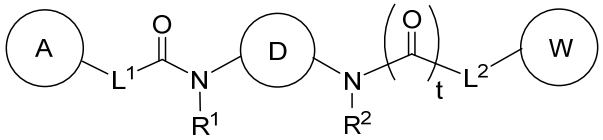
eIF2B4) are also highly homologous to one another and form a "regulatory sub-complex" that provides binding sites for eIF2B's substrate eIF2 (Dev, K. et al, *Mol Cell Biol* (2010) 30:5218-5233). The exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF)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

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;

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 $R^G$;

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 $R^H$;

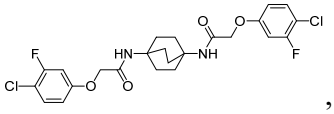
each $R^H$ is independently $C_1$-$C_6$ alkyl or halo-$C_1$-$C_6$ alkyl;

m is 1, 3, or 5;

t is 0 or 1; and

with the proviso that not more than one $R^X$ is $G^2$ and not more than two $R^Y$ are $G^1$.

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

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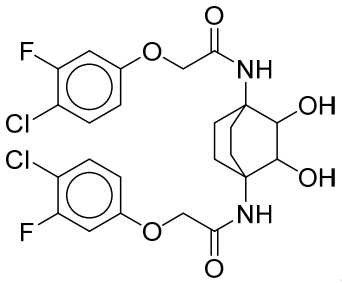

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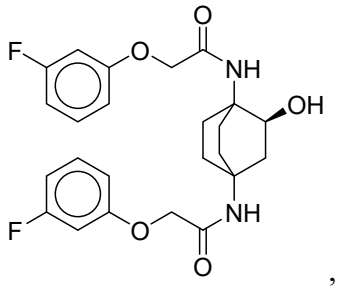

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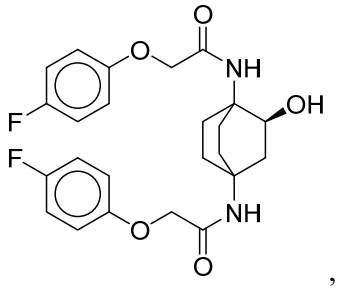

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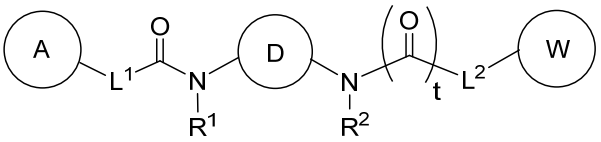
and a pharmaceutically acceptable salt thereof.

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




Formula (I)

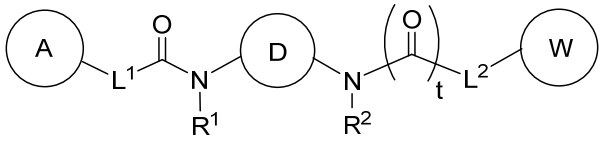
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,

wherein D is a bridged monocyclic cycloalkyl, bridged monocyclic heterocyclyl, or cubanyl,

## CLAIMS

We claim:

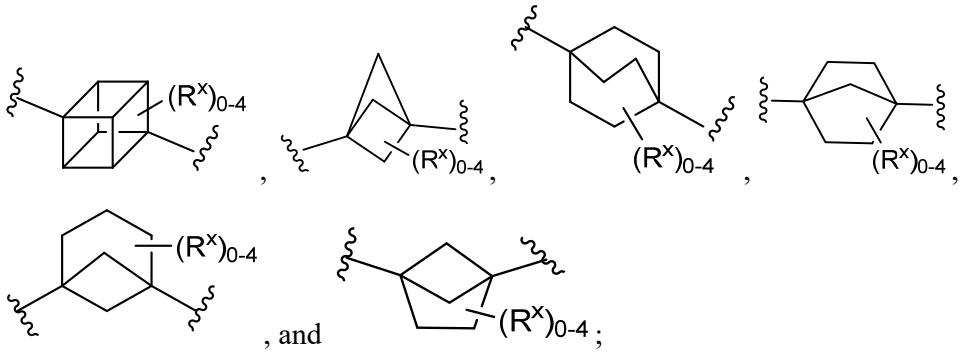
1. A compound of Formula (I):




Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of:




, and ;

$L^1$ 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;

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 $R^G$;

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;

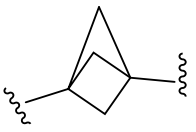
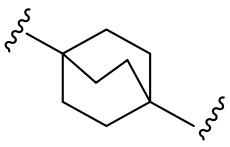
t is 0 or 1; and

with the proviso that not more than one $R^X$ is $G^2$ and not more than two $R^Y$ are $G^1$.

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, $–OCH_3$, $–NH_2$, $–N(CH_3)_2$, $–NHC(O)CH_3$, $–OC(O)CH_3$, $–C(O)NH_2$, $–OS(O)_2CH_3$, $–S(O)_2CH_3$, $–S(O)_2CH_2CH_3$, –C(O)OH, $–OC(O)R^D$, $–C(O)CH_3$, $–SCH_3$, oxadiazolyl, and tetrazolyl.

4. The compound of claim 1, wherein D is substituted with 0 $R^X$.

5. The compound of claim 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.

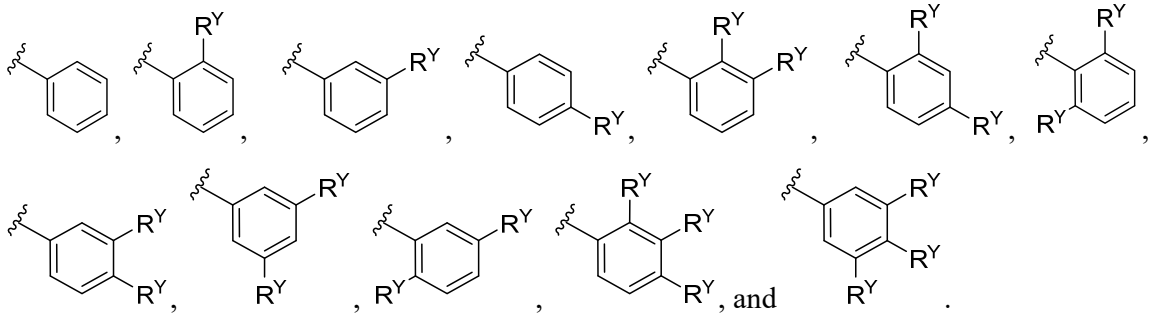
8. The compound of any one of claims 1-7, wherein $R^1$ and $R^2$ are each independently hydrogen, *–$CH_3$, *–$CH_2CH_2OH$, or *–$CH_2CH_2OSi(CH_3)_2C(CH_3)_3$, and "*–" indicates the attachment point to the nitrogen atom.

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.

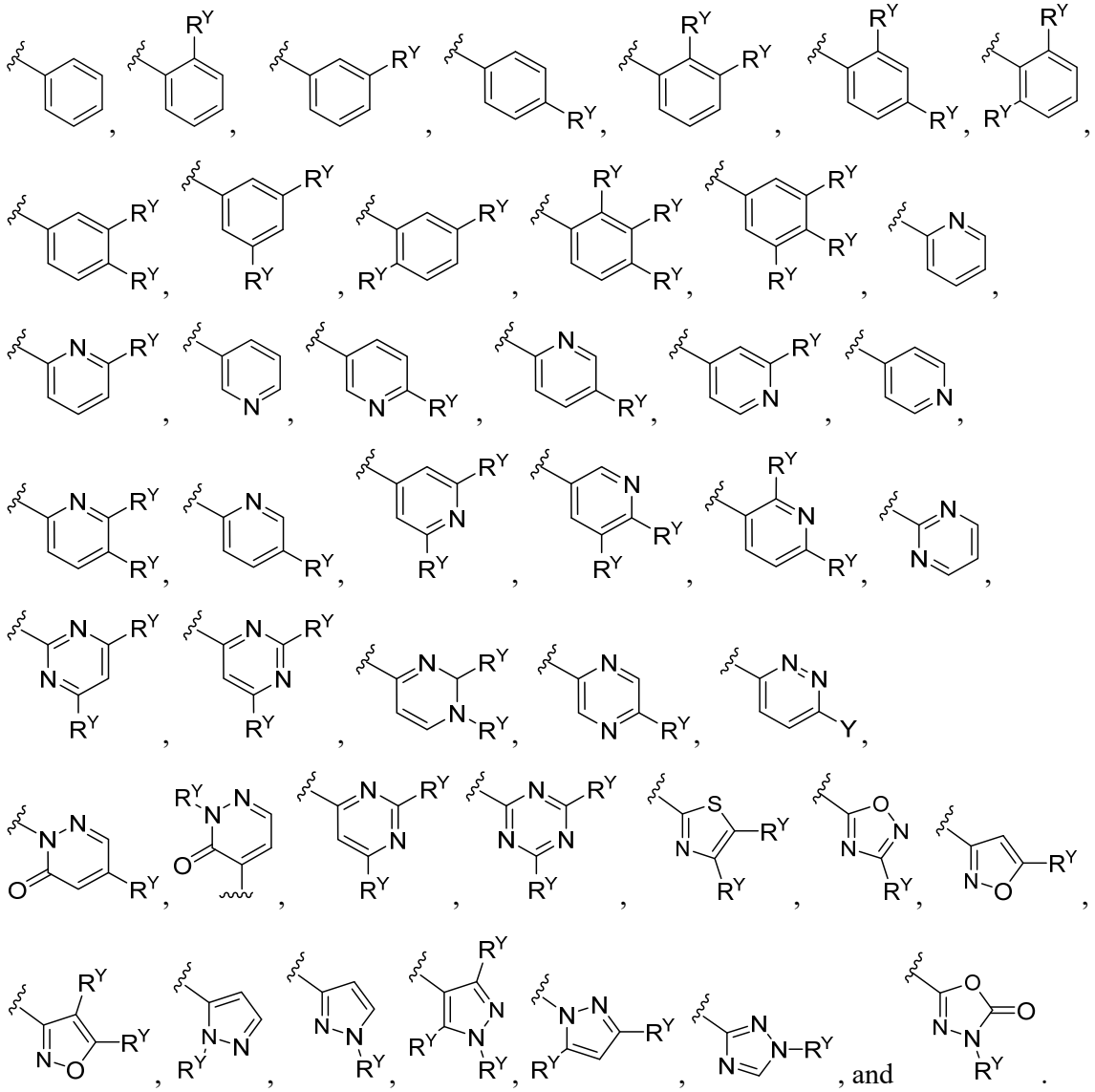
10. The compound of any one of claims 1-9, wherein $R^1$ and $R^2$ are each hydrogen.

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, O–$CHF_2$ 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 $R^X$.

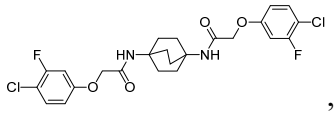
15. The compound of claim 14, wherein the 2 $R^Y$ together with the atoms to which they are attached form a pyrazolyl, pyrrolyl, isoxazolyl, thiophenyl, furanyl, or dioxolanyl ring, each of which is optionally substituted with 1-5 $R^X$.

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 selected from the group consisting of: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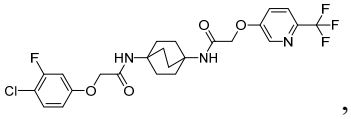
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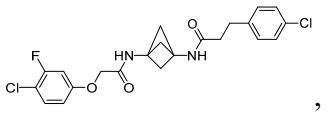
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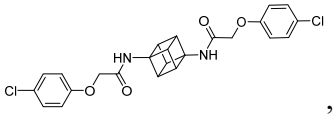
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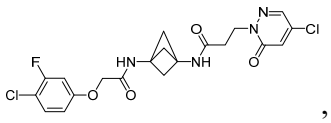
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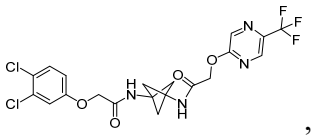
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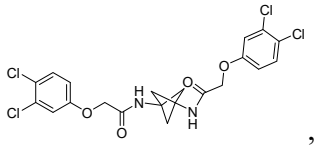
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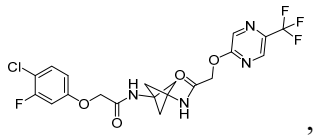
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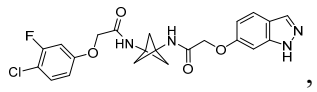
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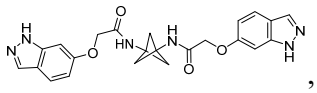
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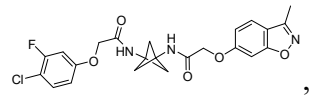
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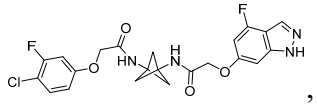
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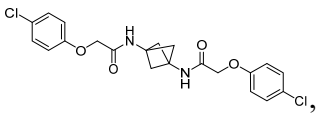
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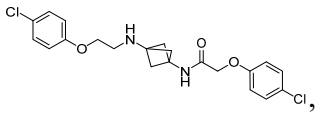
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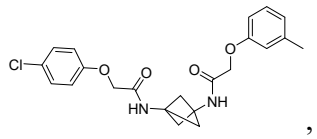
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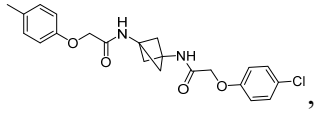
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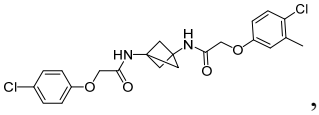
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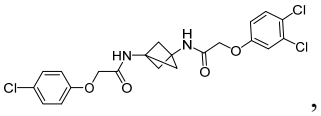
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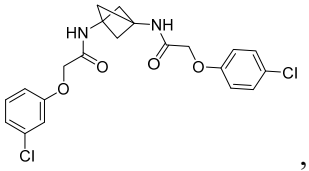
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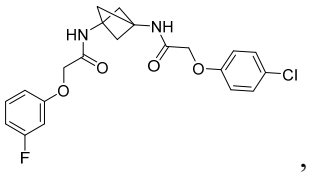
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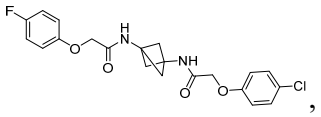
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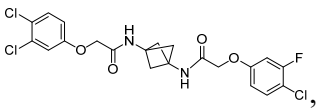
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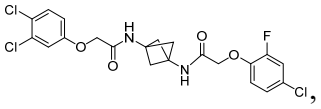
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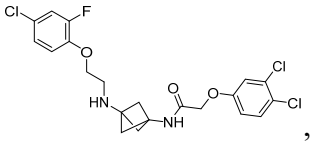
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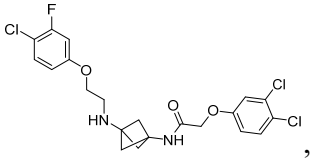
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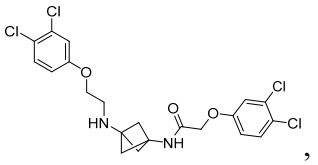
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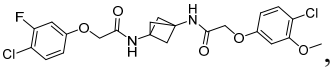
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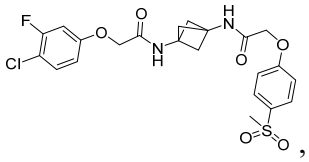
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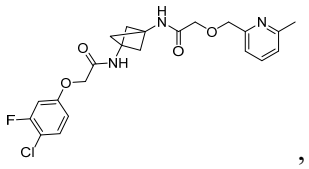
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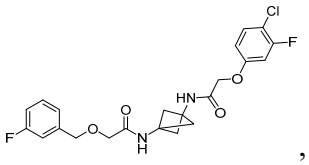
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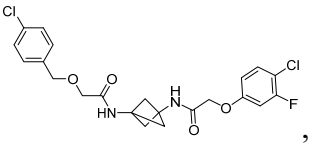
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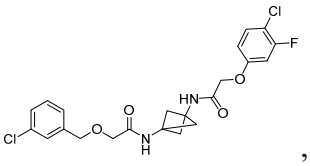
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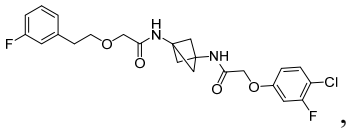
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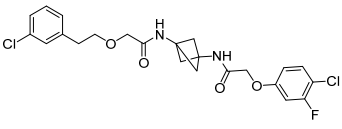
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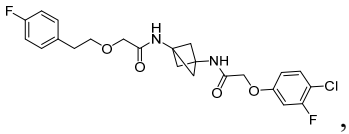
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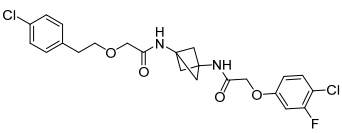
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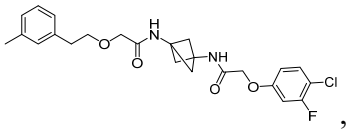
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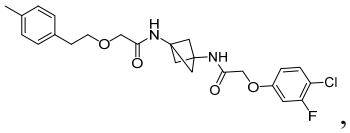
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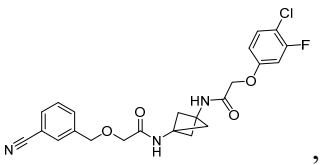
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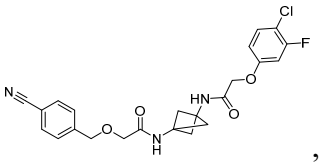
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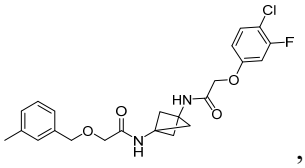
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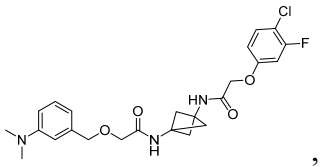
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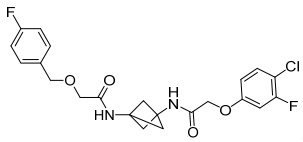
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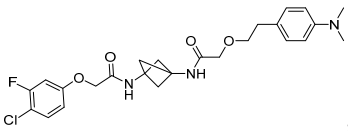
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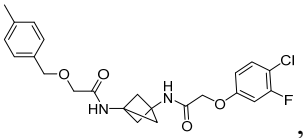
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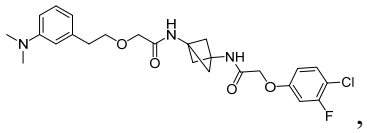
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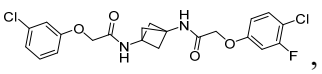
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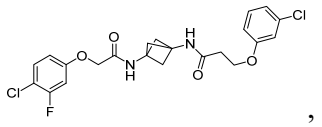
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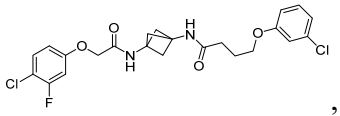
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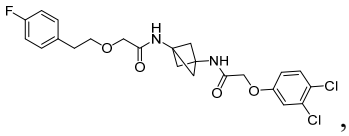
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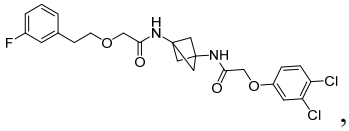
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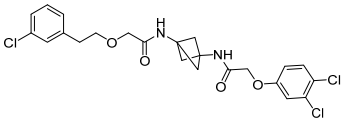
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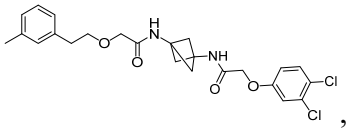
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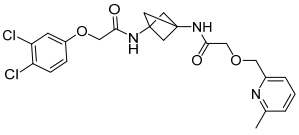
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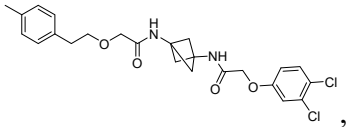
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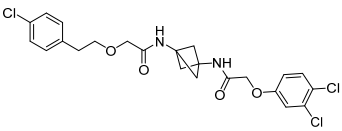
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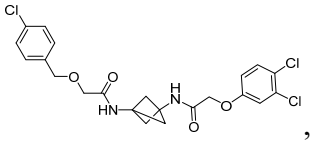
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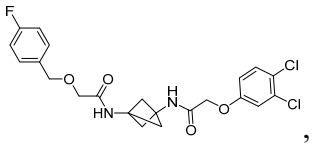
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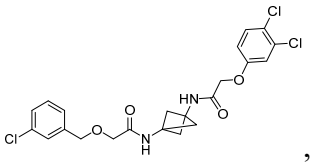
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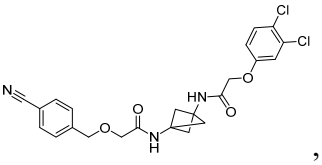
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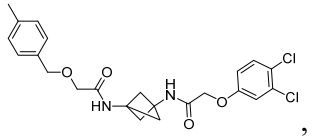
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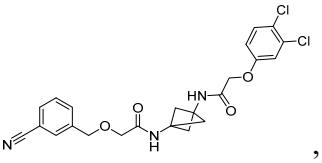
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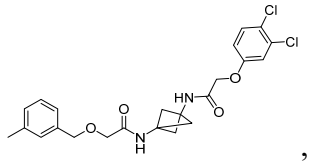
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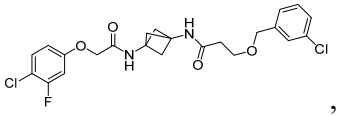
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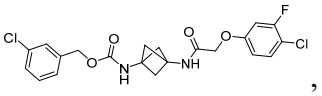
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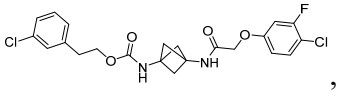
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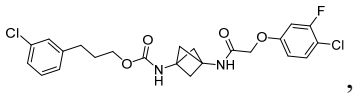
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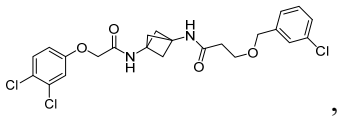
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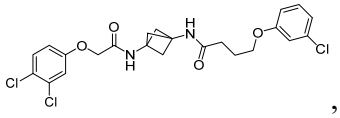
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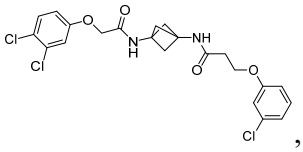
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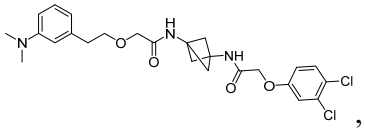
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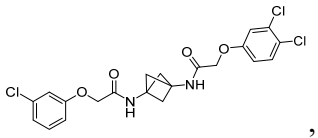
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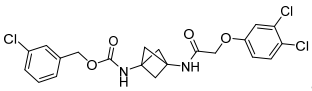
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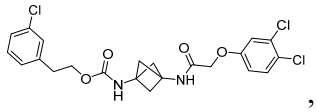
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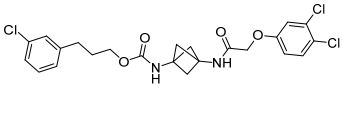
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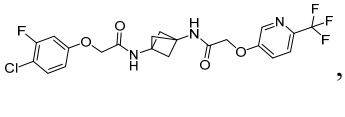
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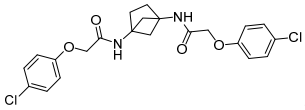
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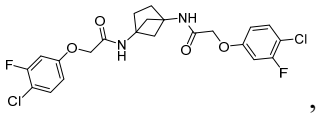
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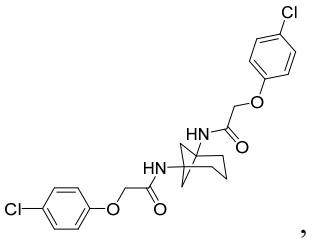
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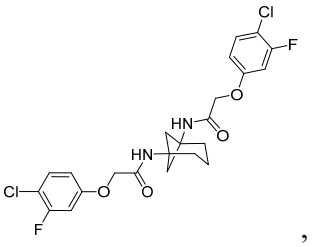
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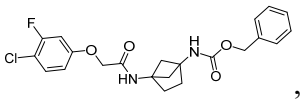
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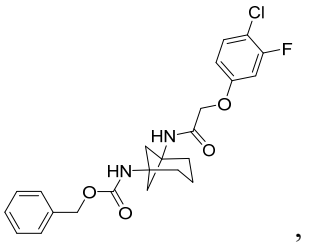
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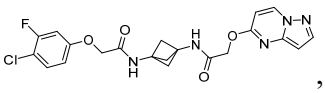
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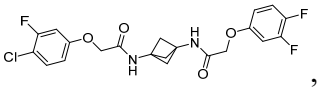
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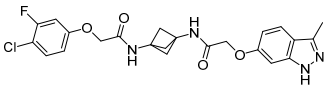
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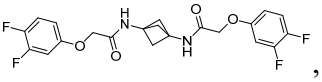
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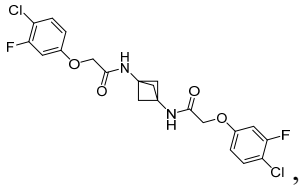
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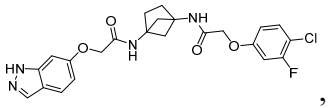
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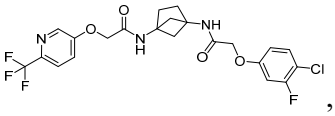
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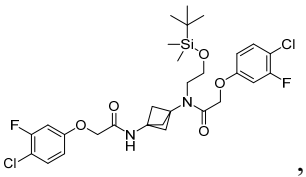
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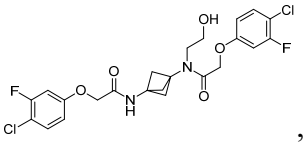
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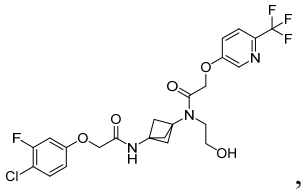
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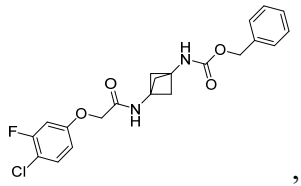
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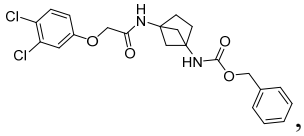
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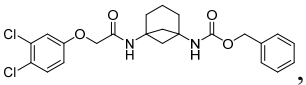
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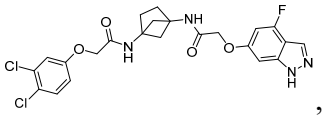
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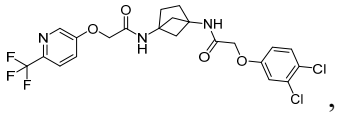
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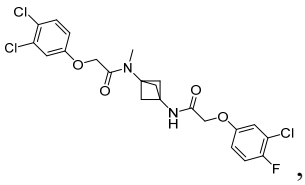
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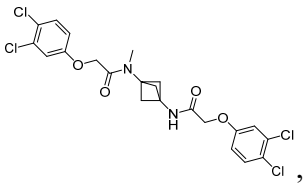
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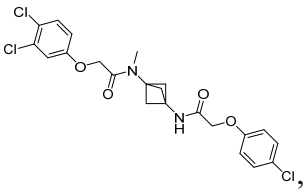
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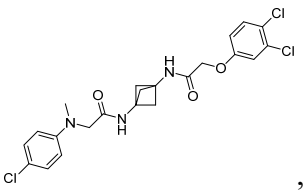
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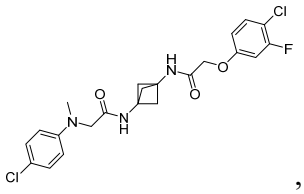
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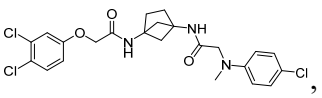
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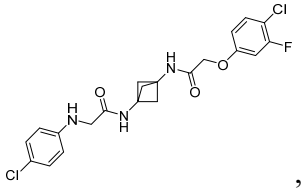
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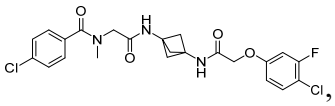
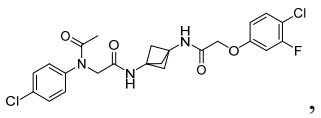
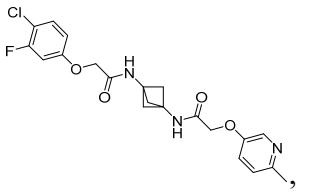
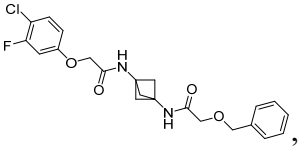
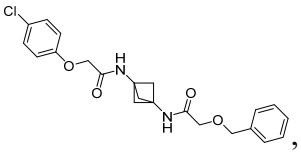
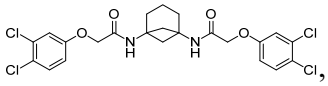
,

