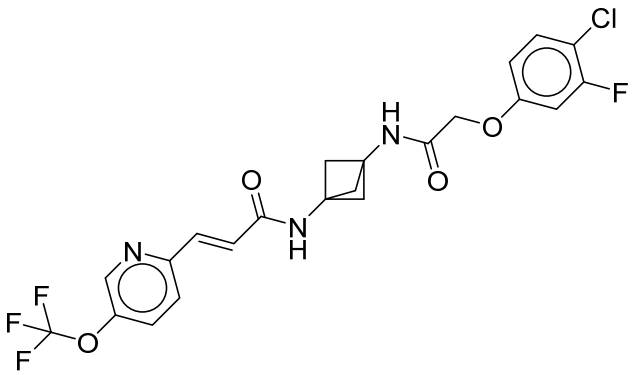

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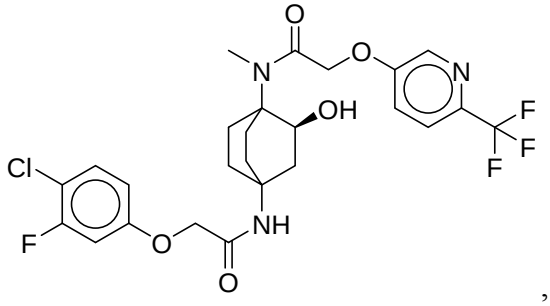

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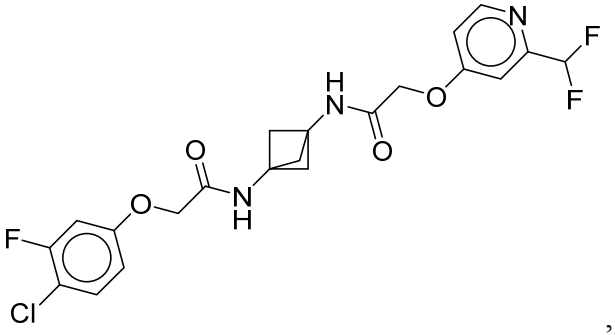

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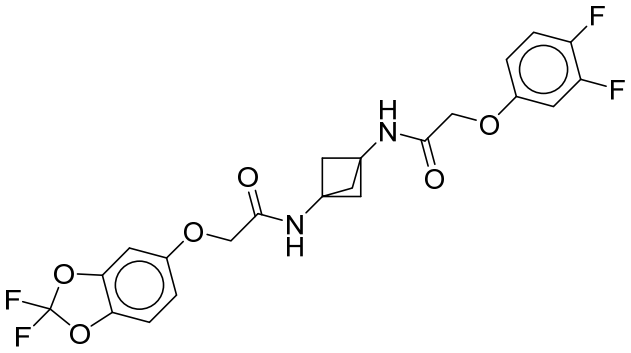

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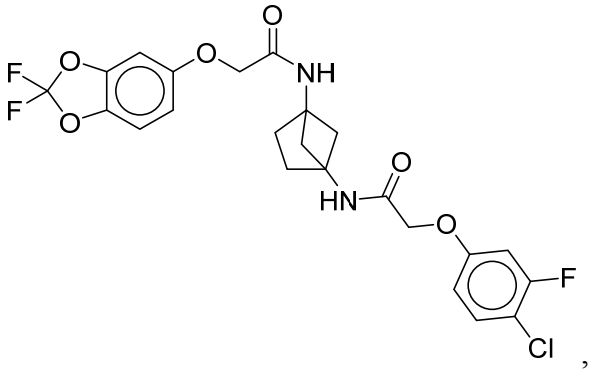

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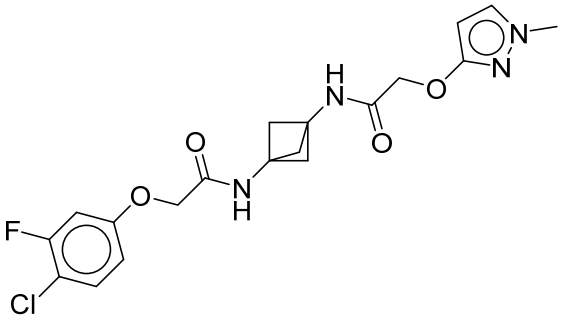

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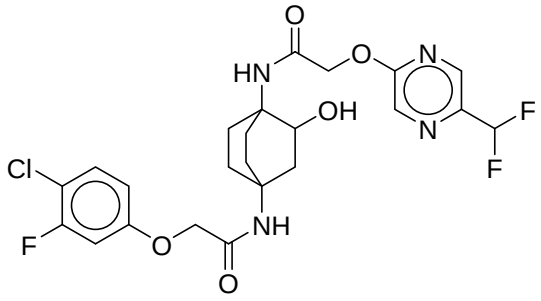

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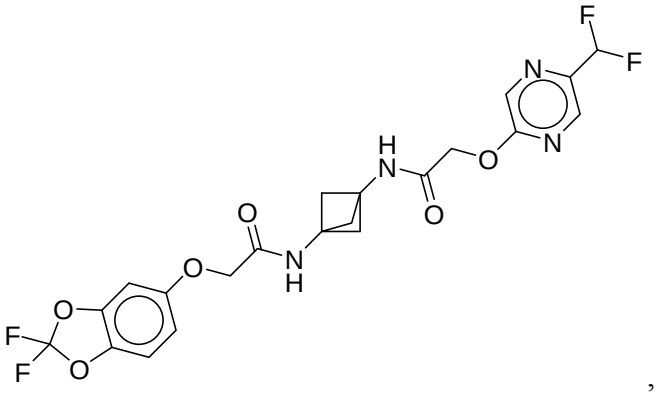

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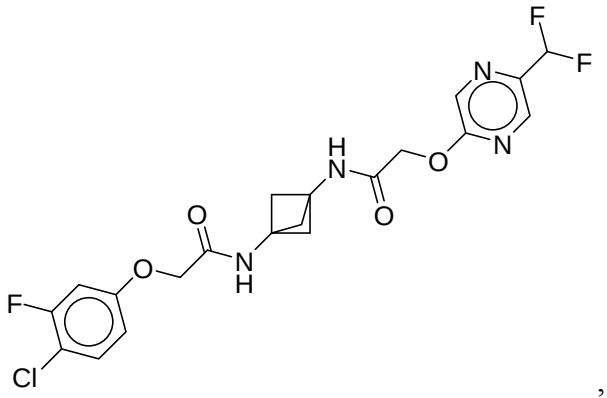

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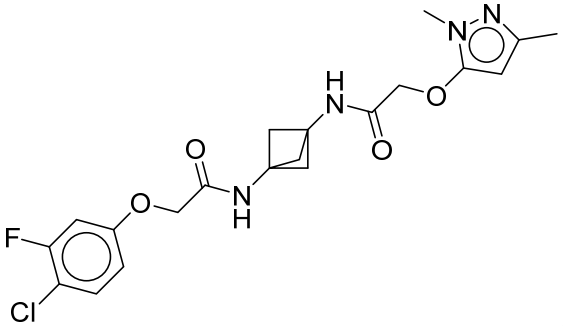

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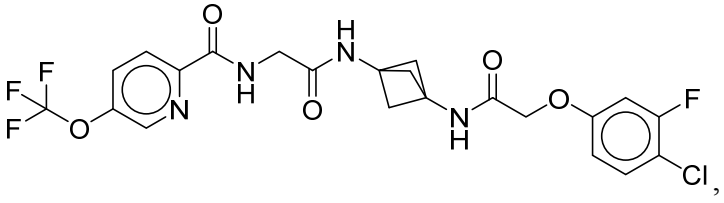

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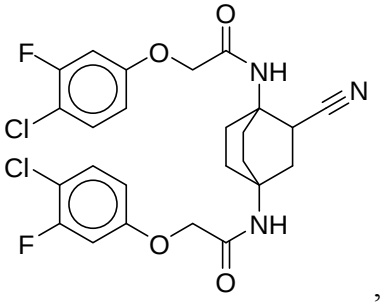

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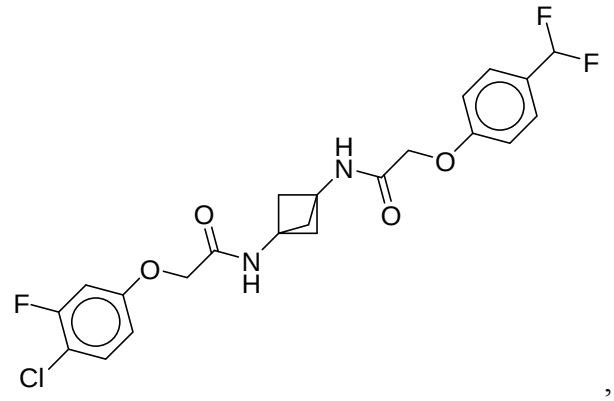

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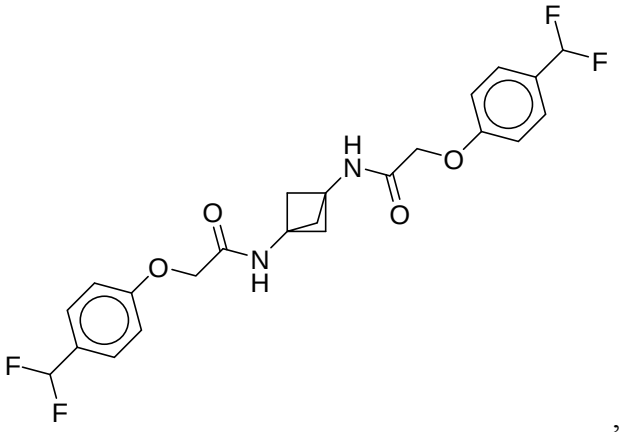

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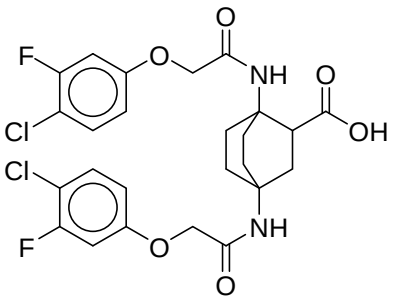

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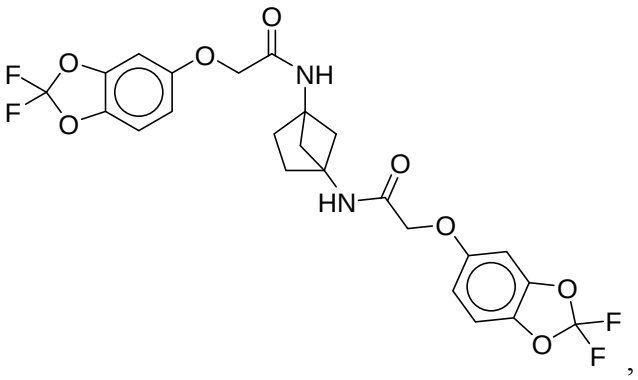

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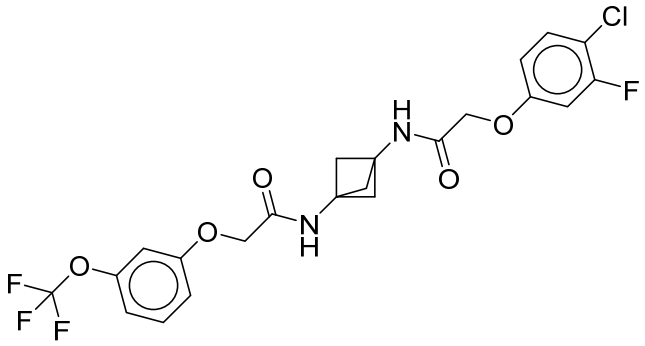

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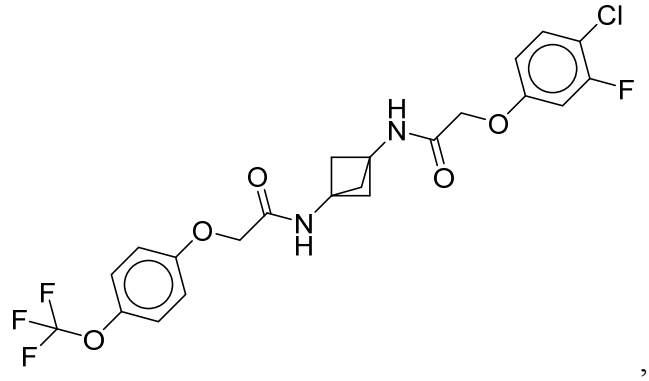

