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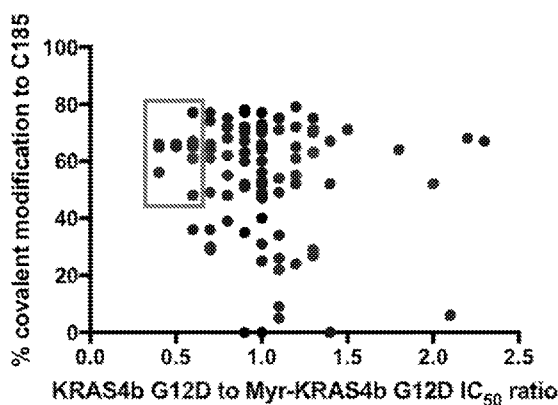


FIG. 7

(57) Abstract: Provided herein are compounds comprising a vinyl sulfonamide moiety. Also provided herein are pharmaceutical compositions comprising such compounds, and methods of using such compounds and pharmaceutical compositions for inhibiting the post-translational processing of K-Ras precursors, and for treating disorders in a subject in need thereof.



DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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- *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

K-RAS MODULATORS WITH A VINYL SULFONAMIDE MOIETY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/659,607, filed April 18, 2018, the disclosure of which is hereby incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Contract No. HHSN261200800001E awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD

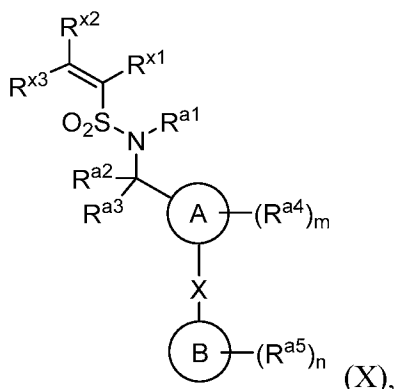
[0003] The present disclosure relates generally to compounds that inhibit K-Ras, or the post-translational processing of Ras that produces a mature, fully-processed K-Ras protein, and more specifically to inhibitors with a vinyl sulfonamide moiety.

BACKGROUND

[0004] *KRAS* is one of the most frequently mutated oncogenes implicated in human cancer. The *KRAS* oncogene encodes the K-Ras protein, which is part of RAS/MAPK signaling pathway. K-Ras is a GTPase that acts as a molecular switch, flipping between an active GTP-bound form and an inactive GDP-bound form. The K-Ras protein plays a crucial role in tissue signaling, and is involved in cell proliferation, cell differentiation, and apoptosis. Activating mutations in *KRAS* are common in many different human cancers. Thus, what is needed are effective inhibitors of K-Ras, and effective inhibitors of the post translational processing of Ras that produces a mature, fully-processed K-Ras protein.

BRIEF SUMMARY

[0005] In some aspects, provided herein is a compound of Formula (X):



or a pharmaceutically acceptable salt thereof, wherein:

R^{x1} , R^{x2} , and R^{x3} are independently hydrogen, -CN, or alkyl; or R^{x2} and R^{x3} together form alkenyl; or R^{x1} and R^{x2} together with the carbon atoms to which they are attached form heterocycloalkenyl or cycloalkenyl; or R^{a1} and R^{x2} together with the atoms to which they are attached form heterocycloalkenyl; wherein each alkyl, alkenyl, heteroaryl, heterocycloalkenyl, and cycloalkenyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo and $-OR^{x4}$, wherein each R^{x4} is independently H, alkyl, or haloalkyl;

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when A is piperidiny and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and =O;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{a7}\text{R}^{a8}$, $-\text{OR}^{a9}$, and $-\text{SO}_2\text{R}^{a10}$, wherein when A is phenyl, R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{a7}\text{R}^{a8}$, $-\text{OR}^{a9}$, and $-\text{SO}_2\text{R}^{a10}$; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{a7}\text{R}^{a8}$, $-\text{OR}^{a9}$, $=\text{O}$, $-\text{SR}^{a47}$, and $-\text{SO}_2\text{R}^{a10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{a46}-$, or $-\text{C}(\text{S})-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or, when X is $-\text{C}(\text{O})-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a spirocycle with ring A, wherein the spirocycle is unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{a48}\text{R}^{a49}$, $-\text{NR}^{a11}\text{R}^{a12}$, $-\text{OR}^{a13}$, $-\text{SO}_2\text{R}^{a14}$, $=\text{O}$, and $-\text{SR}^{a15}$,

wherein each alkenyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{a16}$, $=\text{O}$, $-\text{NR}^{a17}\text{R}^{a18}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{a50}\text{R}^{a51}$, $-\text{SR}^{a52}$, $-\text{SO}_2\text{R}^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{a19}$, $=\text{O}$, $-\text{NR}^{a20}\text{R}^{a21}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{a54}\text{R}^{a55}$, $-\text{SR}^{a56}$, $-\text{SO}_2\text{R}^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a35} , R^{a54} , and R^{a55} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{a22}\text{R}^{a23}$, $-\text{OR}^{a24}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, $=\text{O}$, $-\text{NR}^{a36}\text{R}^{a37}$, $-\text{NR}^{a38}\text{C}(\text{O})\text{R}^{a39}$, $-\text{OR}^{a40}$, and R^{a59} , wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or

substituted with one or more substituents independently selected from the group consisting of =O, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

each $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, $\text{R}^{\text{a}24}$, $\text{R}^{\text{a}36}$, $\text{R}^{\text{a}37}$, $\text{R}^{\text{a}38}$, and $\text{R}^{\text{a}39}$ is independently hydrogen, alkyl, or haloalkyl;

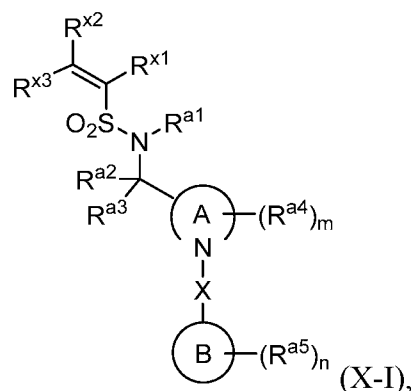
wherein each alkyl or haloalkyl or $\text{R}^{\text{a}22}$ and $\text{R}^{\text{a}23}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

each $\text{R}^{\text{a}40}$ is independently hydrogen, alkyl, haloalkyl, aryl, or heteroaryl, wherein each aryl or heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

m is an integer from 0 to 13; and

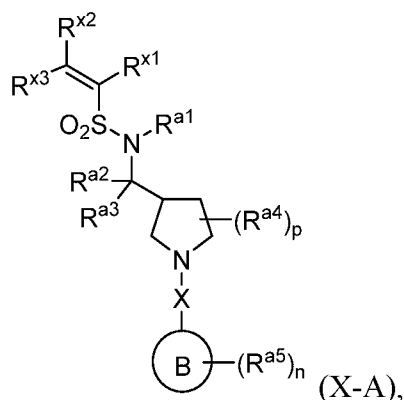
n is an integer from 0 to 11.

[0006] In some variations, the compound of Formula (X) is a compound of Formula (X-I):



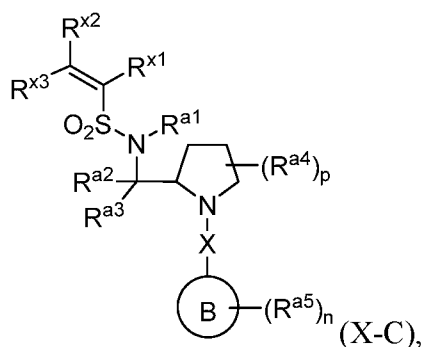
or a pharmaceutically acceptable salt thereof, wherein A is 4- to 10-membered heterocycloalkyl, and B, X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, m, and n are as defined for Formula (X).

[0007] In some variations, the compound of Formula (X) is a compound of Formula (X-A):



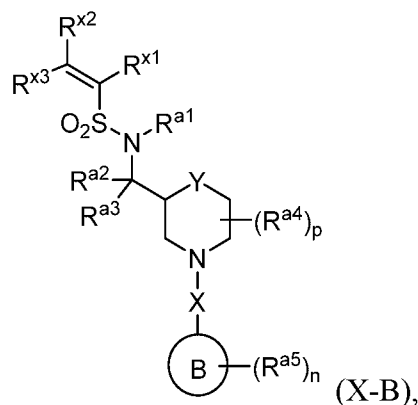
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, and n are as defined for Formula (X).

[0008] In some variations, the compound of Formula (X) is a compound of Formula (X-C):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, and n are as defined for Formula (X).

[0009] In some variations, the compound of Formula (X) is a compound of Formula (X-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, $-\text{S}(\text{O})_r-$, $-\text{O}-$, or $-\text{N}(\text{R}^{\text{a45}})-$, wherein each R^{a45} is independently hydrogen or R^{a4} ;

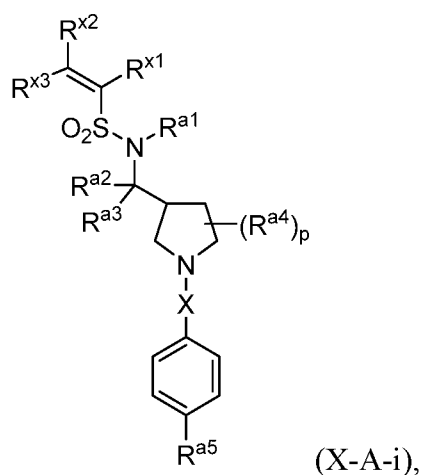
X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$, wherein when Y is $-\text{CH}_2-$ and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

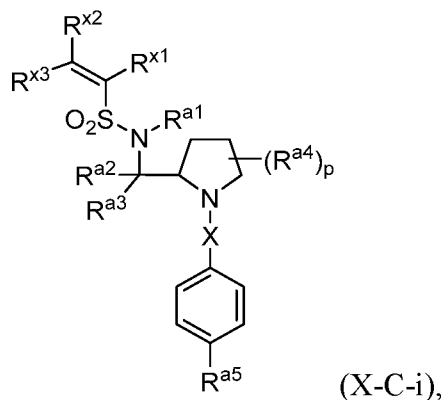
and B, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} , R^{a46} , and n are as defined for Formula (X).

[0010] In some variations, the compound of Formula (X) is a compound of Formula (X-A-i):



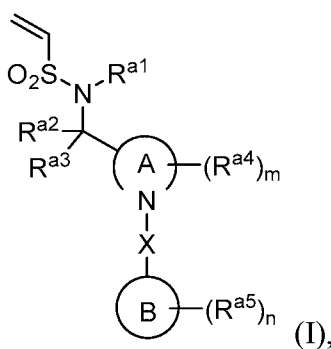
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are as defined in Formula (X).

[0011] In some variations, the compound of Formula (X) is a compound of Formula (X-C-i):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are as defined in Formula (X).

[0012] In some aspects, the compound of Formula (X) is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, -C(S)-, -C(O)-, or -C(R^{a6})₂-, wherein when A is piperidiny and B is phenyl, X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, -C(S)-, or -C(R^{a6})₂-;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and =O;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, $=O$, $-SR^{a47}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or two to four R^{a4} , together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{a48}\text{R}^{a49}$, $-\text{NR}^{a11}\text{R}^{a12}$, $-\text{OR}^{a13}$, $-\text{SO}_2\text{R}^{a14}$, $=\text{O}$, and $-\text{SR}^{a15}$,

wherein each cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{a16}$, $=\text{O}$, $-\text{NR}^{a17}\text{R}^{a18}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{a50}\text{R}^{a51}$, $-\text{SR}^{a52}$, $-\text{SO}_2\text{R}^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{a19}$, $=\text{O}$, $-\text{NR}^{a20}\text{R}^{a21}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{a54}\text{R}^{a55}$, $-\text{SR}^{a56}$, $-\text{SO}_2\text{R}^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{a22}\text{R}^{a23}$, $-\text{OR}^{a24}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, $=\text{O}$, $-\text{NR}^{a36}\text{R}^{a37}$, $-\text{NR}^{a38}\text{C}(\text{O})\text{R}^{a39}$, $-\text{OR}^{a40}$, and R^{a59} , wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or

substituted with one or more substituents independently selected from the group consisting of =O, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

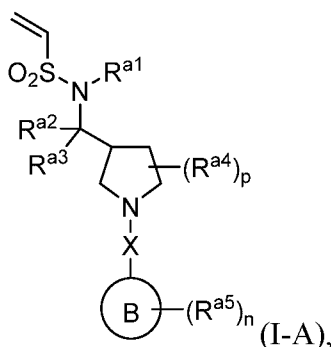
each $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, $\text{R}^{\text{a}24}$, $\text{R}^{\text{a}36}$, $\text{R}^{\text{a}37}$, $\text{R}^{\text{a}38}$, $\text{R}^{\text{a}39}$, and $\text{R}^{\text{a}40}$ is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

n is an integer from 0 to 11.

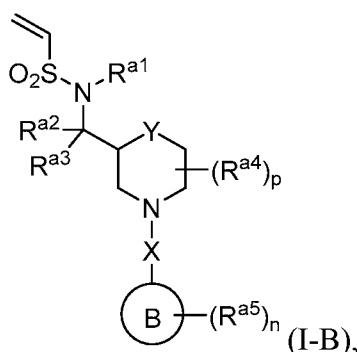
[0013] In some variations of the compound of Formula (X), Formula (X-I), or Formula (I), or a pharmaceutically acceptable salt thereof, A is 5- or 6-membered heterocycloalkyl.

[0014] In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, $\text{R}^{\text{a}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}4}$, $\text{R}^{\text{a}5}$, and n are as defined for Formula (I).

[0015] In other variations, the compound of Formula (X) or Formula (I) is a compound of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, $-\text{S}(\text{O})_r-$, $-\text{O}-$, or $-\text{N}(\text{R}^{\text{a45}})-$, wherein each R^{a45} is independently hydrogen or R^{a4} ;

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$, wherein when Y is $-\text{CH}_2-$ and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$;

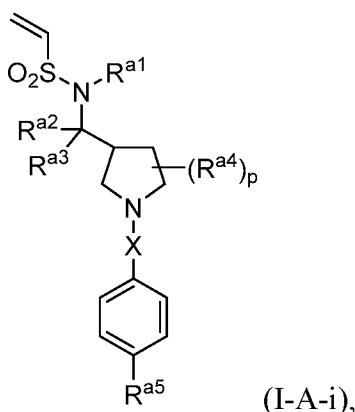
r is 0, 1, or 2;

p is an integer from 0 to 7;

and B, R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} , R^{a46} , and n are as defined for Formula (I).

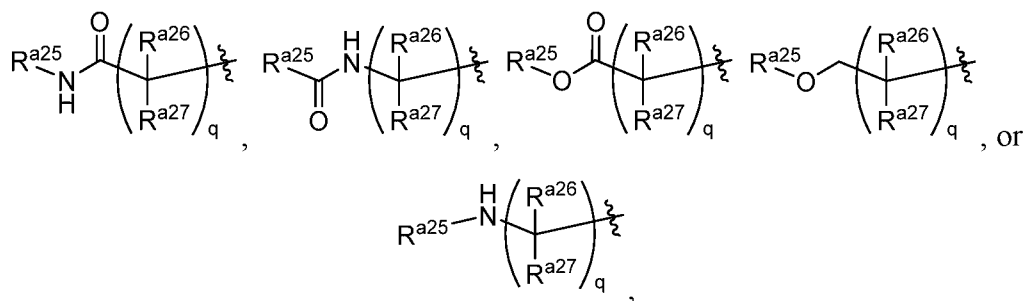
[0016] In certain variations of the compound of Formula (I-B), or a pharmaceutically acceptable salt thereof, Y is $-\text{CH}_2-$. In certain variations of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), or Formula (I-B), or a pharmaceutically acceptable salt thereof, B is heteroaryl, cycloalkyl, or heterocycloalkyl.

[0017] In other variations, the compound of Formula (X) or Formula (I) is a compound of Formula (I-A-i):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and X, R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are as defined for Formula (I).

[0018] In certain variations of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof, at least one of R^{a5} is:



wherein:

R^{a25} is hydrogen, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

wherein the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, $=\text{O}$, $-\text{OR}^{a28}$, $-\text{SF}_5$, and $-\text{NR}^{a29}\text{R}^{a30}$,

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{SF}_5$, $=\text{O}$, $-\text{OR}^{a31}$, $-\text{NR}^{a41}\text{R}^{a42}$, $-\text{NR}^{a43}\text{C}(\text{O})\text{R}^{a44}$, cycloalkyl, and heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $=\text{O}$, halo, $-\text{OH}$, and $-\text{SF}_5$;

each R^{a26} and R^{a27} is independently hydrogen, halo, or alkyl;

wherein each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{OR}^{a32}$, and $-\text{NR}^{a33}\text{R}^{a34}$,

wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, haloalkyl, alkyl, $-\text{OH}$, $=\text{O}$, and $-\text{SF}_5$;

or one R^{a26} and one R^{a27} attached to the same atom, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

each R^{a28}, R^{a29}, R^{a30}, R^{a31}, R^{a32}, R^{a33}, R^{a34}, R^{a41}, R^{a42}, R^{a43}, and R^{a44} is independently hydrogen, alkyl, or haloalkyl;

and q is 1 or 2.

[0019] In certain variations of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof, X is $-S(O)_2-$. In other variations, X is $-C(O)-$. In still further variations, X is $-CH_2-$.

[0020] In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (X) (such as Formula (I)), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof.

[0021] In a further aspect, provided herein is a method of reducing the level of a K-Ras protein in a subject in need thereof, by administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (X) (such as Formula (I)), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I-B), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof.

[0022] In still another aspect, provided herein is a method of treating a disorder in a subject in need thereof, by administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (X) (such as Formula (I)), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i),

Formula (I-B), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof.

[0023] In yet a further aspect, provided herein is the use of a compound of Formula (X) (such as Formula (I)), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of a K-Ras protein in a subject in need thereof. In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I-B), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof.

[0024] In another aspect, provided herein is the use of a compound of Formula (X) (such as Formula (I)), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof. In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I-B), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof.

[0025] In still a further aspect, provided herein is a compound of Formula (X) (such as Formula (I)), or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of a K-Ras protein in a subject in need thereof. In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I-B), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof.

[0026] In yet another aspect, provided herein is a compound of Formula (X) (such as Formula (I)), or a pharmaceutically acceptable salt thereof, for use in a method of treating a disorder in a subject in need thereof. In some variations, the compound of Formula (X) or Formula (I) is a compound of Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I-B), Formula (I-A), Formula (I-A-i), or Formula (I-B), or a pharmaceutically acceptable salt thereof.

[0027] In certain variations of the aspects described herein, the disorder is cancer. In some embodiments, the cancer is a blood cancer, or a solid tumor. In some variations, the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath

tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer. In other variations of the aspects described herein, the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome. In certain variations of the aspects described herein, the disorder is associated with a mutation of K-Ras.

DESCRIPTION OF THE FIGURES

[0028] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0029] FIG. 1 depicts an immunoblot demonstrating the effect of compound I-0175 on the level of K-Ras in mouse embryonic fibroblast (MEF) cell lines expressing *KRAS Q61R*, *KRAS G12D*, or *Myr-KRAS G12D/C185S* genes. Cells were treated with compound (I-0175), or corresponding volume of DMSO (D), or left untreated (0). Seventy-two hours after treatment was initiated, cells were lysed, then 30 micrograms of total protein lysate was resolved by SDS-PAGE, followed by immunoblotting with antibodies as described in the Experimental section.

[0030] FIG. 2 depicts an immunoblot demonstrating the effect of compound I-0175 on K-Ras membrane localization in the different MEF cell lines K-Ras4b G12D, K-Ras4b G12V, and H-Ras wild type (WT). “WCL” refers to whole cell lysate. Cells were treated with I-0175 at 12.5 or 25 μ M, or DMSO volume corresponding to the highest compound dose (D). Seventy-two hours after treatment was initiated, cells were fractionated using digitonin in a sucrose buffer (following the protocol provided in Experimental section). Corresponding cytosolic and membrane lysates (30 μ g protein) were resolved by SDS-PAGE, followed by immunoblot. Anti-MEK antibodies were used as a cytosolic fraction loading control, and anti-Na/K ATPase antibodies as a control for a membrane fraction.

[0031] FIG. 3 depicts confocal images of the effect of compound I-0175 on cell membrane localization of K-Ras4b in HeLa cells.

[0032] FIG. 4 depicts confocal images of the effect of compound I-0176 on HeLa cells expressing *eGFP-KRAS4b G12D* in a doxycycline-inducible system. *KRAS* gene expression was induced with doxycycline, followed immediately with addition of compound I-0176 at

the concentrations depicted on the panels. The presence of compound I-0176 decreased K-Ras membrane localization.

[0033] FIGS. 5A-5D depicts results from cell proliferation assays with selected compounds in MEF cells after 72 h incubation, (IC_{50} values, μM).

[0034] FIG. 6 is a table listing the IC_{50} ratio of selected compounds in G12D vs. Myr-G12D MEFs.

[0035] FIG. 7 is a graph comparing the level of covalent modification to C185 (measured by MALDI-TOF MS) with calculated IC_{50} ratios (of K-Ras4b G12D to Myr-K-Ras G12D/C185 MEFs) for selected compounds.

[0036] FIGS. 8A-8C are heat maps representing IC_{50} values for selected compounds in mouse embryonic fibroblast (MEF) cells. Numbers represent IC_{50} values, with lowest IC_{50} (black) indicating highest sensitivity. In FIG. 8A, bracketed compounds demonstrated desirable selectivity for MEF cells expressing oncogenic mutant of *KRAS4b* (such as G12V, G12D or Q61R), compared to MEFs expressing *HRAS*, or control cell line expressing *Myr-KRASG12D/C185S*. In FIG. 8C, bracketed compounds demonstrated higher activity in MEFs expressing *KRAS4b G12V*, compared to *KRAS4a*, *HRAS*, or *Myr-KRAS G12D/C185S* cells.

[0037] FIG. 9 is a heat map representing IC_{50} values for selected compounds in MEF cells expressing the proteins K-Ras4b G12D, K-Ras4b G12V, Myr-K-Ras G12D/C185S, or Myr-K-Ras G12V/C185S.

[0038] FIG. 10 is a table summarizing the data displayed in FIG. 9.

DETAILED DESCRIPTION

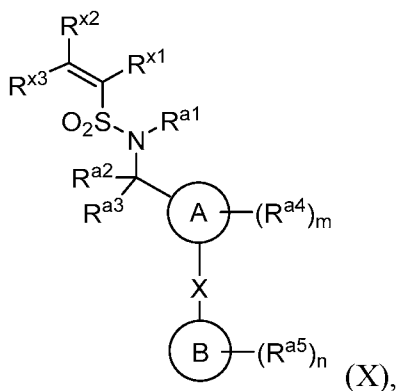
[0039] The following description sets forth numerous exemplary configurations, methods, parameters, and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure, but is instead provided as a description of exemplary embodiments.

[0040] Provided herein is a compound, such as a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically

acceptable salt of any of the foregoing, as described below. In some embodiments, this compound may inhibit K-Ras, or may inhibit the post-translational processing of K-Ras that produces a mature, fully-processed K-Ras protein, such as K-Ras4b. For example, in some embodiments, this compound may block the farnesylation of the newly synthesized K-Ras, preventing its C-terminal processing. In other embodiments, this compound or salt thereof may be administered to a subject in need thereof, for example in a pharmaceutical composition further comprising a pharmaceutically acceptable excipient. In some embodiments, a compound as described herein may be administered in a therapeutically effective amount to a subject in need thereof in a method of treating a disorder in a subject. The disorder may be, for example, a disorder associated with a mutation in K-Ras. In some embodiments, the compound inhibits K-Ras, or decreases the level of K-Ras, or inhibits the post-translational processing of K-Ras to produce a K-Ras protein, such as K-Ras4b. These compounds, compositions comprising said compounds, and methods of using said compounds and compositions are described in greater detail below.

I. Compounds of Formula (X)

[0041] In some aspects, provided herein is a compound of Formula (X):



or a pharmaceutically acceptable salt thereof, wherein:

R^{x1} , R^{x2} , and R^{x3} are independently hydrogen, -CN, or alkyl; or R^{x2} and R^{x3} together form alkenyl; or R^{x1} and R^{x2} together with the carbon atoms to which they are attached form heterocycloalkenyl or cycloalkenyl; or R^{a1} and R^{x2} together with the atoms to which they are attached form heterocycloalkenyl; wherein each alkyl, alkylene, heteroaryl, heterocycloalkenyl, and cycloalkenyl is independently unsubstituted or substituted with one or more substituents

independently selected from the group consisting of halo and $-OR^{x4}$, wherein each R^{x4} is independently H, alkyl, or haloalkyl;

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when A is piperidiny and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=O$;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$, wherein when A is phenyl, R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, $=O$, $-SR^{a47}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

- or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;
- or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;
- or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;
- or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;
- or, when X is $-C(O)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a spirocycle with ring A, wherein the spirocycle is unsubstituted or substituted with one or more halo;
- each R^{a5} is independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-NO_2$, $-CN$, $-SO_2NR^{a48}R^{a49}$, $-NR^{a11}R^{a12}$, $-OR^{a13}$, $-SO_2R^{a14}$, $=O$, and $-SR^{a15}$, wherein each alkenyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;
- each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a19}$, $=O$, $-NR^{a20}R^{a21}$, $-CN$, $-SF_5$, $-SO_2NR^{a54}R^{a55}$, $-SR^{a56}$, $-SO_2R^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;
- each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently

hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl,
heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a35} , R^{a54} , and R^{a55} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-NR^{a22}R^{a23}$, $-OR^{a24}$, and $-SF_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, -CN, $-SF_5$, =O, $-NR^{a36}R^{a37}$, $-NR^{a38}C(O)R^{a39}$, $-OR^{a40}$, and R^{a59} , wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, $-NH_2$, $-SF_5$, -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl;

each R^{a22} , R^{a23} , R^{a24} , R^{a36} , R^{a37} , R^{a38} , and R^{a39} is independently hydrogen, alkyl, or haloalkyl;

wherein each alkyl or haloalkyl or R^{a22} and R^{a23} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of
-OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl;

each R^{a40} is independently hydrogen, alkyl, haloalkyl, aryl, or heteroaryl, wherein each aryl or heteroaryl is independently unsubstituted or

substituted with one or more substituents independently selected from the group consisting of $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

m is an integer from 0 to 13; and

n is an integer from 0 to 11.

[0042] "Alkyl", as used herein, refers to an unbranched or branched saturated hydrocarbon chain. In some embodiments, alkyl as used herein has 1 to 50 carbon atoms ((C₁-C₅₀)alkyl), 1 to 20 carbon atoms ((C₁-C₂₀)alkyl), 1 to 12 carbon atoms ((C₁-C₁₂)alkyl), 1 to 8 carbon atoms ((C₁-C₈)alkyl), 1 to 6 carbon atoms ((C₁-C₆)alkyl), or 1 to 4 carbon atoms ((C₁-C₄)alkyl). Examples of alkyl groups may, for example, include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 2-pentyl, isopentyl, neopentyl, n-hexyl, 2-hexyl, 3-hexyl, and 3-methyl pentyl. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed. Thus, for example, "butyl" can include n-butyl, sec-butyl, isobutyl and t-butyl, and "propyl" can include n-propyl and isopropyl.

[0043] "Haloalkyl", as used herein, refers to an alkyl group substituted with one or more halo, which may be selected independently. Thus, haloalkyl includes alkyl substituted with one or more halo independently selected from the group consisting of fluoro, chloro, iodo, and bromo. Haloalkyl may include, for example, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CHCl}_2$, $-\text{CCl}_3$, $-\text{CH}_2\text{CHFCl}$, $-\text{CHFCH}_3$, $-\text{CH}_2\text{Br}$, and $-\text{CH}_2\text{CHFCH}_2\text{CH}_2\text{Br}$.

[0044] "Alkenyl", as used herein, refers to an unbranched or branched hydrocarbon chain containing at least one carbon-carbon double bond. In some embodiments, alkenyl as used herein has 2 to 50 carbon atoms ((C₂-C₅₀)alkenyl), 2 to 20 carbon atoms ((C₂-C₂₀)alkenyl), 2 to 12 carbon atoms ((C₂-C₁₂)alkenyl), 2 to 10 carbon atoms ((C₂-C₁₀)alkenyl), 2 to 8 carbon atoms ((C₂-C₈)alkenyl), 2 to 6 carbon atoms ((C₂-C₆)alkenyl), or 2 to 4 carbon atoms ((C₂-C₄)alkenyl). Alkenyl may have one, two, three, four, five, or more carbon-carbon double bonds, as valency permits. When an alkenyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed.

[0045] "Cycloalkenyl", as used herein, refers to a non-aromatic monocyclic or polycyclic hydrocarbon comprising one or more carbon-carbon double bonds. In some embodiments, cycloalkenyl has 3 to 50 carbon atoms ((C₃-C₅₀)cycloalkenyl), 3 to 20 carbon atoms ((C₃-

C₂₀)cycloalkenyl), 3 to 12 carbon atoms ((C₃-C₁₂)cycloalkenyl), 3 to 8 carbon atoms ((C₃-C₈)cycloalkenyl), 3 to 6 carbon atoms ((C₃-C₆)cycloalkenyl), or 3 to 5 carbon atoms ((C₃-C₄)cycloalkenyl).

[0046] “Alkynyl”, as used herein, refers to an unbranched or branched hydrocarbon chain containing at least one carbon-carbon triple bond. In some embodiments, alkynyl as used herein has 2 to 50 carbon atoms ((C₂-C₅₀)alkynyl), 2 to 20 carbon atoms ((C₂-C₂₀)alkynyl), 2 to 12 carbon atoms ((C₂-C₁₂)alkynyl), 2 to 10 carbon atoms ((C₂-C₁₀)alkynyl), 2 to 8 carbon atoms ((C₂-C₈)alkynyl), 2 to 6 carbon atoms ((C₂-C₆)alkynyl), or 2 to 4 carbon atoms ((C₂-C₄)alkynyl). Alkynyl may have one, two, three, four, five, or more carbon-carbon triple bonds, as valency permits. When an alkynyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed.

[0047] “Cycloalkyl”, as used herein, refers to a monocyclic or polycyclic saturated hydrocarbon. In some embodiments, cycloalkyl has 3 to 50 carbon atoms ((C₃-C₅₀)cycloalkyl), 3 to 20 carbon atoms ((C₃-C₂₀)cycloalkyl), 3 to 12 carbon atoms ((C₃-C₁₂)cycloalkyl), 3 to 8 carbon atoms ((C₃-C₈)cycloalkyl), 3 to 6 carbon atoms ((C₃-C₆)cycloalkyl), or 3 to 5 carbon atoms ((C₃-C₄)cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, octahydropentalenyl, octahydro-1*H*-indene, decahydronaphthalene, cubane, bicyclo[3.1.0]hexane, and bicyclo[1.1.1]pentane.

[0048] “Halocycloalkyl”, as used herein, refers to a cycloalkyl group substituted with one or more halo, which may be selected independently. Thus, halocycloalkyl includes cycloalkyl substituted with one or more halo independently selected from the group consisting of fluoro, chloro, iodo, and bromo. Halocycloalkyl may include, for example, cyclopropyl substituted with two fluoro, cyclopropyl substituted with one fluoro and one chloro, cyclopentyl substituted with one fluoro, and cyclohexyl substituted with one bromo.

[0049] “Aryl”, as used herein, refers to a monocyclic or polycyclic group having at least one hydrocarbon aromatic ring, wherein all of the ring atoms of the at least one hydrocarbon aromatic ring are carbon. Wherein aryl includes a polycyclic system, no aromatic ring heteroatoms are present. Aryl may include groups with a single aromatic ring (*e.g.*, phenyl) and multiple fused aromatic rings (*e.g.*, naphthyl, anthryl). Aryl may further include groups with one or more aromatic hydrocarbon rings fused to one or more non-aromatic hydrocarbon rings (*e.g.*, fluorenyl; 2,3-dihydro-1*H*-indene; 1,2,3,4-tetrahydronaphthalene). In certain

embodiments, aryl includes groups with an aromatic hydrocarbon ring fused to a non-aromatic ring, wherein the non-aromatic ring comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S. For example, in some embodiments, aryl includes groups with a phenyl ring fused to a non-aromatic ring, wherein the non-aromatic ring comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S (*e.g.*, chromane; thiochromane; 2,3-dihydrobenzofuran; indoline). In some embodiments, aryl as used herein has from 6 to 14 carbon atoms ((C₆-C₁₄)aryl), or 6 to 10 carbon atoms ((C₆-C₁₀)aryl). Where the aryl includes fused rings, the aryl may connect to one or more substituents or moieties of the formulae described herein through any atom for which valency permits. In some embodiments, aryl comprises one ring, two fused rings, three fused rings, four fused rings, or more.

[0050] "Heteroaryl", as used herein, refers to a monocyclic or polycyclic group comprising at least one aromatic ring, wherein the aromatic ring comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S. The heteroaryl group may comprise 5, 6, 7, 8, 9, 10, 11, 12, or more ring atoms, where ring atoms refer to the sum of carbon and heteroatoms in the one or more rings (*e.g.*, be a 5-membered, 6-membered, 7-membered, 8-membered, 9-membered, 10-membered, 11-membered, or 12-membered heteroaryl). In some embodiments, the heteroaryl comprises greater than 12 ring atoms, for example 13 ring atoms, 14 ring atoms, 15 ring atoms, 16 ring atoms, or greater. In certain embodiments, the heteroaryl comprises between 5 to 16 ring atoms, between 5 to 14 ring atoms, between 5 to 12 ring atoms, between 5 to 10 ring atoms, or between 5 to 8 ring atoms. In some embodiments, heteroaryl includes groups with an aromatic ring that comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S, (*e.g.*, pyridinyl, pyrazinyl, furanyl, thiophenyl). In certain embodiments, heteroaryl includes polycyclic groups with an aromatic ring comprising at least one ring heteroatom, fused to a non-aromatic hydrocarbon ring (*e.g.*, 5,6,7,8-tetrahydroquinolinyl; 4,5,6,7-tetrahydroisobenzofuranyl). In some embodiments, heteroaryl includes polycyclic groups with an aromatic ring comprising at least one ring heteroatom fused to an aromatic hydrocarbon ring (*e.g.*, quinolinyl, quinoxalinyl, benzothiazolyl). In still further embodiments, heteroaryl includes polycyclic groups with two fused aromatic rings, wherein each ring comprises at least one ring heteroatom (*e.g.*, naphthyridinyl). In some embodiments, heteroaryl comprises one ring, two rings, three rings, four rings, five rings, between one to four rings, or between one to three rings. Heteroaryl may include groups

comprising 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 or 2 ring heteroatoms, or 1 ring heteroatom, wherein each ring heteroatom is independently selected from the group consisting of N, O, and S. In some embodiments, heteroaryl comprises greater than 5 ring heteroatoms. In one example, a heteroaryl has 3 to 8 ring carbon atoms, with 1 to 3 ring heteroatoms independently selected from N, O, and S. Examples of heteroaryl groups include pyridyl, pyridazinyl, pyrimidinyl, benzothiazolyl, and pyrazolyl. In some embodiments, a heteroaryl substituted with =O is still a heteroaryl.

[0051] “Heterocycloalkyl”, as used herein, refers to non-aromatic, monocyclic or polycyclic ring containing carbon and at least one heteroatom selected from the group consisting of O, N, and S. The heterocycloalkyl group may be saturated or unsaturated, and may comprise 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more ring atoms, where ring atoms refer to the sum of carbon and heteroatoms in the one or more rings (*e.g.*, be a 3-membered, 4-membered, 5-membered, 6-membered, 7-membered, 8-membered, 9-membered, 10-membered, 11-membered, or 12-membered heterocycloalkyl). In some embodiments, the heterocycloalkyl group comprises more than 12 ring atoms, for example 13 ring atoms, 14 ring atoms, 15 ring atoms, or 16 ring atoms, or more. In certain embodiments, the heterocycloalkyl comprises between 5 to 16 ring atoms, between 5 to 14 ring atoms, between 5 to 12 ring atoms, between 5 to 10 ring atoms, or between 5 to 8 ring atoms. Heterocycloalkyl may include groups comprising 1 to 5 ring heteroatoms, 1 to 4 heteroatoms, 1 to 3 ring heteroatoms, 1 or 2 ring heteroatoms, or 1 ring heteroatom, wherein each heteroatom is independently selected from the group consisting of N, O, and S. In one example, a heterocycloalkyl has 2 to 8 ring carbon atoms and with 1 to 3 ring heteroatoms independently selected from N, O, and S. In some embodiments, the heterocycloalkyl comprises one ring, two rings, three rings, four rings, or more, for example as a polycyclic fused system. In some embodiments, heterocycloalkyl comprising multiple rings includes spirocyclic systems in which one or more rings comprise one or more heteroatoms. Examples of heterocycloalkyl include, but are not limited to, oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, oxazoliny, oxazolidinyl, thiazoliny, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, azepinyl, oxepinyl, diazepinyl, and tropanyl. “Heterocycloalkenyl”, as used herein, is a heterocycloalkyl comprising one or more ring double bonds. Heterocycloalkenyl may include, for example, 1,2-dihydropyridine, 2,5-dihydrofuran, and 2,5-dihydro-1*H*-pyrrole.

[0052] “Halo” or “halogen” includes bromo, chloro, fluoro, and iodo.

[0053] The term “substituted” as used herein means a group wherein at least one hydrogen atom or electron pair is replaced by a bond to a non-hydrogen atom. This may include, for example, a halogen atom such as F, Cl, Br, and I; an oxygen atom in a hydroxyl group; a nitrogen atom in an amino group; or an oxygen atom in a sulfur dioxide group.

[0054] It should be understood that when a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “(C₁-C₆)alkyl” (which may also be referred to as C₁-C₆ alkyl, C₁₋₆ alkyl, or C₁₋₆ alkyl) is intended to encompass C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0055] In some embodiments of the compound of Formula (X), A is heteroaryl, cycloalkyl, or heterocycloalkyl. In some embodiments, A is 5- to 10-membered heteroaryl, or 5- to 10-membered heterocycloalkyl, wherein the heteroaryl or heterocycloalkyl comprises one to five ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, A is 5- or 6-membered heteroaryl or 5- or 6-membered heterocycloalkyl, wherein the heterocycloalkyl or heteroaryl comprises one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In other embodiments, A is 9- or 10-membered bicyclic heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S.

[0056] In some embodiments of the compound of Formula (X), or a pharmaceutically acceptable salt thereof, A is heterocycloalkyl. For example, in some embodiments, A is 3- to 10-membered heterocycloalkyl comprising one to five ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, A is 5- to 10-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In other embodiments, A is 5- or 6-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In some embodiments, A is 9- or 10-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, A is a 5,5-ring fused heterocycloalkyl, 6,6-ring fused heterocycloalkyl, or 5,6-ring fused heterocycloalkyl. In some embodiments of the compound of Formula (X), or a pharmaceutically acceptable salt

thereof, A is oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, or tropanyl.

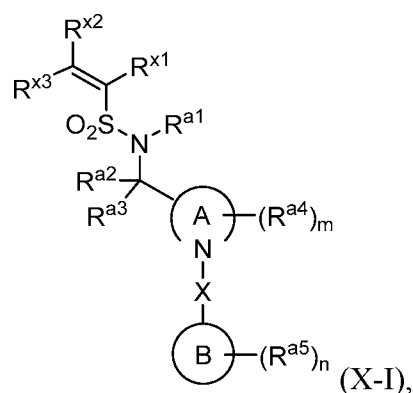
[0057] In other embodiments of the compound of Formula (X), or a pharmaceutically acceptable salt thereof, A is heteroaryl. For example, in some embodiments, A is 5- to 10-membered heteroaryl comprising one to five ring heteroatoms independently selected from the group consisting of O, N, and S. In other embodiments, A is 5- or 6-membered heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, A is 9- or 10-membered heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In some embodiments, A is a 9- or 10-membered bicyclic heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In some embodiments, A is a 5,5-ring fused heteroaryl, 6,6-ring fused heteroaryl, or 5,6-ring fused heteroaryl. In some embodiments of the compound of Formula (X), or a pharmaceutically acceptable salt thereof, A is pyridazinyl, pyrazolyl, pyrrolyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, indazolyl, benzoxazolyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, naphthyridinyl, or pyrrolyl.

[0058] In other embodiments of the compound of Formula (X), or a pharmaceutically acceptable salt thereof, A is aryl. For example, in some embodiments, A is (C₆-C₁₀)aryl, such as C₆-aryl, (C₇-C₁₀)bicyclic aryl, (C₈-C₁₀)bicyclic aryl, or (C₉-C₁₀)bicyclic aryl. In certain embodiments of the compound of Formula (I), Formula (I-A), or Formula (I-B), or a pharmaceutically acceptable salt thereof, A is phenyl or naphthyl. In some embodiments, A is an aryl comprising a phenyl ring fused to a cycloalkyl or heterocycloalkyl ring, for example (C₇-C₁₀)bicyclic aryl, (C₈-C₁₀)bicyclic aryl, or (C₉-C₁₀)bicyclic aryl comprising a phenyl ring fused to a cycloalkyl or heterocycloalkyl ring.

[0059] In still further embodiments of the compound of Formula (X), or a pharmaceutically acceptable salt thereof, A is cycloalkyl. For example, in some embodiments, A is (C₃-C₁₀)cycloalkyl. In certain embodiments, A is (C₅-C₁₀)cycloalkyl. In other embodiments, A is (C₅-C₇)cycloalkyl. In still other embodiments, A is (C₈-C₁₀)cycloalkyl. In some embodiments, A is C₃-cycloalkyl, C₄-cycloalkyl, C₅-cycloalkyl, C₆-cycloalkyl, C₇-cycloalkyl,

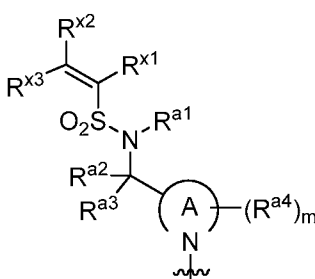
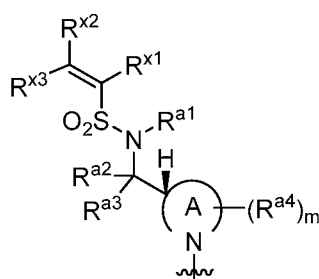
C₈-cycloalkyl, C₉-cycloalkyl, or C₁₀-cycloalkyl. In some embodiments, A is a 5,5-ring fused cycloalkyl, 6,6-ring fused cycloalkyl, or 5,6-ring fused cycloalkyl. In some embodiments of the compound of Formula (X), or a pharmaceutically acceptable salt thereof, A is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, bicyclooctyl, or tricyclooctyl.

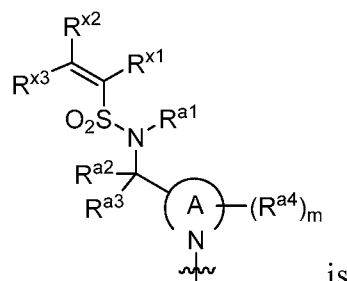
[0060] In some embodiments, the compound of Formula (X) is a compound of Formula (X-I):



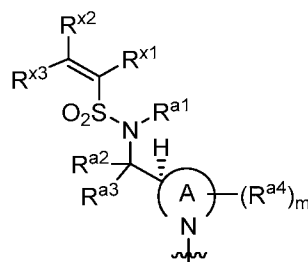
or a pharmaceutically acceptable salt thereof, wherein A is 4- to 10-membered heterocycloalkyl, and B, X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, m, and n are as defined for Formula (X).

[0061] In some embodiments of the compound of Formula (X-I), or a pharmaceutically

acceptable salt thereof,  is , and m is an

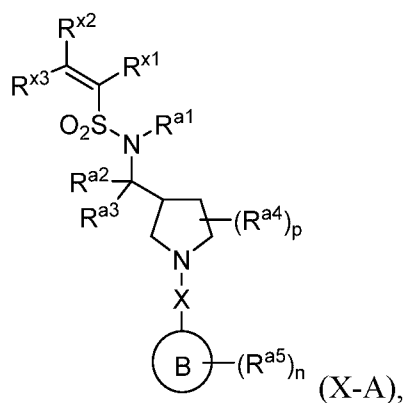


integer from 0 to 12. In other embodiments,



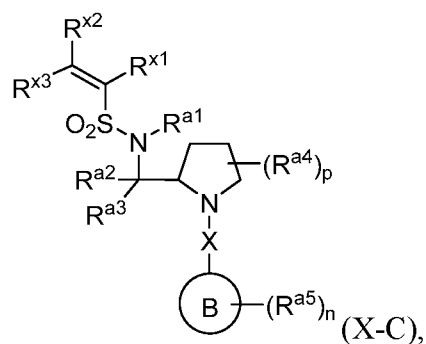
, and m is an integer from 0 to 12.

[0062] In some embodiments, the compound of Formula (X) or Formula (X-I) is a compound of Formula (X-A):



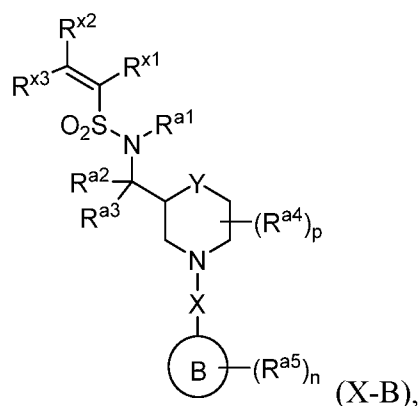
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , and n are as defined for Formula (X).

[0063] In some embodiments, the compound of Formula (X) or Formula (X-I) is a compound of Formula (X-C):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , and n are as defined for Formula (X).

[0064] In some embodiments, the compound of Formula (X) or Formula (X-I) is a compound of Formula (X-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-C(R^{a45})_2-$, $-S(O)_r-$, $-O-$, or $-N(R^{a45})-$, wherein each R^{a45} is independently hydrogen or R^{a4} ;

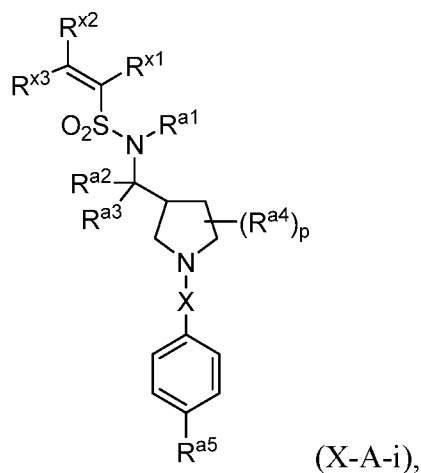
X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when Y is $-CH_2-$ and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

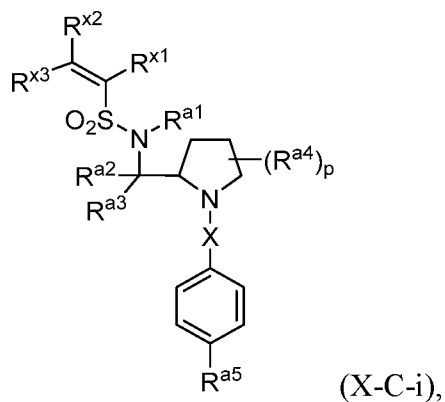
and B, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} , R^{a6} , and n are as defined for Formula (X).

[0065] In some embodiments, the compound of Formula (X) is a compound of Formula (X-A-i):



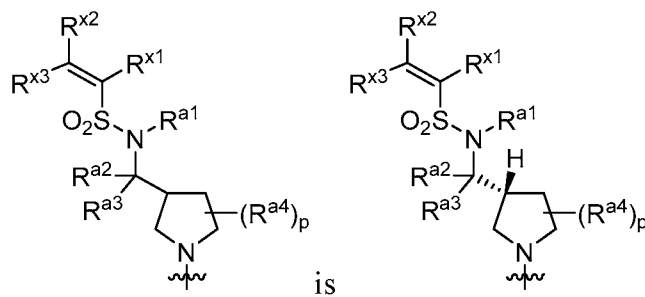
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are as defined in Formula (X).

[0066] In some embodiments, the compound of Formula (X) is a compound of Formula (X-C-i):

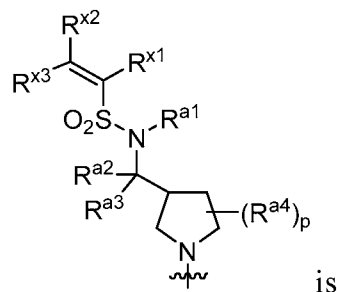


or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are as defined in Formula (X).

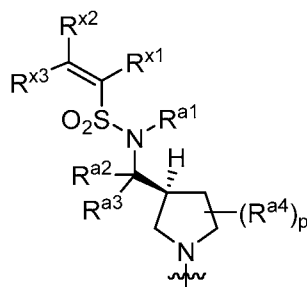
[0067] In some embodiments of the compound of Formula (X-A) or (X-A-i), or a



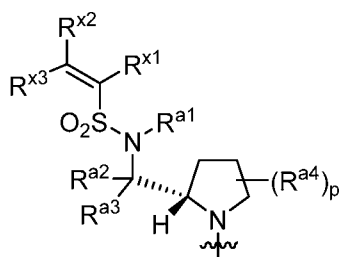
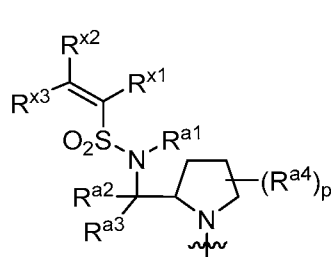
pharmaceutically acceptable salt thereof,



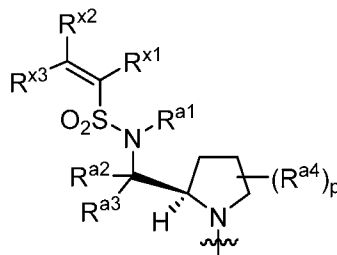
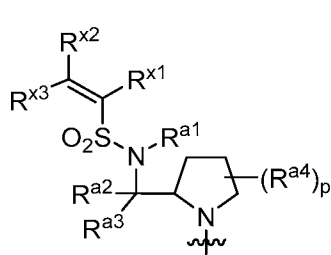
and p is an integer from 0 to 6. In other embodiments,



compound of Formula (X-C) or (X-C-i), or a pharmaceutically acceptable salt thereof,



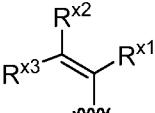
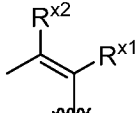
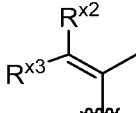
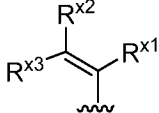
other embodiments,



integer from 0 to 6.

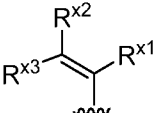
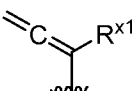
[0068] In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (X-A-i), or Formula (X-C-i), or a

pharmaceutically acceptable salt thereof, one of R^{x1} , R^{x2} , and R^{x3} is unsubstituted or substituted alkyl. In some embodiments, two of R^{x1} , R^{x2} , and R^{x3} is unsubstituted or substituted alkyl. In still further embodiments, three of R^{x1} , R^{x2} , and R^{x3} is unsubstituted or substituted alkyl. In some embodiments, the alkyl is (C₁-C₄)alkyl. In certain embodiments, the alkyl is unsubstituted. In other embodiments, the alkyl is substituted with one or more substituents independently selected from the group consisting of halo, -OH, -O-alkyl, and -O-haloalkyl. In certain embodiments, the alkyl is substituted with one to four substituents independently selected from the group consisting of halo, -OH, -O-(C₁-C₄)alkyl, and -O-(C₁-C₄)haloalkyl.

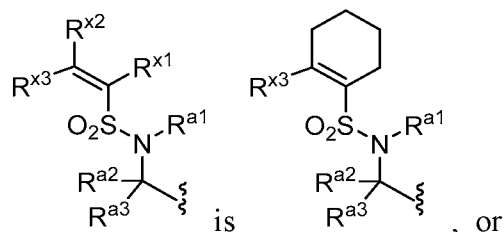
[0069] In some embodiments,  is  or . In certain embodiments,  is  or .

[0070] In some embodiments, one of R^{x1} , R^{x2} , and R^{x3} is -CN.

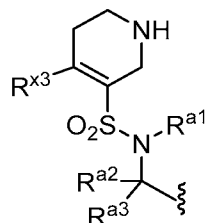
[0071] In still further embodiments, R^{x2} and R^{x3} together form alkenyl. For example, in some embodiments, R^{x2} and R^{x3} together with the carbon to which they are attached form a (C₂-C₁₀)alkenyl. In some embodiments, R^{x2} and R^{x3} together with the carbon to which they are attached form a C₂-alkenyl. In some embodiments, the alkenyl is substituted with one or more substituents independently selected from the group consisting of halo and -OR^{x4}, wherein each R^{x4} is independently H, alkyl, or haloalkyl. Thus, for example, in some embodiments the alkenyl is substituted with one or more substituents independently selected from the group consisting of halo, -OH, -O(C₁-C₆)alkyl, and -O(C₁-C₆)haloalkyl. In some embodiments, each halo is independently chloro or fluoro. In some embodiments, the alkenyl is unsubstituted.

[0072] In some embodiments,  is . In certain embodiments, R^{x1} is hydrogen.

[0073] In some embodiments, R^{x1} and R^{x2} together with the carbon atoms to which they are attached form heterocycloalkenyl, or cycloalkenyl. In some embodiments, the heterocycloalkenyl is a 5- to 10-membered heterocycloalkenyl, or a 5- to 8-membered heterocycloalkenyl. In some embodiments, the cycloalkenyl is a (C₄-C₁₀)cycloalkenyl, or a (C₅-C₈)cycloalkenyl, or a (C₅-C₆)cycloalkenyl. In some embodiments, the heterocycloalkenyl or cycloalkenyl is unsubstituted. In other embodiments, the heterocycloalkenyl or cycloalkenyl is substituted with one or more substituents independently selected from the group consisting of halo and $-OR^{x4}$, wherein each R^{x4} is independently H, alkyl, or haloalkyl. Thus, for example, in some embodiments the heterocycloalkenyl or cycloalkenyl is substituted with one or more substituents independently selected from the group consisting of halo, $-OH$, $-O(C_1-C_6)alkyl$, and $-O(C_1-C_6)haloalkyl$. In some embodiments, each halo is independently chloro or fluoro.

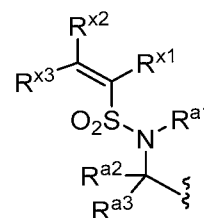


[0074] Thus, for example, in some embodiments,

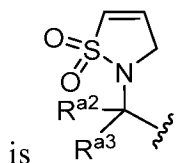


[0075] In certain embodiments, R^{a1} and R^{x2} together with the atoms to which they are attached form heterocycloalkenyl. In some embodiments, the heterocycloalkenyl is a 5- to 10-membered heterocycloalkenyl, or a 5- to 8-membered heterocycloalkenyl, or a 5-membered heterocycloalkenyl, or a 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkenyl comprises one double bond. In certain embodiments, the heterocycloalkyl is substituted with one or more substituents independently selected from the group consisting of halo and $-OR^{x4}$, wherein each R^{x4} is independently H, alkyl, or haloalkyl. Thus, for example, in some embodiments the heterocycloalkenyl is substituted with one or more substituents independently selected from the group consisting of halo, $-OH$, $-O(C_1-C_6)alkyl$, and $-O(C_1-C_6)haloalkyl$. In some embodiments, each halo is independently chloro or fluoro. In other embodiments, the heterocycloalkenyl is unsubstituted. In some

embodiments, R^{a1} and R^{x2} together with the atoms to which they are attached form an

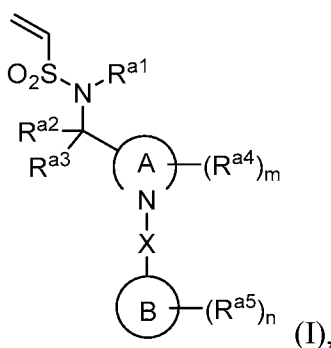


unsubstituted heterocycloalkenyl. Thus, for example, in some embodiments,



[0076] In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (X-A-i), or Formula (X-C-i), or a pharmaceutically acceptable salt thereof, such as other embodiments described herein, one of R^{x1} , R^{x2} , and R^{x3} is hydrogen. In some embodiments, R^{x1} is hydrogen. In some embodiments, R^{x2} is hydrogen. In other embodiments, R^{x3} is hydrogen. In certain embodiments, both R^{x2} and R^{x3} are hydrogen. In still further embodiments, R^{x1} and R^{x2} are hydrogen. In other embodiments, both R^{x1} and R^{x3} are hydrogen. In certain embodiments, each of R^{x1} , R^{x2} , and R^{x3} are hydrogen.

[0077] In some embodiments, the compound of Formula (X) is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when A is piperidiny and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a6} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and =O;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a6}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, $=O$, $-SR^{a47}$, and $-SO_2R^{a10}$,

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-CN$, $-NH_2$, $-NH(alkyl)$, $-COOH$, $-C(O)O-alkyl$, $-CONH_2$, $-NO_2$, $-SH$, $-S-alkyl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-alkyl$, $-NHC(O)O-alkyl$, $-NHC(O)OH$, $-NHOH$, $-OH$, $-O-alkyl$, $-O-haloalkyl$, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; and

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or two to four R^{a4} , together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a3} and one R^{a4}, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2}, together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3}, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, or -C(S)-, R^{a1} and one R^{a4}, together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, -NO₂, -CN, -SO₂NR^{a48}R^{a49}, -NR^{a11}R^{a12}, -OR^{a13}, -SO₂R^{a14}, =O, and -SR^{a15},

wherein each cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -OR^{a16}, =O, -NR^{a17}R^{a18}, -CN, -SF₅, -SO₂NR^{a50}R^{a51}, -SR^{a52}, -SO₂R^{a53}, and R^{a35}, wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -OR^{a19}, =O, -NR^{a20}R^{a21}, -CN, -SF₅, -SO₂NR^{a54}R^{a55}, -SR^{a56}, -SO₂R^{a57}, and R^{a58}, wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11}, R^{a12}, R^{a13}, R^{a14}, R^{a15}, R^{a16}, R^{a17}, R^{a18}, R^{a19}, R^{a20}, R^{a21}, R^{a48}, R^{a49}, R^{a50}, R^{a51}, R^{a52}, R^{a53}, R^{a54}, R^{a55}, R^{a56}, and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -OR^{a24}, and -SF₅;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, -CN, -SF₅, =O, -NR^{a36}R^{a37}, -NR^{a38}C(O)R^{a39}, -OR^{a40}, and R^{a59}, wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, -NH₂, -SF₅, -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl;

each R^{a22}, R^{a23}, R^{a24}, R^{a36}, R^{a37}, R^{a38}, R^{a39}, and R^{a40} is independently hydrogen, alkyl, or haloalkyl;

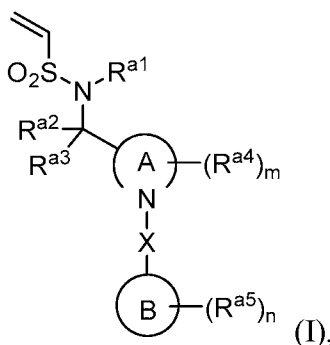
m is an integer from 0 to 13; and

n is an integer from 0 to 11.

[0078] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (X-A-i), Formula (X-C-i), Formula (I), or a pharmaceutically acceptable salt thereof, each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -NO₂, -CN, -SO₂NH₂, -NR^{a7}R^{a8}, -OR^{a9}, =O, -SR^{a47}, and -SO₂R^{a10}, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -CN, -NH₂, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -OH, -COOH, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHC(O)-alkyl,

–NHC(O)O-alkyl, –NHOH, –OCCl₃, –OCBr₃, –OCF₃, –OCl₃, –OCH₂Cl, –OCH₂Br, –OCH₂F, –OCH₂I, –OCHCl₂, –OCHBr₂, –OCHF₂, –OCHI₂, –CONH₂, –NO₂, –NH(alkyl), –C(O)O-alkyl, –O-alkyl, alkyl (such as (C₁–C₈)alkyl, (C₁–C₆)alkyl, or (C₁–C₄)alkyl), cycloalkyl (such as (C₃–C₈)cycloalkyl, (C₃–C₆)cycloalkyl, or (C₅–C₆)cycloalkyl), heterocycloalkyl (such as 3- to 8-membered heterocycloalkyl, 3- to 6-membered heterocycloalkyl, or 5- to 6-membered heterocycloalkyl), aryl (such as (C₆–C₁₀)aryl, (C₁₀)aryl, or phenyl), and heteroaryl (such as 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, or 5- to 6-membered heteroaryl).

[0079] In some embodiments of the compound of Formula (I):



or a pharmaceutically acceptable salt thereof:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is –S(O)–, –S(O)₂–, –S(O)NR^{a46}–, –C(S)–, –C(O)–, or –C(R^{a6})₂–, wherein when A is piperidiny and B is phenyl, X is –S(O)–, –S(O)₂–, –S(O)NR^{a46}–, –C(S)–, or –C(R^{a6})₂–;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and =O;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is –S(O)–, –S(O)₂–, –S(O)NR^{a46}–, –C(S)–, or –C(O)–;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, –NO₂, –CN, –SO₂NH₂, –NR^{a7}R^{a8}, –OR^{a9},

- and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;
- each $\text{R}^{\text{a}4}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, $=\text{O}$, $-\text{SR}^{\text{a}47}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;
- each $\text{R}^{\text{a}7}$, $\text{R}^{\text{a}8}$, $\text{R}^{\text{a}9}$, $\text{R}^{\text{a}10}$, and $\text{R}^{\text{a}47}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;
- or two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo;
- or $\text{R}^{\text{a}2}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;
- or $\text{R}^{\text{a}3}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;
- or $\text{R}^{\text{a}1}$ and $\text{R}^{\text{a}2}$, together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;
- or $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;
- or, when X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, or $-\text{C}(\text{S})-$, $\text{R}^{\text{a}1}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;
- each $\text{R}^{\text{a}5}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{\text{a}48}\text{R}^{\text{a}49}$, $-\text{NR}^{\text{a}11}\text{R}^{\text{a}12}$, $-\text{OR}^{\text{a}13}$, $-\text{SO}_2\text{R}^{\text{a}14}$, $=\text{O}$, and $-\text{SR}^{\text{a}15}$,

wherein each cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a19}$, $=O$, $-NR^{a20}R^{a21}$, $-CN$, $-SF_5$, $-SO_2NR^{a54}R^{a55}$, $-SR^{a56}$, $-SO_2R^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-CN$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-NR^{a22}R^{a23}$, $-OR^{a24}$, and $-SF_5$;

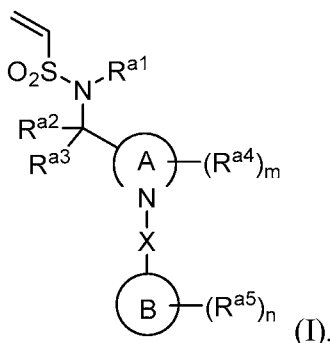
wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-CN$, $-SF_5$, $=O$, $-NR^{a36}R^{a37}$, $-NR^{a38}C(O)R^{a39}$, $-OR^{a40}$, and R^{a59} , wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $=O$, $-NH_2$, $-SF_5$, $-OH$, $-O$ -alkyl, $-O$ -haloalkyl, halo, alkyl, and haloalkyl;

each R^{a22} , R^{a23} , R^{a24} , R^{a36} , R^{a37} , R^{a38} , R^{a39} , and R^{a40} is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

n is an integer from 0 to 11.

[0080] In some embodiments of the compound of Formula (I):



or a pharmaceutically acceptable salt thereof:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when A is piperidiny and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=O$;

R^{a1} is hydrogen, alkyl, or cycloalkyl, wherein when R^{a1} is alkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$,

$-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, $=\text{O}$, $-\text{SR}^{\text{a}47}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each $\text{R}^{\text{a}7}$, $\text{R}^{\text{a}8}$, $\text{R}^{\text{a}9}$, $\text{R}^{\text{a}10}$, and $\text{R}^{\text{a}47}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

or two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

or $\text{R}^{\text{a}2}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or $\text{R}^{\text{a}3}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or $\text{R}^{\text{a}1}$ and $\text{R}^{\text{a}2}$, together with the atoms to which they are attached, form a heterocycloalkyl;

or $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl;

or, when X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, or $-\text{C}(\text{S})-$, $\text{R}^{\text{a}1}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a heterocycloalkyl;

each $\text{R}^{\text{a}5}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{\text{a}48}\text{R}^{\text{a}49}$, $-\text{NR}^{\text{a}11}\text{R}^{\text{a}12}$, $-\text{OR}^{\text{a}13}$, $-\text{SO}_2\text{R}^{\text{a}14}$, $=\text{O}$, and $-\text{SR}^{\text{a}15}$,

wherein each cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a}16}$, $=\text{O}$, $-\text{NR}^{\text{a}17}\text{R}^{\text{a}18}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a}50}\text{R}^{\text{a}51}$, $-\text{SR}^{\text{a}52}$, $-\text{SO}_2\text{R}^{\text{a}53}$, and $\text{R}^{\text{a}35}$, wherein each $\text{R}^{\text{a}35}$ is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{SF}_5$, and $\text{R}^{\text{a}35}$, wherein $\text{R}^{\text{a}35}$ is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a}19}$, $=\text{O}$, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a}54}\text{R}^{\text{a}55}$, $-\text{SR}^{\text{a}56}$, $-\text{SO}_2\text{R}^{\text{a}57}$, and $\text{R}^{\text{a}58}$, wherein each $\text{R}^{\text{a}58}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each $\text{R}^{\text{a}14}$, $\text{R}^{\text{a}15}$, $\text{R}^{\text{a}16}$, $\text{R}^{\text{a}17}$, $\text{R}^{\text{a}18}$, $\text{R}^{\text{a}48}$, $\text{R}^{\text{a}49}$, $\text{R}^{\text{a}50}$, $\text{R}^{\text{a}51}$, $\text{R}^{\text{a}52}$, $\text{R}^{\text{a}53}$, $\text{R}^{\text{a}54}$, $\text{R}^{\text{a}55}$, $\text{R}^{\text{a}56}$, and $\text{R}^{\text{a}57}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

each $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, and $\text{R}^{\text{a}21}$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

each $\text{R}^{\text{a}13}$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or alkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}13}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, $\text{R}^{\text{a}21}$, and $\text{R}^{\text{a}35}$, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}58}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, $-\text{OR}^{\text{a}24}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, $=\text{O}$, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, $-\text{NR}^{\text{a}38}\text{C}(\text{O})\text{R}^{\text{a}39}$, $-\text{OR}^{\text{a}40}$, and $\text{R}^{\text{a}59}$, wherein each $\text{R}^{\text{a}59}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each $\text{R}^{\text{a}59}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $=\text{O}$, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl

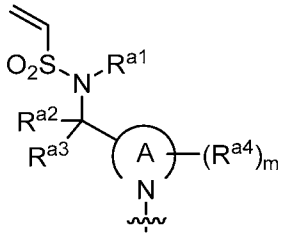
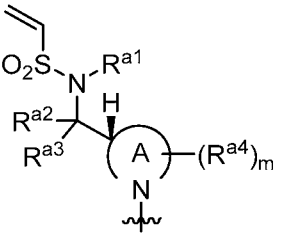
each $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, $\text{R}^{\text{a}24}$, $\text{R}^{\text{a}36}$, $\text{R}^{\text{a}37}$, $\text{R}^{\text{a}38}$, $\text{R}^{\text{a}39}$, and $\text{R}^{\text{a}40}$ is independently hydrogen, alkyl, or haloalkyl;

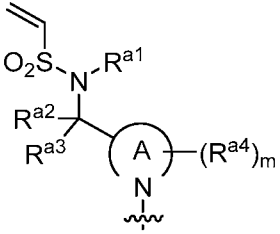
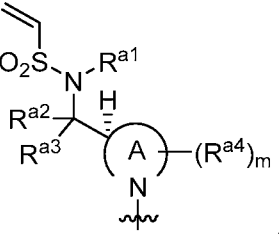
m is an integer from 0 to 13; and

n is an integer from 0 to 11.

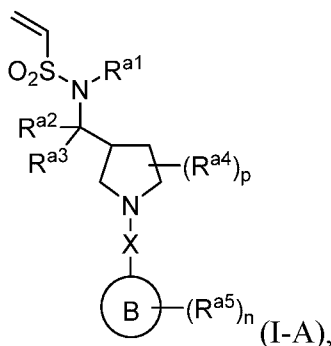
[0081] In certain embodiments of the compound of Formula (X), Formula (X-I), or Formula (I), or a pharmaceutically acceptable salt thereof, A is a 4-, 5-, 6-, or 7-membered heterocycloalkyl. In some embodiments, A is a 5-, 6-, or 7-membered heterocycloalkyl. In some embodiments, A is a 5-, 6-, or 7-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In some embodiments, A is a 5- or 6-membered heterocycloalkyl. In certain embodiments, A is a 5- or 6-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. For example, in some embodiments A is pyrrolidinyl, thiazolidinyl, oxazolidinyl, imidazolidinyl, piperidinyl, thiomorpholinyl, morpholinyl, or piperazinyl. In some embodiments, A is piperidinyl. In other embodiments, A is pyrrolidinyl. In some embodiments, A is a 4-membered heterocycloalkyl.

[0082] In some embodiments of the compound of Formula (I), or a pharmaceutically

acceptable salt thereof,  is , and m is an integer

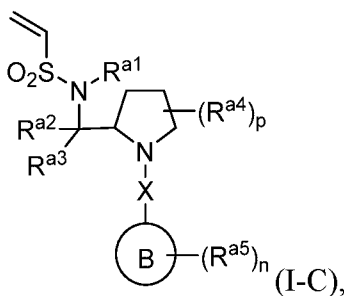
from 0 to 12. In other embodiments,  is , and m is an integer from 0 to 12.

[0083] In some embodiments, the compound of Formula (I) is a compound of Formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B , X , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , and n are as defined for Formula (I).

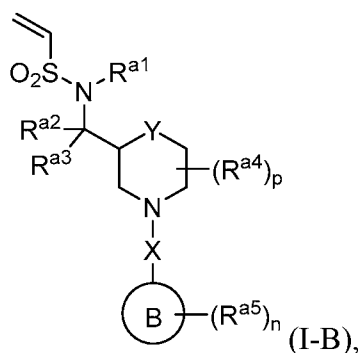
[0084] In some embodiments, the compound of Formula (I) is a compound of Formula (I-C):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B , X , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , and n are as defined for Formula (I).

[0085] In some embodiments of the compound of Formula (X-A), Formula (X-A-i), Formula (X-C), Formula (X-C-i), Formula (I-A), or Formula (I-C), or a pharmaceutically acceptable salt thereof, p is an integer from 0 to 6, or an integer from 0 to 5, or an integer from 0 to 4, or an integer from 0 to 3, or an integer from 0 to 2, or an integer from 3 to 5. In some embodiments, p is 0. In other embodiments, p is 1. In still further embodiments, p is 2. In some embodiments, p is 3. In other embodiments, p is an integer from 4 to 7.

[0086] In other embodiments, the compound of Formula (I) is a compound of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, $-\text{S}(\text{O})_r-$, $-\text{O}-$, or $-\text{N}(\text{R}^{\text{a45}})-$, wherein each R^{a45} is independently hydrogen or R^{a4} ;

X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when Y is $-CH_2-$ and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

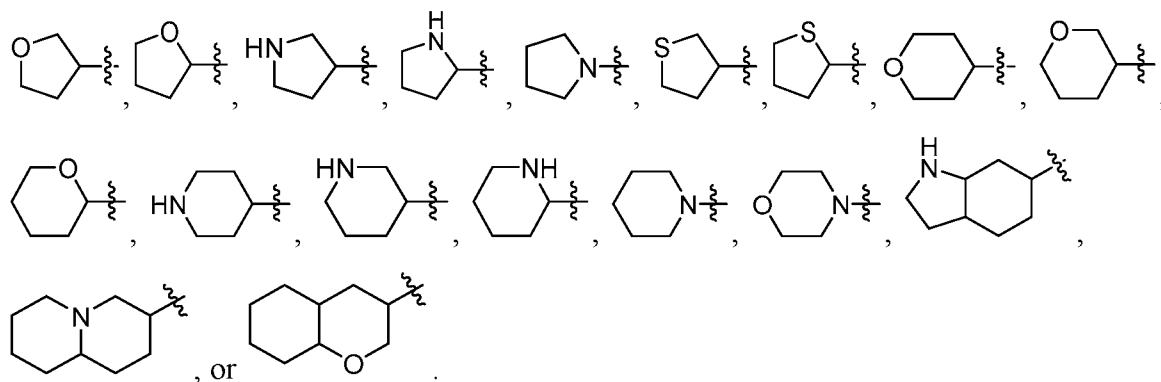
and B, R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} , R^{a6} , and n are as defined for Formula (I).

[0087] In certain embodiments of the compound of Formula (X-B) or Formula (I-B), or a pharmaceutically acceptable salt thereof, Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, wherein each R^{a45} is independently hydrogen or R^{a4} . In certain embodiments, Y is $-\text{CH}_2-$. In other embodiments, Y is $-\text{CHR}^{\text{a4}}-$. In some embodiments, Y is $-\text{C}(\text{R}^{\text{a4}})_2-$. In other embodiments, Y is $-\text{S}(\text{O})_r-$, where r is 0, 1, or 2. For example, in some embodiments, Y is $-\text{S}-$. In other embodiments, Y is $-\text{S}(\text{O})-$. In still further embodiments, Y is $-\text{S}(\text{O})_2-$. In some embodiments, Y is $-\text{O}-$. In other embodiments, Y is $-\text{N}(\text{R}^{\text{a45}})-$, wherein each R^{a45} is independently hydrogen or R^{a4} . For example, in certain embodiments, Y is $-\text{NH}-$. In some embodiments, Y is $-\text{NR}^{\text{a4}}-$.