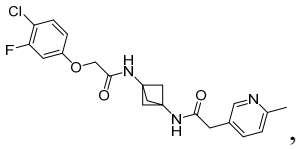
,

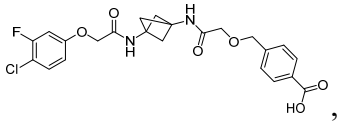
,

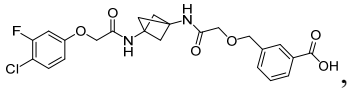
,

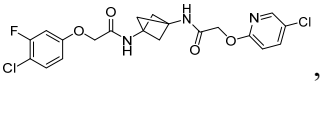
,

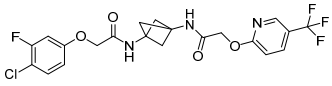
,

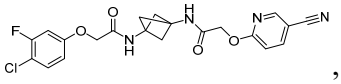
,

,

,

,

,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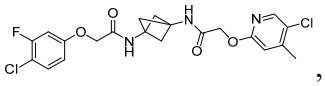
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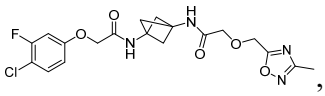
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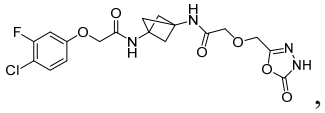
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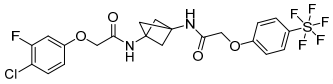
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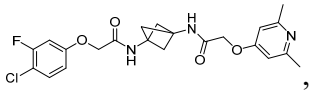
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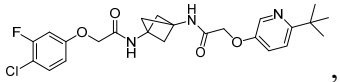
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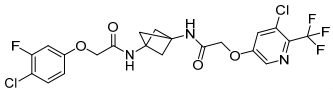
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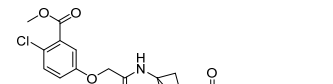
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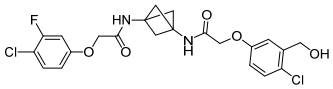
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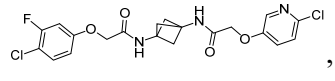
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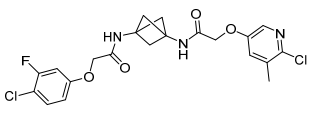
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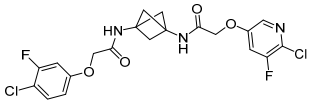
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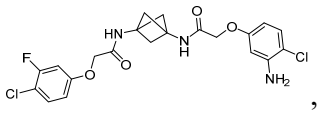
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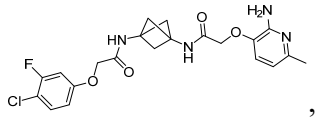
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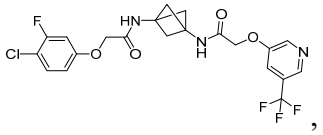
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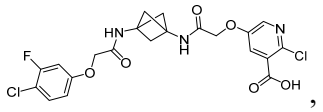
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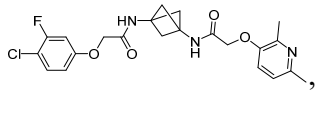
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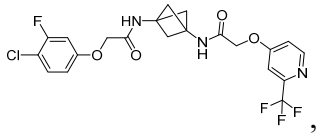
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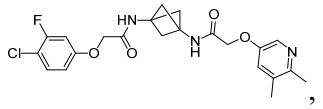
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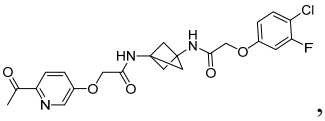
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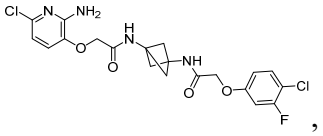
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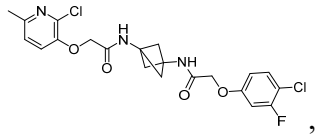
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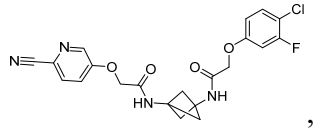
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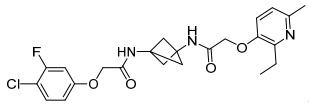
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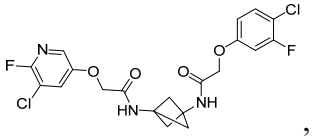
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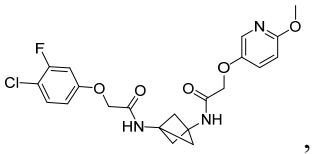
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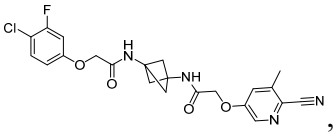
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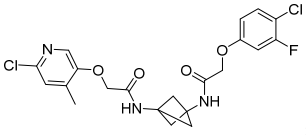
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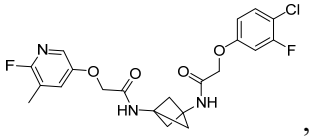
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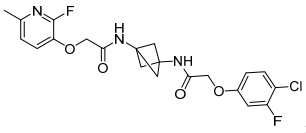
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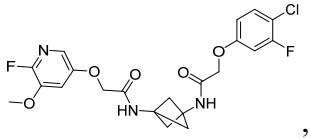
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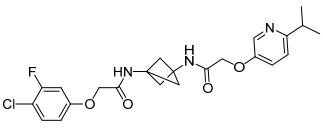
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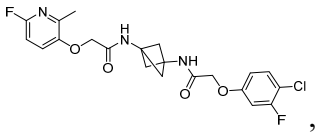
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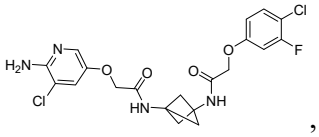
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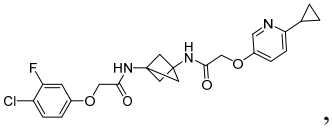
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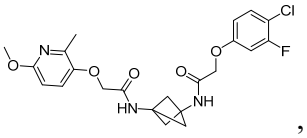
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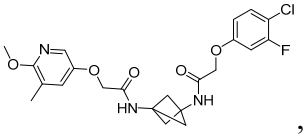
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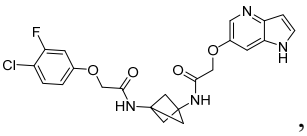
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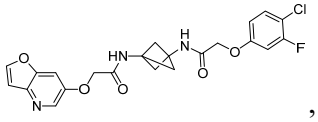
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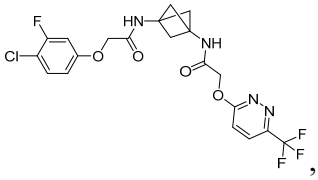
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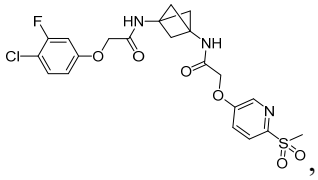
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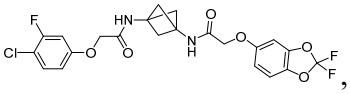
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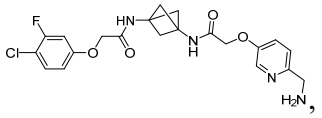
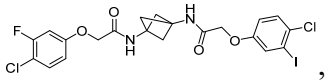
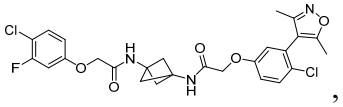
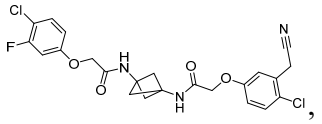
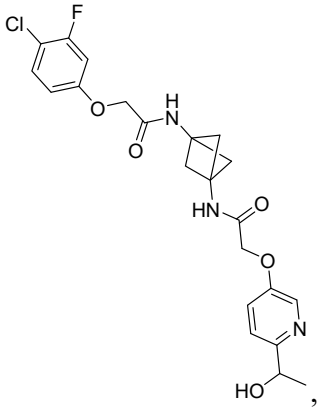
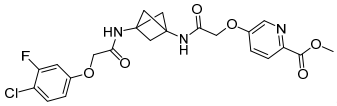


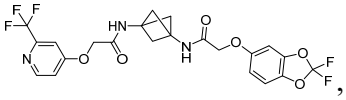


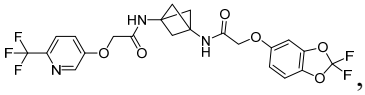


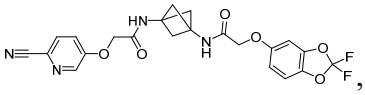


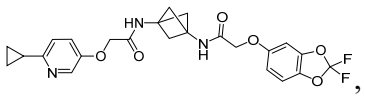


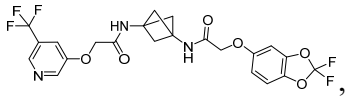


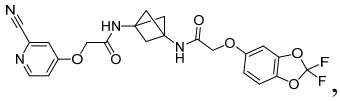


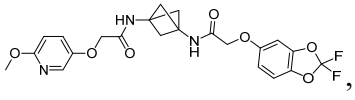


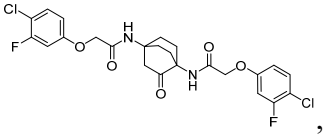


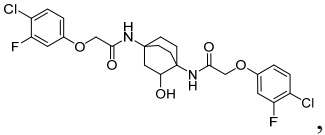


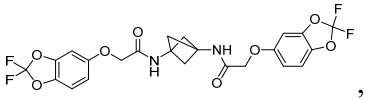
,

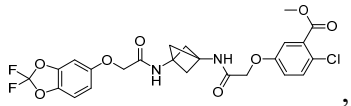
,

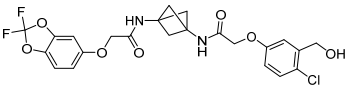
,

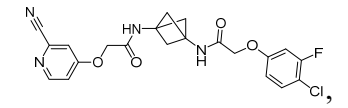
,

,

,

,

,

,

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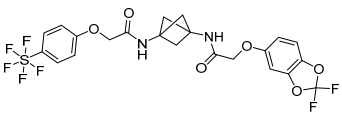
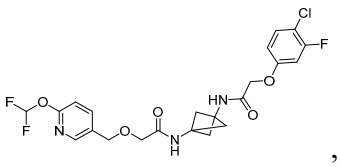
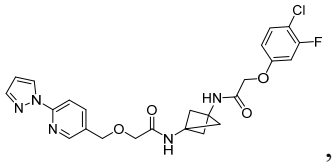
,