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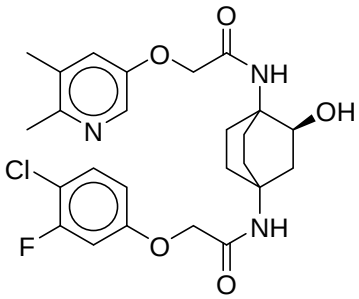

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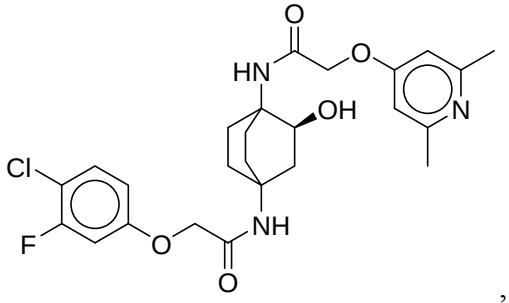

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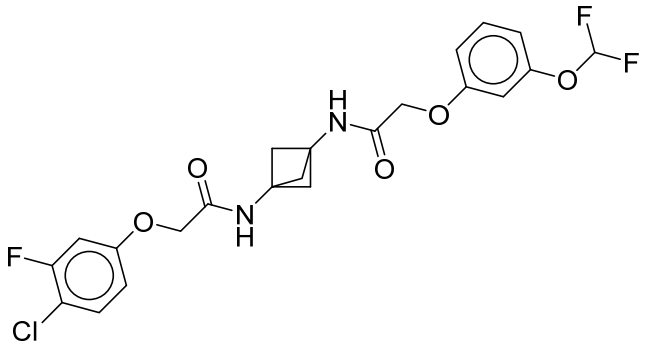

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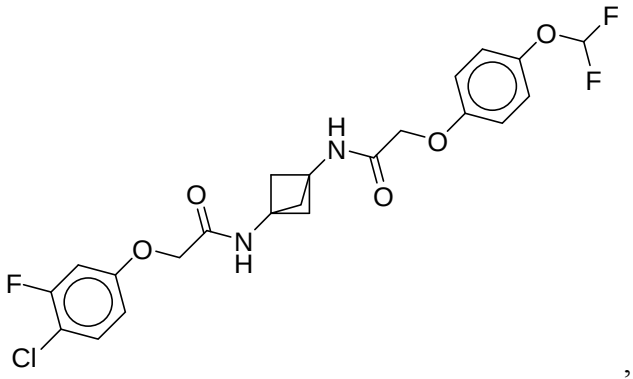

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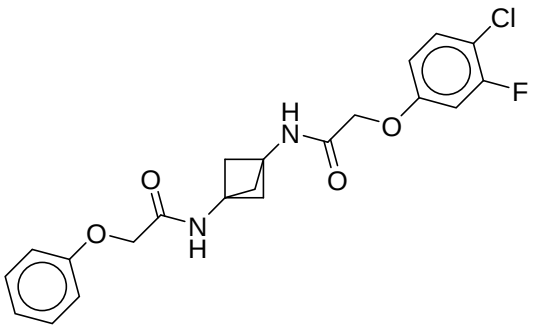

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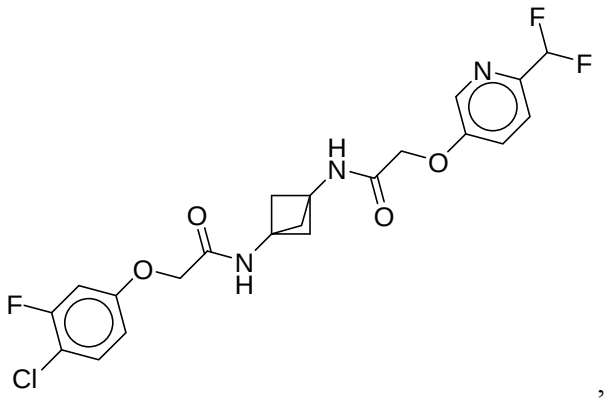

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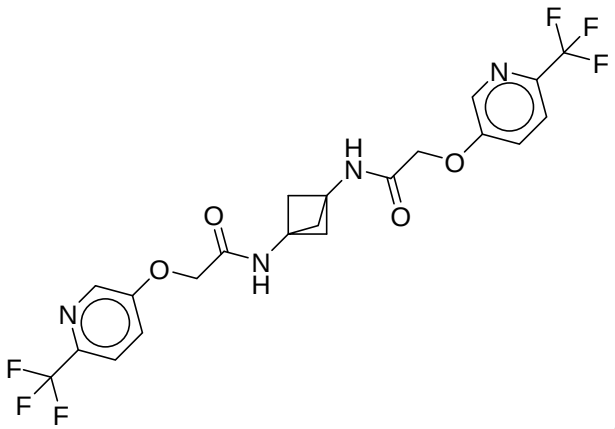

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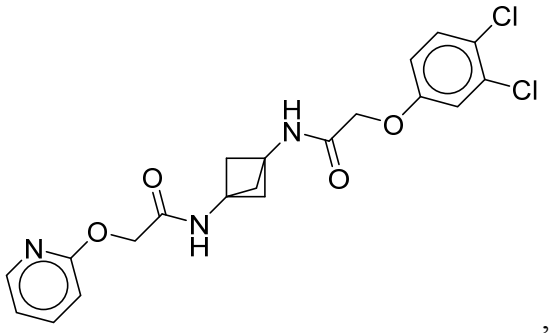

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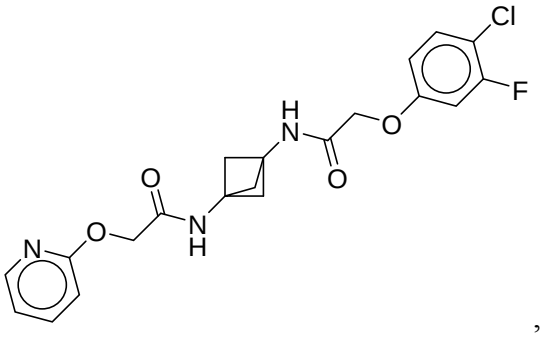

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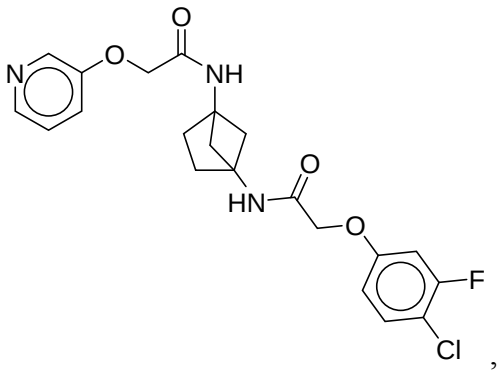

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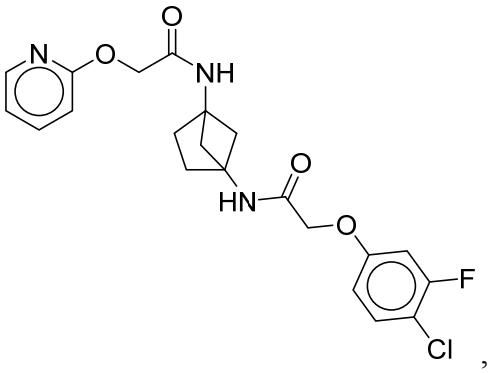

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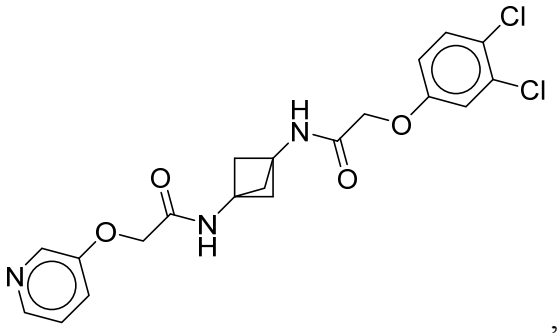

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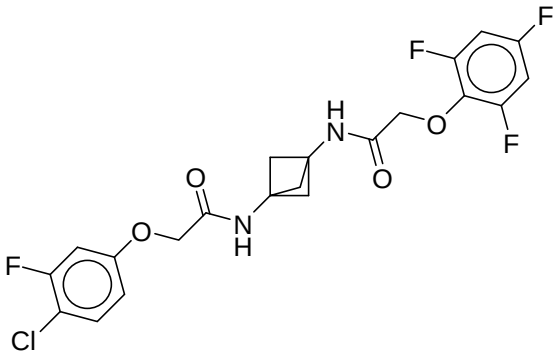

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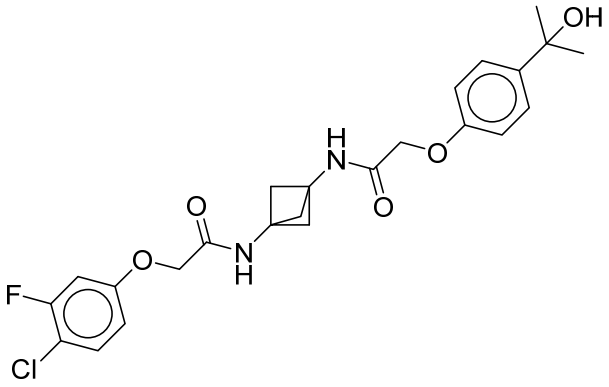

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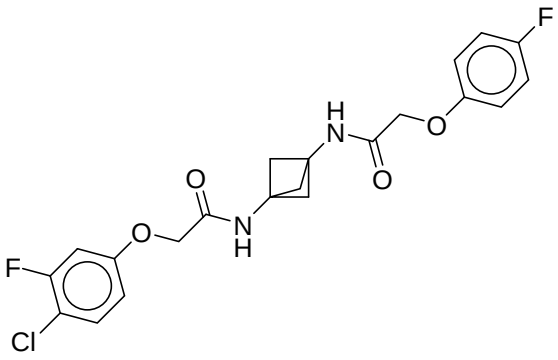

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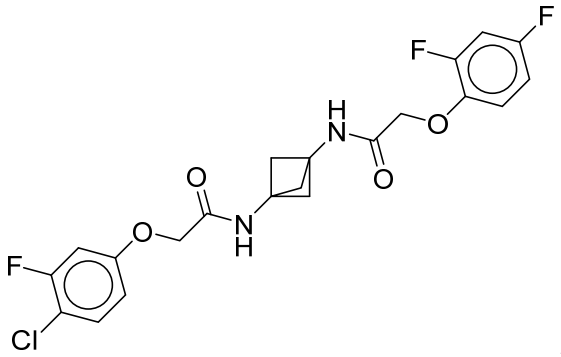

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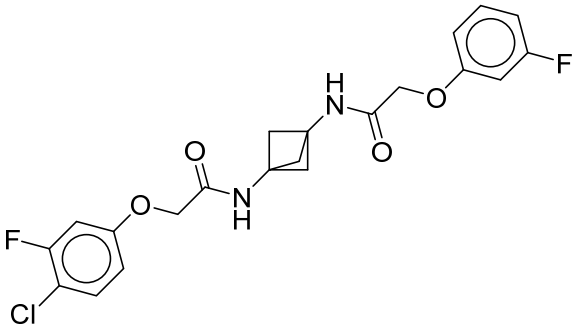

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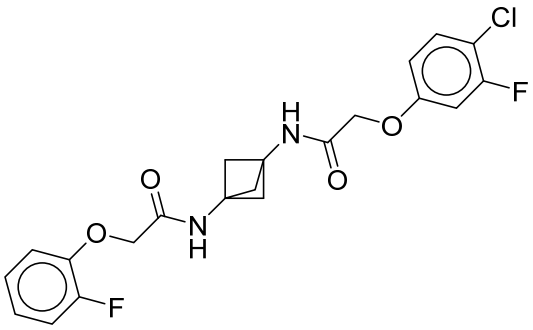

