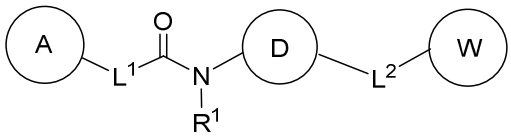
eIF2B4) are also highly homologous to one another and form a "regulatory sub-complex" that provides binding sites for eIF2B's substrate eIF2 (Dev, K. et al, *Mol Cell Biol* (2010) 30:5218-5233). The exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF)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

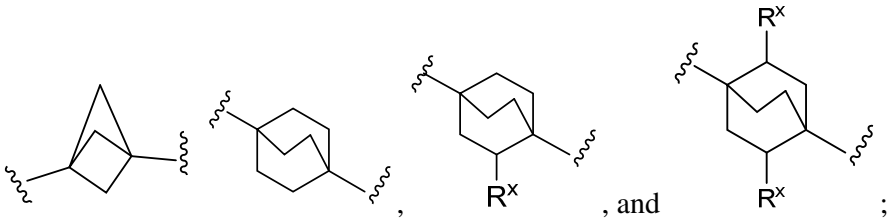
In one aspect of the present disclosure, there is provided a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of



, , and ;

L^1 is CH_2O–* or CH_2OCH_2–*; wherein "–*" indicates the attachment point to A;

L^2 is selected from the group consisting of O–*, OCH_2–*, CH_2O–*, OCH_2CH_2–*, CH_2OCH_2–*, and CH_2CH_2O–*; wherein "–*" indicates the attachment point to W;

R^1 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_2-C_6 alkyl, hydroxy-C_2-C_6 alkyl, and silyloxy-C_2-C_6 alkyl;

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

each R^X is independently selected from the group consisting of oxo, $-OR^A$, $-C(O)OH$, $-C(O)OR^D$, halo, and hydroxy-C_1-C_6 alkyl;

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, oxo, halo, cyano, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2R^D$, and G^1; or

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

each G^1 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, $-C(O)NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

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

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

each R^D is independently C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl, wherein each C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl is optionally substituted with 1-5 R^G;

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

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

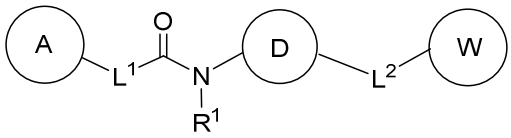
each R^G is independently aryl or 5-6 membered heteroaryl, wherein each aryl or 5-6 membered heteroaryl is optionally substituted with 1-5 R^H;

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

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

t is 0 or 1.

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



Formula (II-a)

or a pharmaceutically acceptable salt thereof, wherein:

D is bicyclo[1.1.1]pentanyl or bicyclo[2.2.2]octanyl, each of which is optionally substituted with 1-4 R^X groups;

L^1 is CH_2O–* or CH_2OCH_2–*, wherein "-*" indicates the attachment point to A;

L^2 is selected from the group consisting of O–*, OCH_2–*, CH_2O–*, OCH_2CH_2–*, CH_2OCH_2–*, and CH_2CH_2O–*; wherein "–*" indicates the attachment point to W;

A is phenyl or pyridyl, each of which is optionally substituted with 1-5 R^Y groups;

W is phenyl, pyridyl, isoxazolyl, or pyrazolyl, each of which is optionally substituted on one or more available carbons with 1-5 R^Y groups; and wherein pyrazolyl may be optionally substituted on an available nitrogen with hydrogen or CH_3;

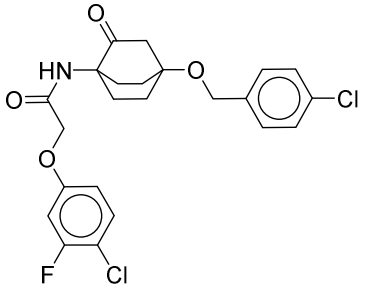
each R^X is independently fluoro, oxo, –OH, $–OCH_3$, –C(O)OH, or $–C(O)OCH_3$;

each R^Y is independently chloro, fluoro, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCH(CH_3)_2$, or –CN; or

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

R^1 is hydrogen.