,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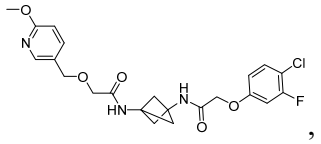
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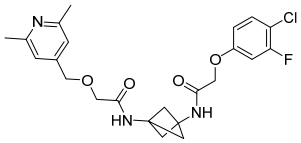
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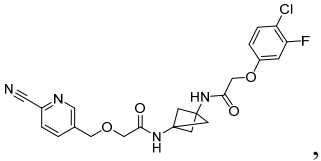
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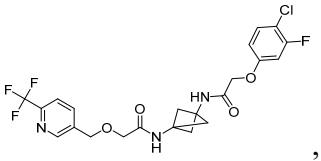
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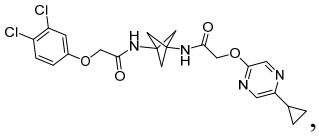
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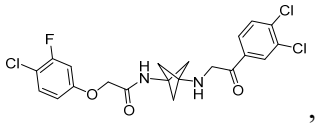
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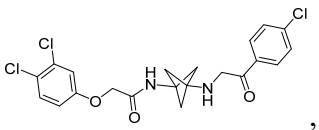
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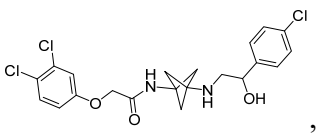
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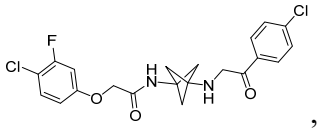
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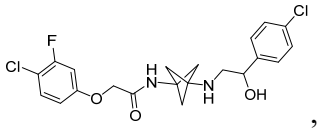
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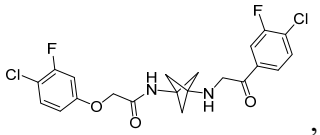
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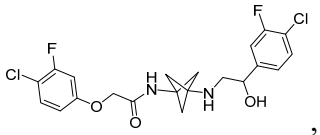
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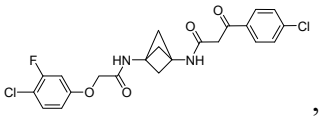
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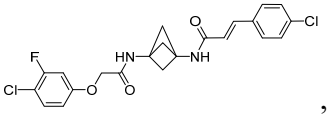
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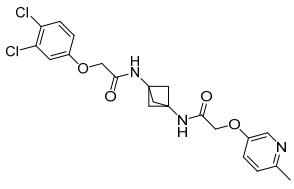
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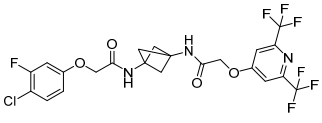
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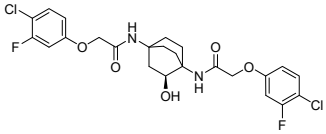
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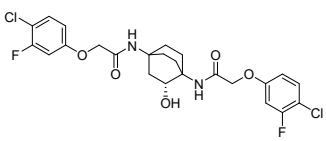
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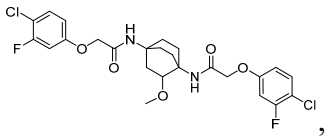
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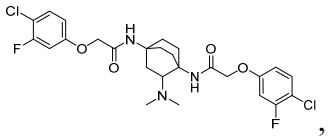
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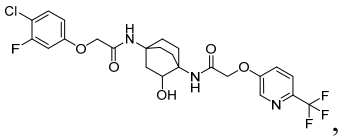
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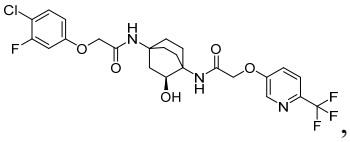
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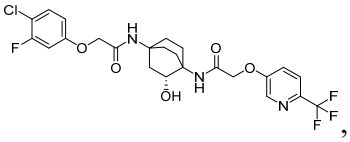
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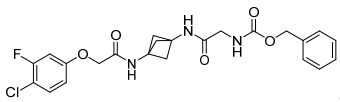
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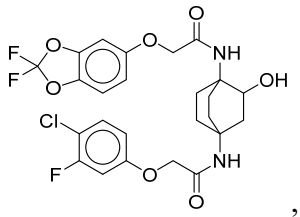
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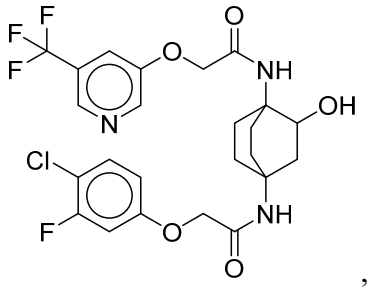
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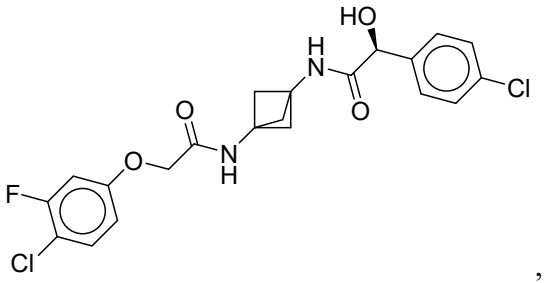

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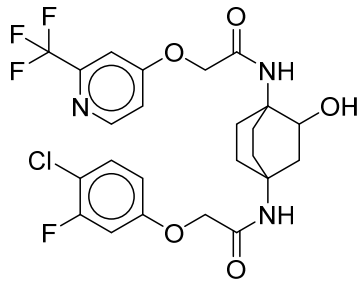

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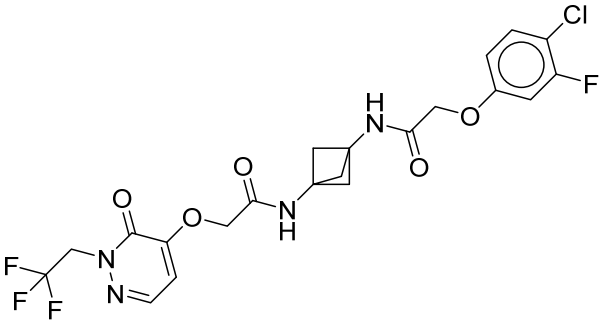

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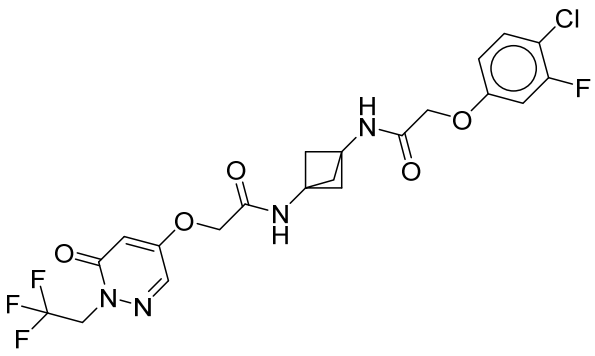

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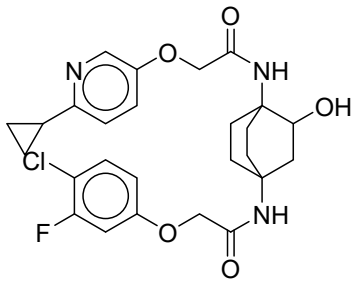

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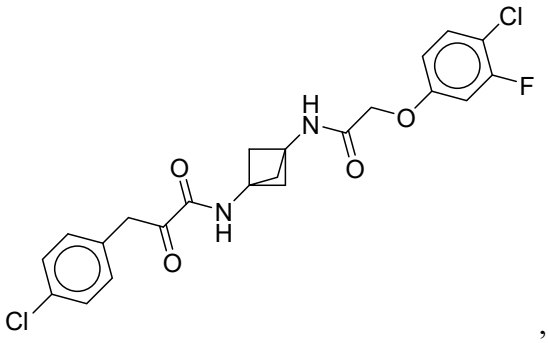
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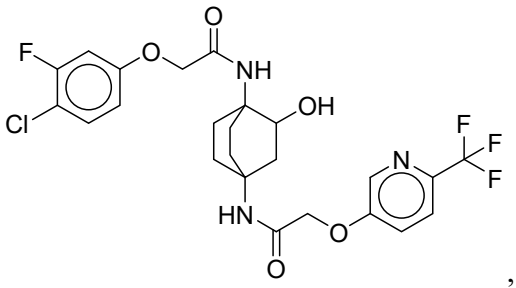
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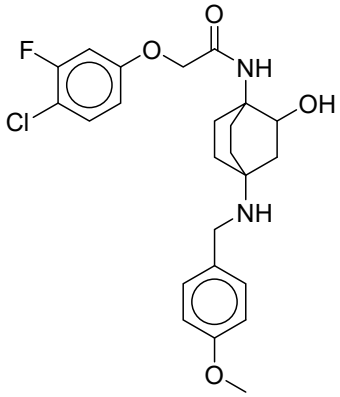
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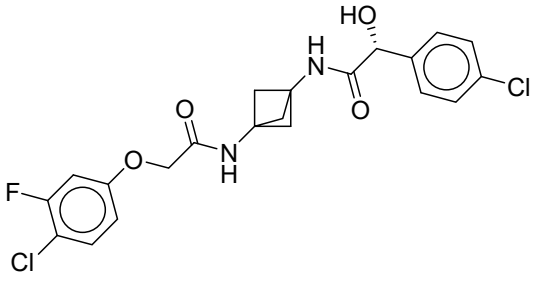
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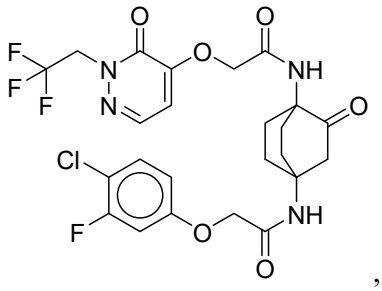

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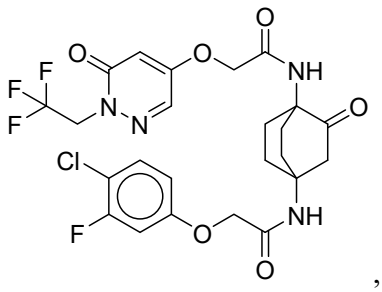

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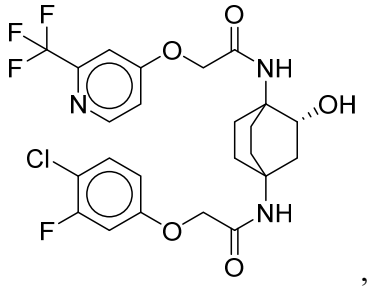

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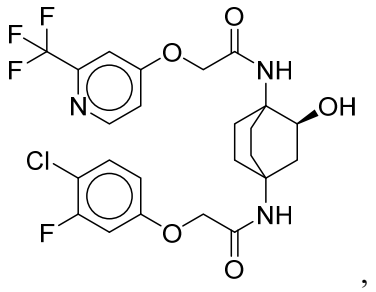

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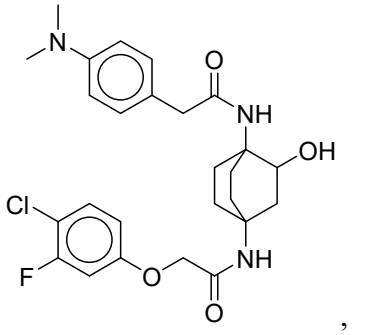

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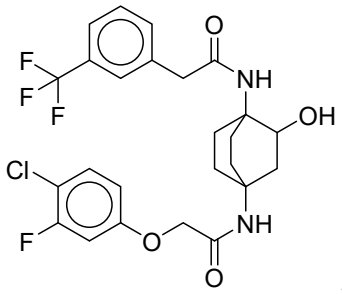
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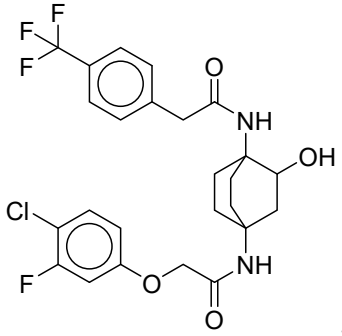
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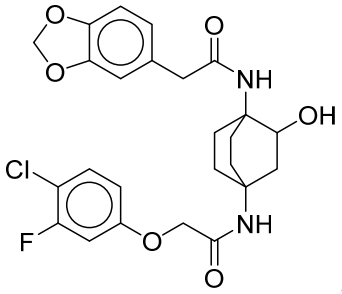
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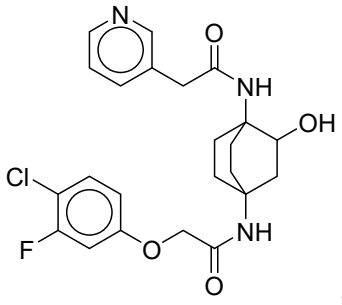
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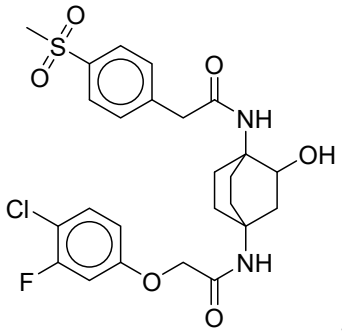
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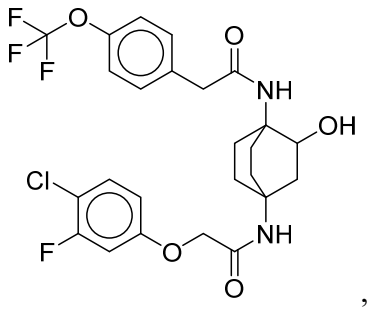
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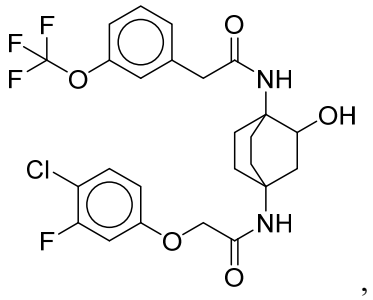
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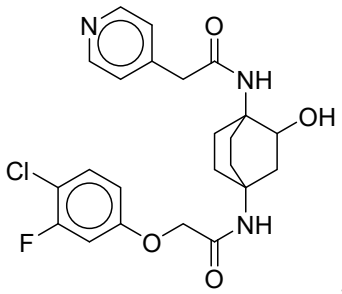
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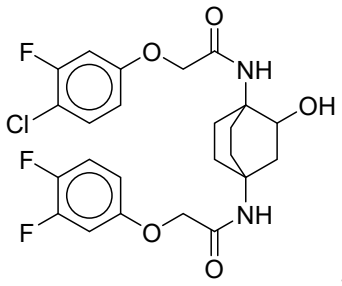
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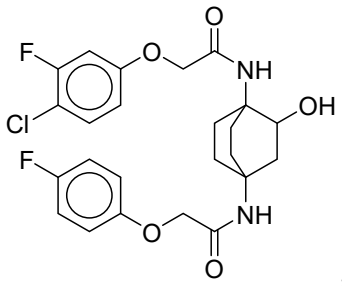
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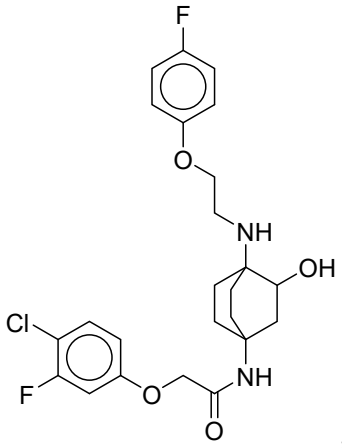

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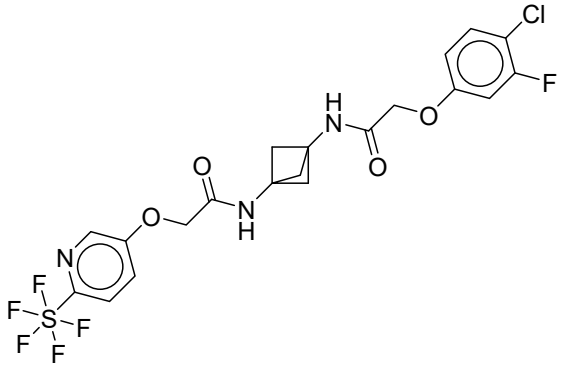

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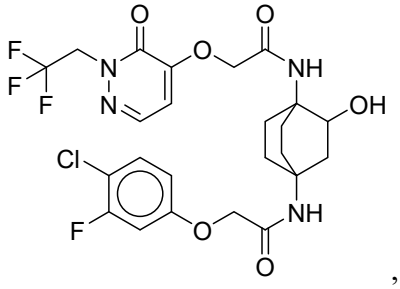

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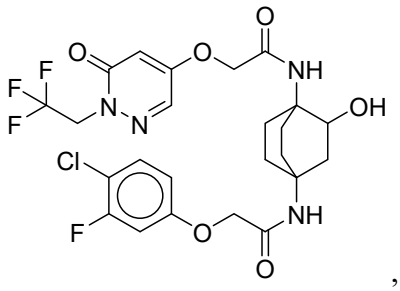

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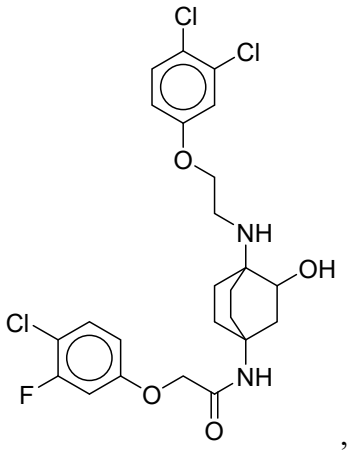
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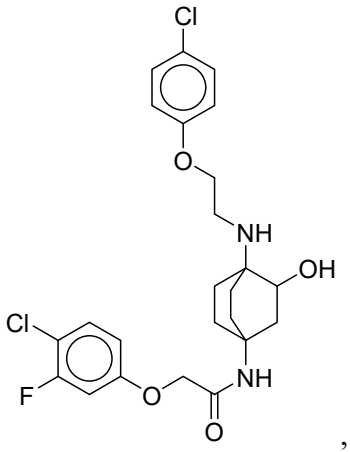
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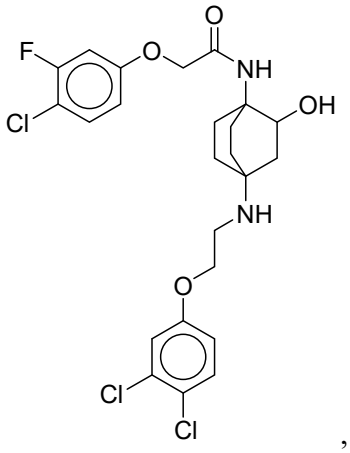
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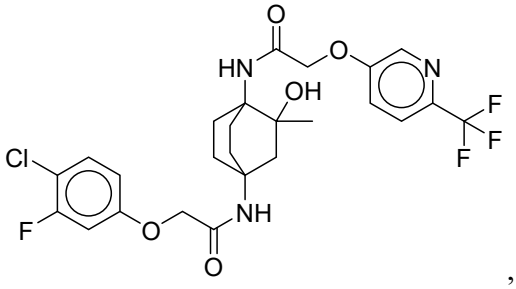

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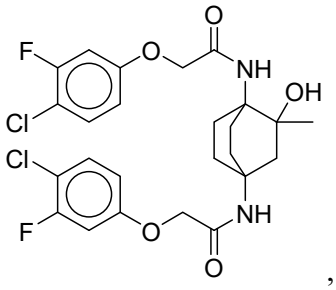

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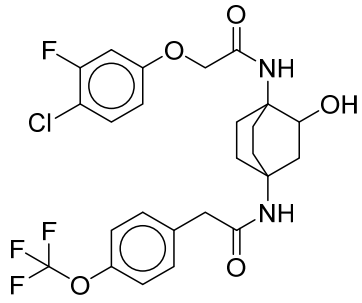

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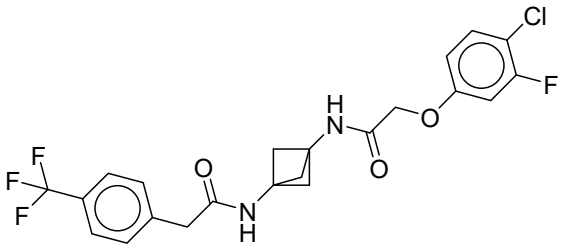

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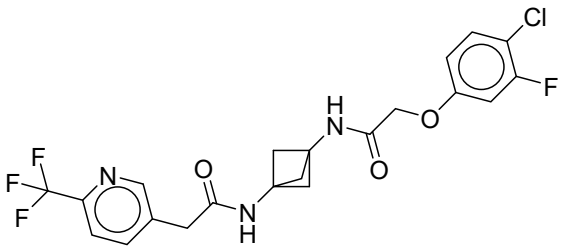