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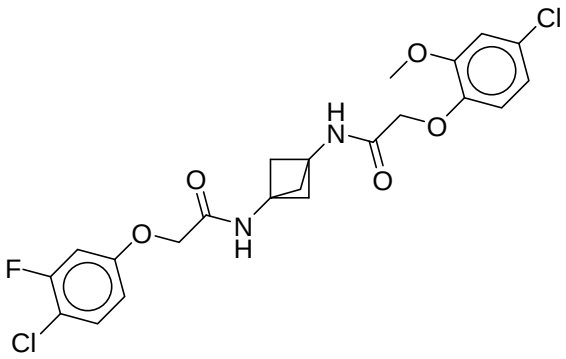

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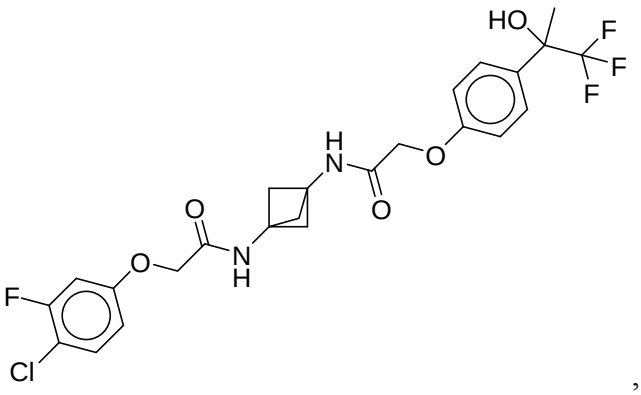

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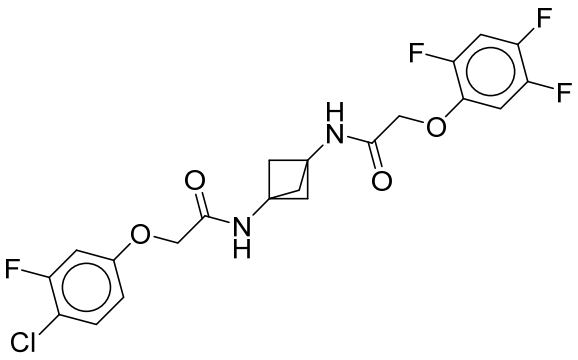

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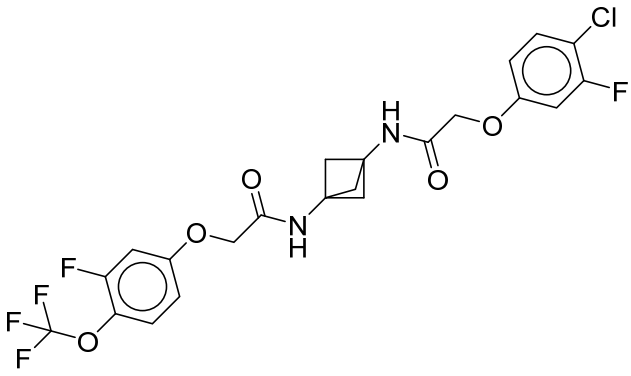

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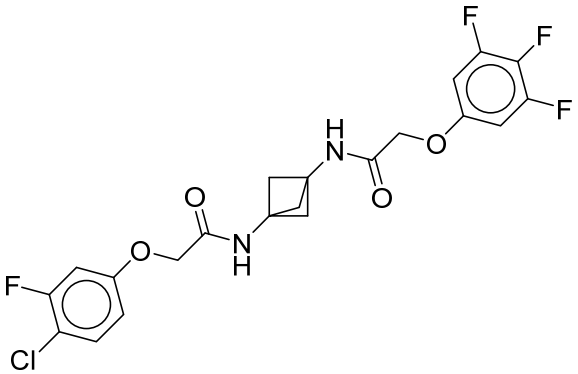

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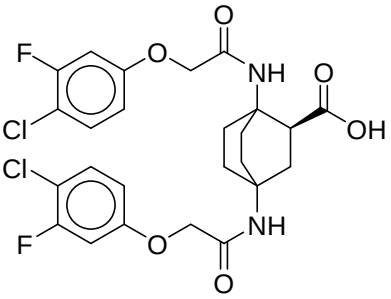

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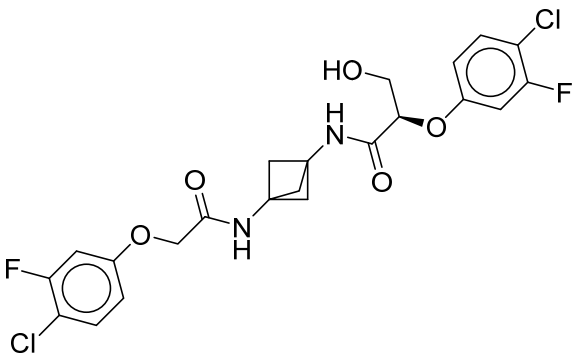

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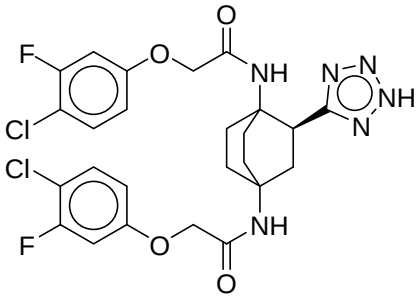

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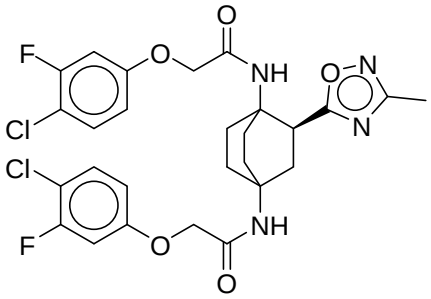

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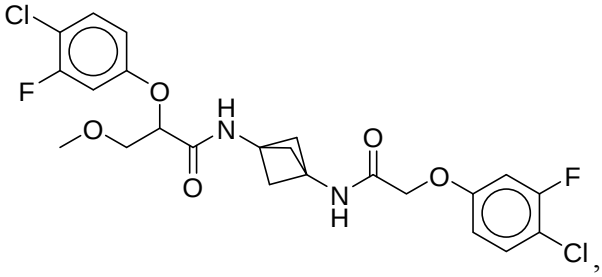

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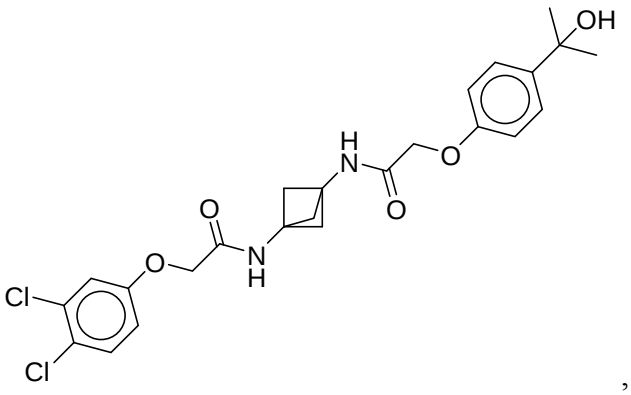

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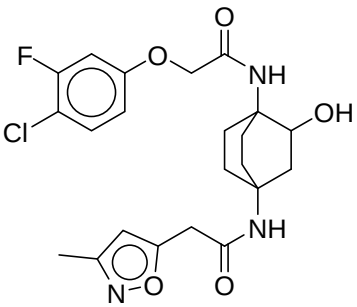

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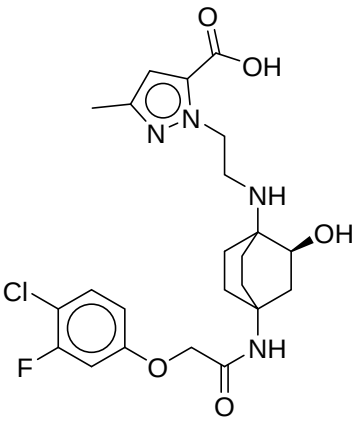

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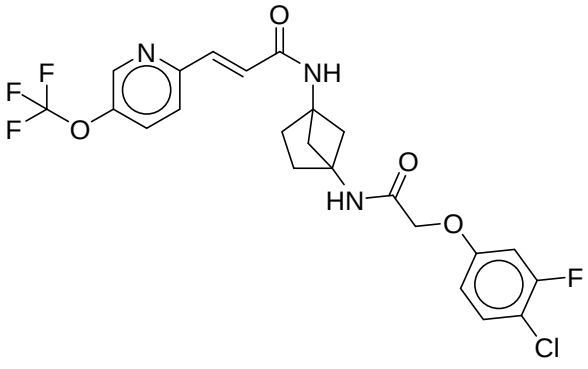

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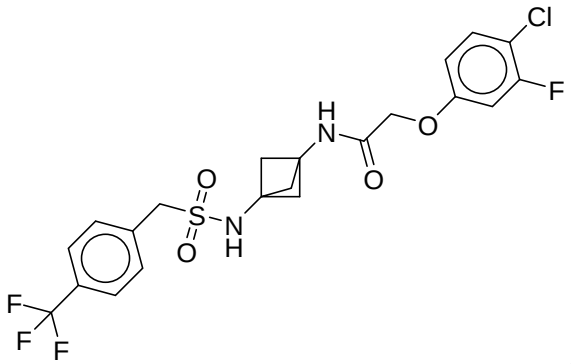

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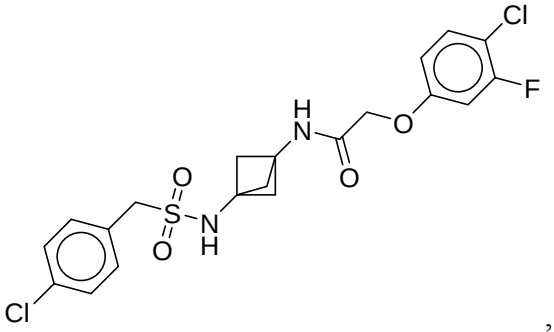

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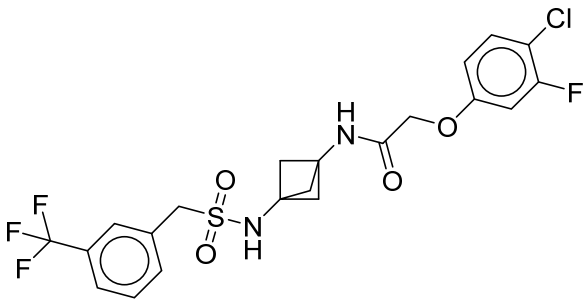

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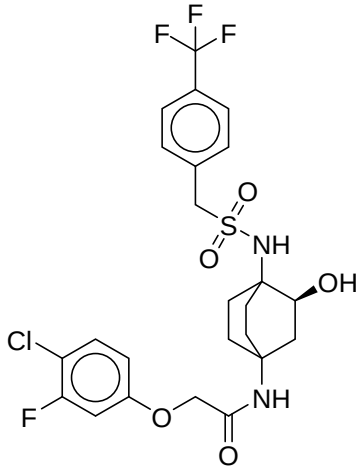

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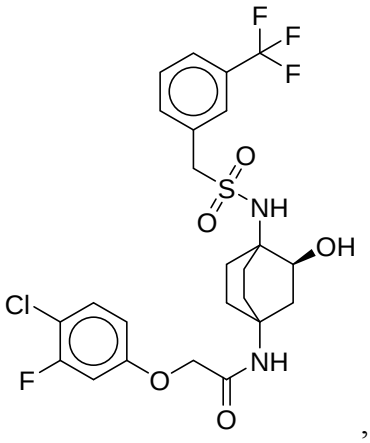

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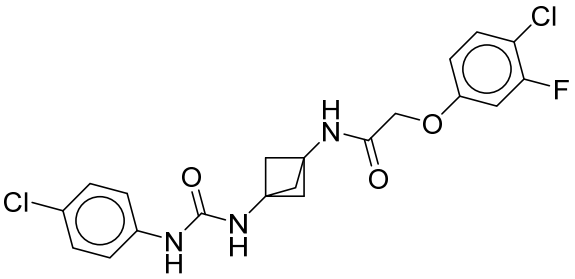

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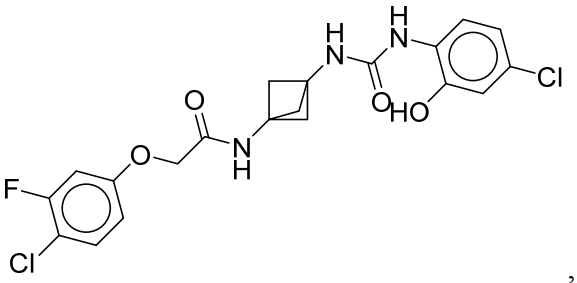