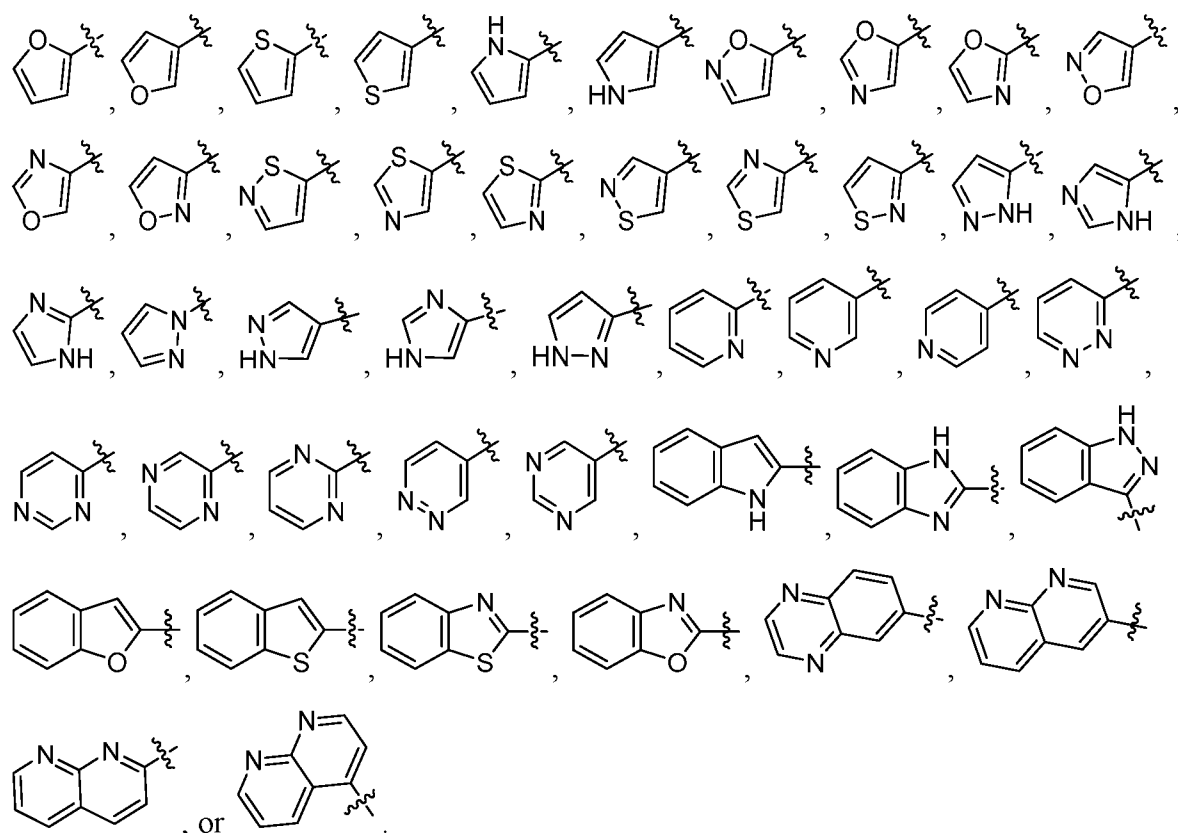
[0088] In some embodiments of the compound of Formula (X-B) or Formula (I-B), or a pharmaceutically acceptable salt thereof, p is an integer from 0 to 6, or an integer from 0 to 5, or an integer from 0 to 4, or an integer from 0 to 3, or an integer from 0 to 2, or an integer from 3 to 5. In some embodiments, p is 0. In other embodiments, p is 1. In still further embodiments, p is 2. In some embodiments, p is 3. In other embodiments, p is an integer from 4 to 7.

[0089] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is heteroaryl, cycloalkyl, or heterocycloalkyl. In some embodiments, B is 5- to 10-membered heteroaryl, or 5- to 10-membered heterocycloalkyl, wherein the heteroaryl or heterocycloalkyl comprises one to five ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, B is 5- or 6-membered heteroaryl or 5- or 6-membered heterocycloalkyl, wherein the heterocycloalkyl or heteroaryl comprises one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In other embodiments, B is 9- or 10-membered bicyclic heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S.

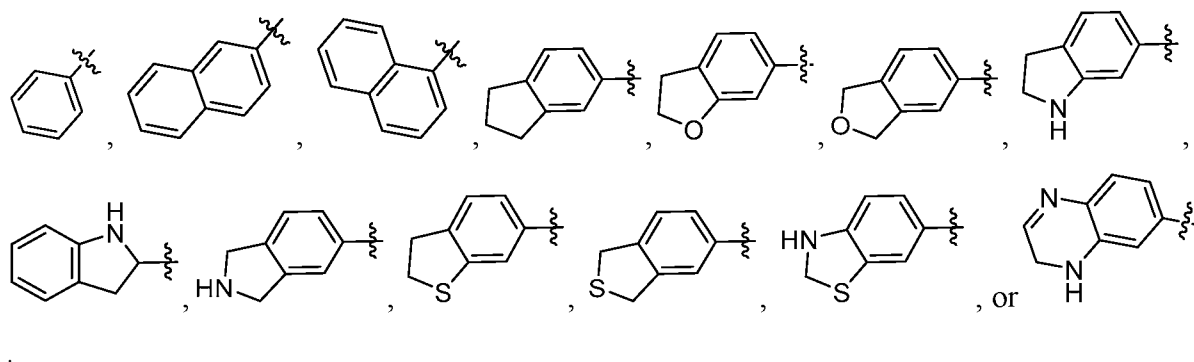
[0090] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is heterocycloalkyl. For example, in some embodiments, B is 3- to 10-membered heterocycloalkyl comprising one to five ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, B is 5- to 10-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In other embodiments, B is 5- or 6-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In some embodiments, B is 9- or 10-membered heterocycloalkyl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, B is a 5,5-ring fused heterocycloalkyl, 6,6-ring fused heterocycloalkyl, or 5,6-ring fused heterocycloalkyl. In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, oxazoliny, oxazolidinyl, thiazolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, or tropanyl. In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is:



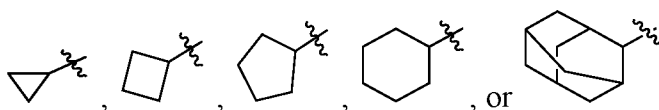
[0091] In other embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is heteroaryl. For example, in some embodiments, B is 5- to 10-membered heteroaryl comprising one to five ring heteroatoms independently selected from the group consisting of O, N, and S. In other embodiments, B is 5- or 6-membered heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In certain embodiments, B is 9- or 10-membered heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In some embodiments, B is a 9- or 10-membered bicyclic heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S. In some embodiments, B is a 5,5-ring fused heteroaryl, 6,6-ring fused heteroaryl, or 5,6-ring fused heteroaryl. In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is pyridazinyl, pyrazolyl, pyrrolyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, indazolyl, benzoxazolyl, benzimidazolyl, benzofuranyl, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxaliny, quinolyl, naphthyridinyl, or pyrrolyl. In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is:



[0092] In other embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is aryl. For example, in some embodiments, B is (C₆-C₁₀)aryl, such as C₆-aryl, (C₇-C₁₀)bicyclic aryl, (C₈-C₁₀)bicyclic aryl, or (C₉-C₁₀)bicyclic aryl. In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is phenyl or naphthyl. In some embodiments, B is an aryl comprising a phenyl ring fused to a cycloalkyl or heterocycloalkyl ring, for example (C₇-C₁₀)bicyclic aryl, (C₈-C₁₀)bicyclic aryl, or (C₉-C₁₀)bicyclic aryl comprising a phenyl ring fused to a cycloalkyl or heterocycloalkyl ring. In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is:

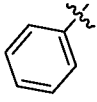
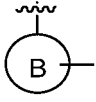
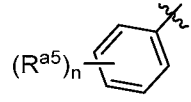


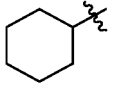
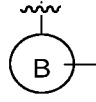
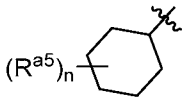
[0093] In still further embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is cycloalkyl. For example, in some embodiments, B is (C₃-C₁₀)cycloalkyl. In certain embodiments, B is (C₅-C₁₀)cycloalkyl. In other embodiments, B is (C₅-C₇)cycloalkyl. In still other embodiments, B is (C₈-C₁₀)cycloalkyl. In some embodiments, B is C₃-cycloalkyl, C₄-cycloalkyl, C₅-cycloalkyl, C₆-cycloalkyl, C₇-cycloalkyl, C₈-cycloalkyl, C₉-cycloalkyl, or C₁₀-cycloalkyl. In some embodiments, B is a 5,5-ring fused cycloalkyl, 6,6-ring fused cycloalkyl, or 5,6-ring fused cycloalkyl. In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, bicyclooctyl, or tricyclooctyl. In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is:

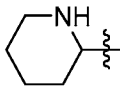
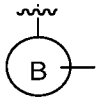
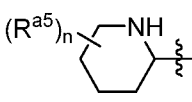


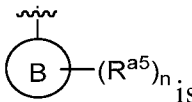
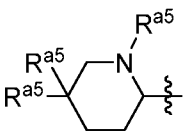
[0094] It should be understood in embodiments described herein, B may be unsubstituted or substituted with one to eleven R^{a5} as described in Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), and Formula (I-C), as valency allows.

[0095] For example, in some embodiments, B is

, as described above, and  is , wherein n is an integer from 0 to 5.

[0096] In other embodiments, B is , as described above, and  is , wherein n is an integer from 0 to 11.

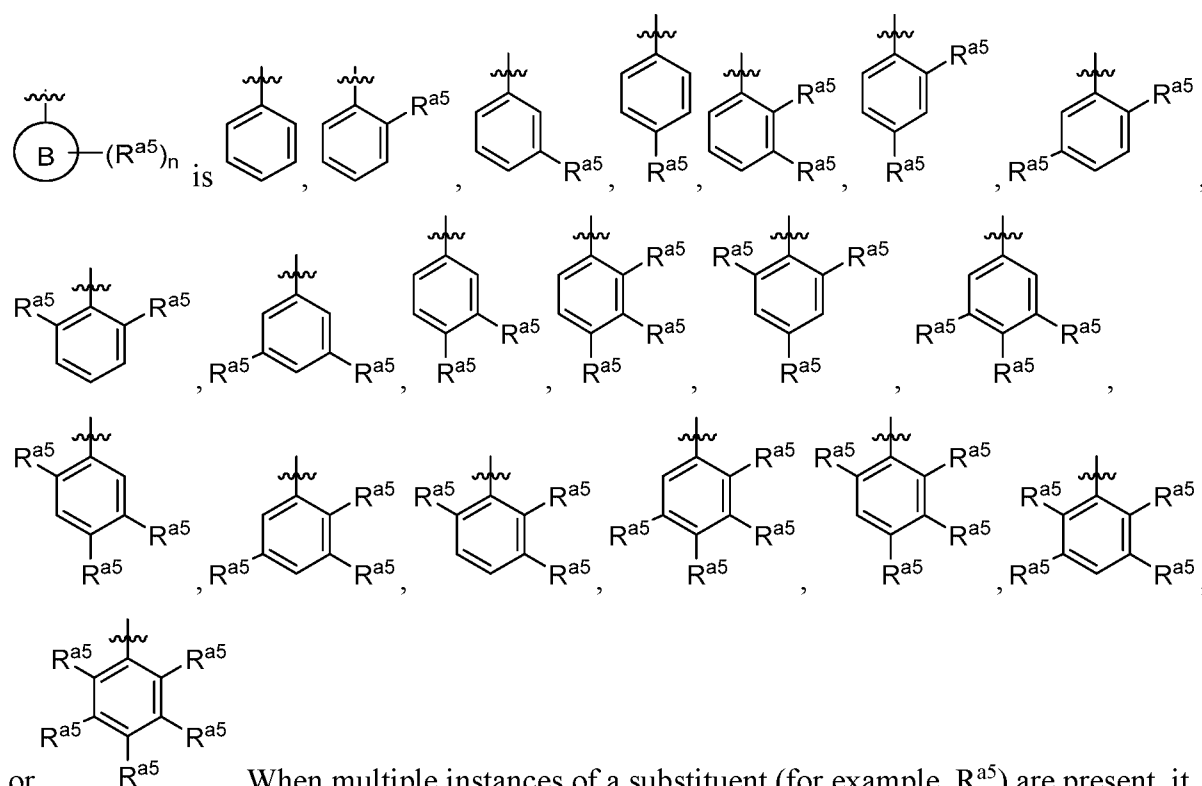
[0097] In still other embodiments B is , as described above, and  is , wherein n is an integer from 0 to 10. For example in some embodiments,

 is . When multiple instances of a substituent (for example, R^{a5}) are present, it should be understood that they may be optionally different unless otherwise indicated.

[0098] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, n is an integer from 0 to 11. In some embodiments, n is an integer from 0 to 9. In other embodiments, n is an integer from 0 to 7. In still further embodiments, n is an integer from 0 to 5. In certain embodiments, n is an integer from 0 to 3. In other embodiments, n is an integer from 3 to 11, or from 5 to 11, or from 7 to 11, or from 3 to 7, or from 3 to 5. In certain embodiments, n is 0. In other embodiments, n is 1. In some embodiments, n is 2. In still other embodiments, n is 3. In still further embodiments, n is 4.

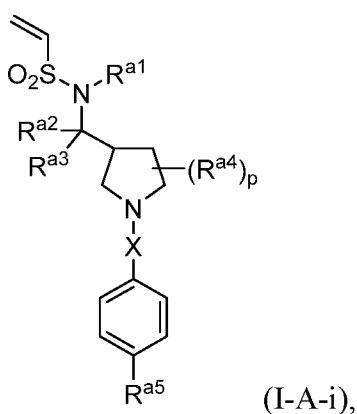
[0099] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof, B is phenyl, and n is an integer from 0 to 5. Thus, for example, in some embodiments of the compound of Formula (X),

Formula (X-I), Formula (X-A), Formula (X-B), Formula (X-C), Formula (I), Formula (I-A), Formula (I-B), or Formula (I-C), or a pharmaceutically acceptable salt thereof,



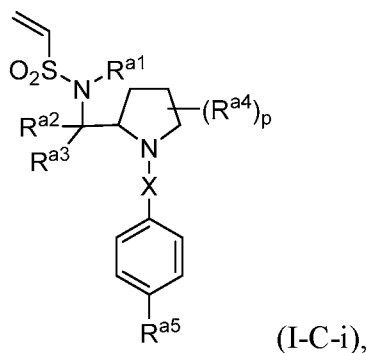
. When multiple instances of a substituent (for example, R^{a5}) are present, it should be understood that they may be optionally different unless otherwise indicated.

[0100] In certain variations, the compound of Formula (I) is a compound of Formula (I-A-i):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and X , R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are as defined for Formula (I).

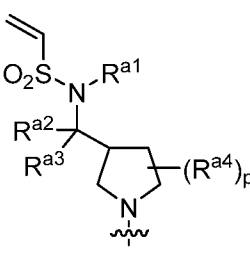
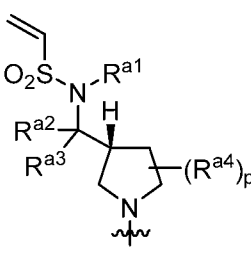
[0101] In some embodiments, the compound of Formula (I) is a compound of Formula (I-C-i):

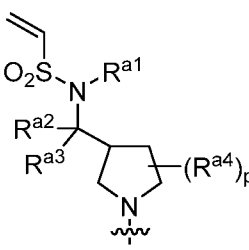
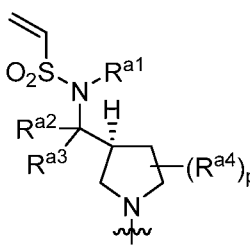


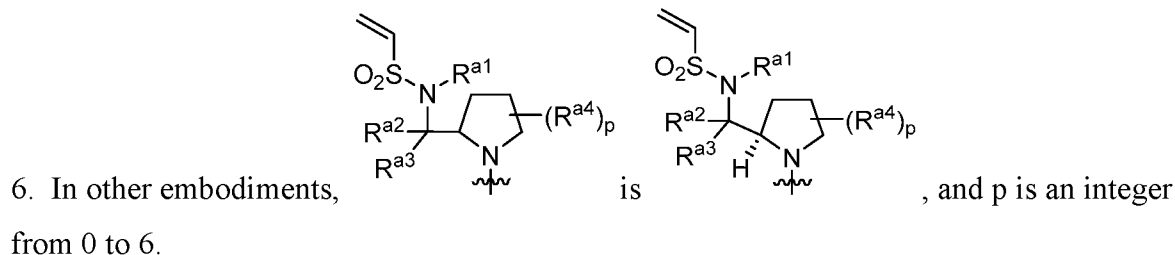
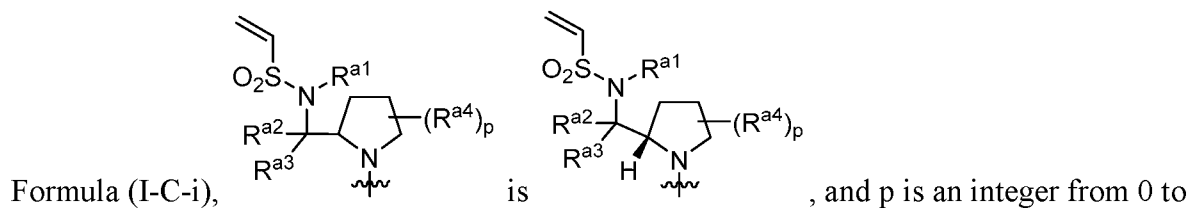
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and X, R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are as defined for Formula (I).

[0102] In some embodiments of the compound of Formula (I-A-i) or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, p is an integer from 0 to 6, or an integer from 0 to 5, or an integer from 0 to 4, or an integer from 0 to 3, or an integer from 0 to 2, or an integer from 3 to 5. In some embodiments, p is 0. In other embodiments, p is 1. In still further embodiments, p is 2. In some embodiments, p is 3. In other embodiments, p is an integer from 4 to 7.

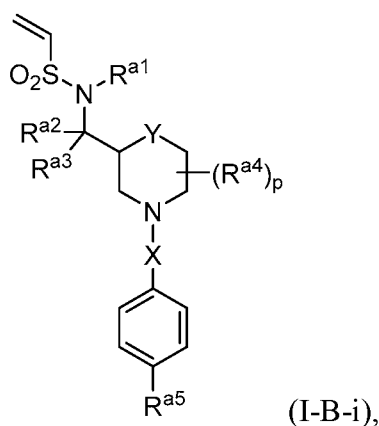
[0103] In some embodiments of the compound of Formula (I-A) or Formula (I-A-i), or a

pharmaceutically acceptable salt thereof,  is , and p is

an integer from 0 to 6. In other embodiments,  is , and p is an integer from 0 to 6. In some embodiments of the compound of Formula (I-C) or



[0104] In other variations, the compound of Formula (I) is a compound of Formula (I-B-i):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, $-\text{S}(\text{O})_r-$, $-\text{O}-$, or $-\text{N}(\text{R}^{\text{a45}})-$, wherein each R^{a45} is independently hydrogen or R^{a4} ;

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$, wherein when Y is $-\text{CH}_2-$, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

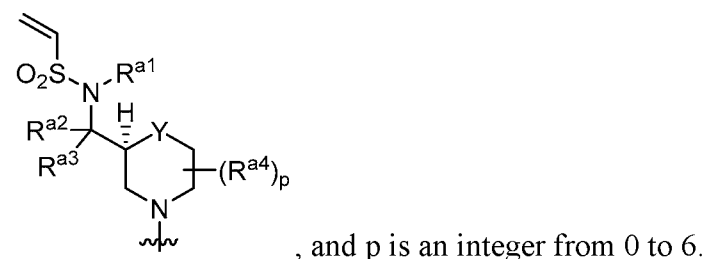
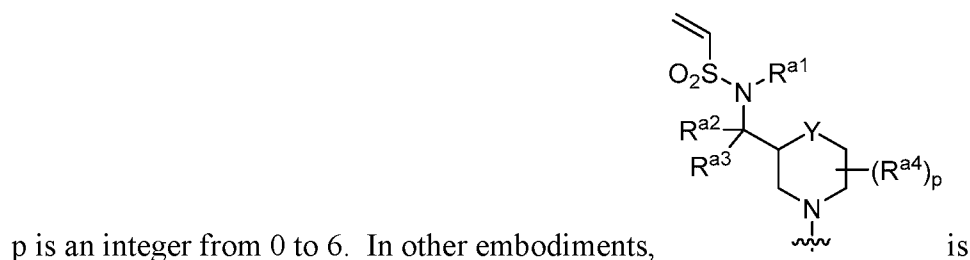
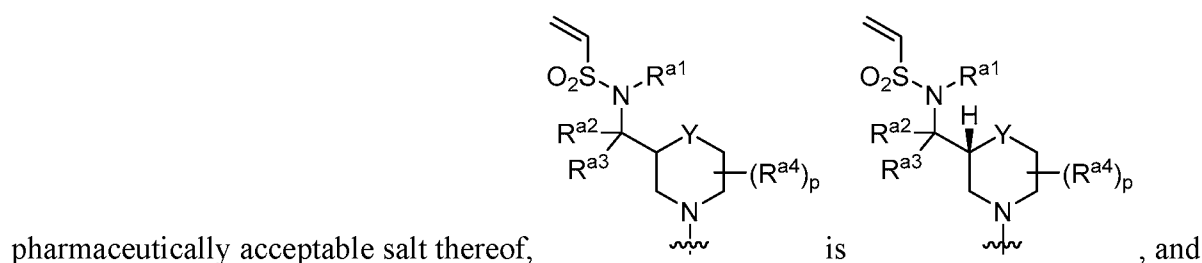
and R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} , R^{a46} , and n are as defined for Formula (I).

[0105] In certain embodiments of the compound of Formula (I-B-i), or a pharmaceutically acceptable salt thereof, Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, wherein each R^{a45} is independently hydrogen or R^{a4} . In certain embodiments, Y is $-\text{CH}_2-$. In other embodiments, Y is $-\text{CHR}^{\text{a4}}-$. In some embodiments, Y is $-\text{C}(\text{R}^{\text{a4}})_2-$. In other embodiments, Y is $-\text{S}(\text{O})_r-$, wherein r is 0, 1, or 2.

For example, in some embodiments, Y is $-S-$. In other embodiments, Y is $-S(O)-$. In still further embodiments, Y is $-S(O)_2-$. In some embodiments, Y is $-O-$. In other embodiments, Y is $-N(R^{a45})-$, wherein each R^{a45} is independently hydrogen or R^{a4} . For example, in certain embodiments, Y is $-NH-$. In some embodiments, Y is $-NR^{a4}-$.

[0106] In some embodiments of the compound of Formula (I-B-i) or a pharmaceutically acceptable salt thereof, p is an integer from 0 to 6, or an integer from 0 to 5, or an integer from 0 to 4, or an integer from 0 to 3, or an integer from 0 to 2, or an integer from 3 to 5. In some embodiments, p is 0. In other embodiments, p is 1. In still further embodiments, p is 2. In some embodiments, p is 3. In other embodiments, p is an integer from 4 to 7.

[0107] In some embodiments of the compound of Formula (I-B) or Formula (I-B-i), or a



[0108] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-NO_2$, $-CN$, $-SO_2NR^{a48}R^{a49}$, $-NR^{a11}R^{a12}$, $-OR^{a13}$, $-SO_2R^{a14}$, $=O$, and $-SR^{a15}$. In some embodiments, one

or more R^{a5} is independently selected from the group consisting of halo; -O-(C₁-C₄)alkyl unsubstituted or substituted with one or more fluoro or chloro; phenyl; heteroaryl; heterocycloalkyl; -SO₂NH₂; -NO₂; -CN; (C₃-C₆)cycloalkyl unsubstituted or substituted with one or more fluoro or chloro; and (C₁-C₆)alkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of (C₃-C₆)cycloalkyl, 3- to 6-membered heterocycloalkyl, aryl, heteroaryl, halo, -OH, -O-(C₁-C₄)alkyl, =O, -NR^{a20}R^{a21}, and -CN. In certain embodiments, one or more R^{a5} is independently selected from the group consisting of halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, and -O-(C₁-C₆)haloalkyl. In certain embodiments, each R^{a5} is independently selected from the group consisting of halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, and -CN. In some embodiments, one or more R^{a5} is independently selected from the group consisting of fluoro, chloro, methyl, ethyl, propyl, butyl, pentyl, hexyl, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -CH₂F, -CHF₂, -CF₃, -OCH₂F, -OCHF₂, -OCF₃, -NO₂, phenyl, =O, -SO₂NH₂, cyclopropyl, and cyclohexyl. In some embodiments, at least one R^{a5} is halo, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, or -CN. In certain embodiments, at least one R^{a5} is chloro, fluoro, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -CH₂F, -CHF₂, -CF₃, -OCH₂F, -OCHF₂, -OCF₃, or -CN. In certain embodiments, at least one R^{a5} is chloro, fluoro, -OCH₃, or -CN. In some embodiments, each R^{a5} is independently chloro, fluoro, -OCH₃, or -CN. In some embodiments, at least one R^{a5} is independently selected from the group consisting of fluoro, chloro, bromo, methyl, ethyl, propyl, butyl, pentyl, hexyl, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -CH₂F, -CHF₂, -CF₃, -CH₂Cl, -CHCl₂, -CCl₃, -CH₂Br, -CHBr₂, -CBr₃, -CH₂I, -CHI₂, -CI₃, -OCH₂Cl, -OCHCl₂, -OCCl₃, -OCH₂Br, -OCHBr₂, -OCBr₃, -OCH₂I, -OCHI₂, -OCI₃, -OCH₂F, -OCHF₂, -OCF₃, -NO₂, phenyl, =O, -SO₂NH₂, -CN, cyclopropyl, cyclohexyl, and -OCH₂CCH.

[0109] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one R^{a5} is alkyl, wherein each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -OR^{a19}, =O, -NR^{a20}R^{a21}, -CN, -SF₅, -SO₂NR^{a54}R^{a55}, -SR^{a56}, -SO₂R^{a57}, and R^{a58}, wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{a58} is independently (C₃-C₆)cycloalkyl, 3- to 8-membered heterocycloalkyl, (C₆-C₁₀)aryl, or 3- to 8-

membered heteroaryl. In some embodiments, the alkyl is unbranched. In other embodiments, the alkyl is branched. In some embodiments, at least one R^{a5} is alkyl, wherein the alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, $-OR^{a19}$, $=O$, $-NR^{a20}R^{a21}$, $-CN$, $-SF_5$, $-SO_2NR^{a54}R^{a55}$, $-SR^{a56}$, and $-SO_2R^{a57}$. In some embodiments, the alkyl is (C_1-C_{12}) alkyl, wherein the alkyl is unsubstituted or substituted as described above. In some embodiments, the alkyl is unbranched. In other embodiments, the alkyl is branched. In other embodiments, the alkyl is (C_1-C_8) alkyl, wherein the alkyl is unsubstituted or substituted as described herein. In further embodiments, the alkyl is (C_1-C_6) alkyl, wherein the alkyl is unsubstituted or substituted as described herein. In still other embodiments, the alkyl is (C_1-C_4) alkyl, wherein the alkyl is unsubstituted or substituted as described herein. In some embodiments, at least one R^{a5} is methyl, ethyl, propyl, butyl, pentyl, hexyl, trifluoromethyl, difluoromethyl, or fluoromethyl.

[0110] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one R^{a5} is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, each R^{a35} is independently (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, 3- to 8-membered heterocycloalkyl, (C_6-C_{10}) aryl, or 3- to 8-membered heteroaryl.

[0111] In some embodiments, R^{a35} is unsubstituted alkyl. In some embodiments, R^{a35} is unsubstituted (C_1-C_6) alkyl. In other embodiments, R^{a35} is alkyl substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-CN$, aryl, heteroaryl, alkynyl, cycloalkyl, heterocycloalkyl, $-NR^{a22}R^{a23}$, $-OR^{a24}$, and $-SF_5$. In certain embodiments, R^{a35} is (C_1-C_6) alkyl substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-CN$, aryl, heteroaryl, alkynyl, cycloalkyl, heterocycloalkyl, $-NR^{a22}R^{a23}$, $-OR^{a24}$, and $-SF_5$. In some embodiments, R^{a35} is (C_1-C_6) alkyl substituted with one or more substituents independently selected from the group consisting of

halo, =O, -CN, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{\text{a22}}\text{R}^{\text{a23}}$, $-\text{SF}_5$, -OH, -O-(C₁-C₆)alkyl, and -O-(C₁-C₆)haloalkyl. In certain embodiments, R^{a35} is alkyl substituted with aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted with haloalkyl or $-\text{SF}_5$.

[0112] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one R^{a5} is branched alkyl. In some embodiments, the branched alkyl is (C₃-C₅) branched alkyl. In some embodiments, the branched alkyl is isopropyl. In some embodiments, the branched alkyl is substituted with two or more substituents independently selected from the group consisting of =O, $-\text{NR}^{\text{a20}}\text{R}^{\text{a21}}$, $-\text{OR}^{\text{a19}}$, and R^{a58} . In some embodiments, each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkynyl, -CN, =O, $-\text{OR}^{\text{a24}}$, and $-\text{NR}^{\text{a22}}\text{R}^{\text{a23}}$, wherein each alkyl is independently unsubstituted or substituted with one or more halo. In some embodiments, each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkynyl, -CN, and =O. In some embodiments, wherein R^{a5} is branched alkyl substituted with one or more $-\text{NR}^{\text{a20}}\text{R}^{\text{a21}}$, each R^{a20} and R^{a21} are independently selected from the group consisting of hydrogen; unsubstituted or substituted cycloalkyl; unsubstituted or substituted heterocycloalkyl; and alkyl, wherein the alkyl is unsubstituted or substituted. In some embodiments, wherein one or both of R^{a20} and R^{a21} are independently alkyl, each alkyl is independently unsubstituted substituted with one or more substituents independently selected from the group consisting of halo, =O, $-\text{NR}^{\text{a22}}\text{R}^{\text{a23}}$, $-\text{OR}^{\text{a24}}$, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl. In some embodiments, each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, $-\text{NR}^{\text{a36}}\text{R}^{\text{a37}}$, and $-\text{OR}^{\text{a40}}$. In some embodiments, at least one of R^{a20} and R^{a21} is not hydrogen. In certain embodiments, both R^{a20} and R^{a21} are not hydrogen.

[0113] In some embodiments, at least one R^{a5} is isopropyl, wherein one terminal methyl of the isopropyl is substituted with phenyl. In some embodiments, the phenyl is unsubstituted.

In other embodiments, the phenyl is substituted with one to three substituents independently selected from the group consisting of halo, haloalkyl, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, and $-\text{OR}^{\text{a}24}$. In some embodiments, $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, and $\text{R}^{\text{a}24}$ are independently hydrogen, (C₁-C₄)alkyl, or (C₁-C₄)haloalkyl. In some embodiments, one terminal methyl of the $\text{R}^{\text{a}5}$ isopropyl is substituted with =O and $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$ or =O and $\text{R}^{\text{a}58}$. In some embodiments, $\text{R}^{\text{a}58}$ is heterocycloalkyl. In some embodiments, the heterocycloalkyl is unsubstituted. In other embodiments, the heterocycloalkyl is substituted.

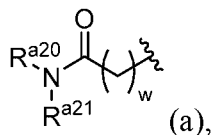
[0114] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one $\text{R}^{\text{a}5}$ is $-\text{NR}^{\text{a}11}\text{R}^{\text{a}12}$. In some embodiments, at least one of $\text{R}^{\text{a}11}$ and $\text{R}^{\text{a}12}$ is not hydrogen. In certain embodiments, both of $\text{R}^{\text{a}11}$ and $\text{R}^{\text{a}12}$ are not hydrogen. In certain embodiments, at least one of $\text{R}^{\text{a}11}$ and $\text{R}^{\text{a}12}$ is substituted alkyl. In certain embodiments, both of $\text{R}^{\text{a}11}$ and $\text{R}^{\text{a}12}$ are substituted alkyl. For example, in some embodiments, $\text{R}^{\text{a}11}$ is alkyl substituted with aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted. In some embodiments, the aryl or heteroaryl is unsubstituted. In other embodiments, the aryl or heteroaryl is substituted with one or more substituents selected from the group consisting of halo, haloalkyl, $-\text{SF}_5$, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, and $-\text{OR}^{\text{a}40}$. In some embodiments, $\text{R}^{\text{a}12}$ is alkyl substituted with one or more substituents independently selected from the group consisting of =O, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, $-\text{OR}^{\text{a}24}$, and heterocycloalkyl, wherein the heterocycloalkyl is independently unsubstituted or substituted. In some embodiments, the heterocycloalkyl is unsubstituted. In other embodiments, the heterocycloalkyl is substituted with one or more substituents independently selected from the group consisting of halo, haloalkyl, $-\text{SF}_5$, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, and $-\text{OR}^{\text{a}40}$. In some embodiments, when $\text{R}^{\text{a}11}$ or $\text{R}^{\text{a}12}$ is alkyl, or both $\text{R}^{\text{a}11}$ and $\text{R}^{\text{a}12}$ are alkyl, each alkyl is independently (C₁-C₄)alkyl.

[0115] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one $\text{R}^{\text{a}5}$ is $-\text{NR}^{\text{a}11}\text{R}^{\text{a}12}$, wherein $\text{R}^{\text{a}11}$ is C₁-alkyl substituted with aryl, heteroaryl, cycloalkyl, or heterocycloalkyl; and $\text{R}^{\text{a}12}$ is hydrogen or alkyl. In some embodiments, where $\text{R}^{\text{a}12}$ is alkyl, the alkyl of $\text{R}^{\text{a}12}$ is substituted

with one or more substituents independently selected from the group consisting of =O, aryl, heteroaryl, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, and $-\text{OR}^{\text{a}24}$. In certain embodiments, each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl (e.g., substituting the C₁-alkyl of $\text{R}^{\text{a}11}$ or alkyl of $\text{R}^{\text{a}12}$) is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, $-\text{SF}_5$, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, and $-\text{OR}^{\text{a}40}$. In some embodiments, each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, and haloalkyl.

[0116] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one $\text{R}^{\text{a}5}$ is alkyl substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a}19}$, =O, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, and $\text{R}^{\text{a}58}$, wherein $\text{R}^{\text{a}58}$ is heterocycloalkyl. In some embodiments, at least one $\text{R}^{\text{a}5}$ is alkyl substituted with one or more substituents independently selected from the group consisting of =O, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, and $\text{R}^{\text{a}58}$, wherein $\text{R}^{\text{a}58}$ is heterocycloalkyl. In certain embodiments, at least one of $\text{R}^{\text{a}20}$ and $\text{R}^{\text{a}21}$ is not hydrogen. In some embodiments, the alkyl is (C₁-C₄)alkyl. In certain embodiments, the alkyl is (C₁-C₂)alkyl. In certain embodiments, at least one $\text{R}^{\text{a}5}$ is C₁-alkyl substituted with $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, wherein at least one of $\text{R}^{\text{a}20}$ and $\text{R}^{\text{a}21}$ is not hydrogen. In some embodiments, at least one $\text{R}^{\text{a}5}$ is C₂-alkyl substituted with =O and $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, wherein at least one of $\text{R}^{\text{a}20}$ and $\text{R}^{\text{a}21}$ is not hydrogen.

[0117] In still further embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, one or more $\text{R}^{\text{a}5}$ is a substituted alkyl of formula (a):



wherein:

w is 0 or 1;

R^{a20} and R^{a21} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl,

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, $-NR^{a22}R^{a23}$, $-OR^{a24}$, alkyl, aryl, and heteroaryl;

wherein each alkyl is independently unsubstituted or substituted with one or more halo; and each aryl and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, and haloalkyl.

[0118] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one R^{a5} is alkenyl, wherein each alkenyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, =O, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{a35} is independently (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 8-membered heterocycloalkyl, (C₆-C₁₀)aryl, or 3- to 8-membered heteroaryl. In some embodiments, at least one R^{a5} is alkenyl, wherein the alkenyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, $-OR^{a16}$, =O, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, and $-SO_2R^{a53}$. In some embodiments, at least one R^{a5} is alkenyl, wherein each alkenyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl, 3- to 6-membered heteroaryl, halo, -OH, -OH-(C₁-C₆)alkyl, =O, $-NR^{a17}R^{a18}$, $-CN$, and $-SF_5$. In some embodiments, at least one R^{a5} is unsubstituted alkenyl. In some embodiments, the alkenyl is (C₂-C₁₀)alkenyl. In other embodiments, the alkenyl is (C₂-C₈)alkenyl. In still further embodiments, the alkenyl is (C₂-C₆)alkenyl. In yet other embodiments, the alkenyl is (C₂-C₄)alkenyl. In some embodiments, the alkenyl is branched. In other embodiments, the alkenyl is unbranched. In some embodiments, the alkenyl is a

branched (C₂-C₆)alkenyl substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, -OR^{a16}, =O, and -NR^{a17}R^{a18}. In some embodiments, the alkenyl comprises between one to three carbon-carbon double bonds. In other embodiments, the alkenyl comprises one carbon-carbon double bond. In some embodiments, the alkenyl comprises two carbon-carbon double bonds. In still further embodiments, the alkenyl comprises three carbon-carbon double bonds.

[0119] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one R^{a5} is cycloalkyl, wherein each cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -OR^{a16}, =O, -NR^{a17}R^{a18}, -CN, -SF₅, -SO₂NR^{a50}R^{a51}, -SR^{a52}, -SO₂R^{a53}, and R^{a35}, wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{a35} is independently (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 8-membered heterocycloalkyl, (C₆-C₁₀)aryl, or 3- to 8-membered heteroaryl. In some embodiments, at least one R^{a5} is cycloalkyl, wherein the cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, -OR^{a16}, =O, -NR^{a17}R^{a18}, -CN, -SF₅, -SO₂NR^{a50}R^{a51}, -SR^{a52}, and -SO₂R^{a53}. In some embodiments, at least one R^{a5} is cycloalkyl, wherein each cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₆-C₁₀)aryl, 3- to 6-membered heteroaryl, halo, -OH, -OH-, (C₁-C₆)alkyl, =O, -NR^{a17}R^{a18}, -CN, and -SF₅. In some embodiments, at least one R^{a5} is unsubstituted cycloalkyl.

[0120] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one R^{a5} is aryl, wherein each aryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -OR^{a16}, =O, -NR^{a17}R^{a18}, -CN, -SF₅, -SO₂NR^{a50}R^{a51}, -SR^{a52}, -SO₂R^{a53}, and R^{a35}, wherein each R^{a35} is independently alkyl,

cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{a35} is independently (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 8-membered heterocycloalkyl, (C₆-C₁₀)aryl, or 3- to 8-membered heteroaryl. In some embodiments, at least one R^{a5} is aryl, wherein the aryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, -SF₅, and R^{a35} . In some embodiments, R^{a35} is unsubstituted (C₁-C₆)alkyl. In other embodiments, R^{a35} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -OR^{a24}, and -SF₅. In some embodiments, R^{a35} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -SF₅, -OH, -O-(C₁-C₆)alkyl, and -O-(C₁-C₆)haloalkyl. In some embodiments, at least one R^{a5} is unsubstituted aryl.

[0121] In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a stereoisomer or pharmaceutically acceptable salt thereof, at least one R^{a5} is heteroaryl, wherein each heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, -OR^{a16}, =O, -NR^{a17}R^{a18}, -CN, -SF₅, -SO₂NR^{a50}R^{a51}, -SR^{a52}, -SO₂R^{a53}, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{a35} is independently (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 8-membered heterocycloalkyl, (C₆-C₁₀)aryl, or 3- to 8-membered heteroaryl. In some embodiments, at least one R^{a5} is heteroaryl, wherein the heteroaryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, -SF₅, and R^{a35} . In some embodiments, R^{a35} is unsubstituted (C₁-C₆)alkyl. In other embodiments, R^{a35} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -OR^{a24}, and -SF₅. In some embodiments, R^{a35} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -SF₅, -OH, -O-(C₁-C₆)alkyl, and -O-(C₁-C₆)haloalkyl. In some embodiments, at least one R^{a5} is unsubstituted heteroaryl.

[0122] In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a stereoisomer or pharmaceutically acceptable salt thereof, at least one R^{a5} is heterocycloalkyl, wherein each heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{a35} is independently (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 8-membered heterocycloalkyl, (C₆-C₁₀)aryl, or 3- to 8-membered heteroaryl. In some embodiments, at least one R^{a5} is heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-SF_5$, and R^{a35} . In some embodiments, R^{a35} is unsubstituted (C₁-C₆)alkyl. In other embodiments, R^{a35} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-CN$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-NR^{a22}R^{a23}$, $-OR^{a24}$, and $-SF_5$. In some embodiments, R^{a35} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-CN$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-NR^{a22}R^{a23}$, $-SF_5$, $-OH$, $-O-(C_1-C_6)alkyl$, and $-O-(C_1-C_6)haloalkyl$. In some embodiments, at least one R^{a5} is unsubstituted heterocycloalkyl.

[0123] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl. In certain embodiments, each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)halocycloalkyl, 3- to 10-membered heterocycloalkyl, (C₆-C₁₀)aryl, 3- to 10-membered heteroaryl, (C₂-C₆)alkynyl, or (C₂-C₆)haloalkynyl.

[0124] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, each R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl. In some embodiments, each R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, and (C₃-C₆)halocycloalkyl. In certain embodiments, each R^{a11} , R^{a12} , R^{a19} , R^{a20} , and R^{a21} is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl. In certain embodiments, each R^{a11} , R^{a12} , R^{a19} , R^{a20} , and R^{a21} is independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heteroaryl, or (C₆-C₁₀)aryl. In some embodiments, each R^{a13} is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or alkynyl. In certain embodiments, each R^{a13} is independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 10-membered heterocycloalkyl, (C₆-C₁₀)aryl, 3- to 10-membered heteroaryl, or (C₃-C₆)alkynyl.

[0125] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -OR^{a24}, and -SF₅;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, -CN, -SF₅, =O, -NR^{a36}R^{a37}, -NR^{a38}C(O)R^{a39}, -OR^{a40}, and R^{a59},

wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the

group consisting of =O, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl.

[0126] In certain embodiments, each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, $-\text{CN}$, $(\text{C}_6\text{-C}_{10})\text{aryl}$, 5- to 10-membered heteroaryl, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, 5- to 10-membered heterocycloalkyl, $-\text{NR}^{\text{a22}}\text{R}^{\text{a23}}$, $-\text{OR}^{\text{a24}}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{haloalkyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$, halo, $-\text{CN}$, $-\text{SF}_5$, =O, $-\text{NR}^{\text{a36}}\text{R}^{\text{a37}}$, $-\text{NR}^{\text{a38}}\text{C}(\text{O})\text{R}^{\text{a39}}$, $-\text{OR}^{\text{a40}}$, and R^{a59} ,

wherein each R^{a59} is independently $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, 5- to 10-membered heterocycloalkyl, $(\text{C}_6\text{-C}_{10})\text{aryl}$, or 5- to 10-membered heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{O}-(\text{C}_1\text{-C}_6)\text{haloalkyl}$, halo, $(\text{C}_1\text{-C}_6)\text{alkyl}$, and $(\text{C}_1\text{-C}_6)\text{haloalkyl}$.

[0127] In certain embodiments, each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently selected from the group consisting of halo, =O, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{\text{a22}}\text{R}^{\text{a23}}$, $-\text{OR}^{\text{a24}}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, =O, $-\text{NR}^{\text{a36}}\text{R}^{\text{a37}}$, $-\text{NR}^{\text{a38}}\text{C}(\text{O})\text{R}^{\text{a39}}$, $-\text{OR}^{\text{a40}}$, and R^{a59} ,

wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group

consisting of =O, -NH₂, -SF₅, -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl.

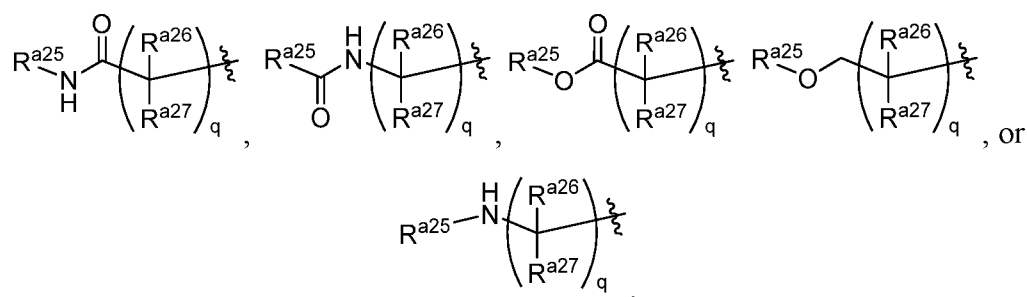
[0128] In certain embodiments, each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11}, R^{a12}, R^{a13}, R^{a19}, R^{a20}, R^{a21}, and R^{a35}, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently selected from the group consisting of halo, =O, -CN, (C₆-C₁₀)aryl, 5- to 10-membered heteroaryl, (C₁-C₆)alkyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heterocycloalkyl, -NR^{a22}R^{a23}, -OR^{a24}, and -SF₅;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkynyl, halo, -CN, -SF₅, =O, -NR^{a36}R^{a37}, -NR^{a38}C(O)R^{a39}, -OR^{a40}, and R^{a59},

wherein each R^{a59} is independently (C₃-C₆)cycloalkyl, 5- to 10-membered heterocycloalkyl, (C₆-C₁₀)aryl, or 5- to 10-membered heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, -NH₂, -SF₅, -OH, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, halo, (C₁-C₆)alkyl, and (C₁-C₆)haloalkyl.

[0129] In some embodiments, each R^{a22}, R^{a23}, R^{a24}, R^{a36}, R^{a37}, R^{a38}, R^{a39}, and R^{a40} is independently hydrogen, alkyl, or haloalkyl. In certain embodiments, each R^{a22}, R^{a23}, R^{a24}, R^{a36}, R^{a37}, R^{a38}, R^{a39}, and R^{a40} is independently hydrogen, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl.

[0130] In certain variations of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, at least one of R^{a5} is:



wherein:

R^{a25} is hydrogen, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

wherein the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, =O, $-OR^{a28}$, $-SF_5$, and $-NR^{a29}R^{a30}$,

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-SF_5$, =O, $-OR^{a31}$, $-NR^{a41}R^{a42}$, $-NR^{a43}C(O)R^{a44}$, cycloalkyl, and heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, halo, $-OH$, and $-SF_5$;

each R^{a26} and R^{a27} is independently hydrogen, halo, or alkyl;

wherein each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-OR^{a32}$, and $-NR^{a33}R^{a34}$,

wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, haloalkyl, alkyl, $-OH$, =O, and $-SF_5$;

or one R^{a26} and one R^{a27} attached to the same atom, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

each R^{a28} , R^{a29} , R^{a30} , R^{a31} , R^{a32} , R^{a33} , R^{a34} , R^{a41} , R^{a42} , R^{a43} , and R^{a44} is independently hydrogen, alkyl, or haloalkyl;

and q is 1 or 2.

[0131] In some embodiments, each R^{a28} , R^{a29} , R^{a30} , R^{a31} , R^{a32} , R^{a33} , R^{a34} , R^{a41} , R^{a42} , R^{a43} , and R^{a44} is independently hydrogen, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl. In some embodiments, each R^{a28} , R^{a29} , R^{a30} , R^{a31} , R^{a32} , R^{a33} , R^{a34} , R^{a41} , R^{a42} , R^{a43} , and R^{a44} is independently hydrogen, methyl, ethyl, propyl, butyl, halomethyl, haloethyl, halopropyl, or halobutyl.

[0132] In some embodiments, R^{a25} is hydrogen. In other embodiments, R^{a25} is alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, aryl, heteroaryl, heterocycloalkyl, =O, $-OR^{a28}$, $-SF_5$, and $-NR^{a29}R^{a30}$. In still other embodiments, R^{a25} is aryl, wherein the aryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, aryl, heteroaryl, heterocycloalkyl, =O, $-OR^{a28}$, $-SF_5$, and $-NR^{a29}R^{a30}$.

[0133] In certain embodiments, R^{a25} is alkyl, wherein the alkyl is unsubstituted or substituted with aryl or heteroaryl, wherein the aryl or heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkynyl, alkyl, haloalkyl, halo, $-SF_5$, =O, $-OR^{a31}$, $-NR^{a41}R^{a42}$, $-NR^{a43}C(O)R^{a44}$, and heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with =O. In some embodiments, the aryl or heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of (C₂-C₆)alkynyl, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, halo, $-SF_5$, =O, $-OH$, $-O(C_1-C_6)alkyl$, $-O(C_1-C_6)haloalkyl$, $-NHC(O)H$, $-NHC(O)-(C_1-C_6)alkyl$, $-NH_2$, $-NH(C_1-C_6)alkyl$, and 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with =O.

[0134] In some embodiments, R^{a25} is alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-SF_5$, (C₃-C₆)cycloalkyl, (C₃-C₆)heterocycloalkyl, (C₆-C₁₀)aryl, and 3- to 6-membered heteroaryl; wherein the aryl and heteroaryl are independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, (C₁-C₆)haloalkyl, (C₁-C₆)alkyl, $-SF_5$, $-OH$, $-O(C_1-C_6)alkyl$, =O, $-NR^{a41}R^{a42}$, and $-NR^{a43}C(O)R^{a44}$. In some embodiments, R^{a25} is alkyl substituted with one or more (C₆-C₁₀)aryl, wherein each aryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, $-OH$, $-O(C_1-C_6)alkyl$,

–SF₅, –NHC(O)–(C₁–C₆)alkyl, and 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with =O. In certain embodiments, R^{a25} is (C₁–C₆)alkyl, wherein the alkyl is unsubstituted or substituted with one or more (C₆–C₁₀)aryl or 3- to 6-membered heteroaryl.

[0135] In certain embodiments, R^{a25} is unsubstituted (C₁–C₆)alkyl. In other embodiments, R^{a25} is (C₁–C₆)alkyl substituted with 3- to 6-membered heteroaryl. In other embodiments, R^{a25} is (C₁–C₆)alkyl substituted with phenyl, wherein the phenyl is unsubstituted or substituted with one more substituents independently selected from the group consisting of (C₁–C₆)alkyl, (C₂–C₆)alkynyl, (C₁–C₆)haloalkyl, –OH, –O(C₁–C₆)alkyl, –SF₅, –NHC(O)H, and –NHC(O)–(C₁–C₆)alkyl. In other embodiments, R^{a25} is (C₁–C₆)alkyl substituted with phenyl, wherein the phenyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of (C₁–C₆)alkyl, (C₁–C₆)haloalkyl, –OH, –O(C₁–C₆)alkyl, –SF₅, –NHC(O)H, –NHC(O)–(C₁–C₆)alkyl, =O, –NH₂, and –NH(C₁–C₆)alkyl.

[0136] In some embodiments, R^{a25} is (C₁–C₆)alkyl substituted with (C₃–C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, –OH, and –O(C₁–C₆)alkyl. In other embodiments, R^{a25} is (C₁–C₆)alkyl substituted with 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, –OH, and –O(C₁–C₆)alkyl.

[0137] In some embodiments, R^{a25} is (C₃–C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, (C₁–C₆)alkyl, (C₁–C₆)haloalkyl, –OH, –O(C₁–C₆)alkyl, –SF₅, –NHC(O)–(C₁–C₆)alkyl, and 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with =O. In other embodiments, R^{a25} is (C₃–C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, –OH, and –O(C₁–C₆)alkyl.

[0138] In some embodiments, R^{a25} is 3- to 10-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, (C₁–C₆)alkyl, (C₁–C₆)haloalkyl, –OH, –O(C₁–

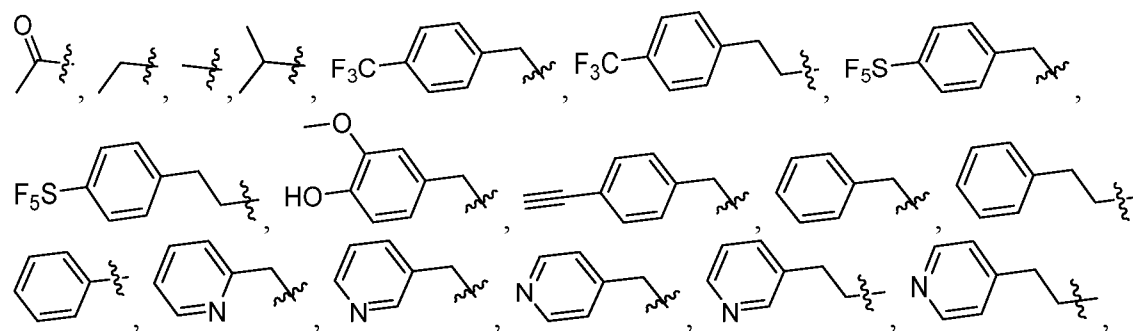
C₆alkyl, -SF₅, -NHC(O)-(C₁-C₆)alkyl, and 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with =O. In other embodiments, R^{a25} is 3- to 10-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, -OH, and -O(C₁-C₆)alkyl.

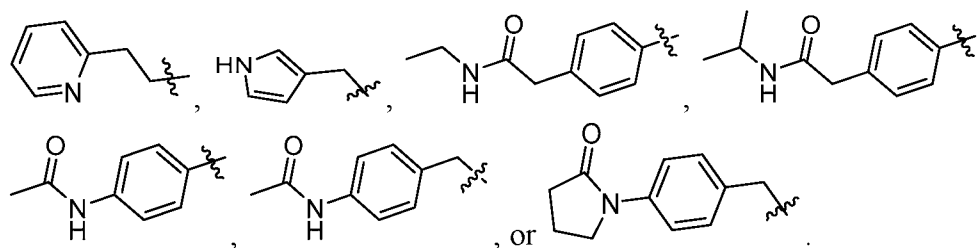
[0139] In still further embodiments, R^{a25} is aryl, wherein the aryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -OH, -O(C₁-C₆)alkyl, -SF₅, -NHC(O)-(C₁-C₆)alkyl, and 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with =O. In other embodiments, R^{a25} is phenyl, wherein the phenyl is unsubstituted or substituted with one or more (C₁-C₆)alkyl, wherein each alkyl is independently unsubstituted or substituted with (C₁-C₆)haloalkyl, -OH, -O(C₁-C₆)alkyl, -SF₅, -NHC(O)H, -NHC(O)-(C₁-C₆)alkyl, =O, -NH₂, and -NH(C₁-C₆)alkyl.

[0140] In still further embodiments, R^{a25} is heteroaryl, wherein the heteroaryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -OH, -O(C₁-C₆)alkyl, -SF₅, -NHC(O)-(C₁-C₆)alkyl, and 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with =O.

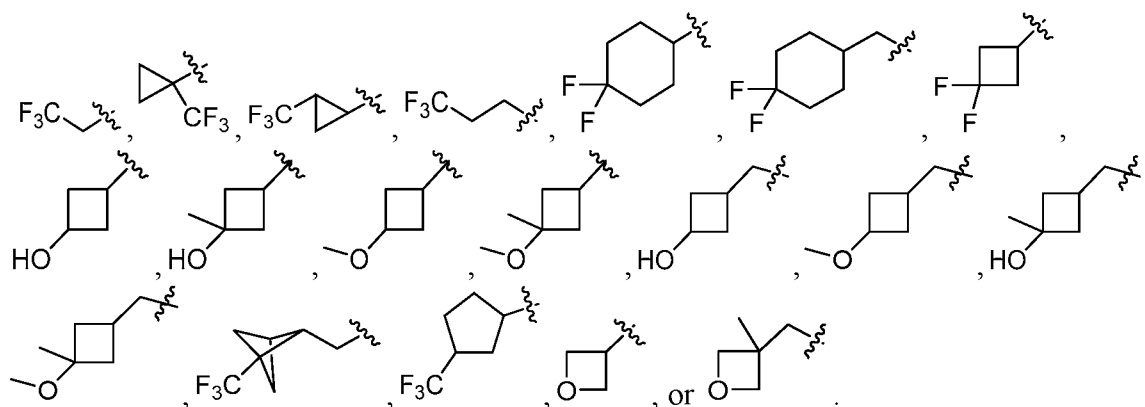
[0141] In some embodiments, R^{a25} is alkynyl. In certain embodiments, R^{a25} is (C₂-C₆)alkynyl.

[0142] In certain embodiments, R^{a25} is:





[0143] In certain embodiments, R^{a25} is:



[0144] In some embodiments, R^{a26} and R^{a27} attached to the same carbon form a cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the cycloalkyl is a (C₃-C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more halo. In certain embodiments, R^{a26} and R^{a27} attached to the same carbon form an unsubstituted cyclopropyl or cyclobutyl. In some embodiments, R^{a26} and R^{a27} attached to the same carbon form a cyclopropyl or cyclobutyl, wherein the cyclopropyl or cyclobutyl are substituted with one or more halo.

[0145] In some embodiments, each R^{a26} and R^{a27} is hydrogen. In some embodiments, at least one R^{a26} or R^{a27} is alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-OR^{a32}$, and $-NR^{a33}R^{a34}$. In some embodiments, at least one R^{a26} or R^{a27} is alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, bromo, (C₃-C₆)cycloalkyl, (C₃-C₆)halocycloalkyl, 3- to 6-membered heterocycloalkyl, aryl, 3- to 6-membered heteroaryl, $-OH$, $-O-(C_1-C_6)alkyl$, $-O-(C_1-C_6)haloalkyl$, $-NH_2$, $-NH(C_1-C_6)alkyl$, $-N((C_1-C_6)alkyl)((C_1-C_6)alkyl)$. In some embodiments, one R^{a26} or one R^{a27} is (C₁-C₆)alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of

fluoro, chloro, (C₃-C₆)cycloalkyl, (C₃-C₆)halocycloalkyl, and –OH. In certain embodiments, one R^{a26} or one R^{a27} is (C₁-C₆)alkyl, wherein the alkyl is unsubstituted or substituted with fluoro, chloro, (C₃-C₆)cycloalkyl, (C₃)halocycloalkyl, or –OH. In some embodiments, one R^{a26} or one R^{a27} is ethyl substituted with difluorocyclopropyl.

[0146] In some embodiments, at least one R^{a26} or R^{a27} is alkyl substituted with 3- to 10-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, haloalkyl, alkyl, and =O. In certain embodiments, at least one R^{a26} or R^{a27} is alkyl substituted with 4- to 10-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of fluoro, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, and =O. In certain embodiments, the 4- to 10-membered heterocycloalkyl is a polycyclic heterocycloalkyl. In some embodiments, at least one R^{a26} or R^{a27} is alkyl substituted with 5- to 6-membered heteroaryl.

[0147] In some embodiments, q is 1. In still other embodiments, q is 2. In some embodiments, q is 1, and one of R^{a26} and R^{a27} is hydrogen. In other embodiments, q is 2, and one R^{a26} and two R^{a27} are hydrogen. In other embodiments, q is 2, and two R^{a26} and one R^{a27} are hydrogen. In some embodiments, q is 2, and two R^{a26} and three R^{a27} are hydrogen. In some embodiments, q is 2, and three R^{a26} and two R^{a27} are hydrogen.

[0148] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl. In some embodiments, R^{a1} is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)halocycloalkyl. In some embodiments, R^{a1} is hydrogen, (C₁-C₆)alkyl, or (C₃-C₆)cycloalkyl. In certain embodiments, R^{a1} is hydrogen. In other embodiments, R^{a1} is (C₁-C₆)alkyl. For example, in some embodiments, R^{a1} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{a1} is (C₃-C₆)cycloalkyl. For example, in some embodiments, R^{a1} is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0149] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula

(I-C-i), or a pharmaceutically acceptable salt thereof, R^{a2} is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{a7}\text{R}^{a8}$, $-\text{OR}^{a9}$, and $-\text{SO}_2\text{R}^{a10}$, wherein the alkyl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, each R^{a7} , R^{a8} , R^{a9} , and R^{a10} , is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl. In some embodiments, each R^{a7} , R^{a8} , R^{a9} , and R^{a10} , is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl. In some embodiments, each R^{a7} , R^{a8} , R^{a9} , and R^{a10} , is independently hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)$ haloalkyl, $(\text{C}_3\text{-C}_6)$ cycloalkyl, $(\text{C}_3\text{-C}_6)$ halocycloalkyl, 3- to 8-membered heterocycloalkyl, or 3- to 8-membered haloheterocycloalkyl. In certain embodiments, each R^{a7} , R^{a8} , R^{a9} , and R^{a10} , is independently hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)$ haloalkyl, $(\text{C}_3\text{-C}_6)$ cycloalkyl, or $(\text{C}_3\text{-C}_6)$ halocycloalkyl. In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, R^{a2} is hydrogen, fluoro, chloro, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_3\text{-C}_6)$ cycloalkyl, 3- to 6-membered heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NH}_2$, $-\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{SO}_2\text{H}$, or $-\text{SO}_2(\text{C}_1\text{-C}_6)\text{alkyl}$. In certain embodiments, R^{a2} is hydrogen. In some embodiments, wherein R^{a2} is alkyl, cycloalkyl, or heterocycloalkyl, the alkyl, cycloalkyl, or heterocycloalkyl is unsubstituted. In other embodiments, the alkyl, cycloalkyl, or heterocycloalkyl is substituted with one or more halo. In certain embodiments, the alkyl, cycloalkyl, or heterocycloalkyl is substituted with one to four fluoro, chloro, or bromo, or any combinations thereof.

[0150] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, R^{a3} is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{a7}\text{R}^{a8}$, $-\text{OR}^{a9}$, and $-\text{SO}_2\text{R}^{a10}$, wherein the alkyl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, each R^{a7} , R^{a8} , R^{a9} , and R^{a10} , is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl. In certain embodiments, each R^{a7} , R^{a8} , R^{a9} , and R^{a10} , is independently hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)$ haloalkyl, $(\text{C}_3\text{-C}_6)$ cycloalkyl, or $(\text{C}_3\text{-C}_6)$ halocycloalkyl. In certain embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B),

Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, R^{a3} is hydrogen, fluoro, chloro, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 6-membered heterocycloalkyl, -NO₂, -CN, -SO₂NH₂, -NH₂, -NH(C₁-C₆)alkyl, -N((C₁-C₆)alkyl)((C₁-C₆)alkyl), -OH, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, -SO₂H, or -SO₂-(C₁-C₆)alkyl. In certain embodiments, R^{a3} is hydrogen. In some embodiments, wherein R^{a3} is alkyl, cycloalkyl, or heterocycloalkyl, the alkyl, cycloalkyl, or heterocycloalkyl is unsubstituted. In other embodiments, the alkyl, cycloalkyl, or heterocycloalkyl is substituted with one or more halo. In certain embodiments, the alkyl, cycloalkyl, or heterocycloalkyl is substituted with one to four fluoro, chloro, or bromo, or any combinations thereof.

[0151] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -NO₂, -CN, -SO₂NH₂, -NR^{a7}R^{a8}, -OR^{a9}, =O, -SR^{a47}, and -SO₂R^{a10}, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo. In some embodiments, each R^{a4} is independently selected from the group consisting of halo, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 3- to 10-membered heterocycloalkyl, (C₆-C₁₀)aryl, 5- to 10-membered heteroaryl, -NO₂, -CN, -SO₂NH₂, -NR^{a7}R^{a8}, -OR^{a9}, =O, -SR^{a47}, and -SO₂R^{a10}, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo. In some embodiments, each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl. In certain embodiments, each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)halocycloalkyl, 3- to 10-membered heterocycloalkyl, or 3- to 10-membered haloheterocycloalkyl. In some embodiments, each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl. In certain embodiments, each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, or (C₃-C₆)halocycloalkyl. In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt

thereof, each R^{a4} is independently selected from the group consisting of fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)halocycloalkyl, 3- to 6-membered heterocycloalkyl, -NO₂, -CN, -SO₂NH₂, -NH₂, -NH(C₁-C₆)alkyl, -N((C₁-C₆)alkyl)((C₁-C₆)alkyl), -OH, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, -SO₂H, =O, and -SO₂-(C₁-C₆)alkyl. In some embodiments, each R^{a4} is independently selected from the group consisting of fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -OH, -O-(C₁-C₆)alkyl, and -O-(C₁-C₆)haloalkyl. In certain embodiments, at least one R^{a4} is fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)halocycloalkyl, 3- to 6-membered heterocycloalkyl, -NO₂, -CN, -SO₂NH₂, -NH₂, -NH(C₁-C₆)alkyl, -N((C₁-C₆)alkyl)((C₁-C₆)alkyl), -OH, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, -SO₂H, =O, or -SO₂-(C₁-C₆)alkyl. In some embodiments, at least one R^{a4} is fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -OH, -O-(C₁-C₆)alkyl, or -O-(C₁-C₆)haloalkyl. In certain embodiments, at least one R^{a4} is fluoro, chloro, methyl, ethyl, propyl, -OH, methoxy, ethoxy, propoxy, -OCH₂F, -OCHF₂, -OCF₃, -CH₂F, -CHF₂, or -CF₃.

[0152] In some embodiments of the compound of Formula (X) or Formula (I), or a pharmaceutically acceptable salt thereof m is an integer from 0 to 13. In some embodiments, m is an integer from 0 to 10. In other embodiments, m is an integer from 0 to 7. In certain embodiments, m is an integer from 0 to 5. In certain embodiments, m is 0, 1, 2, or 3. In still other embodiments, m is an integer from 3 to 13. In further embodiments, m is an integer from 7 to 13. In some embodiments, m is an integer from 3 to 10. In some embodiments, m is 0. In other embodiments, m is 1.

[0153] In some embodiments of the compound of Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, p is an integer from 0 to 7. In certain embodiments, p is an integer from 0 to 5. In some embodiments, p is an integer from 3 to 5. In other embodiments, p is 0, 1, 2, or 3. In some embodiments, p is 0.

[0154] In some embodiments, R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, -NO₂, -CN, -SO₂NH₂, -NR^{a7}R^{a8}, -OR^{a9}, and -SO₂R^{a10}, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo. In certain embodiments, R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)halocycloalkyl, 3- to 6-membered

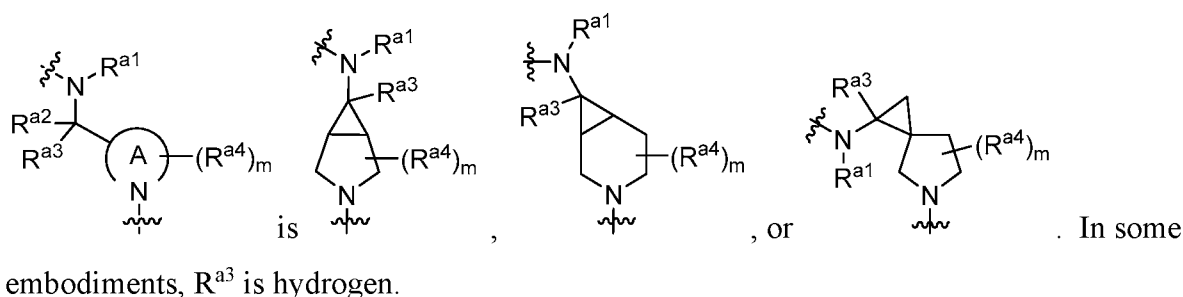
heterocycloalkyl, 3- to 6-membered haloheterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$, and $-\text{OH}$. In some embodiments, $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, and $-\text{OH}$. In some embodiments, $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ are independently selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, and $-\text{OH}$. In certain embodiments, $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ are independently hydrogen, methyl, or ethyl. In some embodiments, $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ are both hydrogen. In certain embodiments, one of $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ is $(\text{C}_1\text{-C}_6)\text{alkyl}$.

[0155] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, $\text{R}^{\text{a}1}$ and $\text{R}^{\text{a}2}$, together with the atoms to which they are attached, form a heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, $\text{R}^{\text{a}1}$ and $\text{R}^{\text{a}2}$, together with the atoms to which they are attached, form a 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the heterocycloalkyl is unsubstituted.

[0156] In some embodiments of the compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a $(\text{C}_6\text{-C}_{10})\text{aryl}$, 3- to 6-membered heteroaryl, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, or 3- to 6-membered heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is fused with ring A. In other embodiments, the cycloalkyl or heterocycloalkyl forms a spirocyclic system with ring A. In some embodiments, wherein two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo; there may exist one or more other $\text{R}^{\text{a}4}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, $=\text{O}$, $-\text{SR}^{\text{a}47}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl,

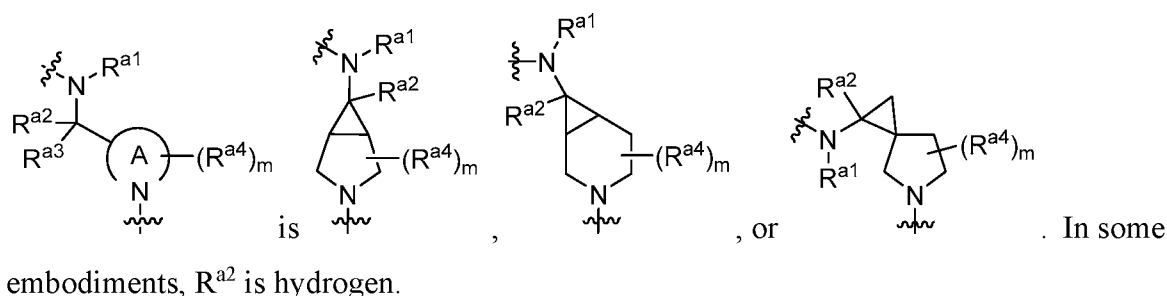
heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo.

[0157] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a (C₃-C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the cycloalkyl is unsubstituted. In other embodiments, R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the heterocycloalkyl is unsubstituted. In certain embodiments, R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a C₃-cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more halo. The cycloalkyl or heterocycloalkyl formed by R^{a2} and R^{a4} may be fused to ring A. For example, in some embodiments,

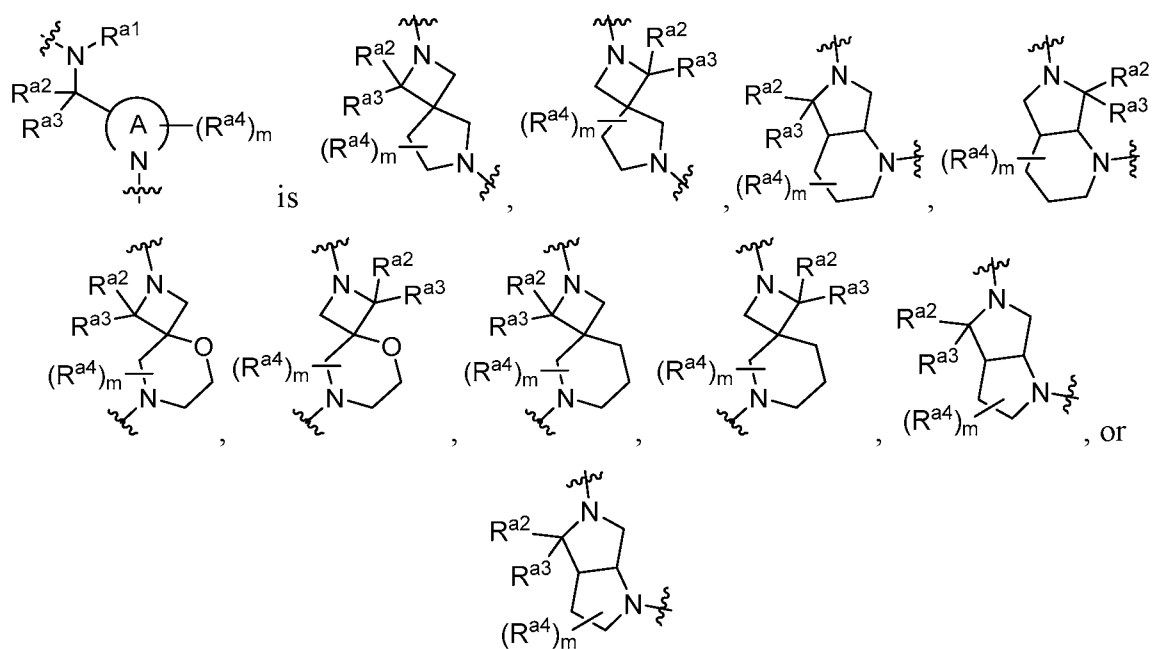


[0158] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a (C₃-C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the

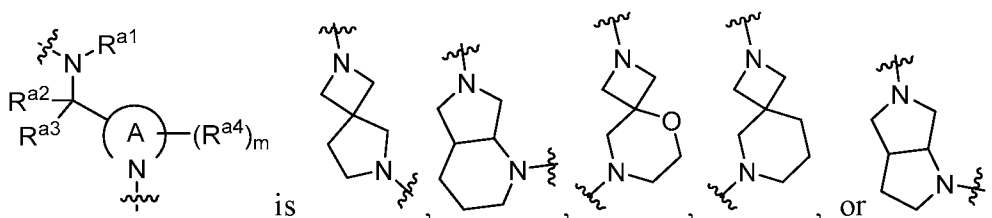
cycloalkyl is unsubstituted. In other embodiments, R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a 3- to 6-membered heterocycloalkyl. wherein the heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the heterocycloalkyl is unsubstituted. In certain embodiments, R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a C₃-cycloalkyl. The cycloalkyl or heterocycloalkyl formed by R^{a3} and R^{a4} may be fused to ring A. For example, in some embodiments,



[0159] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl. For example, in certain embodiments, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a 3- to 6-membered heterocycloalkyl. For example, in some embodiments,



[0160] In some embodiments, R^{a2} or R^{a3} is hydrogen. In other embodiments, both of R^{a2} and R^{a3} are hydrogen. In some embodiments, m is 0. Thus, in some embodiments,



[0161] In some embodiments, when X is $-C(O)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a spirocycle with ring A . In certain embodiments, the spirocycle is unsubstituted. In some embodiments, the spirocycle is substituted with one or more halo.

[0162] It should be understood that in some embodiments, wherein R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl; or wherein R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl; or wherein R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl; or wherein two to four R^{a4} , together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl; there may exist one or more other R^{a4} independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, $=O$, $-SR^{a10}$, and $-SO_2R^{a10}$, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are independently unsubstituted or substituted with one or more halo. For example, in some embodiments of Formula (I), m is 3; R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl; and the remaining two R^{a4} are independently halo or alkyl. In some embodiments of Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), p is 4; R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl; and the remaining three R^{a4} are independently $-OH$, halo, alkyl, or haloalkyl.

[0163] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or

substituted with one or more halo. For example, in some embodiments, R^{a2} and R^{a3} , together with the atom to which they are attached, form a (C₃-C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the cycloalkyl is unsubstituted. In other embodiments, R^{a2} and R^{a3} , together with the atom to which they are attached, form a 3- to 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with one or more halo. In some embodiments, the heterocycloalkyl is unsubstituted.

[0164] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$. In some embodiments, X is $-S(O)_2-$, $-C(O)-$, or $-C(R^{a6})_2-$. In certain embodiments, X is $-S(O)-$, $-S(O)_2-$, or $-S(O)NR^{a46}-$. In other embodiments, X is $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$.

[0165] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is $-S(O)-$.

[0166] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is $-S(O)_2-$.

[0167] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is $-S(O)NR^{a46}-$, wherein R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=O$. In some embodiments, R^{a46} is hydrogen or (C₁-C₆)alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl,

heteroaryl, and =O. In certain embodiments, R^{a46} is hydrogen. In other embodiments, R^{a46} is unsubstituted (C₁-C₆)alkyl, such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still other embodiments, R^{a46} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, (C₃-C₆)cycloalkyl, 3- to 6-membered heterocycloalkyl, (C₆-C₁₀)aryl, 5- to 7-membered heteroaryl, and =O. In still further embodiments, R^{a46} is (C₁-C₆)alkyl substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, (C₃-C₆)cycloalkyl, and =O.