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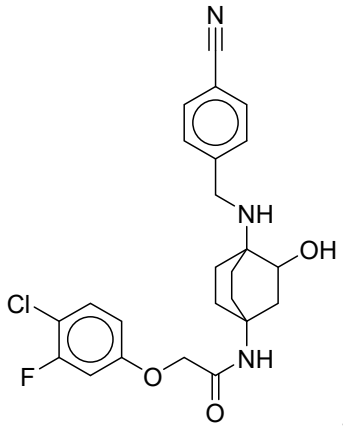
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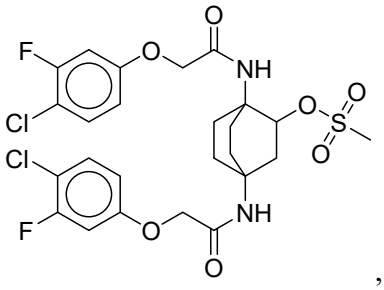
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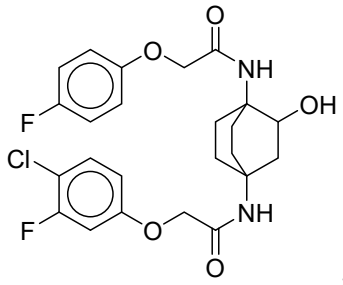
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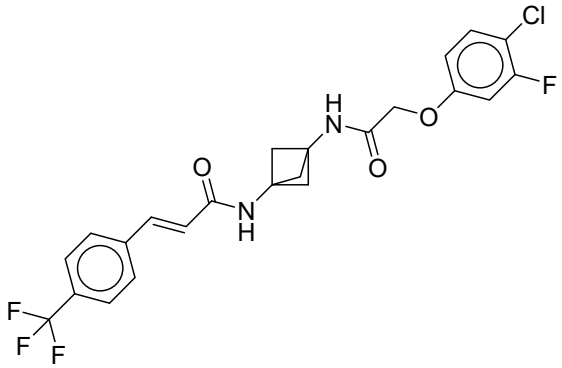
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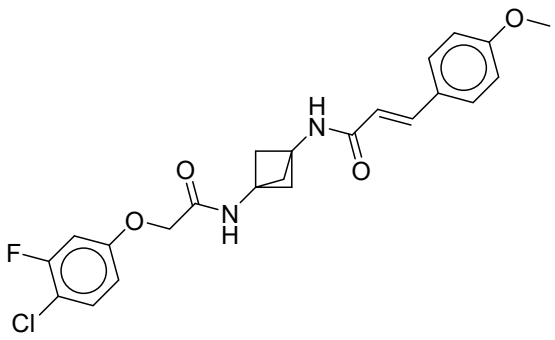
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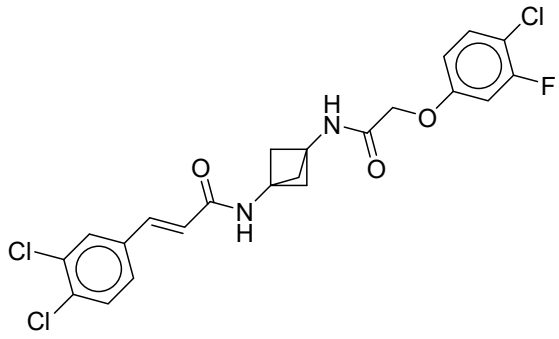
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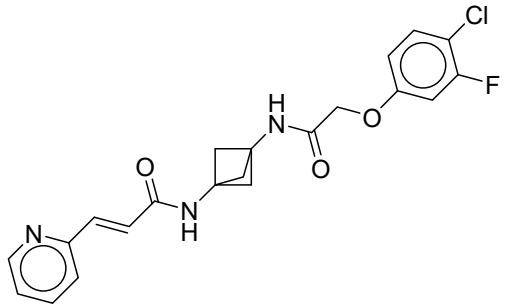
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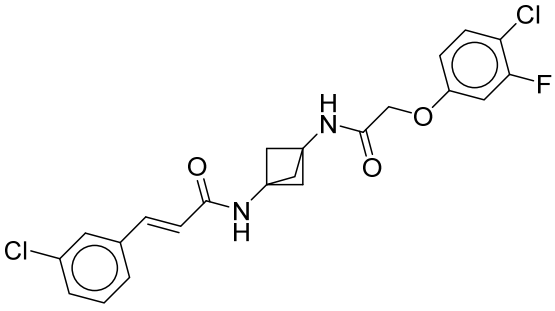
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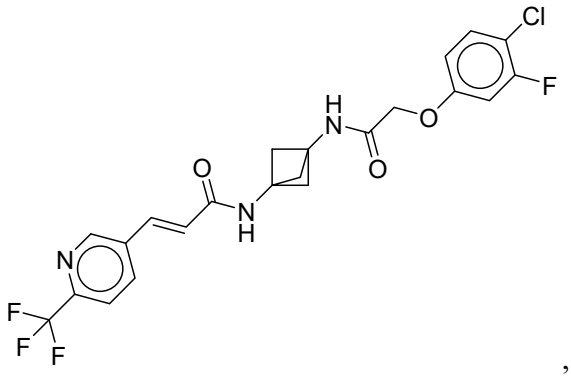
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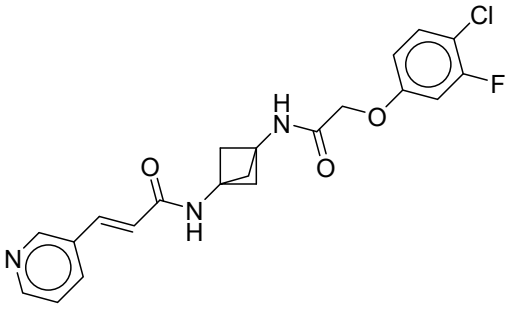
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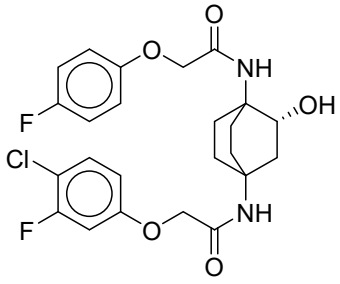
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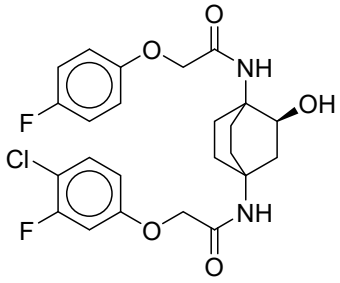
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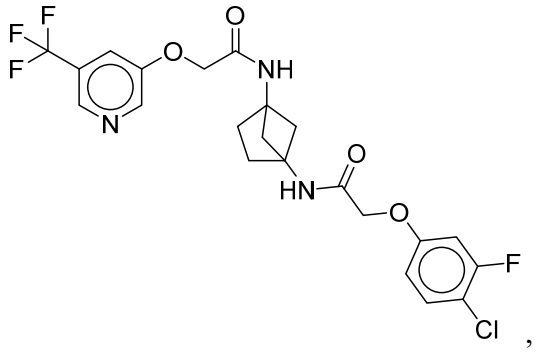

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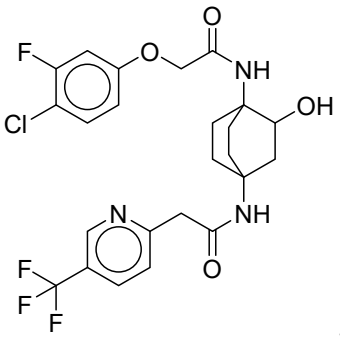

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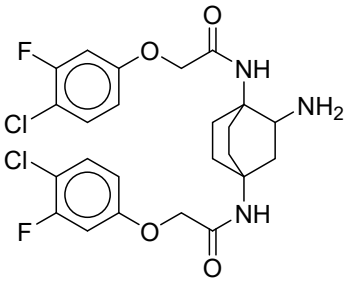

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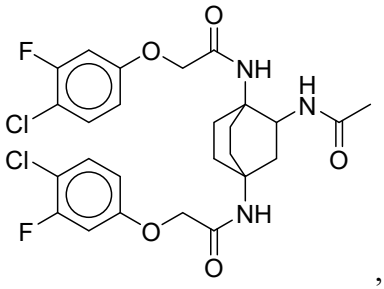

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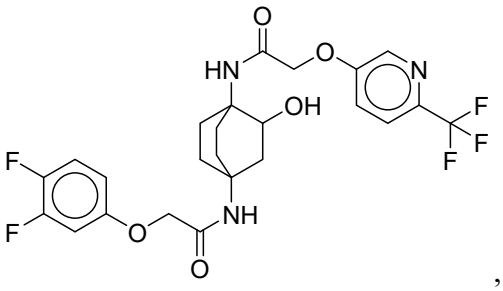

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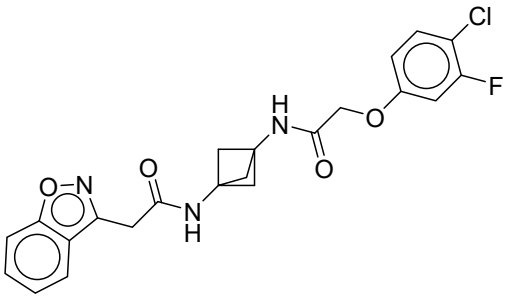

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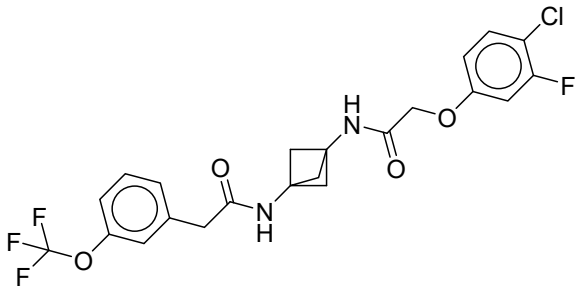

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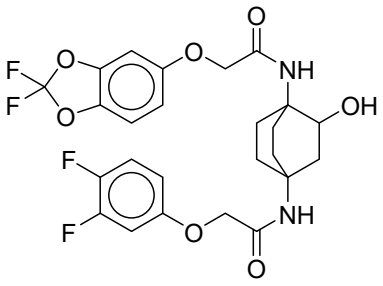

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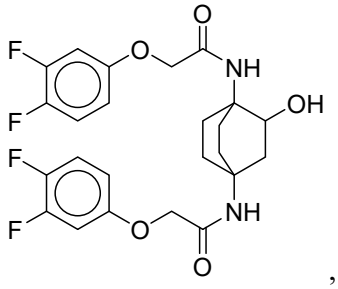

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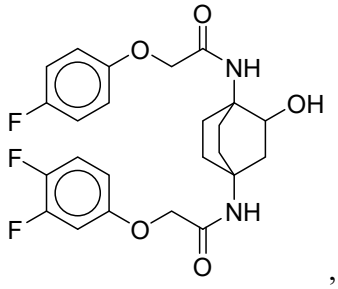

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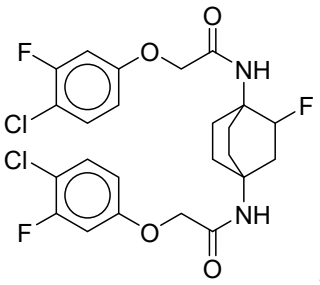

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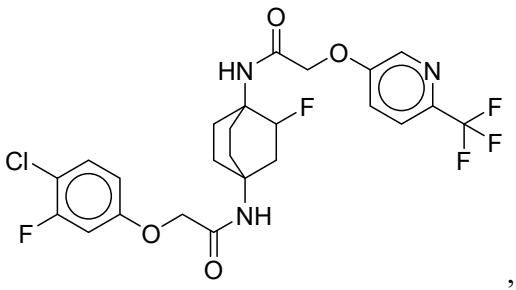

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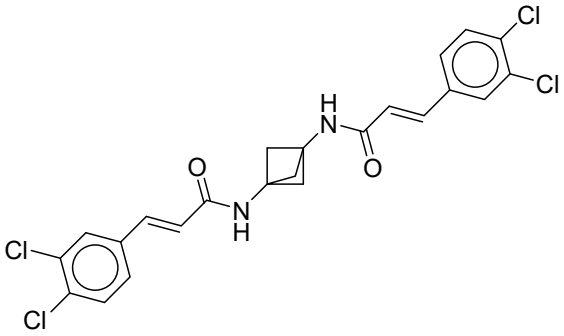

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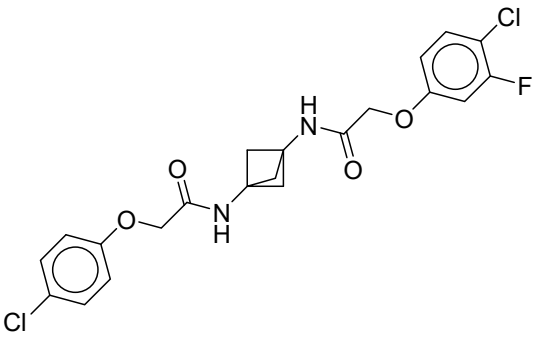

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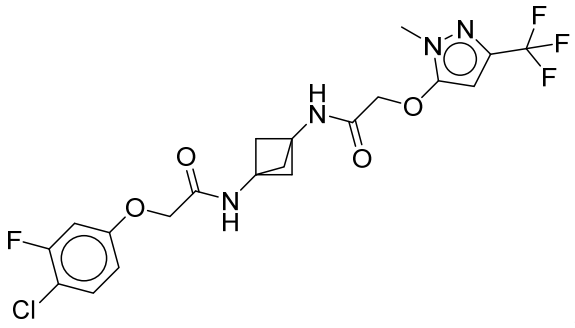

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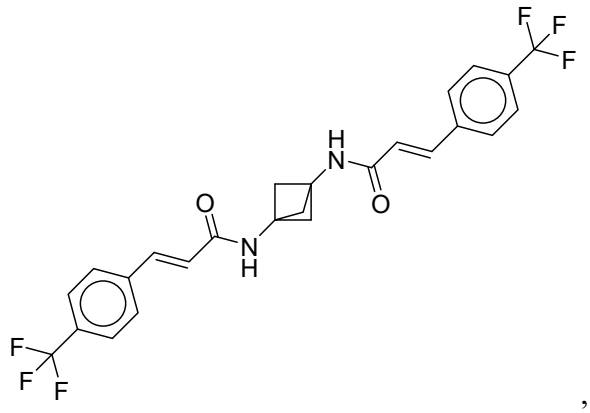

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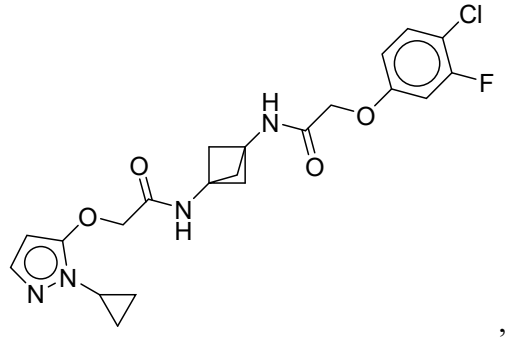

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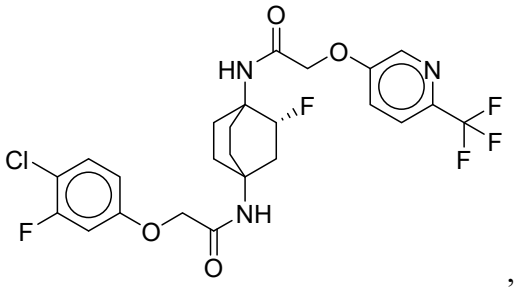

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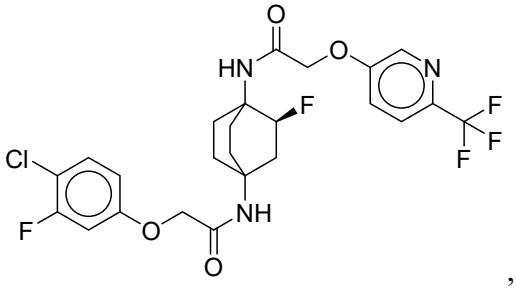

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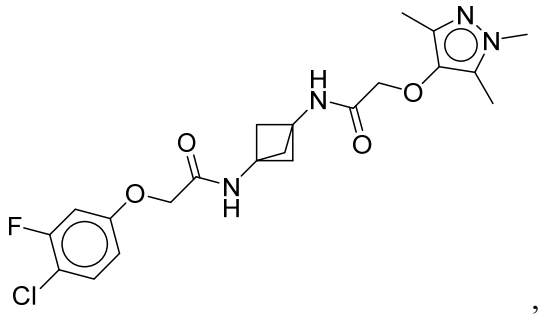

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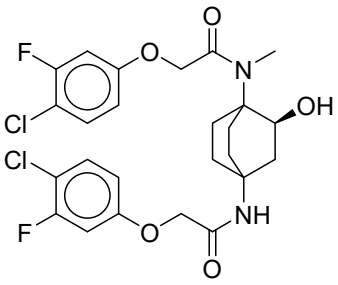

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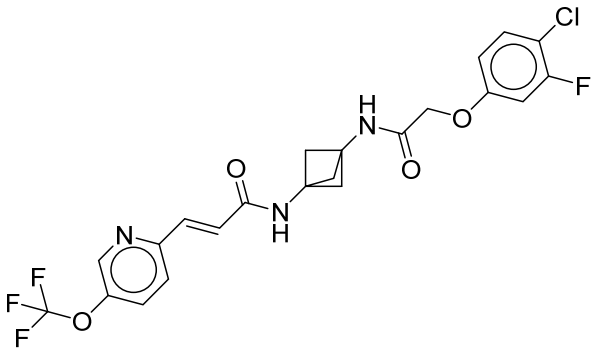

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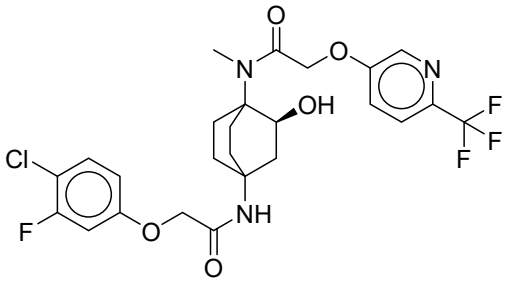

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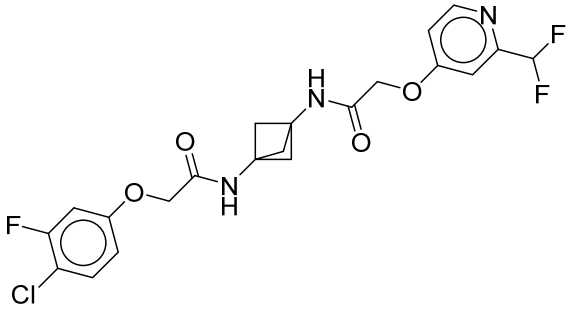

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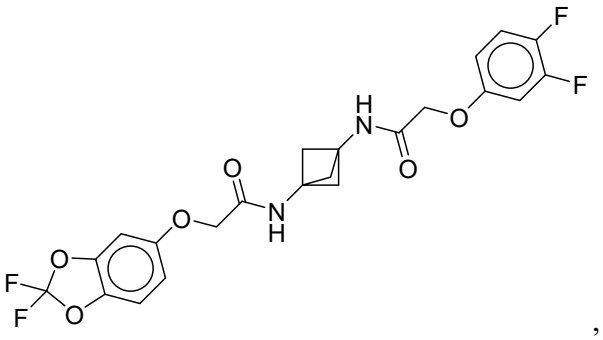

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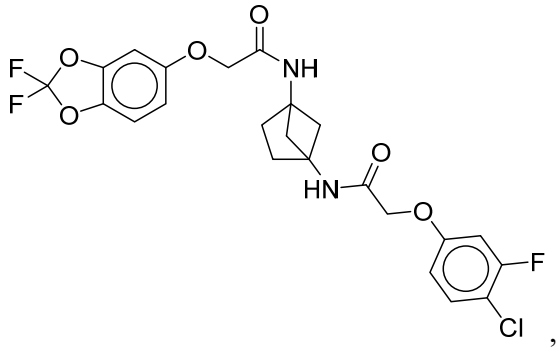

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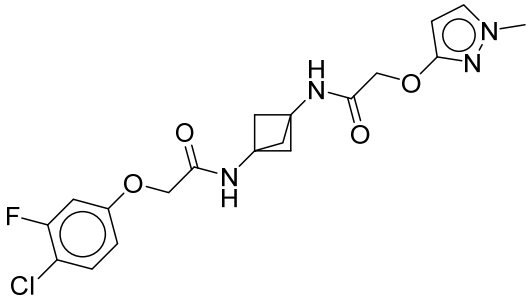

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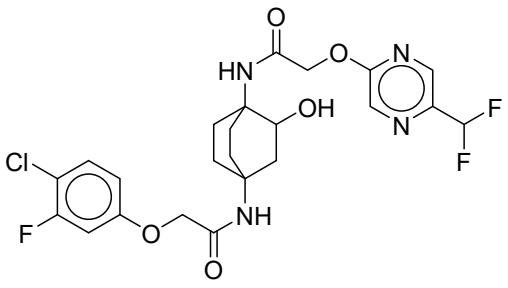

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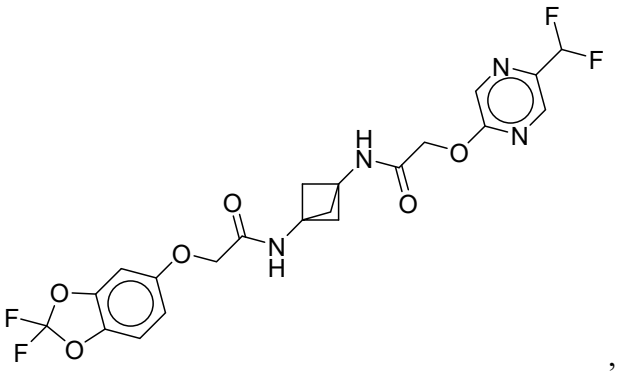