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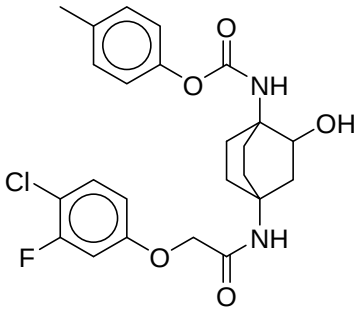

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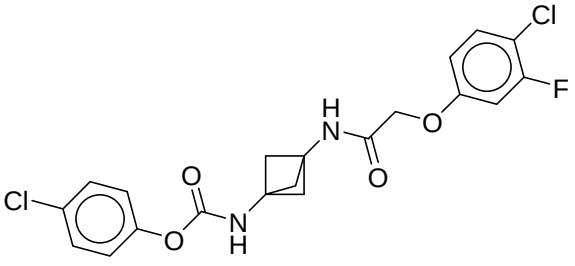

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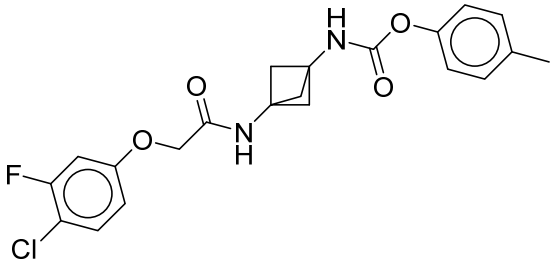

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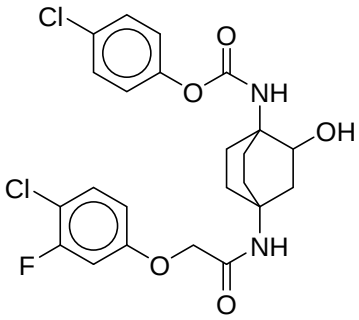

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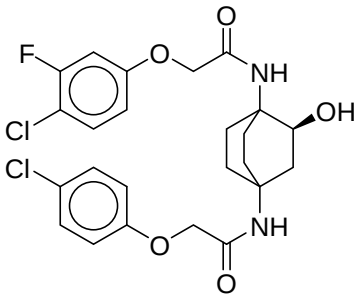

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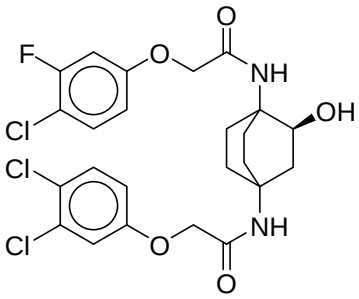

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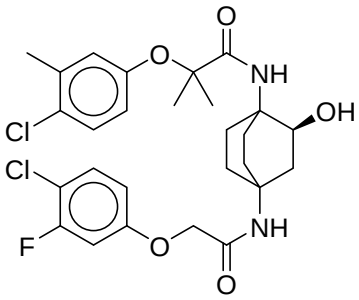

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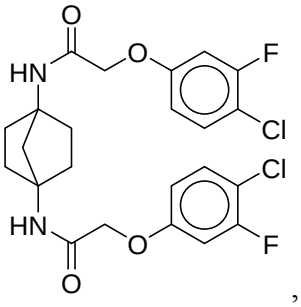
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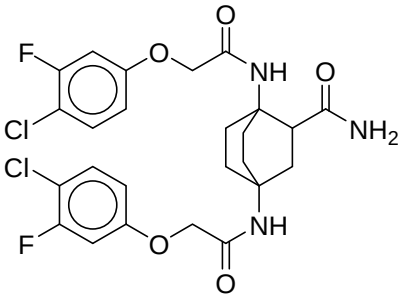
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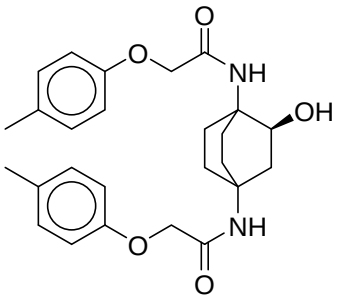
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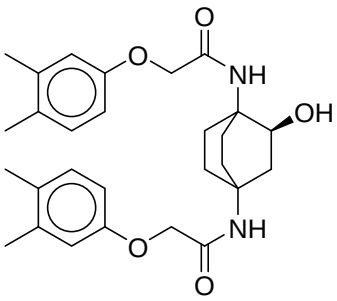
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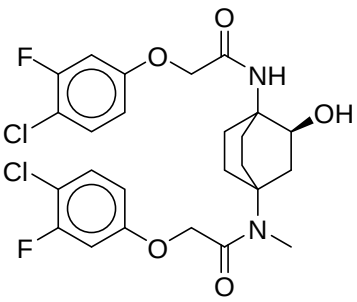
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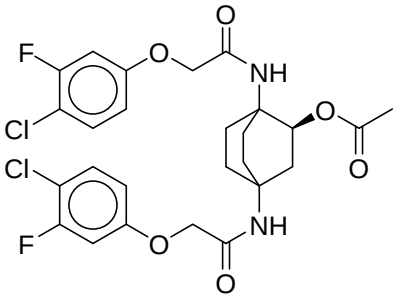
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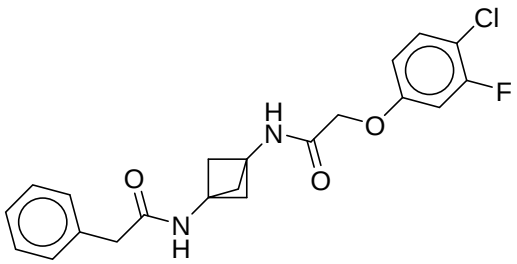
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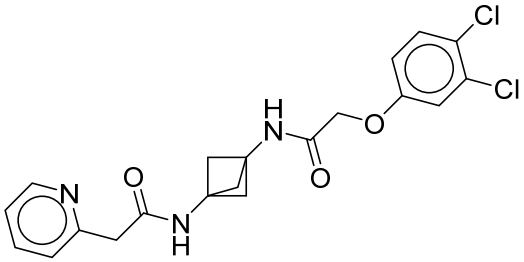
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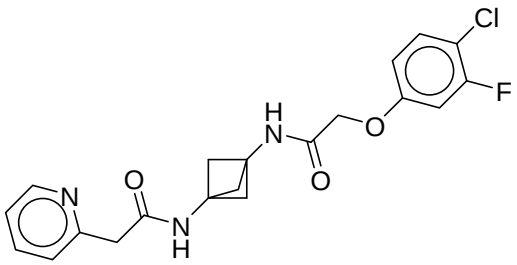
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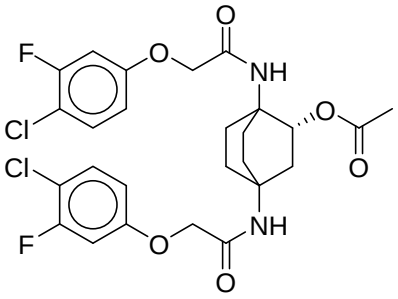
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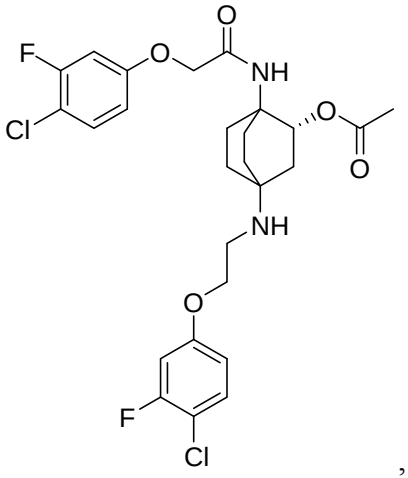

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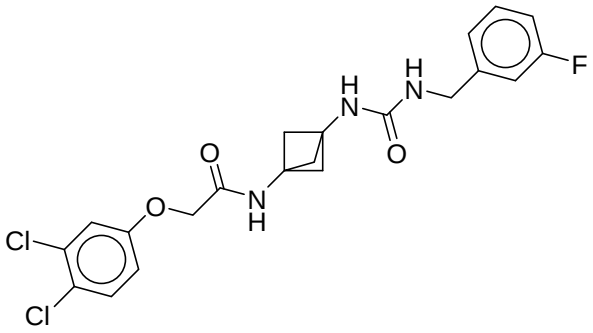

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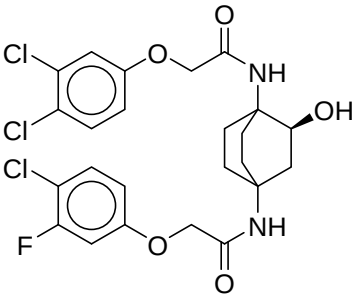

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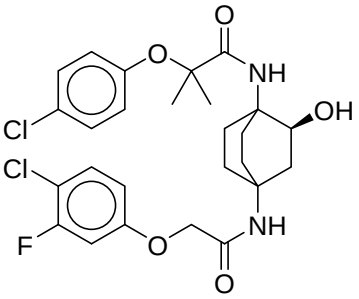

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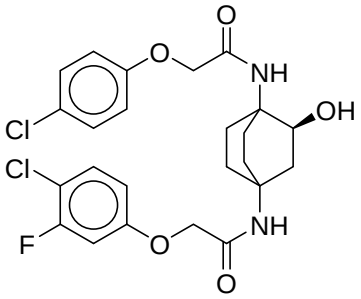
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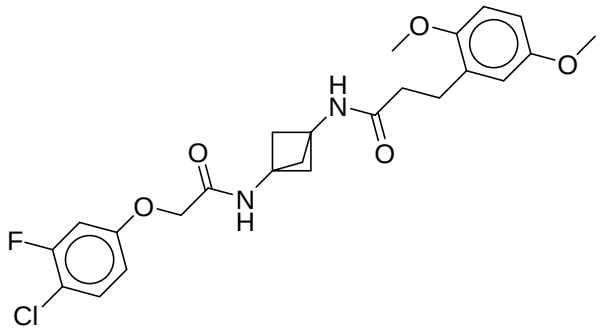
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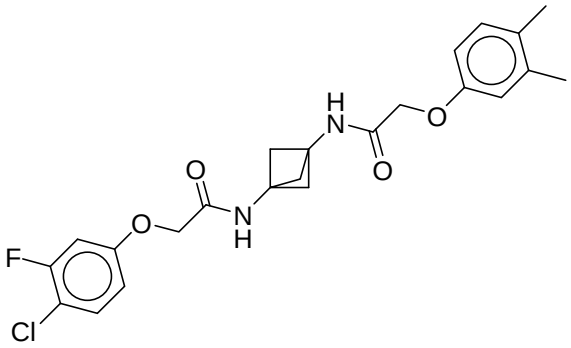
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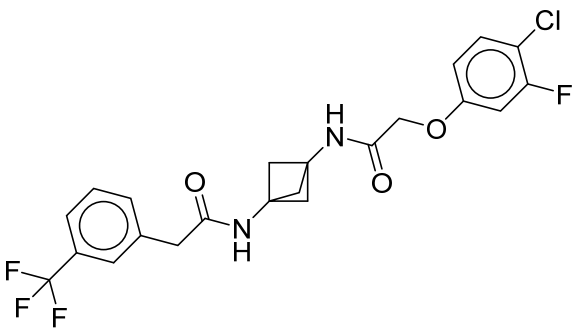
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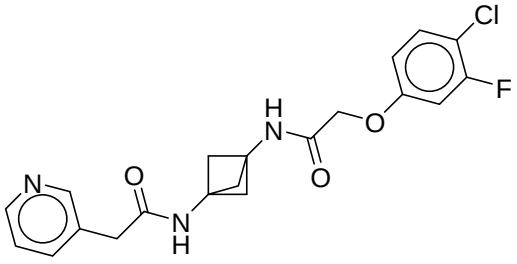
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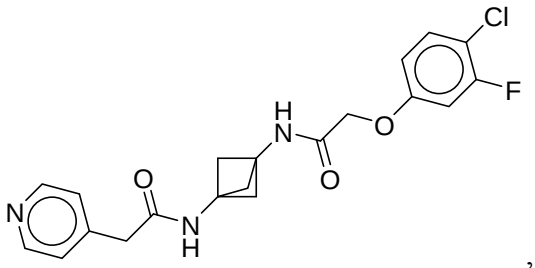