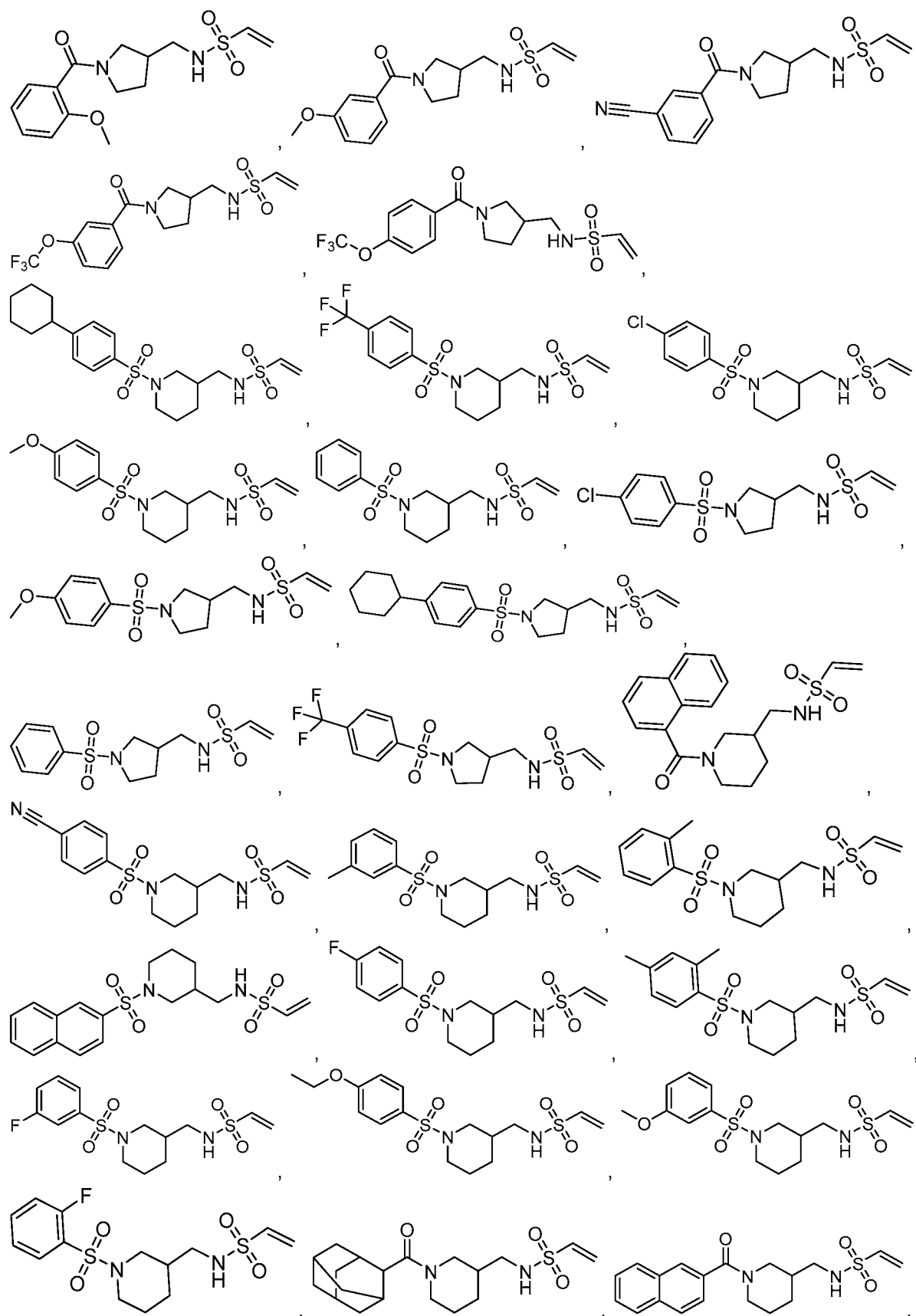
[0168] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is -C(S)-.

[0169] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is -C(O)-.

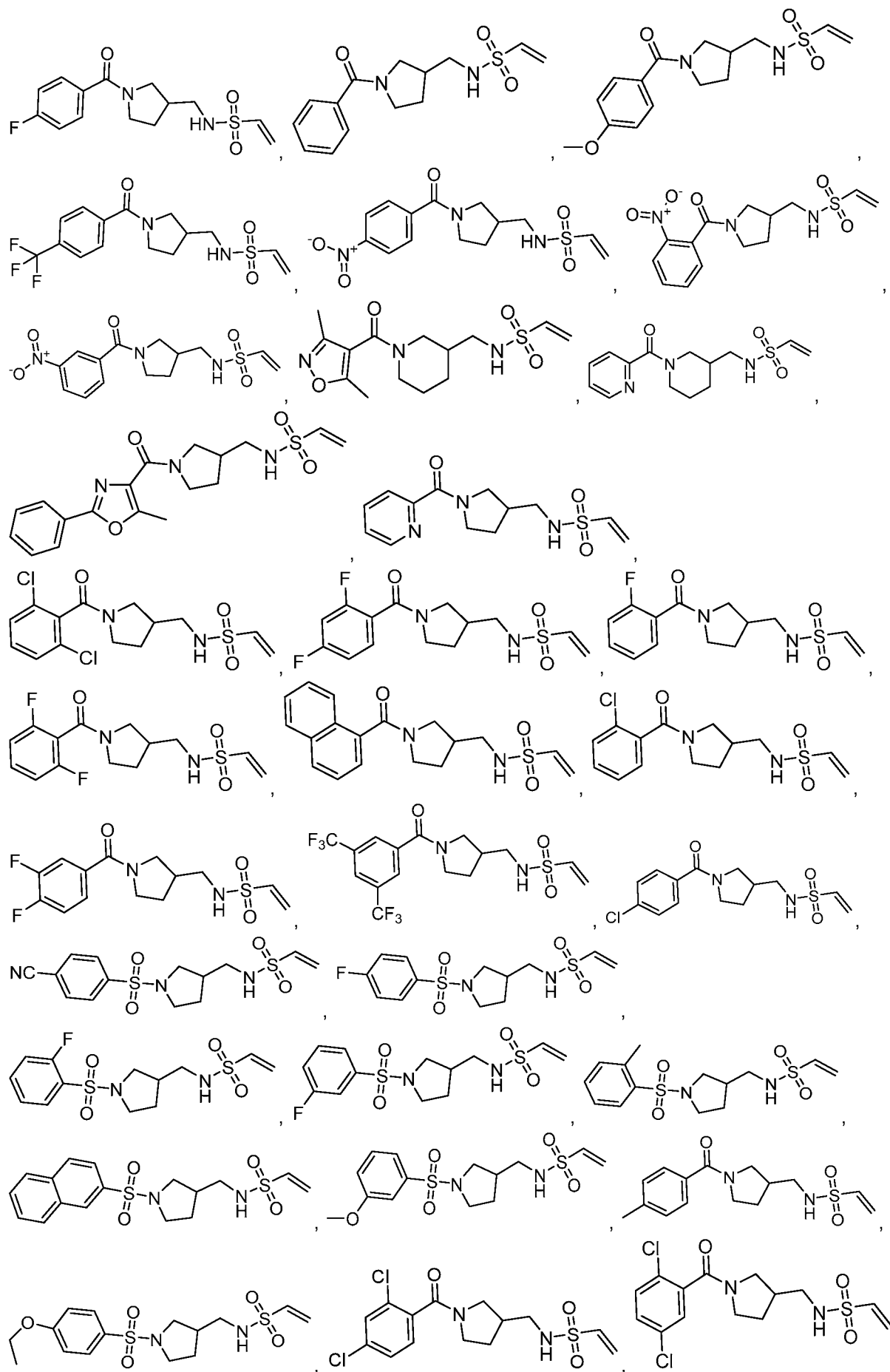
[0170] In some embodiments, of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is -C(R^{a6})₂-, wherein each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl. In certain embodiments, each R^{a6} is independently hydrogen, halo, (C₁-C₆)alkyl, or (C₁-C₆)haloalkyl. In some embodiments, each R^{a6} is independently hydrogen, chloro, fluoro, methyl, ethyl, propyl, -CH₂F, -CHF₂, or -CF₃. In some embodiments, each R^{a6} is H, and X is -CH₂-.

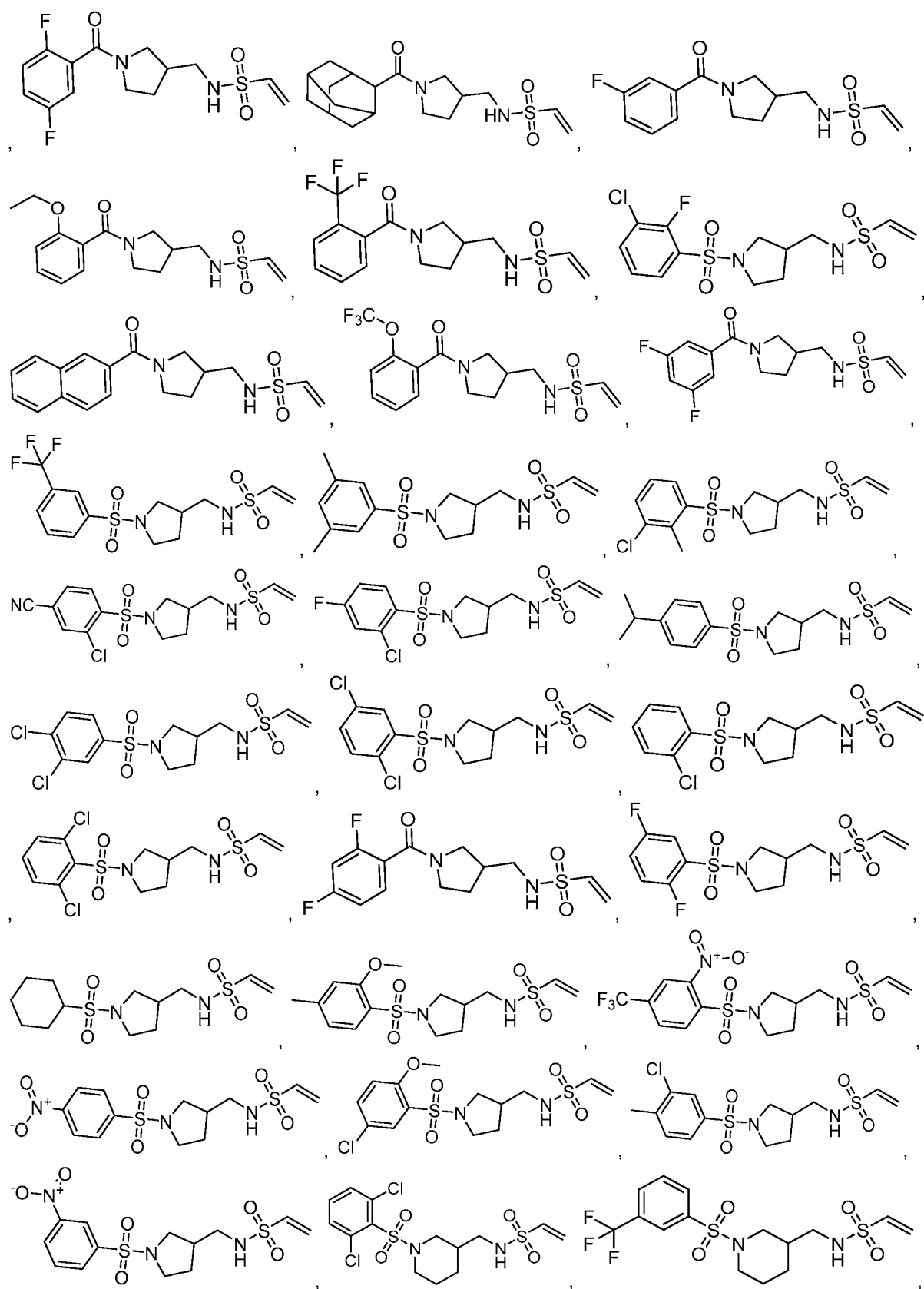
[0171] In some embodiments of the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, X is -S(O)₂-, -C(O)-, or -CH₂-.

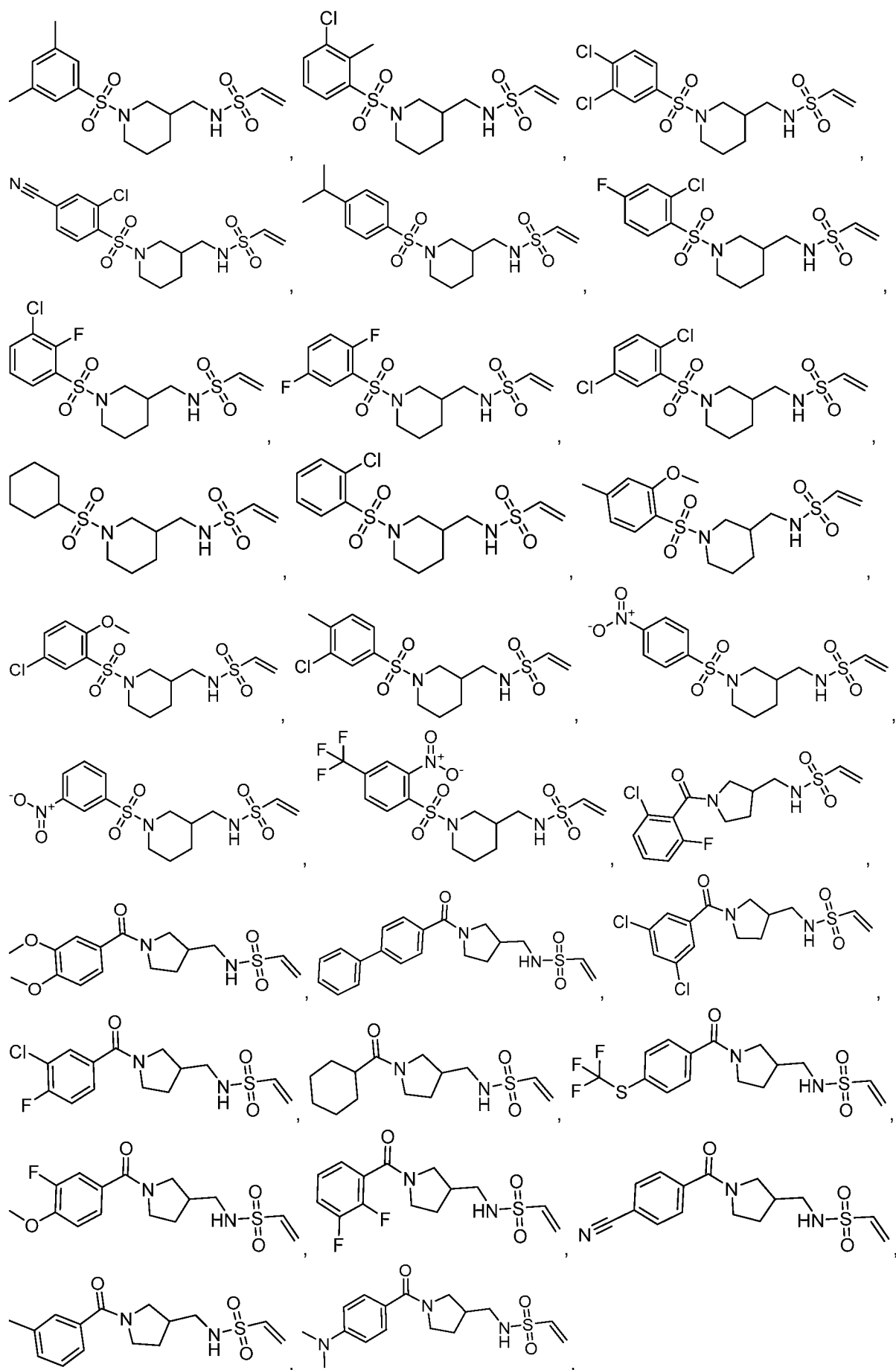
[0172] In some embodiments, the compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), is:

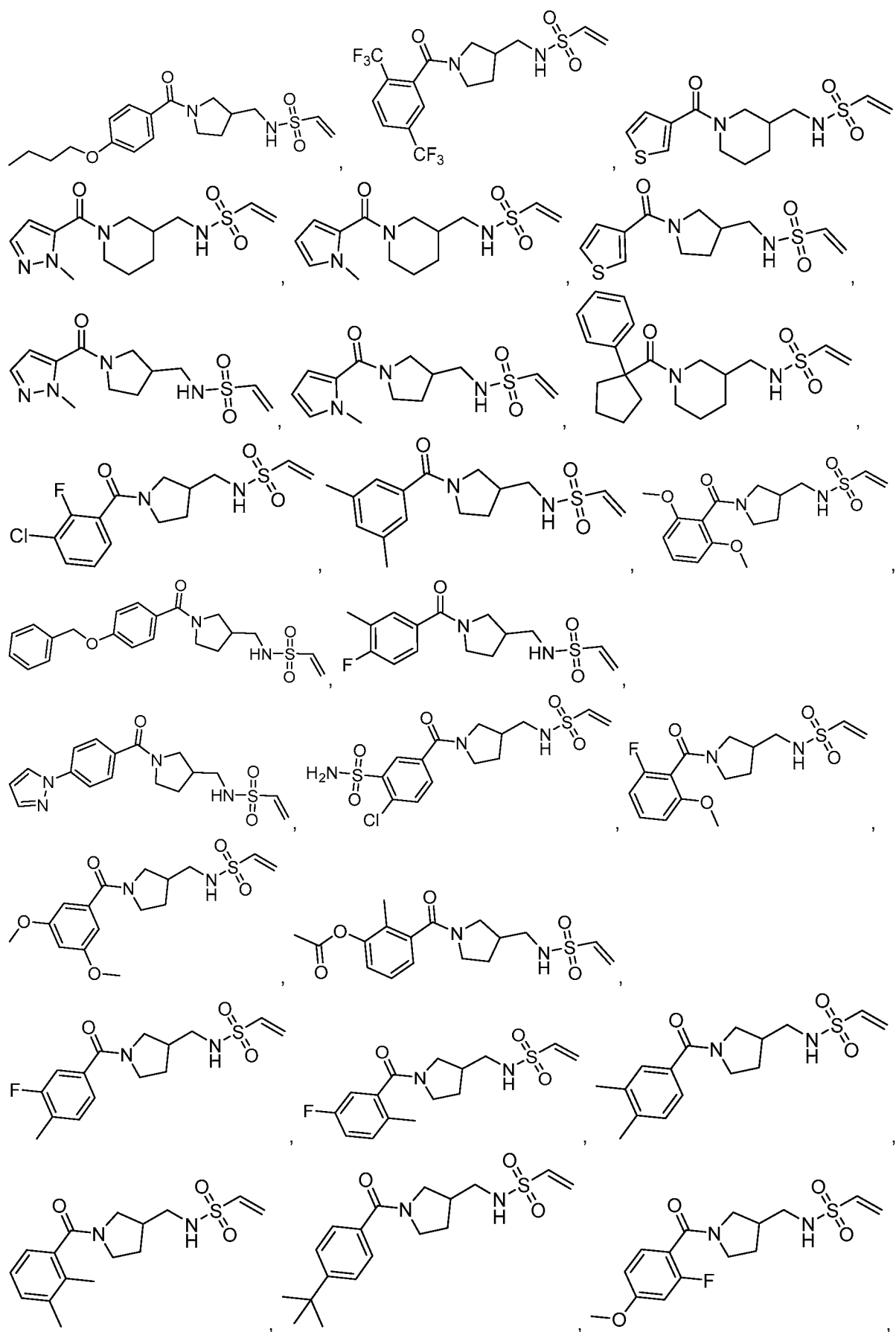


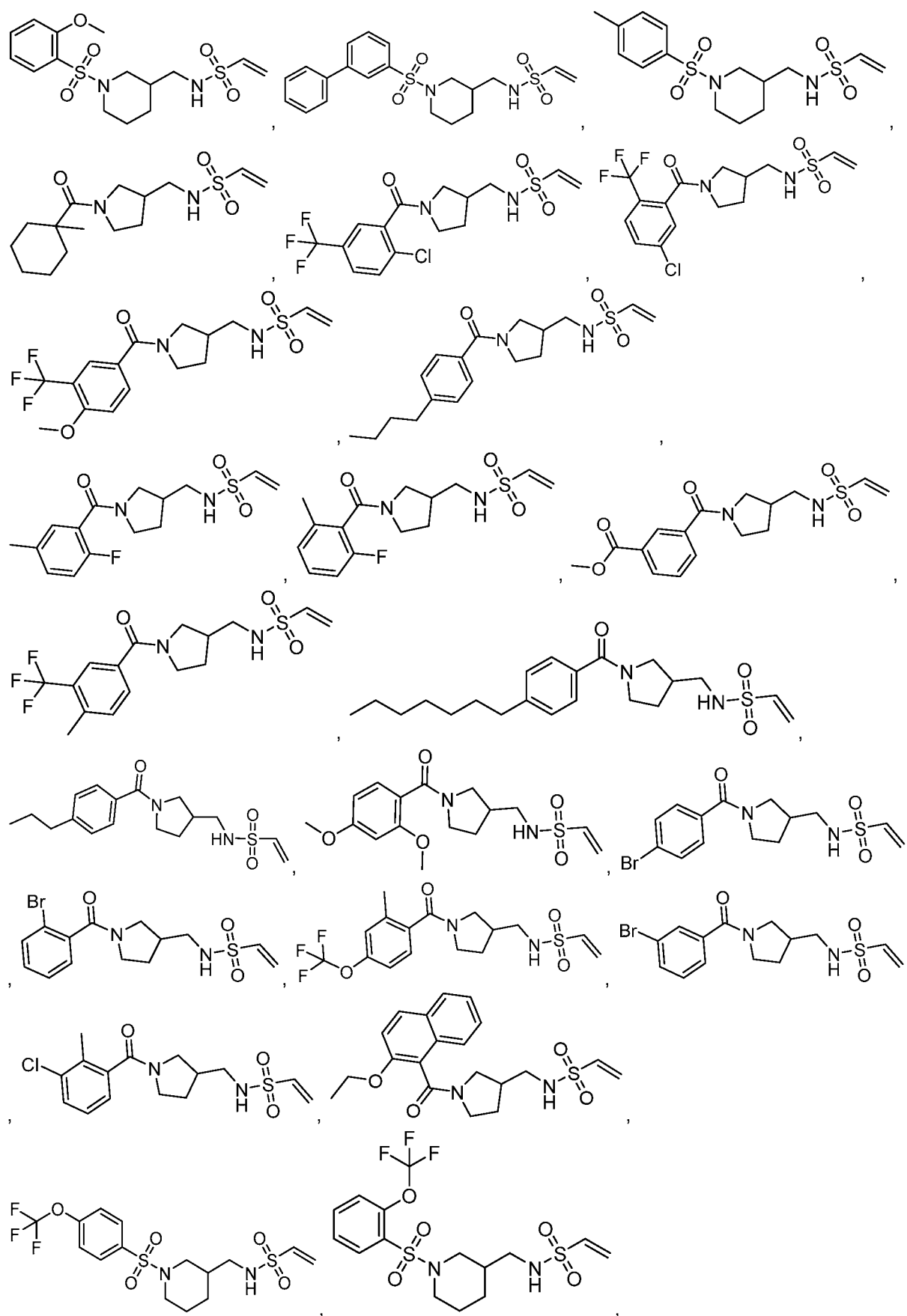


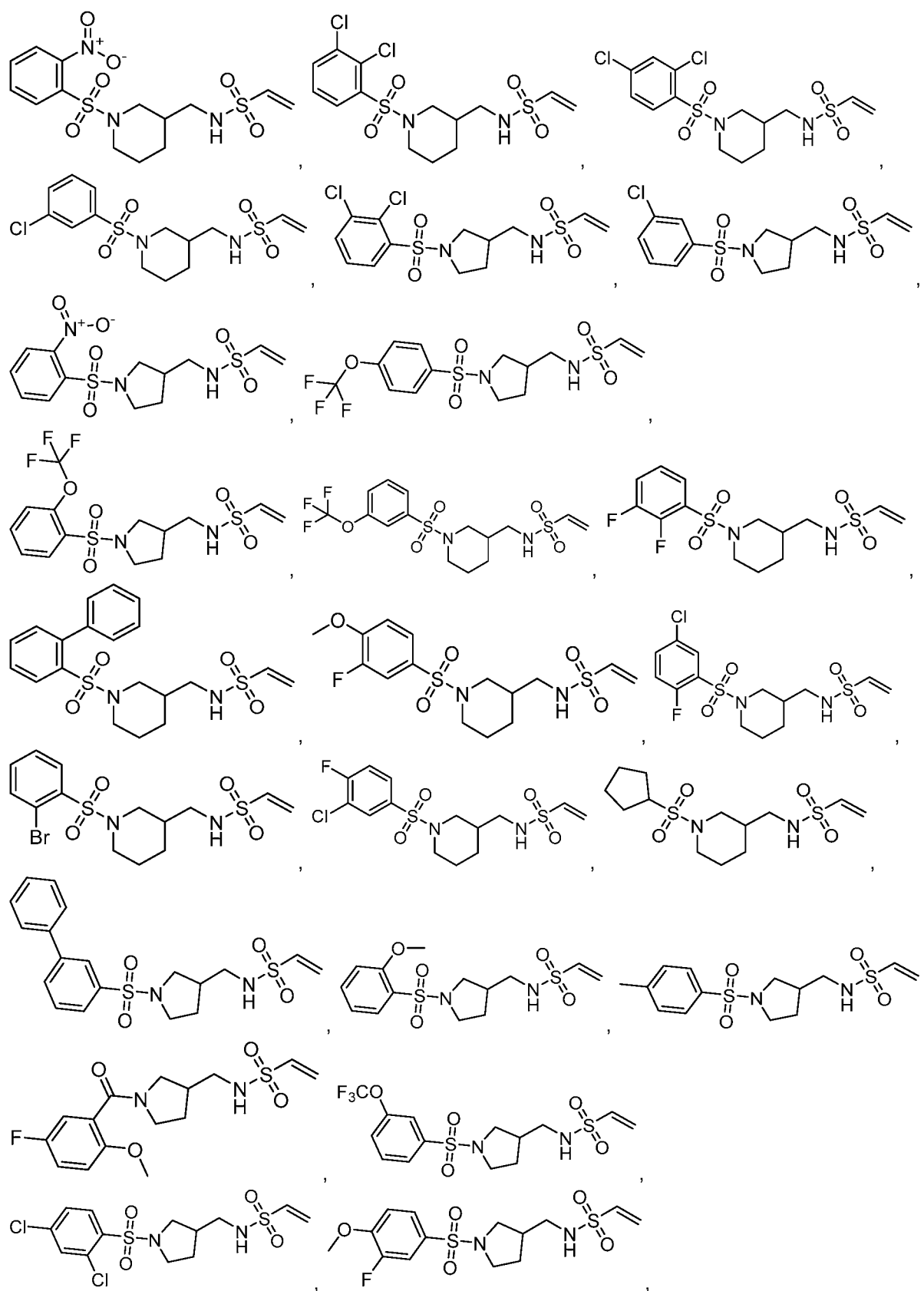


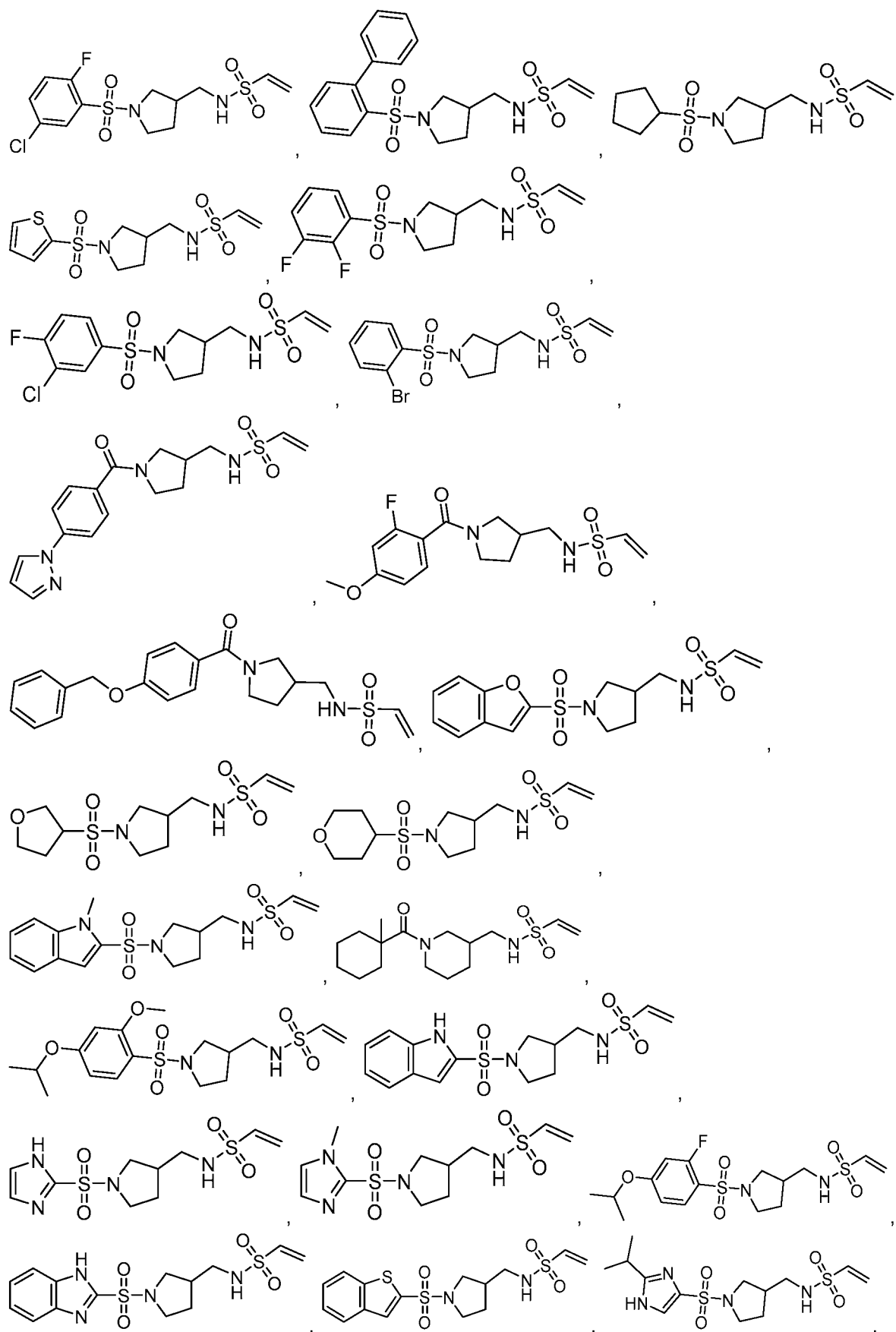


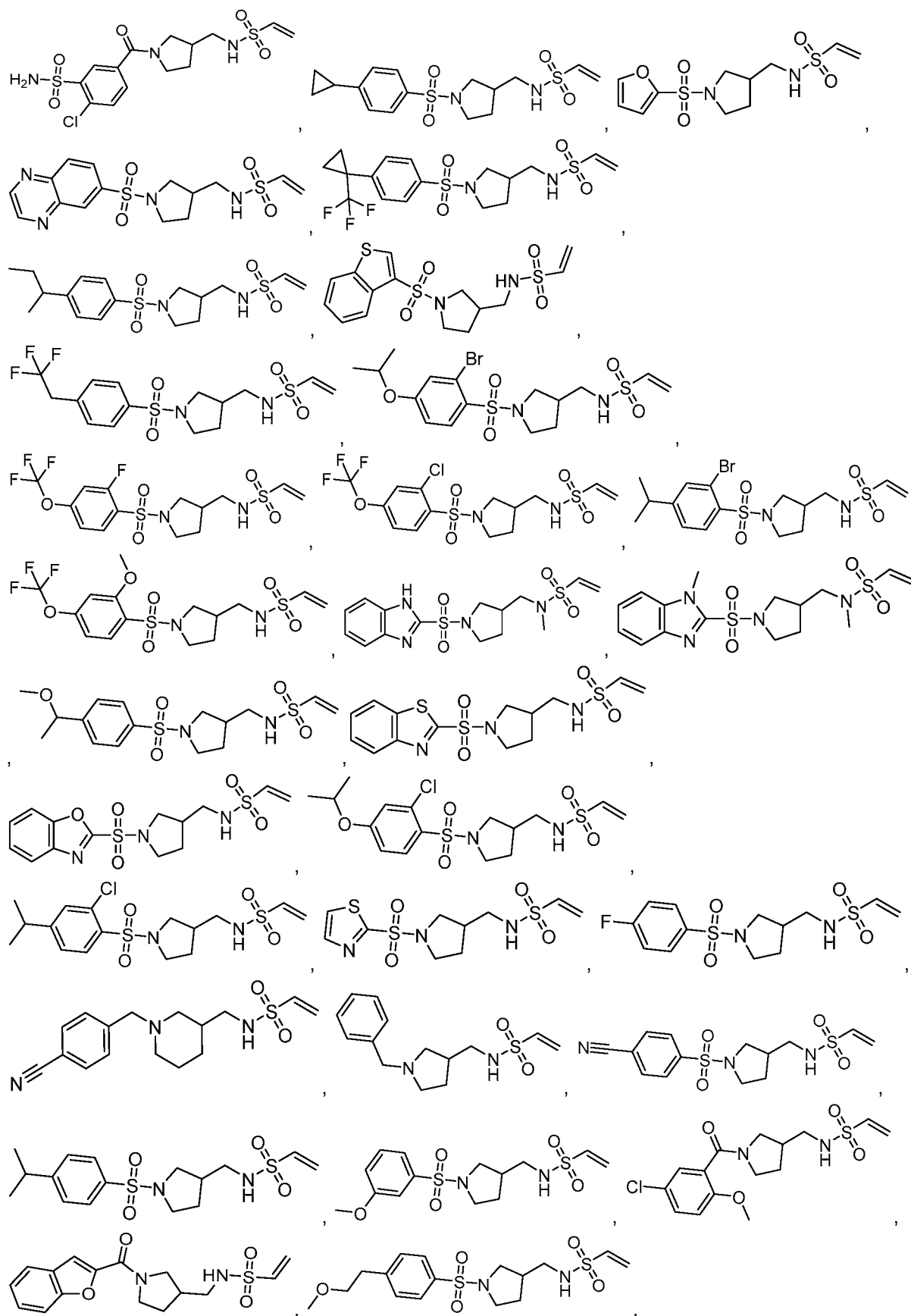




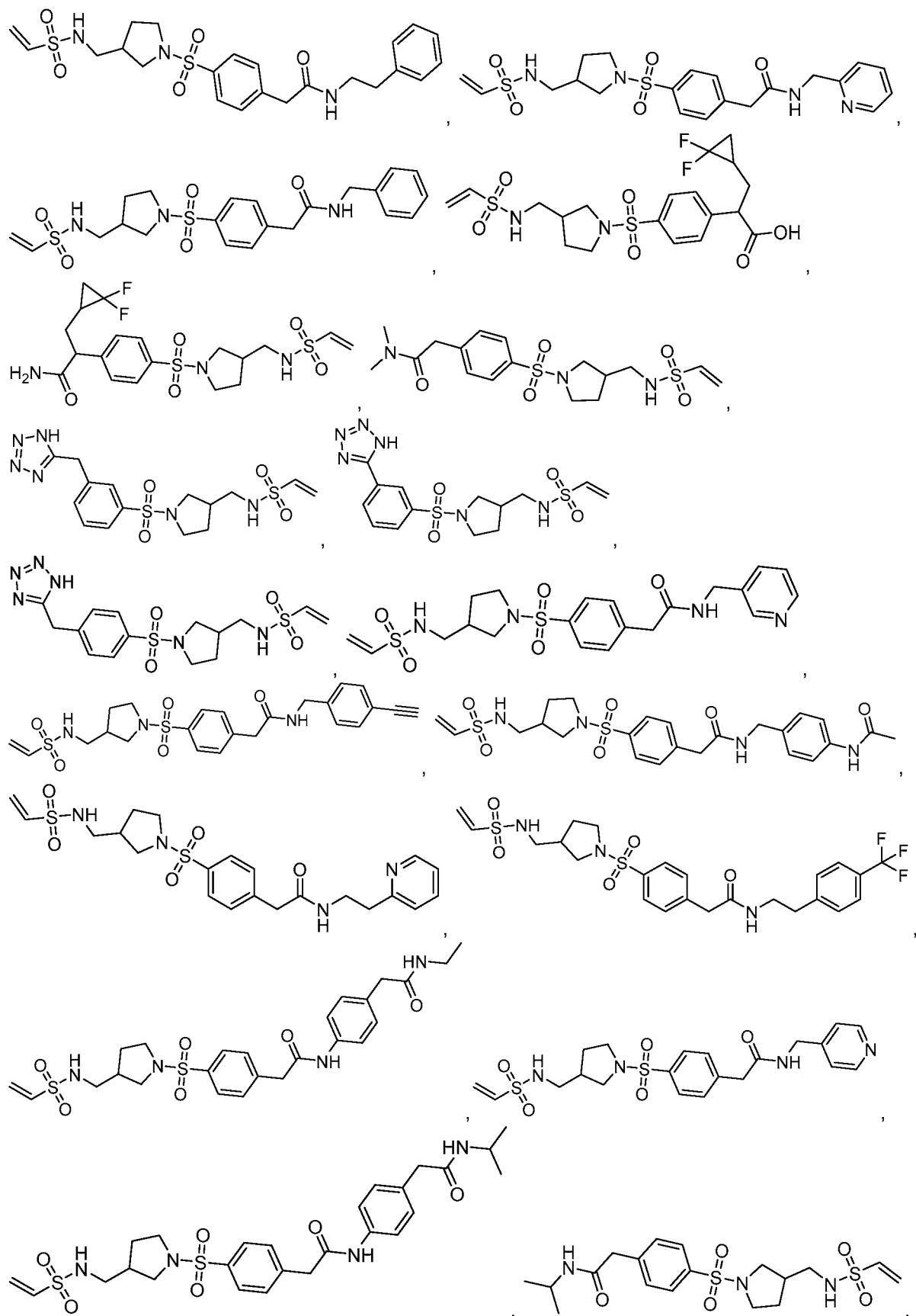


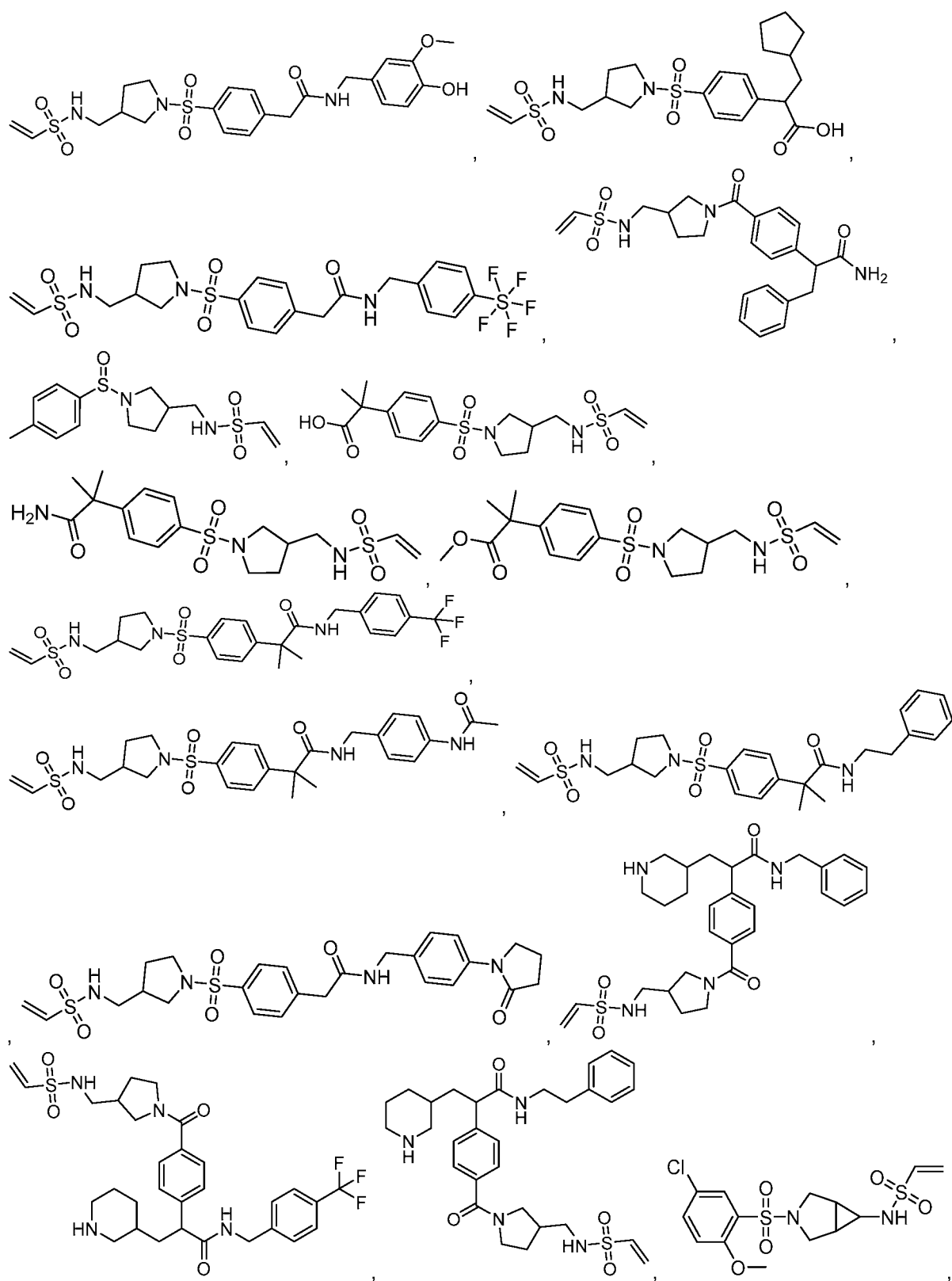


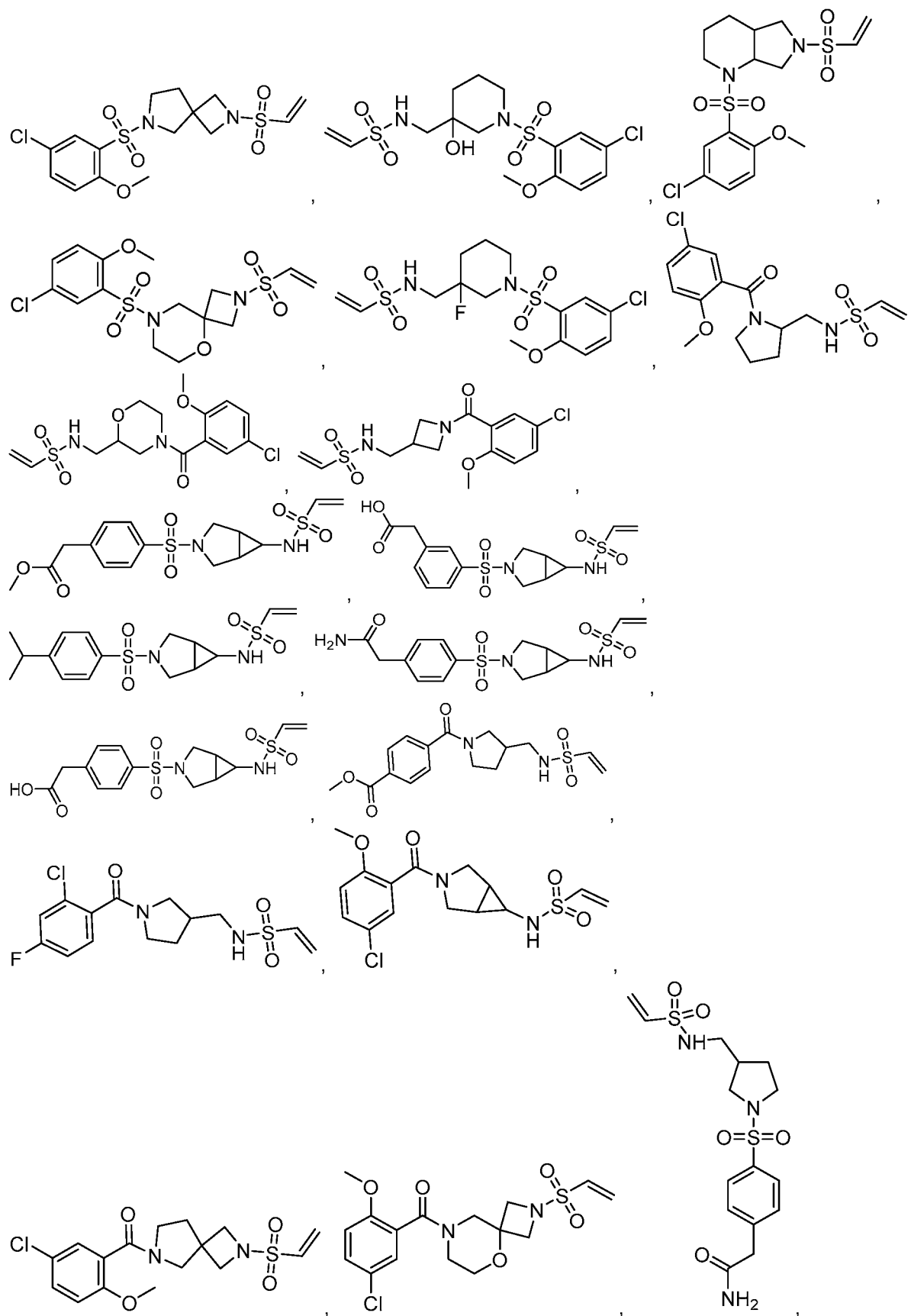


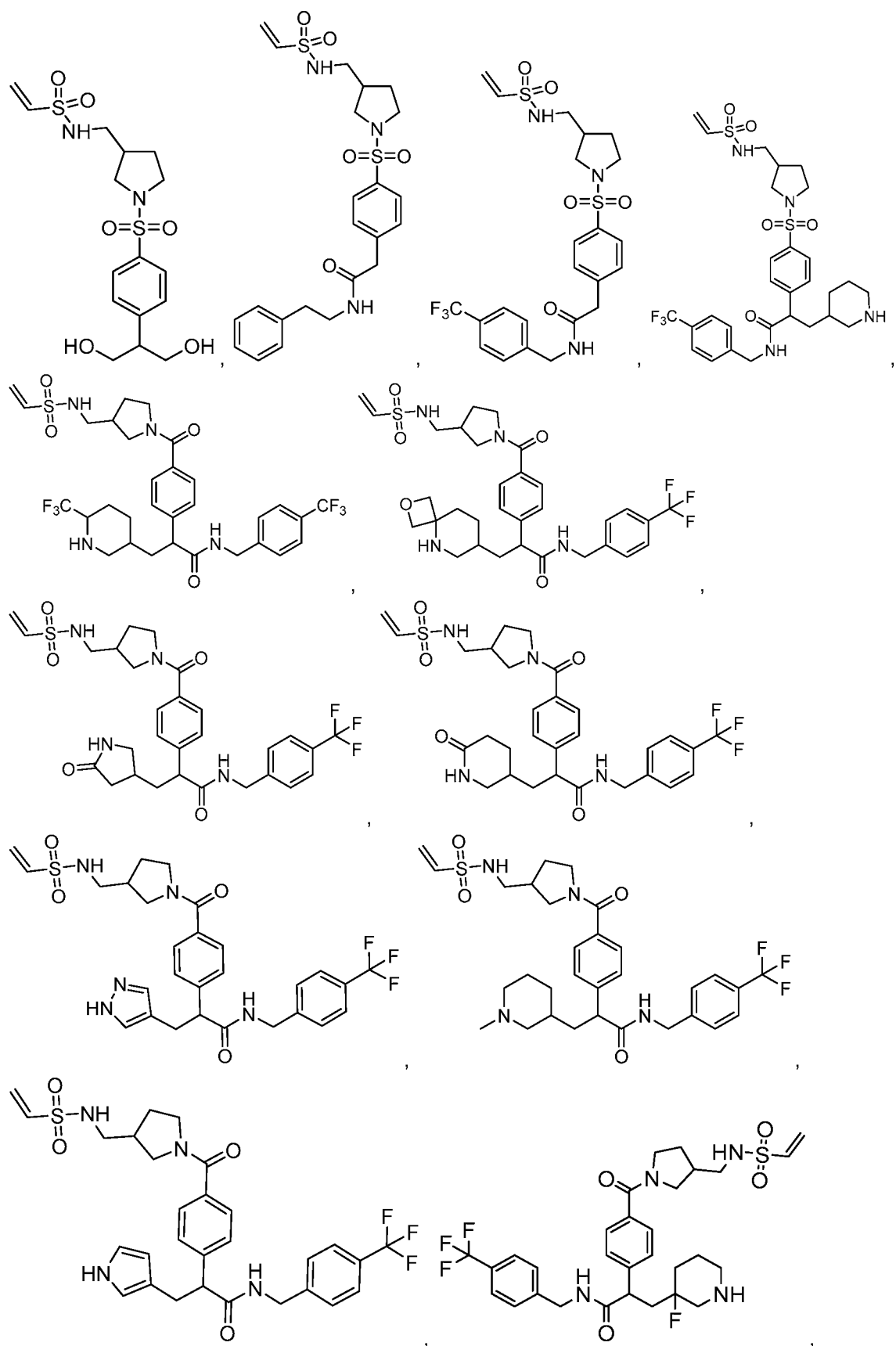


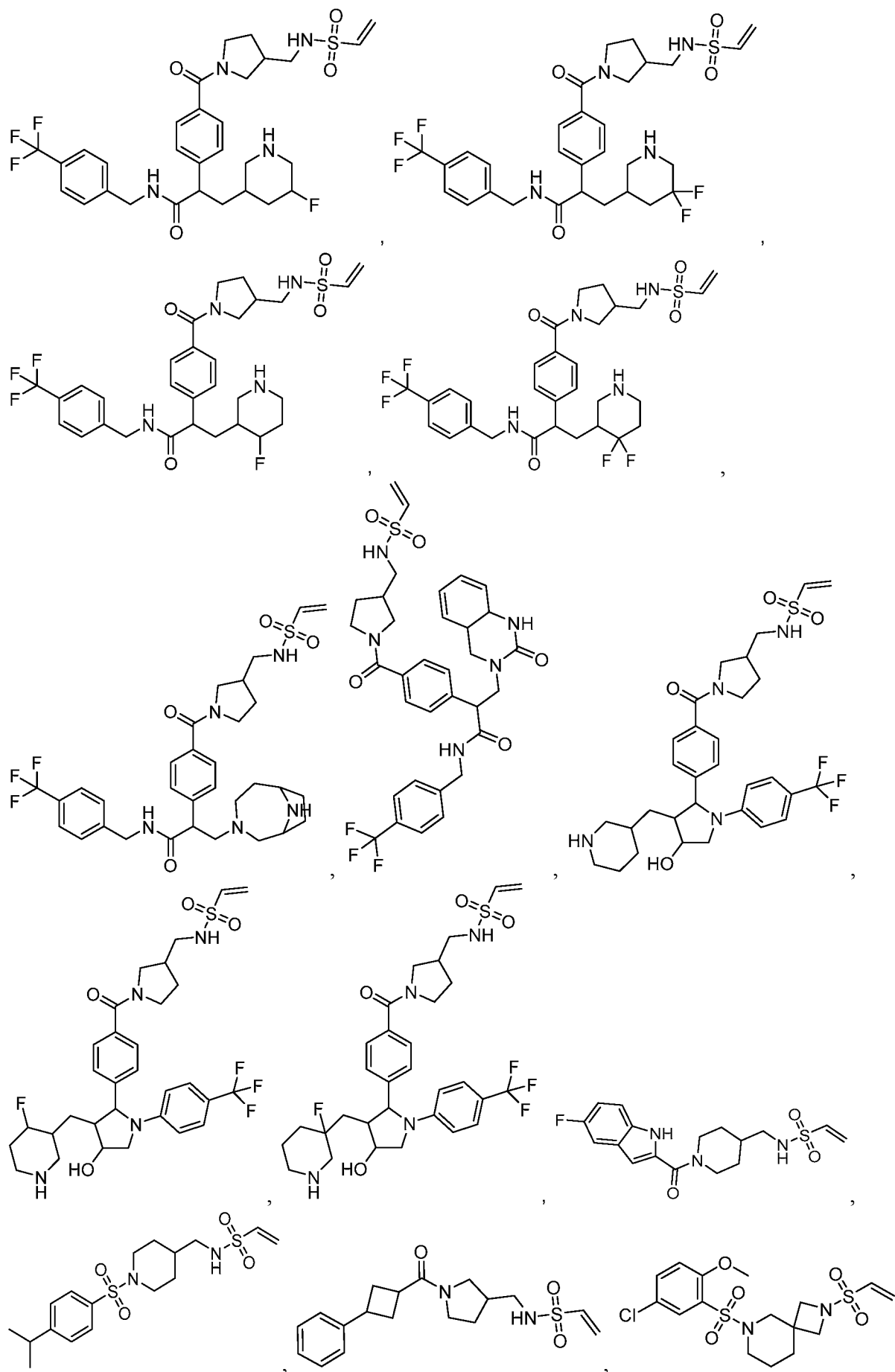


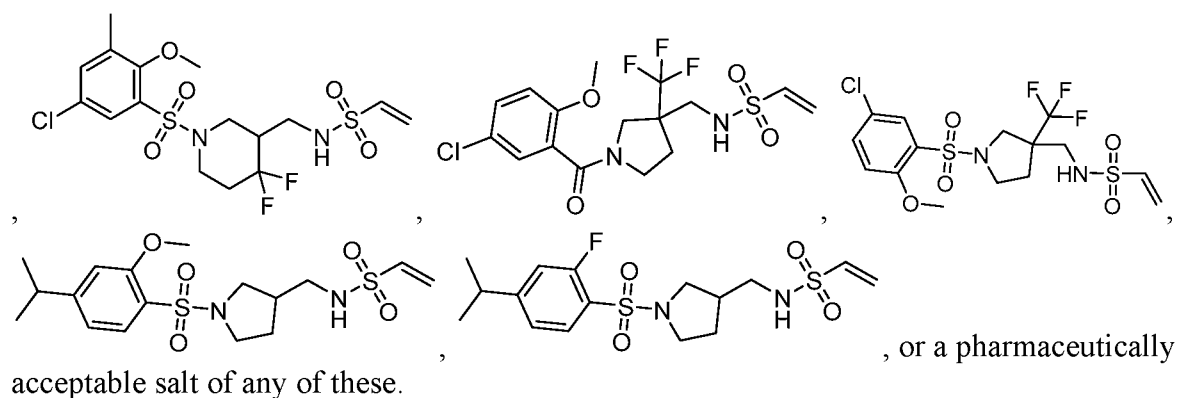




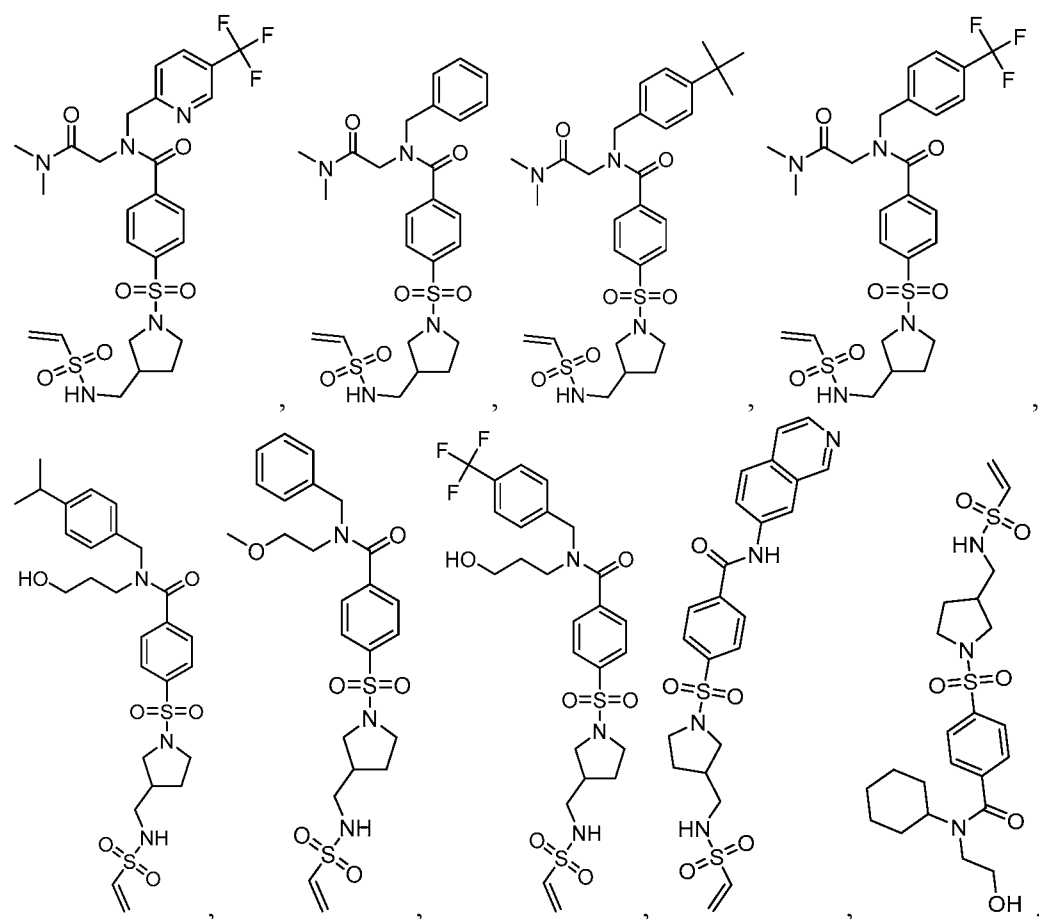


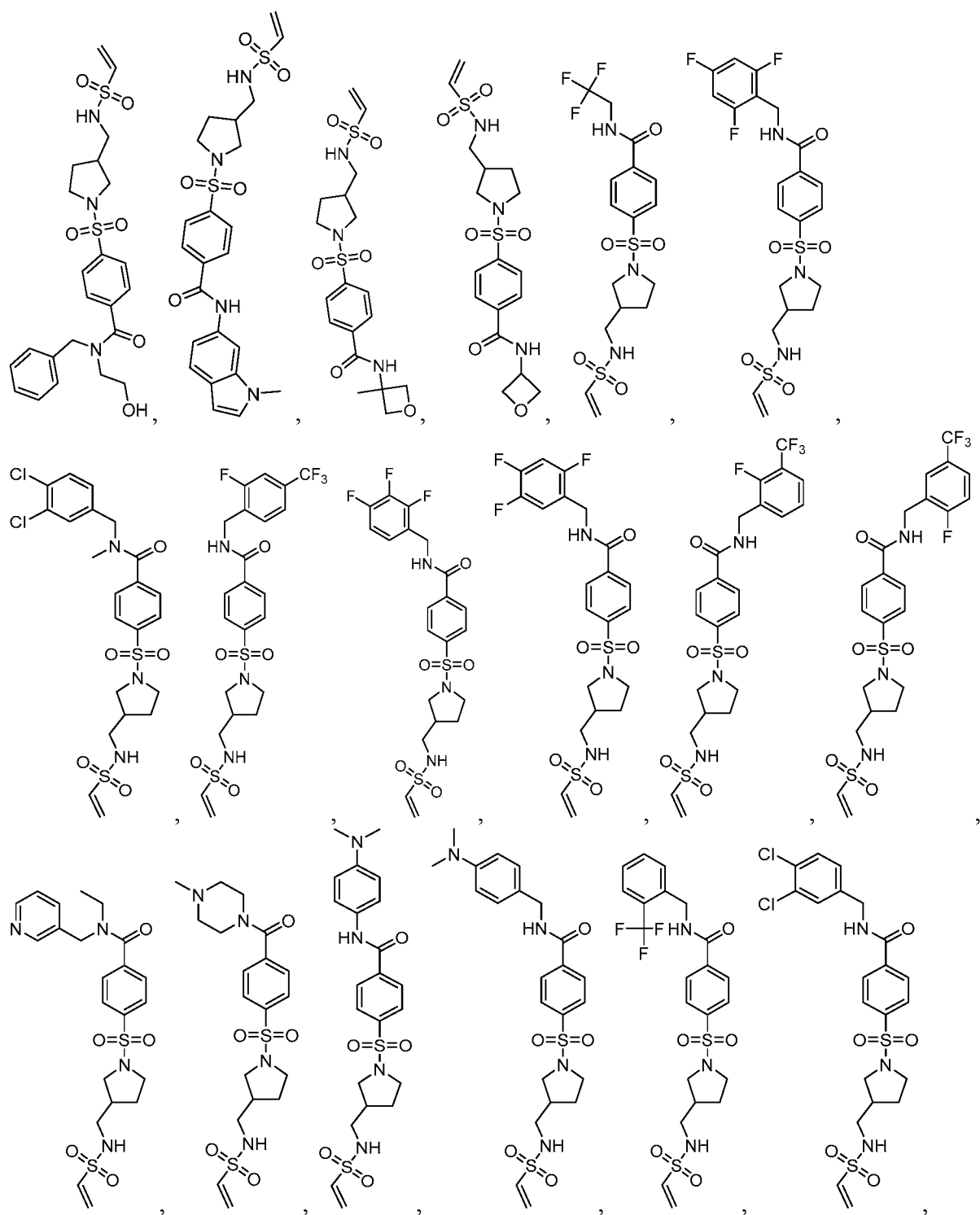


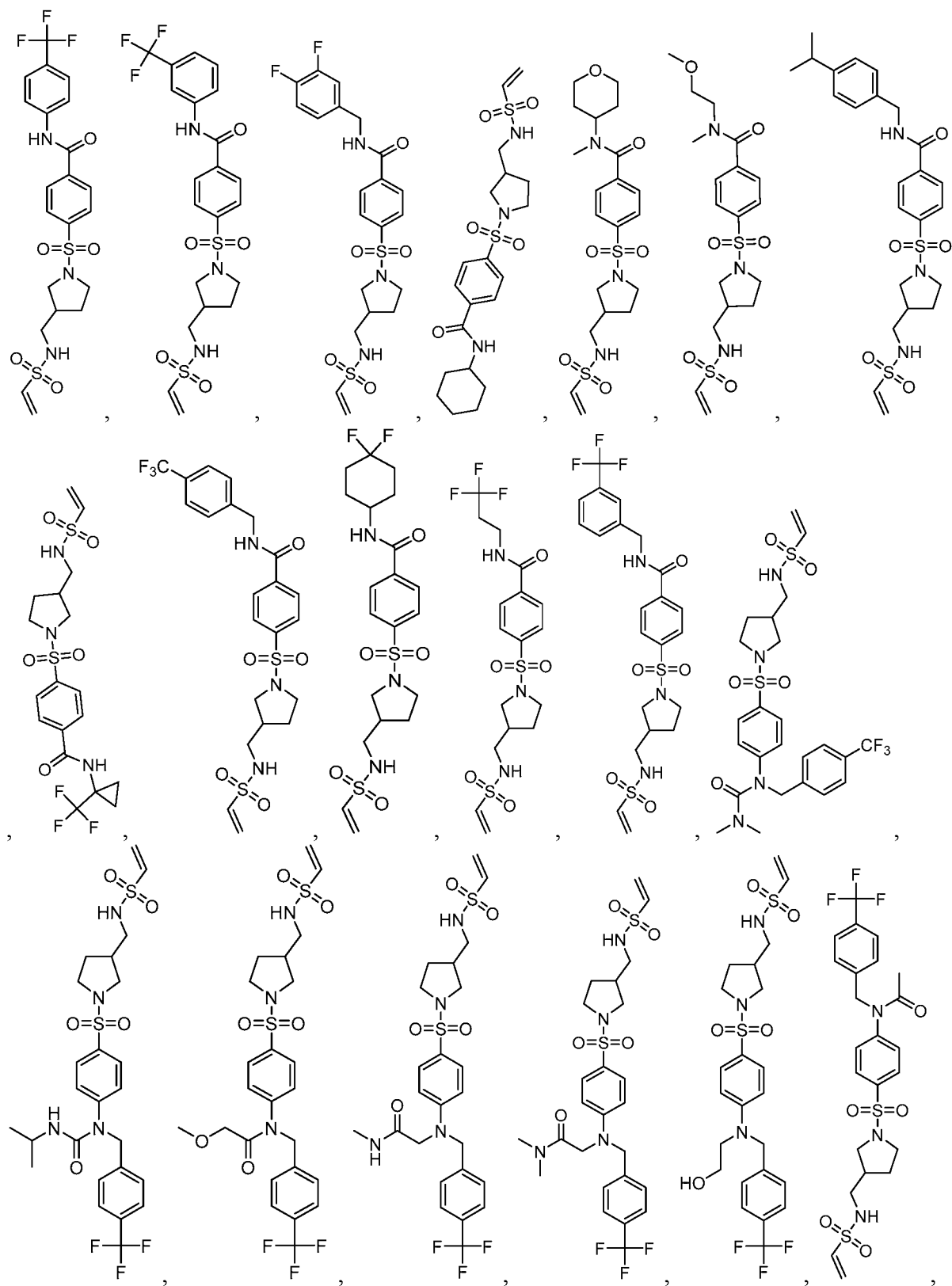


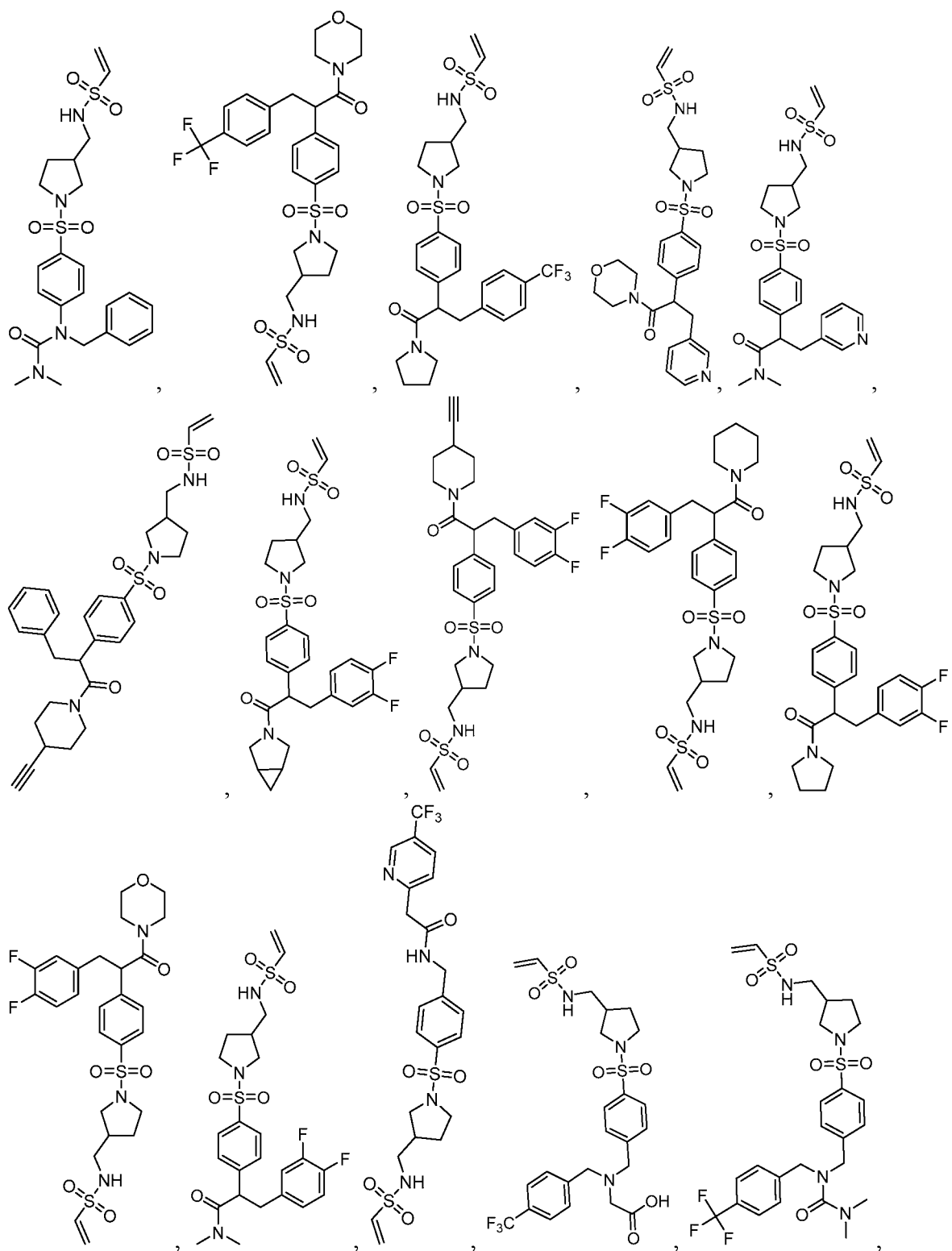


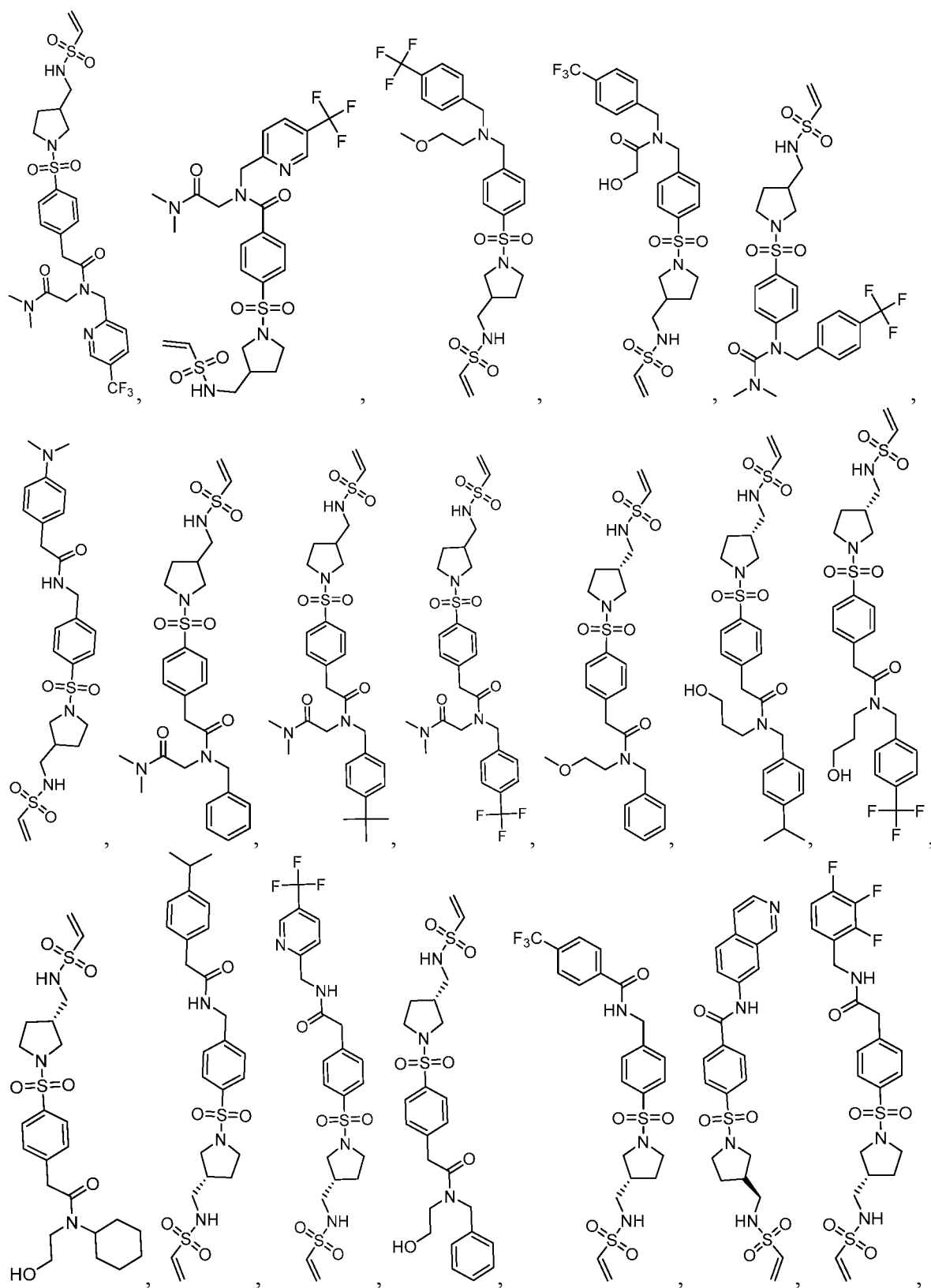
[0173] In some embodiments, the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i) is:



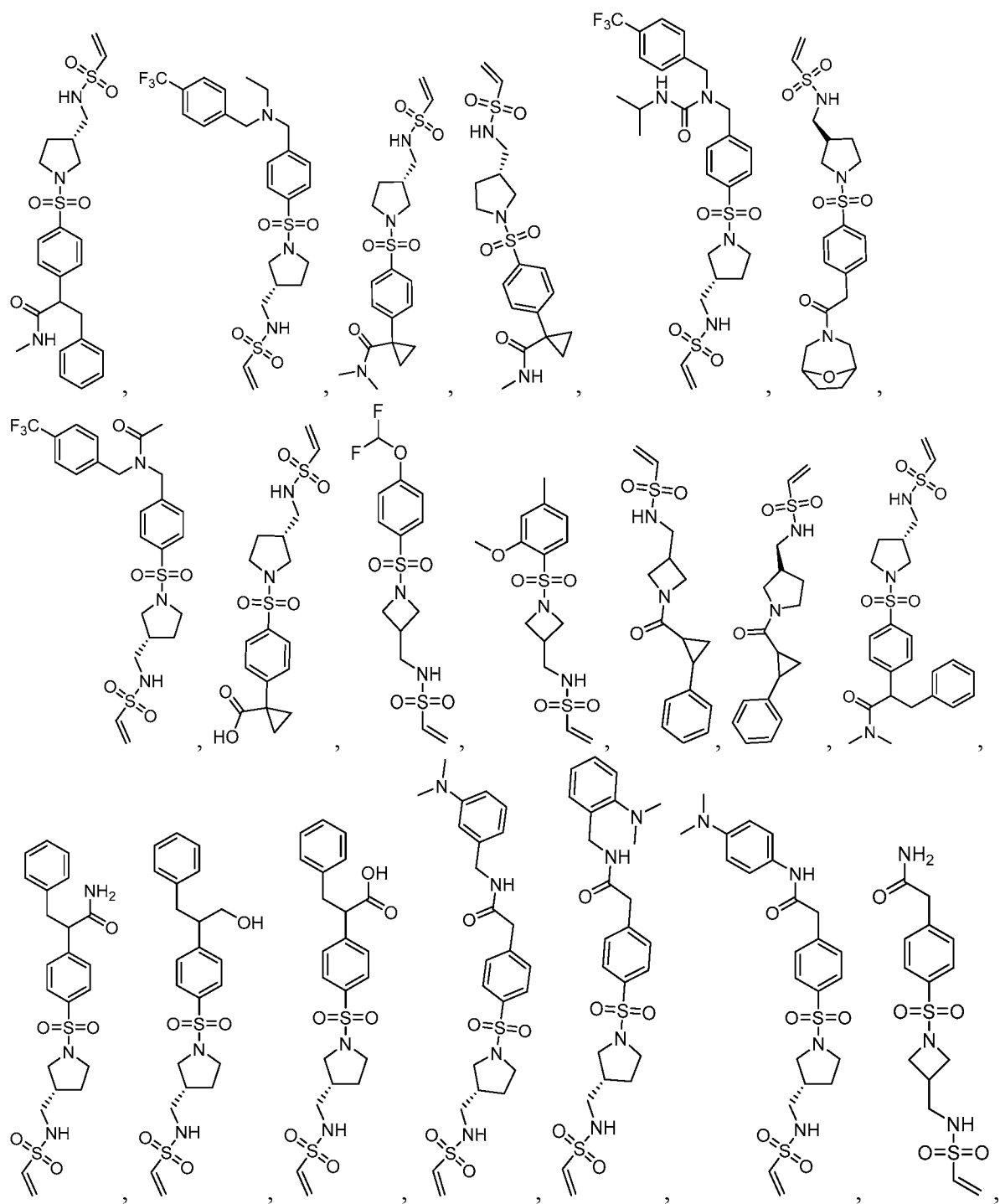


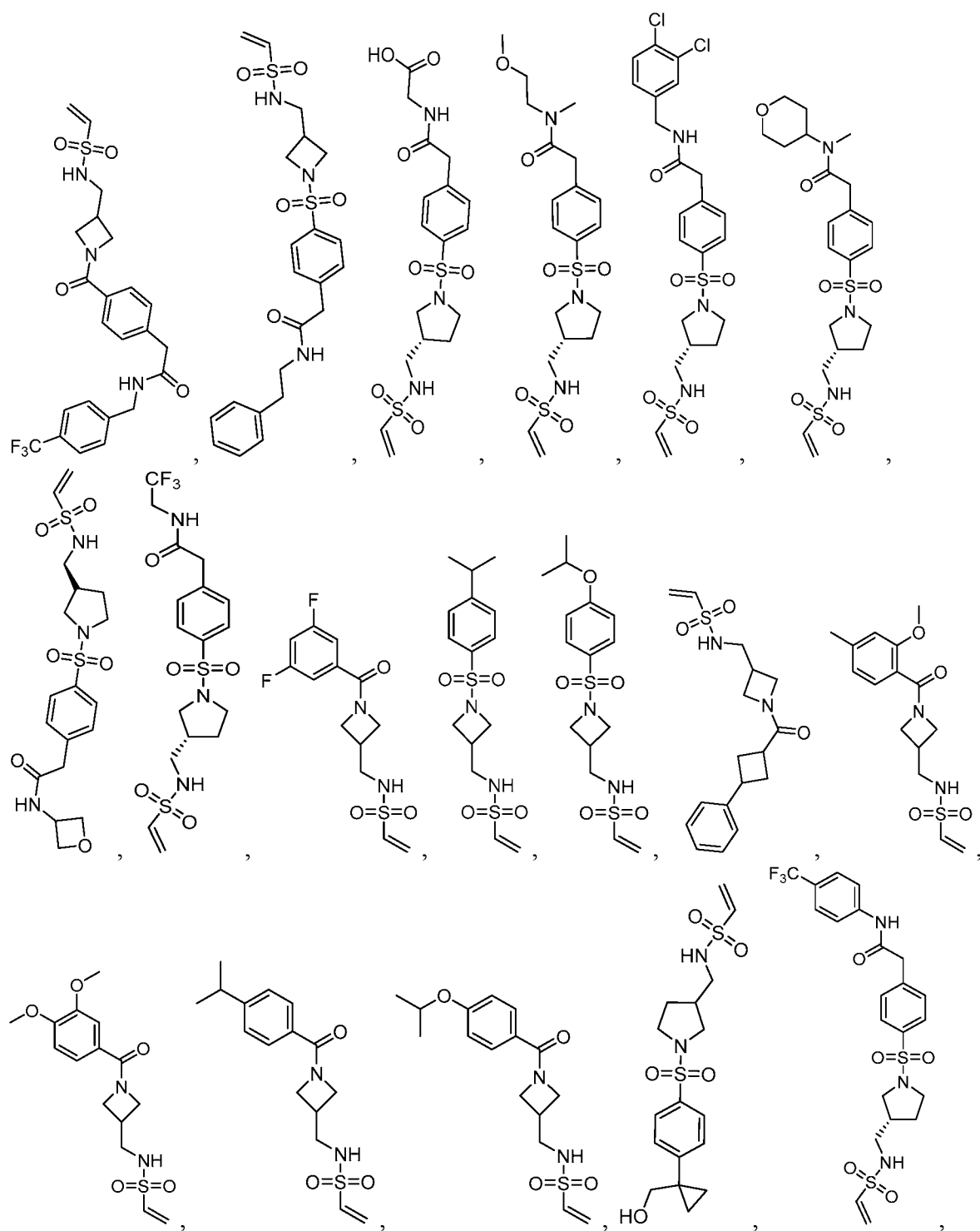


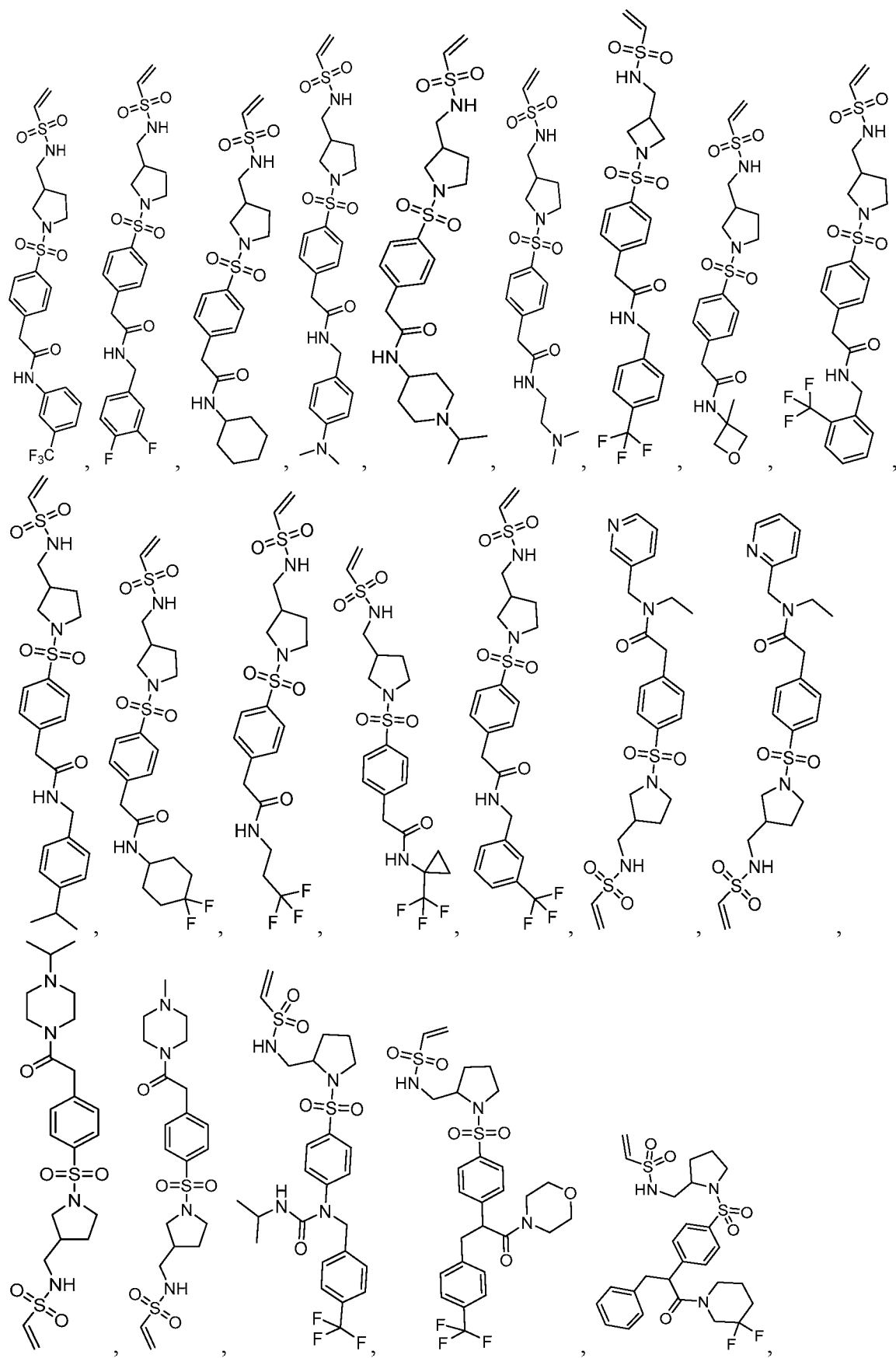


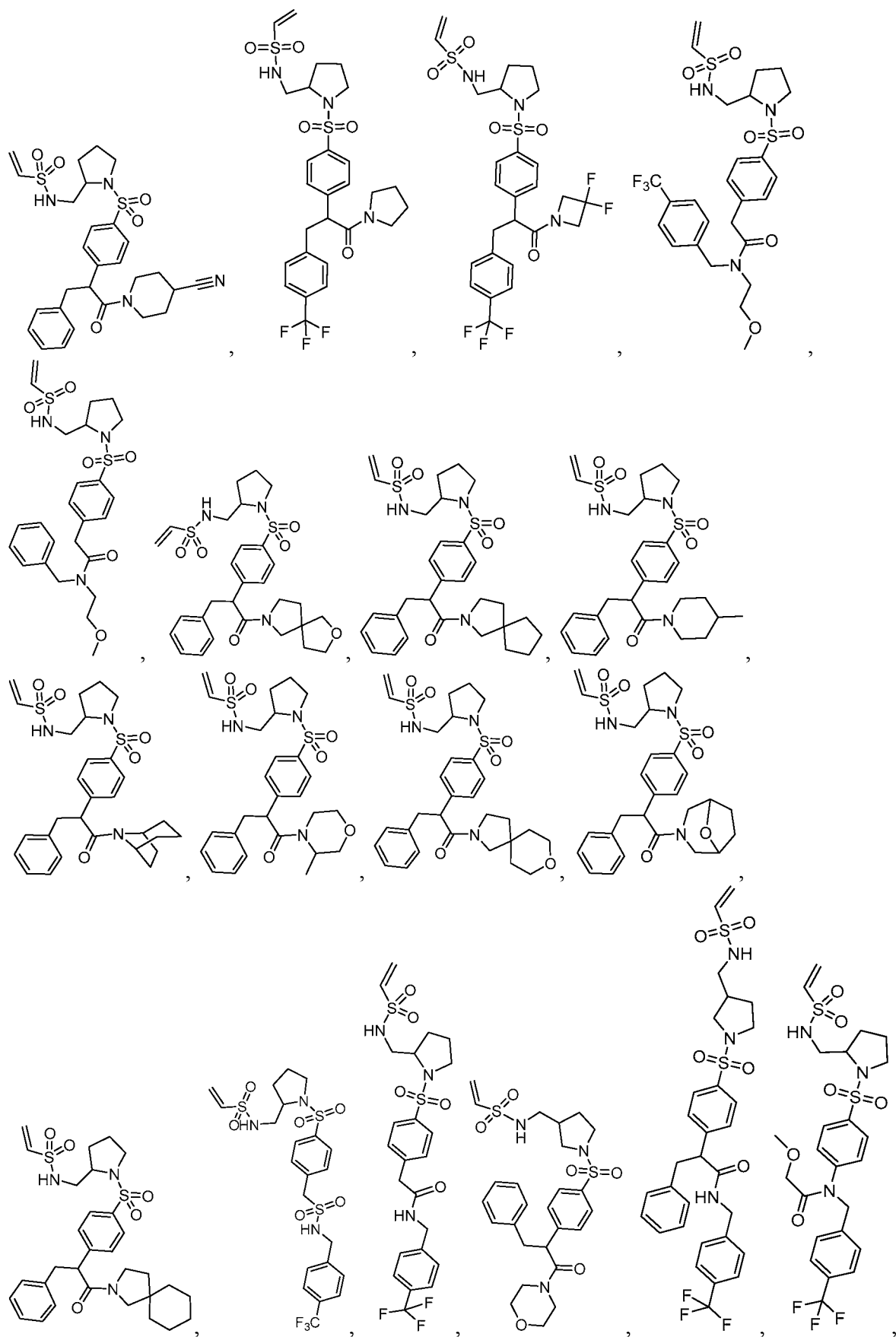


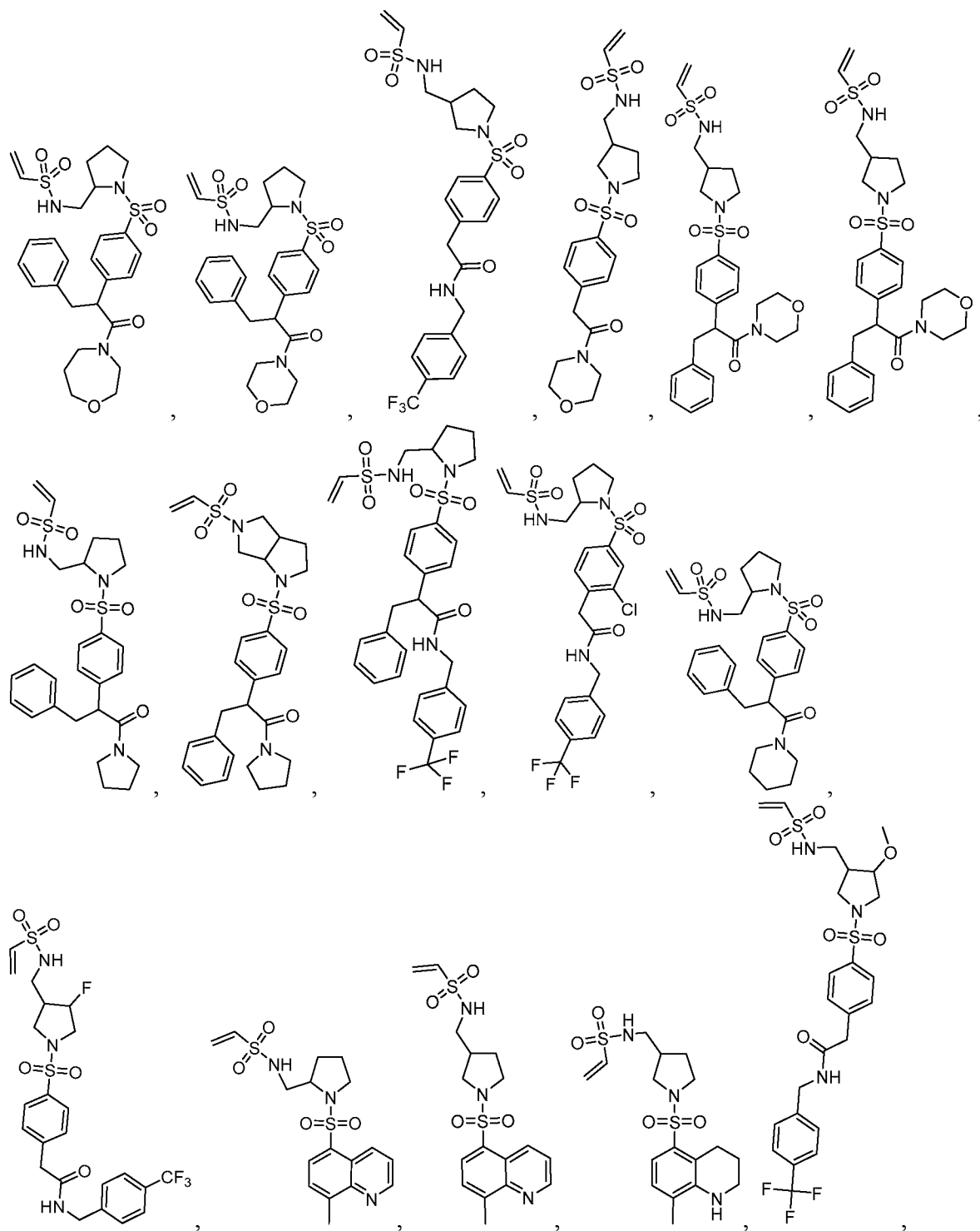


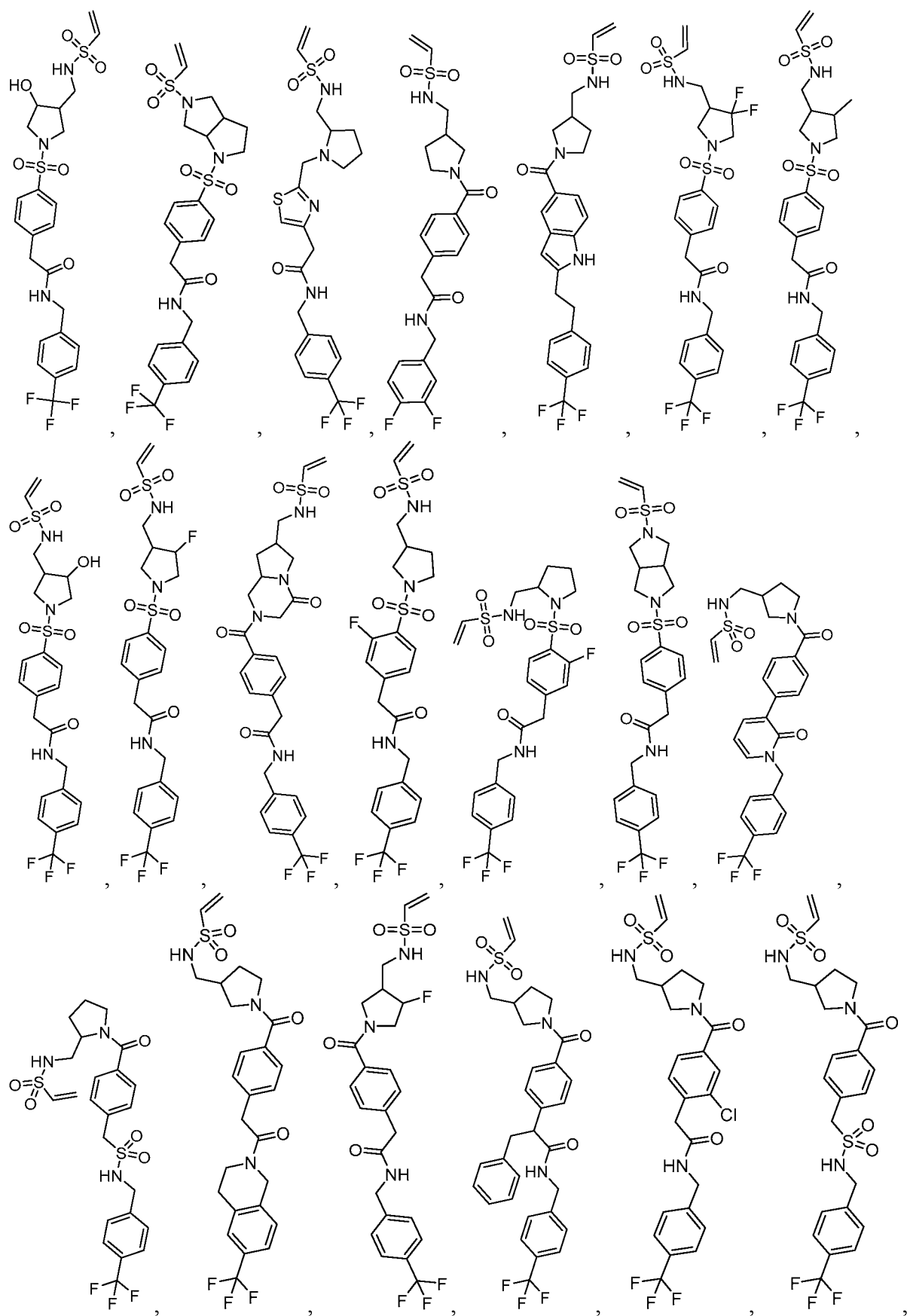




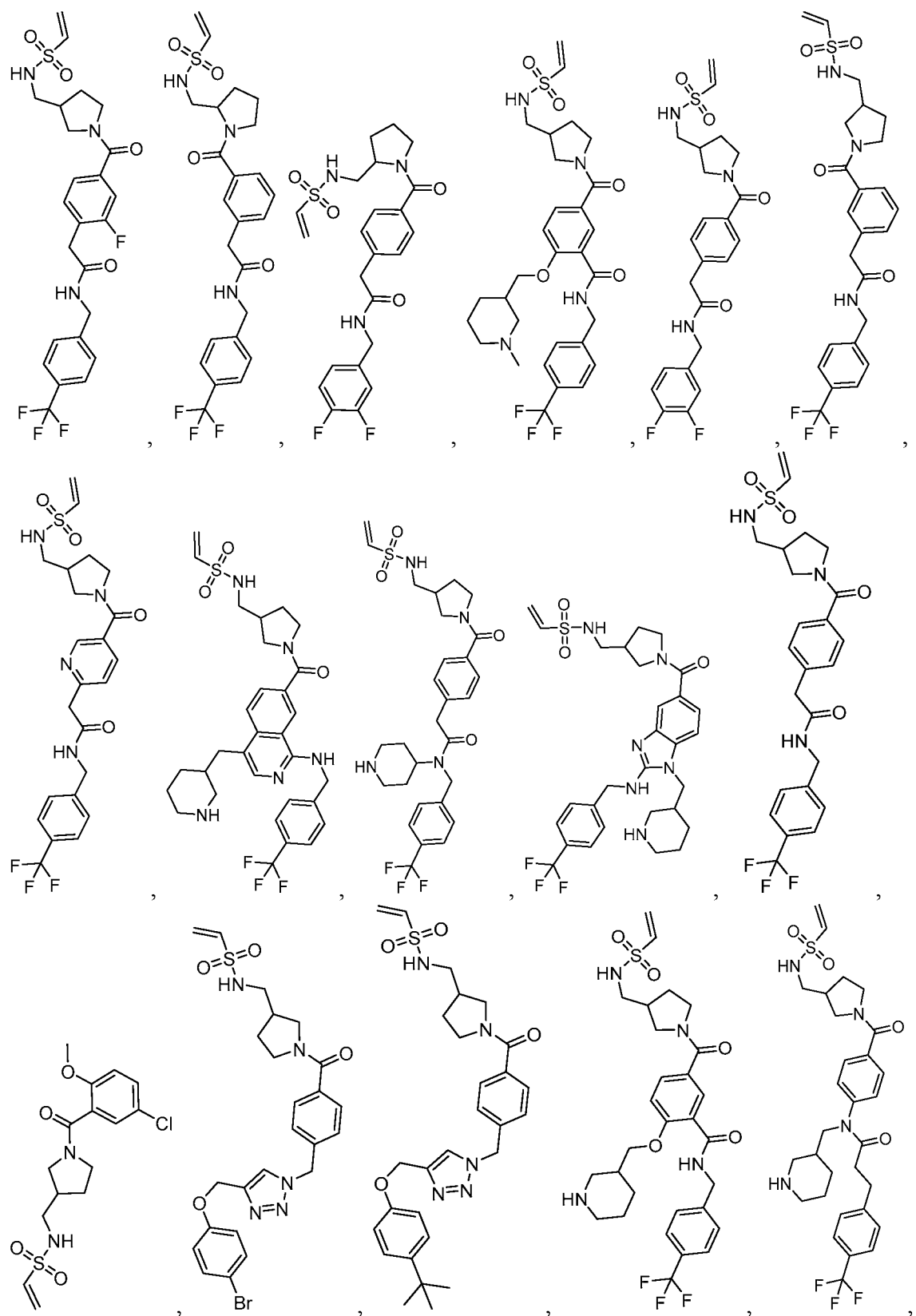


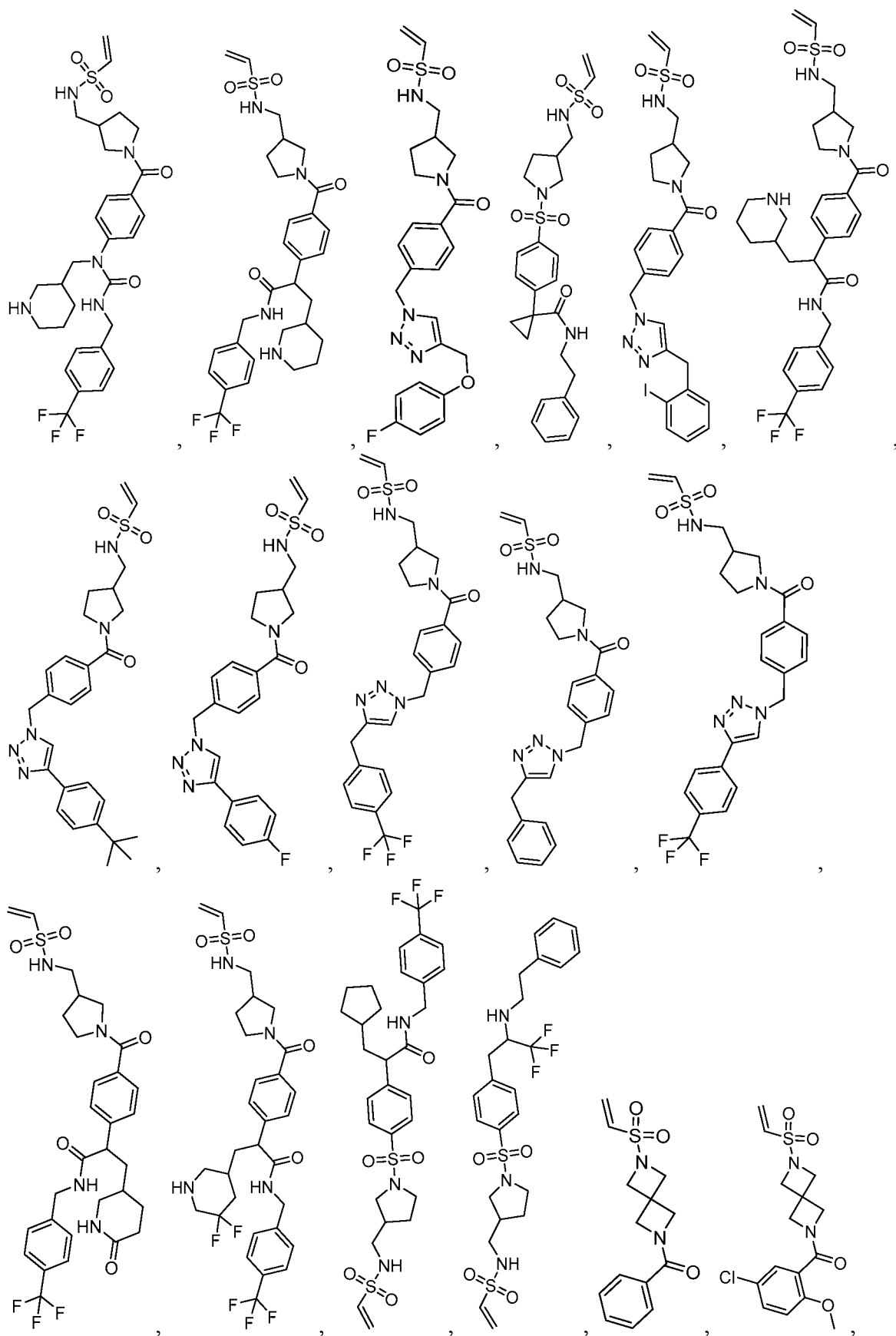


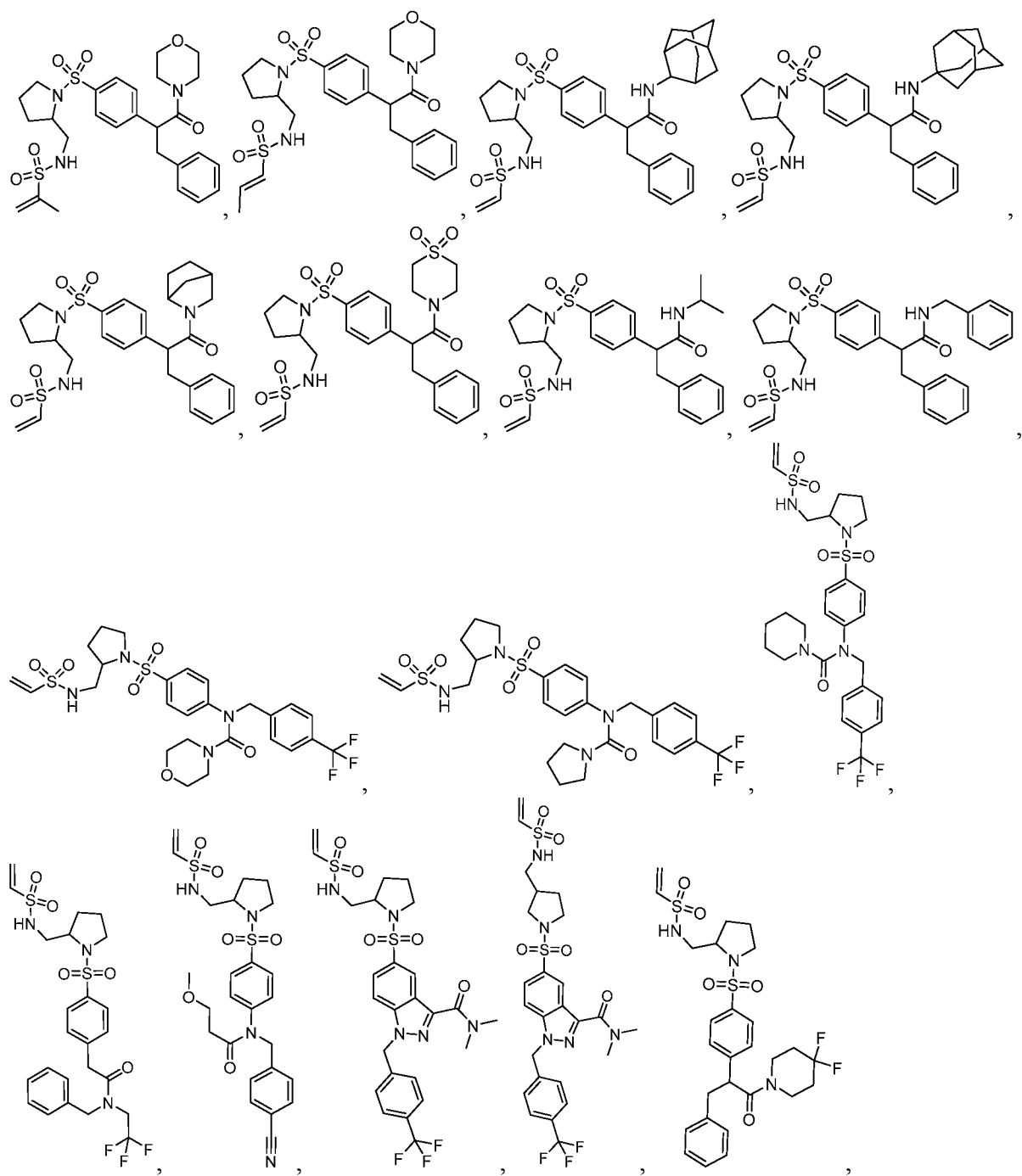




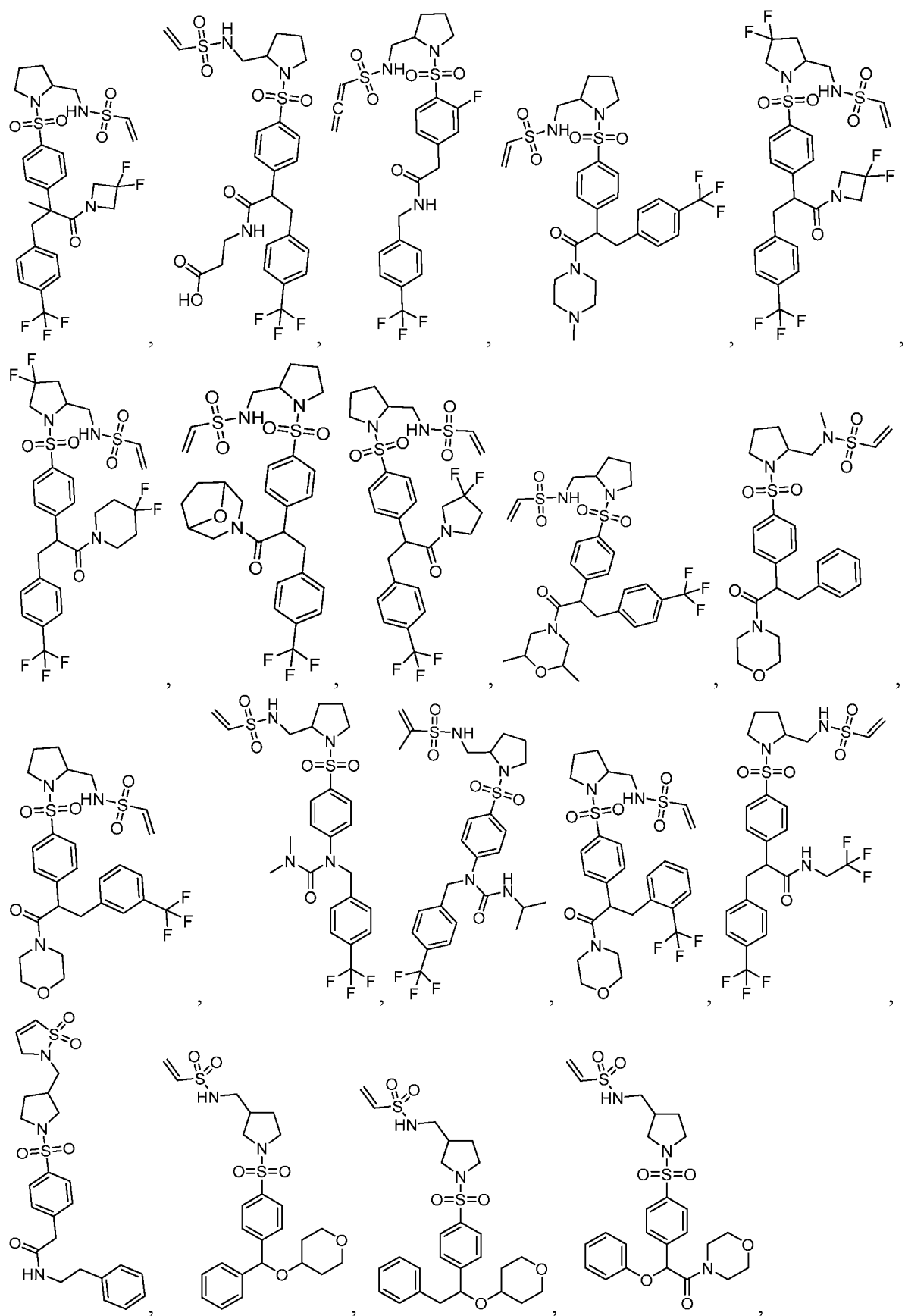


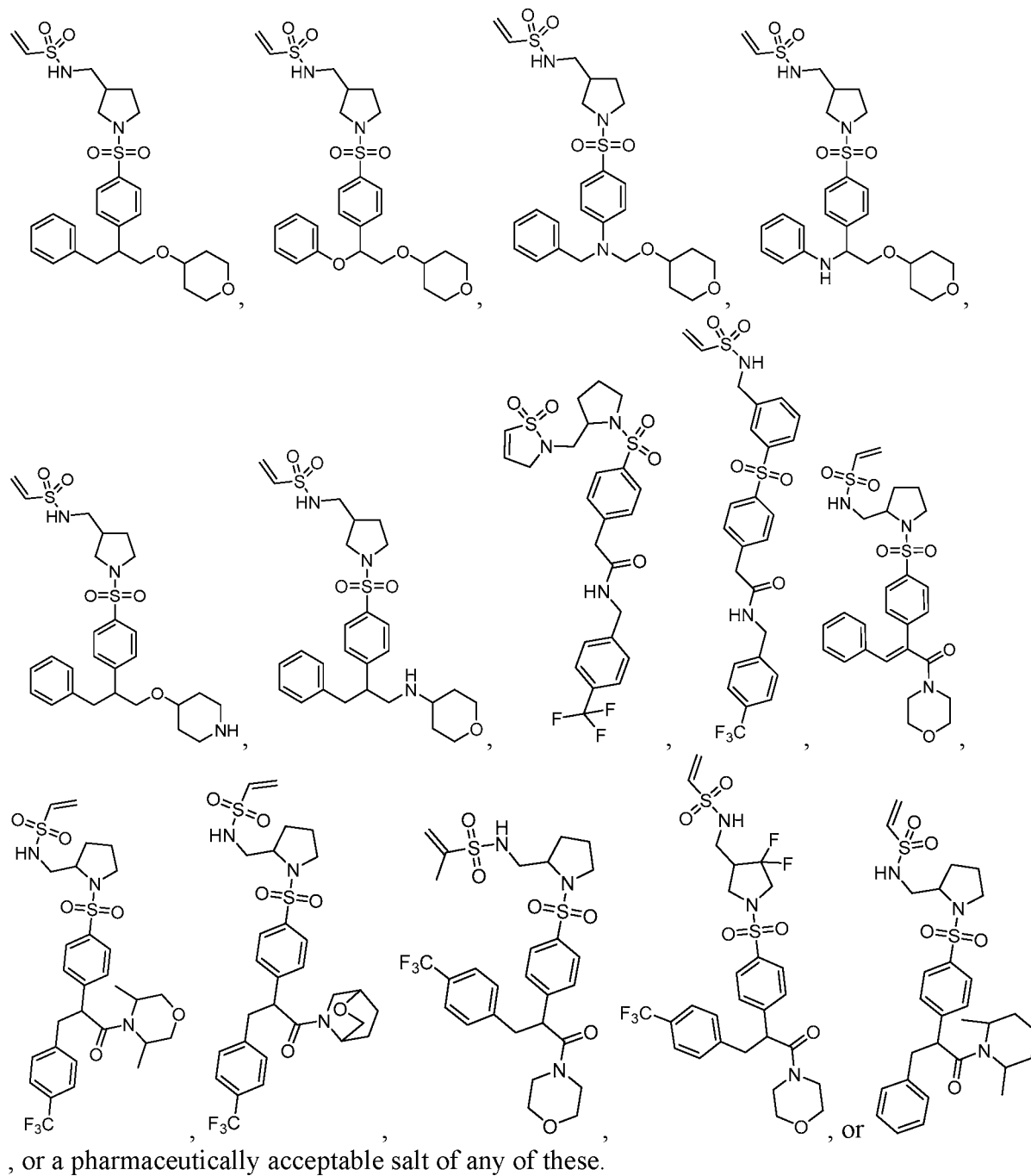




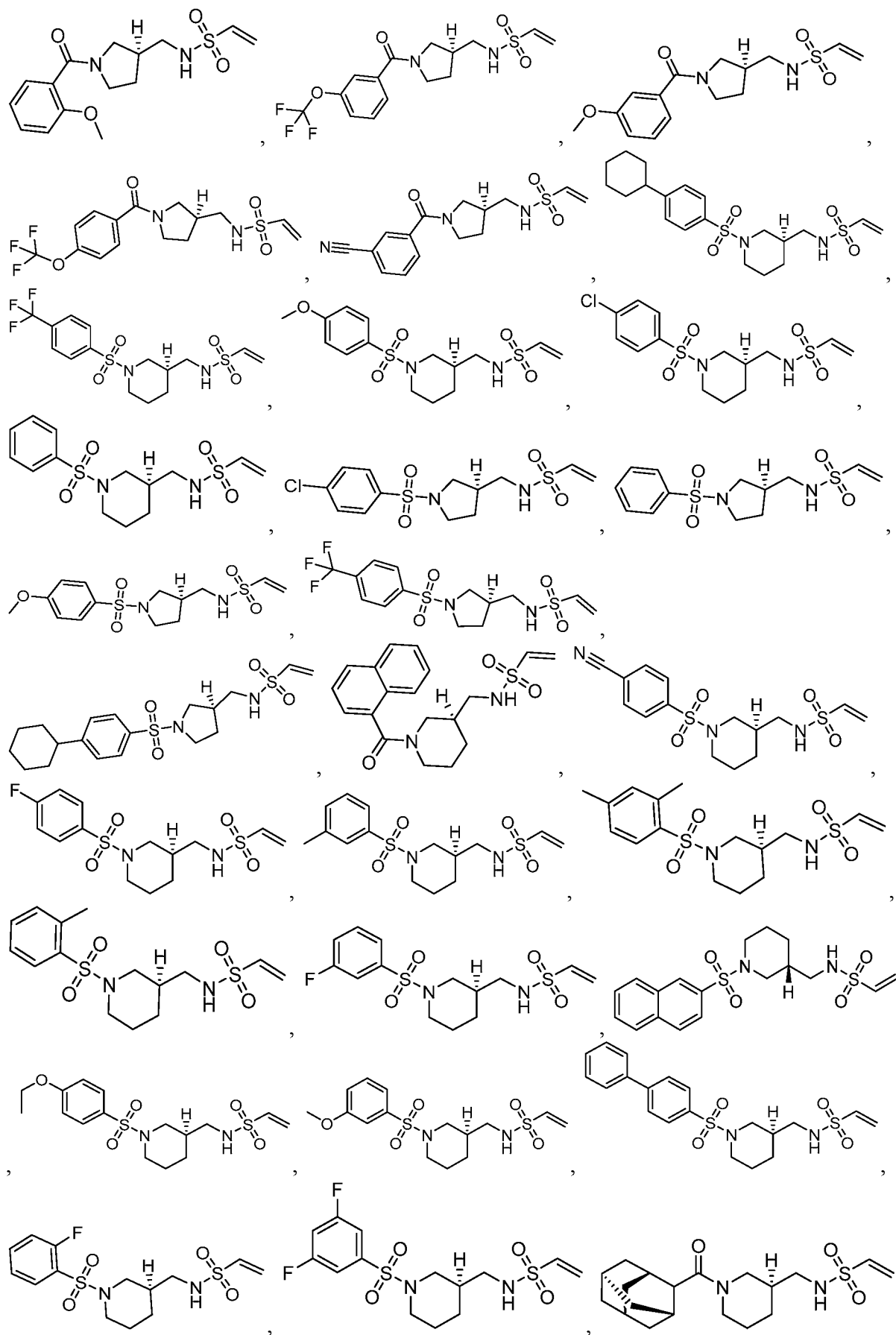


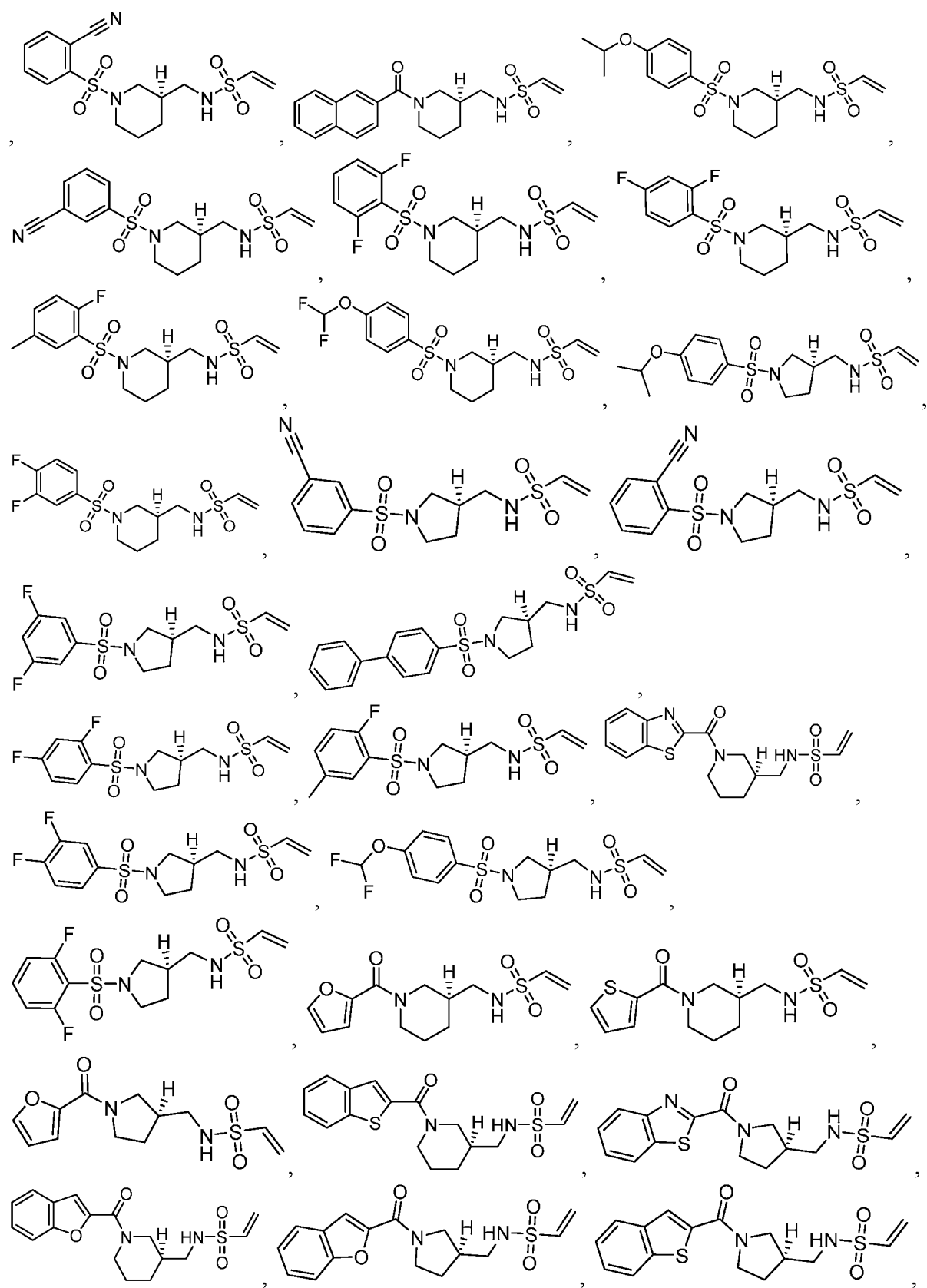


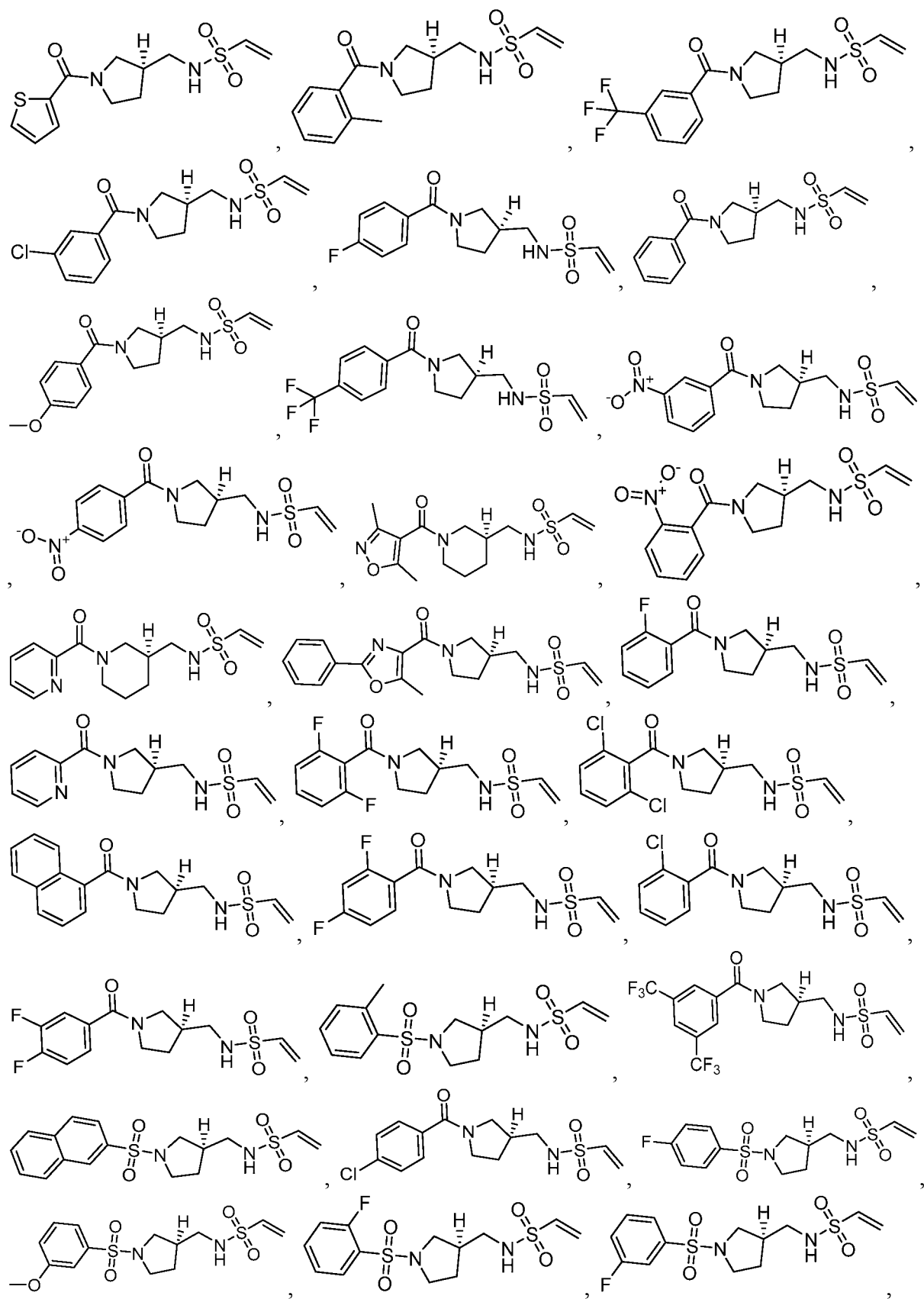


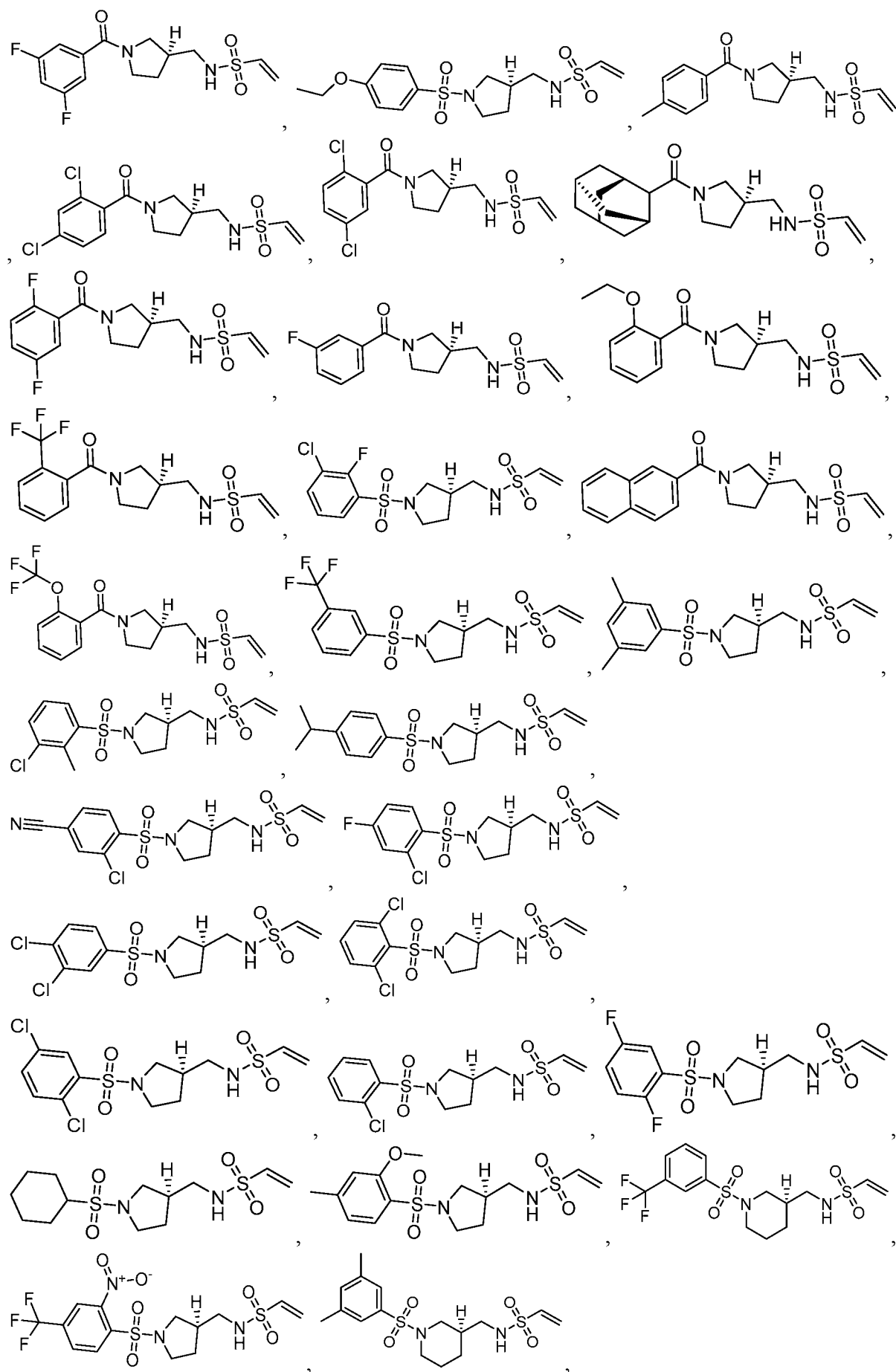


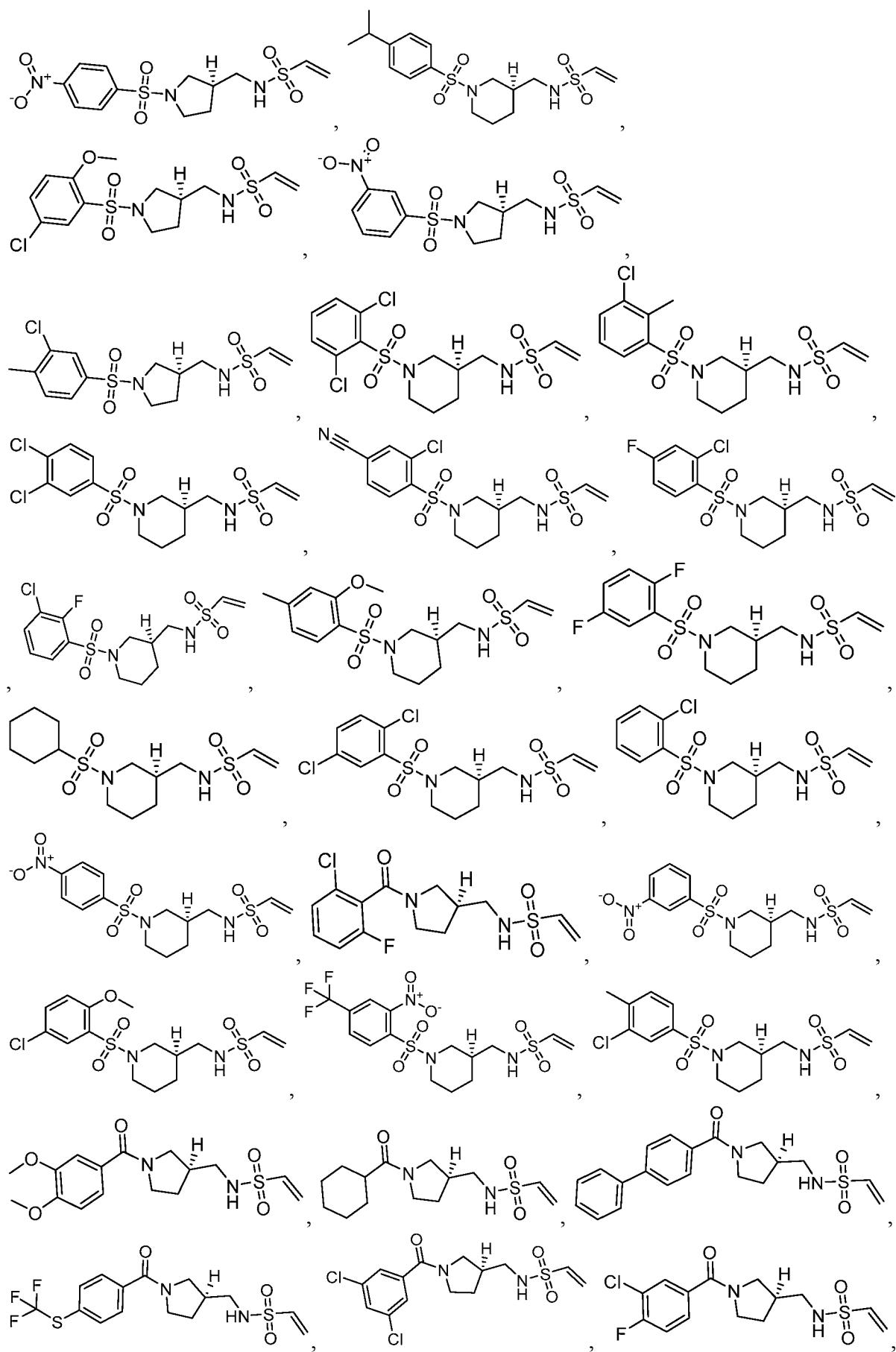
[0174] In some embodiments, the compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), is:

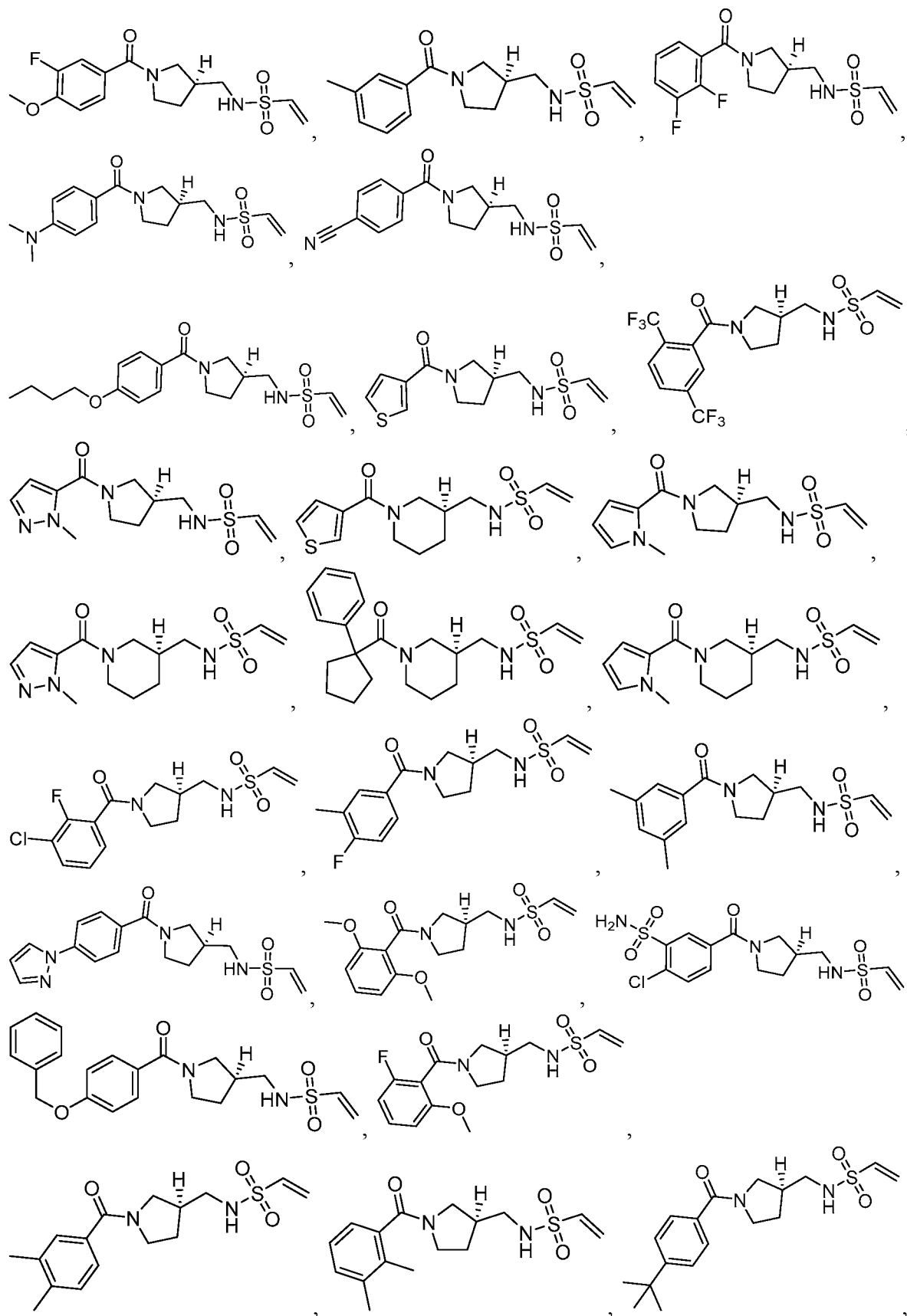


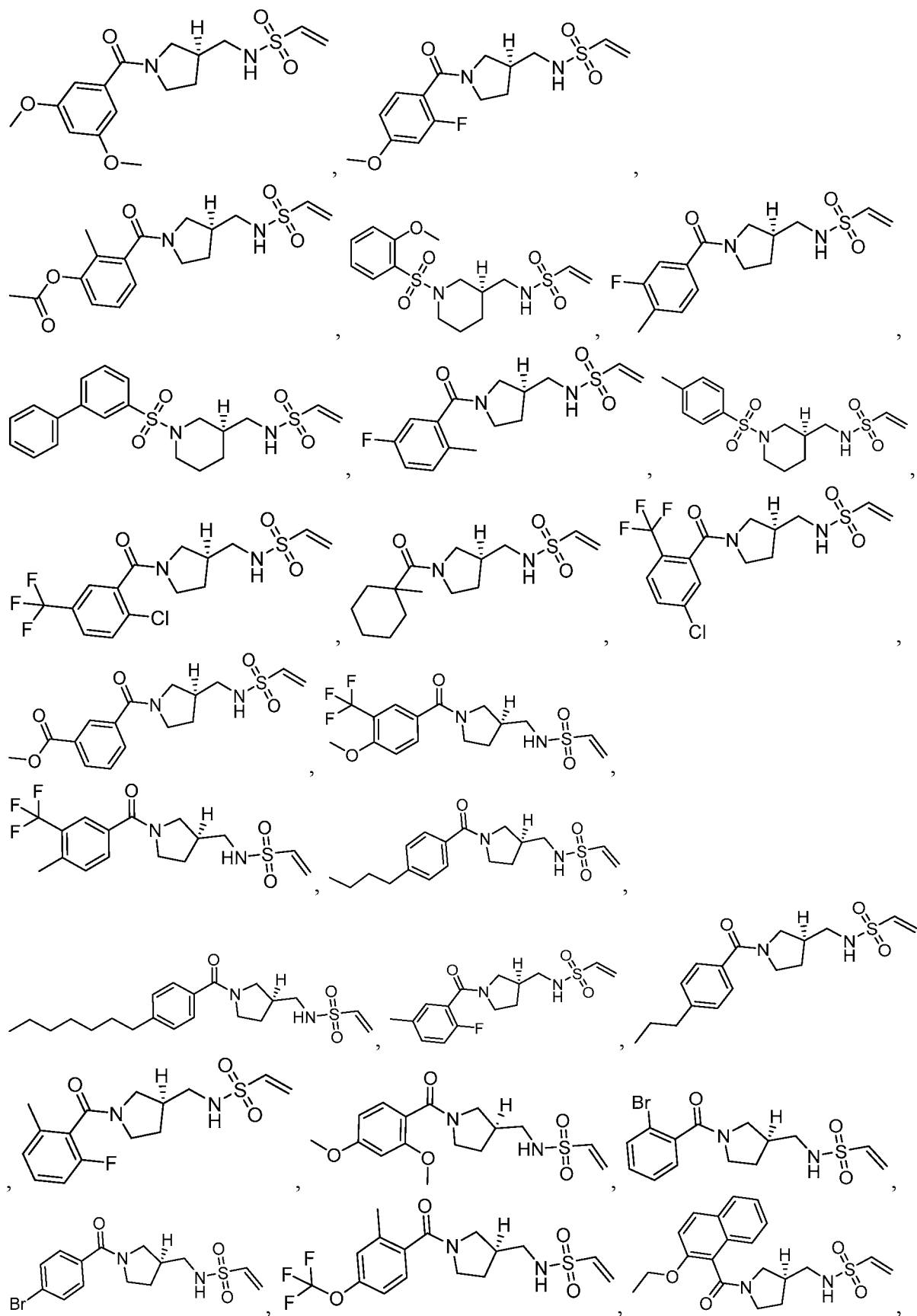




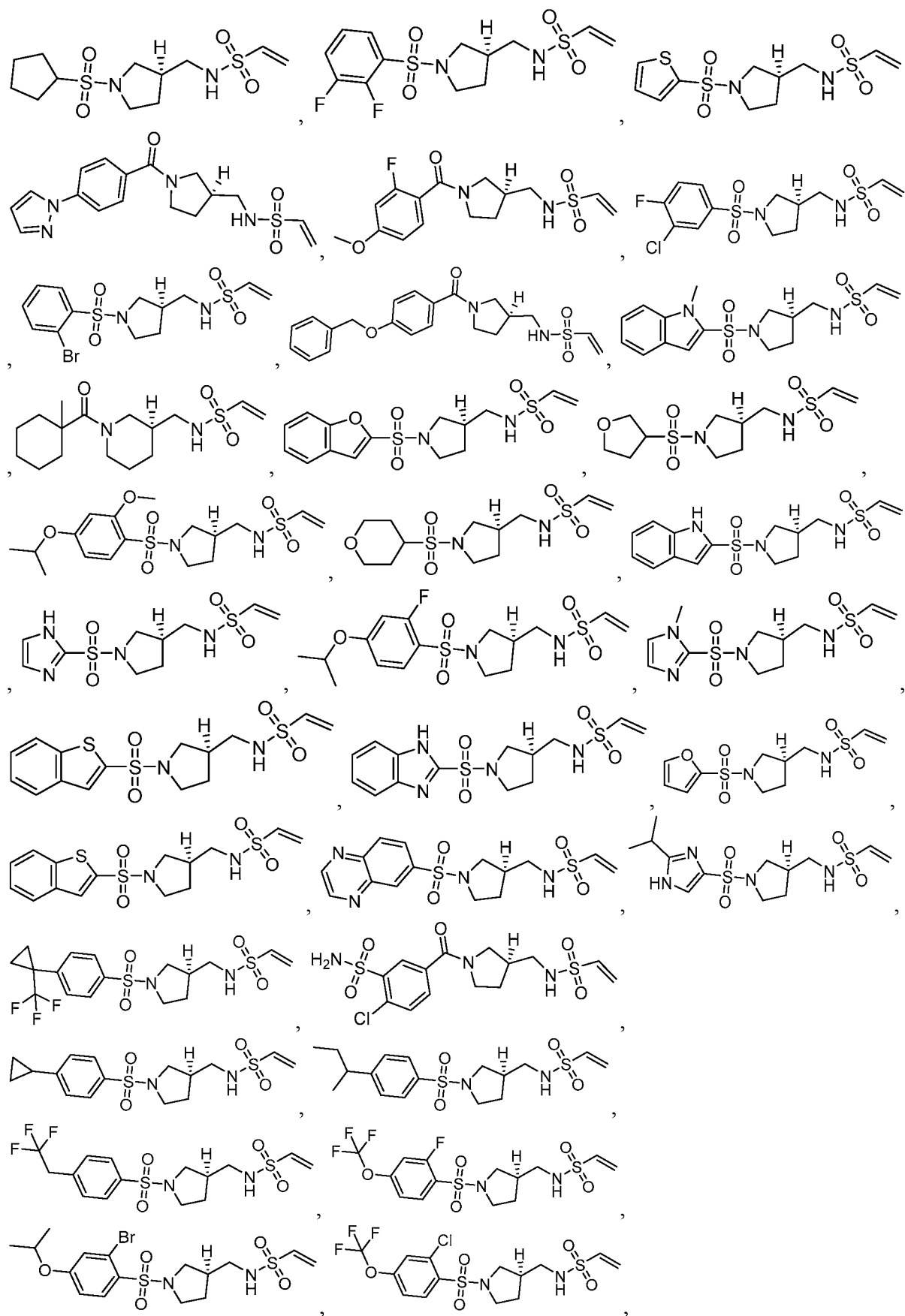




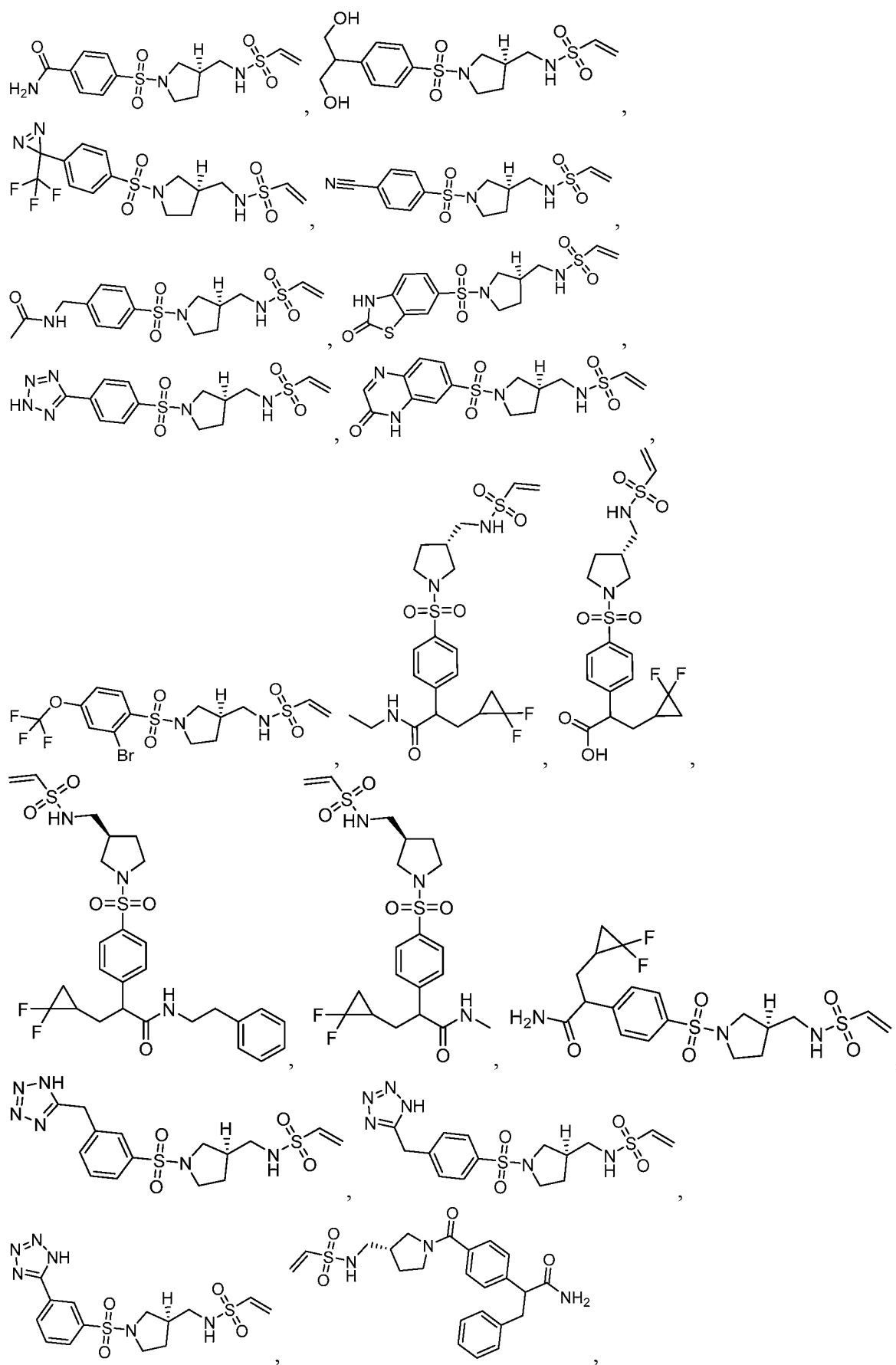


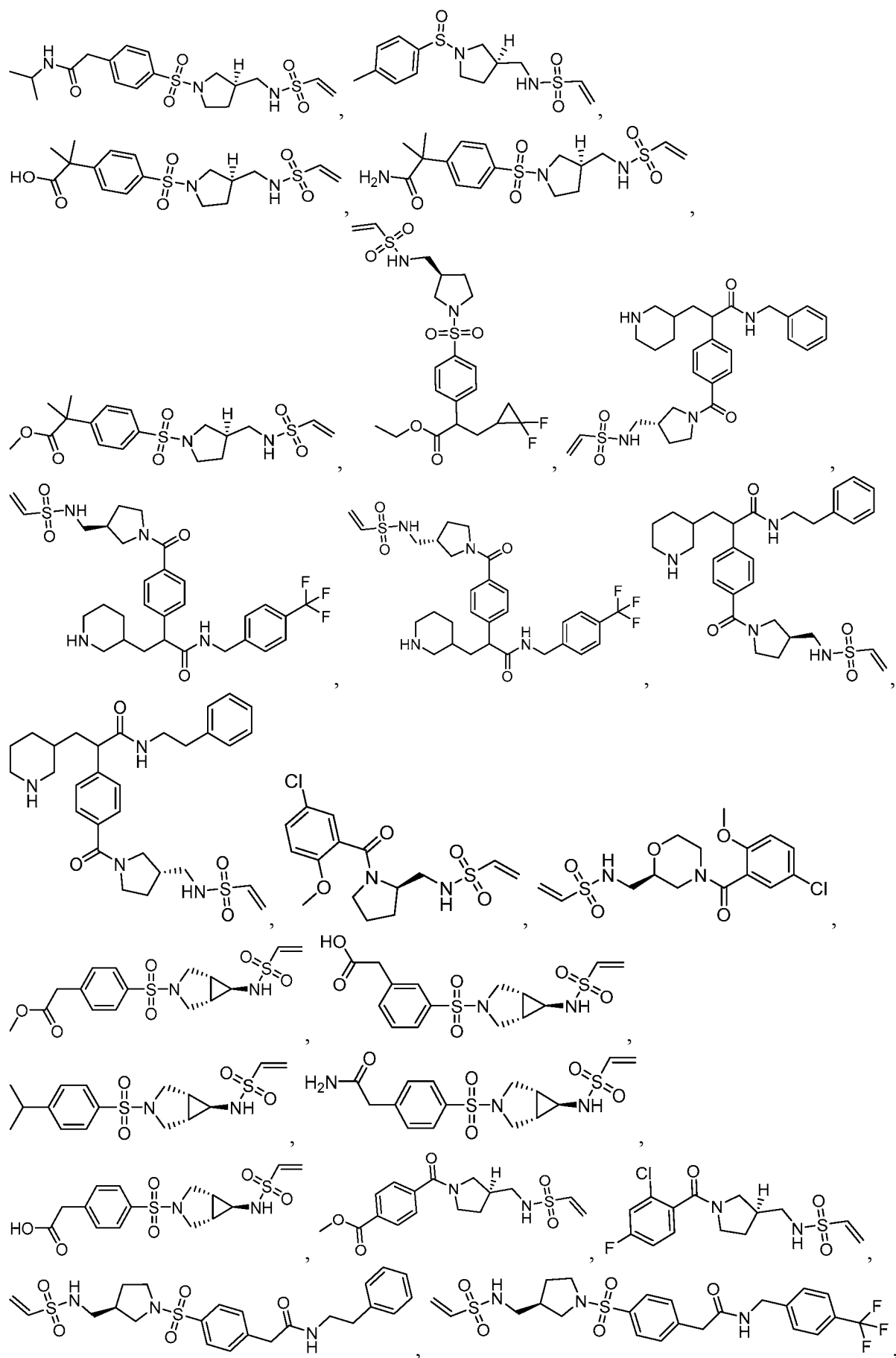


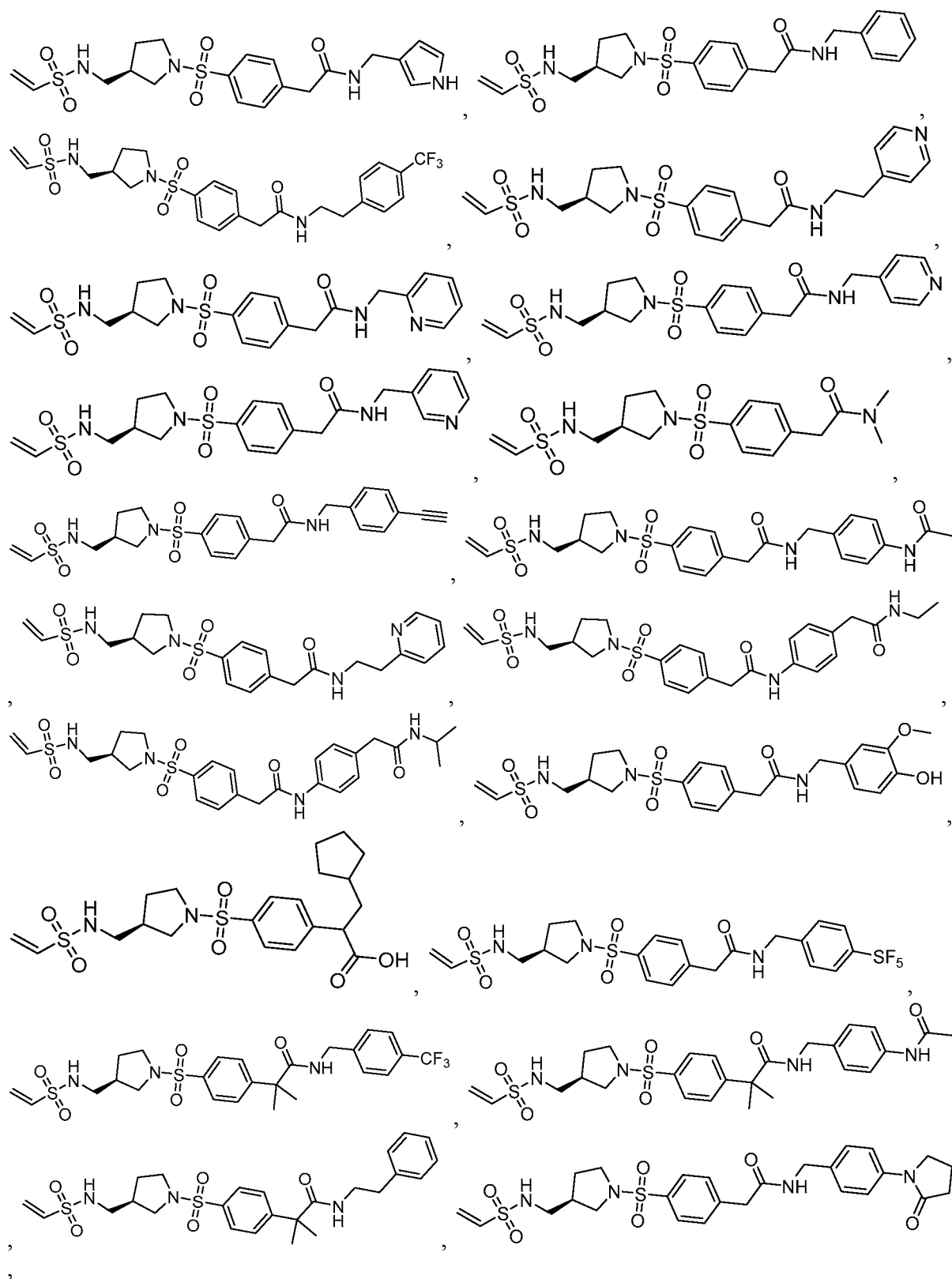


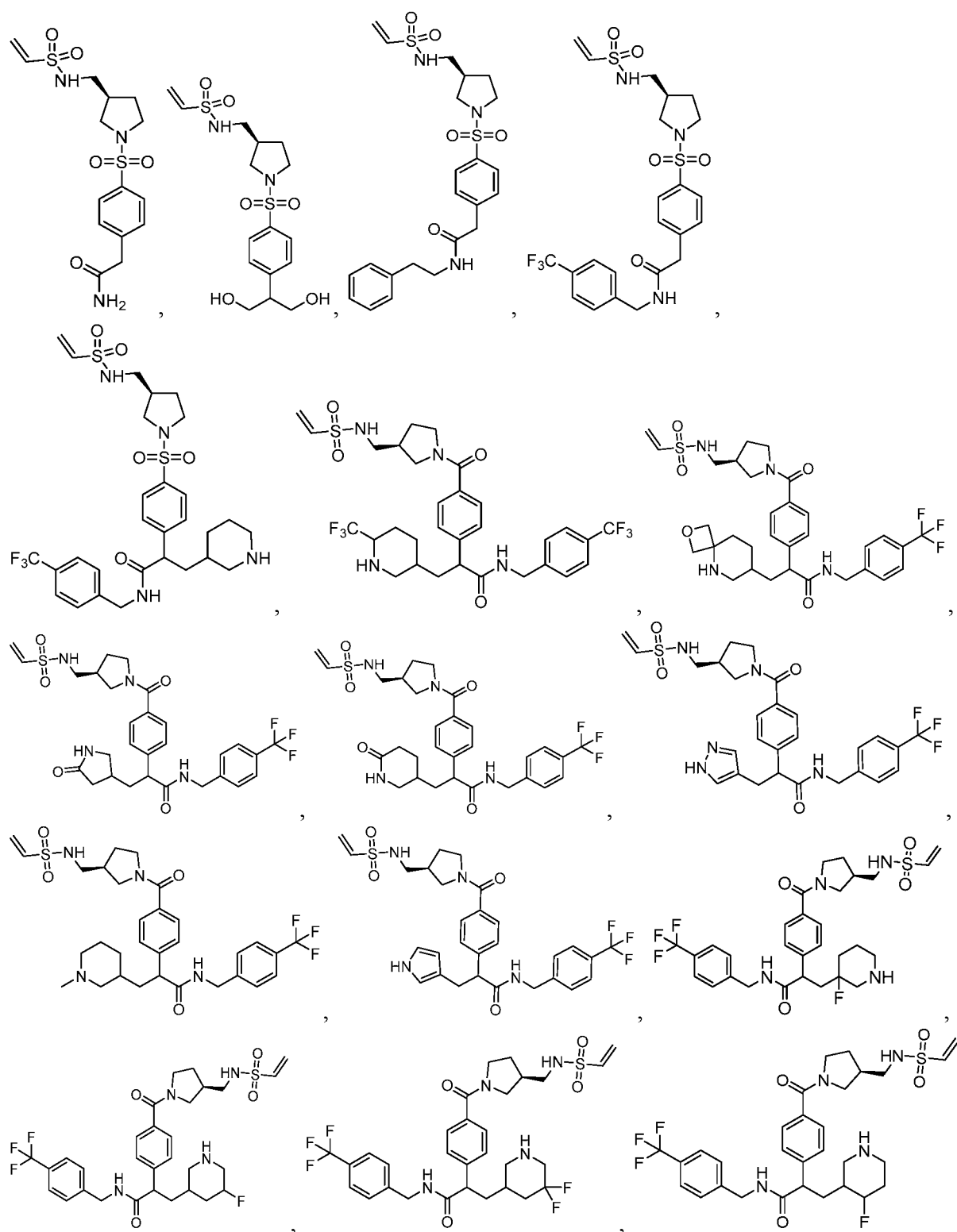


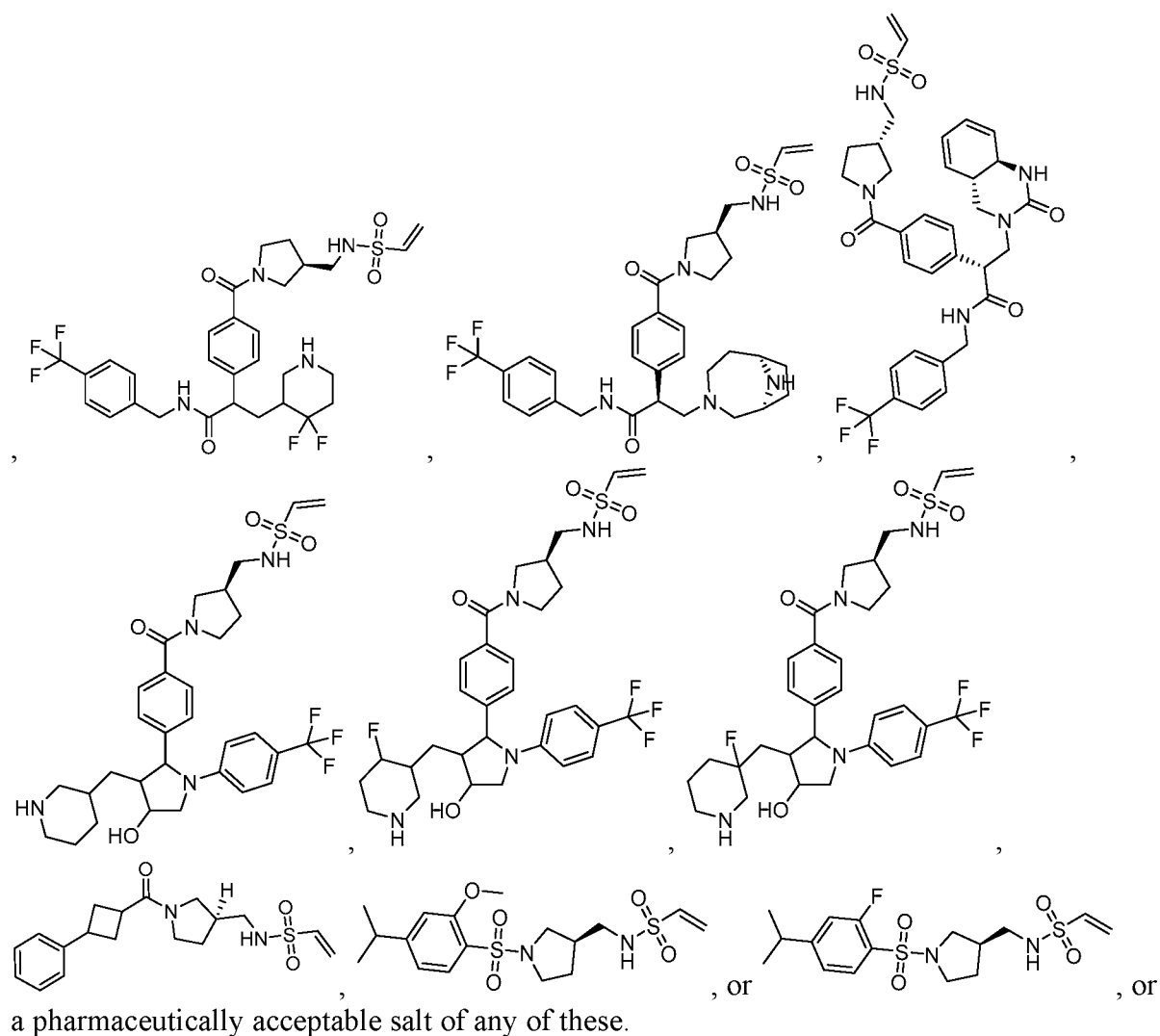




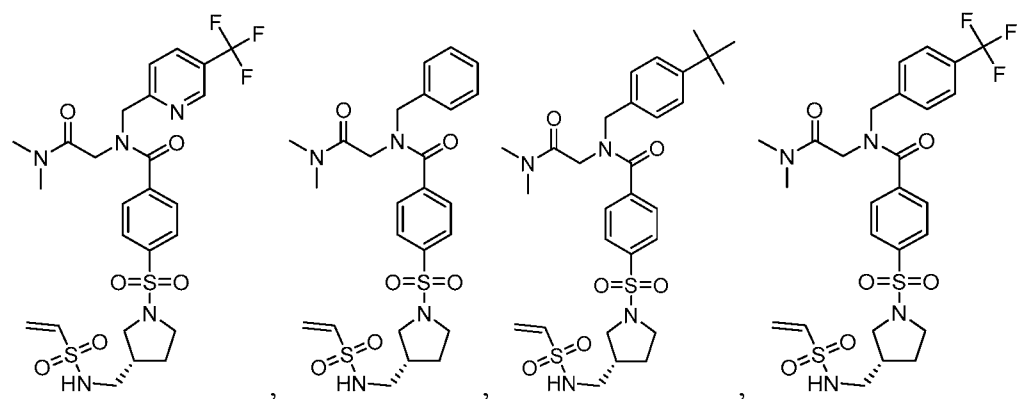


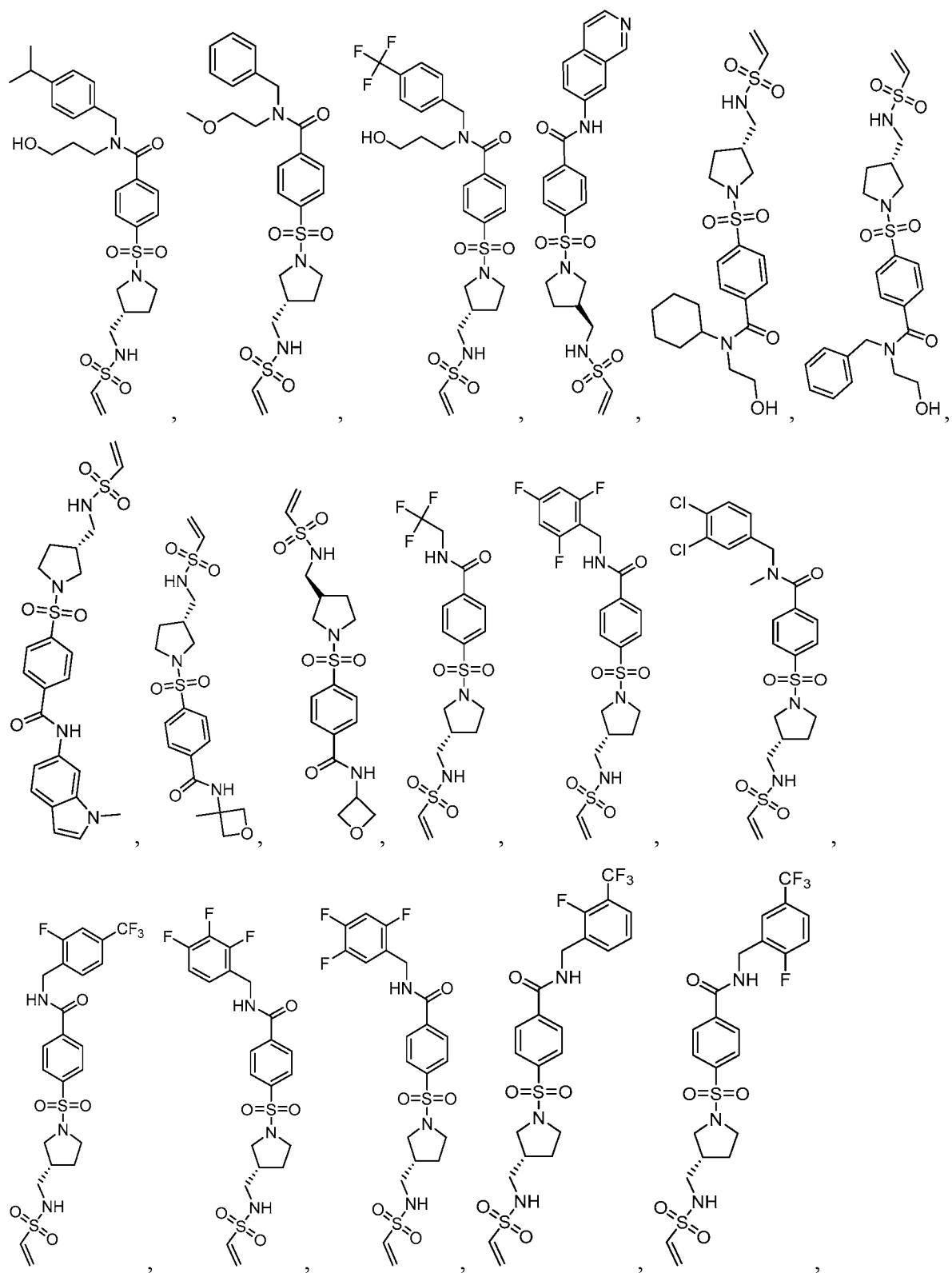


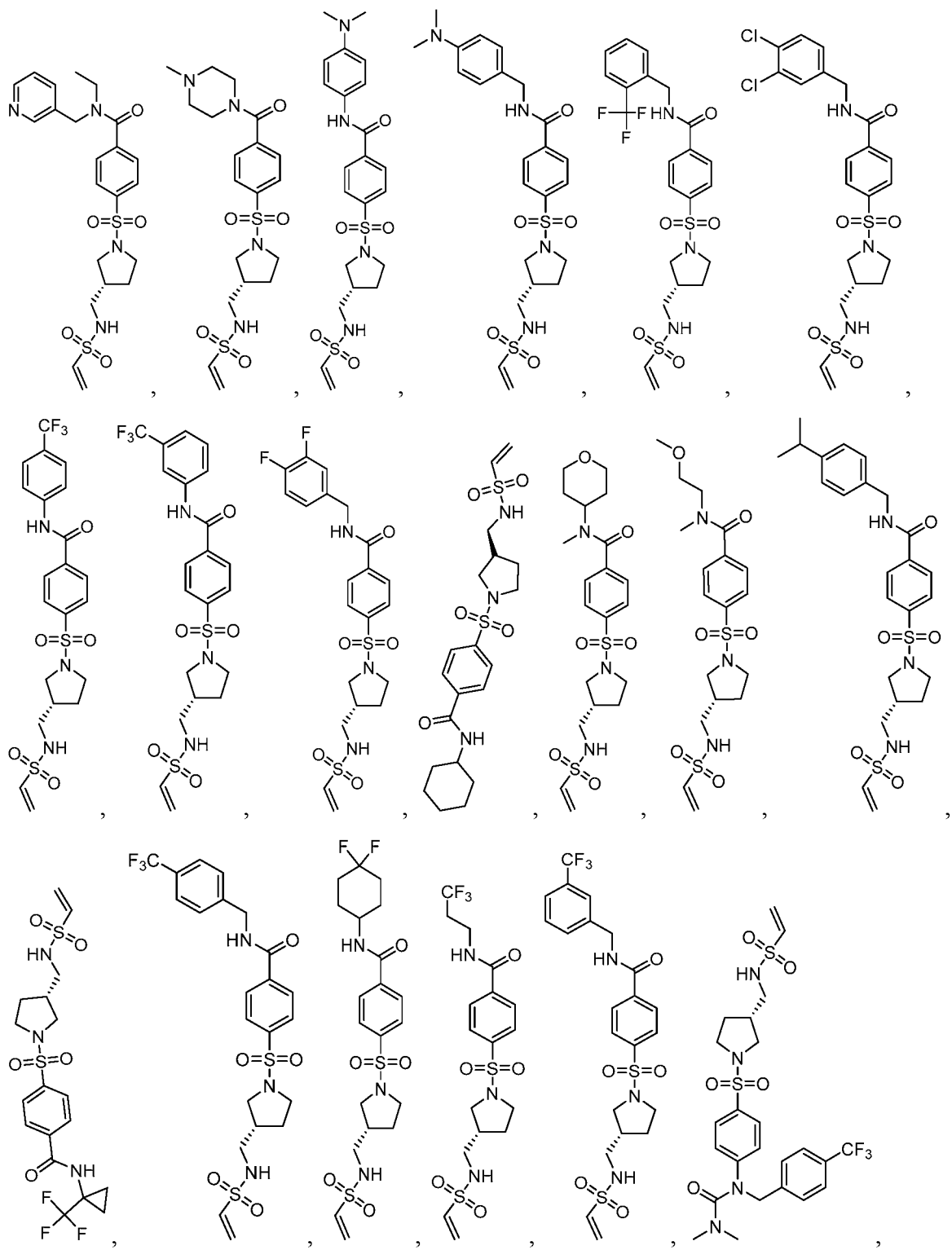


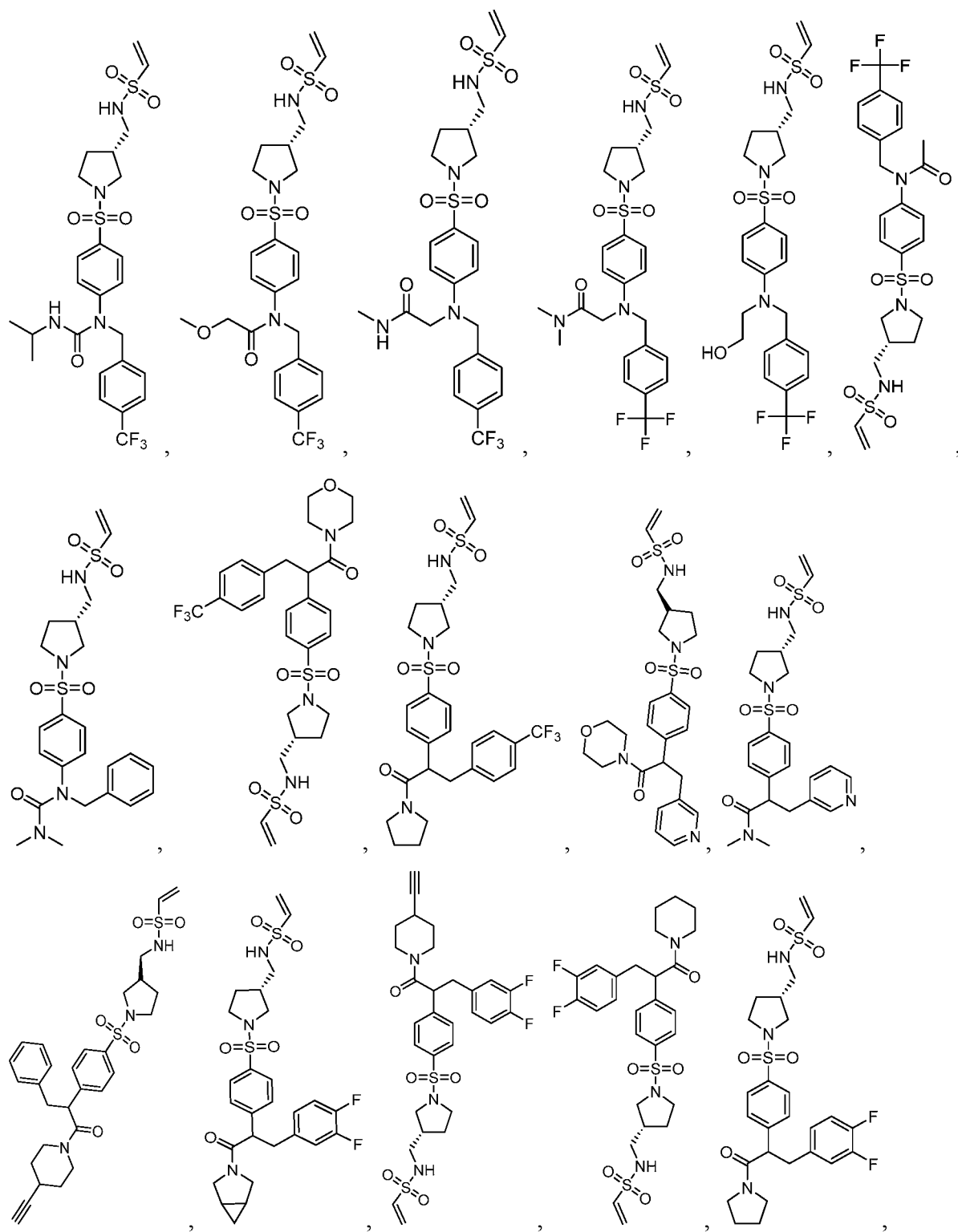


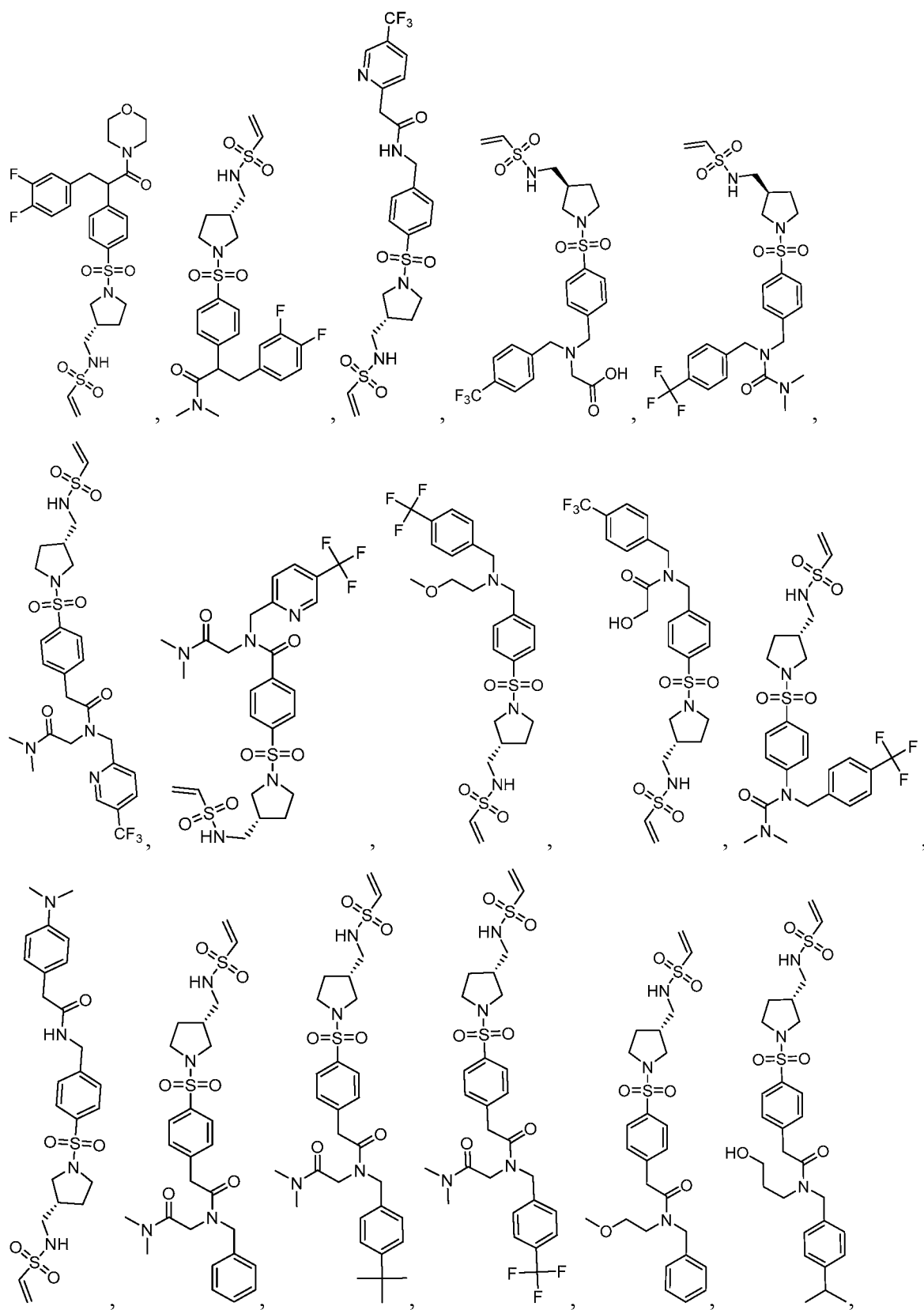
[0175] In some embodiments, the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i) is:



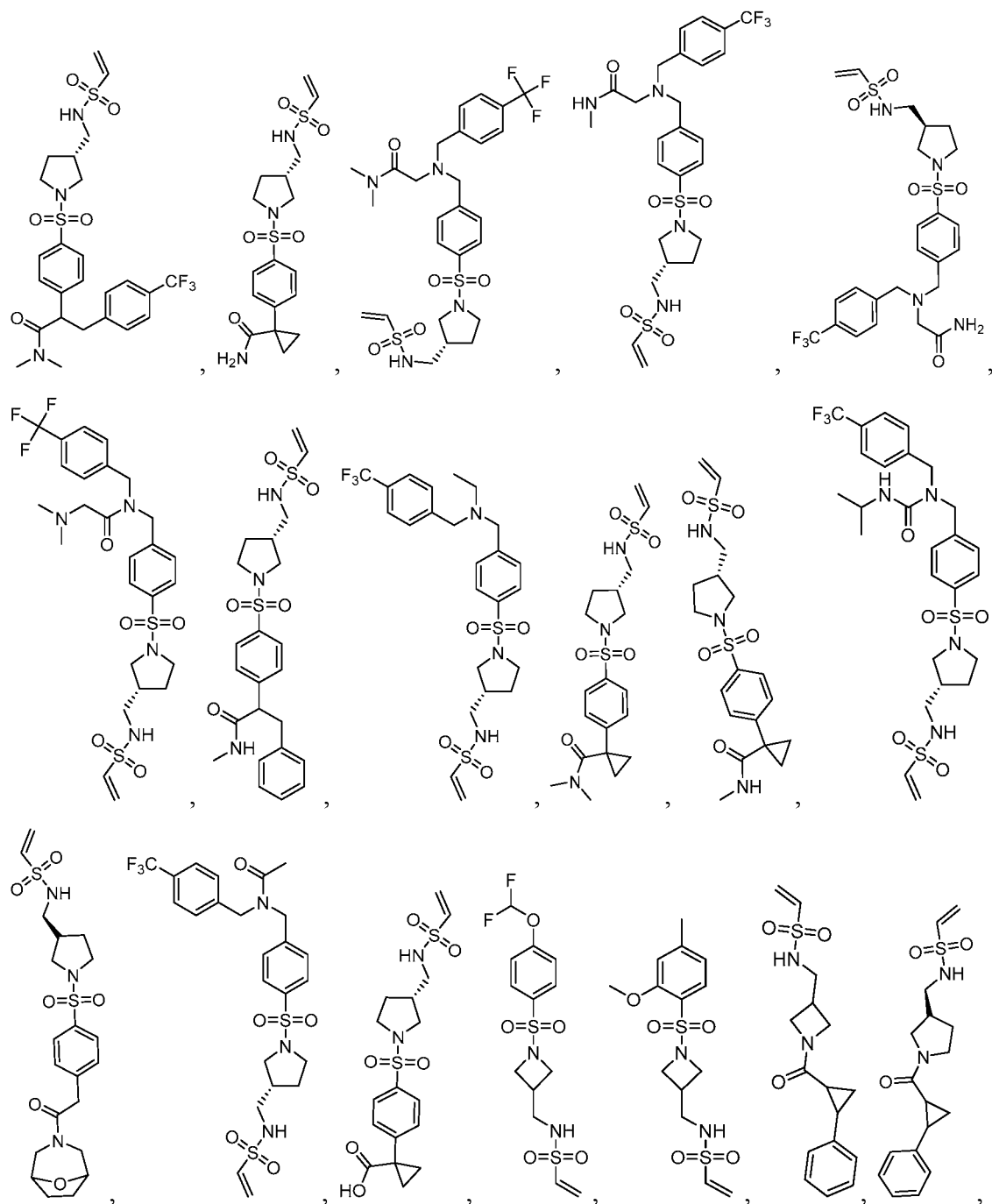


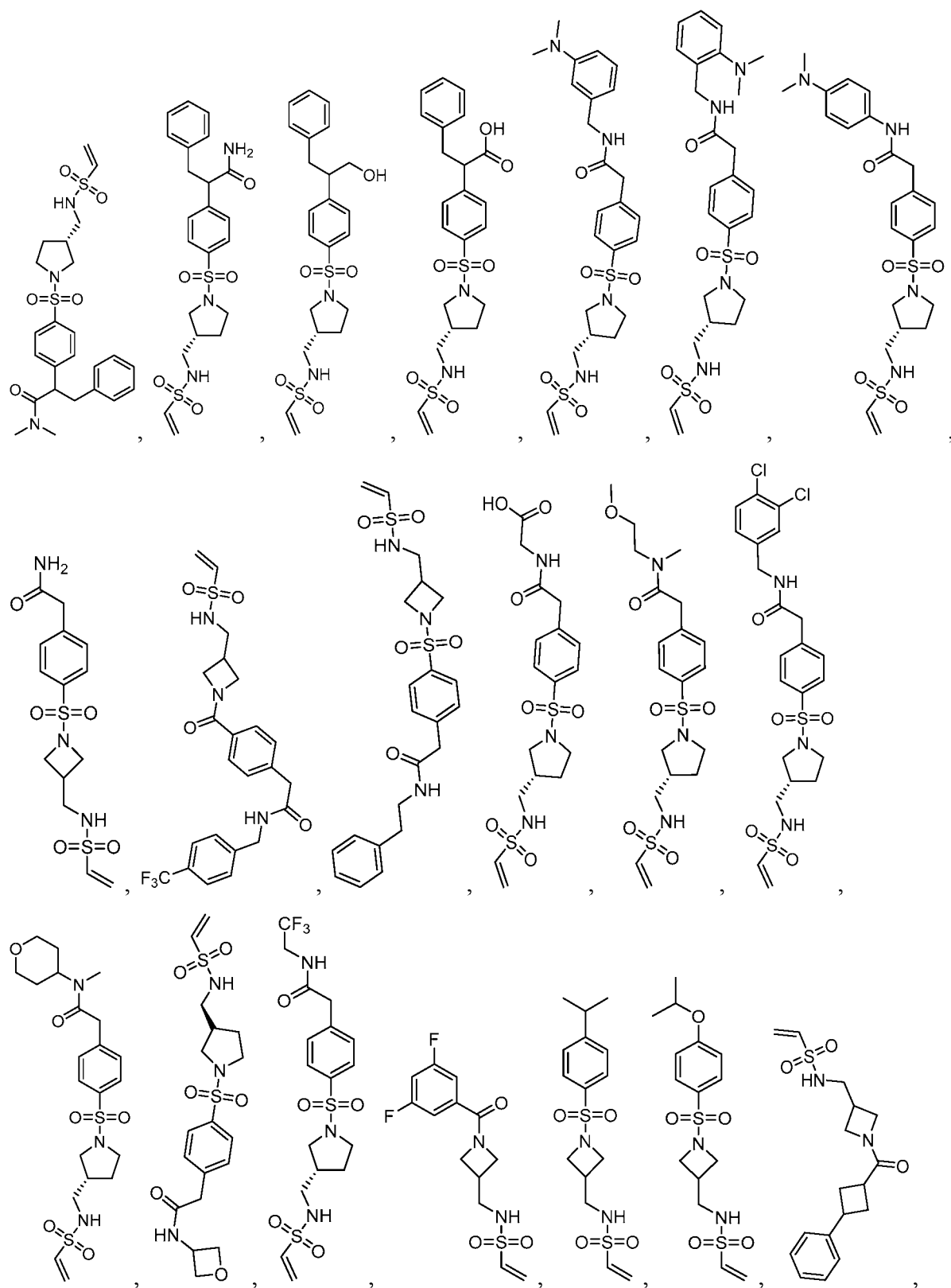


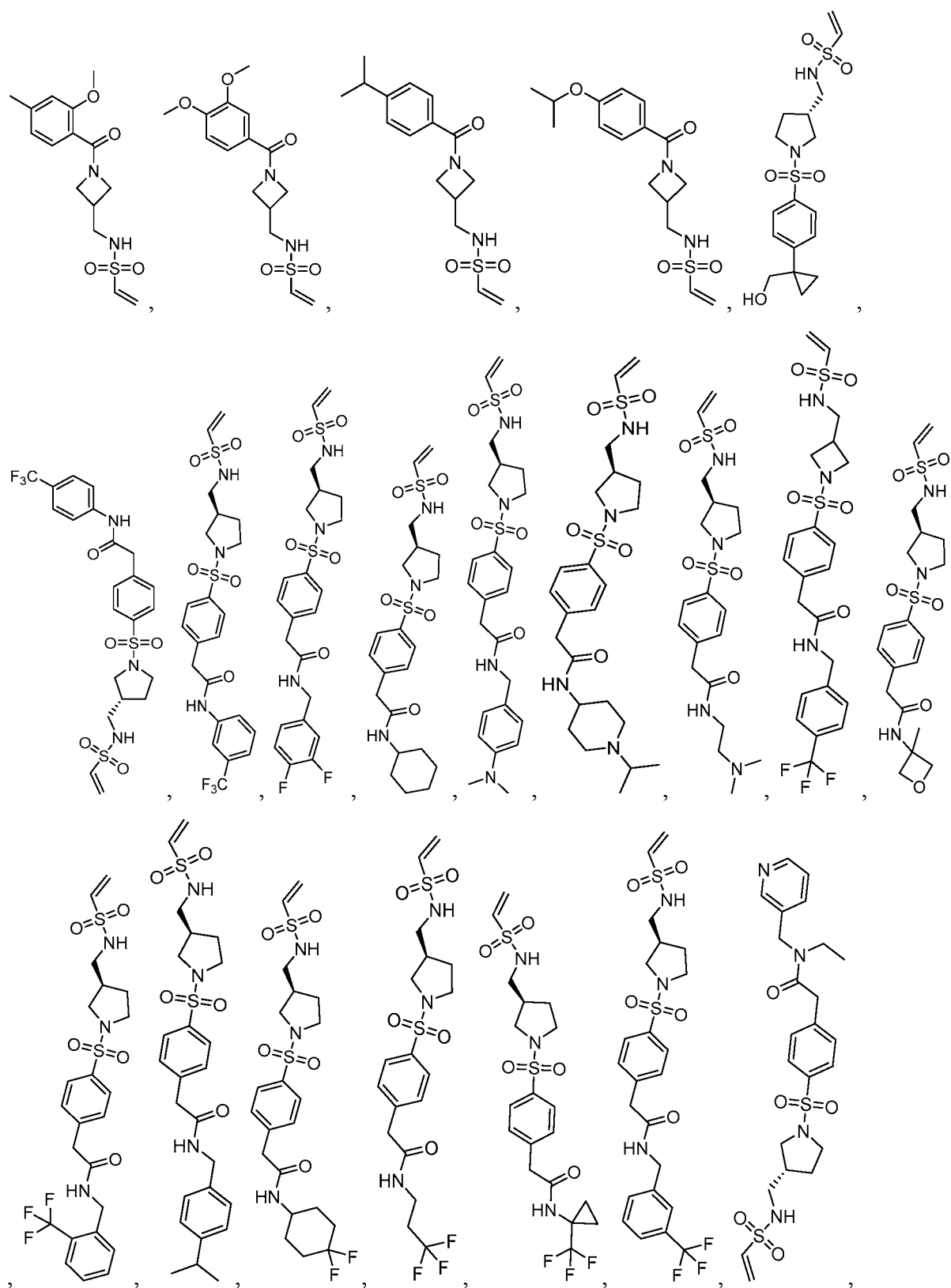


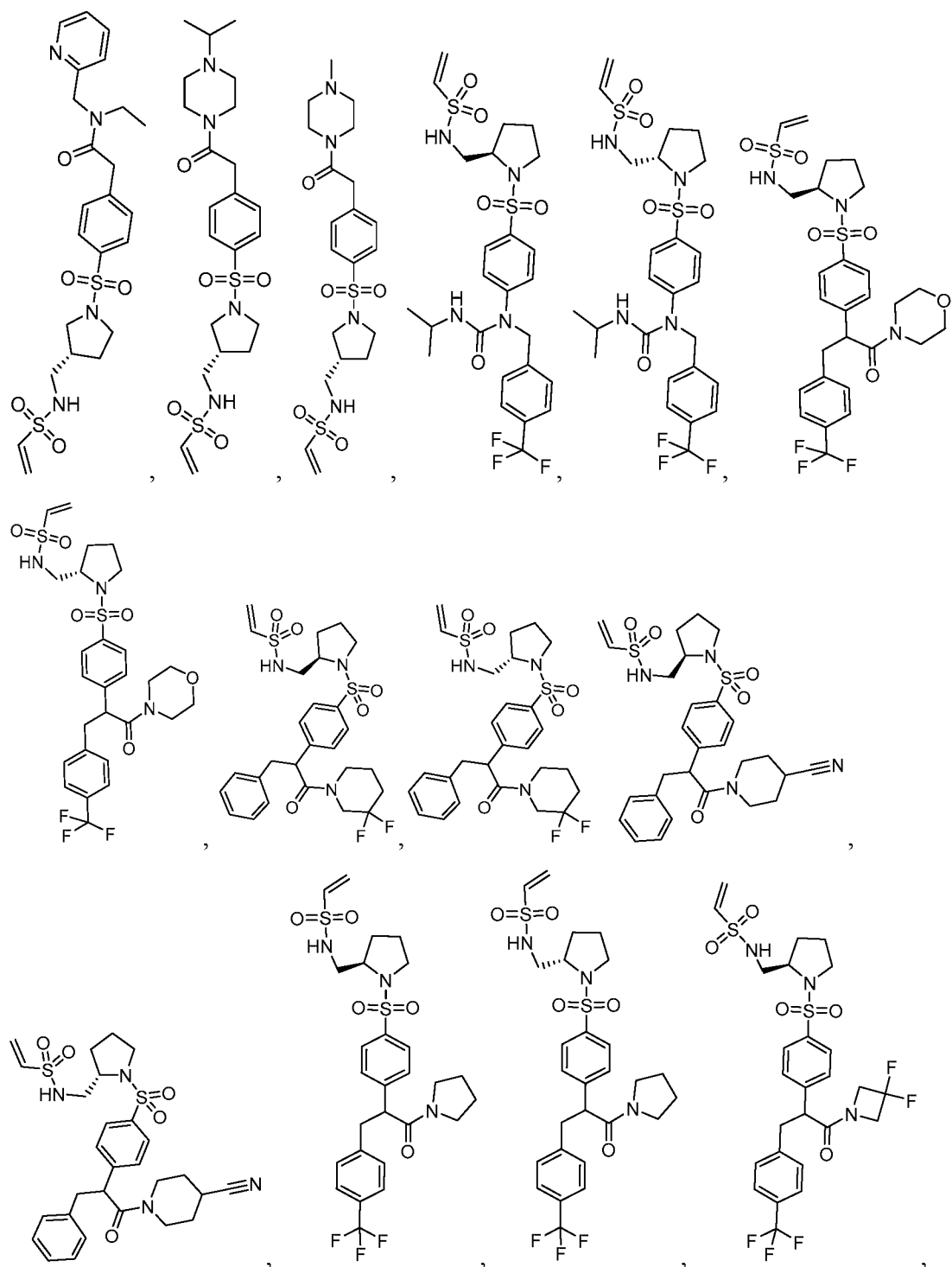


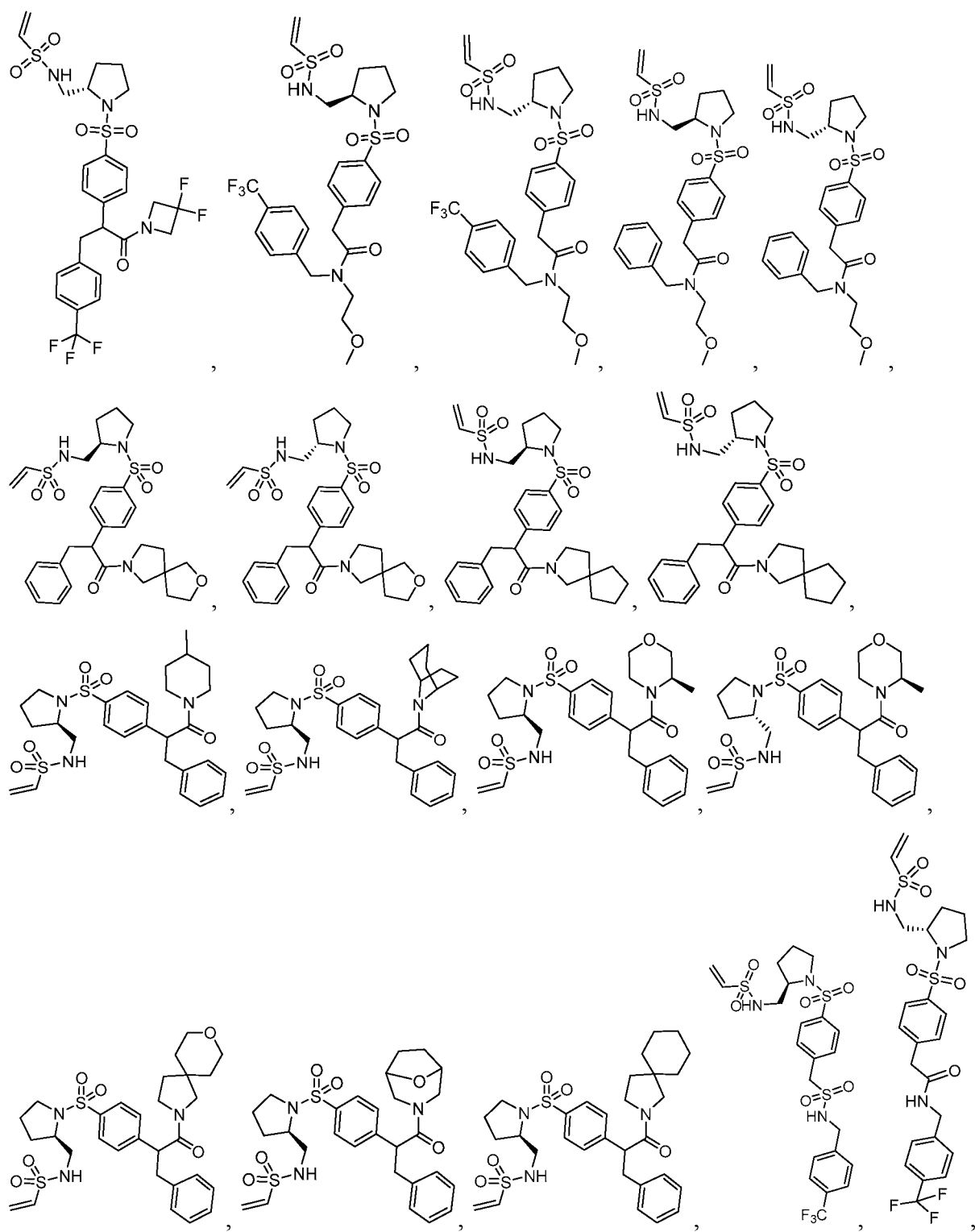


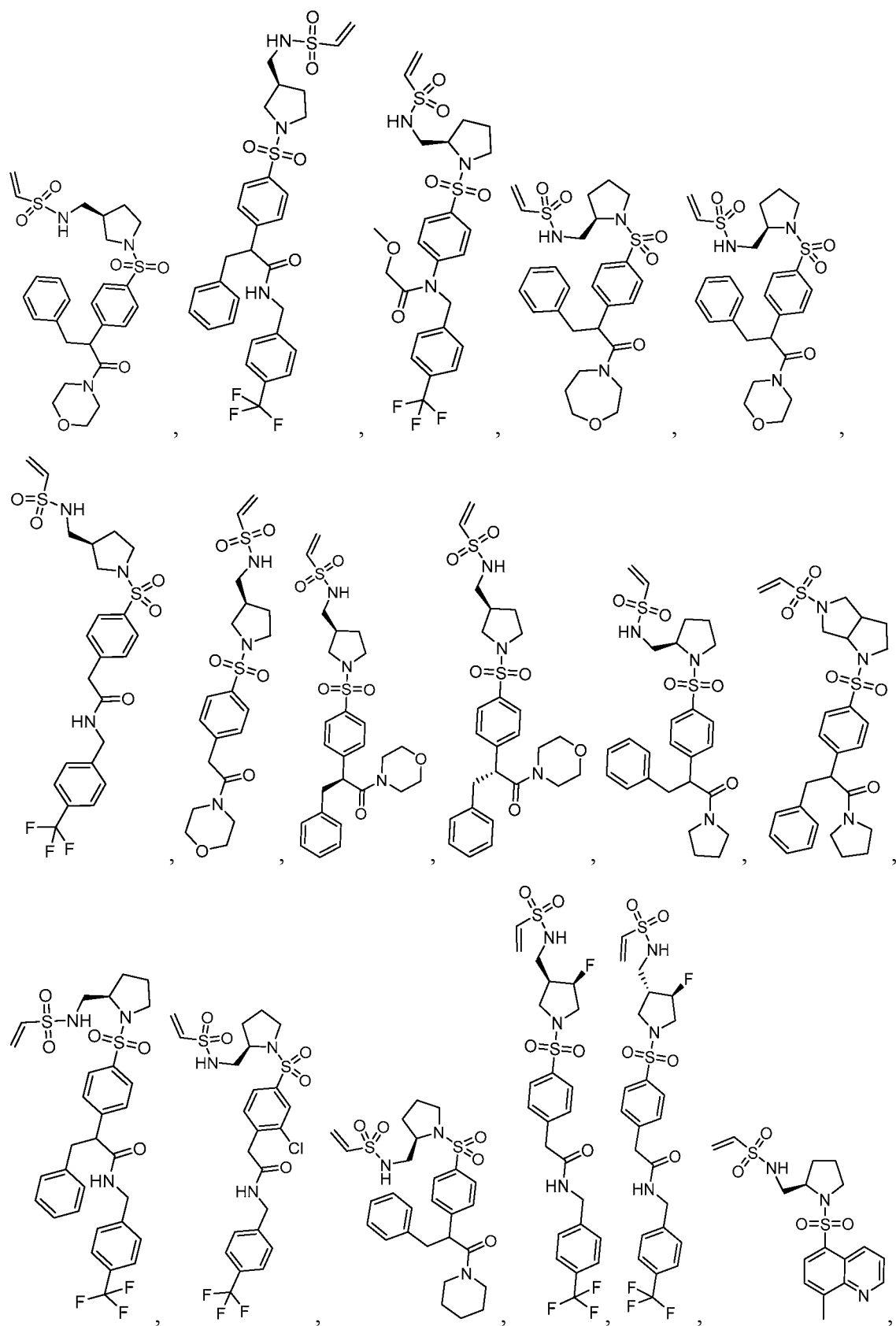


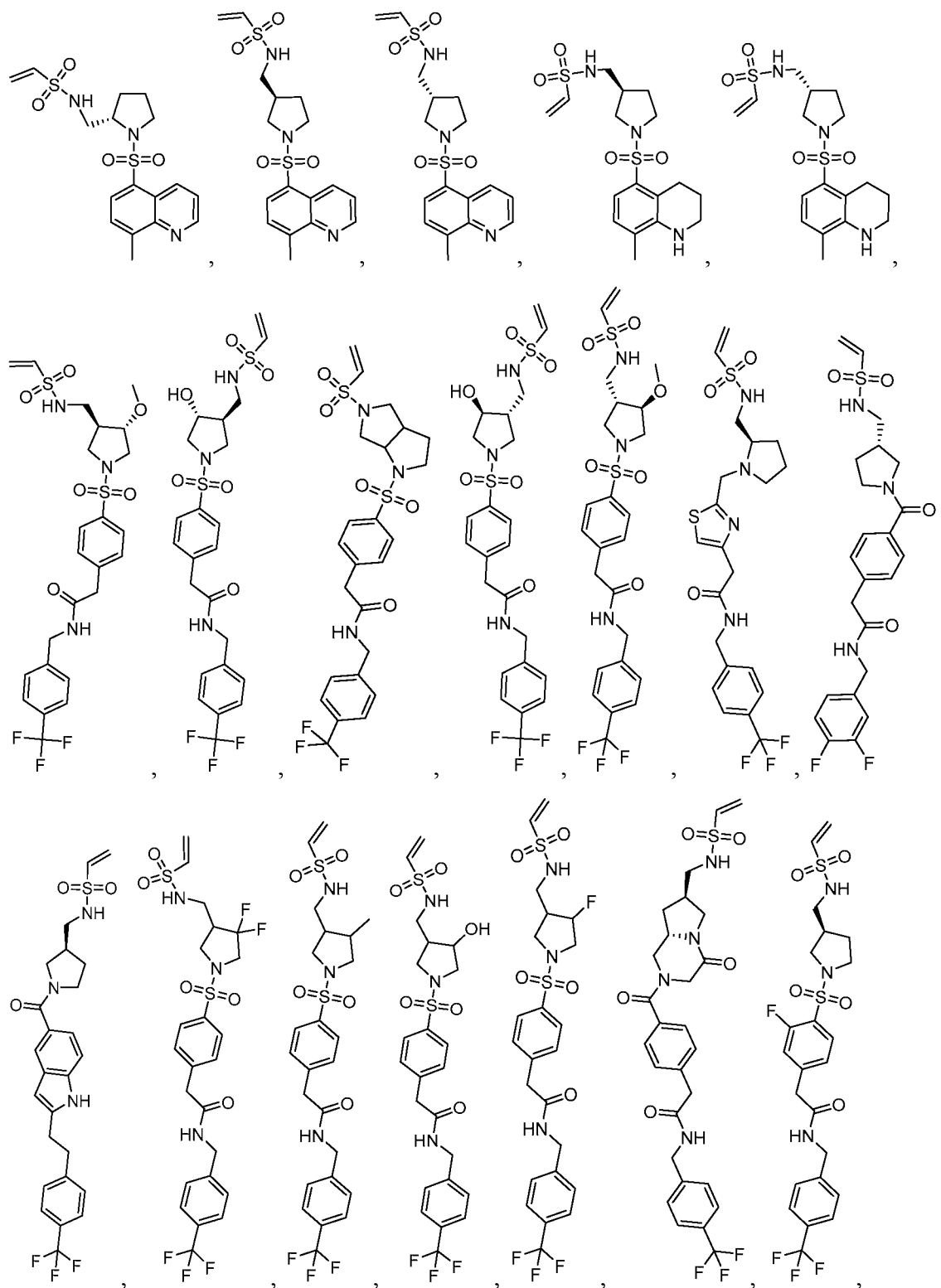


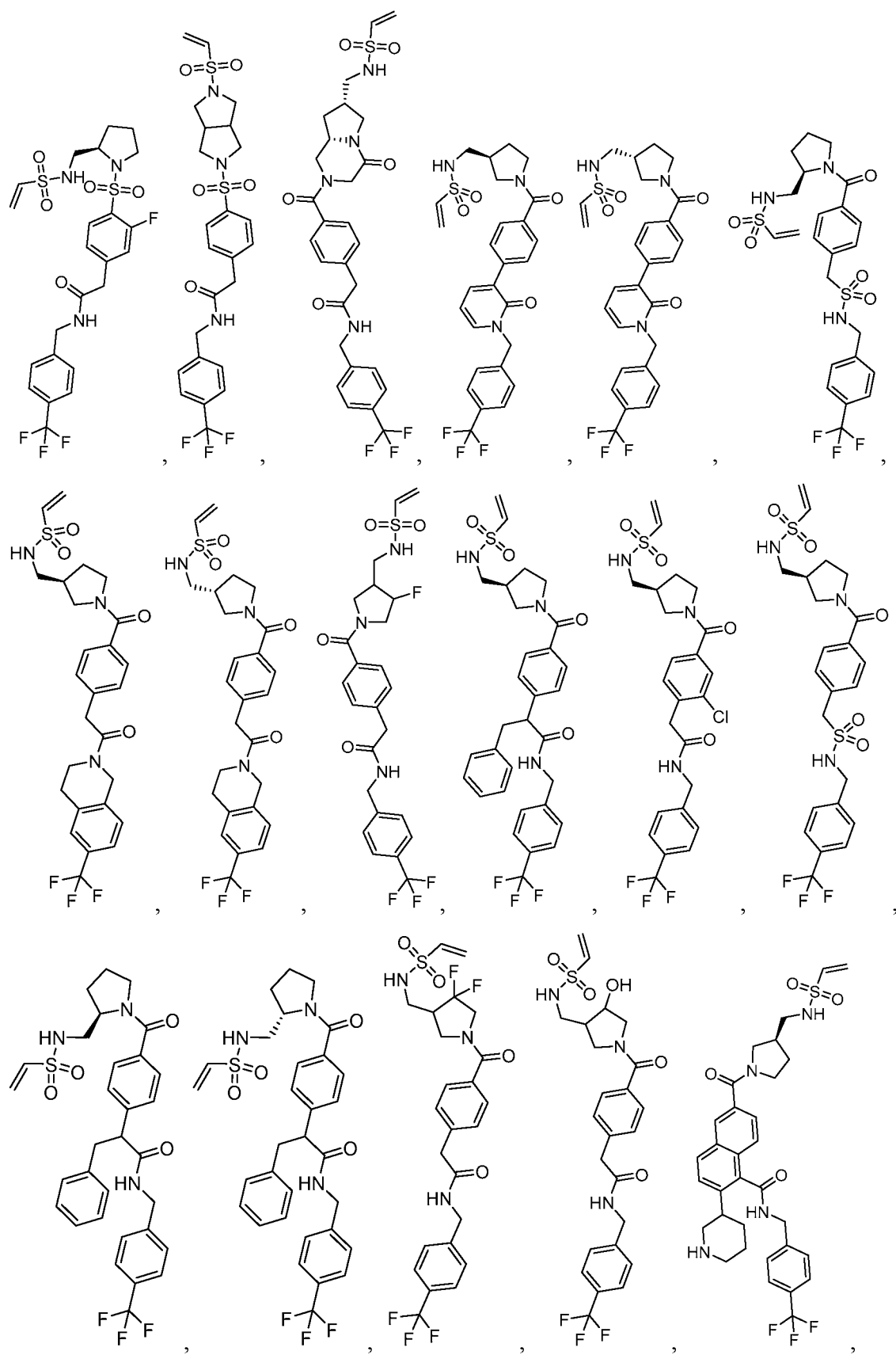




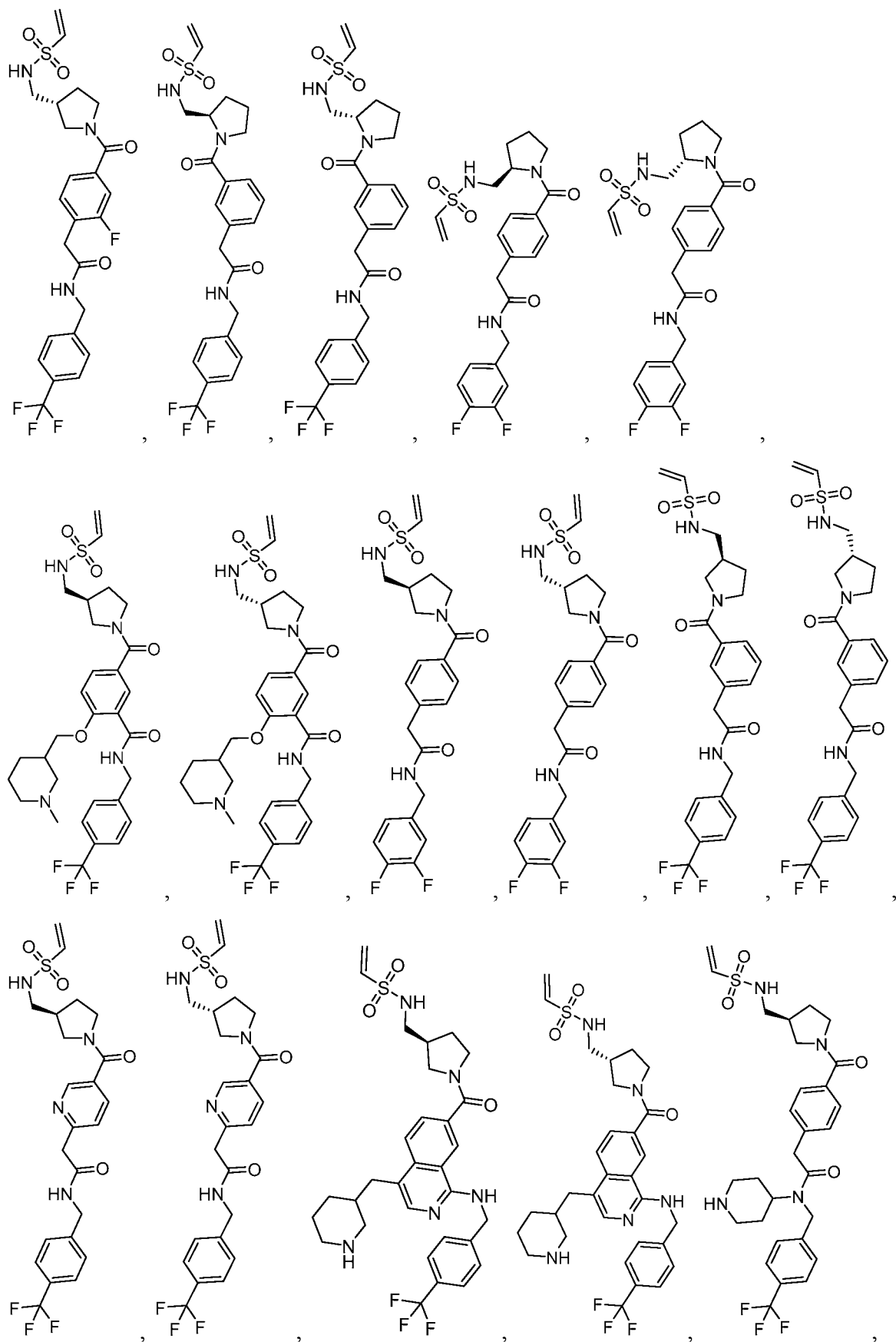


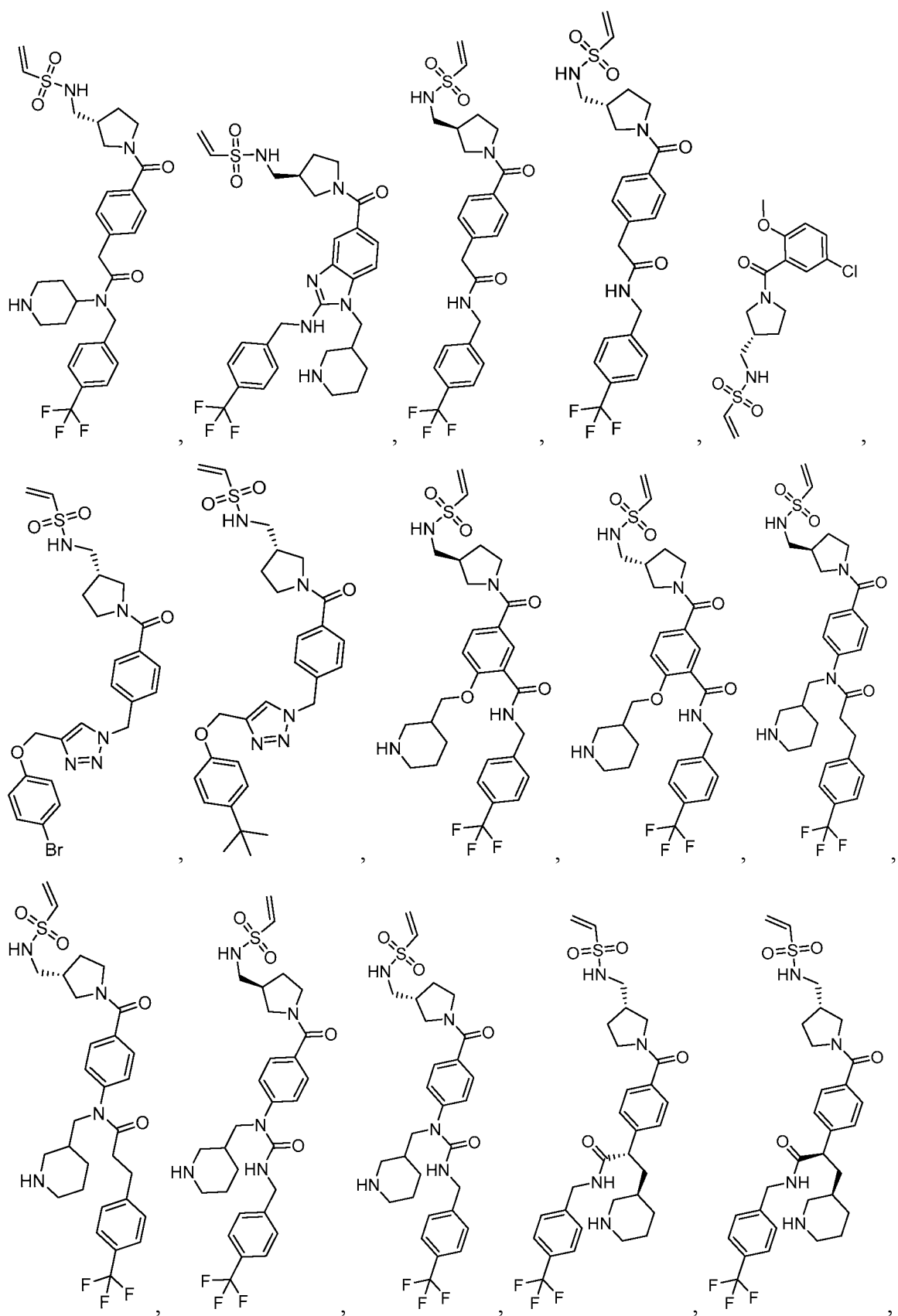


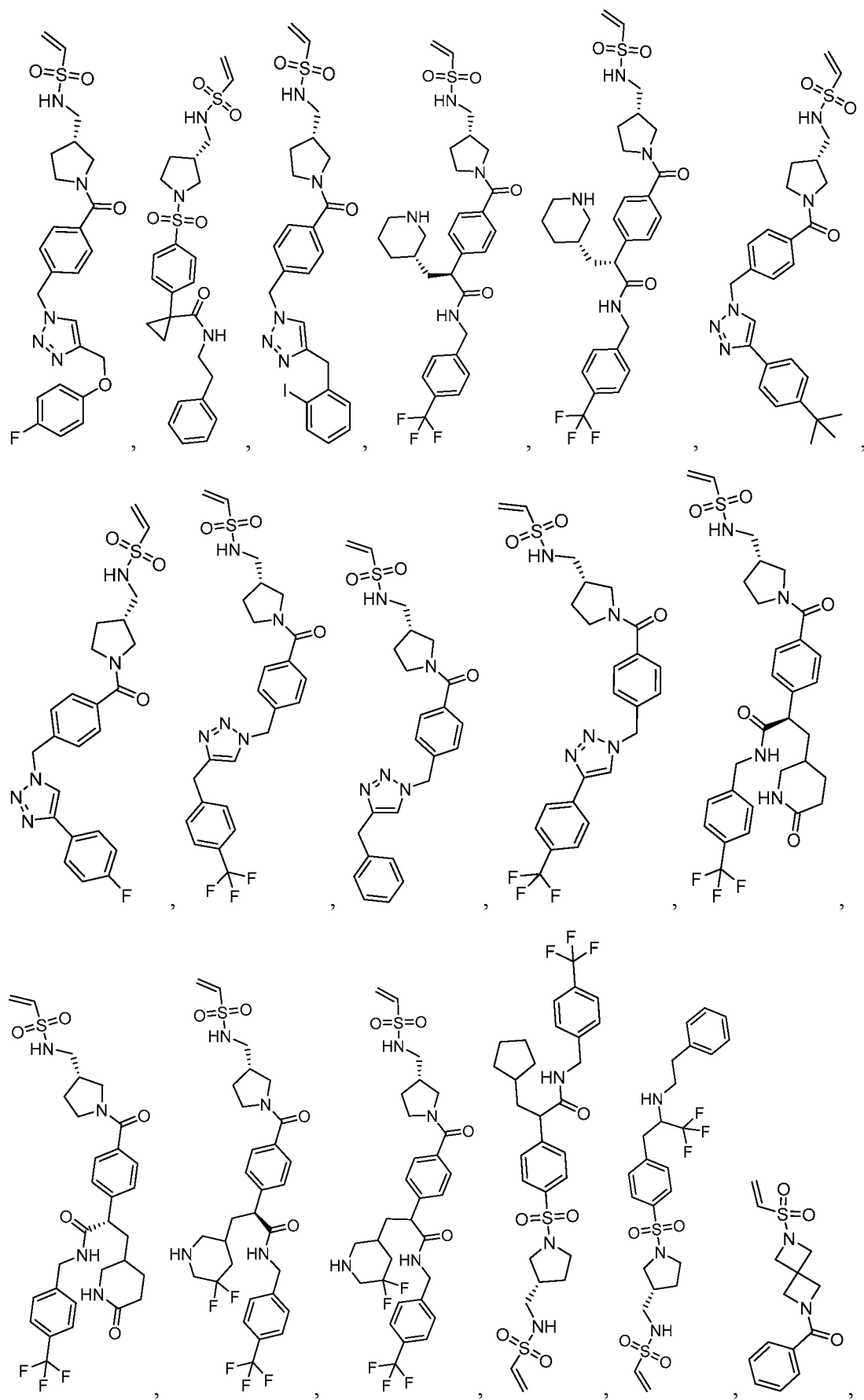


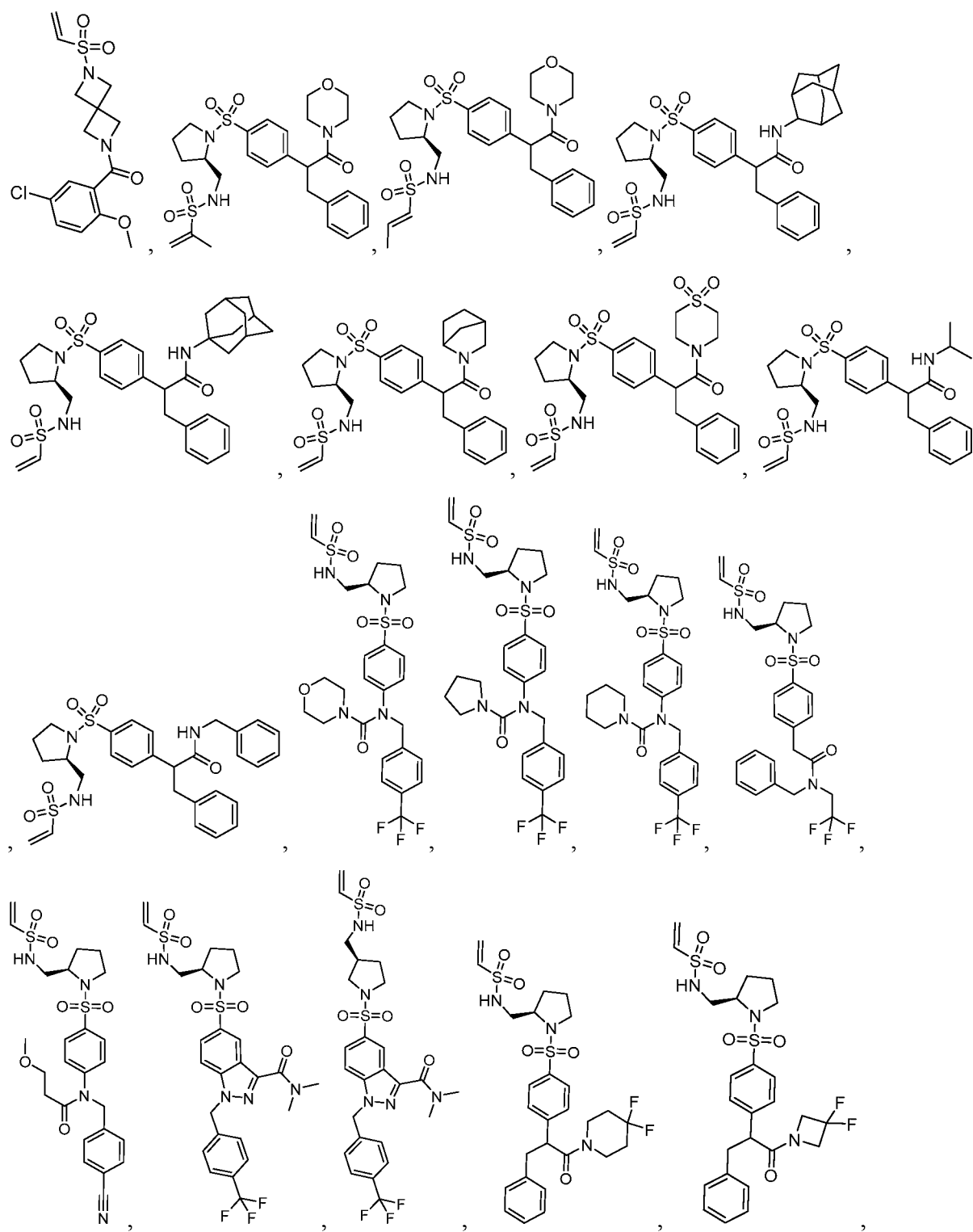


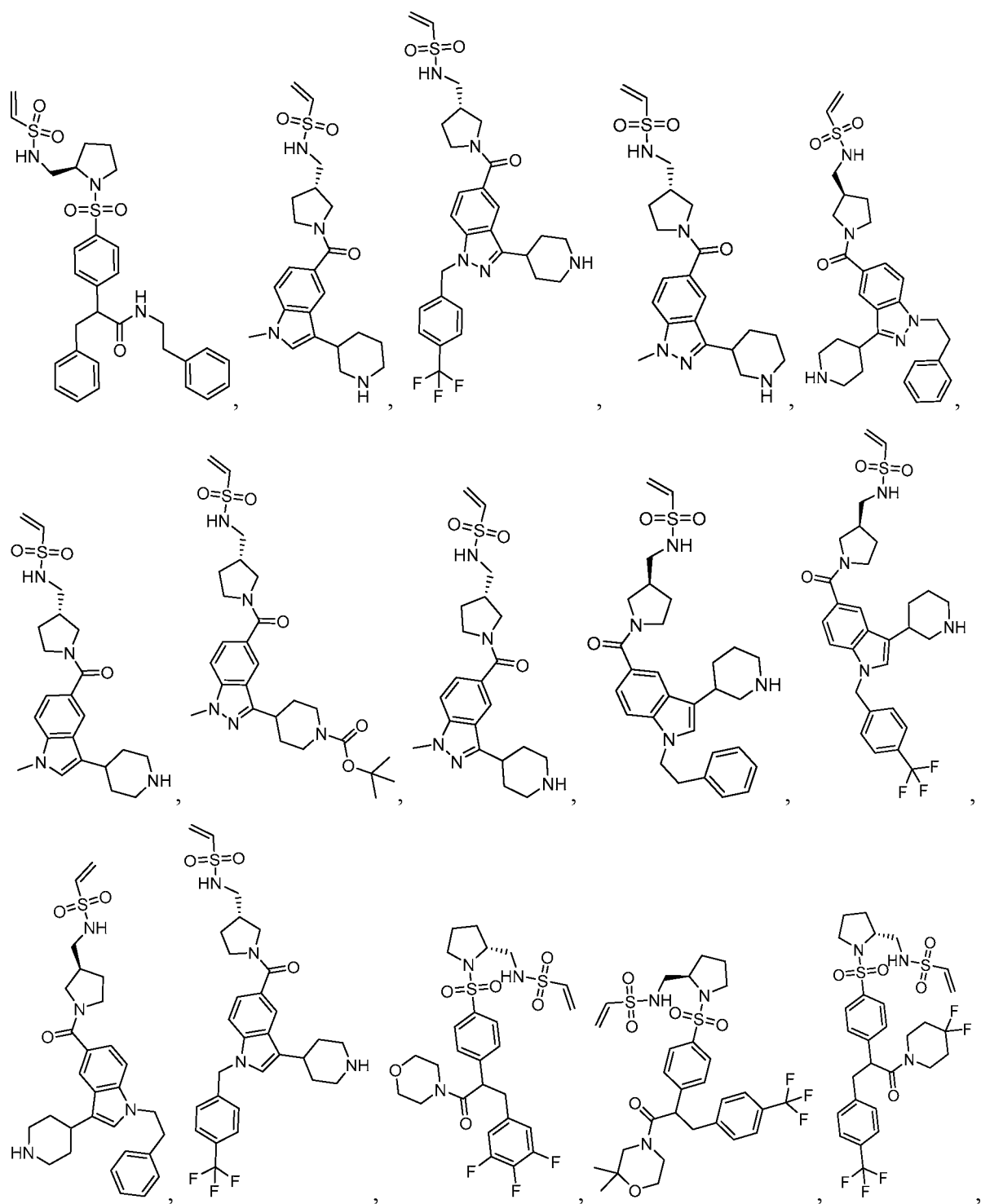


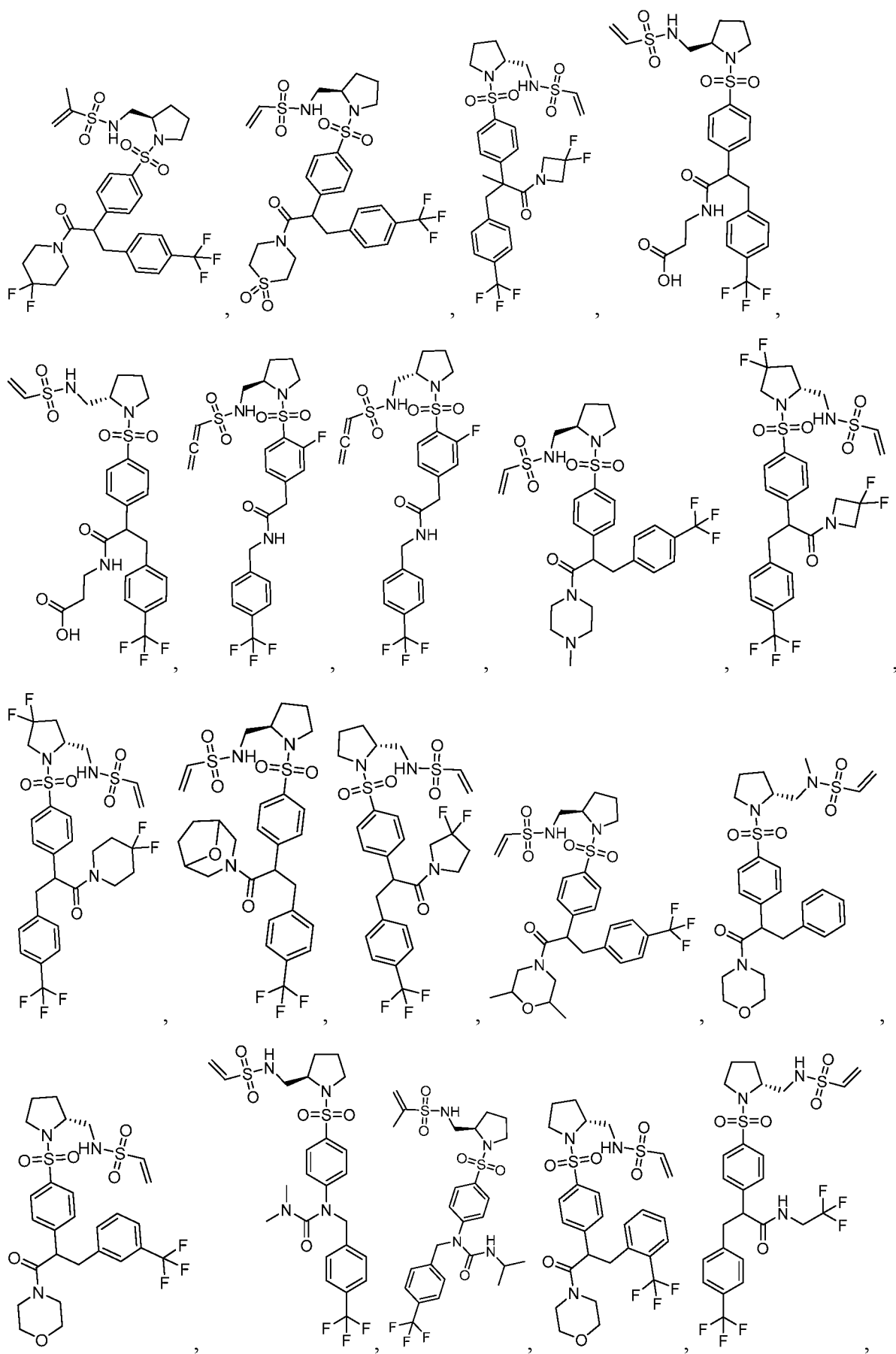


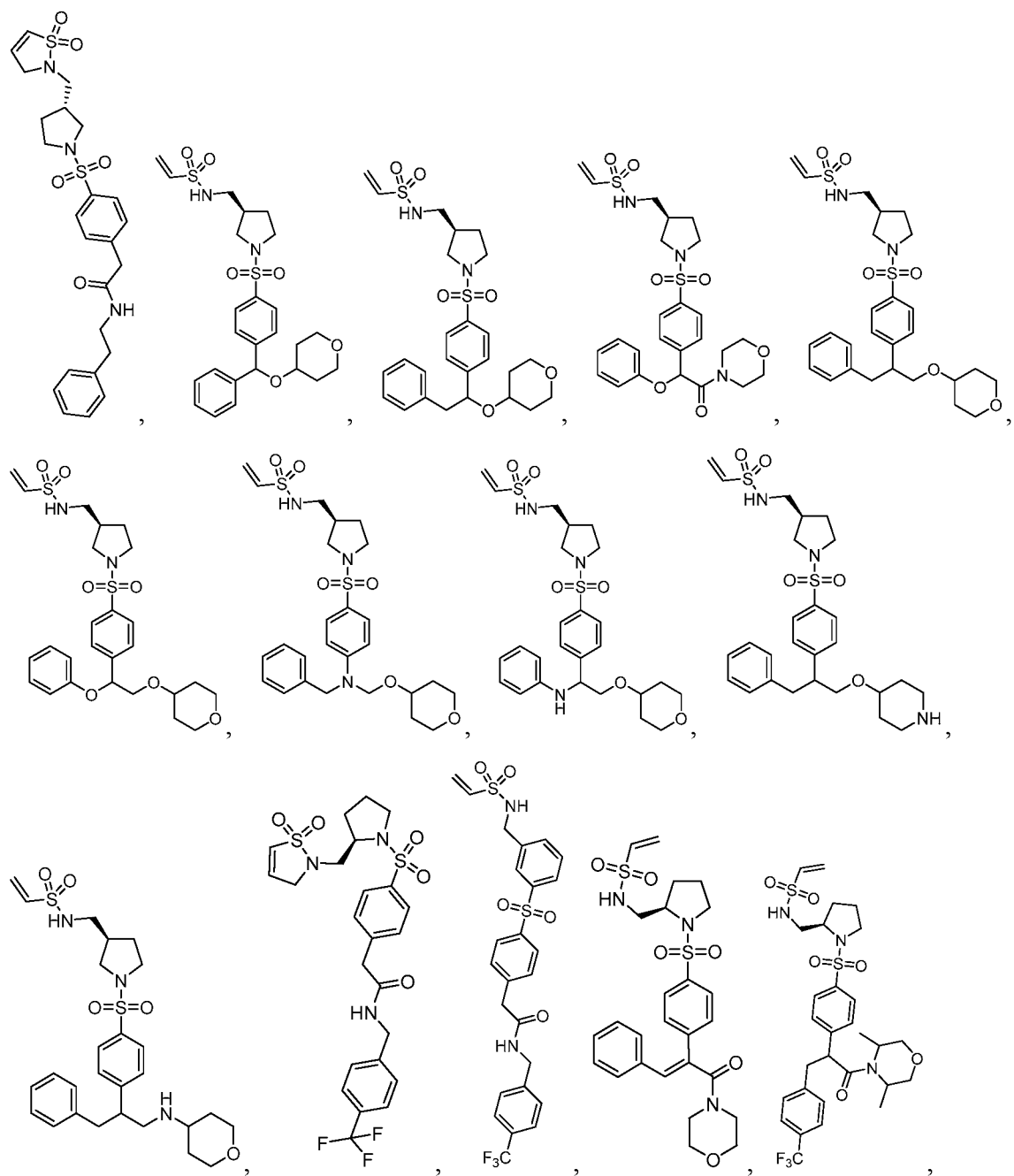


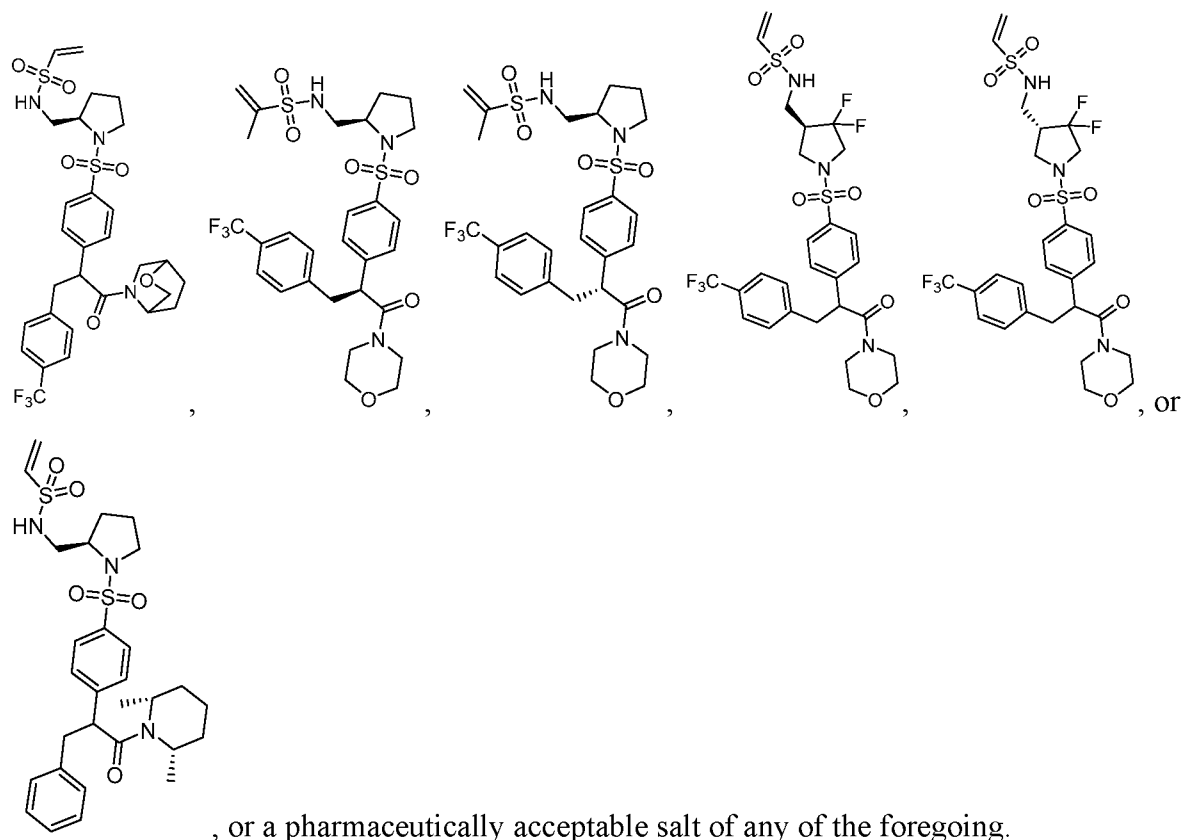












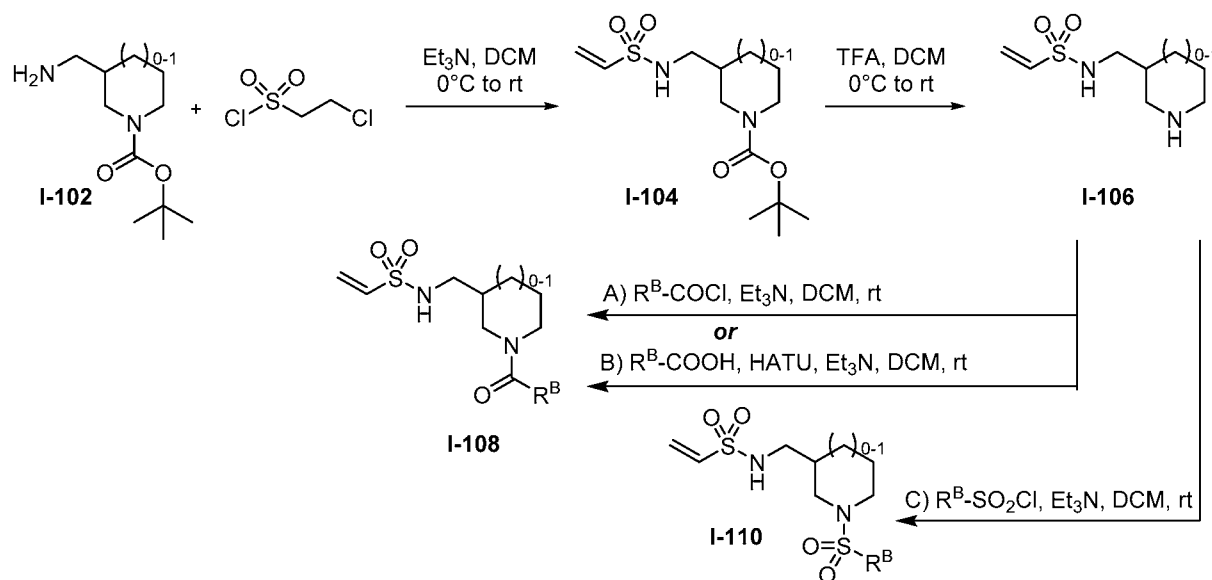
[0176] The compounds described herein, including compounds of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or their pharmaceutically acceptable salts, may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, or other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (−), or (*R*)- and (*S*)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-performance liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0177] “Pharmaceutically acceptable salt” includes a salt which is generally safe, non-toxic and not biologically or otherwise undesirable, and includes that which is acceptable for veterinary use as well as human pharmaceutical use. Such salts may include acid addition salts and base addition salts. Acid addition salts may be formed with inorganic acid such as, but not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or an organic acid such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, or undecylenic acid. Salts derived from inorganic bases may include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from organic bases may include, but are not limited to, salts of primary, secondary, or tertiary amines; substituted amines including naturally occurring substituted amines; cyclic amines; ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, or N-ethylpiperidine. In some embodiments, a compound provided herein, including compounds of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), and including any of the species provided herein, is a hydrochloric acid salt.

[0178] Unless otherwise stated, the compounds provided herein, including compounds of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or their pharmaceutically acceptable salts, also include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds may have the present structures except for the replacement of a hydrogen by a deuterium (D or ^2H) or tritium (^3H), or the replacement of a carbon-12 by a carbon-13 (^{13}C) or carbon-14 (^{14}C).

[0179] The compounds disclosed herein, such as a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, may be prepared, for example, through the reaction routes depicted in General Scheme I-1.

General Scheme I-1:



[0180] General Scheme I-1 provides three routes to prepare a compound disclosed herein, such as a compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof. In this scheme, compound **I-102** is combined with 2-chloroethanesulfonyl chloride, triethylamine (Et_3N), and solvent (such as dichloromethane, DCM), and that mixture is stirred from 0 °C to room temperature to produce compound **I-104**. This compound is then combined with trifluoroacetic acid (TFA) and solvent (such as DCM) and stirred from 0 °C to room temperature to remove the BOC

protecting group and produce compound **I-106**. This compound can be combined with triethylamine, solvent (such as DCM), and an R^B -carbonyl chloride reactant, wherein the R^B is a substituted or unsubstituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl. This mixture is then stirred at room temperature to produce compound **I-108**, an example of a compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, wherein X is $-C(O)-$. Alternatively, compound **I-106** may be combined with triethylamine, solvent (such as DCM), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), and an R^B -COOH reactant, and stirred at room temperature to produce compound **I-108**, an example of a compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, wherein X is $-C(O)-$. In still another route, compound **I-106** is combined with triethylamine, a solvent (such as DCM), and an R^B -SO₂Cl reactant and stirred at room temperature to produce compound **I-110**, an example of a compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, wherein X is $-S(O)_2-$. In some embodiments of any of the these routes, a different solvent is used in one or more steps, such as acetonitrile. In some embodiments, a different amine is used. In certain embodiments, the temperature may be adjusted.

[0181] While General Scheme I-1 depicts the preparation of a compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, with certain substituents or moieties, other compounds according to the Formulae may also in some embodiments be prepared following analogous reaction schemes. For example, compounds with a 4-, 7- or 8-membered heterocycloalkyl ring A, or compounds with R^{a2} or R^{a3} other than hydrogen, or other compounds disclosed herein may, in some embodiments, be prepared following analogous reaction schemes. The reactants, solvents, and other compounds used to prepare a compound of Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), or Formula (I-B-i), or a pharmaceutically acceptable salt thereof, by following General Reaction Scheme I-1, or by another route, may be commercially available or may be prepared following organic chemical techniques.

[0182] Further provided herein is a pharmaceutical composition comprising a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-

B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. A pharmaceutically acceptable excipient may include, for example, an adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans. Pharmaceutically acceptable excipients may include, but are not limited to, water, NaCl, normal saline solutions, lactated Ringer's solution, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates (such as lactose, amylose or starch), fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors.

II. Methods of Treatment

[0183] Provided herein are methods of treating a disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof. Also provided are methods of treating a disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, the compound administered to the subject in need thereof according to the methods described herein is a compound described in an embodiment, example, figure, or table herein, or a stereoisomer or pharmaceutically acceptable salt thereof.

[0184] Also provided herein is the use of a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

[0185] Further provided herein is a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, for use in a method of treating a disorder in a subject in need thereof.

[0186] In some embodiments of the methods and uses provided herein, the disorder is related to K-Ras, for example a disorder associated with a mutation of K-Ras or dysregulation of K-Ras. In some embodiments of the methods and uses provided herein, the disorder is related to the *KRAS* gene, for example a disorder associated with a mutation of the *KRAS* gene or dysregulation of the *KRAS* gene. Mutation or dysregulation of K-Ras or *KRAS* may include mutation or dysregulation of human K-Ras4a and/or human K-Ras4b. In some embodiments, the disorder is related to the K-Ras (for example, human K-Ras4a and/or human K-Ras4b) signaling pathway activity, for example a disorder related to aberrant K-Ras signaling pathway activity. In some embodiments, the disorder is related mutation or dysregulation of human K-Ras4b. In certain embodiments, the disorder is related to aberrant K-Ras4b signaling pathway activity. In some embodiments, the disorder is related mutation or dysregulation of human K-Ras4a. In certain embodiments, the disorder is related to aberrant K-Ras4a signaling pathway activity.

[0187] In some embodiments, the disorder is neurofibromatosis type 1 (NF1), Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome. In some embodiments, the disorder is neurofibromatosis type 1 (NF1). NF1 is a disorder that predisposes subjects to cancer. Subjects with NF1 are at greater risk than the general population for developing malignancies, which may include pediatric malignancies or adult malignancies. Pediatric malignancies may include optic pathway glioma, rhabdomyosarcoma, neuroblastoma, and juvenile myelomonocytic leukemia. Adult malignancies may include malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, and breast cancer.

[0188] In some embodiments of the methods and uses provided herein, the disorder is cancer. In some embodiments, the cancer is related to K-Ras, for example a cancer associated with a mutation of K-Ras or dysregulation of K-Ras. In some embodiments of the methods and uses provided herein, the cancer is related to the *KRAS* gene, for example a cancer associated with a mutation of the *KRAS* gene or dysregulation of the *KRAS* gene.

Mutation or dysregulation of K-Ras or *KRAS* may include mutation or dysregulation of human K-Ras4a and/or human K-Ras4b. In some embodiments, the cancer is related to the K-Ras (for example, human K-Ras4a and/or human K-Ras4b) signaling pathway activity, for example cancer related to aberrant K-Ras signaling pathway activity. In some embodiments, the cancer is related mutation or dysregulation of human K-Ras4b. In certain embodiments, the cancer is related to aberrant K-Ras4b signaling pathway activity. In some embodiments, the cancer is related mutation or dysregulation of human K-Ras4a. In certain embodiments, the cancer is related to aberrant K-Ras4a signaling pathway activity.

[0189] In some embodiments, the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer. Thus, in one aspect, provided herein is a method of treating cancer in a subject in need thereof, comprising administering to the subject a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer. In some embodiments, the cancer is breast cancer. In other embodiments, the cancer is pancreatic cancer. In still further embodiments, the cancer is colorectal cancer. In certain embodiments, the cancer is lung cancer. In some embodiments, the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, is co-administered with one or more chemotherapeutic agents to a subject in need thereof.

[0190] In another aspect, provided herein is a method of reducing the level of a K-Ras protein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a

pharmaceutically acceptable salt thereof. In still another aspect, provided herein is a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of a K-Ras protein in a subject in need thereof. In a further aspect, provided herein is the use of a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of a K-Ras protein in a subject in need thereof. In some embodiments of these aspects, the K-Ras protein is human K-Ras4a and/or human K-Ras4b. In certain embodiments, the K-Ras is human K-Ras4b. In certain embodiments, the K-Ras is human K-Ras4a. Reduction of the level of K-Ras may be evaluated, for example, by immunoblot of a biological sample using one or more specific anti-K-Ras antibodies, or by mass spectrometry-based methods.

[0191] In some embodiments, administering a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, to a subject may block one or more post-translational processing steps of a K-Ras precursor (such as K-Ras4a precursor or K-Ras4b precursor). This unprocessed precursor may then be degraded by the body, thus reducing the level of K-Ras protein. In some embodiments, the compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, covalently binds to the C185 amino acid residue of a K-Ras precursor (such as K-Ras4a precursor or K-Ras4b precursor) to block one or more post-translational modifications. In certain embodiments, the post-translational modification that is blocked is farnesylation.

[0192] In another aspect, provided herein is a method of reducing the activity of a K-Ras protein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A),

Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof. In still another aspect, provided herein is a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, for use in a method of reducing the activity of a K-Ras protein in a subject in need thereof. In a further aspect, provided herein is the use of a compound of Formula (X), Formula (X-I), Formula (X-A), Formula (X-A-i), Formula (X-B), Formula (X-C), Formula (X-C-i), Formula (I), Formula (I-A), Formula (I-A-i), Formula (I-B), Formula (I-B-i), Formula (I-C), or Formula (I-C-i), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the activity of a K-Ras protein in a subject in need thereof. In some embodiments of these aspects, the K-Ras protein is human K-Ras4a and/or human K-Ras4b. In certain embodiments, the K-Ras is human K-Ras4b. In certain embodiments, the K-Ras is human K-Ras4a.

[0193] In some embodiments, both the activity of K-Ras and the level of K-Ras are reduced in a subject in need thereof. In certain embodiments, the K-Ras is human K-Ras4b. In certain embodiments, the K-Ras is human K-Ras4a.

[0194] “Effective amount” or “therapeutically effective amount” refer to that amount of a compound of the disclosure that, when administered to a mammal, for example a human, is sufficient to effect treatment. The amount of a compound of the disclosure which constitutes a “therapeutically effective amount” may vary depending on the compound, the condition and its severity, the manner of administration, and the age of the mammal to be treated.

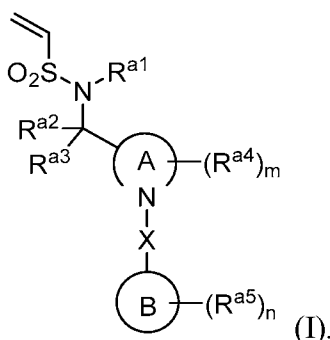
[0195] The terms “treat,” “treating,” or “treatment” refer to any indicia of success in the amelioration of an injury, disease, disorder, pathology, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, disease, disorder, pathology, or condition more tolerable to the subject; slowing or stopping the rate of degeneration, decline, or development; slowing the progression of injury, disease, disorder, pathology, or condition; making the final point of degeneration less debilitating; improving a subject’s physical or mental well-being; or relieving or causing regression of the injury, disease, disorder, pathology, or condition. The treatment of symptoms, including the amelioration of symptoms, can be based on objective or subjective parameters, which may include the results of a physical examination, a neuropsychiatric

exam, and/or a psychiatric evaluation. Certain methods disclosed herein may treat cancer by, for example, decreasing the incidence of cancer, causing remission of cancer, slowing the rate of growth of cancer cells, slowing the rate of spread of cancer cells, reducing metastasis, or reducing the growth of metastatic tumors, reducing the size of one or more tumors, reducing the number of one or more tumors, or any combinations thereof.

[0196] “Co-administer” includes administering a compound, salt thereof, or composition comprising any of these as described herein at the same time, just prior to, or just after the administration of one or more additional therapies, such as a chemotherapeutic agent. One or more compounds or salts thereof disclosed herein and one or more additional therapies may be co-administered as a single combination form, or may be co-administered as two or more separate forms simultaneously or sequentially.

ENUMERATED EMBODIMENTS

[0197] Embodiment I-1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$, wherein when A is piperidiny1 and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$;

each $\text{R}^{\text{a}6}$ is independently hydrogen, halo, alkyl, or haloalkyl;

$\text{R}^{\text{a}46}$ is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=\text{O}$;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, $=O$, $-SR^{a47}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or two to four R^{a4} , together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{a48}\text{R}^{a49}$, $-\text{NR}^{a11}\text{R}^{a12}$, $-\text{OR}^{a13}$, $-\text{SO}_2\text{R}^{a14}$, $=\text{O}$, and $-\text{SR}^{a15}$,

wherein each cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{a16}$, $=\text{O}$, $-\text{NR}^{a17}\text{R}^{a18}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{a50}\text{R}^{a51}$, $-\text{SR}^{a52}$, $-\text{SO}_2\text{R}^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{a19}$, $=\text{O}$, $-\text{NR}^{a20}\text{R}^{a21}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{a54}\text{R}^{a55}$, $-\text{SR}^{a56}$, $-\text{SO}_2\text{R}^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{a22}\text{R}^{a23}$, $-\text{OR}^{a24}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, $=\text{O}$, $-\text{NR}^{a36}\text{R}^{a37}$, $-\text{NR}^{a38}\text{C}(\text{O})\text{R}^{a39}$, $-\text{OR}^{a40}$, and R^{a59} , wherein each R^{a59} is

independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $=O$, $-NH_2$, $-SF_5$, $-OH$, $-O$ -alkyl, $-O$ -haloalkyl, halo, alkyl, and haloalkyl;

each R^{a22} , R^{a23} , R^{a24} , R^{a36} , R^{a37} , R^{a38} , R^{a39} , and R^{a40} is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

n is an integer from 0 to 11.

[0198] Embodiment I-2. The compound of Embodiment I-1, or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when A is piperidiny and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=O$;

R^{a1} is hydrogen, alkyl, or cycloalkyl, wherein when R^{a1} is alkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, $=O$,

$-\text{SR}^{\text{a}47}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each $\text{R}^{\text{a}7}$, $\text{R}^{\text{a}8}$, $\text{R}^{\text{a}9}$, $\text{R}^{\text{a}10}$, and $\text{R}^{\text{a}47}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

or two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

or $\text{R}^{\text{a}2}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or $\text{R}^{\text{a}3}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or $\text{R}^{\text{a}1}$ and $\text{R}^{\text{a}2}$, together with the atoms to which they are attached, form a heterocycloalkyl;

or $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl;

or, when X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, or $-\text{C}(\text{S})-$, $\text{R}^{\text{a}1}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a heterocycloalkyl;

each $\text{R}^{\text{a}5}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{\text{a}48}\text{R}^{\text{a}49}$, $-\text{NR}^{\text{a}11}\text{R}^{\text{a}12}$, $-\text{OR}^{\text{a}13}$, $-\text{SO}_2\text{R}^{\text{a}14}$, $=\text{O}$, and $-\text{SR}^{\text{a}15}$,

wherein each cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a}16}$, $=\text{O}$, $-\text{NR}^{\text{a}17}\text{R}^{\text{a}18}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a}50}\text{R}^{\text{a}51}$, $-\text{SR}^{\text{a}52}$, $-\text{SO}_2\text{R}^{\text{a}53}$, and $\text{R}^{\text{a}35}$, wherein each $\text{R}^{\text{a}35}$ is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{SF}_5$, and $\text{R}^{\text{a}35}$, wherein $\text{R}^{\text{a}35}$ is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a}19}$, $=\text{O}$, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a}54}\text{R}^{\text{a}55}$, $-\text{SR}^{\text{a}56}$, $-\text{SO}_2\text{R}^{\text{a}57}$, and $\text{R}^{\text{a}58}$, wherein each $\text{R}^{\text{a}58}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each $\text{R}^{\text{a}14}$, $\text{R}^{\text{a}15}$, $\text{R}^{\text{a}16}$, $\text{R}^{\text{a}17}$, $\text{R}^{\text{a}18}$, $\text{R}^{\text{a}48}$, $\text{R}^{\text{a}49}$, $\text{R}^{\text{a}50}$, $\text{R}^{\text{a}51}$, $\text{R}^{\text{a}52}$, $\text{R}^{\text{a}53}$, $\text{R}^{\text{a}54}$, $\text{R}^{\text{a}55}$, $\text{R}^{\text{a}56}$, and $\text{R}^{\text{a}57}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

each $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, and $\text{R}^{\text{a}21}$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

each $\text{R}^{\text{a}13}$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or alkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}13}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, $\text{R}^{\text{a}21}$, and $\text{R}^{\text{a}35}$, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}58}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, $-\text{OR}^{\text{a}24}$, and $-\text{SF}_5$;

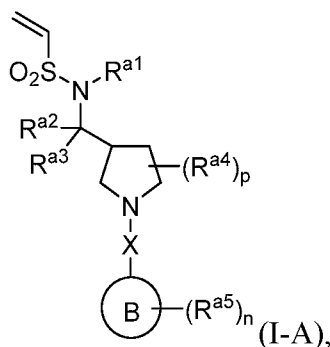
wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, $=\text{O}$, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, $-\text{NR}^{\text{a}38}\text{C}(\text{O})\text{R}^{\text{a}39}$, $-\text{OR}^{\text{a}40}$, and $\text{R}^{\text{a}59}$, wherein each $\text{R}^{\text{a}59}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each $\text{R}^{\text{a}59}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $=\text{O}$, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl

each $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, $\text{R}^{\text{a}24}$, $\text{R}^{\text{a}36}$, $\text{R}^{\text{a}37}$, $\text{R}^{\text{a}38}$, $\text{R}^{\text{a}39}$, and $\text{R}^{\text{a}40}$ is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

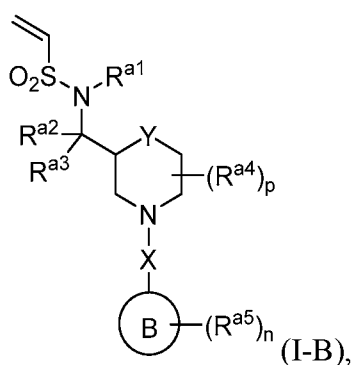
n is an integer from 0 to 11.

[0199] Embodiment I-3. The compound of Embodiment I-1 or I-2, wherein the compound is of Formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, and n are as defined for Formula (I).

[0200] Embodiment I-4. The compound of Embodiment I-1 or I-2, wherein the compound is of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, $-\text{S}(\text{O})_r-$, $-\text{O}-$, or $-\text{N}(\text{R}^{\text{a45}})-$, wherein each R^{a45} is independently hydrogen or R^{a4};

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$, wherein when Y is $-\text{CH}_2-$ and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

and B, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a46}, and n are as defined for Formula (I).

[0201] Embodiment I-5. The compound of Embodiment I-4, or a pharmaceutically acceptable salt thereof, wherein Y is $-\text{CH}_2-$.

[0202] Embodiment I-6. The compound of Embodiment I-1 or I-2, or a pharmaceutically acceptable salt thereof, wherein A is 5- or 6-membered heterocycloalkyl.

[0203] Embodiment I-7. The compound of any one of Embodiments I-1 to I-6, or a pharmaceutically acceptable salt thereof, wherein B is heteroaryl, cycloalkyl, or heterocycloalkyl.

[0204] Embodiment I-8. The compound of any one of Embodiments I-1 to I-7, or a pharmaceutically acceptable salt thereof, wherein B is 5- or 6-membered heterocycloalkyl or 5- or 6-membered heteroaryl, and wherein the heterocycloalkyl or heteroaryl comprises one to three ring heteroatoms independently selected from the group consisting of O, N, and S.

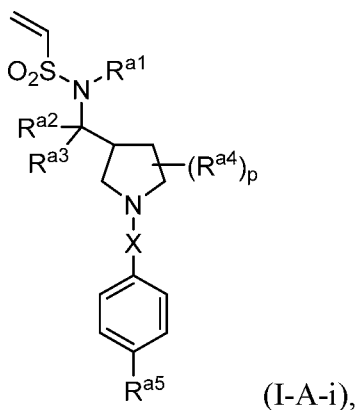
[0205] Embodiment I-9. The compound of any one of Embodiments I-1 to I-7, or a pharmaceutically acceptable salt thereof, wherein B is 9- or 10-membered bicyclic heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S.

[0206] Embodiment I-10. The compound of any one of Embodiments I-1 to I-6, or a pharmaceutically acceptable salt thereof, wherein B is $(\text{C}_9\text{-C}_{10})$ bicyclic aryl.

[0207] Embodiment I-11. The compound of any one of Embodiments I-1 to I-7, or a pharmaceutically acceptable salt thereof, wherein B is $(\text{C}_5\text{-C}_{10})$ cycloalkyl.

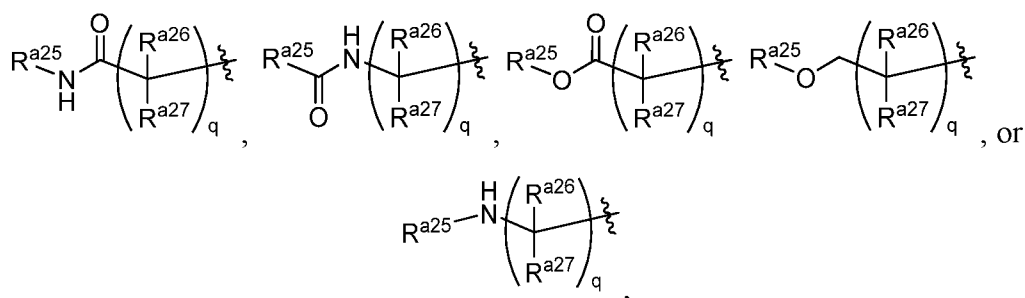
[0208] Embodiment I-12. The compound of any one of Embodiments I-1 to I-11, or a pharmaceutically acceptable salt thereof, wherein one or more R^{a5} are independently selected from the group consisting of halo; $-\text{O}-(\text{C}_1\text{-C}_4)$ alkyl unsubstituted or substituted with one or more fluoro or chloro; phenyl; heteroaryl; heterocycloalkyl; $-\text{SO}_2\text{NH}_2$; $-\text{NO}_2$; $-\text{CN}$; $(\text{C}_3\text{-C}_6)$ cycloalkyl unsubstituted or substituted with one or more fluoro or chloro; and $(\text{C}_1\text{-C}_6)$ alkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of $(\text{C}_3\text{-C}_6)$ cycloalkyl, $(\text{C}_3\text{-C}_6)$ heterocycloalkyl, aryl, heteroaryl, halo, $-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_4)$ alkyl, $=\text{O}$, $-\text{NR}^{\text{a20}}\text{R}^{\text{a21}}$, and $-\text{CN}$.

[0209] Embodiment I-13. The compound of any one of Embodiments I-1 to I-3, or I-6 to I-12, wherein the compound is of Formula (I-A-i):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7.

[0210] Embodiment I-14. The compound of any one of Embodiments I-1 to I-13, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{a5} is:



wherein:

R^{a25} is hydrogen, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

wherein the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl is

unsubstituted or substituted with one or more substituents

independently selected from the group consisting of halo, alkyl,

cycloalkyl, aryl, heteroaryl, heterocycloalkyl, =O, -OR^{a28}, -SF₅, and

-NR^{a29}R^{a30},

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is

independently unsubstituted or substituted with one or more

substituents independently selected from the group consisting

of alkyl, haloalkyl, alkynyl, halo, -SF₅, =O, -OR^{a31},

-NR^{a41}R^{a42}, -NR^{a43}C(O)R^{a44}, cycloalkyl, and heterocycloalkyl,

wherein each cycloalkyl and heterocycloalkyl is independently

unsubstituted or substituted with one or more substituents
independently selected from the group consisting of =O, halo,
–OH, and –SF₅;

each R^{a26} and R^{a27} is independently hydrogen, halo, or alkyl;

wherein each alkyl is independently unsubstituted or substituted with one or
more substituents independently selected from the group consisting of
halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, –OR^{a32}, and
–NR^{a33}R^{a34},

wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is
independently unsubstituted or substituted with one or more
substituents independently selected from the group consisting
of halo, haloalkyl, alkyl, –OH, =O, and –SF₅;

or one R^{a26} and one R^{a27} attached to the same atom, together with the atom to which
they are attached, form a cycloalkyl or heterocycloalkyl, wherein the
cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more
halo;

each R^{a28}, R^{a29}, R^{a30}, R^{a31}, R^{a32}, R^{a33}, R^{a34}, R^{a41}, R^{a42}, R^{a43}, and R^{a44} is independently
hydrogen, alkyl, or haloalkyl;

and q is 1 or 2.

[0211] Embodiment I-15. The compound of Embodiment I-14, or a pharmaceutically
acceptable salt thereof, wherein q is 1 and R^{a26} is hydrogen.

[0212] Embodiment I-16. The compound of any one of Embodiments I-1 to I-15, or a
pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is heteroaryl or
heterocycloalkyl, wherein the heteroaryl or heterocycloalkyl is unsubstituted or substituted
with one or more substituents independently selected from the group consisting of =O, –SF₅,
and R^{a35}.

[0213] Embodiment I-17. The compound of Embodiment I-14, or a pharmaceutically
acceptable salt thereof, wherein R^{a35} is alkyl substituted with aryl or heteroaryl, wherein the
aryl or heteroaryl is unsubstituted or substituted with haloalkyl or –SF₅.

[0214] Embodiment I-18. The compound of any one of Embodiments I-1 to I-17, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and R^{a3} , together with the atom to which they are attached, form a (C₃-C₅)cycloalkyl or a 3- to 5-membered heterocycloalkyl.

[0215] Embodiment I-19. The compound of any one of Embodiments I-1 to I-17, or a pharmaceutically acceptable salt thereof, wherein X is $-S(O)_2-$, and R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a 3- to 6-membered heterocycloalkyl.

[0216] Embodiment I-20. The compound of any one of Embodiments I-1 to I-17, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a (C₃-C₆)cycloalkyl or a 3- to 6-membered heterocycloalkyl.

[0217] Embodiment I-21. The compound of any one of Embodiments I-1 to I-17, or I-19, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and R^{a3} are each hydrogen.

[0218] Embodiment I-22. The compound of any one of Embodiments I-1 to I-21, or a pharmaceutically acceptable salt thereof, wherein X is $-S(O)_2-$.

[0219] Embodiment I-23. The compound of any one of Embodiments I-1 to I-18, I-20, or I-21, or a pharmaceutically acceptable salt thereof, wherein X is $-C(O)-$.

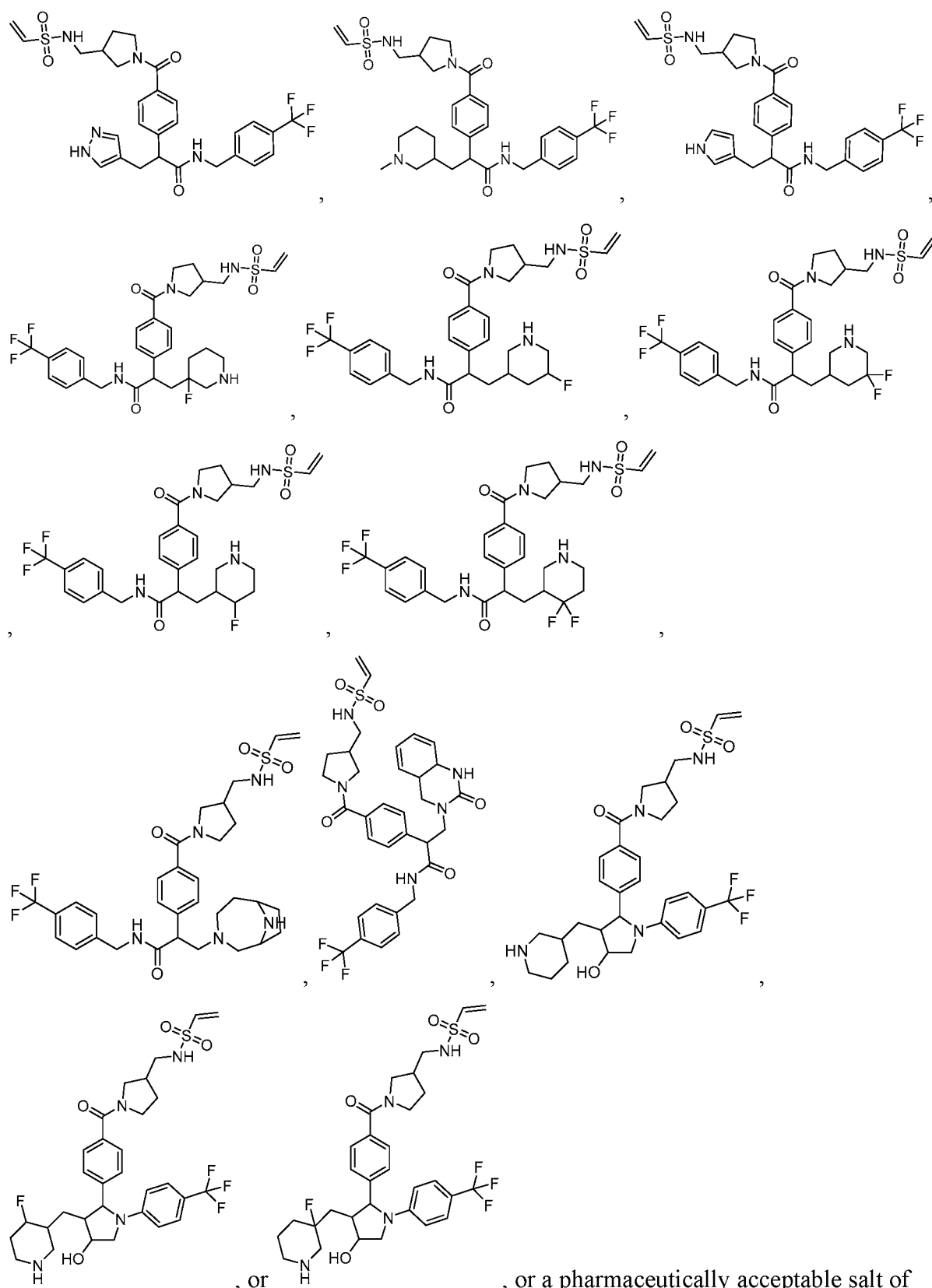
[0220] Embodiment I-24. The compound of any one of Embodiments I-1 to I-18, I-20, or I-21, or a pharmaceutically acceptable salt thereof, wherein X is $-CH_2-$.

[0221] Embodiment I-25. The compound of any one of Embodiments I-1 to I-12 or I-14 to I-24, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

[0222] Embodiment I-26. The compound of any one of Embodiments I-1, I-2, I-6 to I-12, or I-14 to I-25, or a pharmaceutically acceptable salt thereof, wherein m is 0.

[0223] Embodiment I-27. The compound of any one of Embodiments I-3 to I-5, or I-7 to I-26, or a pharmaceutically acceptable salt thereof, wherein p is 0.

[0224] Embodiment I-28. The compound of any one of Embodiments I-1 to I-6, I-12, or I-14 to I-26, or a pharmaceutically acceptable salt thereof, wherein B is phenyl and n is an integer from 0 to 5.



any of the foregoing.

[0227] Embodiment I-31. A pharmaceutical composition comprising a compound according to any one of Embodiments I-1 to I-30, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0228] Embodiment I-32. A method of reducing the level of a K-Ras protein in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of Embodiments I-1 to I-30, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0229] Embodiment I-33. The method of Embodiment I-32, wherein the K-Ras protein is human K-Ras4b.

[0230] Embodiment I-34. A method of treating a disorder in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of Embodiments I-1 to I-30, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0231] Embodiment I-35. The method of Embodiment I-34, wherein the disorder is cancer.

[0232] Embodiment I-36. The method of Embodiment I-35, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.

[0233] Embodiment I-37. The method of Embodiment I-34, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.

[0234] Embodiment I-38. The method of any one of Embodiments I-34 to I-37, wherein the disorder is associated with a mutation of K-Ras.

[0235] Embodiment I-39. Use of a compound of any one of Embodiments I-1 to I-30, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of a K-Ras protein in a subject in need thereof.

[0236] Embodiment I-40. The use of Embodiment I-39, wherein the K-Ras protein is human K-Ras4b.

[0237] Embodiment I-41. Use of a compound of any one of Embodiments I-1 to I-30, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

[0238] Embodiment I-42. The use of Embodiment I-41, wherein the disorder is cancer.

[0239] Embodiment I-43. The use of Embodiment I-42, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.

[0240] Embodiment I-44. The use of Embodiment I-41, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.

[0241] Embodiment I-45. The use of any one of Embodiments I-41 to I-44, wherein the disorder is associated with a mutation of K-Ras.

[0242] Embodiment I-46. A compound according to any one of Embodiments I-1 to I-30, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of a K-Ras protein in a subject in need thereof.

[0243] Embodiment I-47. The compound for use of Embodiment I-46, wherein the K-Ras protein is human K-Ras4b.

[0244] Embodiment I-48. A compound according to any one of Embodiments I-1 to I-30, or a pharmaceutically acceptable salt thereof, for use in a method of treating a disorder in a subject in need thereof.

[0245] Embodiment I-49. The compound for use in Embodiment I-48, wherein the disorder is cancer.

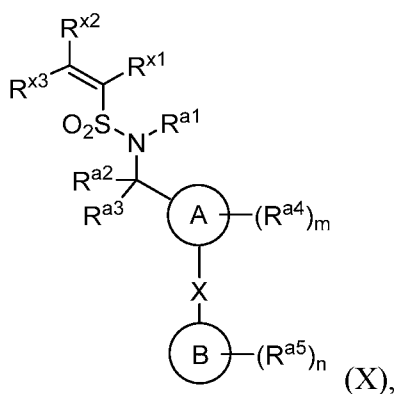
[0246] Embodiment I-50. The compound for use of Embodiment I-49, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma,

rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.

[0247] Embodiment I-51. The compound for use of Embodiment I-48, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.

[0248] Embodiment I-52. The compound for use of any one of Embodiments I-48 to I-51, wherein the disorder is associated with a mutation of K-Ras.

[0249] Embodiment II-1. A compound of Formula (X):



or a pharmaceutically acceptable salt thereof, wherein:

R^{x1} , R^{x2} , and R^{x3} are independently hydrogen, -CN, or alkyl; or R^{x2} and R^{x3} together form alkenyl; or R^{x1} and R^{x2} together with the carbon atoms to which they are attached form heteroaryl, heterocycloalkenyl, or cycloalkenyl; or R^{a1} and R^{x2} together with the atoms to which they are attached form heterocycloalkenyl; wherein each alkyl, alkenyl, heteroaryl, heterocycloalkenyl, and cycloalkenyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo and $-OR^{x4}$, wherein each R^{x4} is independently H, alkyl, or haloalkyl;

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$, wherein when A is piperidiny1 and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=\text{O}$;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{O})-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a7}}\text{R}^{\text{a8}}$, $-\text{OR}^{\text{a9}}$, and $-\text{SO}_2\text{R}^{\text{a10}}$, wherein when A is phenyl, R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a7}}\text{R}^{\text{a8}}$, $-\text{OR}^{\text{a9}}$, and $-\text{SO}_2\text{R}^{\text{a10}}$; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a7}}\text{R}^{\text{a8}}$, $-\text{OR}^{\text{a9}}$, $=\text{O}$, $-\text{SR}^{\text{a47}}$, and $-\text{SO}_2\text{R}^{\text{a10}}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or, when X is $-C(O)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a spirocycle with ring A, wherein the spirocycle is unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-NO_2$, $-CN$, $-SO_2NR^{a48}R^{a49}$, $-NR^{a11}R^{a12}$, $-OR^{a13}$, $-SO_2R^{a14}$, $=O$, and $-SR^{a15}$,

wherein each alkenyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a19}$, $=O$, $-NR^{a20}R^{a21}$, $-CN$, $-SF_5$, $-SO_2NR^{a54}R^{a55}$, $-SR^{a56}$, $-SO_2R^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a35} , R^{a54} , and R^{a55} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo,

=O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -OR^{a24}, and -SF₅;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, -CN, -SF₅, =O, -NR^{a36}R^{a37}, -NR^{a38}C(O)R^{a39}, -OR^{a40}, and R^{a59}, wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, -NH₂, -SF₅, -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl;

each R^{a22}, R^{a23}, R^{a24}, R^{a36}, R^{a37}, R^{a38}, and R^{a39} is independently hydrogen, alkyl, or haloalkyl;

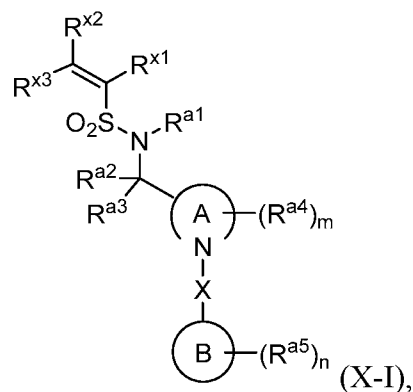
wherein each alkyl or haloalkyl or R^{a22} and R^{a23} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl;

each R^{a40} is independently hydrogen, alkyl, haloalkyl, aryl, or heteroaryl, wherein each aryl or heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl;

m is an integer from 0 to 13; and

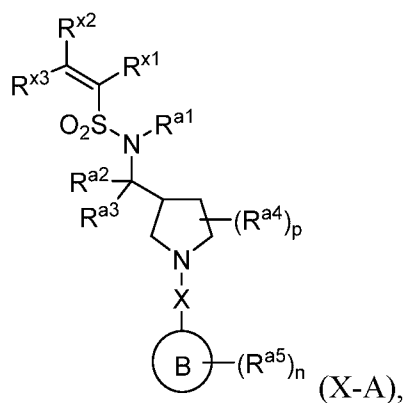
n is an integer from 0 to 11.

[0250] Embodiment II-2. The compound of Embodiment II-1, wherein the compound is of Formula (X-I):



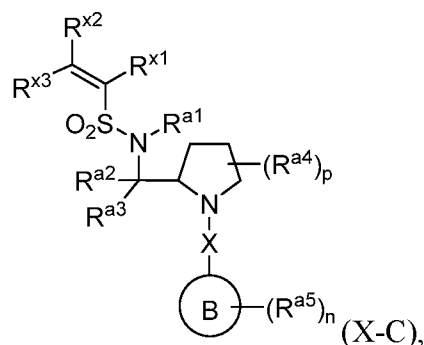
or a pharmaceutically acceptable salt thereof, wherein A is 4- to 10-membered heterocycloalkyl, and B, X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, m, and n are as defined for Formula (X).

[0251] Embodiment II-3. The compound of Embodiment II-1 or II-2, wherein the compound is of Formula (X-A):



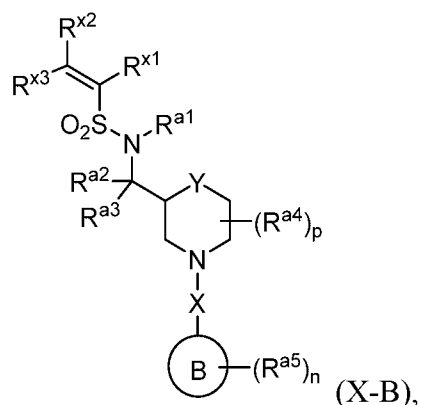
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, and n are as defined for Formula (X).

[0252] Embodiment II-4. The compound of Embodiment II-1 or II-2, wherein the compound is of Formula (X-C):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , and n are as defined for Formula (X).

[0253] Embodiment II-5. The compound of Embodiment II-1 or II-2, wherein the compound is of Formula (X-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-C(R^{a45})_2-$, $-S(O)_r-$, $-O-$, or $-N(R^{a45})-$, wherein each R^{a45} is independently hydrogen or R^{a4} ;

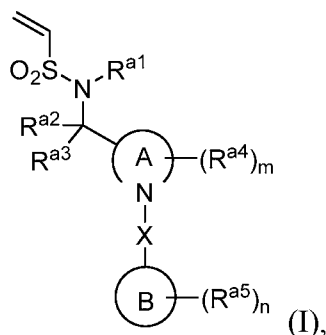
X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when Y is $-CH_2-$ and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

and B, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} , R^{a46} , and n are as defined for Formula (X).

[0254] Embodiment II-6. The compound of Embodiment II-1, wherein the compound is of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$, wherein when A is piperidiny and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$;

each $\text{R}^{\text{a}6}$ is independently hydrogen, halo, alkyl, or haloalkyl;

$\text{R}^{\text{a}46}$ is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=\text{O}$;

$\text{R}^{\text{a}1}$ is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when $\text{R}^{\text{a}1}$ is alkyl or haloalkyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{O})-$;

$\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each $\text{R}^{\text{a}4}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, $=\text{O}$, $-\text{SR}^{\text{a}47}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or two to four R^{a4} , together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-NO_2$, $-CN$, $-SO_2NR^{a48}R^{a49}$, $-NR^{a11}R^{a12}$, $-OR^{a13}$, $-SO_2R^{a14}$, $=O$, and $-SR^{a15}$,

wherein each cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a}19}$, $=\text{O}$, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a}54}\text{R}^{\text{a}55}$, $-\text{SR}^{\text{a}56}$, $-\text{SO}_2\text{R}^{\text{a}57}$, and $\text{R}^{\text{a}58}$, wherein each $\text{R}^{\text{a}58}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}13}$, $\text{R}^{\text{a}14}$, $\text{R}^{\text{a}15}$, $\text{R}^{\text{a}16}$, $\text{R}^{\text{a}17}$, $\text{R}^{\text{a}18}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, $\text{R}^{\text{a}21}$, $\text{R}^{\text{a}48}$, $\text{R}^{\text{a}49}$, $\text{R}^{\text{a}50}$, $\text{R}^{\text{a}51}$, $\text{R}^{\text{a}52}$, $\text{R}^{\text{a}53}$, $\text{R}^{\text{a}54}$, $\text{R}^{\text{a}55}$, $\text{R}^{\text{a}56}$, and $\text{R}^{\text{a}57}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}13}$, $\text{R}^{\text{a}16}$, $\text{R}^{\text{a}17}$, $\text{R}^{\text{a}18}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, $\text{R}^{\text{a}21}$, and $\text{R}^{\text{a}35}$, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}58}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, $-\text{OR}^{\text{a}24}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, $=\text{O}$, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, $-\text{NR}^{\text{a}38}\text{C}(\text{O})\text{R}^{\text{a}39}$, $-\text{OR}^{\text{a}40}$, and $\text{R}^{\text{a}59}$, wherein each $\text{R}^{\text{a}59}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each $\text{R}^{\text{a}59}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $=\text{O}$, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

each $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, $\text{R}^{\text{a}24}$, $\text{R}^{\text{a}36}$, $\text{R}^{\text{a}37}$, $\text{R}^{\text{a}38}$, $\text{R}^{\text{a}39}$, and $\text{R}^{\text{a}40}$ is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

n is an integer from 0 to 11.

[0255] Embodiment II-7. The compound of Embodiment II-6, or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$, wherein when A is piperidiny1 and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$;

each $\text{R}^{\text{a}6}$ is independently hydrogen, halo, alkyl, or haloalkyl;

$\text{R}^{\text{a}6}$ is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=\text{O}$;

$\text{R}^{\text{a}1}$ is hydrogen, alkyl, or cycloalkyl, wherein when $\text{R}^{\text{a}1}$ is alkyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{O})-$;

$\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each $\text{R}^{\text{a}4}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, $=\text{O}$, $-\text{SR}^{\text{a}47}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each $\text{R}^{\text{a}7}$, $\text{R}^{\text{a}8}$, $\text{R}^{\text{a}9}$, $\text{R}^{\text{a}10}$, and $\text{R}^{\text{a}47}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

or two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

or $\text{R}^{\text{a}2}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or $\text{R}^{\text{a}3}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl;

or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl;

each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-NO_2$, $-CN$, $-SO_2NR^{a48}R^{a49}$, $-NR^{a11}R^{a12}$, $-OR^{a13}$, $-SO_2R^{a14}$, $=O$, and $-SR^{a15}$,

wherein each cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-SF_5$, and R^{a35} , wherein R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a19}$, $=O$, $-NR^{a20}R^{a21}$, $-CN$, $-SF_5$, $-SO_2NR^{a54}R^{a55}$, $-SR^{a56}$, $-SO_2R^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

each R^{a11} , R^{a12} , R^{a19} , R^{a20} , and R^{a21} is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

each R^{a13} is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or alkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-NR^{a22}R^{a23}$, $-OR^{a24}$, and $-SF_5$;

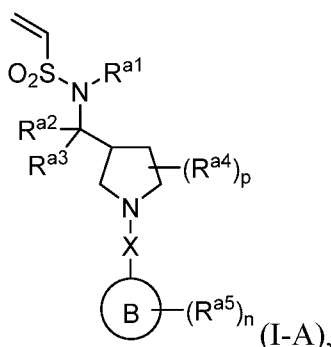
wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, -CN, $-SF_5$, =O, $-NR^{a36}R^{a37}$, $-NR^{a38}C(O)R^{a39}$, $-OR^{a40}$, and R^{a59} , wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, $-NH_2$, $-SF_5$, -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl

each R^{a22} , R^{a23} , R^{a24} , R^{a36} , R^{a37} , R^{a38} , R^{a39} , and R^{a40} is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

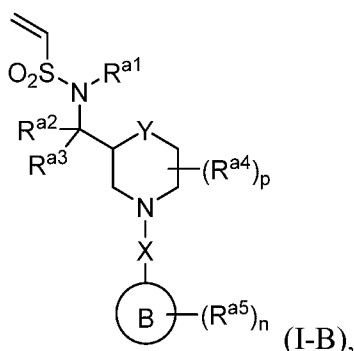
n is an integer from 0 to 11.

[0256] Embodiment II-8. The compound of Embodiment II-6 or II-7, wherein the compound is of Formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, and n are as defined for Formula (I).

[0257] Embodiment II-9. The compound of Embodiment II-6 or II-7, wherein the compound is of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{C}(\text{R}^{\text{a45}})_2-$, $-\text{S}(\text{O})_r-$, $-\text{O}-$, or $-\text{N}(\text{R}^{\text{a45}})-$, wherein each R^{a45} is independently hydrogen or R^{a4},

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$, wherein when Y is $-\text{CH}_2-$ and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a46}}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a6}})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

and B, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a46}, and n are as defined for Formula (I).

[0258] Embodiment II-10. The compound of Embodiment II-5 or II-9, or a pharmaceutically acceptable salt thereof, wherein Y is $-\text{CH}_2-$.

[0259] Embodiment II-11. The compound of any one of Embodiments II-1, II-2, II-6, or II-7, or a pharmaceutically acceptable salt thereof, wherein A is 5- or 6-membered heterocycloalkyl.

[0260] Embodiment II-12. The compound of Embodiment II-1, or a pharmaceutically acceptable salt thereof, wherein A is 5- or 6-membered heteroaryl.

[0261] Embodiment II-13. The compound of any one of Embodiments II-1 to II-12, or a pharmaceutically acceptable salt thereof, wherein B is heteroaryl, cycloalkyl, or heterocycloalkyl.

[0262] Embodiment II-14. The compound of any one of Embodiments II-1 to II-13, or a pharmaceutically acceptable salt thereof, wherein B is 5- or 6-membered heterocycloalkyl or 5- or 6-membered heteroaryl, and wherein the heterocycloalkyl or heteroaryl comprises one to three ring heteroatoms independently selected from the group consisting of O, N, and S.

[0263] Embodiment II-15. The compound of any one of Embodiments II-1 to II-13, or a pharmaceutically acceptable salt thereof, wherein B is 9- or 10-membered bicyclic heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S.

[0264] Embodiment II-16. The compound of any one of Embodiments II-1 to II-12, or a pharmaceutically acceptable salt thereof, wherein B is (C₉-C₁₀)bicyclic aryl.

[0265] Embodiment II-17. The compound of any one of Embodiments II-1 to II-13, or a pharmaceutically acceptable salt thereof, wherein B is (C₅-C₁₀)cycloalkyl.

[0266] Embodiment II-18. The compound of any one of Embodiments II-1 to II-12, or a pharmaceutically acceptable salt thereof, wherein B is phenyl.

[0267] Embodiment II-19. The compound of any one of Embodiments II-1 to II-18, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is:

unsubstituted or substituted alkyl, wherein the alkyl is branched;

-NR^{a11}R^{a12}, wherein at least one of R^{a11} and R^{a12} is not hydrogen; or

(C₁-C₂)alkyl substituted with one or more substituents independently selected from the group consisting of =O, -NR^{a20}R^{a21}, and R^{a58}, wherein R^{a58} is heterocycloalkyl and at least one of R^{a20} and R^{a21} is not hydrogen.

[0268] Embodiment II-20. The compound of Embodiment II-19, or a pharmaceutically acceptable salt thereof, wherein both R^{a11} and R^{a12} are not hydrogen.

[0269] Embodiment II-21. The compound of Embodiment II-19 or II-20, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{a11} and R^{a12} is substituted alkyl.

[0270] Embodiment II-22. The compound of any one of Embodiments II-19 to II-21, or a pharmaceutically acceptable salt thereof, wherein R^{a11} is alkyl substituted with aryl, wherein the aryl is unsubstituted or substituted.

[0271] Embodiment II-23. The compound of any one of Embodiments II-19 to II-22, or a pharmaceutically acceptable salt thereof, wherein R^{a12} is alkyl substituted with one or more substituents independently selected from the group consisting of $=O$, $-NR^{a22}R^{a23}$, $-OR^{a24}$, and heterocycloalkyl, wherein the heterocycloalkyl is independently unsubstituted or substituted.

[0272] Embodiment II-24. The compound of Embodiment II-19, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is C_1 -alkyl substituted with $-NR^{a20}R^{a21}$, wherein at least one of R^{a20} and R^{a21} is not hydrogen.

[0273] Embodiment II-25. The compound of Embodiment II-19, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is C_2 -alkyl substituted with $=O$ and $-NR^{a20}R^{a21}$, wherein at least one of R^{a20} and R^{a21} is not hydrogen.

[0274] Embodiment II-26. The compound of Embodiment II-19, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is substituted alkyl, wherein the alkyl is isopropyl, wherein the isopropyl is substituted with two or more substituents independently selected from the group consisting of $=O$, $-NR^{a20}R^{a21}$, $-OR^{a19}$, and R^{a58} ,

wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkynyl, $-CN$, and $=O$, and wherein each alkyl is independently unsubstituted or substituted with one or more halo.

[0275] Embodiment II-27. The compound of any one of Embodiments II-19 or II-24 to II-26, or a pharmaceutically acceptable salt thereof, wherein R^{a20} and R^{a21} are independently selected from the group consisting of:

hydrogen;

unsubstituted or substituted cycloalkyl;

unsubstituted or substituted heterocycloalkyl; and

alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=O$, $-NR^{a22}R^{a23}$,

$-\text{OR}^{\text{a}24}$, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl; wherein each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, haloalkyl, and $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$; and

wherein at least one of $\text{R}^{\text{a}20}$ and $\text{R}^{\text{a}21}$ is not hydrogen.

[0276] Embodiment II-28. The compound of Embodiment II-27, or a pharmaceutically acceptable salt thereof, wherein both $\text{R}^{\text{a}20}$ and $\text{R}^{\text{a}21}$ are not hydrogen.

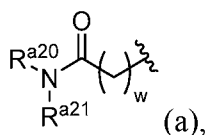
[0277] Embodiment II-29. The compound of any one of Embodiments II-1 to II-18, or a pharmaceutically acceptable salt thereof, wherein one or more $\text{R}^{\text{a}5}$ is $-\text{NR}^{\text{a}11}\text{R}^{\text{a}12}$, wherein:

$\text{R}^{\text{a}11}$ is C_1 -alkyl substituted with aryl, heteroaryl, cycloalkyl, or heterocycloalkyl; and

$\text{R}^{\text{a}12}$ is hydrogen or alkyl, wherein the alkyl is substituted with one or more substituents independently selected from the group consisting of $=\text{O}$, aryl, heteroaryl, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, and $-\text{OR}^{\text{a}24}$.

wherein each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, and haloalkyl.

[0278] Embodiment II-30. The compound of any one of Embodiments II-1 to II-18, or a pharmaceutically acceptable salt thereof, wherein one or more $\text{R}^{\text{a}5}$ is a substituted alkyl of formula (a):



wherein:

w is 0 or 1;

$\text{R}^{\text{a}20}$ and $\text{R}^{\text{a}21}$ are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl,

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents

independently selected from the group consisting of halo, =O, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, $-\text{OR}^{\text{a}24}$, alkyl, aryl, and heteroaryl;

wherein each alkyl is independently unsubstituted or substituted with one or more halo; and each aryl and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, and haloalkyl.

[0279] Embodiment II-31. The compound of any one of Embodiments II-1 to II-18, or a pharmaceutically acceptable salt thereof, wherein one or more $\text{R}^{\text{a}5}$ is alkyl, wherein the alkyl is isopropyl, wherein each terminal methyl of the isopropyl is independently substituted with one or more substituents independently selected from the group consisting of =O, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, $-\text{OR}^{\text{a}19}$, and $\text{R}^{\text{a}58}$;

wherein each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl of $\text{R}^{\text{a}58}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, $-\text{CN}$, alkynyl, halo, and alkyl, and wherein each alkyl is independently unsubstituted or substituted with one or more halo.

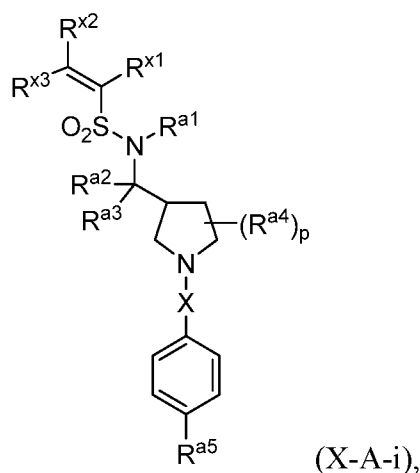
[0280] Embodiment II-32. The compound of Embodiment II-31, or a pharmaceutically acceptable salt thereof, wherein one terminal methyl of the isopropyl is substituted with phenyl, wherein the phenyl is unsubstituted or substituted with one to three substituents independently selected from the group consisting of halo and haloalkyl.

[0281] Embodiment II-33. The compound of Embodiment II-31 or II-32, or a pharmaceutically acceptable salt thereof, wherein one terminal methyl of the isopropyl is substituted with =O and $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$ or =O and $\text{R}^{\text{a}58}$, wherein $\text{R}^{\text{a}58}$ is heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted.

[0282] Embodiment II-34. The compound of any one of Embodiments II-1 to II-18, or a pharmaceutically acceptable salt thereof, wherein one or more $\text{R}^{\text{a}5}$ are independently selected from the group consisting of halo; $-\text{O}-(\text{C}_1\text{-C}_4)\text{alkyl}$ unsubstituted or substituted with one or more fluoro or chloro; phenyl; heteroaryl; heterocycloalkyl; $-\text{SO}_2\text{NH}_2$; $-\text{NO}_2$; $-\text{CN}$; $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ unsubstituted or substituted with one or more fluoro or chloro; and $(\text{C}_1\text{-C}_6)\text{alkyl}$ unsubstituted or substituted with one or more substituents independently selected from the group consisting of $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_6)\text{heterocycloalkyl}$, aryl, heteroaryl,

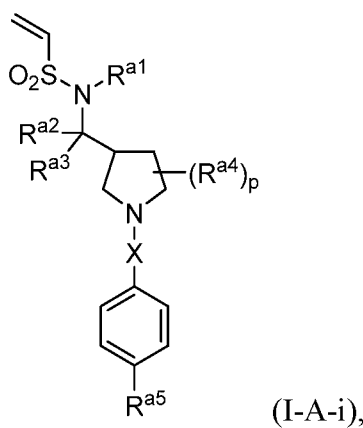
halo, $-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_4)\text{alkyl}$, $=\text{O}$,
 $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, and $-\text{CN}$.

[0283] Embodiment II-35. The compound of any one of Embodiments II-1 to II-3 or II-19 to II-34, wherein the compound is of Formula (X-A-i):



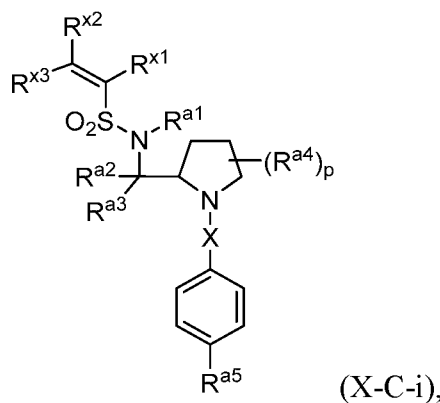
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X , $R^{\text{x}1}$, $R^{\text{x}2}$, $R^{\text{x}3}$, $R^{\text{a}1}$, $R^{\text{a}2}$, $R^{\text{a}3}$, $R^{\text{a}4}$, and $R^{\text{a}5}$ are as defined in Formula (X).

[0284] Embodiment II-36. The compound of any one of Embodiments II-6 to II-8 or II-19 to II-34, wherein the compound is of Formula (I-A-i):



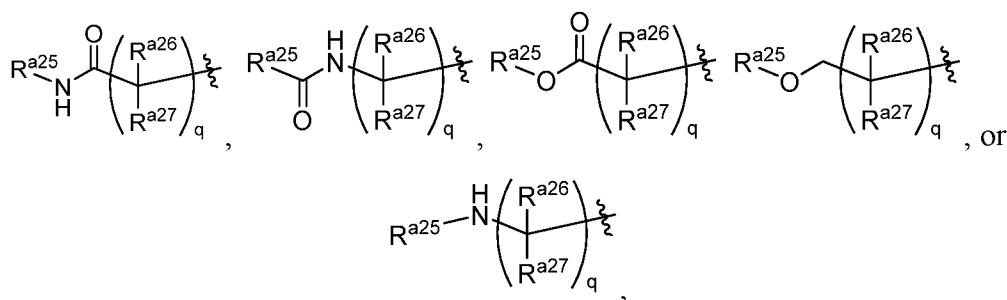
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7.

[0285] Embodiment II-37. The compound of any one of Embodiments II-1, II-2, II-4, or II-19 to II-34, wherein the compound is of Formula (X-C-i):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X , R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are as defined in Formula (X).

[0286] Embodiment II-38. The compound of any one of Embodiments II-1 to II-18 or II-34 to II-37, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{a5} is:



wherein:

R^{a25} is hydrogen, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

wherein the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, $=O$, $-OR^{a28}$, $-SF_5$, and $-NR^{a29}R^{a30}$,

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-SF_5$, $=O$, $-OR^{a31}$, $-NR^{a41}R^{a42}$, $-NR^{a43}C(O)R^{a44}$, cycloalkyl, and heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents

independently selected from the group consisting of =O, halo, –OH, and –SF₅;

each R^{a26} and R^{a27} is independently hydrogen, halo, or alkyl;

wherein each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, –OR^{a32}, and –NR^{a33}R^{a34},

wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, haloalkyl, alkyl, –OH, =O, and –SF₅;

or one R^{a26} and one R^{a27} attached to the same atom, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

each R^{a28}, R^{a29}, R^{a30}, R^{a31}, R^{a32}, R^{a33}, R^{a34}, R^{a41}, R^{a42}, R^{a43}, and R^{a44} is independently hydrogen, alkyl, or haloalkyl;

and q is 1 or 2.

[0287] Embodiment II-39. The compound of Embodiment II-38, or a pharmaceutically acceptable salt thereof, wherein q is 1 and R^{a26} is hydrogen.

[0288] Embodiment II-40. The compound of any one of Embodiments II-1 to II-18 or II-34 to II-39, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is heteroaryl or heterocycloalkyl, wherein the heteroaryl or heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, –SF₅, and R^{a35}.

[0289] Embodiment II-41. The compound of Embodiment II-40, or a pharmaceutically acceptable salt thereof, wherein R^{a35} is alkyl substituted with aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted with haloalkyl or –SF₅.

[0290] Embodiment II-42. The compound of any one of Embodiments II-1 to II-41, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and R^{a3} , together with the atom to which they are attached, form a (C₃-C₅)cycloalkyl or a 3- to 5-membered heterocycloalkyl.

[0291] Embodiment II-43. The compound of any one of Embodiments II-1 to II-41, or a pharmaceutically acceptable salt thereof, wherein X is $-S(O)_2-$, and R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a 3- to 6-membered heterocycloalkyl.

[0292] Embodiment II-44. The compound of any one of Embodiments II-1 to II-41, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a (C₃-C₆)cycloalkyl or a 3- to 6-membered heterocycloalkyl.

[0293] Embodiment II-45. The compound of any one of Embodiments II-1 to II-41, or II-43, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and R^{a3} are each hydrogen.

[0294] Embodiment II-46. The compound of any one of Embodiments II-1 to II-42, II-44, or II-45, or a pharmaceutically acceptable salt thereof, wherein X is $-S(O)_2-$.

[0295] Embodiment II-47. The compound of any one of Embodiments II-1 to II-42, II-44, or II-45, or a pharmaceutically acceptable salt thereof, wherein X is $-C(O)-$.