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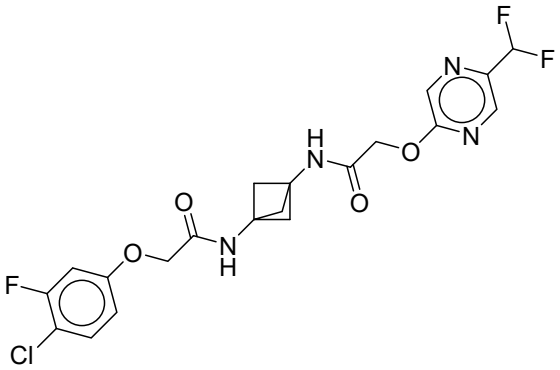

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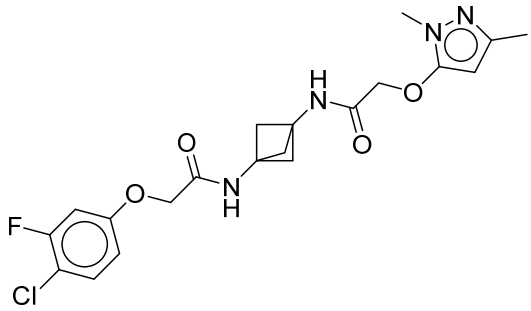

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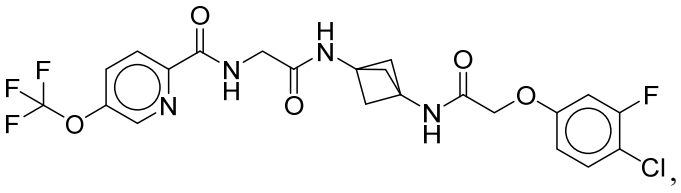

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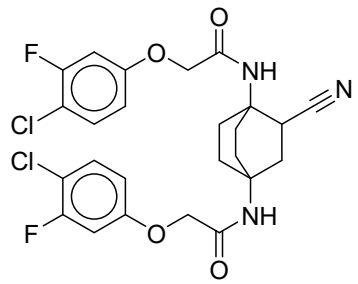

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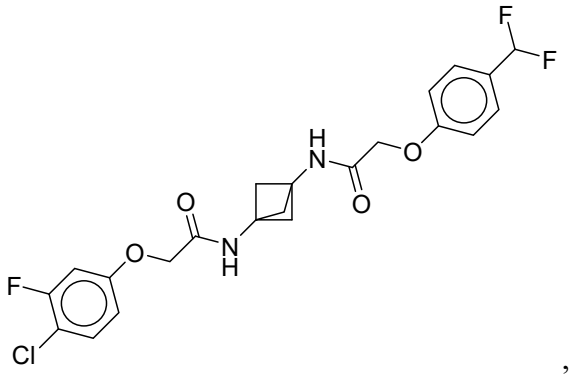

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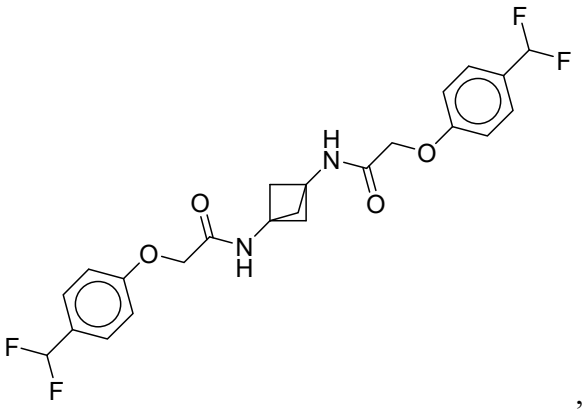

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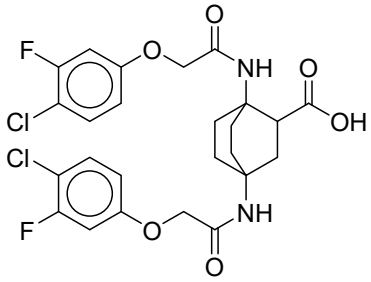

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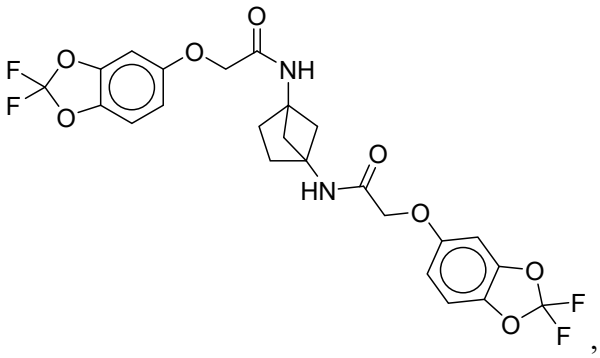

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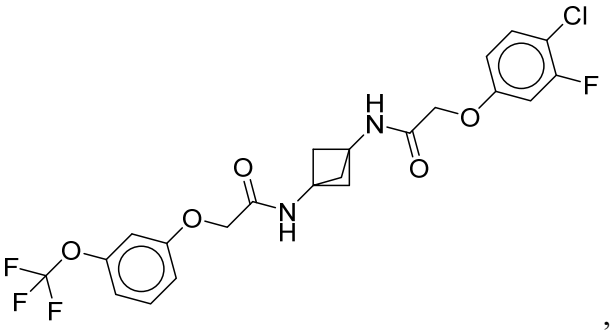

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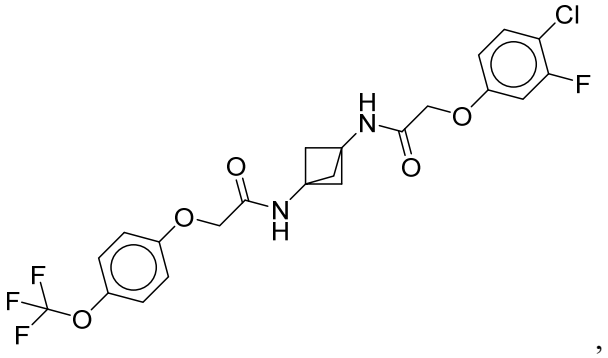

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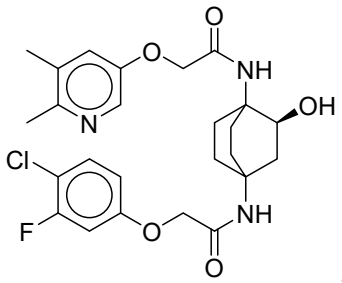

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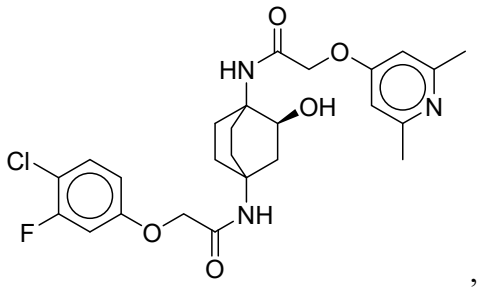

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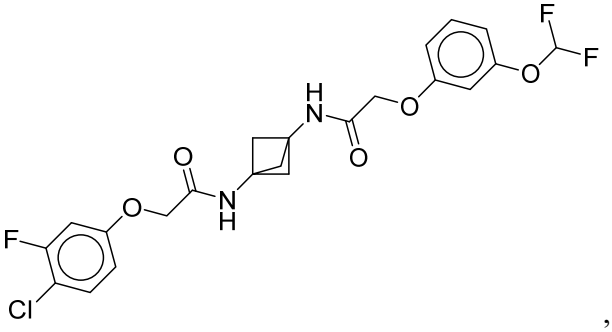

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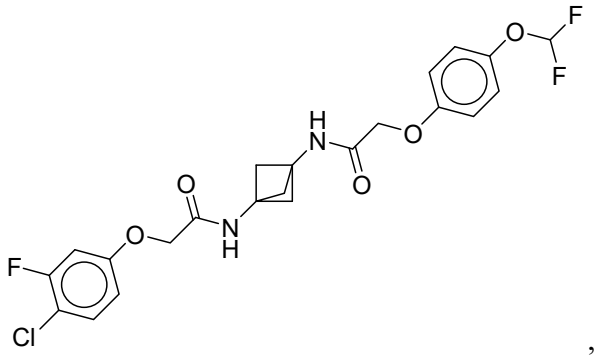

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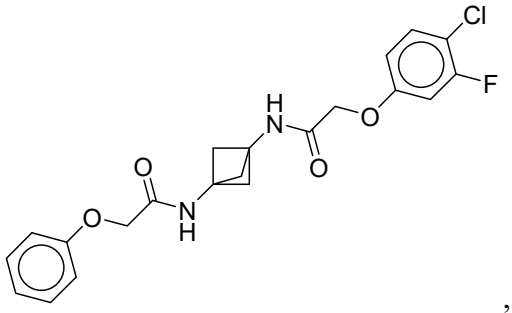

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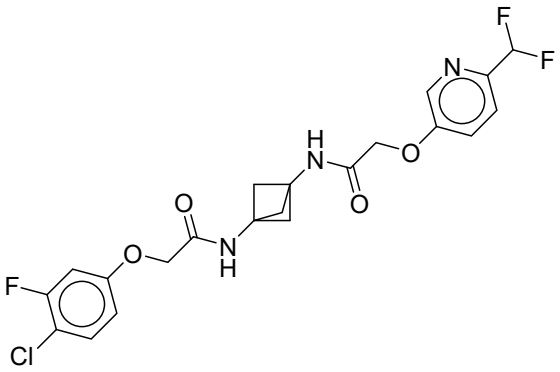

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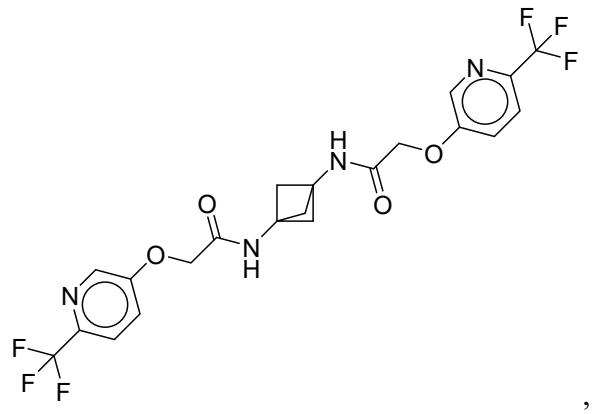

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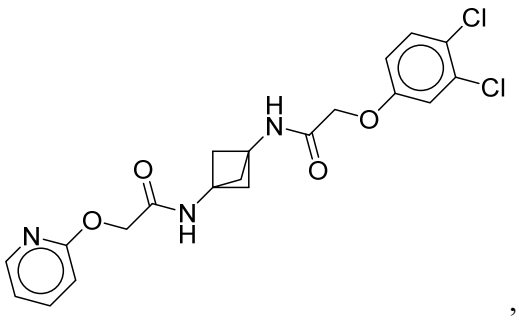
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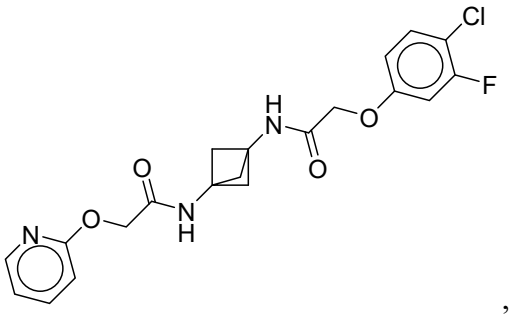
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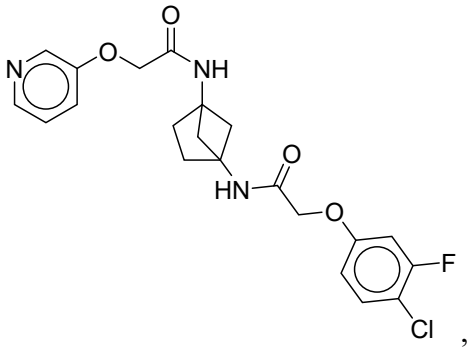
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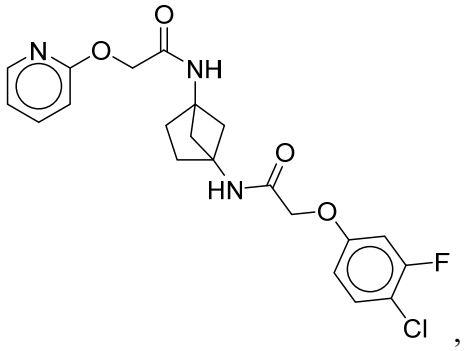
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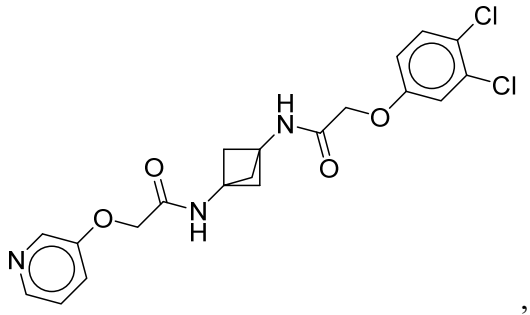

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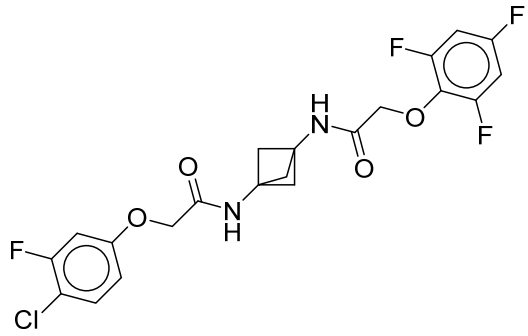

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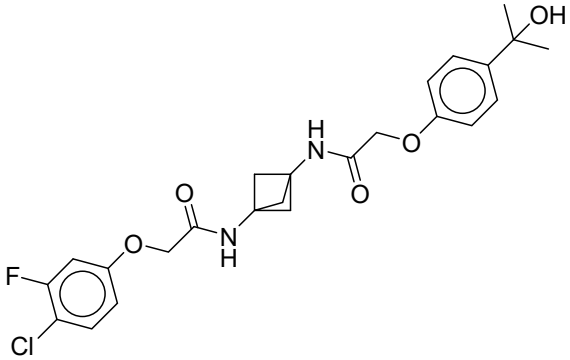

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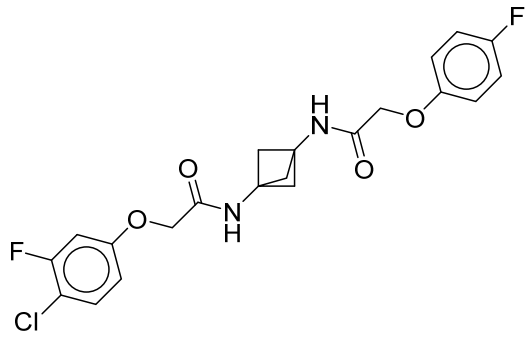

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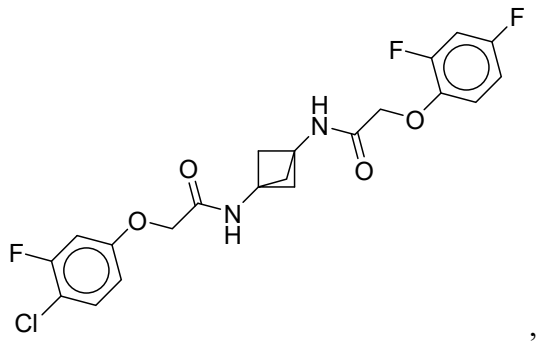

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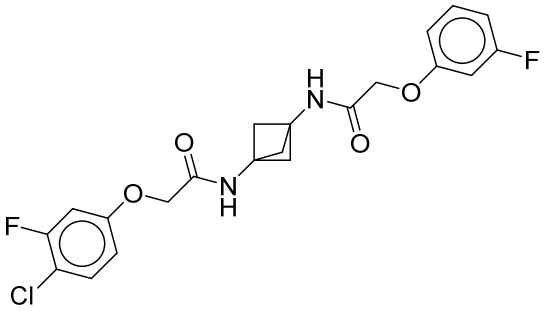

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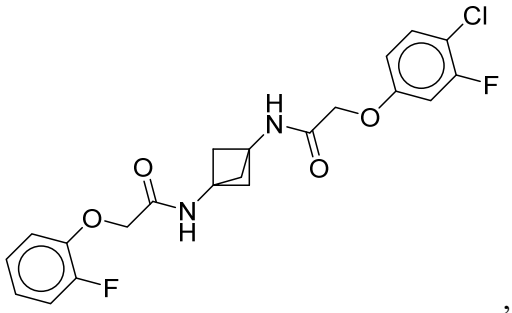

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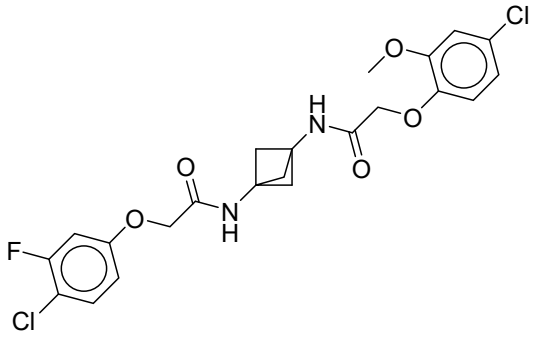

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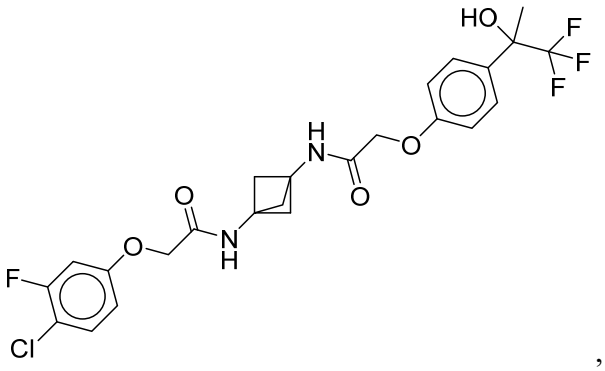
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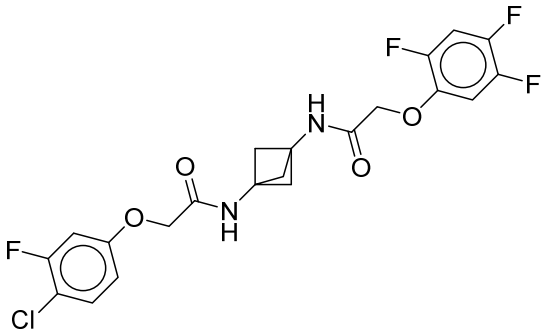
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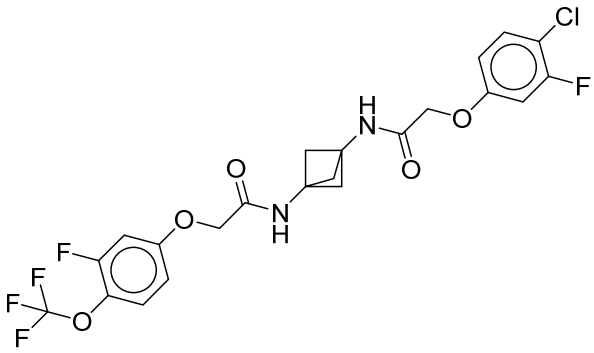
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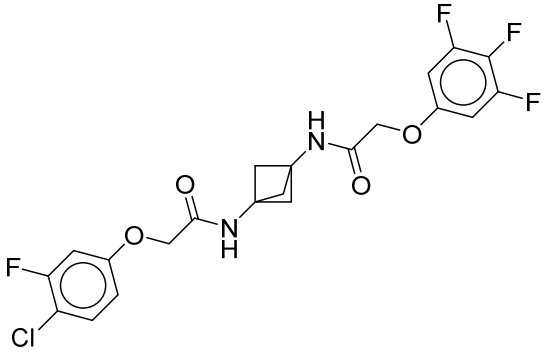
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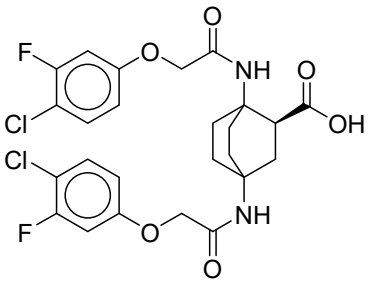