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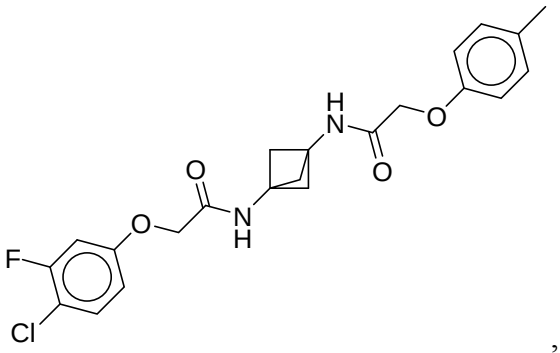

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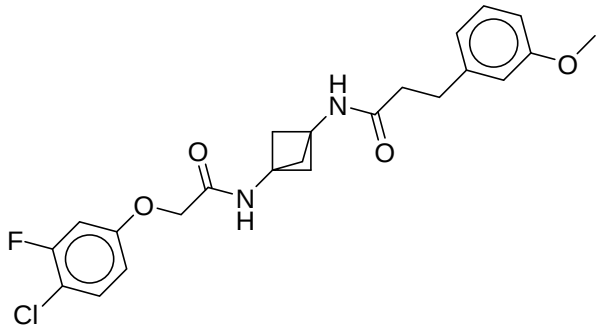

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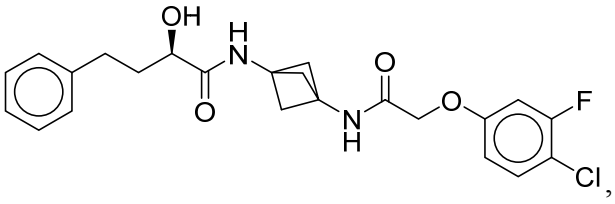

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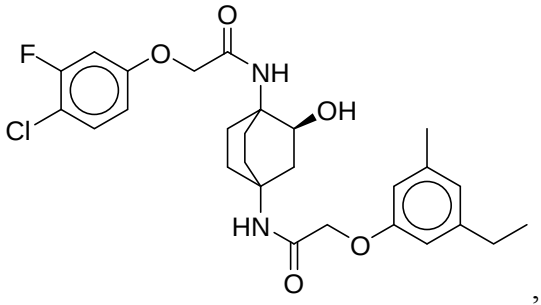

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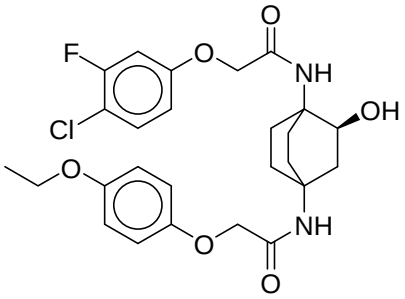
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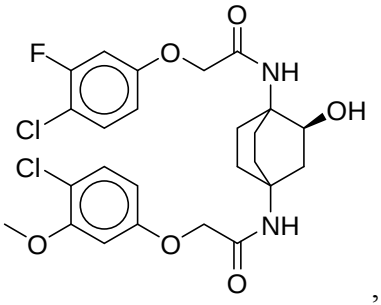
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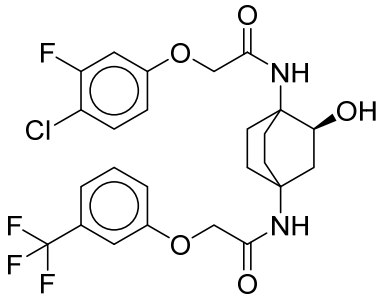
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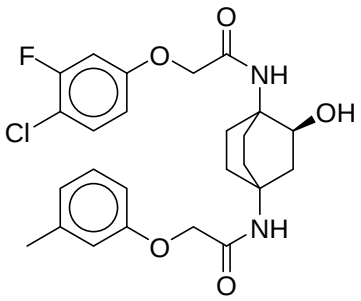
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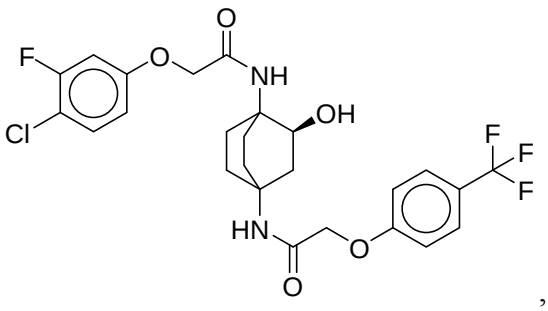
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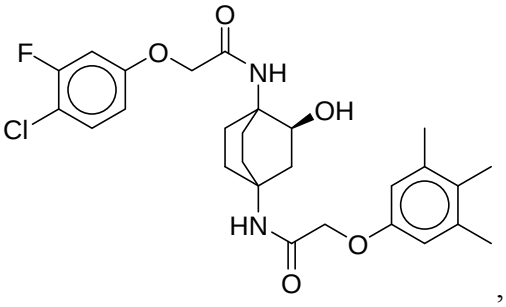
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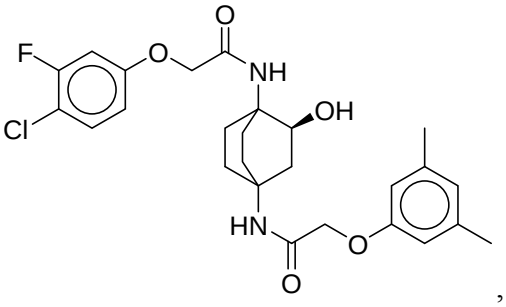
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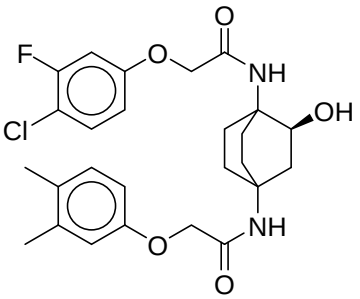
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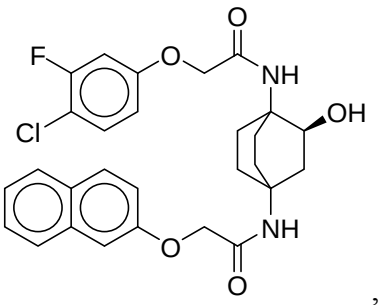
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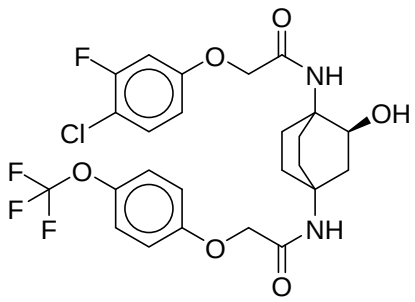
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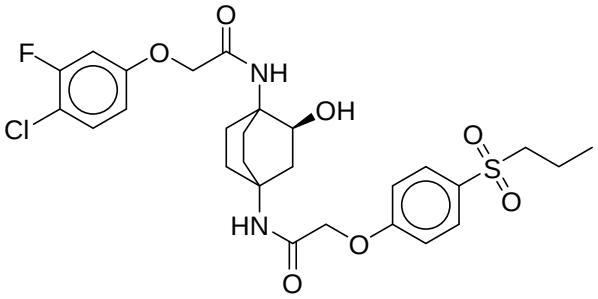
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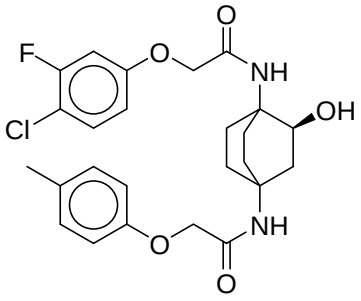
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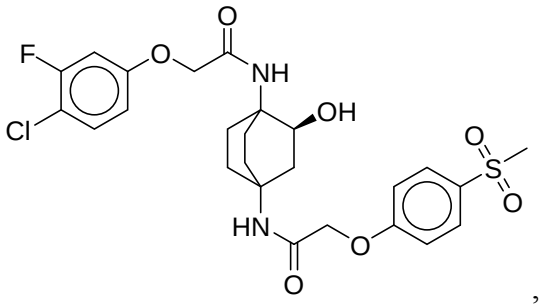
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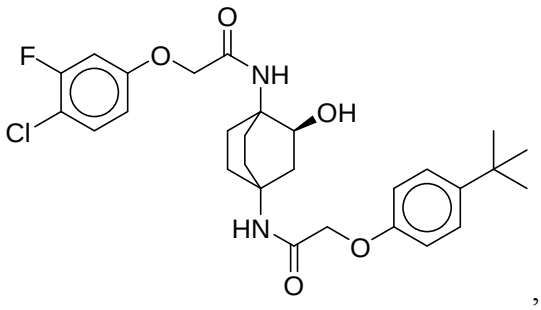
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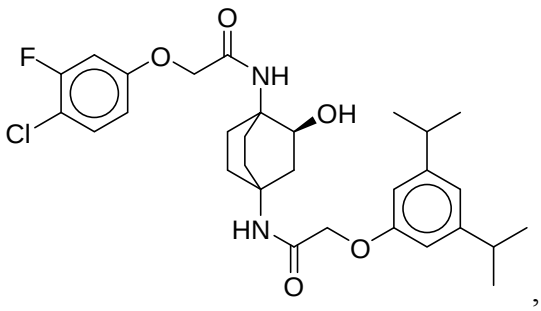
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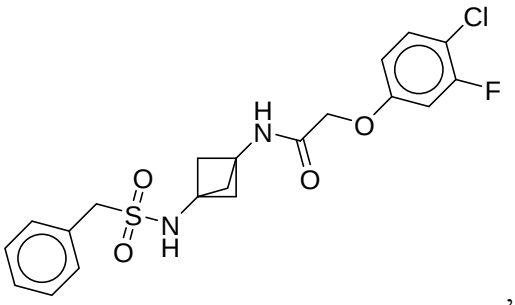

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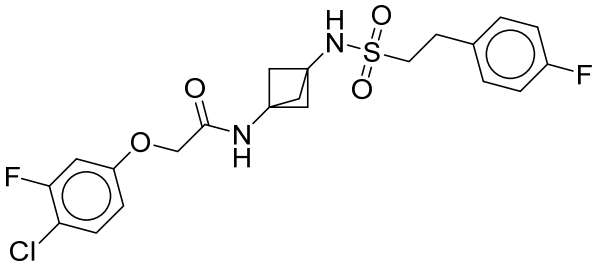

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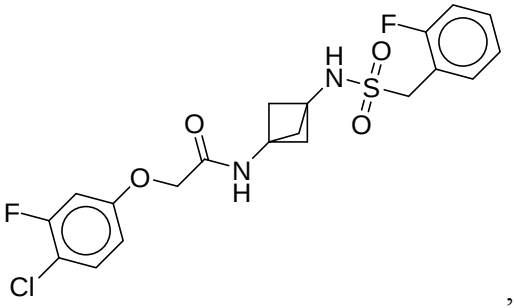

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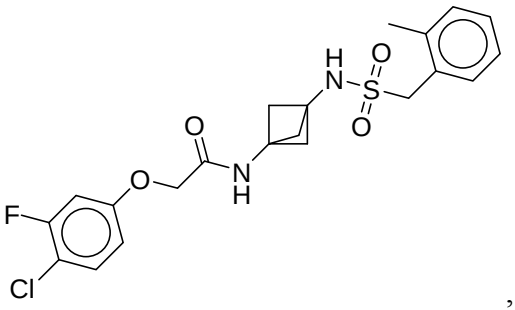

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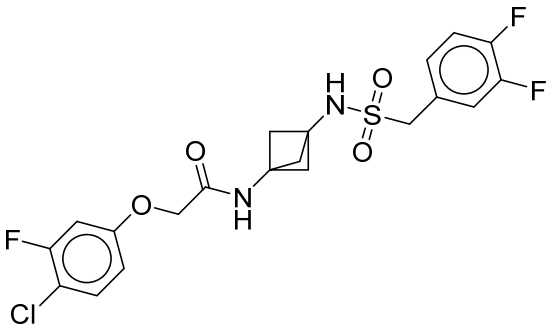