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



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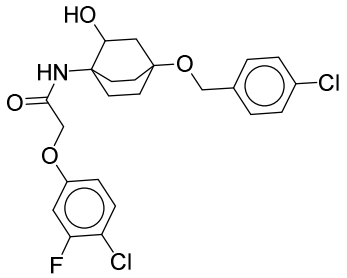

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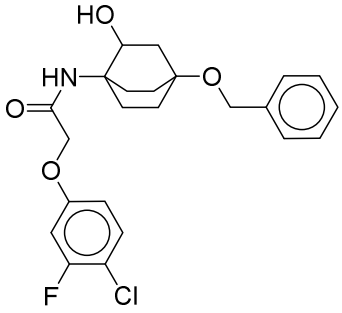

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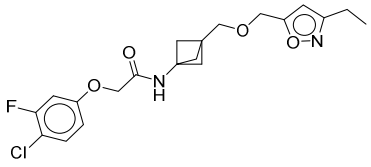

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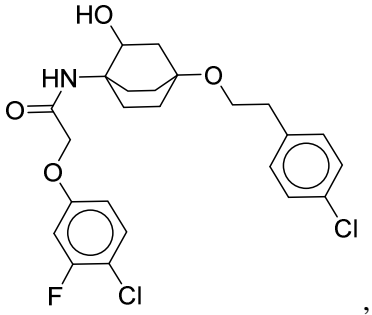

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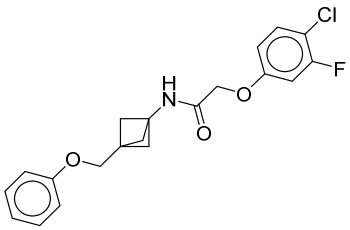

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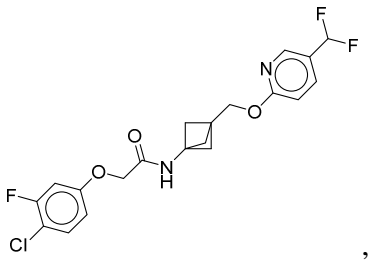
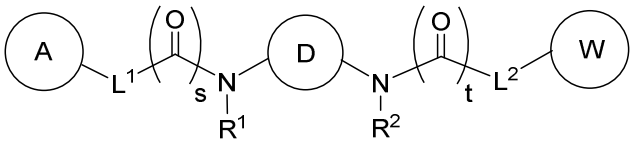


,
or a pharmaceutically acceptable salt thereof.

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 examples, the present disclosure features an eIF2B modulator (e.g., an eIF2B activator) comprising a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide or stereoisomer thereof. In other examples, the present disclosure features methods of using a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, ester, N-oxide 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 example, the present disclosure features a compound of Formula (I):

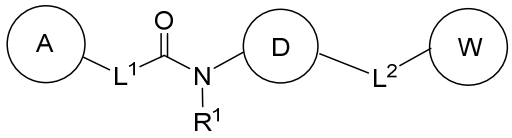


Formula (I)

CLAIMS

We claim:

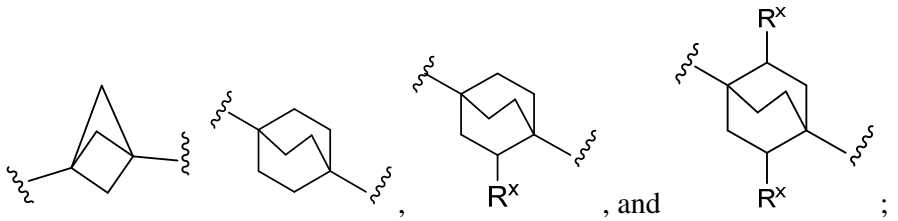
1. A compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of



, , and ;

L^1 is CH_2O–* or CH_2OCH_2–*; wherein "–*" indicates the attachment point to A;

L^2 is selected from the group consisting of O–*, OCH_2–*, CH_2O–*, OCH_2CH_2–*, CH_2OCH_2–*, and CH_2CH_2O–*; wherein "–*" indicates the attachment point to W;