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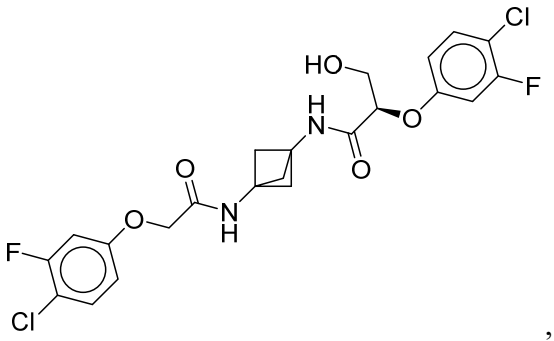

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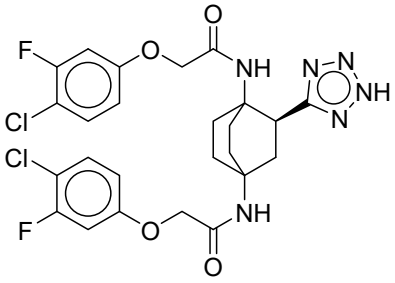

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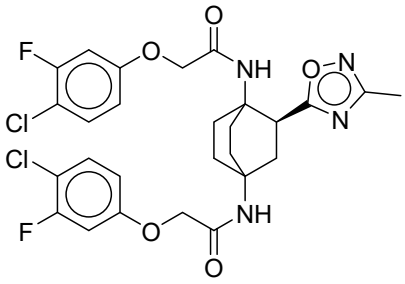

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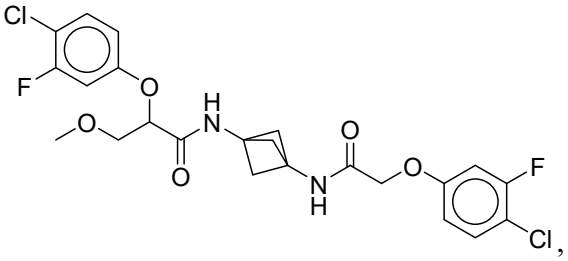

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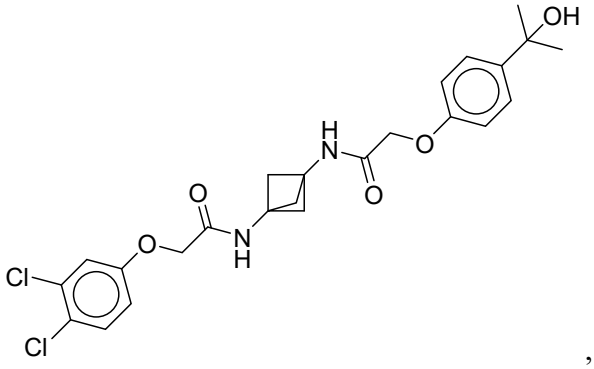
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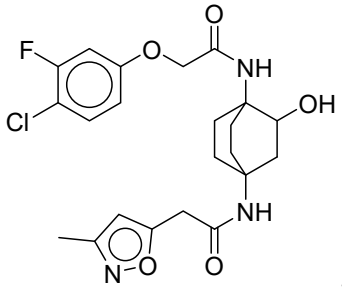
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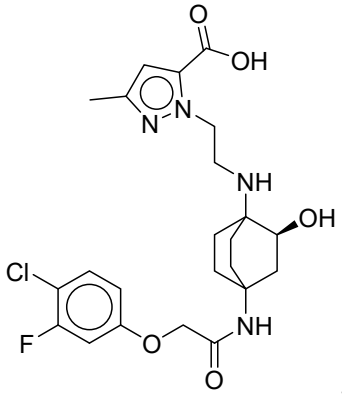
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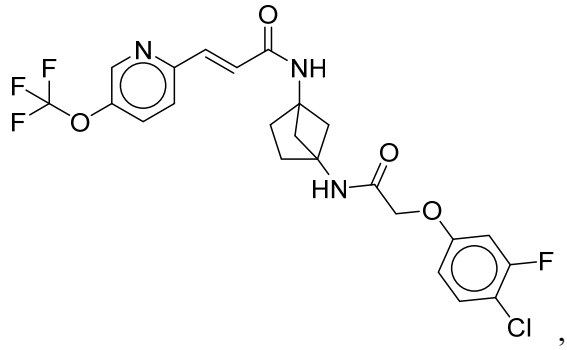
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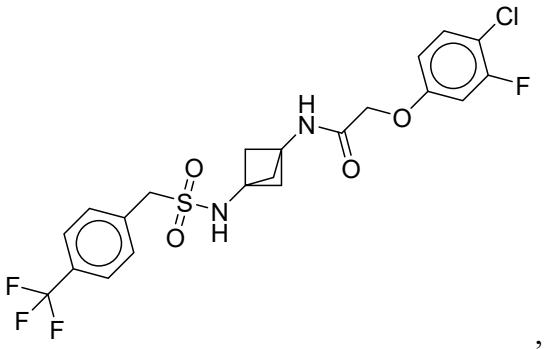

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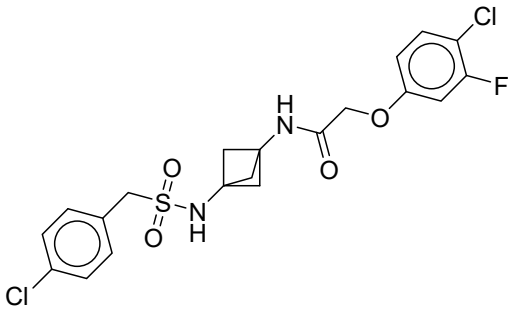

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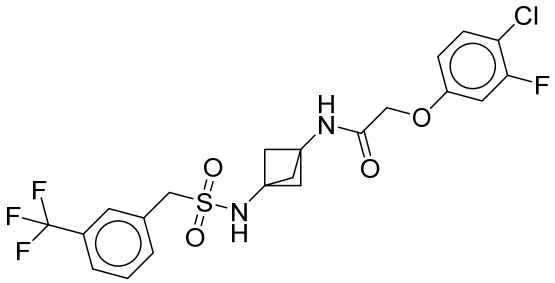

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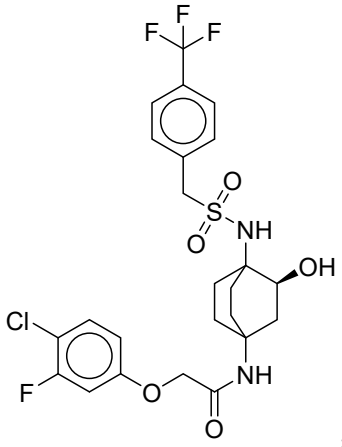

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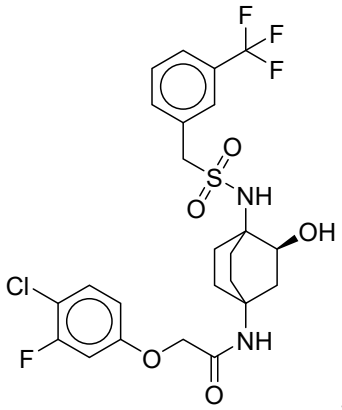

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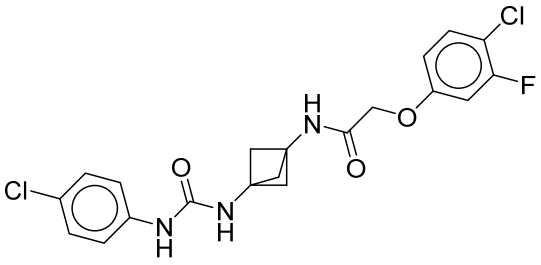

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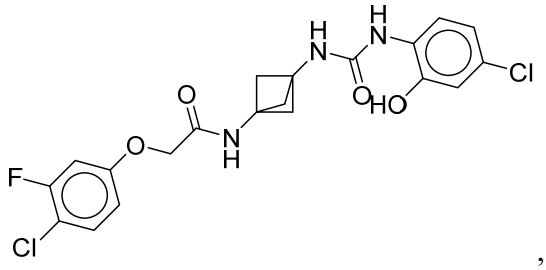

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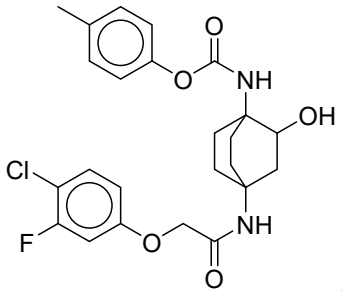

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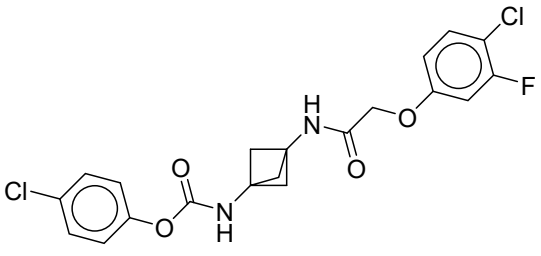

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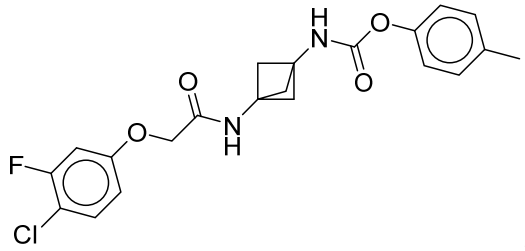

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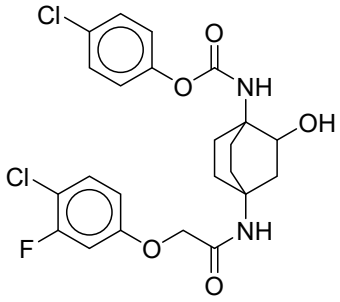

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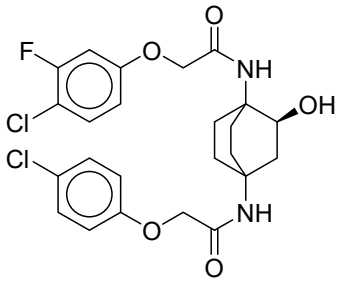

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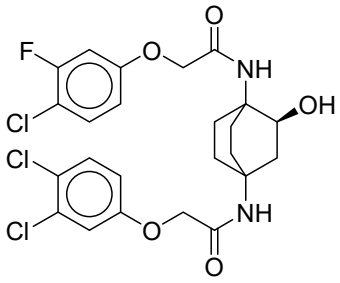

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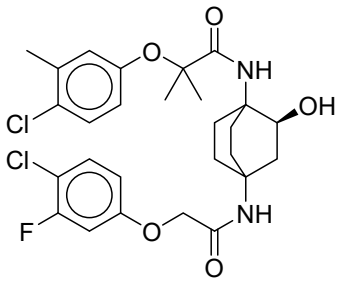

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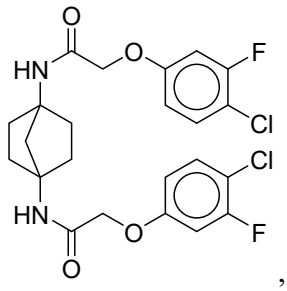

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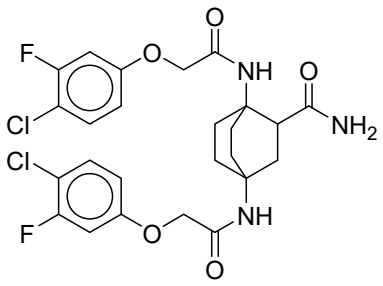

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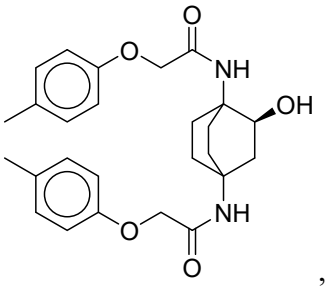

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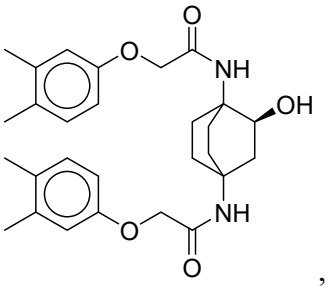

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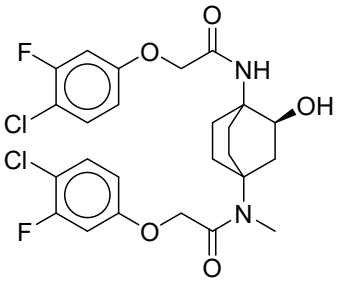

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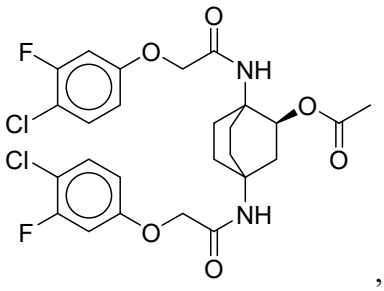
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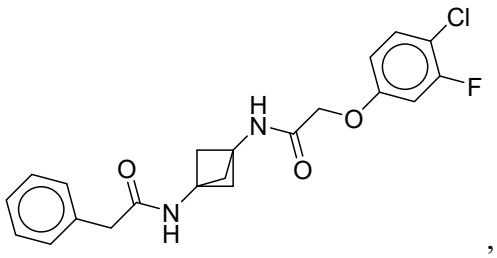
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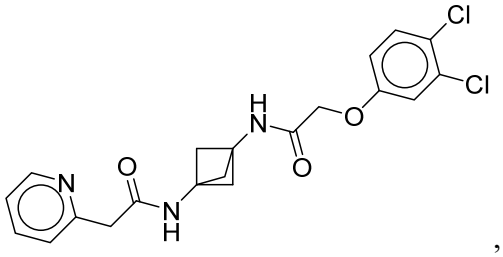
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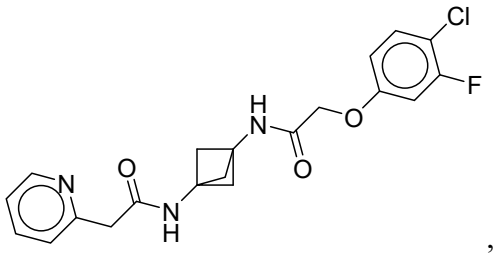
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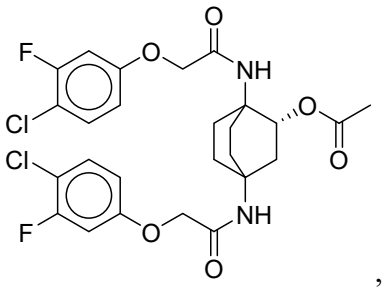
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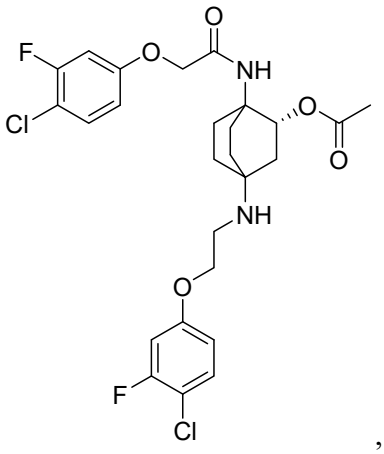

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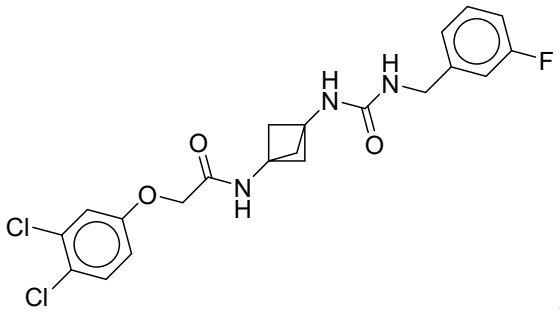

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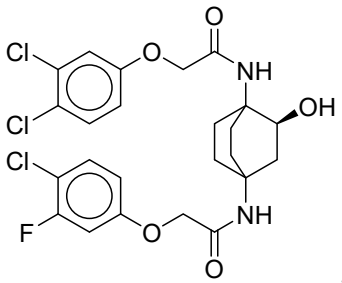

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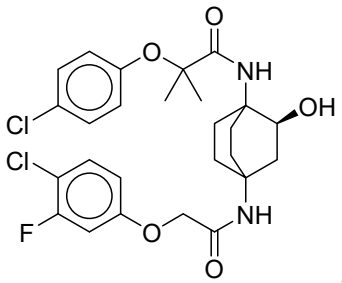

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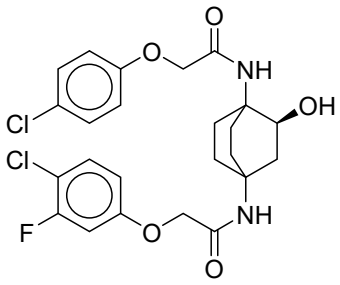

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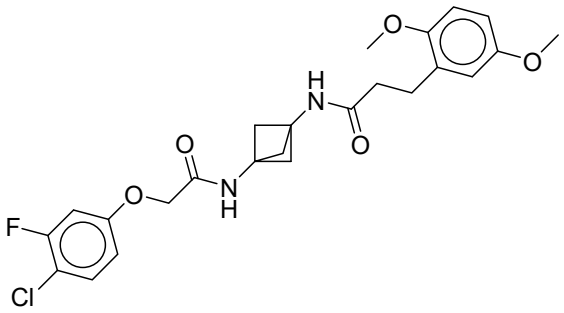

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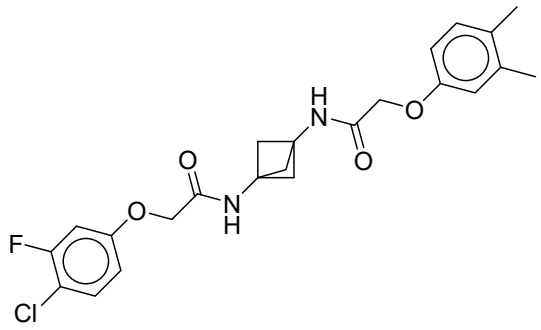

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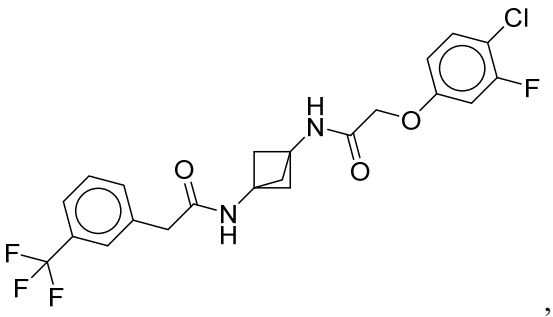

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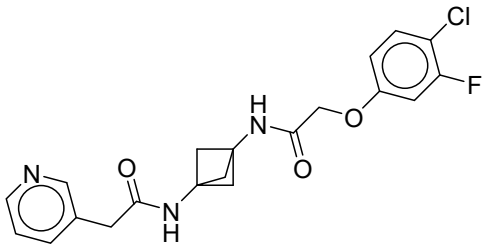

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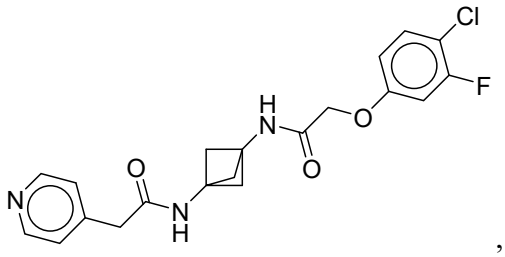

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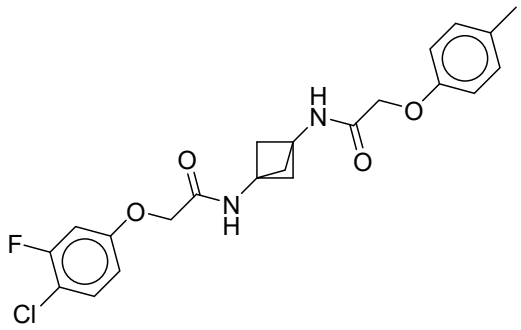

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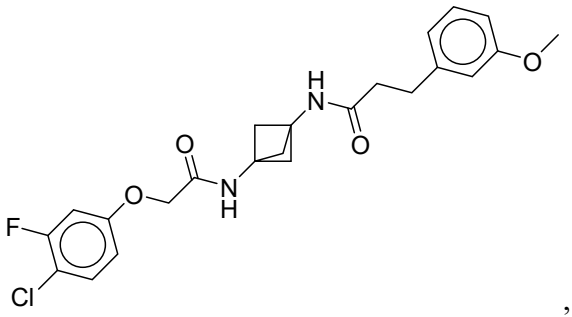