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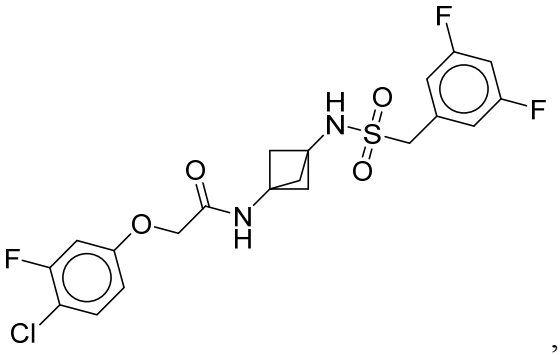

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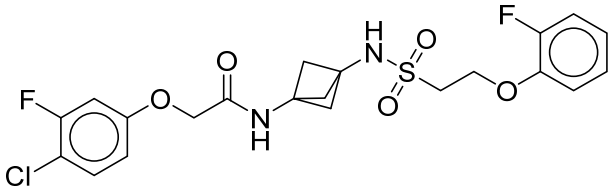

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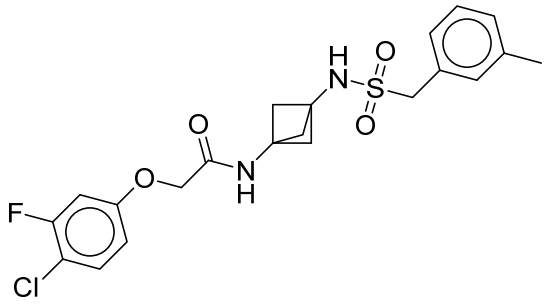

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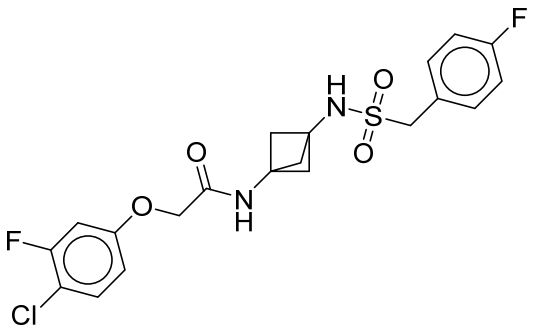

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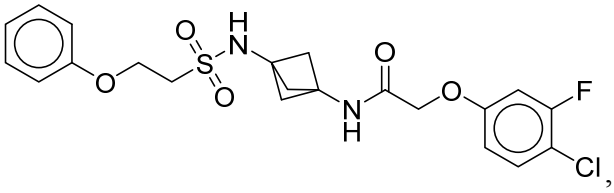

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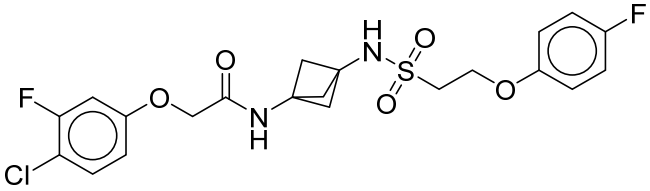

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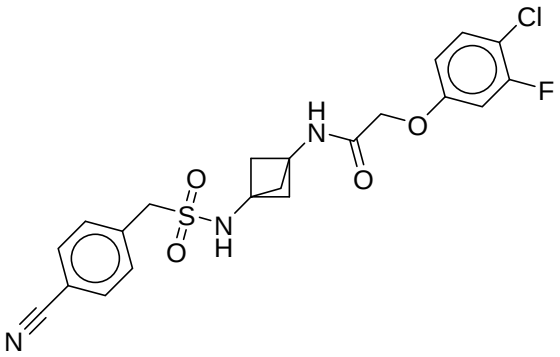

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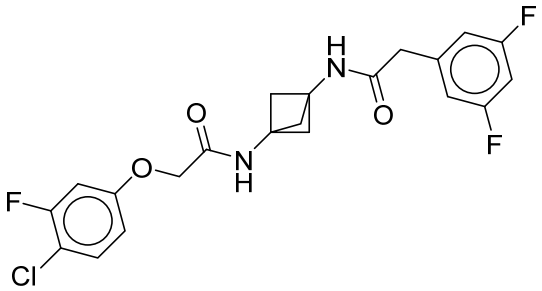

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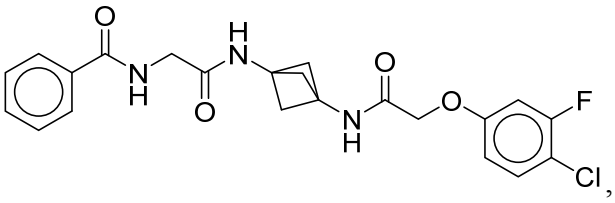

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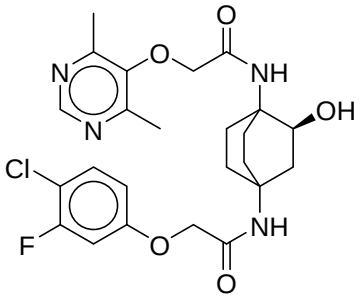

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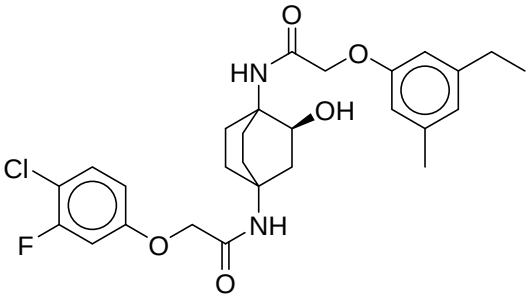

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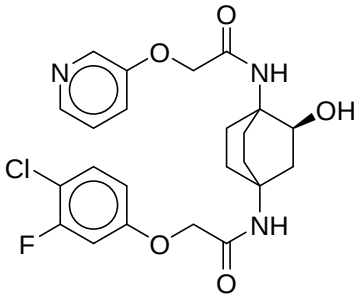
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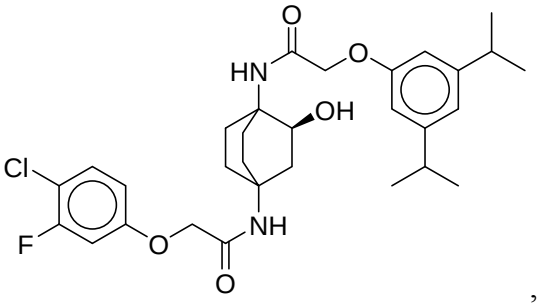
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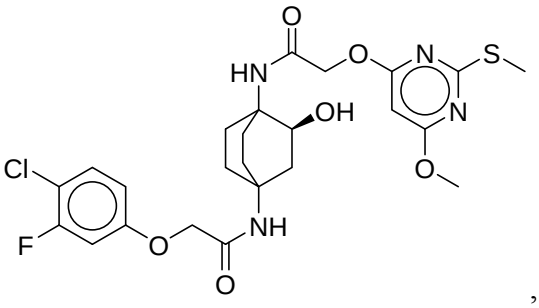
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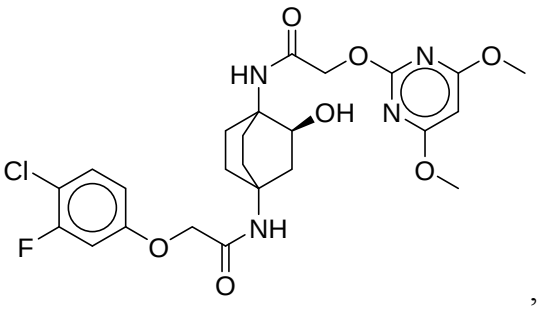
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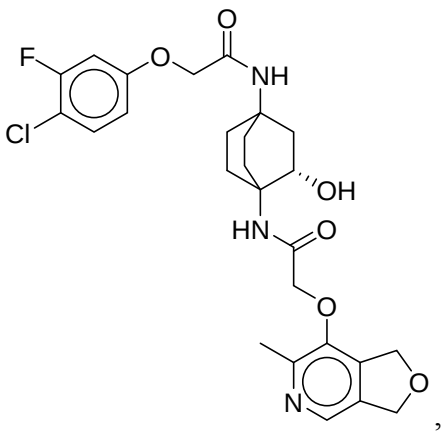
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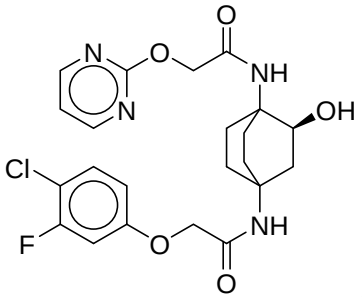

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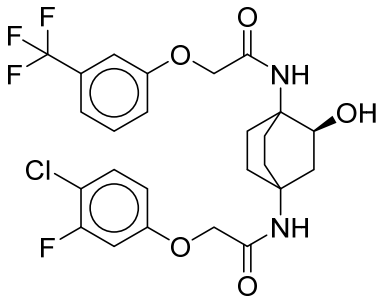

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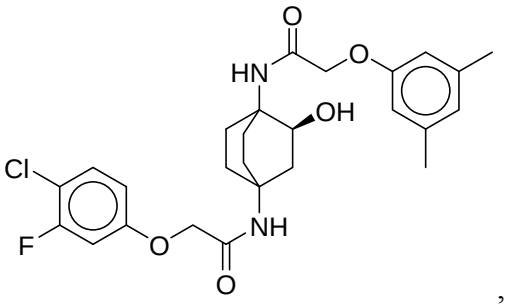

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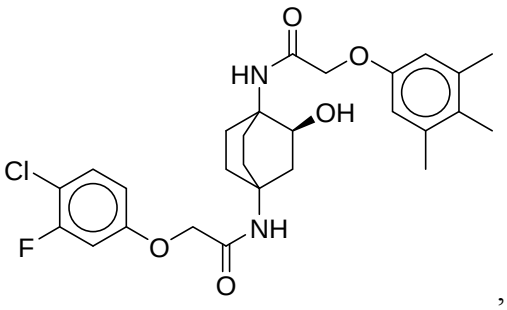

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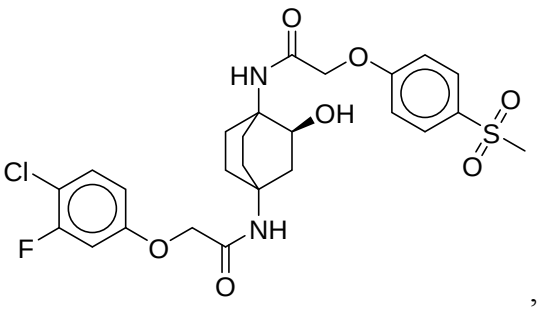

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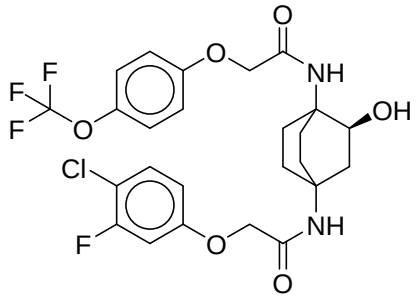

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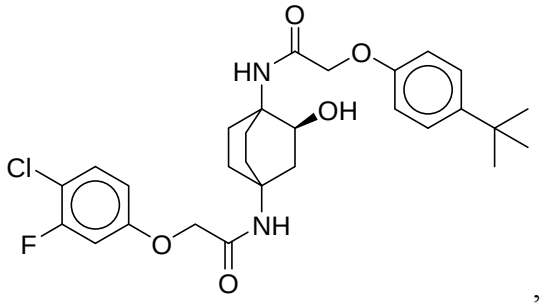

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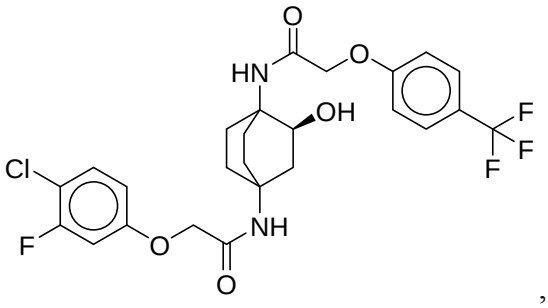