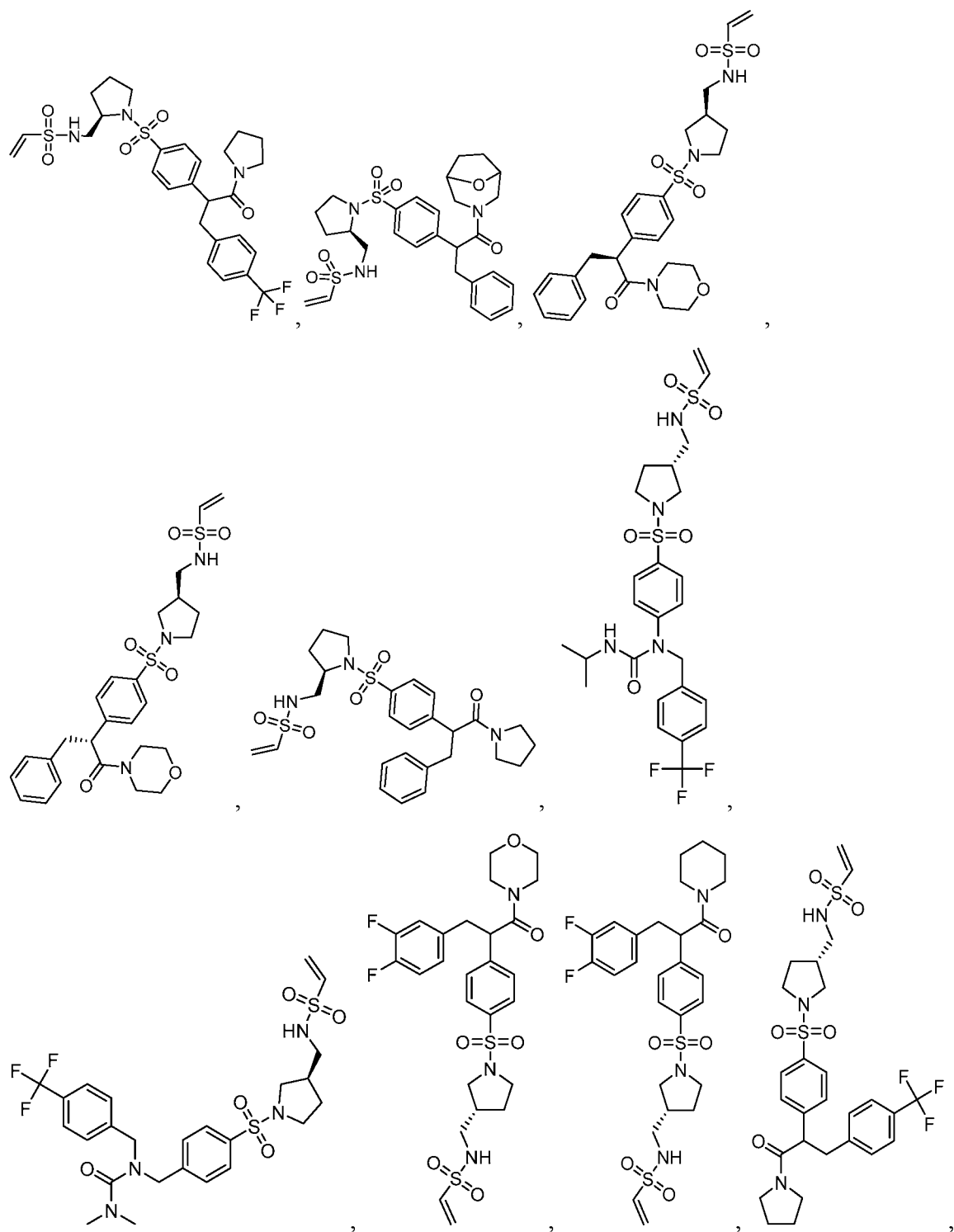
[0296] Embodiment II-48. The compound of any one of Embodiments II-1 to II-42, II-44, or II-45, or a pharmaceutically acceptable salt thereof, wherein X is $-CH_2-$.

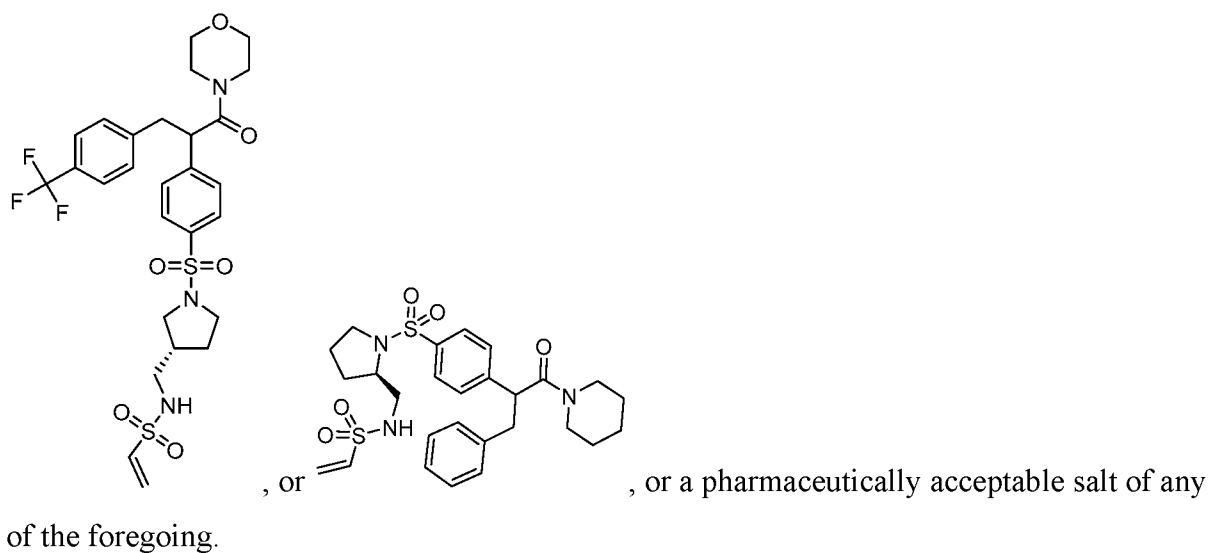
[0297] Embodiment II-49. The compound of any one of Embodiments II-1 to II-34 or II-38 to II-48, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

[0298] Embodiment II-50. The compound of any one of Embodiments II-1, II-2, II-6, II-7, II-11 to II-34, or II-38 to II-49, or a pharmaceutically acceptable salt thereof, wherein m is 0.

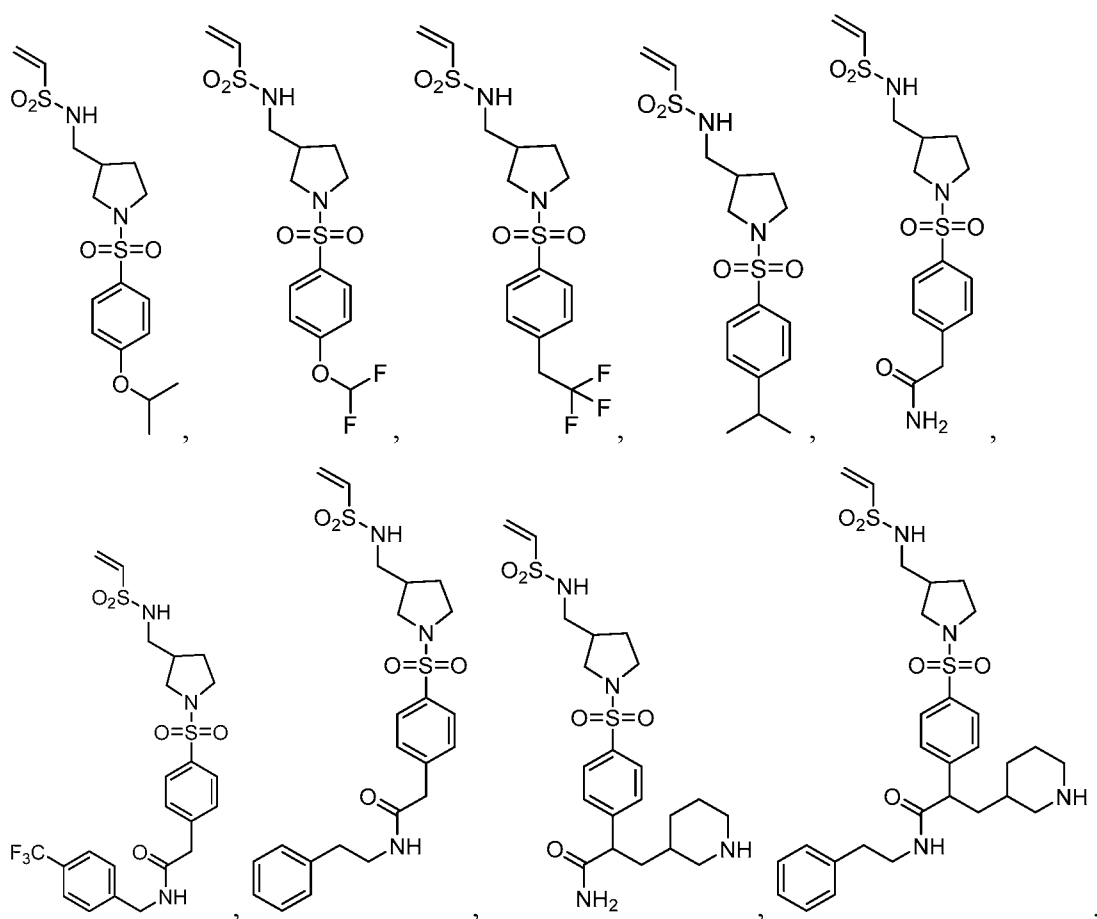
[0299] Embodiment II-51. The compound of any one of Embodiments II-3 to II-5, II-8 to II-10, or II-13 to II-49, or a pharmaceutically acceptable salt thereof, wherein p is 0.

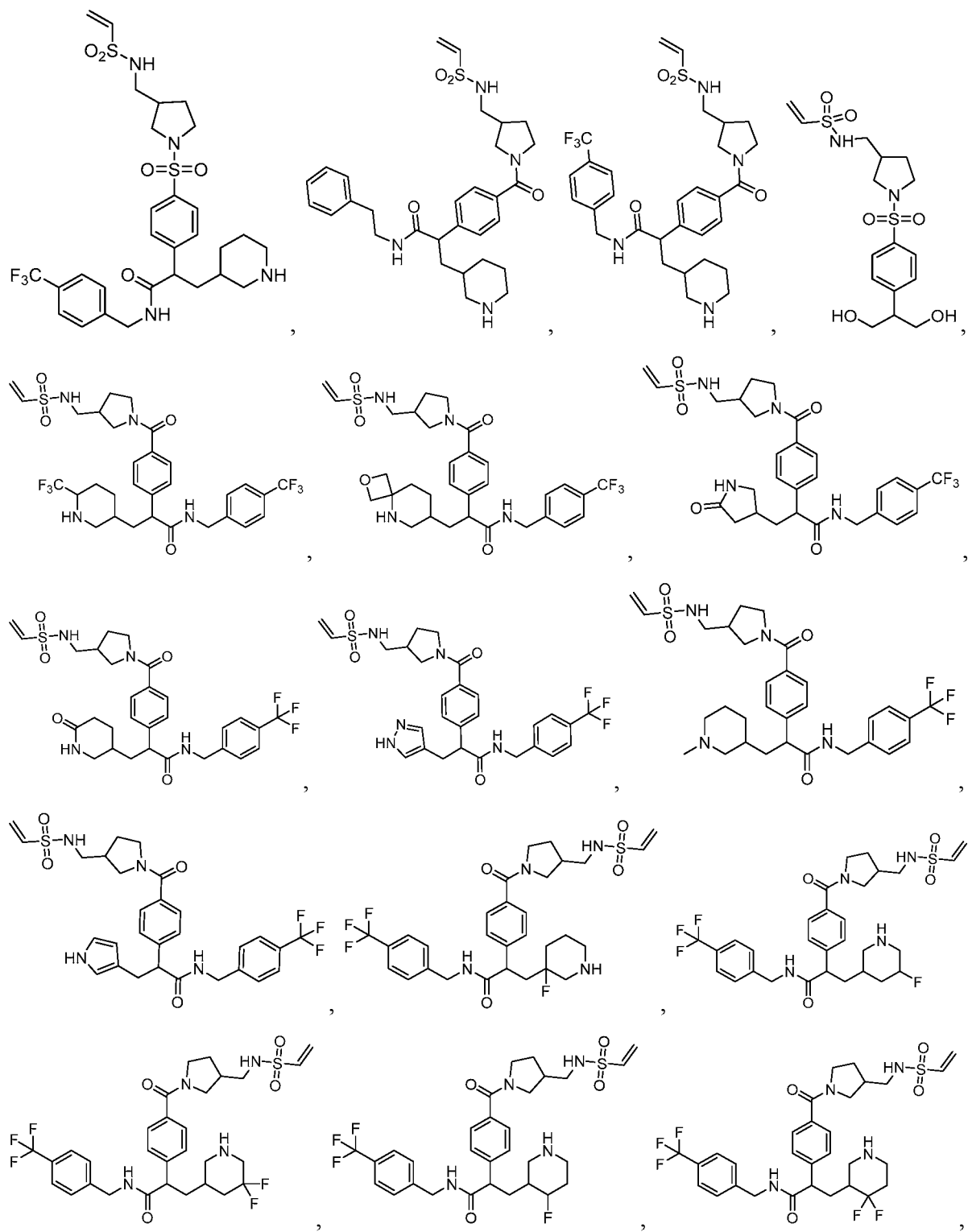
[0300] Embodiment II-52. The compound of any one of Embodiments II-1 to II-12, II-19 to II-34, II-38 to II-48, II-50, or II-51, or a pharmaceutically acceptable salt thereof, wherein B is phenyl and n is an integer from 0 to 5.

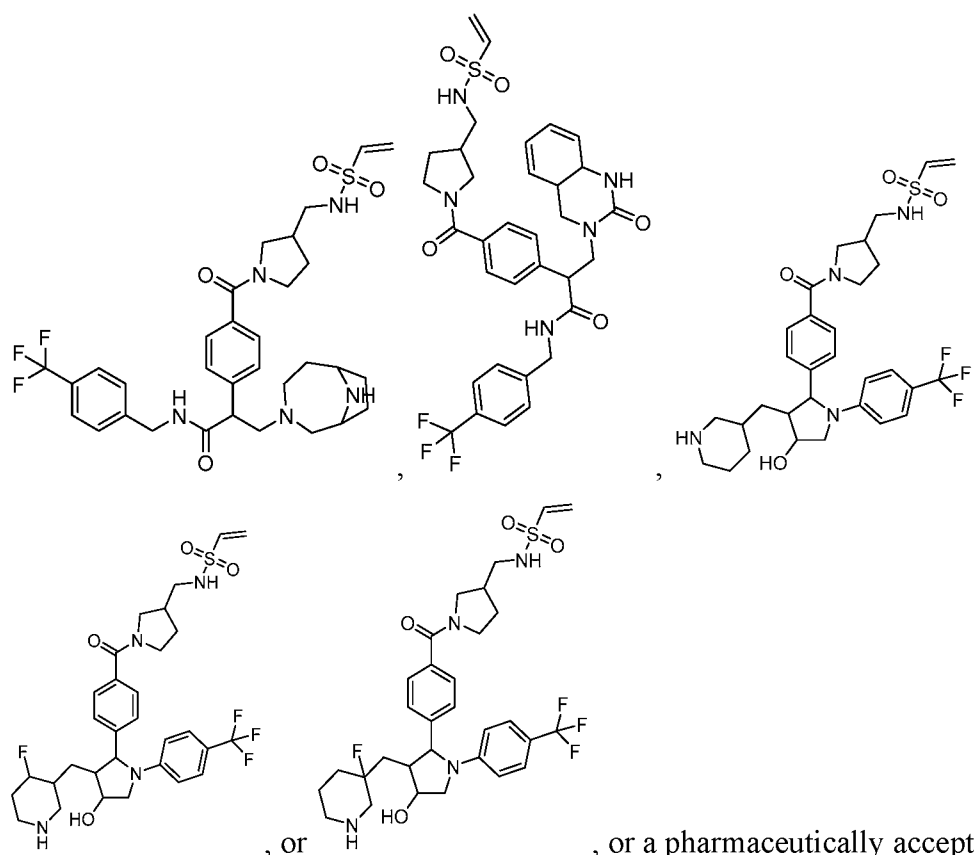




[0306] Embodiment II-58. The compound of Embodiment II-1 or II-6, wherein the compound is:

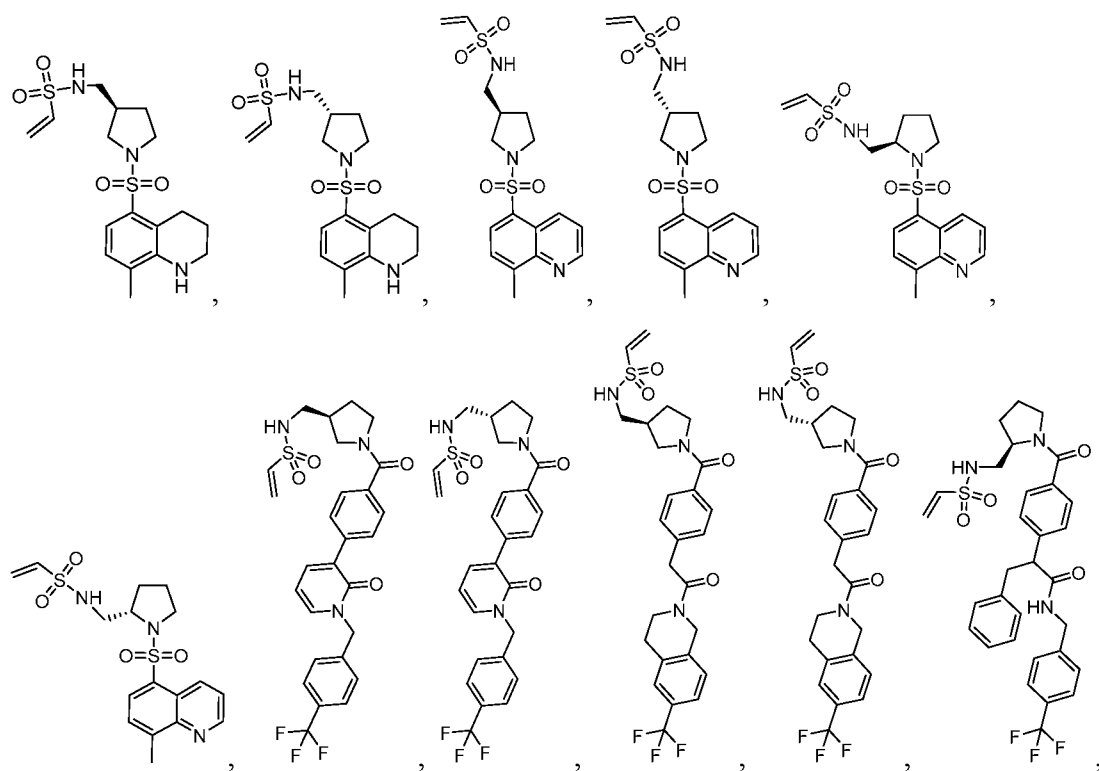


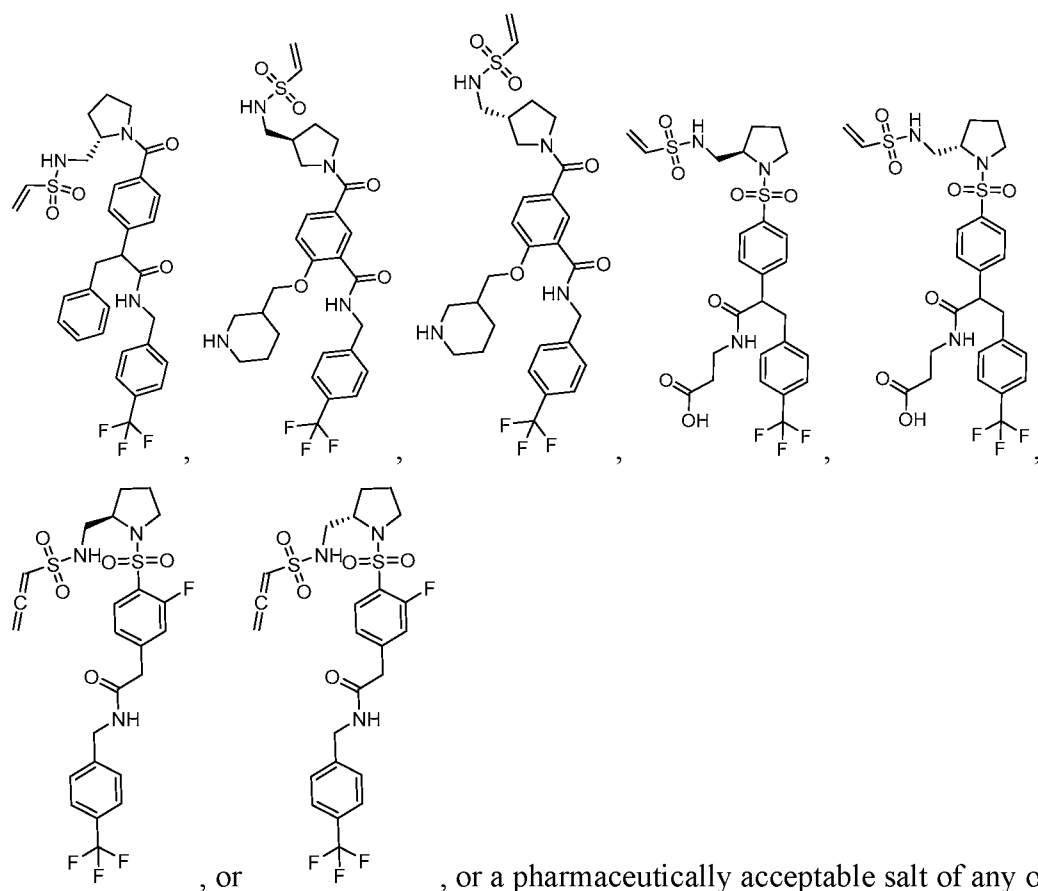




the foregoing.

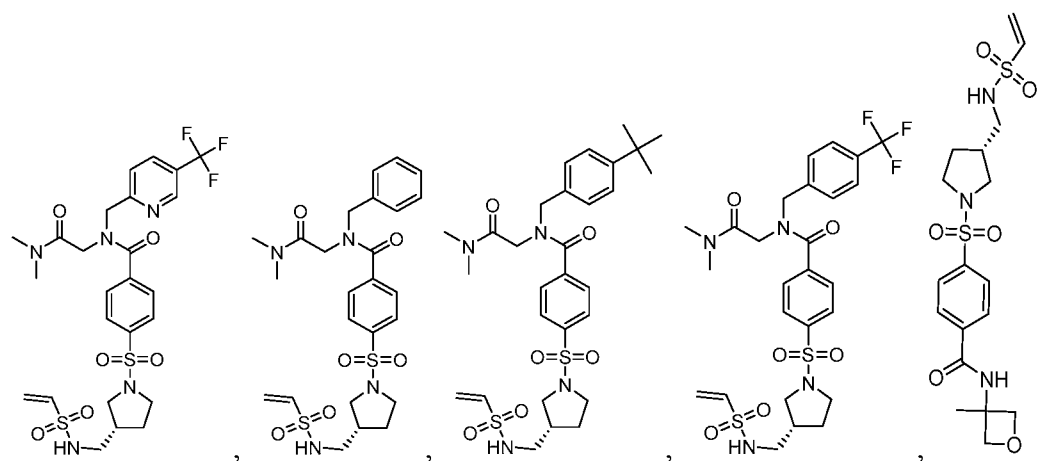
[0307] Embodiment II-59. The compound of Embodiment II-1 or II-6, wherein the compound is:

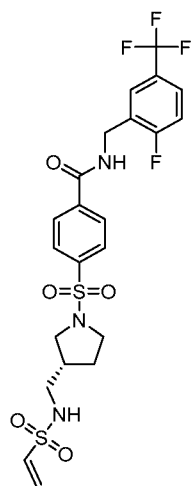
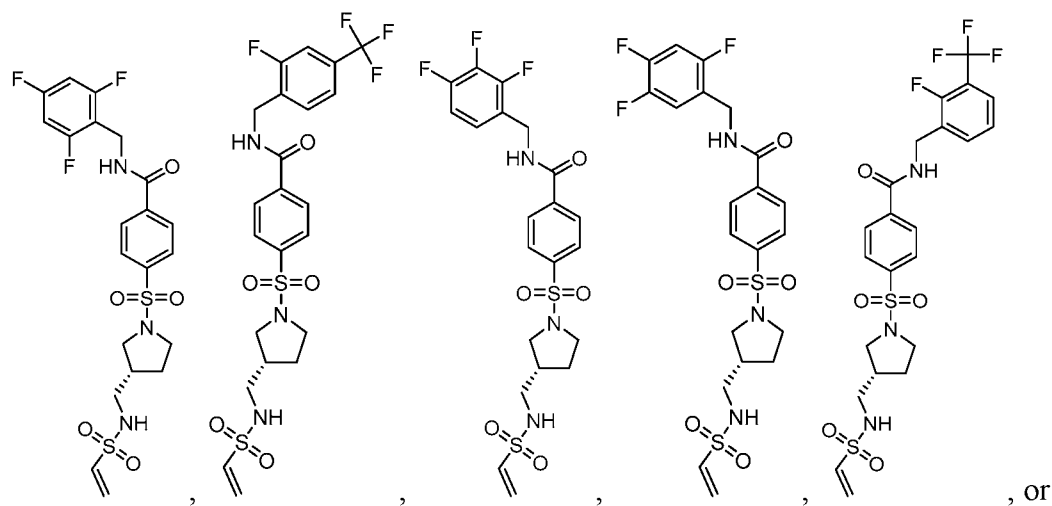
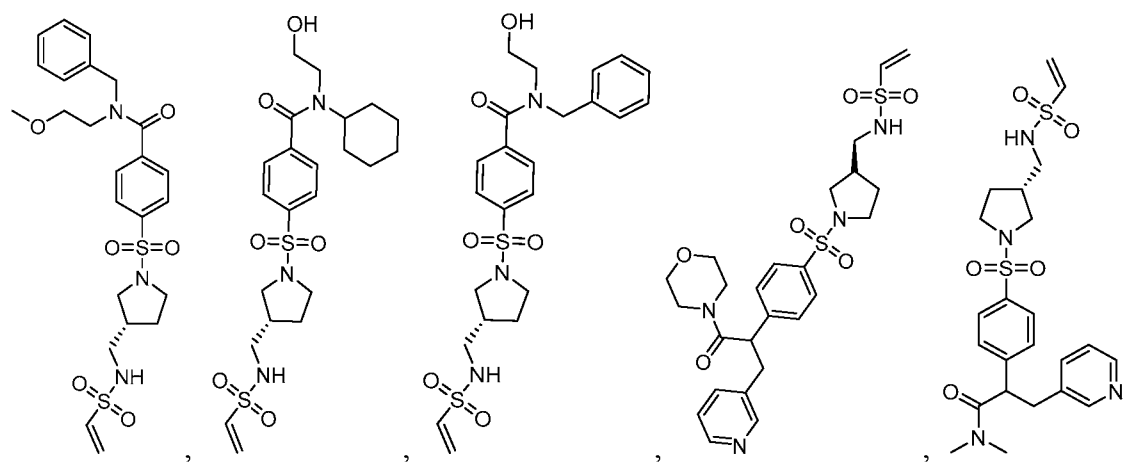




foregoing.

[0308] Embodiment II-60. The compound of Embodiment II-1, wherein the compound is:





, or a pharmaceutically acceptable salt of any of the foregoing.

[0309] Embodiment II-61. A pharmaceutical composition comprising a compound according to any one of Embodiments II-1 to II-60, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0310] Embodiment II-62. A method of reducing the level of a K-Ras protein in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of Embodiments II-1 to II-60, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0311] Embodiment II-63. The method of Embodiment II-62, wherein the K-Ras protein is human K-Ras4b.

[0312] Embodiment II-63-ii. The use of Embodiment II-62, wherein the K-Ras protein is human K-Ras4a.

[0313] Embodiment II-64. A method of treating a disorder in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of Embodiments II-1 to II-60, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0314] Embodiment II-65. The method of Embodiment II-64, wherein the disorder is cancer.

[0315] Embodiment II-66. The method of Embodiment II-65, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.

[0316] Embodiment II-67. The method of Embodiment II-64, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.

[0317] Embodiment II-68. The method of any one of Embodiments II-64 to II-67, wherein the disorder is associated with a mutation of K-Ras.

[0318] Embodiment II-69. Use of a compound of any one of Embodiments II-1 to II-60, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of a K-Ras protein in a subject in need thereof.

[0319] Embodiment II-70. The use of Embodiment II-69, wherein the K-Ras protein is human K-Ras4b.

[0320] Embodiment II-70-ii. The use of Embodiment II-69, wherein the K-Ras protein is human K-Ras4a.

[0321] Embodiment II-71. Use of a compound of any one of Embodiments II-1 to II-60, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

[0322] Embodiment II-72. The use of Embodiment II-71, wherein the disorder is cancer.

[0323] Embodiment II-73. The use of Embodiment II-72, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.

[0324] Embodiment II-74. The use of Embodiment II-71, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.

[0325] Embodiment II-75. The use of any one of Embodiments II-71 to II-74, wherein the disorder is associated with a mutation of K-Ras.

[0326] Embodiment II-76. A compound according to any one of Embodiments II-1 to II-60, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of a K-Ras protein in a subject in need thereof.

[0327] Embodiment II-77. The compound for use of Embodiment II-76, wherein the K-Ras protein is human K-Ras4b.

[0328] Embodiment II-77-ii. The use of Embodiment II-76, wherein the K-Ras protein is human K-Ras4a.

[0329] Embodiment II-78. A compound according to any one of Embodiments II-1 to II-60, or a pharmaceutically acceptable salt thereof, for use in a method of treating a disorder in a subject in need thereof.

[0330] Embodiment II-79. The compound for use in Embodiment II-78, wherein the disorder is cancer.

[0331] Embodiment II-80. The compound for use of Embodiment II-79, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.

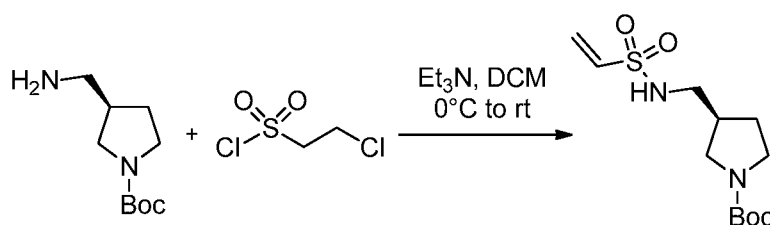
[0332] Embodiment II-81. The compound for use of Embodiment II-78, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.

[0333] Embodiment II-82. The compound for use of any one of Embodiments II-78 to II-81, wherein the disorder is associated with a mutation of K-Ras.

EXAMPLES

[0334] The following Examples are merely illustrative and are not meant to limit any aspects of the present disclosure in any way.

Example I-1: Synthesis of (*S*)-*tert*-butyl 3-(vinylsulfonamidomethyl)pyrrolidine-1-carboxylate



[0335] A mixture of (*R*)-*tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (10.0 g, 49.9 mmol) in anhydrous dichloromethane (180 mL) was cooled to 0 °C under an inert atmosphere. 2-chloroethanesulfonyl chloride (4.8 mL, 46.2 mmol) was added with stirring followed by gradual addition of Et₃N (13.9 mL, 99.9 mmol) maintaining a temperature below 5 °C to give a thick white suspension. The reaction mixture was stirred at 0 °C for 1 h, then additional Et₃N (13.9 mL, 99.9 mmol) was added. The resulting orange suspension was warmed to room temperature and stirred overnight. The mixture was transferred to a separating funnel, and washed with 1 N HCl (2 x 100 mL) and water (100 mL), then dried (Na₂SO₄), filtered, and the solvent removed under vacuum. The residue was adsorbed onto

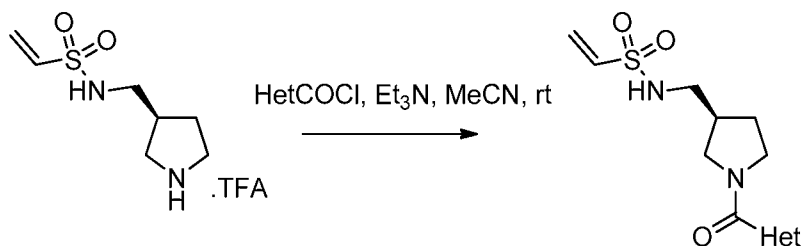
silica gel (21 g) and purified through silica gel (2 x 120g cartridge) using EtOAc/hexanes (1:9 to 7:3) as eluent to give the product (7.71 g) as an oil. R_f (product) = 0.57 (3:2 EtOAc/hexanes, using $KMnO_4$ stain)

Example I-2: Synthesis of (*S*)-*N*-(pyrrolidin-3-ylmethyl)ethenesulfonamide trifluoroacetic acid salt



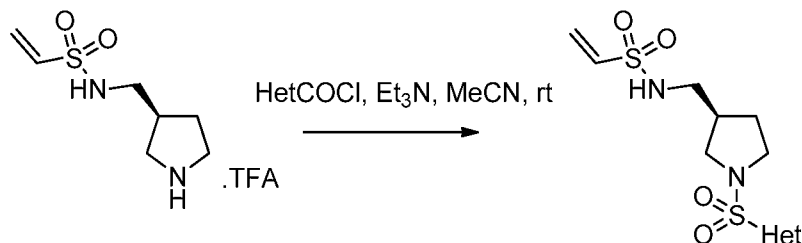
[0336] A solution of (*S*)-*tert*-butyl 3-(vinylsulfonamidomethyl)pyrrolidine-1-carboxylate (1.0 g, 3.4 mmol) in anhydrous dichloromethane (40 mL) was cooled to 0 °C. Trifluoroacetic acid (7.4 mL, 68.9 mmol) was added, and the mixture stirred at room temperature for 2h. The mixture was concentrated to dryness to give a light yellow oil, which was used without further purification. $KMnO_4$ stain was used for visualization.

Example I-3: Synthesis of Formula (I) compounds comprising a pyrrolidinyl, heteroaryl, and carbonyl linker



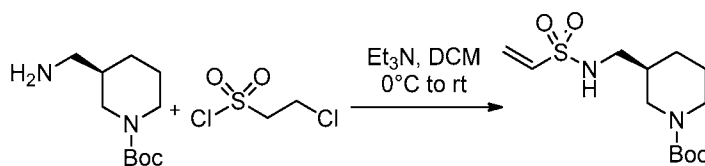
[0337] To a stirred solution of (*S*)-*N*-(pyrrolidin-3-ylmethyl)ethenesulfonamide trifluoroacetic acid salt (80 mg, 0.30 mmol) in MeCN (1.0 mL) was added a solution of the desired heteroaryl acid chloride (0.26 mmol) in MeCN (0.5 mL) followed by Et_3N (0.15 mL, 1.1 mmol). The reaction mixture was stirred at room temperature for 3h, resulting in consumption of the starting material (confirmed by TLC). The crude reaction mixture was purified by Medium Pressure Liquid Chromatography on reverse-phase using 20-90 % MeCN/ H_2O (H_2O mobile-phase contained 0.1% TFA) as eluent to give the product.

Example I-4: Synthesis of Formula (I) compounds comprising a pyrrolidinyl, heteroaryl, and SO₂ linker



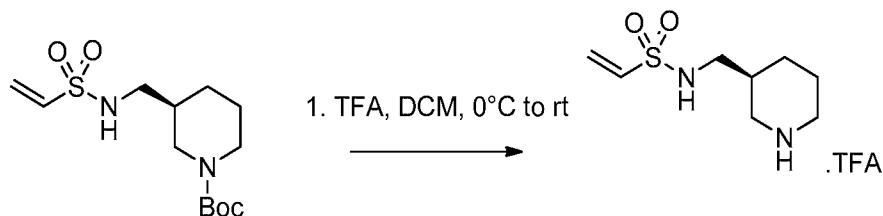
[0338] To a stirred solution of (*S*)-*N*-(pyrrolidin-3-ylmethyl)ethanesulfonamide trifluoroacetic acid salt (80 mg, 0.30 mmol) in MeCN (1.0 mL) was added a solution of the desired sulfonyl chloride (0.26 mmol) in MeCN (0.5 mL) followed by Et₃N (0.15 mL, 1.1 mmol). The reaction mixture was stirred at room temperature for 3h, resulting in consumption of the starting material (confirmed by TLC). The crude reaction mixture was purified by Medium Pressure Liquid Chromatography on reverse-phase using 20-90 % MeCN/H₂O (H₂O mobile-phase contained 0.1% TFA) as eluent to give the product.

Example I-5: Synthesis of (*S*)-*tert*-butyl 3-(vinylsulfonamidomethyl)piperidine-1-carboxylate



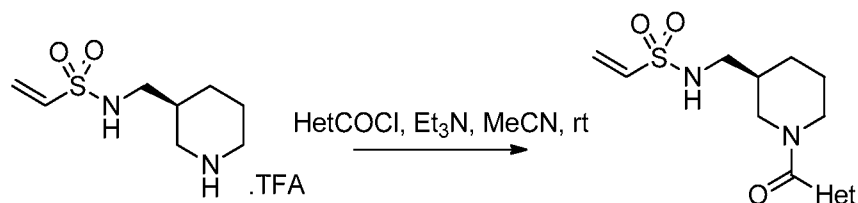
[0339] A solution of (*R*)-*tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (25.0 g, 116.7 mmol) in anhydrous dichloromethane (180 mL) was cooled to 0 °C under an inert atmosphere. 2-chloroethanesulfonyl chloride (12.1 mL, 115.5 mmol) was added with stirring followed by gradual addition of Et₃N (34.8 mL, 249.6 mmol) maintaining a temperature below 5 °C to give a thick white suspension. The reaction mixture was stirred at 0 °C for 1h, then additional Et₃N (34.8 mL, 249.6 mmol) was added. The resulting orange suspension was warmed to room temperature and stirred overnight. The mixture was transferred to a separating funnel, and washed with 1N HCl (2 x 100 mL) and water (100 mL), then dried (Na₂SO₄), filtered and the solvent removed under vacuum. The residue was adsorbed onto silica gel (21 g) and purified through silica gel (2 x 120g cartridge) using EtOAc/hexanes (1:9 to 7:3) as eluent to give the product as an oil. R_f (product) = 0.57 (3:2 EtOAc/hexanes; using KMnO₄ for visualization)

Example I-6: Synthesis of (*S*)-*N*-(piperidin-3-ylmethyl)ethenesulfonamide trifluoroacetic acid salt



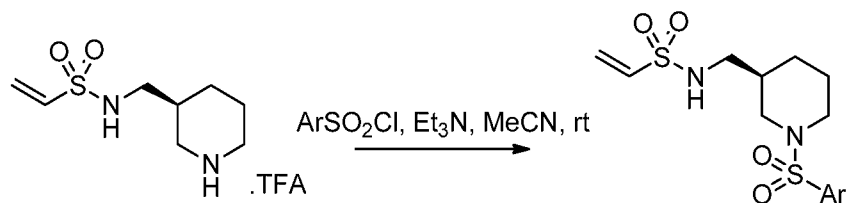
[0340] A solution of (*S*)-*tert*-butyl 3-(vinylsulfonamidomethyl)piperidine-1-carboxylate (2.0 g, 6.6 mmol) in anhydrous dichloromethane (80 mL) was cooled to 0 °C. Trifluoroacetic acid (14.2 mL, 131.4 mmol) was added, and the mixture stirred at room temperature for 3h. The mixture was concentrated to dryness to give a light yellow oil, which was used without further purification.

Example I-7: Synthesis of Formula (I) compounds with piperidinyl, heteroaryl, and carbonyl linker



[0341] To a solution of (*S*)-*N*-(piperidin-3-ylmethyl)ethenesulfonamide trifluoroacetic acid salt (84 mg, 0.30 mmol) in MeCN (1.0 mL) was added a solution of the desired heteroaryl acid chloride (0.26 mmol) in MeCN (0.5 mL) followed by Et₃N (0.15 mL, 1.1 mmol). The reaction mixture was stirred at room temperature for 3h, resulting in consumption of the starting material (confirmed by TLC). The crude reaction mixture was purified by Medium Pressure Liquid Chromatography on reverse-phase using 20-90 % MeCN/H₂O (H₂O mobile-phase contained 0.1% TFA) as eluent to give the desired product.

Example I-8: Synthesis of Formula (I) compounds with piperidinyl, heteroaryl, and SO₂ linker

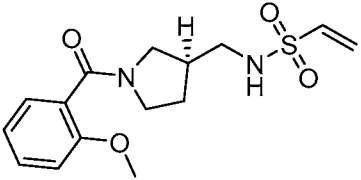
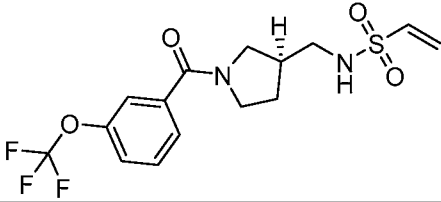
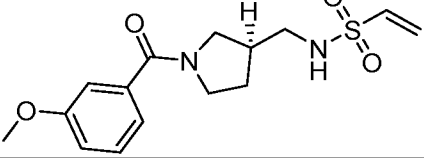
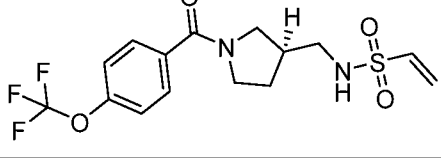
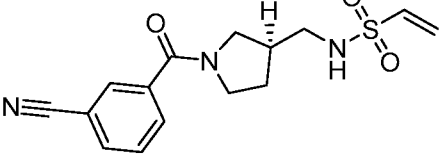
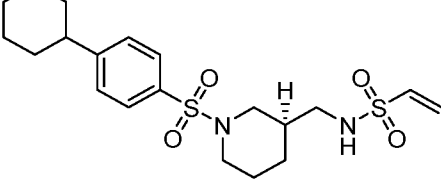
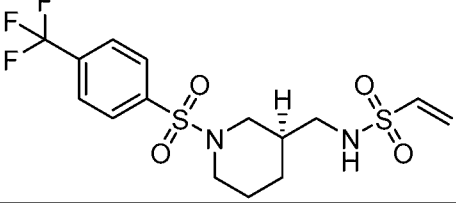
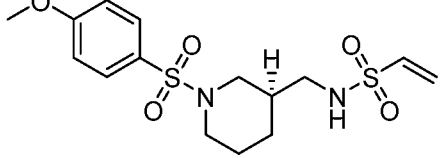
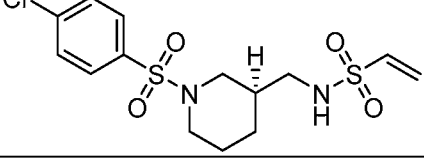
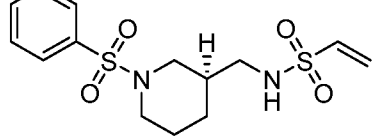
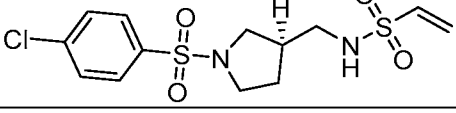
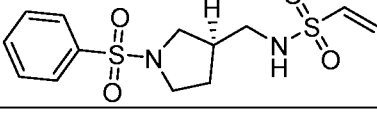
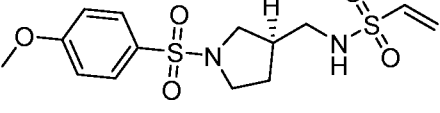
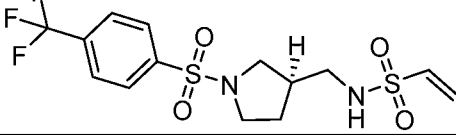


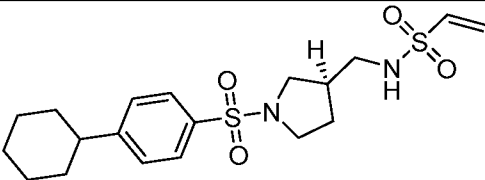
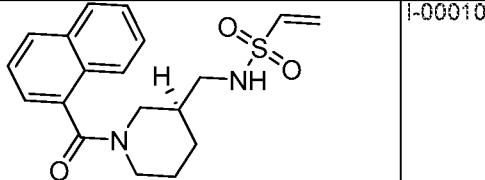
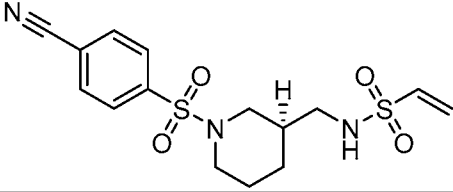
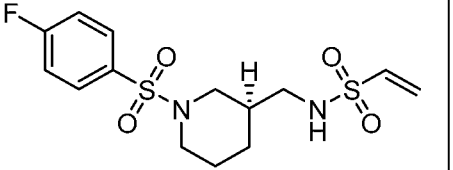
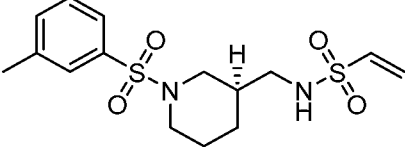
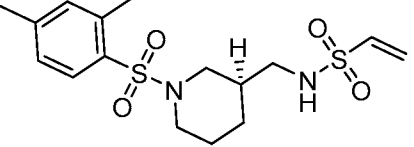
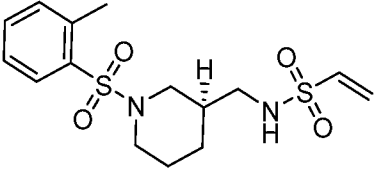
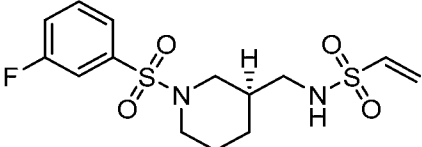
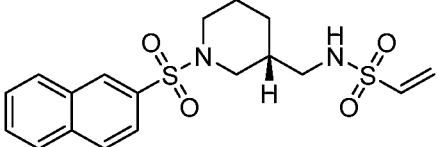
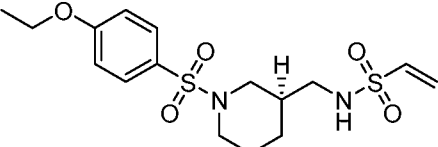
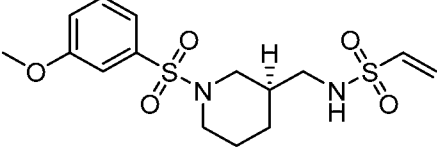
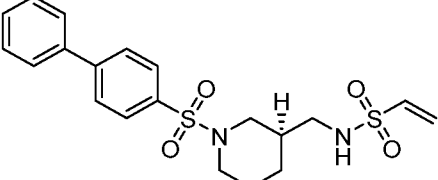
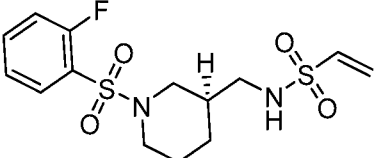
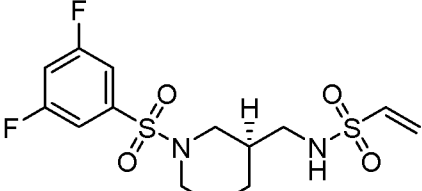
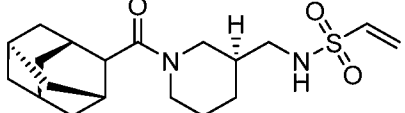
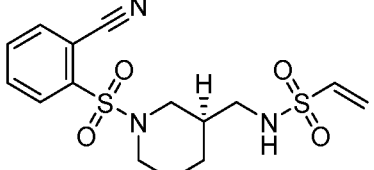
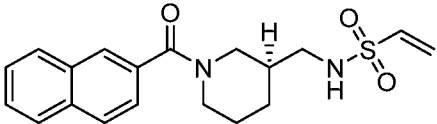
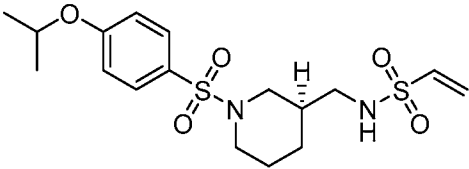
[0342] To a stirred solution of (*S*)-*N*-(piperidin-3-ylmethyl)ethenesulfonamide trifluoroacetic acid salt (84 mg, 0.30 mmol) in MeCN (1.0 mL) was added a solution of the

desired aryl sulfonyl chloride (0.26 mmol) in MeCN (0.5 mL) followed by Et₃N (0.15 mL, 1.1 mmol). The reaction mixture was stirred at room temperature for 3h, resulting in consumption of the starting material (confirmed by TLC). The crude reaction mixture was purified by Medium Pressure Liquid Chromatography on reverse-phase using 20-90 % MeCN/H₂O (H₂O mobile-phase contained 0.1% TFA) as eluent to give the desired product.

[0343] Compounds synthesized using methods similar to those described in the above Examples are provided in Table I-1 and Table I-2 below.

Table I-1. Synthesized Compounds

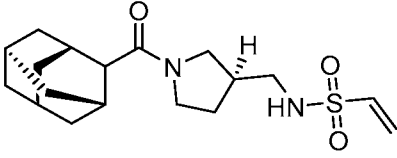
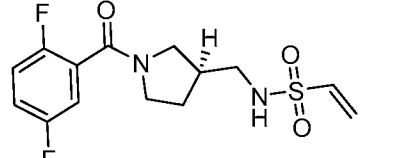
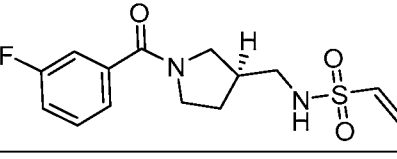
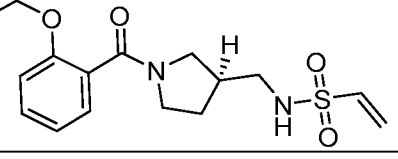
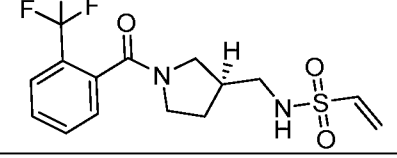
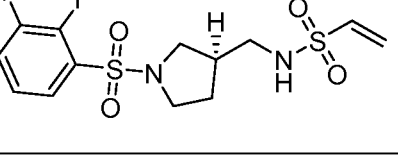
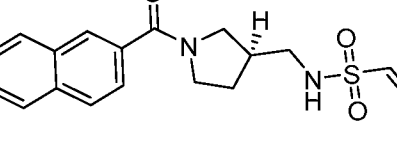
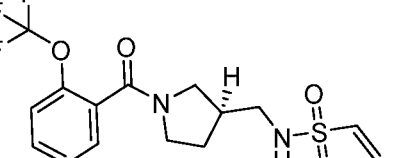
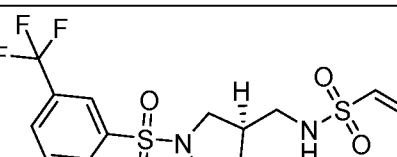
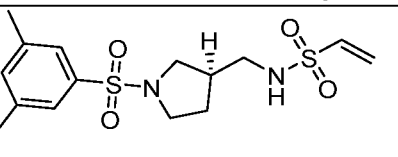
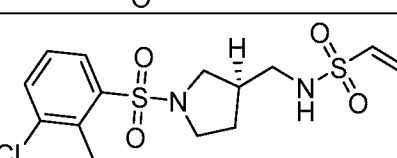
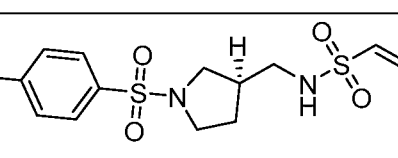
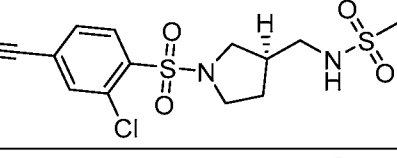
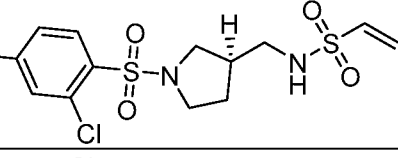
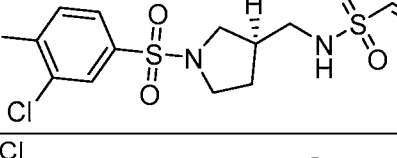
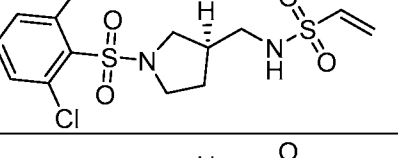
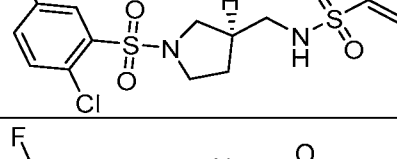
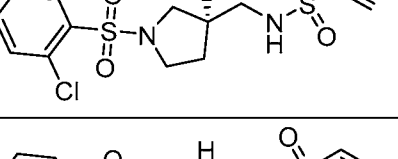
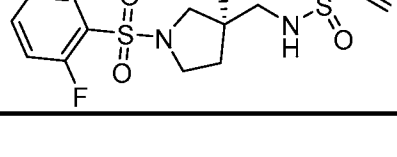
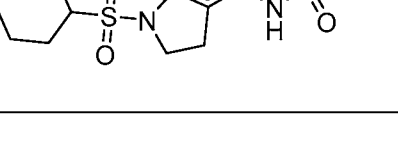
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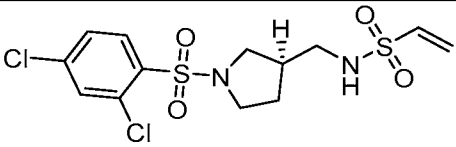
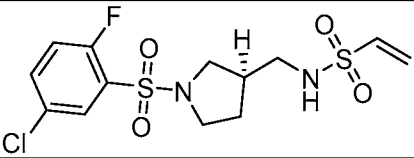
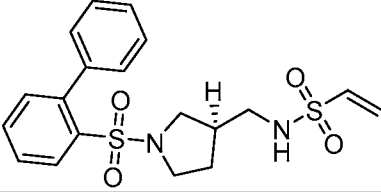
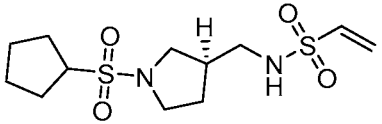
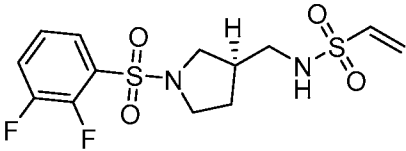
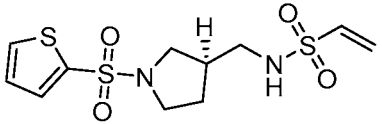
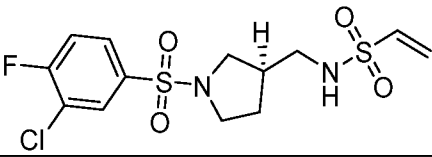
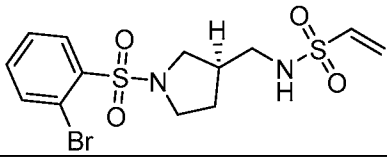
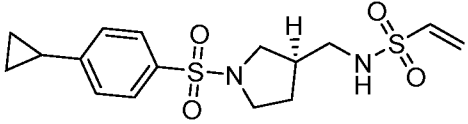
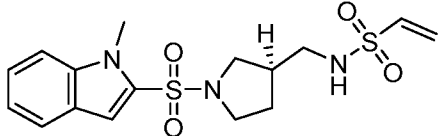
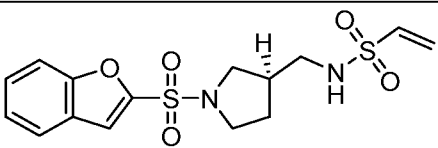
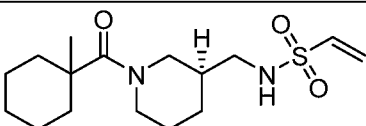
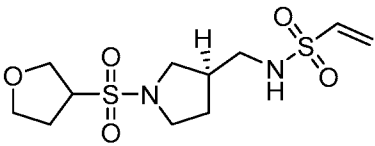
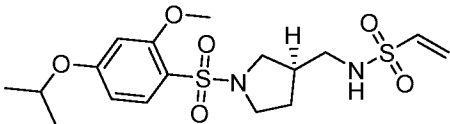
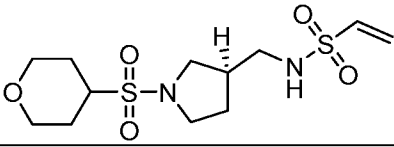
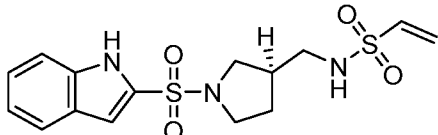
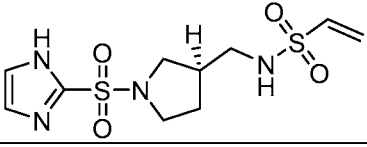
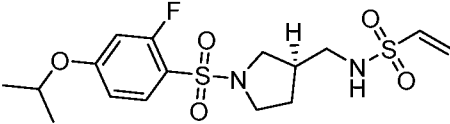
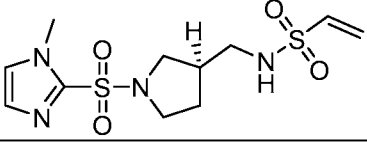
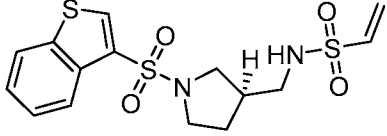
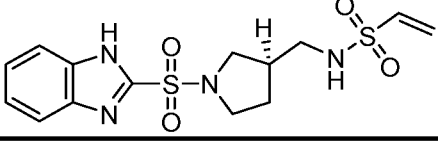
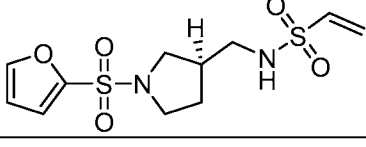
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	I-0001443		I-0001317
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	I-0001445		I-0001442
	I-0001318		I-0001322
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	I-0001326		I-0001330
	I-0001328		I-0001331

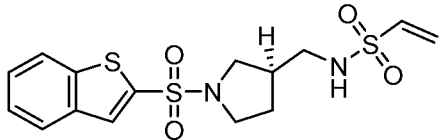
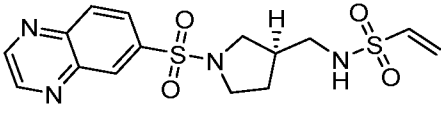
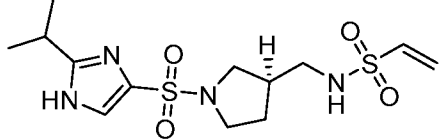
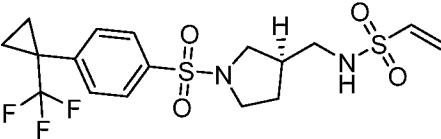
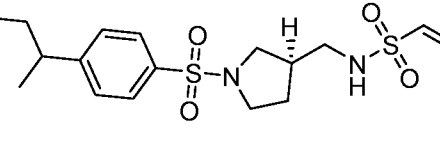
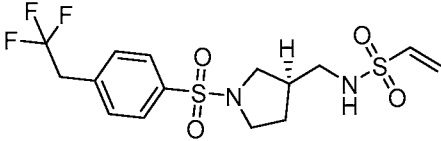
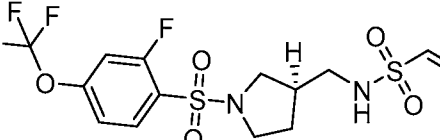
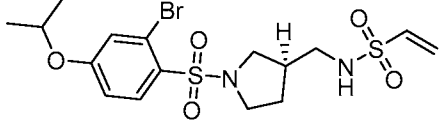
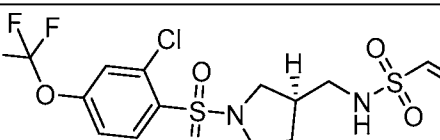
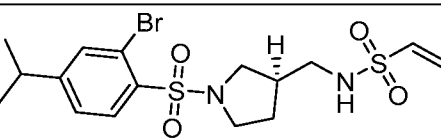
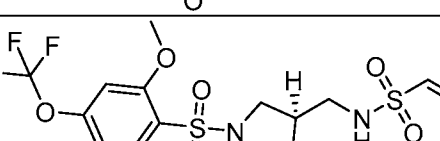
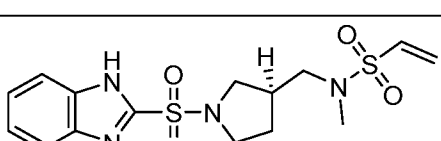
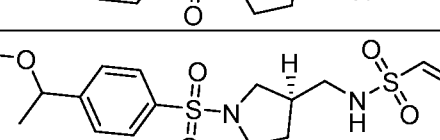
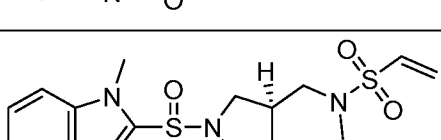
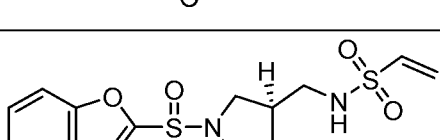
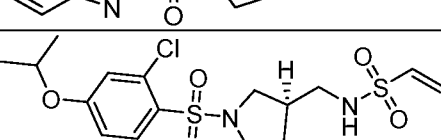
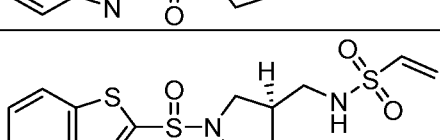
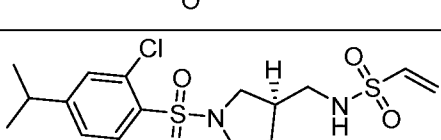
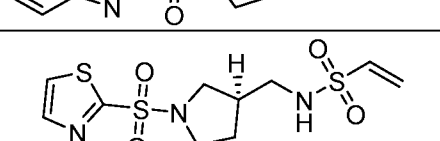
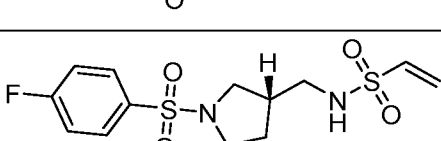
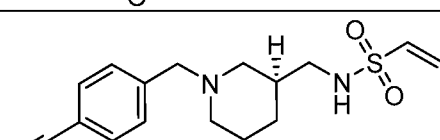
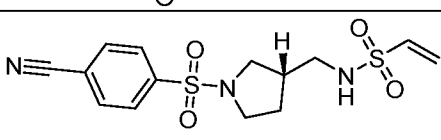
Structure	Cmpd. #	Structure	Cmpd. #
	I-0001329		I-0001482
	I-0001516		I-0001483
	I-0001528		I-0001512
	I-0001532		I-0001524
	I-0001348		I-0001488
	I-0001351		I-0001356
	I-0001352		I-0001358
	I-0001353		I-0001359
	I-0001354		I-0001360

Structure	Cmpd. #	Structure	Cmpd. #
	I-0001365		I-0001366
	I-0001367		I-0001361
	I-0001369		I-0001362
	I-0001371		I-0001363
	I-0001372		I-0001364
	I-0001374		I-0001412
	I-0001411		I-0001413
	I-0001419		I-0001415
	I-0001421		I-0001416

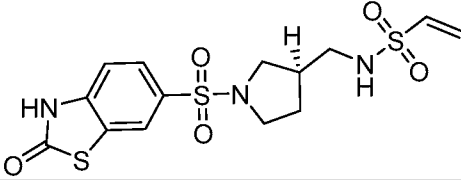
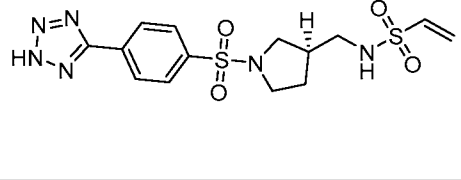
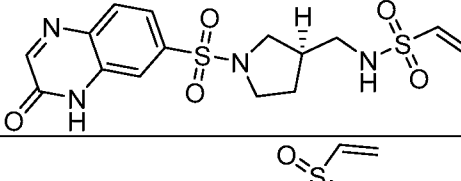
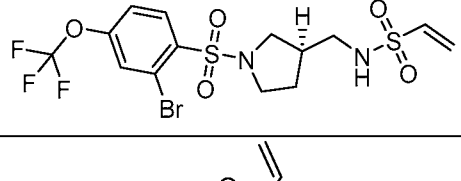
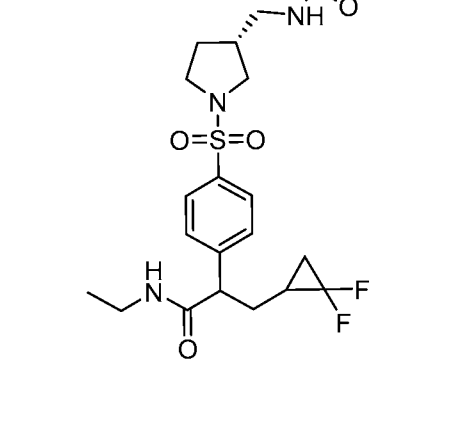
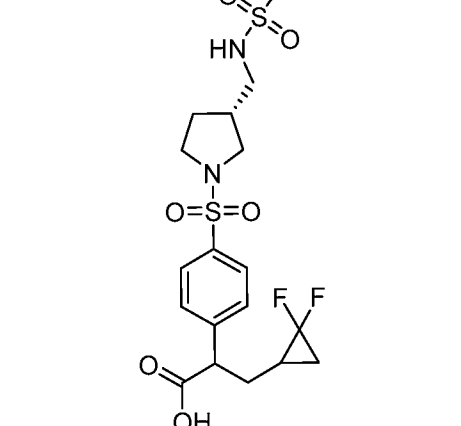
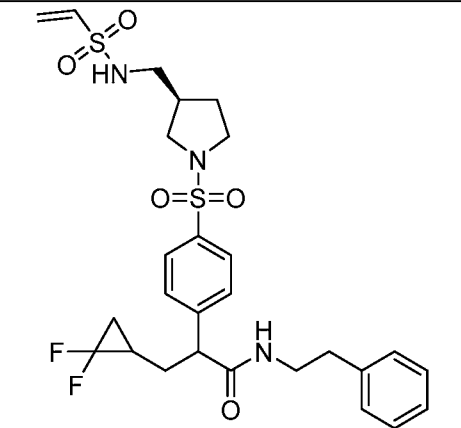
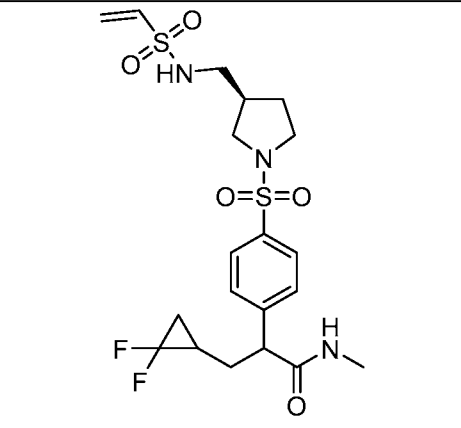
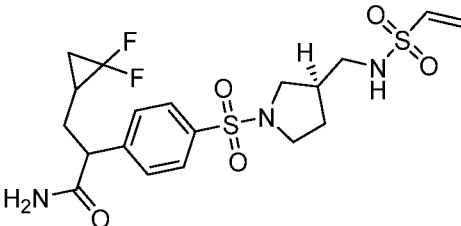
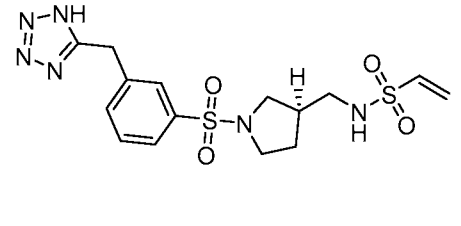
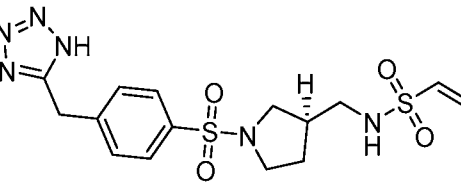
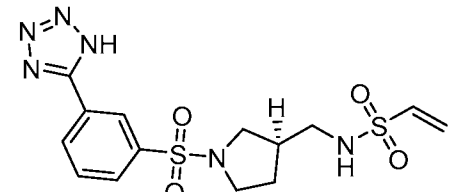
Structure	Cmpd. #	Structure	Cmpd. #
	I-0001422		I-0001417
	I-0001423		I-0001418
	I-0001424		I-0001429
	I-0001425		I-0001430
	I-0001426		I-0001212
	I-0001427		I-0001428
	I-0001213		I-0001216
	I-0001214		I-0001217
	I-0001215		I-0001376

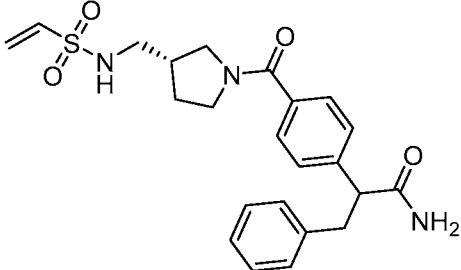
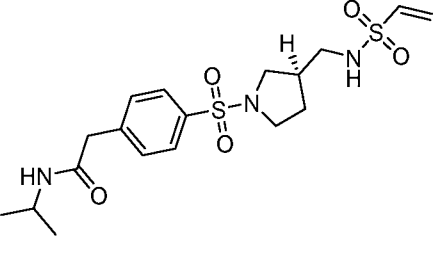
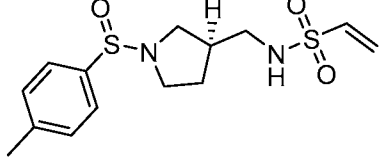
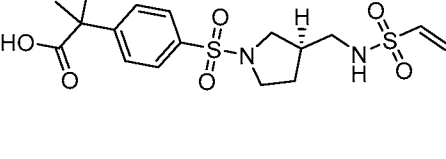
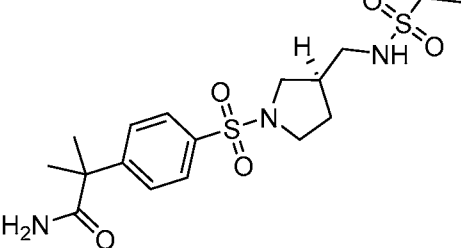
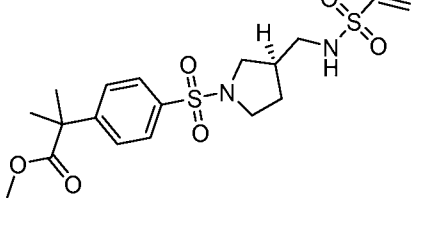
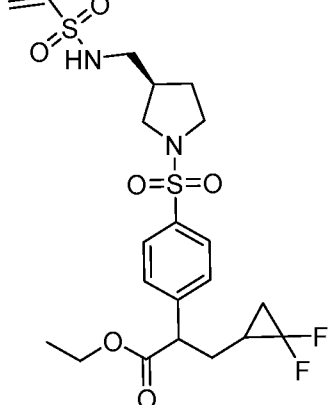
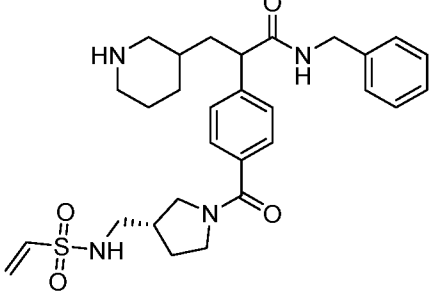
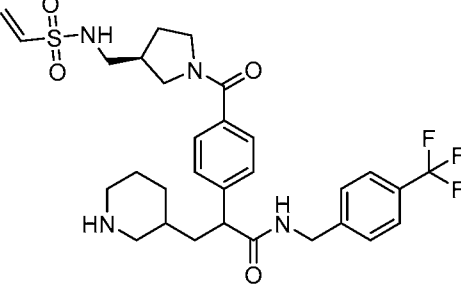
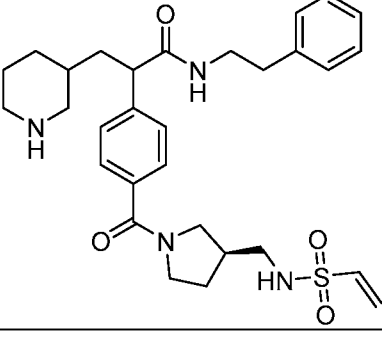
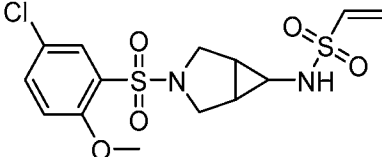
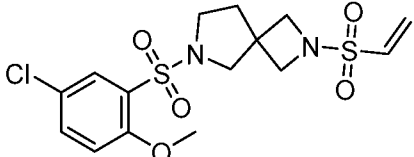
Structure	Cmpd. #	Structure	Cmpd. #
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	I-0001375		I-0001383
	I-0001377		I-0001447
	I-0001378		I-0001448
	I-0001379		I-0001449
	I-0001380		I-0001510
	I-0001381		I-0001382
	I-0001384		I-0001389

Structure	Cmpd. #	Structure	Cmpd. #
	I-0001385		I-0001390
	I-0001386		I-0001391
	I-0001465		I-0001537
	I-0001387		I-0001388
	I-0001541		I-0001550
	I-0001546		I-0001396
	I-0001548		I-0001551
	I-0001549		I-0001559
	I-0001547		I-0001555
	I-0001552		I-0001544
	I-0001554		I-0001545

Structure	Cmpd. #	Structure	Cmpd. #
	I-0001560		I-0001540
	I-0001561		I-0001538
	I-0001542		I-0001543
	I-0001539		I-0001558
	I-0001556		I-0001557
	I-0001564		I-0001565
	I-0001562		I-0001566
	I-0001580		I-0001563
	I-0001579		I-0001581
	I-0001582		I-0132
	I-0091		I-0133

Structure	Cmpd. #	Structure	Cmpd. #
	I-0130		I-0151
	I-0136		I-0134
	I-0137		I-0135
	I-0152		I-0154
	I-0153		I-0155
	I-0156		I-0163
	I-0157		I-0174
	I-0184		I-0180
	I-0001236		I-0182

Structure	Cmpd. #	Structure	Cmpd. #
	I-0195		I-0183
	I-0196		I-0001553
	I-0193		I-0202
	I-0204		I-0203
	I-0206		I-0210
	I-0213		I-0211

Structure	Cmpd. #	Structure	Cmpd. #
	I-0235		I-0229
	I-0236		I-0237
	I-0238		I-0239
	I-0201		I-0244 and I-0245 (diast.)
	I-0246 and I-0247 (diast.)		I-0248 and I-0249 (diast.)
	I-0001568		I-0001569

Structure	Cmpd. #	Structure	Cmpd. #
	I-0001572		I-0001574
	I-0001576		I-0001578
	I-0011		I-0029
	I-0031		I-0167
	I-0168		I-0169
	I-0170		I-0171
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	I-0001567		I-0001570
	I-0001575		I-0225