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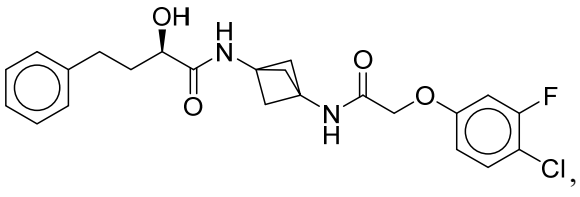

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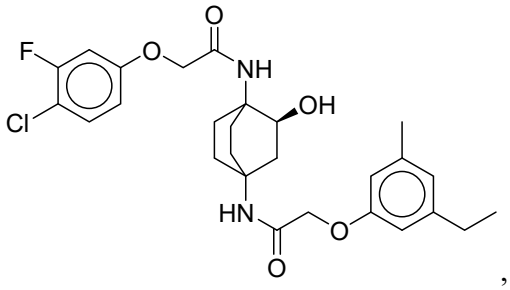

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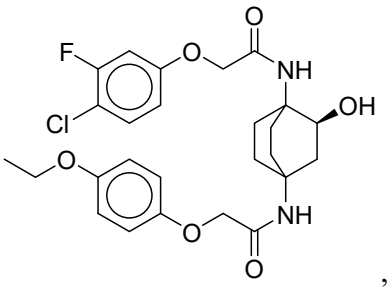
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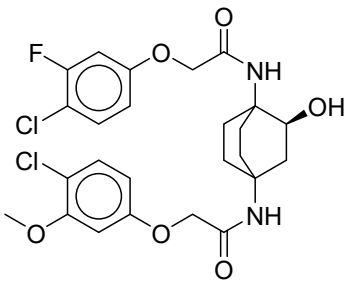
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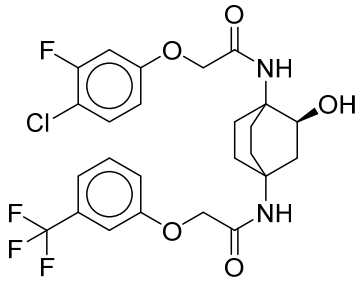
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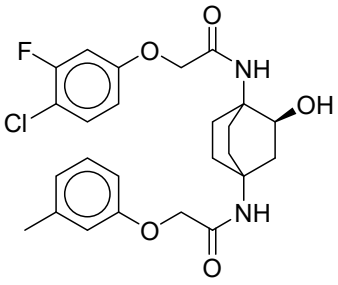
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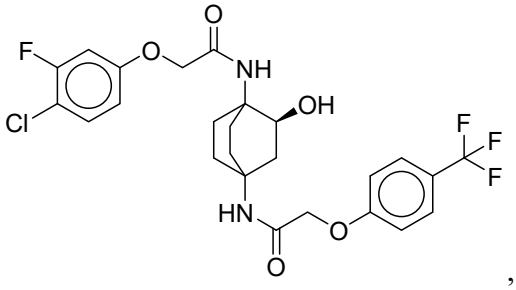
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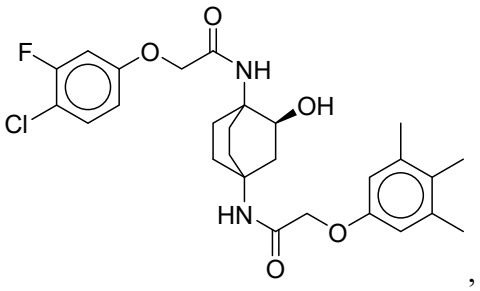
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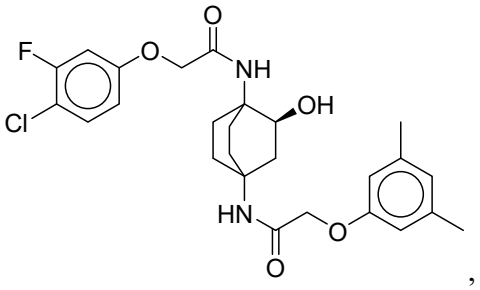
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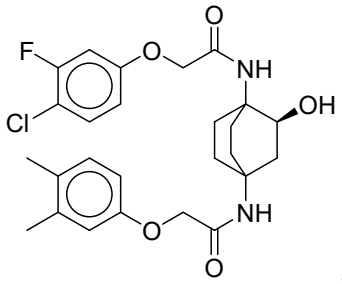
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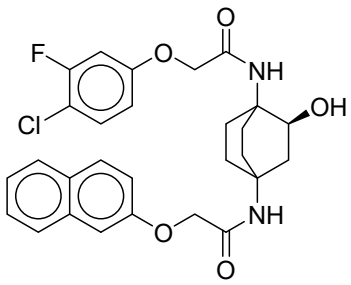
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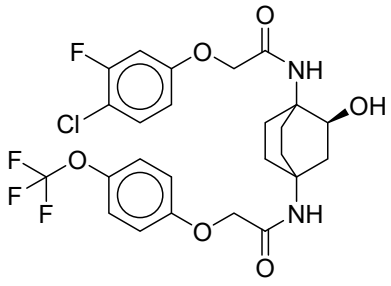
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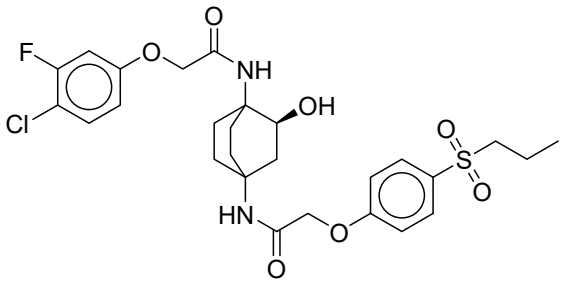

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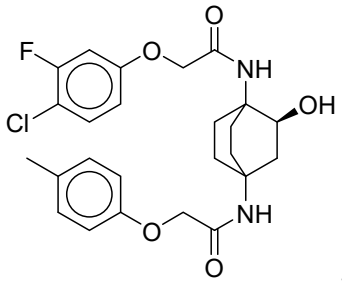

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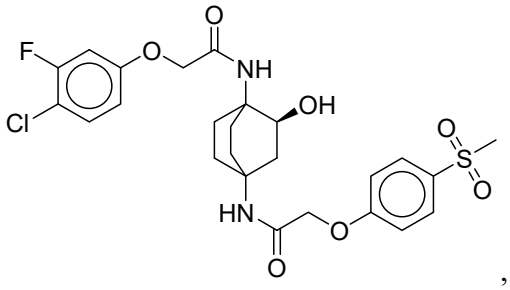

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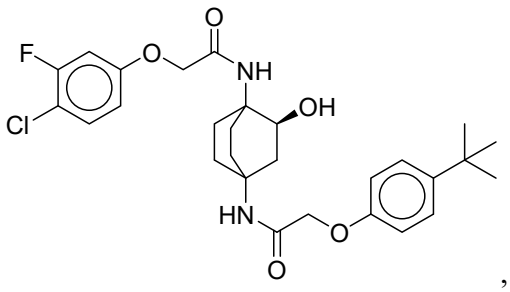

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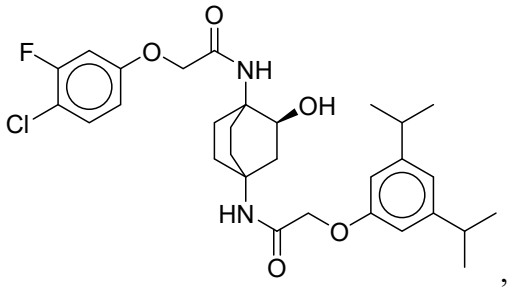

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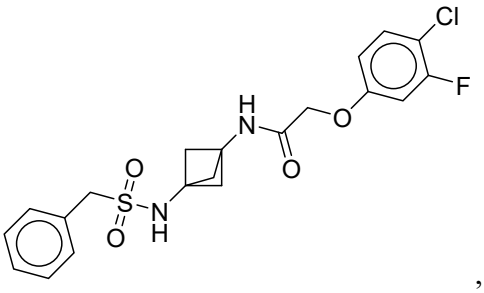

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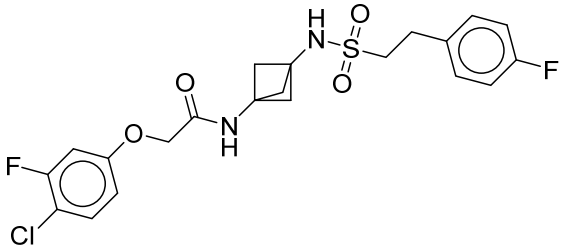

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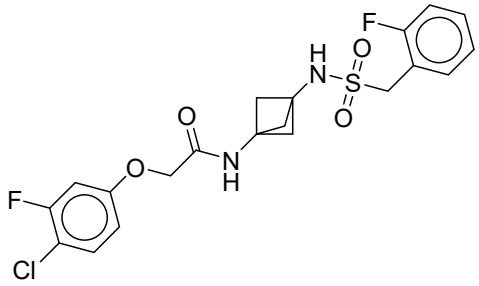

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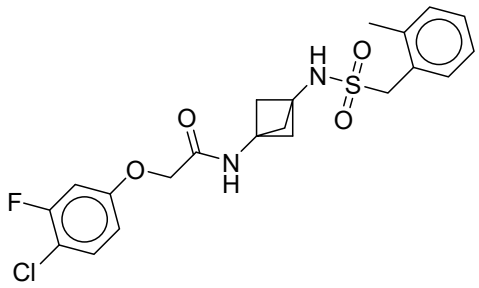

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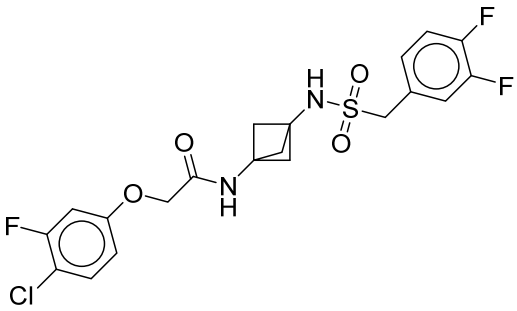

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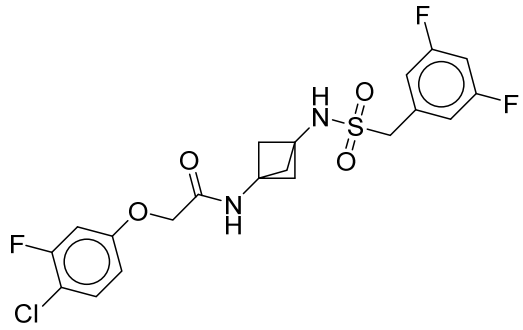

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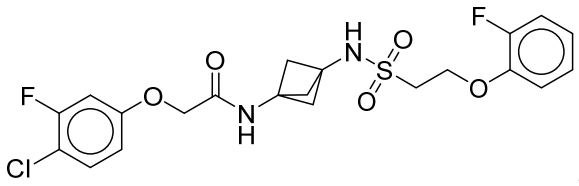

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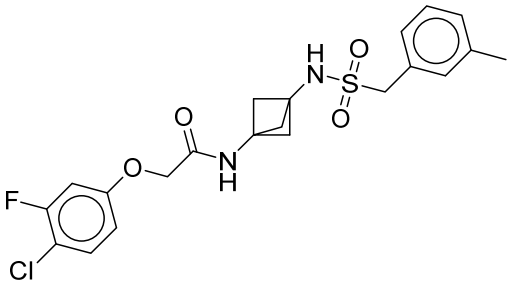

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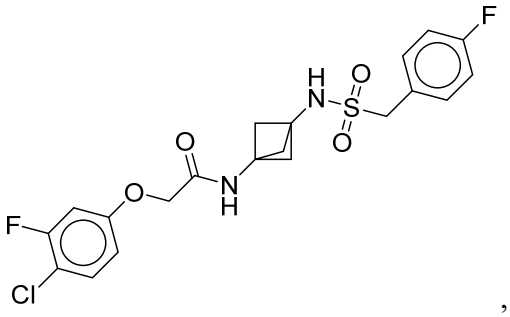

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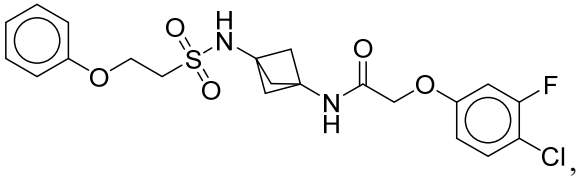

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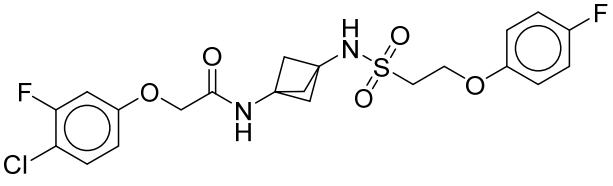

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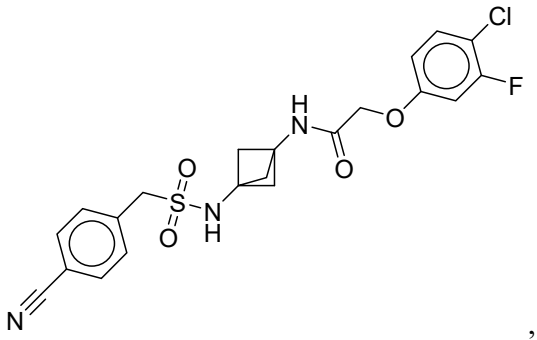

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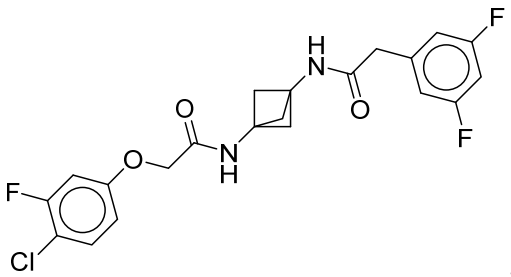

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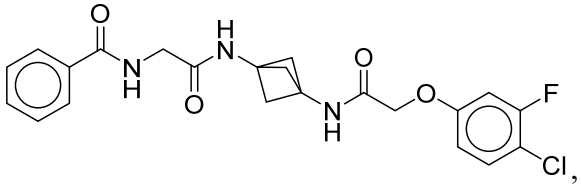

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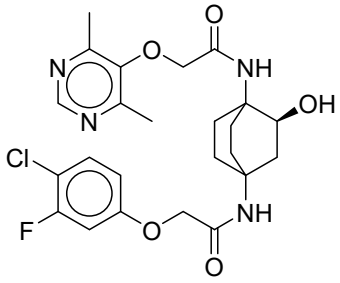

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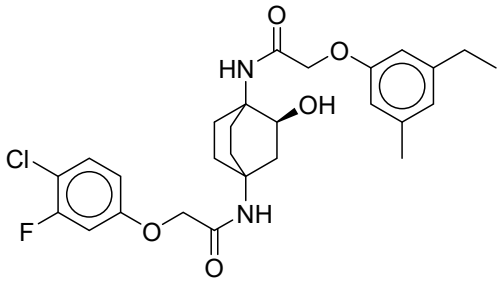

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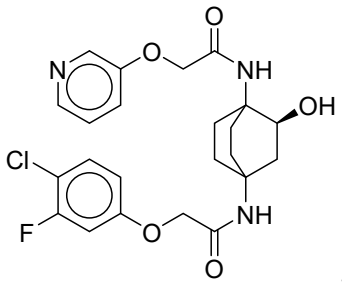

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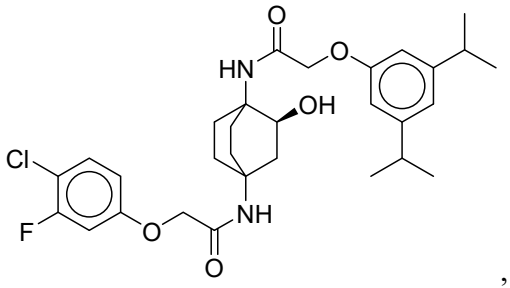

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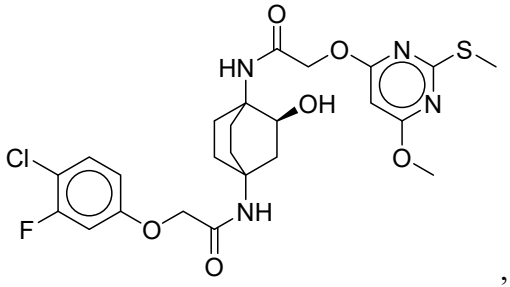

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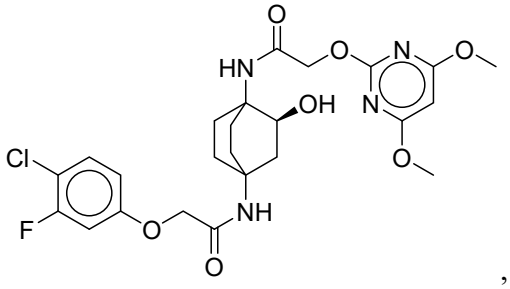

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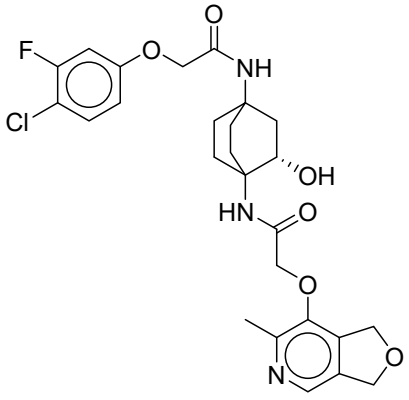

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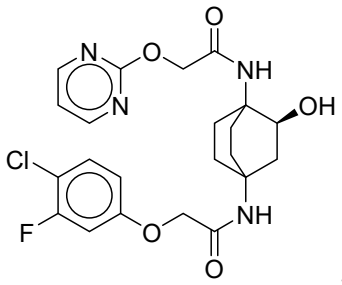

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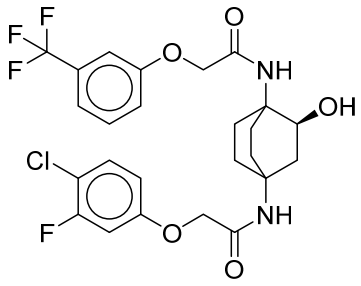

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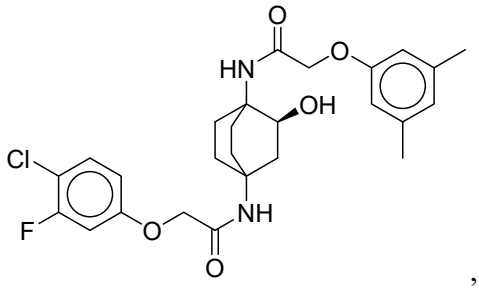

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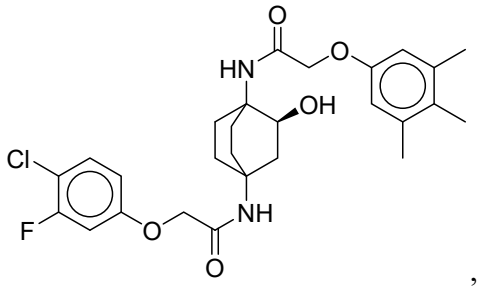

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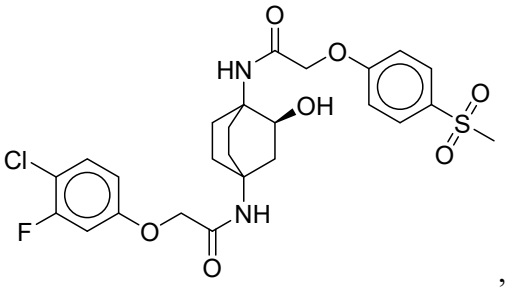