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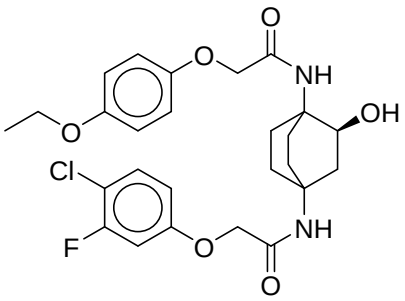

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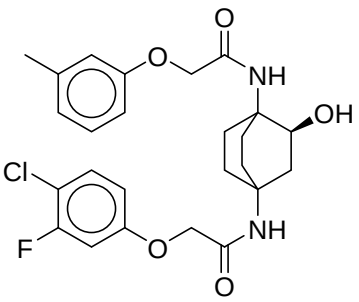

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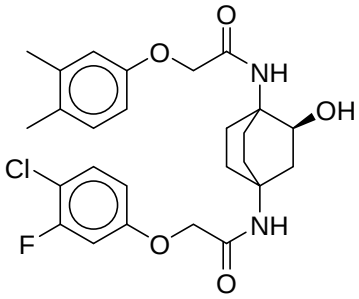
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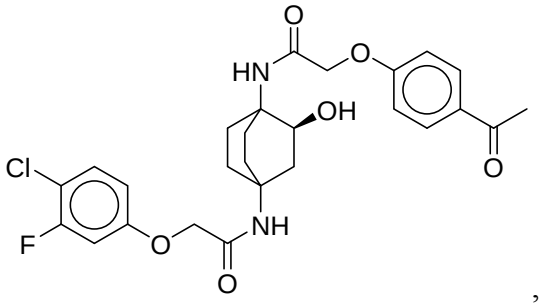
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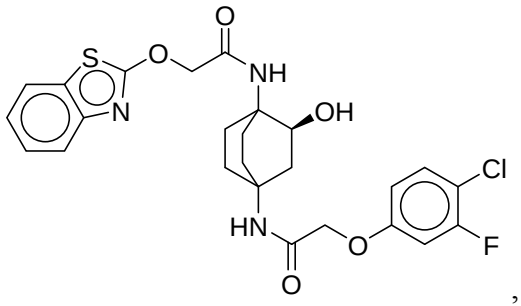
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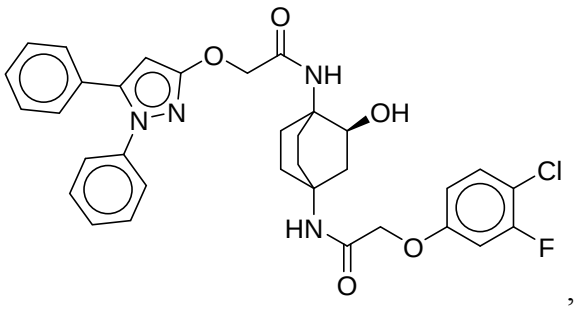
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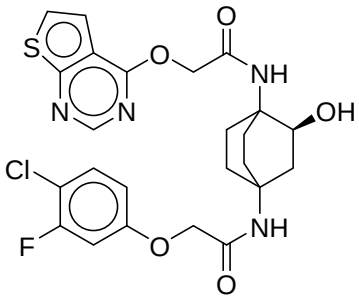
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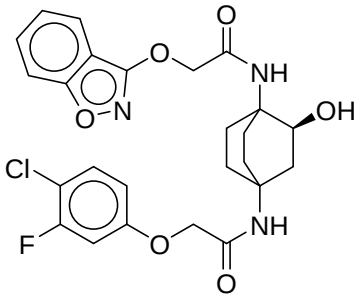

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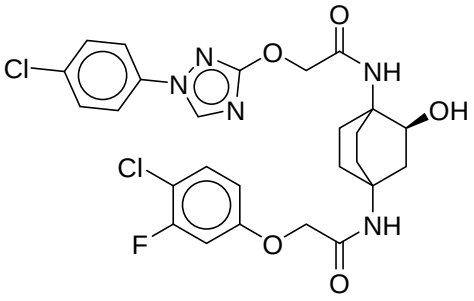

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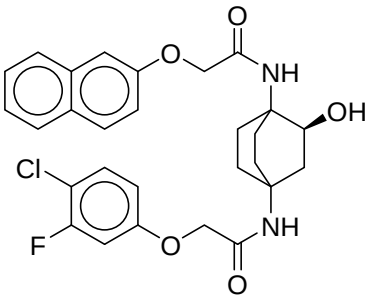

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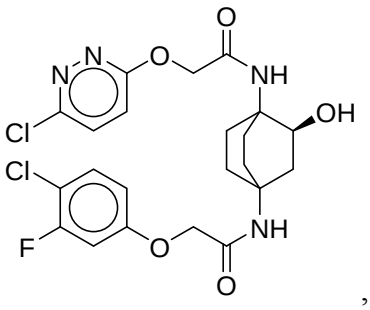

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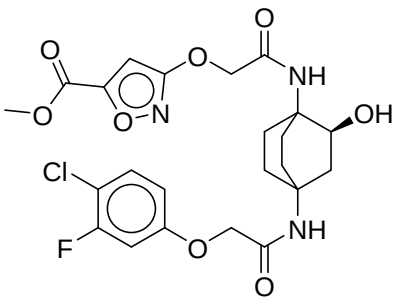

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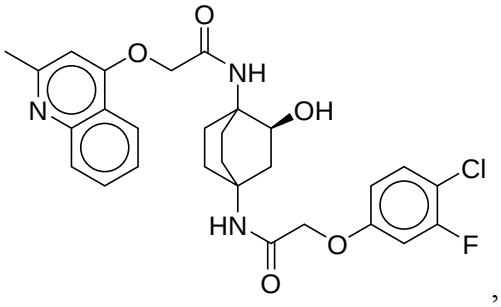

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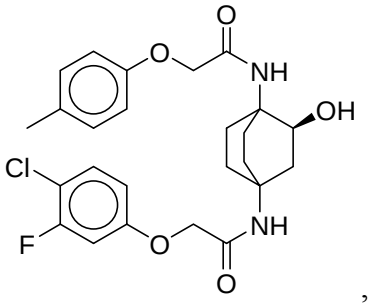

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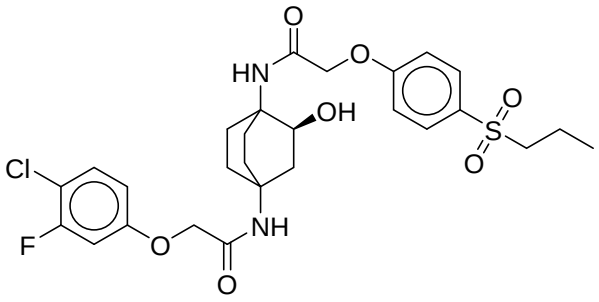

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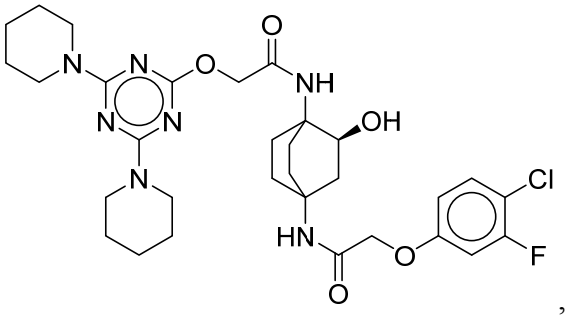

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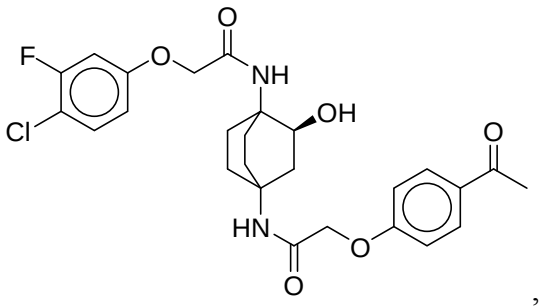

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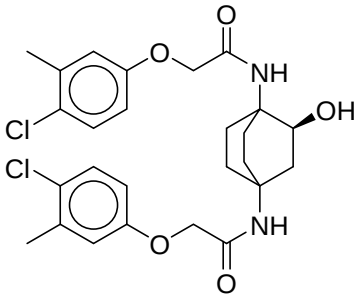
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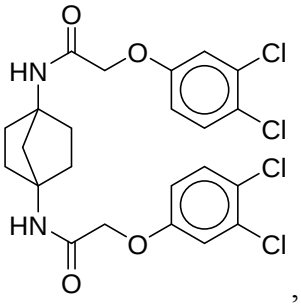
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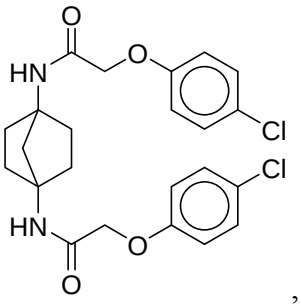
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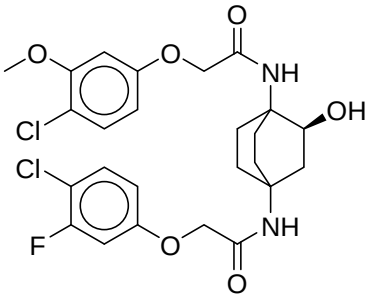
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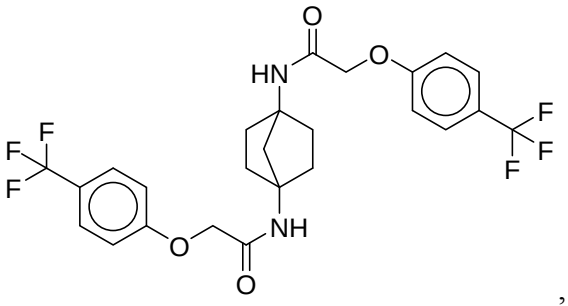
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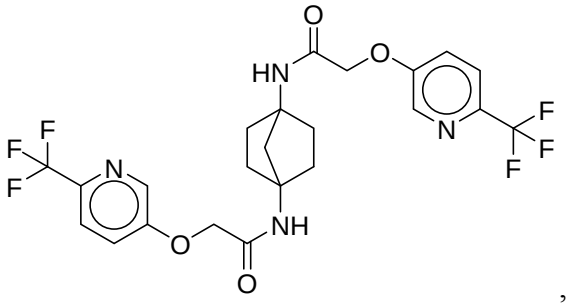

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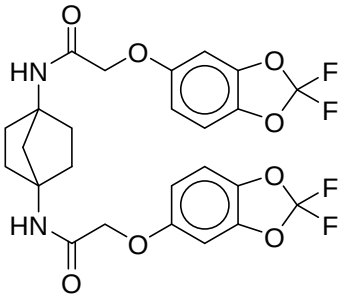

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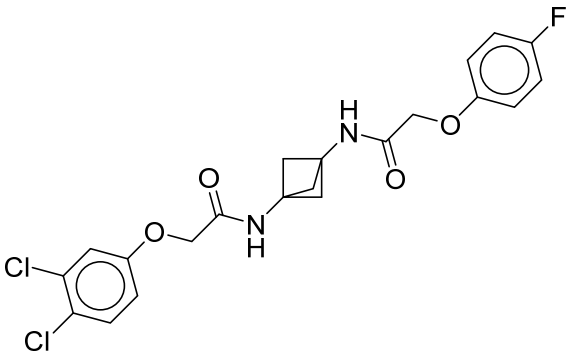

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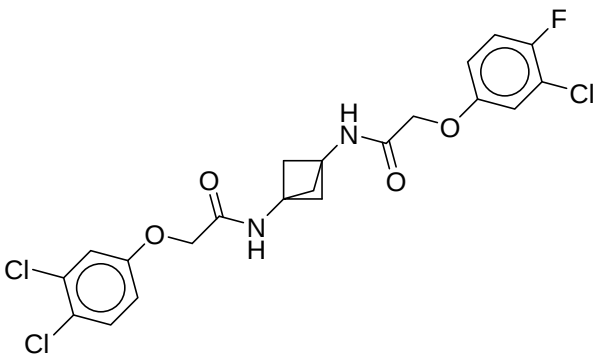