R^1 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_2-C_6 alkyl, hydroxy-C_2-C_6 alkyl, and silyloxy-C_2-C_6 alkyl;

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

each R^X is independently selected from the group consisting of oxo, $–OR^A$, $–C(O)OH$, $–C(O)OR^D$, halo, and hydroxy-C_1-C_6 alkyl;

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, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OH$, $–C(O)OR^D$, $–S(R^F)_m$, $–S(O)R^D$, $–S(O)_2R^D$, and G^1; or

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

each G^1 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, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

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

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

each R^D is independently C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl, wherein each C_1-C_6 alkyl, 2-7-membered heteroalkyl, or halo-C_1-C_6 alkyl is optionally substituted with 1-5 R^G;

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

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

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

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

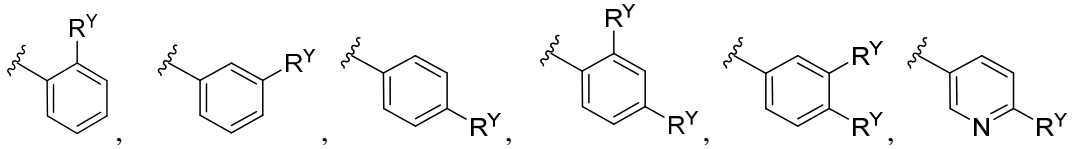
m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo; and

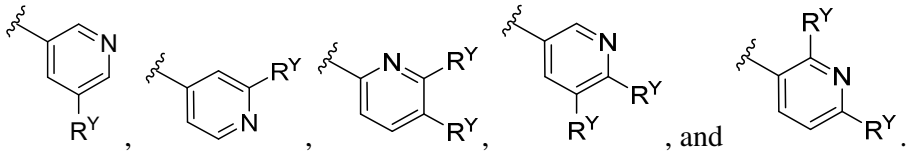
t is 0 or 1.

2. The compound of claim 1, wherein each R^X is independently selected from the group consisting of oxo, –OH, $–OCH_3$, –C(O)OH, $–C(O)OCH_3$, halo, and hydroxy-C_1-C_6 alkyl.

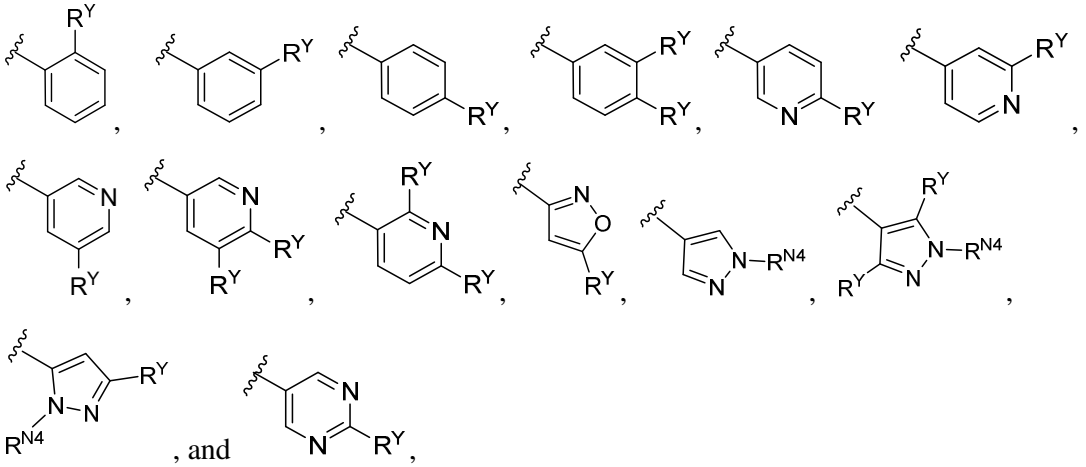
3. The compound of claim 1 or 2, wherein R^1 is hydrogen or $–CH_3$.

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





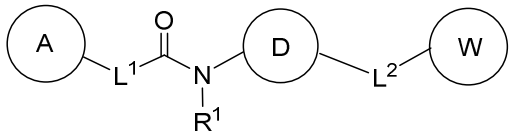
5. The compound of any one of claims 1-4, wherein W is selected from the group consisting of:



wherein R^{N4} is hydrogen or $–CH_3$.