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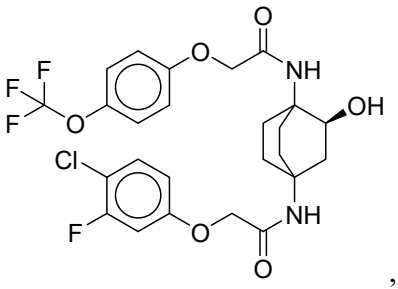
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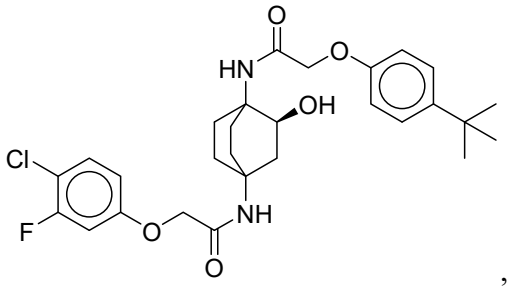
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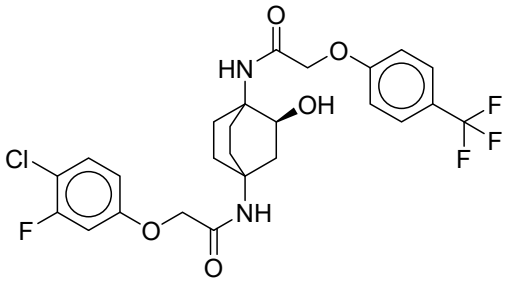
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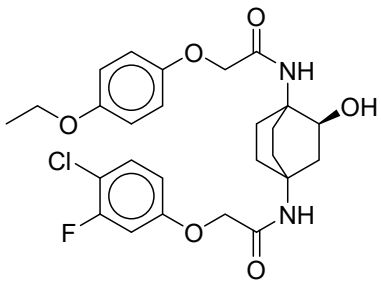
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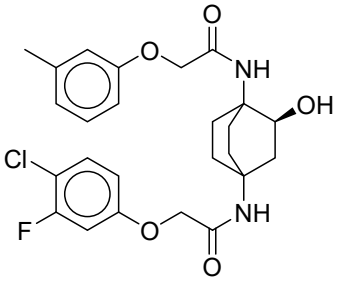
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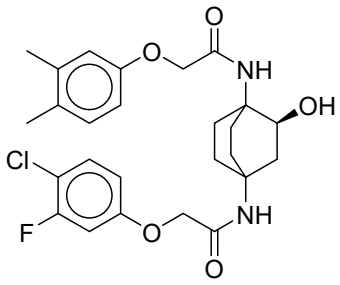
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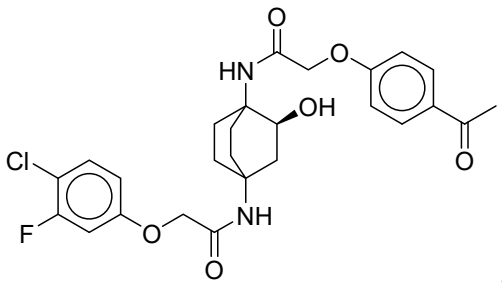
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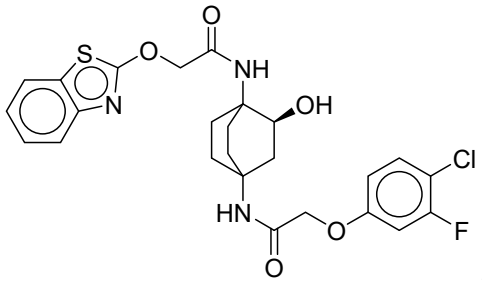
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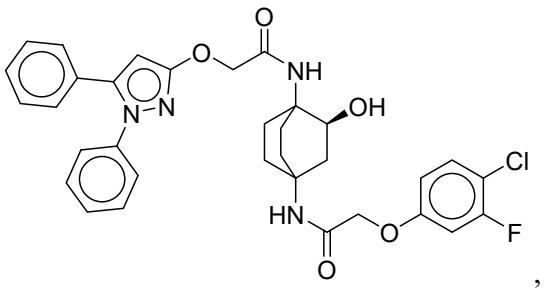
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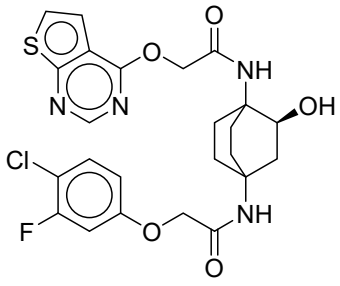
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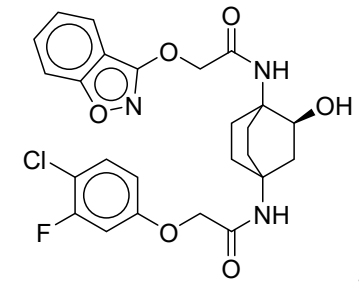

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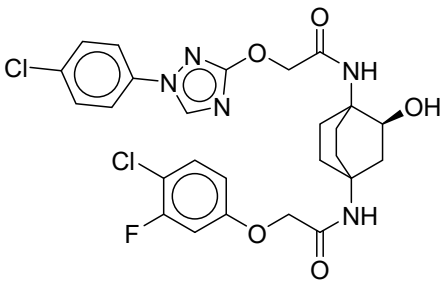

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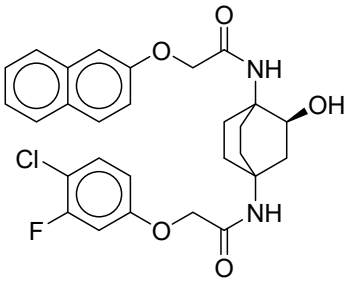

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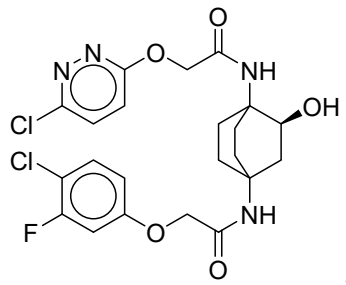

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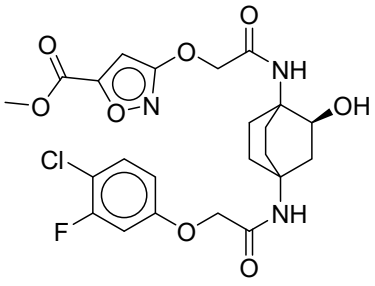

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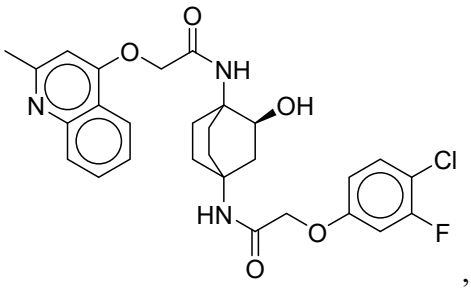

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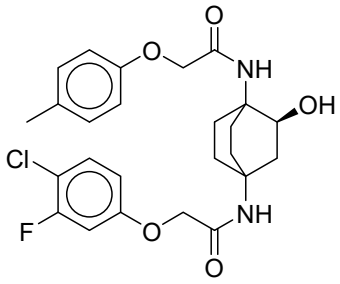

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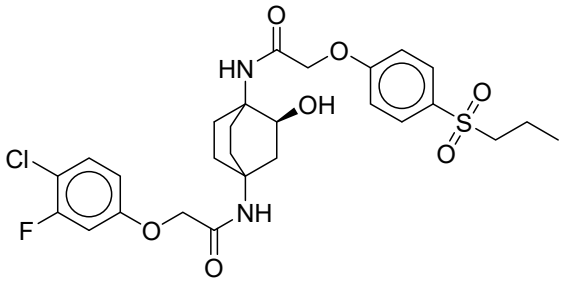

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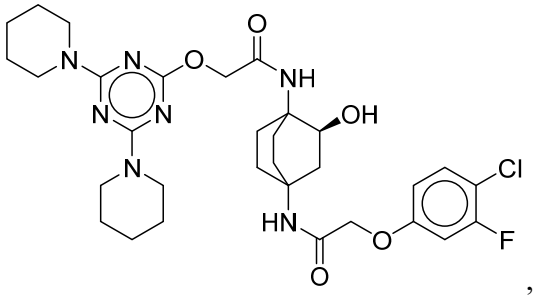

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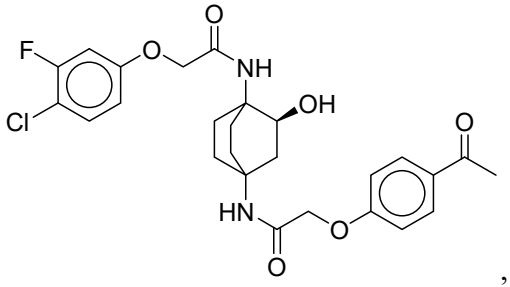

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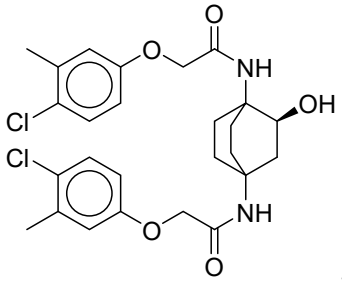

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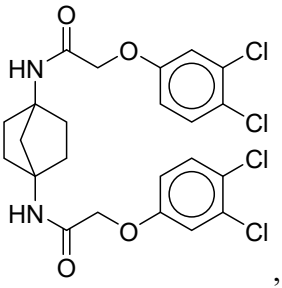

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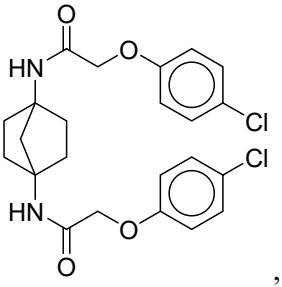

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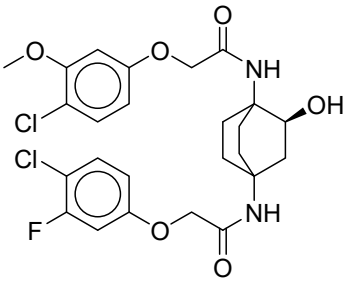

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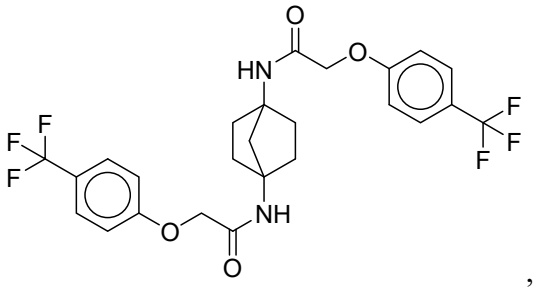

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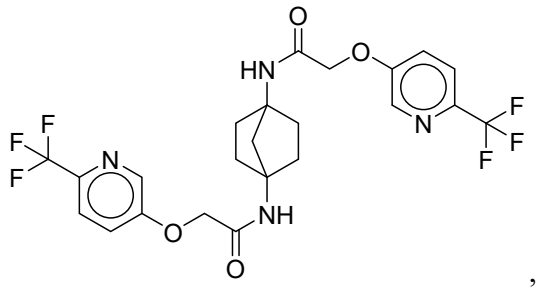

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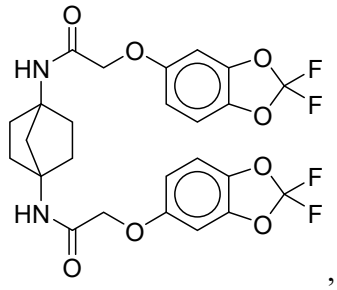

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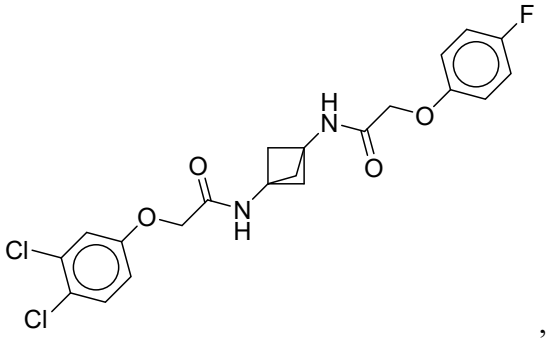

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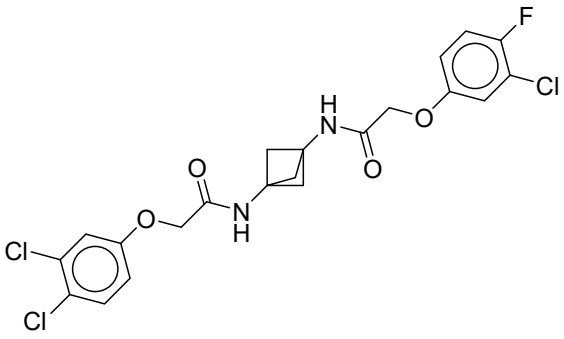

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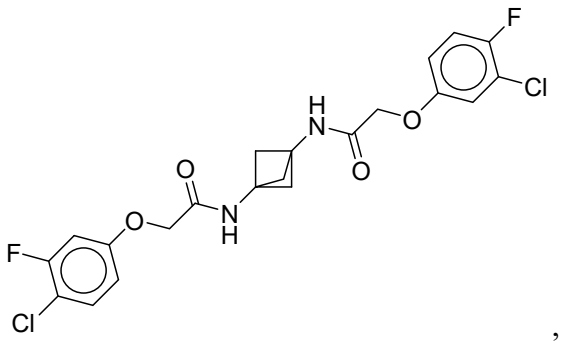

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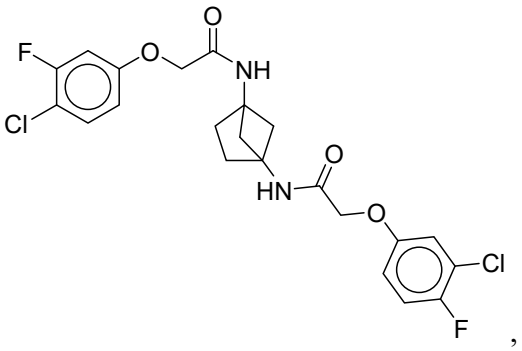

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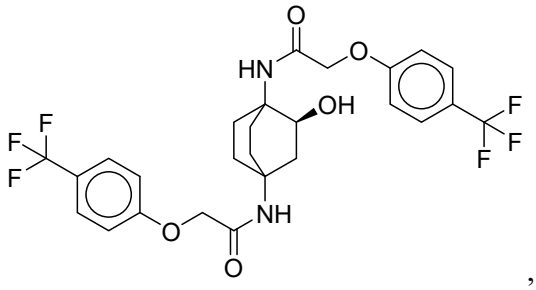

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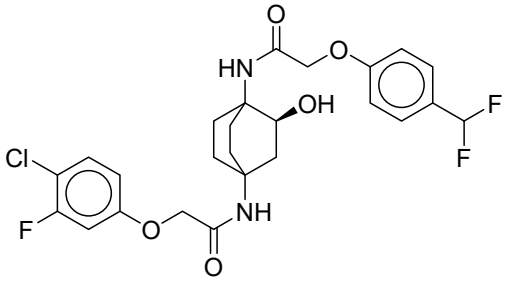

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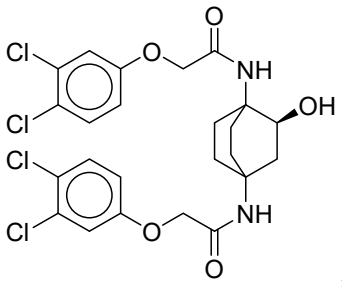

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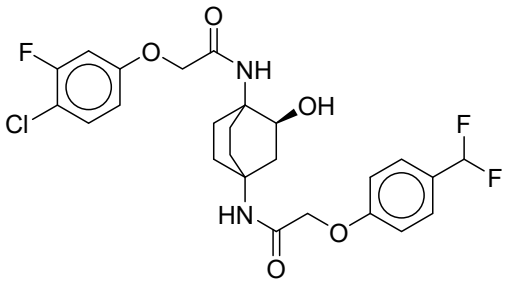

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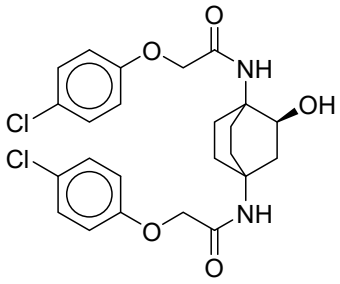

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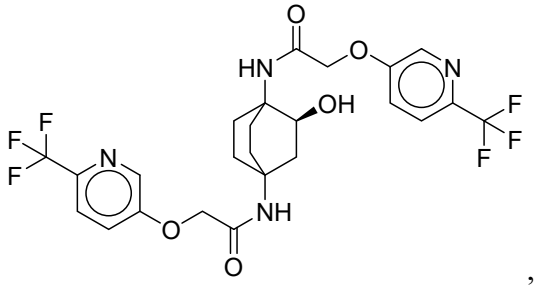

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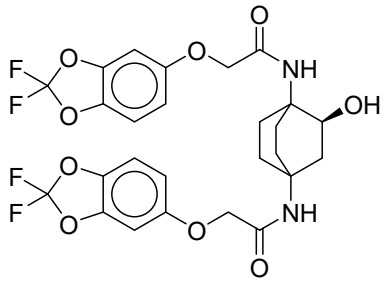

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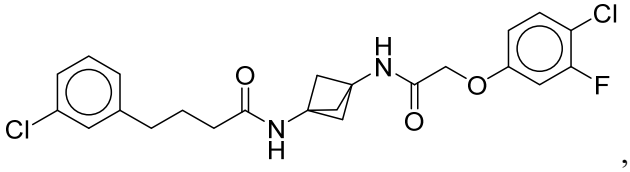

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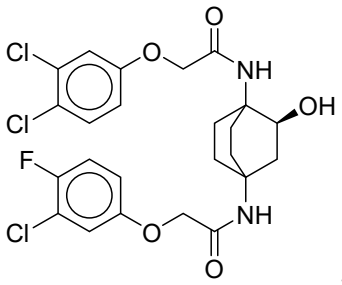

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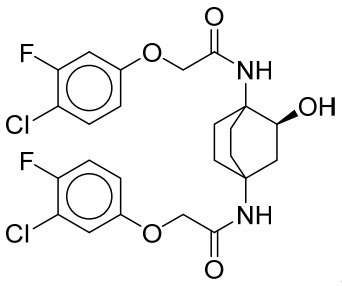

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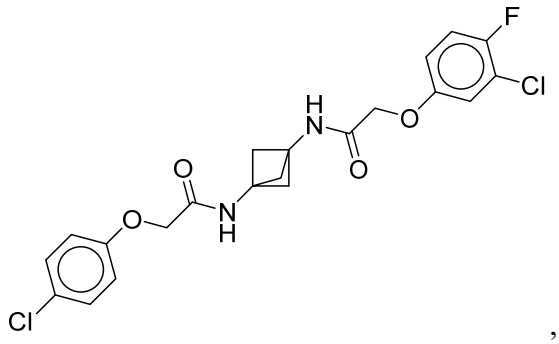

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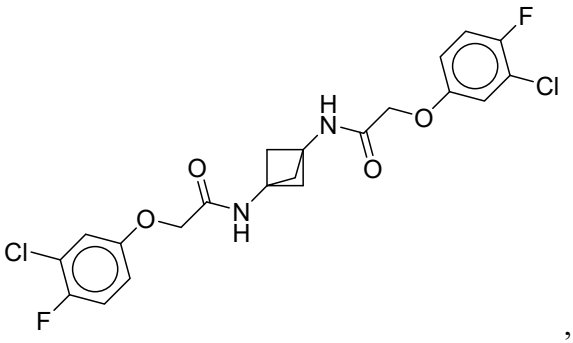

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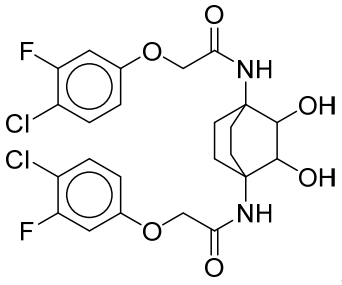

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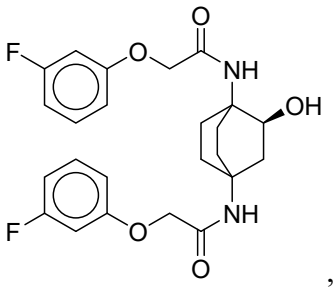
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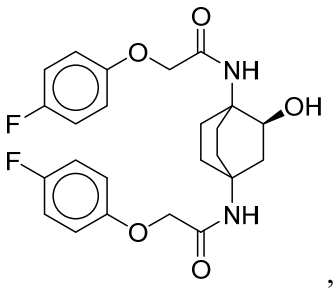
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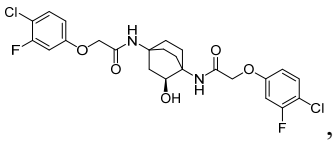
and a pharmaceutically acceptable salt thereof.

20. The compound of any one of claims 1-19, wherein the compound is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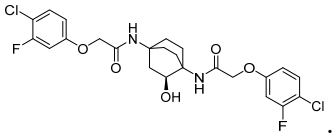
or a pharmaceutically acceptable salt thereof.

21. The compound of claim 20, wherein the compound is a pharmaceutical acceptable salt of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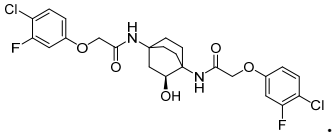
22. The compound of claim 20, wherein the compound is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