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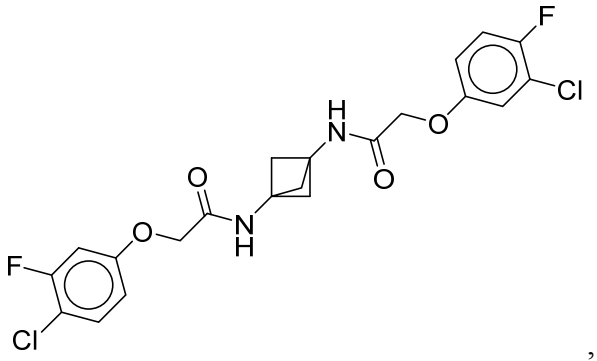

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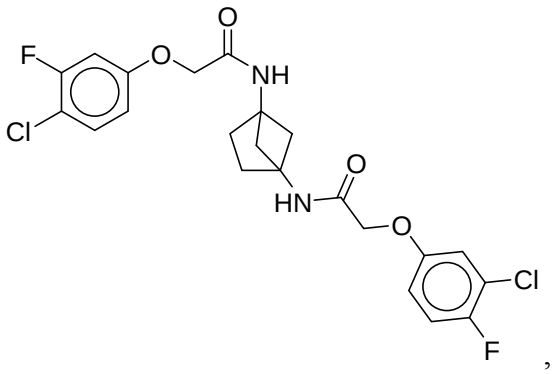

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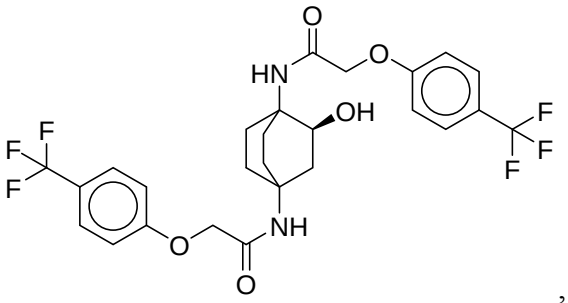

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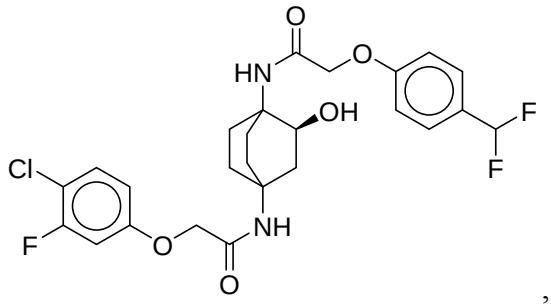

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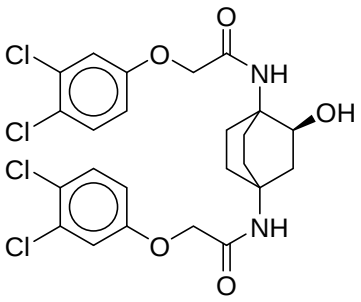

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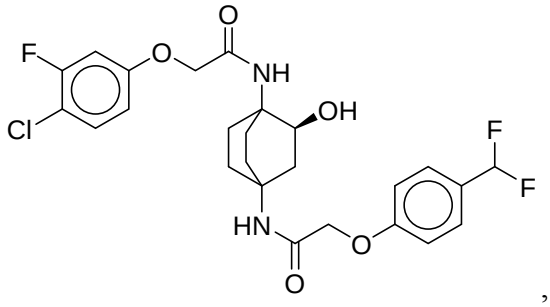

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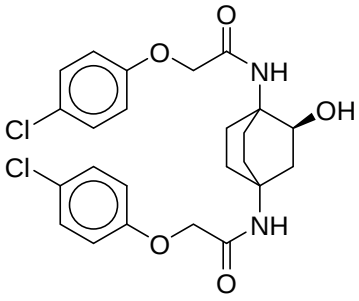

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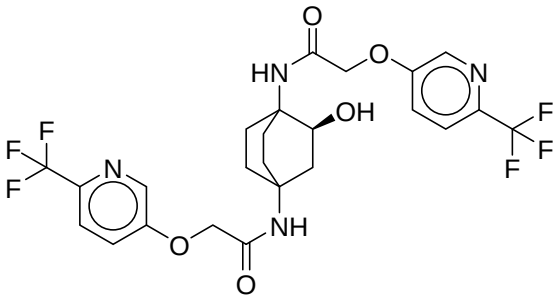

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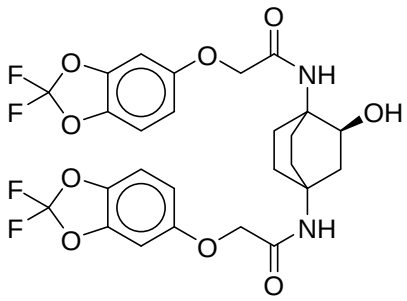

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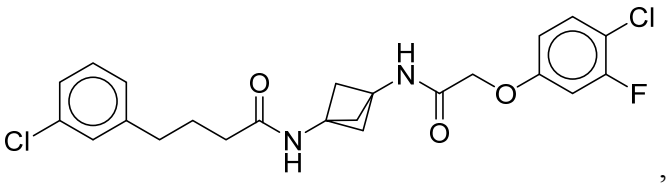

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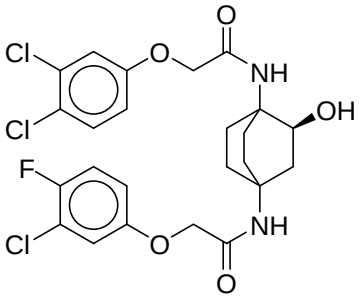
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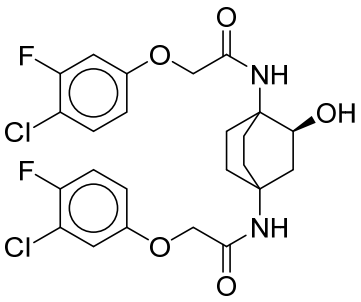
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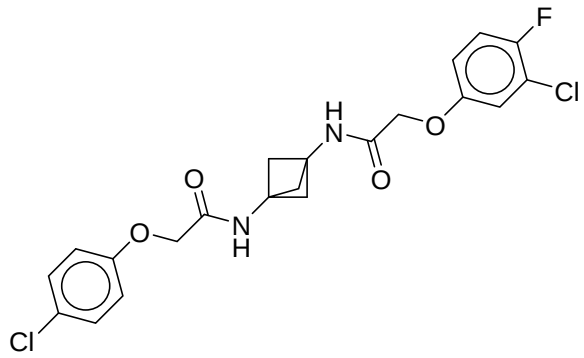
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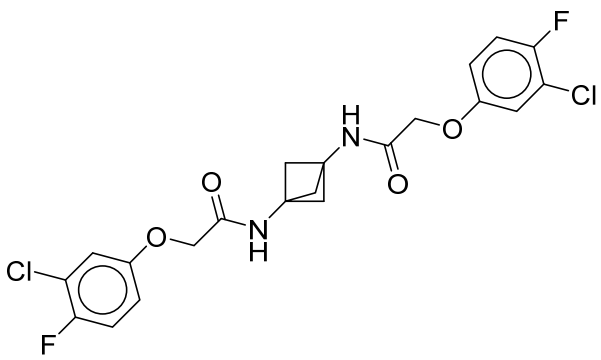
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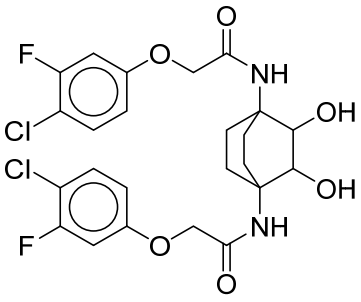
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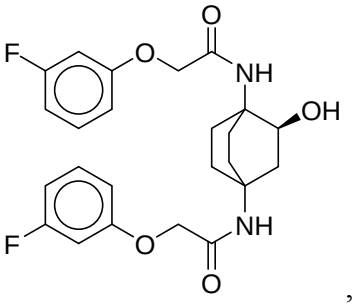

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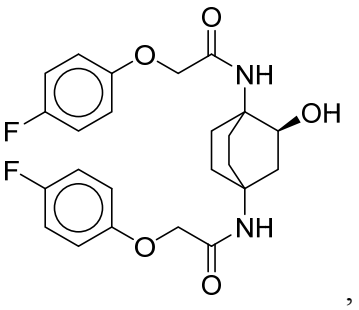

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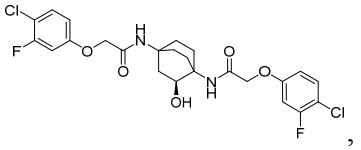
and a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

21. The compound of any one of claims 1-20, wherein the compound is



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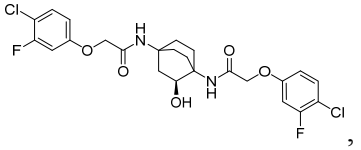
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

22. The compound of any one of claims 1-20, wherein the compound is



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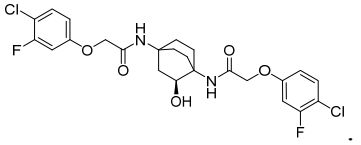
or a pharmaceutically acceptable salt thereof.

23. The compound of any one of claims 1-20, wherein the compound is



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24. A pharmaceutically acceptable composition comprising a compound of claims 1-23 and a pharmaceutically acceptable carrier.

25. Use of a composition comprising a compound of any one of claims 1-23 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in the manufacture of a medicament for treating a disease associated with impaired function of eIF2B or

a component of integrated stress response (ISR) pathway in a subject, wherein the disease is a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, or a metabolic disease.

26. The use of claim 25, wherein the neurodegenerative disease comprises a leukodystrophy, a leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome, a cognitive impairment, a glial cell dysfunction, a traumatic brain injury, or a toxin induced brain injury.

27. The use of any one of claims 25 or 26, wherein the neurodegenerative disease comprises vanishing white matter disease, childhood ataxia with CNS hypo myelination, Alzheimer's disease, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, Frontotemporal dementia, Gerstmann-Straussler-Scheinker disease, Huntington's disease, dementia, HIV-associated dementia, Lewy body dementia, Kuru, multiple sclerosis, Parkinson's disease, or a prion disease.

28. The use of any one of claims 25-27, wherein the neurodegenerative disease comprises vanishing white matter disease.

29. The use of claim 225, wherein the cancer comprises pancreatic cancer, breast cancer, multiple myeloma, or a cancer of the secretory cells.

30. The use of claim 25, wherein the inflammatory disease comprises postoperative cognitive dysfunction, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), myasthenia gravis, juvenile onset diabetes, diabetes mellitus type 1, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves' ophthalmopathy, inflammatory bowel disease, Addison's disease, vitiligo, asthma, acne vulgaris, celiac disease, chronic prostatitis, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis, or atopic dermatitis.

31. The use of claim 25, wherein the musculoskeletal disease comprises muscular dystrophy, Duchenne muscular dystrophy, Becker muscular dystrophy, distal muscular

dystrophy, congenital muscular dystrophy, Emery-Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic muscular dystrophy, multiple sclerosis, amyotropic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, neuralgia, fibromyalgia, Machado-Joseph disease, cramp fasciculation syndrome, Freidrich's ataxia, a muscle wasting disorder, muscle atrophy, sarcopenia, cachexia, an inclusion body myopathy, motor neuron disease, or paralysis.

32. The use of claim 25, wherein the metabolic disease comprises non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, Type I diabetes, Type II diabetes, gestational diabetes, phenylketonuria, proliferative retinopathy, or Kearns-Sayre disease.

33. The use of any one of claims 25-32, wherein a compound of any one of claims 1-23 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or a composition thereof, is to be administered to a subject in combination with a second agent selected from a group consisting of an agent for treating cancer, an agent for treating a neurodegenerative disease, an agent for treating a leukodystrophy, an agent for treating an inflammatory disease, an agent for treating a musculoskeletal disease, an agent for treating a metabolic disease, or an agent for treating a disease or disorder associated with impaired function of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway.

34. The use of claim 25, wherein the disease may be caused by a mutation to a gene or protein sequence related to a member of the eIF2 pathway.

35. A composition for use in treating a disease associated with impaired function of eIF2B or a component of ISR pathway in a subject, wherein the disease is a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, or a metabolic disease, and wherein the composition comprises a compound of any one of claims 1-23 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.