6. The compound of any one of claims 1-5, wherein each R^Y is independently hydrogen, chloro, fluoro, $–CF_3$, $–CHF_2$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCF_3$, $–OCH(CH_3)_2$, or –CN.

7. A compound of Formula (II-a):



Formula (II-a)

or a pharmaceutically acceptable salt thereof, wherein:

D is bicyclo[1.1.1]pentanyl or bicyclo[2.2.2]octanyl, each of which is optionally substituted with 1-4 R^X groups;

L^1 is $CH_2O–*$ or $CH_2OCH_2–*$, wherein "-*" indicates the attachment point to A;

L^2 is selected from the group consisting of $O–*$, $OCH_2–*$, $CH_2O–*$, $OCH_2CH_2–*$, $CH_2OCH_2–*$, and $CH_2CH_2O–*$; wherein "–*" indicates the attachment point to W;

A is phenyl or pyridyl, each of which is optionally substituted with 1-5 R^Y groups;

W is phenyl, pyridyl, isoxazolyl, or pyrazolyl, each of which is optionally substituted on one or more available carbons with 1-5 R^Y groups; and wherein pyrazolyl may be optionally substituted on an available nitrogen with hydrogen or CH_3;

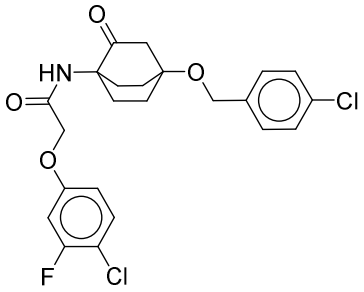
each R^X is independently fluoro, oxo, –OH, $–OCH_3$, –C(O)OH, or $–C(O)OCH_3$;

each R^Y is independently chloro, fluoro, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCH(CH_3)_2$, or –CN; or

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

R^1 is hydrogen.

8. A compound, wherein the compound is selected from the group consisting of:



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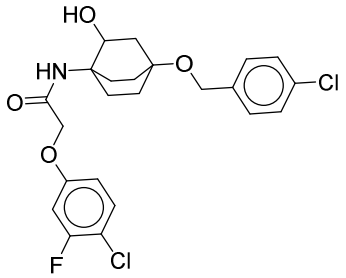

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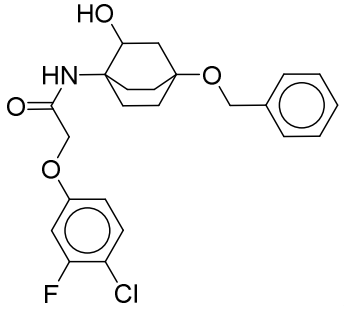

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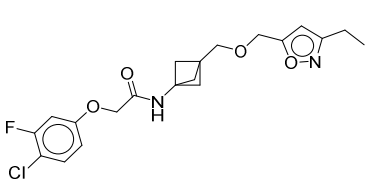

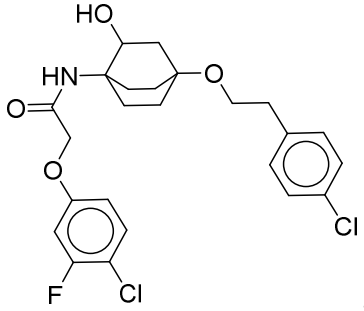

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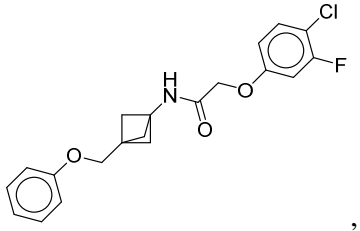

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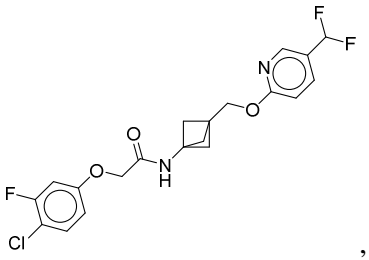

,

or a pharmaceutically acceptable salt thereof.