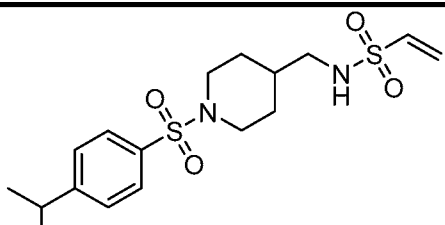
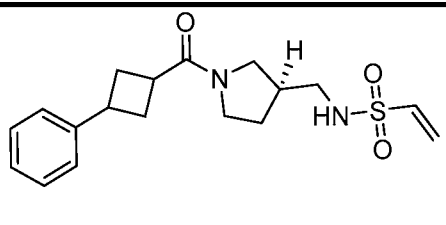
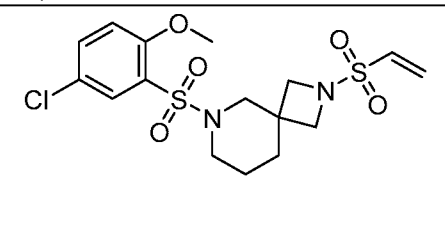
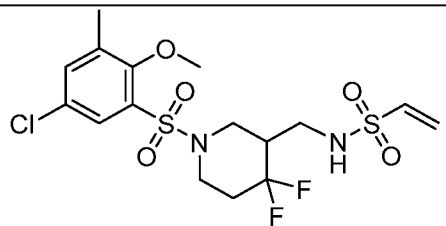
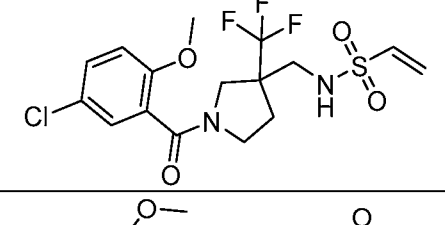
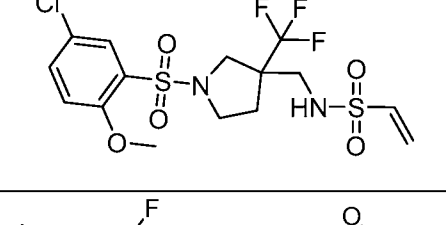
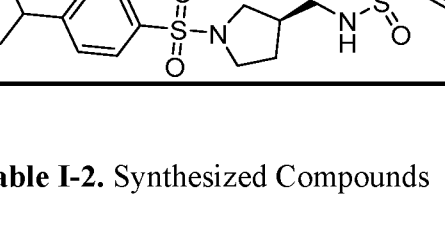
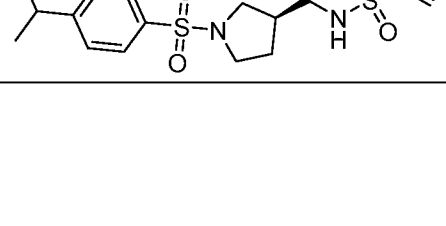
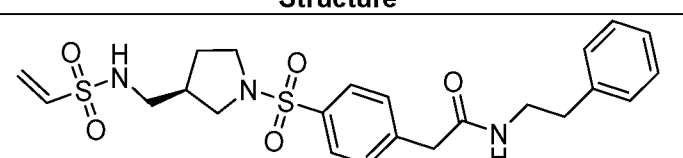
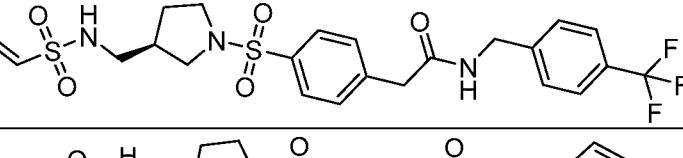
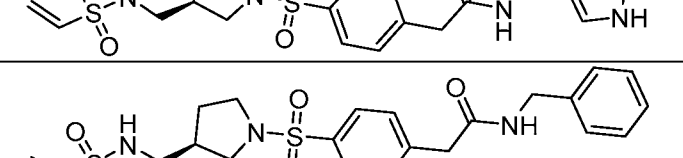
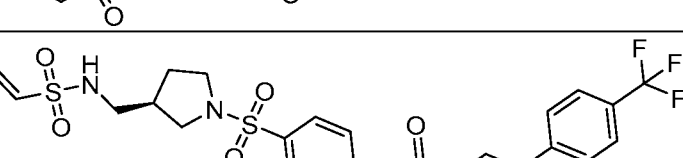
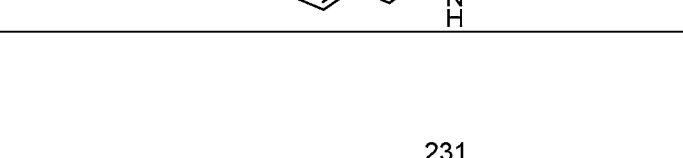
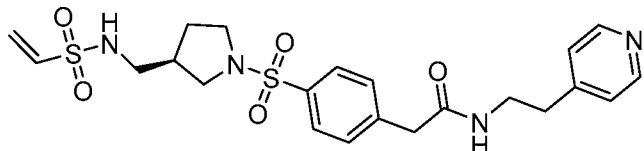
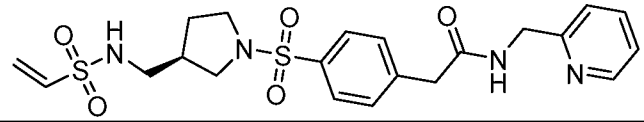
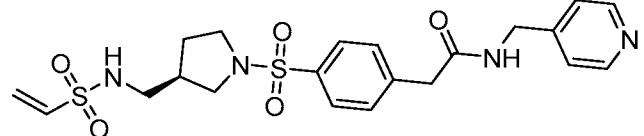
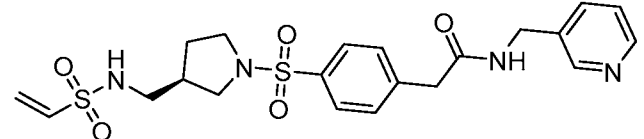
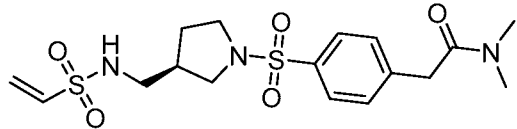
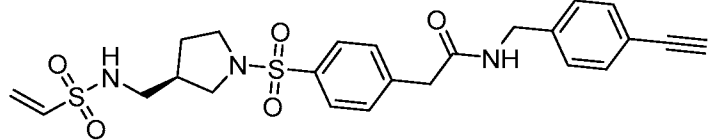
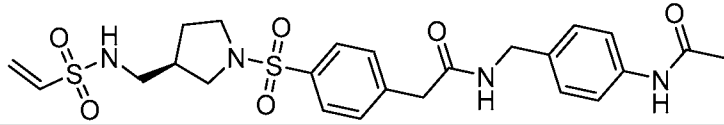
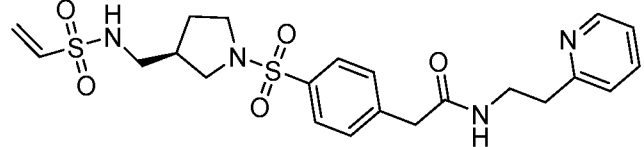
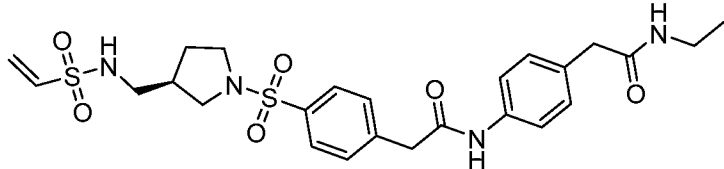
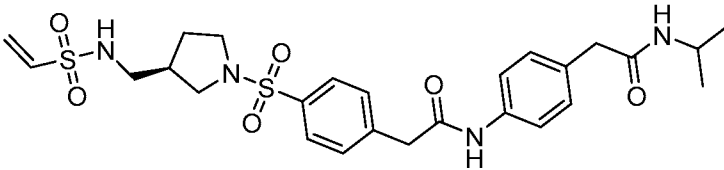
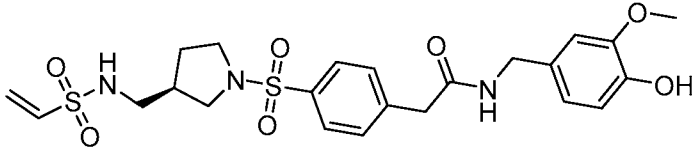
Structure	Cmpd. #	Structure	Cmpd. #
	I-0219		I-0250
	I-0001584		I-0001586
	I-0001587		I-0001588
	I-0001592		I-0001591

Table I-2. Synthesized Compounds

Structure	Cmpd. #
	I-0175
	I-0176
	I-0177
	I-0192
	I-0197

Structure	Cmpd. #
	I-0198
	I-0199
	I-0200
	I-0208
	I-0209
	I-0221
	I-0222
	I-0223
	I-0224
	I-0228
	I-0232

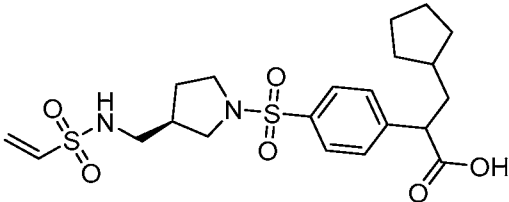
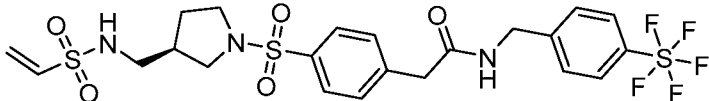
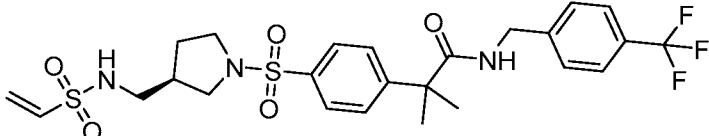
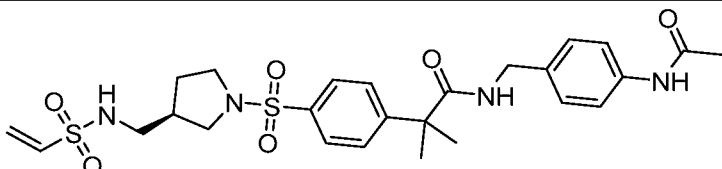
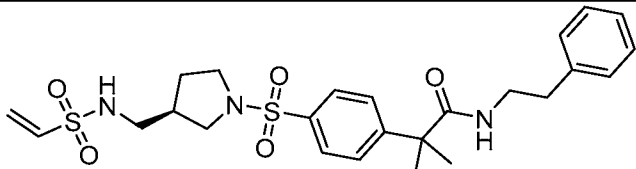
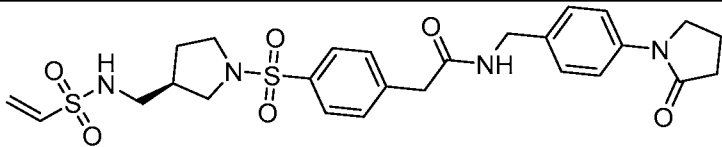
Structure	Cmpd. #
	I-0233
	I-0234
	I-0240
	I-0241
	I-0242
	I-0243

Table I-3. Characterization of synthesized compounds

Compound Identifier	Analytical Analysis
I-0001053	m/z = 325.1 [M+H] ⁺
I-0001054	m/z = 325.1 [M+H] ⁺
I-0001055	m/z = 320.1 [M+H] ⁺
I-0001056	m/z = 379.1 [M+H] ⁺
I-0001057	m/z = 379.1 [M+H] ⁺
I-0001058	m/z = 345.1 [M+H] ⁺
I-0001059	m/z = 413.1 [M+H] ⁺
I-0001060	¹ H-NMR (400 MHz, CDCl ₃) δ 7.69 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.68 (t, J = 6.5 Hz, 1H), 3.48 (dd, J = 11.8, 3.6 Hz, 1H), 3.36 (dt, J = 10.6, 4.4 Hz, 1H), 3.01 – 2.92 (m, 2H), 2.67 – 2.56 (m, 1H), 2.43 (dd, J = 11.7, 8.7 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.82 – 1.67 (m, 2H), 1.67 – 1.56 (m, 1H), 1.18 – 1.04 (m, 1H); m/z = 379.1 [M+H] ⁺
I-0001061	m/z = 375.1 [M+H] ⁺
I-0001062	¹ H-NMR (400 MHz, CDCl ₃) δ 7.79 – 7.71 (m, 2H), 7.65 – 7.57 (m, 1H), 7.57 – 7.50 (m, 2H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 4.74 (t, J = 6.5 Hz, 1H), 3.48 (dd, J = 11.7, 3.6 Hz, 1H), 3.36 (dt, J = 10.6, 4.4 Hz, 1H), 2.96 (t, J = 6.8 Hz, 2H), 2.67 – 2.56 (m, 1H), 2.42 (dd, J = 11.7, 8.6 Hz, 1H), 1.97 – 1.85 (m, 1H), 1.79 – 1.55 (m, 3H), 1.16 – 1.04 (m, 1H); m/z = 345.1 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001063	¹ H-NMR (400 MHz, CDCl ₃) δ 7.76 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.66 (t, J = 6.4 Hz, 1H), 3.43 – 3.30 (m, 2H), 3.17 (dt, J = 9.8, 7.6 Hz, 1H), 3.04 (dd, J = 10.1, 6.2 Hz, 1H), 2.95 – 2.86 (m, 2H), 2.42 – 2.30 (m, 1H), 2.01 – 1.91 (m, 1H), 1.67 – 1.55 (m, 1H); m/z = 365.1 [M+H] ⁺
I-0001064	¹ H-NMR (400 MHz, CDCl ₃) δ 7.75 (d, J = 8.9 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.70 (t, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.38 – 3.25 (m, 2H), 3.14 (dt, J = 9.9, 7.6 Hz, 1H), 3.00 (dd, J = 10.2, 6.1 Hz, 1H), 2.93 – 2.84 (m, 2H), 2.40 – 2.28 (m, 1H), 1.98 – 1.88 (m, 1H), 1.63 – 1.51 (m, 1H); m/z = 361.1 [M+H] ⁺
I-0001065	m/z = 331.1 [M+H] ⁺
I-0001066	¹ H-NMR (400 MHz, CDCl ₃) δ 7.86 – 7.78 (m, 2H), 7.67 – 7.58 (m, 1H), 7.58 – 7.50 (m, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.69 (t, J = 6.4 Hz, 1H), 3.43 – 3.29 (m, 2H), 3.17 (dt, J = 10.0, 7.6 Hz, 1H), 3.04 (dd, J = 10.1, 6.1 Hz, 1H), 2.93 – 2.85 (m, 2H), 2.40 – 2.26 (m, 1H), 2.00 – 1.87 (m, 1H), 1.65 – 1.51 (m, 1H); m/z = 331.1 [M+H] ⁺
I-0001067	¹ H-NMR (400 MHz, CDCl ₃) δ 7.96 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.54 (t, J = 6.2 Hz, 1H), 3.46 – 3.34 (m, 2H), 3.25 – 3.17 (m, 1H), 3.11 – 3.05 (m, 1H), 2.97 – 2.86 (m, 2H), 2.43 – 2.31 (m, 1H), 2.04 – 1.94 (m, 1H), 1.69 – 1.58 (m, 1H); m/z = 399.1 [M+H] ⁺
I-0001069	m/z = 359.1 [M+H] ⁺
I-0001073	m/z = 370.1 [M+H] ⁺
I-0001074	¹ H-NMR (400 MHz, CDCl ₃) δ 7.58 – 7.49 (m, 2H), 7.46 – 7.36 (m, 2H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.6 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.74 (t, J = 6.5 Hz, 1H), 3.45 (dd, J = 11.7, 3.6 Hz, 1H), 3.34 (dt, J = 10.6, 4.5 Hz, 1H), 3.01 – 2.93 (m, 2H), 2.68 – 2.58 (m, 1H), 2.51 – 2.37 (m, 4H), 1.97 – 1.86 (m, 1H), 1.80 – 1.66 (m, 2H), 1.66 – 1.51 (m, 1H), 1.17 – 1.04 (m, 1H); m/z = 359.1 [M+H] ⁺
I-0001075	m/z = 359.1 [M+H] ⁺
I-0001076	m/z = 395.1 [M+H] ⁺
I-0001077	m/z = 363.1 [M+H] ⁺
I-0001078	m/z = 373.1 [M+H] ⁺
I-0001079	m/z = 363.1 [M+H] ⁺
I-0001080	m/z = 389.1 [M+H] ⁺
I-0001081	¹ H-NMR (400 MHz, CDCl ₃) δ 7.48 – 7.39 (m, 1H), 7.32 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.12 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.6 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.67 (t, J = 6.6 Hz, 1H), 3.87 (s, 3H), 3.47 (dd, J = 11.8, 3.6 Hz, 1H), 3.36 (dt, J = 10.5, 4.5 Hz, 1H), 3.01 – 2.93 (m, 2H), 2.69 – 2.58 (m, 1H), 2.45 (dd, J = 11.7, 8.6 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.80 – 1.58 (m, 3H), 1.18 – 1.04 (m, 1H); m/z = 375.1 [M+H] ⁺
I-0001082	m/z = 363.1 [M+H] ⁺
I-0001086	
I-0001092	m/z = 359.1 [M+H] ⁺
I-0001095	¹ H-NMR (400 MHz, CDCl ₃) δ 7.81 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.65 – 7.57 (m, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.47 – 7.37 (m, 1H), 6.54 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.6 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.71 (t, J = 6.5 Hz, 1H), 3.51 (dd, J = 11.8, 3.6 Hz, 1H), 3.40 (dt, J = 10.4, 4.3 Hz, 1H), 2.99 (t, J = 6.8 Hz, 2H), 2.68 (ddd, J = 12.0, 9.2, 3.0 Hz, 1H), 2.50 (dd, J = 11.6, 8.6 Hz, 1H), 1.94 (dq, J = 12.4, 8.8, 4.3 Hz, 1H), 1.74 (ddq, J = 19.0, 13.8, 5.2, 4.5 Hz, 2H), 1.69 – 1.57 (m, 1H), 1.14 (ddt, J = 13.5, 9.4, 4.5 Hz, 1H); m/z = 421.1 [M+H] ⁺
I-0001096	¹ H-NMR (400 MHz, CDCl ₃) δ 7.34 – 7.26 (m, 2H), 7.10 – 7.00 (m, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.26 (d, J = 16.5 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.65 (t, J = 6.5 Hz, 1H), 3.49 (dd, J = 11.8, 3.7 Hz, 1H), 3.39 (dt, J = 10.9, 4.5 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.75 – 2.64 (m, 1H), 2.50 (dd, J = 11.7, 8.6 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.84 – 1.69 (m, 2H), 1.68 – 1.56 (m, 1H), 1.24 – 1.09 (m, 1H); m/z = 381.1 [M+H] ⁺
I-0001097	m/z = 370.1 [M+H] ⁺
I-0001098	m/z = 403.1 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001099	¹ H-NMR (400 MHz, CDCl ₃) δ 8.08 – 8.02 (m, 1H), 8.02 – 7.96 (m, 1H), 7.92 – 7.84 (m, 1H), 7.75 – 7.66 (m, 1H), 6.54 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.6 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.73 (t, J = 6.6 Hz, 1H), 3.54 (dd, J = 11.8, 3.6 Hz, 1H), 3.42 (dt, J = 10.9, 4.4 Hz, 1H), 3.02 – 2.92 (m, 2H), 2.70 – 2.59 (m, 1H), 2.46 (dd, J = 11.7, 8.8 Hz, 1H), 1.97 – 1.90 (m, 1H), 1.83 – 1.70 (m, 2H), 1.68 – 1.58 (m, 1H), 1.20 – 1.06 (m, 1H); m/z = 370.1 [M+H] ⁺
I-0001100	m/z = 381.1 [M+H] ⁺
I-0001101	¹ H-NMR (400 MHz, CDCl ₃) δ 7.77 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 6.62 (t, J = 72.6 Hz, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.72 (t, J = 6.6 Hz, 1H), 3.49 (dd, J = 11.7, 3.6 Hz, 1H), 3.43 – 3.31 (m, 1H), 3.01 – 2.91 (m, 2H), 2.67 – 2.56 (m, 1H), 2.43 (dd, J = 11.6, 8.7 Hz, 1H), 1.99 – 1.85 (m, 1H), 1.81 – 1.67 (m, 2H), 1.65 – 1.52 (m, 1H), 1.20 – 1.04 (m, 1H); m/z = 411.1 [M+H] ⁺
I-0001102	¹ H-NMR (400 MHz, CDCl ₃) δ 7.64 – 7.57 (m, 1H), 7.57 – 7.50 (m, 1H), 7.40 – 7.29 (m, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.66 (t, J = 6.6 Hz, 1H), 3.49 (dd, J = 11.7, 3.7 Hz, 1H), 3.38 (dt, J = 10.5, 4.4 Hz, 1H), 3.02 – 2.93 (m, 2H), 2.70 – 2.59 (m, 1H), 2.46 (dd, J = 11.7, 8.7 Hz, 1H), 2.00 – 1.85 (m, 1H), 1.82 – 1.69 (m, 2H), 1.67 – 1.58 (m, 1H), 1.20 – 1.06 (m, 1H); m/z = 381.1 [M+H] ⁺
I-0001103	¹ H-NMR (400 MHz, Chloroform-d) δ 7.59 – 7.44 (m, 1H), 7.12 – 6.95 (m, 2H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.67 (t, J = 6.6 Hz, 1H), 3.58 (dd, J = 12.5, 3.6 Hz, 1H), 3.55 – 3.42 (m, 1H), 3.09 – 2.93 (m, 3H), 2.83 (dd, J = 12.4, 8.0 Hz, 1H), 2.00 – 1.87 (m, 1H), 1.85 – 1.72 (m, 2H), 1.63 (m, 1H), 1.37 – 1.18 (m, 1H); m/z = 381.1 [M+H] ⁺
I-0001468	¹ H-NMR (400 MHz, CDCl ₃) δ 7.62 (dd, J = 6.7, 1.6 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.08 (dd, J = 10.0, 8.4 Hz, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.6 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.61 (t, J = 6.6 Hz, 1H), 3.48 (dd, J = 12.4, 3.5 Hz, 1H), 3.45 – 3.35 (m, 1H), 3.09 – 2.90 (m, 3H), 2.76 (dd, J = 12.3, 7.9 Hz, 1H), 2.38 (s, 3H), 1.97 – 1.86 (m, 1H), 1.82 – 1.70 (m, 2H), 1.66 – 1.54 (m, 1H), 1.31 – 1.19 (m, 1H); m/z = 377.1 [M+H] ⁺
I-0001105	¹ H-NMR (400 MHz, CDCl ₃) δ 7.72 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.78 (t, J = 6.4 Hz, 1H), 4.63 (p, J = 6.1 Hz, 1H), 3.38 – 3.24 (m, 2H), 3.13 (dt, J = 9.9, 7.6 Hz, 1H), 3.01 (dd, J = 10.1, 6.0 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.40 – 2.27 (m, 1H), 1.98 – 1.87 (m, 1H), 1.64 – 1.51 (m, 1H), 1.37 (d, J = 6.0 Hz, 6H); m/z = 389.1 [M+H] ⁺
I-0001106	¹ H-NMR (400 MHz, CDCl ₃) δ 8.15 – 8.09 (m, 1H), 8.09 – 8.01 (m, 1H), 7.93 – 7.85 (m, 1H), 7.75 – 7.66 (m, 1H), 6.49 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.76 (t, J = 6.5 Hz, 1H), 3.47 – 3.34 (m, 2H), 3.21 (dt, J = 9.9, 7.6 Hz, 1H), 3.08 (dd, J = 10.1, 6.5 Hz, 1H), 2.99 – 2.89 (m, 2H), 2.46 – 2.34 (m, 1H), 2.07 – 1.94 (m, 1H), 1.71 – 1.57 (m, 1H); m/z = 356.1 [M+H] ⁺
I-0001107	m/z = 356.1 [M+H] ⁺
I-0001108	¹ H-NMR (400 MHz, CDCl ₃) δ 7.88 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.52 – 7.45 (m, 2H), 7.45 – 7.38 (m, 1H), 6.46 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.92 (d, J = 9.9 Hz, 1H), 4.66 (t, J = 6.4 Hz, 1H), 3.47 – 3.34 (m, 2H), 3.22 (dt, J = 10.0, 7.6 Hz, 1H), 3.08 (dd, J = 10.1, 6.1 Hz, 1H), 2.95 – 2.88 (m, 2H), 2.43 – 2.31 (m, 1H), 2.03 – 1.91 (m, 1H), 1.67 – 1.57 (m, 1H); m/z = 407.1 [M+H] ⁺
I-0001109	¹ H-NMR (400 MHz, CDCl ₃) δ 7.39 – 7.31 (m, 2H), 7.06 (tt, J = 8.5, 2.3 Hz, 1H), 6.49 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.6 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.64 (s, 1H), 3.46 – 3.40 (m, 1H), 3.37 (dd, J = 10.1, 7.2 Hz, 1H), 3.26 – 3.18 (m, 1H), 3.07 (dd, J = 10.1, 6.3 Hz, 1H), 2.98 – 2.91 (m, 2H), 2.46 – 2.34 (m, 1H), 2.05 – 1.95 (m, 1H), 1.70 – 1.60 (m, 1H); m/z = 367.1 [M+H] ⁺
I-0001110	¹ H-NMR (400 MHz, CDCl ₃) δ 7.96 – 7.85 (m, 1H), 7.05 – 6.92 (m, 2H), 6.49 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.63 (t, J = 6.4 Hz, 1H), 3.57 – 3.41 (m, 2H), 3.31 (dtd, J = 10.0, 7.6, 0.9 Hz, 1H), 3.13 (dd, J = 10.1, 6.5 Hz, 1H), 3.05 – 2.94 (m, 2H), 2.50 – 2.38 (m, 1H), 2.09 – 1.98 (m, 1H), 1.74 – 1.62 (m, 1H); m/z = 367.1 [M+H] ⁺
I-0001111	¹ H-NMR (400 MHz, CDCl ₃) δ 7.67 (dd, J = 6.6, 2.3 Hz, 1H), 7.40 – 7.31 (m, 1H), 7.09 (dd, J = 10.0, 8.4 Hz, 1H), 6.49 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.6 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 3.56 – 3.43 (m, 2H), 3.36 – 3.25 (m, 1H), 3.13 (dd, J = 10.1, 6.5 Hz, 1H), 3.05 – 2.91 (m, 2H), 2.49 – 2.40 (m, 1H), 2.38 (s, 3H), 2.07 – 1.97 (m, 1H), 1.73 – 1.61 (m, 1H); m/z = 363.1 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001112	¹ H-NMR (400 MHz, CDCl ₃) δ 7.72 – 7.64 (m, 1H), 7.64 – 7.57 (m, 1H), 7.42 – 7.31 (m, 1H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.65 (t, J = 6.4 Hz, 1H), 3.45 – 3.30 (m, 2H), 3.19 (dt, J = 9.9, 7.6 Hz, 1H), 3.05 (dd, J = 10.1, 6.3 Hz, 1H), 2.97 – 2.89 (m, 2H), 2.45 – 2.33 (m, 1H), 2.05 – 1.93 (m, 1H), 1.68 – 1.58 (m, 1H); m/z = 367.1 [M+H] ⁺
I-0001113	¹ H-NMR (400 MHz, CDCl ₃) δ 7.57 – 7.45 (m, 1H), 7.09 – 6.98 (m, 2H), 6.50 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 3.63 – 3.51 (m, 2H), 3.45 – 3.34 (m, 1H), 3.24 – 3.15 (m, 1H), 3.08 – 2.95 (m, 2H), 2.56 – 2.43 (m, 1H), 2.12 – 2.03 (m, 1H), 1.79 – 1.66 (m, 1H); m/z = 367.1 [M+H] ⁺
I-0001023	m/z = 366.2 [M+H] ⁺
I-0001114	¹ H-NMR (400 MHz, CDCl ₃) δ 7.84 (d, J = 8.9 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 6.62 (t, J = 72.5 Hz, 1H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.21 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.65 (t, J = 6.4 Hz, 1H), 3.42 – 3.29 (m, 2H), 3.22 – 3.14 (m, 1H), 3.04 (dd, J = 10.1, 6.2 Hz, 1H), 2.96 – 2.83 (m, 2H), 2.42 – 2.31 (m, 1H), 2.01 – 1.92 (m, 1H), 1.66 – 1.55 (m, 1H); m/z = 397.1 [M+H] ⁺
I-0001024	m/z = 299.1 [M+H] ⁺
I-0001025	
I-0001026	m/z = 365.1 [M+H] ⁺
I-0001027	¹ H-NMR (400 MHz, CDCl ₃) δ 7.65 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.40 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.34 – 7.26 (m, 2H), 6.61 – 6.42 (m, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.91 (d, J = 9.9 Hz, 1H), 5.34 – 4.63 (m, 1H), 4.43 – 3.87 (m, 2H), 3.83 – 3.53 (m, 1H), 3.50 – 3.24 (m, 1H), 3.08 – 2.92 (m, 2H), 2.10 – 1.84 (m, 2H), 1.81 – 1.71 (m, 1H), 1.64 – 1.54 (m, 1H), 1.52 – 1.34 (m, 1H); m/z = 349.1 [M+H] ⁺
I-0001028	¹ H-NMR (400 MHz, CDCl ₃) δ 7.51 (dd, J = 1.8, 0.8 Hz, 1H), 7.08 (dd, J = 3.5, 0.8 Hz, 1H), 6.58 – 6.51 (m, 1H), 6.48 (dd, J = 3.5, 1.7 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 5.45 – 4.97 (m, 1H), 4.11 – 3.92 (m, 1H), 3.92 – 3.36 (m, 4H), 3.21 – 2.95 (m, 2H), 2.67 – 2.35 (m, 1H), 2.16 – 2.06 (m, 1H), 1.92 – 1.59 (m, 1H); m/z = 285.1 [M+H] ⁺
I-0001029	m/z = 352.1 [M+H] ⁺
I-0001030	¹ H-NMR (400 MHz, CDCl ₃) δ 7.71 – 7.59 (m, 1H), 7.56 – 7.46 (m, 1H), 7.46 – 7.34 (m, 2H), 7.32 – 7.22 (m, 1H), 6.61 – 6.44 (m, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 5.40 – 5.04 (m, 1H), 4.20 – 4.03 (m, 1H), 3.99 – 3.40 (m, 3H), 3.21 – 3.00 (m, 2H), 2.68 – 2.44 (m, 1H), 2.25 – 2.04 (m, 1H), 1.95 – 1.65 (m, 1H); m/z = 335.1 [M+H] ⁺
I-0001031	m/z = 351.1 [M+H] ⁺
I-0001032	m/z = 301.1 [M+H] ⁺
I-0001048	
I-0001049	m/z = 329.1 [M+H] ⁺
I-0001050	m/z = 363.1 [M+H] ⁺
I-0001051	m/z = 313.1 [M+H] ⁺
I-0001052	m/z = 295.1 [M+H] ⁺
I-0001436	m/z = 325.1 [M+H] ⁺
I-0001437	m/z = 325.1 [M+H] ⁺
I-0001438	m/z = 340.1 [M+H] ⁺
I-0001439	m/z = 340.1 [M+H] ⁺
I-0001440	m/z = 340.1 [M+H] ⁺
I-0001475	m/z = 328.1 [M+H] ⁺
I-0001476	m/z = 310.2 [M+H] ⁺
I-0001479	
I-0001481	m/z = 296.1 [M+H] ⁺
I-0001225	m/z = 363.0 [M+H] ⁺ ; m/z = 363.1 [M+H] ⁺
I-0001227	m/z = 313.1 [M+H] ⁺
I-0001228	m/z = 331.1 [M+H] ⁺
I-0001230	
I-0001226	m/z = 331.1 [M+H] ⁺
I-0001231	m/z = 329.1 [M+H] ⁺
I-0001232	m/z = 331.1 [M+H] ⁺
I-0001233	

Compound Identifier	Analytical Analysis
I-0001234	m/z = 329.1 [M+H] ⁺
I-0001237	¹ H-NMR (400 MHz, CDCl ₃) δ 7.84 (dd, J = 8.8, 5.1 Hz, 2H), 7.27 – 7.18 (m, 3H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.21 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.71 (t, J = 6.4 Hz, 1H), 3.42 – 3.28 (m, 2H), 3.22 – 3.12 (m, 1H), 3.04 (dd, J = 10.1, 6.2 Hz, 1H), 2.95 – 2.86 (m, 2H), 2.42 – 2.30 (m, 1H), 2.02 – 1.89 (m, 1H), 1.67 – 1.53 (m, 1H); m/z = 349.1 [M+H] ⁺
I-0001238	¹ H-NMR (400 MHz, CDCl ₃) δ 7.90 (dd, J = 8.2, 1.4 Hz, 1H), 7.46 (td, J = 7.5, 1.5 Hz, 1H), 7.36 – 7.29 (m, 2H), 6.49 (dd, J = 16.6, 9.9 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.69 (t, J = 6.4 Hz, 1H), 3.48 – 3.33 (m, 2H), 3.33 – 3.19 (m, 1H), 3.09 (dd, J = 10.1, 6.2 Hz, 1H), 3.05 – 2.93 (m, 2H), 2.63 (s, 3H), 2.54 – 2.25 (m, 1H), 2.12 – 1.85 (m, 1H), 1.76 – 1.50 (m, 1H); m/z = 345.1 [M+H] ⁺
I-0001239	¹ H-NMR (400 MHz, CDCl ₃) δ 8.39 (d, J = 1.1 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.96 – 7.89 (m, 1H), 7.81 (dd, J = 8.6, 1.8 Hz, 1H), 7.69 – 7.58 (m, 2H), 6.41 (dd, J = 16.5, 9.9 Hz, 1H), 6.13 (d, J = 16.5 Hz, 1H), 5.86 (d, J = 9.9 Hz, 1H), 4.66 (t, J = 6.4 Hz, 1H), 3.51 – 3.35 (m, 2H), 3.23 (dt, J = 9.9, 7.6 Hz, 1H), 3.10 (dd, J = 10.2, 6.0 Hz, 1H), 2.93 – 2.80 (m, 2H), 2.40 – 2.25 (m, 1H), 1.97 – 1.87 (m, 1H), 1.64 – 1.53 (m, 1H); m/z = 381.1 [M+H] ⁺
I-0001240	m/z = 361.0 & 361.1 [M+H] ⁺
I-0001241	m/z = 349.1 [M+H] ⁺
I-0001242	m/z = 349.1 [M+H] ⁺
I-0001243	m/z = 375.3 [M+H] ⁺
I-0001245	m/z = 331.1 [M+H] ⁺
I-0001246	m/z = 309.1 [M+H] ⁺
I-0001247	m/z = 363.0 [M+H] ⁺
I-0001248	m/z = 353.2 [M+H] ⁺
I-0001251	m/z = 363.0 & 363.1 [M+H] ⁺
I-0001253	m/z = 331.1 [M+H] ⁺
I-0001249	m/z = 313.1 [M+H] ⁺
I-0001250	m/z = 363.1 [M+H] ⁺
I-0001254	
I-0001291	¹ H-NMR (400 MHz, DMSO-d ₆) δ 7.94 (ddd, J = 8.4, 6.9, 1.7 Hz, 1H), 7.78 (ddd, J = 7.9, 6.2, 1.7 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.40 (t, 1H), 6.67 (dd, J = 16.5, 10.0 Hz, 1H), 5.99 (d, J = 16.8 Hz, 1H), 5.95 (d, J = 10.1 Hz, 1H), 3.40 (dd, J = 10.0, 7.3 Hz, 1H), 3.37 – 3.29 (m, 1H), 3.28 – 3.19 (m, 1H), 2.99 (dd, J = 10.0, 7.1 Hz, 1H), 2.81 – 2.69 (m, 2H), 2.35 – 2.25 (m, 1H), 1.99 – 1.86 (m, 1H), 1.64 – 1.52 (m, 1H); m/z = 383.0 [M+H] ⁺
I-0001255	m/z = 345.0 [M+H] ⁺
I-0001256	m/z = 379.1 [M+H] ⁺
I-0001284	¹ H-NMR (400 MHz, CDCl ₃) δ 8.07 (s, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.76 – 7.67 (m, 1H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.66 (t, J = 6.5 Hz, 1H), 3.42 (ddd, J = 9.9, 8.2, 4.8 Hz, 1H), 3.36 (dd, J = 10.1, 7.2 Hz, 1H), 3.19 (dt, J = 9.9, 7.6 Hz, 1H), 3.08 (dd, J = 10.1, 6.2 Hz, 1H), 2.97 – 2.88 (m, 2H), 2.44 – 2.33 (m, 1H), 2.04 – 1.95 (m, 1H), 1.70 – 1.58 (m, 1H); m/z = 399.1 [M+H] ⁺
I-0001285	¹ H-NMR (400 MHz, CDCl ₃) δ 7.42 (s, 2H), 7.22 (s, 1H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.21 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.64 (t, J = 6.4 Hz, 1H), 3.37 (ddd, J = 9.9, 8.2, 4.9 Hz, 1H), 3.30 (dd, J = 10.1, 7.3 Hz, 1H), 3.15 (dt, J = 9.9, 7.6 Hz, 1H), 3.03 (dd, J = 10.1, 6.0 Hz, 1H), 2.96 – 2.85 (m, 2H), 2.39 (s, 6H), 2.38 – 2.27 (m, 1H), 2.01 – 1.88 (m, 1H), 1.65 – 1.51 (m, 1H); m/z = 359.1 [M+H] ⁺
I-0001286	¹ H-NMR (400 MHz, CDCl ₃) δ 7.86 (dd, J = 8.0, 1.3 Hz, 1H), 7.58 (dd, J = 7.9, 1.3 Hz, 1H), 7.33 – 7.18 (m, 1H), 6.50 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.63 (t, J = 6.5 Hz, 1H), 3.51 – 3.35 (m, 2H), 3.29 (dt, J = 9.8, 7.5 Hz, 1H), 3.11 (dd, J = 10.1, 6.2 Hz, 1H), 3.08 – 2.94 (m, 2H), 2.68 (s, 3H), 2.57 – 2.42 (m, 1H), 2.15 – 2.00 (m, 1H), 1.80 – 1.67 (m, 1H); m/z = 379.1 [M+H] ⁺
I-0001287	

Compound Identifier	Analytical Analysis
I-0001288	¹ H-NMR (400 MHz, CDCl ₃) δ 8.10 (dd, J = 8.9, 5.9 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.11 (ddd, J = 8.8, 7.5, 2.6 Hz, 1H), 6.50 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.6 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.50 (t, J = 6.5 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.38 (dt, J = 9.7, 7.5 Hz, 1H), 3.17 (dd, J = 10.0, 6.3 Hz, 1H), 3.10 – 2.93 (m, 2H), 2.55 – 2.43 (m, 1H), 2.13 – 2.03 (m, 1H), 1.79 – 1.67 (m, 1H); m/z = 383.0 [M+H] ⁺
I-0001289	¹ H-NMR (400 MHz, CDCl ₃) δ 7.73 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.47 (dd, J = 16.6, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.57 (t, J = 6.4 Hz, 1H), 3.43 – 3.35 (m, 1H), 3.35 – 3.27 (m, 1H), 3.19 – 3.12 (m, 1H), 3.07 – 2.95 (m, 2H), 2.95 – 2.85 (m, 2H), 2.41 – 2.30 (m, 1H), 2.00 – 1.90 (m, 1H), 1.64 – 1.54 (m, 2H), 1.28 (d, J = 6.9 Hz, 6H); m/z = 373.1 [M+H] ⁺
I-0001290	m/z = 399.2 & 401.2 [M+H] ⁺
I-0001282	¹ H-NMR (400 MHz, CDCl ₃) δ 7.46 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 8.6, 7.4 Hz, 1H), 6.51 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.6 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.64 (t, J = 6.4 Hz, 1H), 3.68 – 3.57 (m, 2H), 3.52 – 3.43 (m, 1H), 3.27 (dd, J = 10.0, 6.3 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.58 – 2.46 (m, 1H), 2.15 – 2.05 (m, 1H), 1.81 – 1.69 (m, 1H); m/z = 399.0 [M+H] ⁺
I-0001292	¹ H-NMR (400 MHz, CDCl ₃) δ 8.09 – 8.02 (m, 1H), 7.51 – 7.39 (m, 2H), 6.50 (dd, J = 16.6, 9.8 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.8 Hz, 1H), 4.64 (t, J = 6.5 Hz, 1H), 3.61 – 3.49 (m, 2H), 3.40 (dt, J = 9.8, 7.6 Hz, 1H), 3.19 (dd, J = 10.0, 6.4 Hz, 1H), 3.08 – 2.95 (m, 2H), 2.55 – 2.43 (m, 1H), 2.14 – 2.03 (m, 1H), 1.80 – 1.66 (m, 1H); m/z = 399.0 [M+H] ⁺
I-0001293	¹ H-NMR (400 MHz, CDCl ₃) δ 7.60 (ddd, J = 7.9, 5.2, 3.1 Hz, 1H), 7.31 – 7.16 (m, 3H), 6.50 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.66 (t, J = 6.4 Hz, 1H), 3.56 – 3.48 (m, 2H), 3.38 – 3.30 (m, 1H), 3.15 (dd, J = 10.2, 6.6 Hz, 1H), 3.05 – 2.93 (m, 2H), 2.52 – 2.39 (m, 1H), 2.09 – 2.01 (m, 1H), 1.74 – 1.64 (m, 1H); m/z = 367.1 [M+H] ⁺
I-0001294	¹ H-NMR (400 MHz, CDCl ₃) δ 6.52 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.79 (t, J = 6.4 Hz, 1H), 3.59 – 3.45 (m, 2H), 3.37 (dt, J = 9.9, 7.5 Hz, 1H), 3.21 (dd, J = 10.2, 6.2 Hz, 1H), 3.09 – 2.87 (m, 3H), 2.54 – 2.43 (m, 1H), 2.11 – 2.02 (m, 2H), 1.92 – 1.83 (m, 2H), 1.77 – 1.60 (m, 3H), 1.60 – 1.44 (m, 2H), 1.36 – 1.11 (m, 3H); m/z = 337.1 [M+H] ⁺
I-0001295	m/z = 375.1 [M+H] ⁺
I-0001296	m/z = 365.0 & 365.1 [M+H] ⁺
I-0001269	m/z = 413.0 & 413.1 [M+H] ⁺
I-0001270	¹ H-NMR (400 MHz, CDCl ₃) δ 7.21 (s, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.6 Hz, 1H), 5.96 (d, J = 9.8 Hz, 1H), 4.70 (t, J = 6.6 Hz, 1H), 3.41 (dd, J = 11.7, 3.6 Hz, 1H), 3.37 – 3.27 (m, 1H), 3.06 – 2.90 (m, 2H), 2.71 – 2.60 (m, 1H), 2.46 (dd, J = 11.7, 8.4 Hz, 1H), 2.39 (s, 6H), 1.96 – 1.86 (m, 1H), 1.80 – 1.67 (m, 2H), 1.65 – 1.56 (m, 1H), 1.19 – 1.05 (m, 1H); m/z = 373.1 [M+H] ⁺
I-0001297	
I-0001298	¹ H-NMR (400 MHz, Chloroform-d) δ 8.40 (d, J = 8.9 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.8 Hz, 1H), 4.34 (t, J = 6.5 Hz, 1H), 3.48 – 3.37 (m, 2H), 3.25 (dt, J = 9.9, 7.6 Hz, 1H), 3.10 (dd, J = 10.1, 6.3 Hz, 1H), 2.98 – 2.90 (m, 2H), 2.40 (p, J = 7.1 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.70 – 1.59 (m, 1H); m/z = 376.0 & 376.1 [M+H] ⁺
I-0001299	m/z = 395.1 [M+H] ⁺
I-0001300	m/z = 379.1 [M+H] ⁺
I-0001274	
I-0001301	¹ H-NMR (400 MHz, CDCl ₃) δ 8.69 – 8.59 (m, 1H), 8.46 (ddd, J = 8.2, 2.2, 1.1 Hz, 1H), 8.16 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H), 7.83 – 7.74 (m, 1H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.21 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.63 (t, J = 6.4 Hz, 1H), 3.49 – 3.37 (m, 2H), 3.25 (dt, J = 9.9, 7.6 Hz, 1H), 3.11 (dd, J = 10.1, 6.4 Hz, 1H), 3.00 – 2.88 (m, 2H), 2.46 – 2.35 (m, 1H), 2.06 – 1.96 (m, 1H), 1.71 – 1.60 (m, 1H); m/z = 376.0 & 376.1 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001268	¹ H-NMR (400 MHz, CDCl ₃) δ 7.53 – 7.40 (m, 2H), 7.32 (dd, J = 8.6, 7.4 Hz, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.67 (t, J = 6.6 Hz, 1H), 3.58 (dd, J = 13.3, 3.6 Hz, 1H), 3.53 – 3.43 (m, 1H), 3.28 (ddd, J = 12.1, 8.2, 3.3 Hz, 1H), 3.14 – 2.94 (m, 3H), 1.99 – 1.88 (m, 1H), 1.86 – 1.71 (m, 2H), 1.67 – 1.53 (m, 1H), 1.44 – 1.31 (m, 1H); m/z = 413.0 [M+H] ⁺
I-0001271	¹ H-NMR (400 MHz, CDCl ₃) δ 7.81 (dd, J = 8.0, 1.3 Hz, 1H), 7.58 (dd, J = 8.0, 1.3 Hz, 1H), 7.26 (d, J = 15.9 Hz, 1H), 6.50 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.64 (t, J = 6.6 Hz, 1H), 3.51 (dd, J = 12.6, 3.6 Hz, 1H), 3.46 – 3.33 (m, 1H), 3.05 – 2.93 (m, 3H), 2.80 (dd, J = 12.6, 8.2 Hz, 1H), 2.65 (s, 3H), 1.95 – 1.85 (m, 1H), 1.85 – 1.71 (m, 2H), 1.65 – 1.51 (m, 1H), 1.35 – 1.20 (m, 1H); m/z = 393.1 [M+H] ⁺
I-0001272	¹ H-NMR (400 MHz, CDCl ₃) δ 7.83 (d, J = 2.0 Hz, 1H), 7.65 – 7.54 (m, 2H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.68 (t, J = 6.6 Hz, 1H), 3.49 (dd, J = 11.7, 3.6 Hz, 1H), 3.43 – 3.32 (m, 1H), 3.03 – 2.89 (m, 2H), 2.66 (ddd, J = 11.9, 9.3, 3.0 Hz, 1H), 2.48 (dd, J = 11.7, 8.7 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.83 – 1.68 (m, 2H), 1.69 – 1.55 (m, 1H), 1.22 – 1.07 (m, 1H); m/z = 413.0 [M+H] ⁺
I-0001273	
I-0001275	m/z = 397.0 [M+H] ⁺
I-0001276	m/z = 397.0 [M+H] ⁺
I-0001277	¹ H-NMR (400 MHz, CDCl ₃) δ 7.55 (ddd, J = 7.5, 5.2, 3.1 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.19 (ddd, J = 9.0, 4.1 Hz, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.64 (t, J = 6.5 Hz, 1H), 3.55 (dd, J = 12.5, 3.6 Hz, 1H), 3.45 (dt, J = 11.8, 5.8 Hz, 1H), 3.05 – 2.90 (m, 3H), 2.76 (dd, J = 12.4, 8.2 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.84 – 1.71 (m, 2H), 1.68 – 1.53 (m, 1H), 1.32 – 1.18 (m, 1H); m/z = 381.0 & 381.1 [M+H] ⁺
I-0001278	¹ H-NMR (400 MHz, CDCl ₃) δ 8.07 – 7.97 (m, 1H), 7.50 – 7.39 (m, 2H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.61 (t, J = 6.6 Hz, 1H), 3.56 (dd, J = 12.9, 3.6 Hz, 1H), 3.46 (dt, J = 10.2, 5.2 Hz, 1H), 3.14 (ddd, J = 12.3, 8.7, 3.2 Hz, 1H), 3.09 – 2.90 (m, 3H), 1.98 – 1.86 (m, 1H), 1.86 – 1.69 (m, 2H), 1.65 – 1.52 (m, 1H), 1.39 – 1.24 (m, 1H); m/z = 413.0 [M+H] ⁺
I-0001279	
I-0001280	¹ H-NMR (400 MHz, CDCl ₃) δ 8.04 (dd, J = 7.8, 1.5 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.43 – 7.36 (m, 1H), 6.52 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.6 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.59 (t, J = 6.6 Hz, 1H), 3.51 (dd, J = 12.9, 3.6 Hz, 1H), 3.48 – 3.35 (m, 1H), 3.17 (ddd, J = 12.2, 8.4, 3.2 Hz, 1H), 3.10 – 2.89 (m, 3H), 1.97 – 1.85 (m, 1H), 1.85 – 1.70 (m, 2H), 1.67 – 1.51 (m, 2H), 1.37 – 1.23 (m, 1H); m/z = 379.0 & 379.1 [M+H] ⁺
I-0001443	m/z = 390.1 [M+H] ⁺
I-0001444	¹ H-NMR (400 MHz, CDCl ₃) δ 8.61 – 8.55 (m, 1H), 8.46 (ddd, J = 8.3, 2.3, 1.1 Hz, 1H), 8.14 – 8.06 (m, 1H), 7.83 – 7.74 (m, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.26 (d, J = 16.5 Hz, 1H), 5.99 (d, J = 9.9 Hz, 1H), 4.52 (t, J = 6.7 Hz, 1H), 3.53 (dd, J = 11.8, 3.6 Hz, 1H), 3.48 – 3.39 (m, 1H), 3.04 – 2.95 (m, 2H), 2.78 – 2.67 (m, 1H), 2.54 (dd, J = 11.8, 8.6 Hz, 1H), 2.01 – 1.87 (m, 1H), 1.86 – 1.68 (m, 2H), 1.68 – 1.59 (m, 1H), 1.23 – 1.09 (m, 1H); m/z = 390.0 & 390.1 [M+H] ⁺
I-0001445	
I-0001317	m/z = 347.1 [M+H] ⁺
I-0001441	
I-0001442	m/z = 393.1 [M+H] ⁺
I-0001318	m/z = 355.1 [M+H] ⁺
I-0001319	m/z = 371.1 [M+H] ⁺
I-0001320	
I-0001321	m/z = 347.1 [M+H] ⁺
I-0001322	m/z = 301.1 & 301.2 [M+H] ⁺
I-0001323	m/z = 395.1 [M+H] ⁺
I-0001326	m/z = 343.1 [M+H] ⁺
I-0001328	m/z = 331.1 [M+H] ⁺
I-0001329	m/z = 320.1 [M+H] ⁺
I-0001330	
I-0001331	m/z = 338.3 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001482	m/z = 367.3 [M+H] ⁺
I-0001516	m/z = 301.2 [M+H] ⁺
I-0001528	m/z = 299.2 [M+H] ⁺
I-0001532	
I-0001483	m/z = 431.3 [M+H] ⁺
I-0001512	m/z = 315.3 [M+H] ⁺
I-0001524	m/z = 312.3 [M+H] ⁺
I-0001348	m/z = 377.2 [M+H] ⁺
I-0001351	m/z = 347.1 [M+H] ⁺
I-0001488	
I-0001356	m/z = 327.1 [M+H] ⁺
I-0001352	m/z = 323.1 & 323.2 [M+H] ⁺
I-0001353	
I-0001360	m/z = 343.2 [M+H] ⁺
I-0001365	m/z = 323.2 [M+H] ⁺
I-0001366	m/z = 323.2 [M+H] ⁺
I-0001367	m/z = 351.2 [M+H] ⁺
I-0001361	m/z = 355.2 [M+H] ⁺
I-0001371	¹ H-NMR (400 MHz, CDCl ₃) δ 7.87 (dd, J = 7.8, 1.7 Hz, 1H), 7.52 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.08 – 6.97 (m, 2H), 6.52 (dd, J = 16.6, 9.9 Hz, 1H), 6.23 (d, J = 16.6 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.71 (t, J = 6.6 Hz, 1H), 3.93 (s, 3H), 3.46 (dd, J = 12.8, 3.5 Hz, 1H), 3.40 – 3.29 (m, 1H), 3.16 – 2.87 (m, 4H), 1.95 – 1.83 (m, 1H), 1.79 – 1.69 (m, 2H), 1.59 – 1.50 (m, 1H), 1.35 – 1.24 (m, 1H); m/z = 347.1 [M+H] ⁺ m/z = 375.1 & 375.2 [M+H] ⁺
I-0001372	m/z = 413.1 [M+H] ⁺
I-0001362	
I-0001363	m/z = 327.2 [M+H] ⁺
I-0001364	m/z = 327.2 [M+H] ⁺
I-0001374	m/z = 359.1 & 359.2 [M+H] ⁺
I-0001411	
I-0001412	m/z = 397.2 [M+H] ⁺
I-0001413	m/z = 397.2 [M+H] ⁺
I-0001419	m/z = 353.2 [M+H] ⁺
I-0001421	m/z = 377.2 [M+H] ⁺
I-0001422	m/z = 393.3 [M+H] ⁺
I-0001415	m/z = 393.3 [M+H] ⁺
I-0001416	m/z = 351.3 [M+H] ⁺
I-0001417	m/z = 327.1 & 327.2 [M+H] ⁺
I-0001423	
I-0001424	m/z = 355.2 [M+H] ⁺
I-0001425	
I-0001418	m/z = 327.2 [M+H] ⁺
I-0001429	m/z = 373.0 [M+H] ⁺
I-0001430	m/z = 393.2 [M+H] ⁺
I-0001426	
I-0001427	m/z = 373.1 & 375.1 [M+H] ⁺
I-0001212	¹ H-NMR (400 MHz, CDCl ₃) δ 7.81 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.71 (t, J = 6.6 Hz, 1H), 3.51 (dd, J = 11.8, 3.6 Hz, 1H), 3.38 (dt, J = 10.7, 4.5 Hz, 1H), 3.02 – 2.93 (m, 2H), 2.69 – 2.58 (m, 1H), 2.46 (dd, J = 11.7, 8.6 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.83 – 1.68 (m, 2H), 1.68 – 1.57 (m, 1H), 1.20 – 1.06 (m, 1H); m/z = 429.1 & 429.2 [M+H] ⁺
I-0001428	m/z = 343.1 & 343.2 [M+H] ⁺
I-0001213	¹ H-NMR (400 MHz, CDCl ₃) δ 7.99 (dd, J = 8.1, 1.7 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.45 – 7.36 (m, 2H), 6.52 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.61 (t, J = 6.5 Hz, 1H), 3.46 (dd, J = 12.7, 3.5 Hz, 1H), 3.44 – 3.38 (m, 1H), 3.13 – 2.92 (m, 3H), 2.85 (dd, J = 12.7, 7.7 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.83 – 1.70 (m, 2H), 1.65 – 1.52 (m, 1H), 1.35 – 1.23 (m, 1H); m/z = 429.1 & 429.2 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001214	m/z = 390.2 [M+H] ⁺
I-0001215	m/z = 413.1 & 415.1 [M+H] ⁺
I-0001216	m/z = 379.1 & 379.2 [M+H] ⁺
I-0001217	¹ H-NMR (400 MHz, CDCl ₃) δ 8.02 (dd, J = 8.0, 1.6 Hz, 1H), 7.67 (dd, J = 8.0, 1.6 Hz, 1H), 7.40 – 7.31 (m, 1H), 6.50 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.54 (t, J = 6.5 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.41 (dt, J = 9.8, 7.5 Hz, 1H), 3.19 (dd, J = 10.0, 6.3 Hz, 1H), 3.08 – 2.95 (m, 2H), 2.56 – 2.44 (m, 1H), 2.14 – 2.04 (m, 1H), 1.80 – 1.69 (m, 1H); m/z = 399.0 & 399.1 [M+H] ⁺
I-0001376	¹ H-NMR (400 MHz, CDCl ₃) δ 7.98 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.38 (dd, J = 8.5, 2.1 Hz, 1H), 6.52 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.66 (t, J = 6.6 Hz, 1H), 3.54 (dd, J = 12.9, 3.6 Hz, 1H), 3.45 (dt, J = 12.7, 5.1 Hz, 1H), 3.10 (ddd, J = 12.3, 8.8, 3.2 Hz, 1H), 3.04 – 2.95 (m, 2H), 2.90 (dd, J = 12.9, 7.9 Hz, 1H), 1.96 – 1.86 (m, 1H), 1.86 – 1.68 (m, 2H), 1.66 – 1.50 (m, 1H), 1.36 – 1.22 (m, 1H); m/z = 413.0 & 413.1 [M+H] ⁺
I-0001218	m/z = 376.1 [M+H] ⁺
I-0001219	¹ H-NMR (400 MHz, CDCl ₃) δ 7.88 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.62 (t, J = 6.5 Hz, 1H), 3.45 – 3.31 (m, 2H), 3.18 (dt, J = 9.9, 7.6 Hz, 1H), 3.11 – 3.04 (m, 1H), 2.93 (ddd, J = 7.6, 6.5, 1.5 Hz, 2H), 2.45 – 2.33 (m, 1H), 2.05 – 1.92 (m, 1H), 1.70 – 1.56 (m, 1H); m/z = 415.1 & 415.2 [M+H] ⁺
I-0001220	m/z = 415.1 & 415.2 [M+H] ⁺
I-0001221	m/z = 365.0 & 365.1 [M+H] ⁺
I-0001375	¹ H-NMR (400 MHz, CDCl ₃) δ 7.74 – 7.66 (m, 1H), 7.65 – 7.56 (m, 2H), 7.50 – 7.42 (m, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.64 (t, J = 6.6 Hz, 1H), 3.48 (dd, J = 11.8, 3.6 Hz, 1H), 3.37 (dt, J = 10.8, 4.5 Hz, 1H), 3.02 – 2.94 (m, 2H), 2.73 – 2.62 (m, 1H), 2.48 (dd, J = 11.7, 8.5 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.82 – 1.69 (m, 2H), 1.68 – 1.57 (m, 1H), 1.21 – 1.08 (m, 1H); m/z = 429.1 & 429.2 [M+H] ⁺
I-0001377	m/z = 381.1 & 382.2 [M+H] ⁺
I-0001383	
I-0001447	m/z = 407.2 [M+H] ⁺
I-0001378	m/z = 421.2 [M+H] ⁺
I-0001379	¹ H-NMR (400 MHz, CDCl ₃) δ 7.53 (ddd, J = 8.6, 2.2, 1.2 Hz, 1H), 7.46 (dd, J = 10.3, 2.2 Hz, 1H), 7.12 – 7.03 (m, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.6 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.69 (t, J = 6.5 Hz, 1H), 3.96 (s, 3H), 3.46 (dd, J = 11.7, 3.6 Hz, 1H), 3.35 (dt, J = 10.8, 4.6 Hz, 1H), 3.01 – 2.92 (m, 2H), 2.66 – 2.55 (m, 1H), 2.41 (dd, J = 11.6, 8.7 Hz, 1H), 1.99 – 1.85 (m, 1H), 1.80 – 1.66 (m, 2H), 1.66 – 1.51 (m, 1H), 1.18 – 1.04 (m, 1H); m/z = 393.1 & 393.2 [M+H] ⁺
I-0001380	¹ H-NMR (400 MHz, CDCl ₃) δ 7.82 (dd, J = 5.9, 2.7 Hz, 1H), 7.52 (ddd, J = 8.8, 4.2, 2.7 Hz, 1H), 7.22 – 7.12 (m, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.6 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.60 (t, J = 6.6 Hz, 1H), 3.53 (dd, J = 12.4, 3.6 Hz, 1H), 3.45 (dt, J = 11.2, 5.1 Hz, 1H), 3.09 – 2.92 (m, 3H), 2.78 (dd, J = 12.4, 8.1 Hz, 1H), 1.97 – 1.87 (m, 1H), 1.84 – 1.72 (m, 2H), 1.68 – 1.53 (m, 1H), 1.32 – 1.20 (m, 1H); m/z = 397.0 & 397.1 [M+H] ⁺
I-0001381	¹ H-NMR (400 MHz, CDCl ₃) δ 8.08 (dd, J = 7.8, 1.8 Hz, 1H), 7.74 (dd, J = 7.8, 1.4 Hz, 1H), 7.46 (td, J = 7.6, 1.4 Hz, 1H), 7.39 (td, J = 7.6, 1.8 Hz, 1H), 6.51 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.6 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.62 (t, J = 6.6 Hz, 1H), 3.54 (dd, J = 13.0, 3.6 Hz, 1H), 3.50 – 3.37 (m, 1H), 3.15 (ddd, J = 12.3, 8.7, 3.2 Hz, 1H), 3.09 – 2.87 (m, 3H), 1.97 – 1.86 (m, 1H), 1.86 – 1.68 (m, 2H), 1.67 – 1.52 (m, 1H), 1.38 – 1.22 (m, 1H); m/z = 423.0 [M+H] ⁺
I-0001448	¹ H-NMR (400 MHz, CDCl ₃) δ 7.91 (dd, J = 7.7, 1.8 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.09 – 6.99 (m, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.93 (d, J = 9.9 Hz, 1H), 4.72 (t, J = 6.3 Hz, 1H), 3.95 (s, 3H), 3.56 (dd, J = 10.2, 7.2 Hz, 1H), 3.50 (ddd, J = 9.9, 8.1, 4.8 Hz, 1H), 3.32 (dt, J = 9.9, 7.6 Hz, 1H), 3.13 (dd, J = 10.1, 6.6 Hz, 1H), 3.03 – 2.90 (m, 2H), 2.48 – 2.34 (m, 1H), 2.06 – 1.93 (m, 1H), 1.71 – 1.58 (m, 1H); m/z = 361.1 & 361.2 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001449	¹ H-NMR (400 MHz, CDCl ₃) δ 7.70 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 3.40 – 3.33 (m, 1H), 3.31 (dd, J = 10.0, 7.1 Hz, 1H), 3.14 (dt, J = 9.9, 7.6 Hz, 1H), 3.01 (dd, J = 10.1, 6.1 Hz, 1H), 2.94 – 2.84 (m, 2H), 2.44 (s, 3H), 2.37 – 2.28 (m, 1H), 1.99 – 1.87 (m, 1H), 1.62 – 1.51 (m, 1H); m/z = 345.1 & 345.2 [M+H] ⁺
I-0001510	
I-0001382	¹ H-NMR (400 MHz, CDCl ₃) δ 7.83 (dd, J = 6.7, 2.2 Hz, 1H), 7.66 (ddd, J = 8.6, 4.4, 2.3 Hz, 1H), 7.36 – 7.26 (m, 1H), 6.53 (dd, J = 16.5, 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.69 (t, J = 6.5 Hz, 1H), 3.49 (dd, J = 11.8, 3.6 Hz, 1H), 3.38 (dt, J = 10.5, 4.4 Hz, 1H), 3.02 – 2.93 (m, 2H), 2.70 – 2.59 (m, 1H), 2.46 (dd, J = 11.7, 8.6 Hz, 1H), 2.00 – 1.86 (m, 1H), 1.82 – 1.69 (m, 2H), 1.68 – 1.57 (m, 1H), 1.20 – 1.07 (m, 1H); m/z = 397.0 & 397.1 [M+H] ⁺
I-0001384	¹ H-NMR (400 MHz, CDCl ₃) δ 7.80 – 7.73 (m, 1H), 7.70 – 7.57 (m, 2H), 7.51 – 7.43 (m, 1H), 6.48 (dd, J = 16.6, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.63 (t, J = 6.4 Hz, 1H), 3.46 – 3.30 (m, 2H), 3.19 (dt, J = 9.8, 7.6 Hz, 1H), 3.06 (dd, J = 10.1, 6.2 Hz, 1H), 2.96 – 2.88 (m, 2H), 2.44 – 2.32 (m, 1H), 2.04 – 1.91 (m, 1H), 1.70 – 1.56 (m, 1H); m/z = 415.1 [M+H] ⁺
I-0001385	m/z = 399.9 & 401.9 [M+H] ⁺
I-0001386	m/z = 407.2 [M+H] ⁺
I-0001465	m/z = 367.1 [M+H] ⁺
I-0001389	¹ H-NMR (400 MHz, CDCl ₃) δ 7.59 (ddd, J = 8.5, 2.2, 1.3 Hz, 1H), 7.53 (dd, J = 10.3, 2.2 Hz, 1H), 7.14 – 7.01 (m, 1H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.8 Hz, 1H), 4.66 (t, J = 6.3 Hz, 1H), 3.97 (s, 3H), 3.40 – 3.26 (m, 2H), 3.16 (dt, J = 9.9, 7.6 Hz, 1H), 3.02 (dd, J = 10.1, 6.2 Hz, 1H), 2.95 – 2.86 (m, 2H), 2.43 – 2.28 (m, 1H), 2.01 – 1.91 (m, 1H), 1.67 – 1.52 (m, 1H); m/z = 379.1 & 379.2 [M+H] ⁺
I-0001390	
I-0001391	
I-0001537	m/z = 337.0 & 337.3 [M+H] ⁺
I-0001358	
I-0001387	¹ H-NMR (400 MHz, CDCl ₃) δ 7.90 (dd, J = 6.7, 2.3 Hz, 1H), 7.73 (ddd, J = 8.6, 4.4, 2.3 Hz, 1H), 7.35 – 7.28 (m, 1H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.6 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.61 (t, J = 6.4 Hz, 1H), 3.44 – 3.37 (m, 1H), 3.35 (dd, J = 9.9, 7.1 Hz, 1H), 3.19 (dt, J = 9.9, 7.6 Hz, 1H), 3.06 (dd, J = 10.1, 6.2 Hz, 1H), 2.98 – 2.90 (m, 2H), 2.45 – 2.33 (m, 1H), 2.05 – 1.95 (m, 1H), 1.69 – 1.60 (m, 1H); m/z = 383.0 & 383.1 [M+H] ⁺
I-0001354	
I-0001546	¹ H-NMR (400 MHz, CDCl ₃) δ 7.70 (d, J = 7.8 Hz, 1H), 7.57 (dd, J = 8.4, 1.0 Hz, 1H), 7.48 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.42 – 7.31 (m, 2H), 6.41 (dd, J = 16.5, 9.9 Hz, 1H), 6.15 (d, J = 16.5 Hz, 1H), 5.88 (d, J = 9.9 Hz, 1H), 4.61 (t, J = 6.4 Hz, 1H), 3.65 – 3.51 (m, 2H), 3.43 (dt, J = 10.2, 7.5 Hz, 1H), 3.22 (dd, J = 10.5, 6.4 Hz, 1H), 2.92 (t, J = 6.9 Hz, 2H), 2.49 – 2.33 (m, 1H), 2.08 – 1.95 (m, 1H), 1.75 – 1.61 (m, 1H); m/z = 371.1 [M+H] ⁺
I-0001548	m/z = 325.2 [M+H] ⁺
I-0001549	m/z = 339.2 [M+H] ⁺
I-0001547	m/z = 321.2 [M+H] ⁺
I-0001552	m/z = 335.2 [M+H] ⁺
I-0001554	m/z = 371.2 [M+H] ⁺
I-0001369	
I-0001388	¹ H-NMR (400 MHz, CDCl ₃) δ 8.11 (dd, J = 7.8, 1.8 Hz, 1H), 7.75 (dd, J = 7.8, 1.4 Hz, 1H), 7.46 (ddd, J = 7.6, 1.4 Hz, 1H), 7.40 (ddd, J = 7.6, 1.9 Hz, 1H), 6.49 (dd, J = 16.5, 9.9 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.63 (t, J = 6.4 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.39 (dt, J = 9.7, 7.5 Hz, 1H), 3.18 (dd, J = 10.0, 6.2 Hz, 1H), 3.08 – 2.95 (m, 2H), 2.55 – 2.44 (m, 1H), 2.13 – 2.03 (m, 1H), 1.79 – 1.68 (m, 1H); m/z = 409.0 [M+H] ⁺
I-0001550	m/z = 384.2 [M+H] ⁺
I-0001396	
I-0001551	m/z = 419.3 [M+H] ⁺
I-0001559	m/z = 370.2 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0001555	m/z = 407.3 [M+H] ⁺
I-0001544	m/z = 387.2 [M+H] ⁺
I-0001545	¹ H-NMR (400 MHz, CDCl ₃) δ 7.61 – 7.56 (m, 1H), 7.05 (d, J = 3.5 Hz, 1H), 6.57 – 6.43 (m, 2H), 6.23 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.70 (t, J = 6.4 Hz, 1H), 3.56 – 3.42 (m, 2H), 3.33 (dt, J = 10.2, 7.5 Hz, 1H), 3.12 (dd, J = 10.5, 6.5 Hz, 1H), 2.98 – 2.89 (m, 2H), 2.45 – 2.33 (m, 1H), 2.06 – 1.93 (m, 1H), 1.70 – 1.56 (m, 1H); m/z = 321.1 [M+H] ⁺
I-0001560	m/z = 387.0 & 387.2 [M+H] ⁺
I-0001561	m/z = 363.3 [M+H] ⁺
I-0001359	
I-0001542	¹ H-NMR (400 MHz, CDCl ₃) δ 7.72 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.21 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.72 (t, J = 6.4 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.32 (dd, J = 10.1, 7.3 Hz, 1H), 3.15 (dt, J = 9.9, 7.6 Hz, 1H), 3.04 (dd, J = 10.1, 6.1 Hz, 1H), 2.97 – 2.85 (m, 2H), 2.74 – 2.63 (m, 1H), 2.41 – 2.30 (m, 1H), 1.99 – 1.88 (m, 1H), 1.66 – 1.53 (m, 3H), 1.26 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H); m/z = 387.1 & 387.3 [M+H] ⁺
I-0001539	m/z = 433.2 [M+H] ⁺
I-0001556	
I-0001564	¹ H-NMR (300 MHz, CDCl ₃) δ 7.96 (d, 1H, J = 8.7 Hz), 7.88 (d, 1H, J = 8.7 Hz), 6.83 (brs, 1H), 6.49 (dd, J = 9.9, 16.2 Hz, 1H), 6.23 (d, J = 7.5 Hz, 1H), 5.96 (d, J = 9.6 Hz, 1H), 4.46 (m, 1H), 3.96 (s, 3H), 3.58-3.48 (m, 2H), 3.38-3.30 (m, 1H), 3.16-3.11 (dd, J = 6.3, 9.9 Hz, 1H), 3.02-2.97 (m, 2H), 2.43 (m, 1H), 2.18-1.95 (m, 1H), 1.71-1.64 (m, 1H); m/z = 445.3 [M+H] ⁺
I-0001562	¹ H-NMR (400 MHz, CDCl ₃) δ 7.80 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.23 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.43 – 4.32 (m, 2H), 3.41 (ddd, J = 9.9, 8.2, 4.8 Hz, 1H), 3.33 (dd, J = 10.1, 7.3 Hz, 1H), 3.27 (s, 3H), 3.24 – 3.13 (m, 1H), 3.05 (dd, J = 10.1, 6.1 Hz, 1H), 2.94 (t, J = 6.9 Hz, 2H), 2.44 – 2.29 (m, 1H), 1.97 (dtd, J = 12.5, 7.6, 4.8 Hz, 1H), 1.68 – 1.56 (m, 3H), 1.56 (s, 2H), 1.45 (d, J = 6.5 Hz, 3H); m/z = 389.1 [M+H] ⁺
I-0001580	m/z = 372.2 [M+H] ⁺
I-0001579	¹ H-NMR (400 MHz, CDCl ₃) δ 8.24 – 8.15 (m, 1H), 8.04 – 7.95 (m, 1H), 7.66 – 7.54 (m, 2H), 6.44 (dd, J = 16.5, 9.9 Hz, 1H), 6.19 (d, J = 16.6 Hz, 1H), 5.91 (d, J = 9.9 Hz, 1H), 4.49 (t, J = 6.5 Hz, 1H), 3.75 (dd, J = 10.6, 7.2 Hz, 1H), 3.70 – 3.55 (m, 2H), 3.41 (dd, J = 10.6, 6.1 Hz, 1H), 3.07 – 2.90 (m, 2H), 2.55 – 2.43 (m, 1H), 2.14 – 2.03 (m, 1H), 1.81 – 1.70 (m, 1H); m/z = 388.0 [M+H] ⁺
I-0001540	m/z = 383.2 [M+H] ⁺
I-0001538	m/z = 439.3 [M+H] ⁺
I-0001541	¹ H-NMR (400 MHz, Chloroform-d) δ 7.68 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.21 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.65 (t, J = 6.4 Hz, 1H), 3.40 – 3.24 (m, 2H), 3.14 (dt, J = 9.9, 7.6 Hz, 1H), 3.01 (dd, J = 10.1, 6.0 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.41 – 2.24 (m, 1H), 2.03 – 1.86 (m, 2H), 1.64 – 1.50 (m, 1H), 1.14 – 1.02 (m, 2H), 0.84 – 0.74 (m, 2H); m/z = 371.1 & 371.2 [M+H] ⁺
I-0001543	¹ H-NMR (400 MHz, CDCl ₃) δ 7.82 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.21 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.8 Hz, 1H), 4.62 (t, J = 6.5 Hz, 1H), 3.47 (q, J = 10.6 Hz, 2H), 3.41 – 3.31 (m, 2H), 3.18 (dt, J = 9.9, 7.6 Hz, 1H), 3.06 (dd, J = 10.1, 6.1 Hz, 1H), 2.97 – 2.85 (m, 2H), 2.43 – 2.31 (m, 1H), 2.01 – 1.91 (m, 1H), 1.66 – 1.55 (m, 1H); m/z = 413.1 & 413.3 [M+H] ⁺
I-0001558	m/z = 467.2 & 469.2 [M+H] ⁺
I-0001557	m/z = 451.3 & 453.3 [M+H] ⁺
I-0001565	
I-0001566	
I-0001563	
I-0001581	
I-0001582	

Compound Identifier	Analytical Analysis
I-0091	¹ H-NMR (400 MHz, CDCl ₃) δ 7.60 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 6.46 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.92 (d, J = 9.9 Hz, 1H), 4.61 (s, 1H), 3.57 – 3.45 (m, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.77 – 2.68 (m, 1H), 2.65 – 2.54 (m, 1H), 2.16 – 2.04 (m, 1H), 1.99 – 1.88 (m, 1H), 1.87 – 1.78 (m, 1H), 1.78 – 1.65 (m, 3H), 1.61 – 1.48 (m, 1H), 1.17 – 1.03 (m, 1H); m/z = 320.1 [M+H] ⁺
I-0130	
I-0136	¹ H-NMR (400 MHz, CDCl ₃) δ 7.35 – 7.27 (m, 1H), 7.24 – 7.17 (m, 1H), 6.86 (dd, J = 8.9, 5.4 Hz, 1H), 6.49 (ddd, J = 24.2, 16.5, 9.9 Hz, 1H), 6.22 (dd, J = 16.5, 9.0 Hz, 1H), 5.94 (dd, J = 9.9, 4.6 Hz, 1H), 5.15 – 4.81 (m, 1H), 3.83 (s, 3H), 3.80 – 3.71 (m, 1H), 3.65 – 3.55 (m, 1H), 3.45 – 3.21 (m, 2H), 3.14 – 2.91 (m, 2H), 2.58 – 2.37 (m, 1H), 2.14 – 1.97 (m, 1H), 1.80 – 1.64 (m, 1H); m/z = 359.0 & 359.1 [M+H] ⁺
I-0137	¹ H-NMR (400 MHz, CDCl ₃) δ 7.71 – 7.59 (m, 1H), 7.56 – 7.46 (m, 1H), 7.46 – 7.34 (m, 2H), 7.32 – 7.22 (m, 1H), 6.61 – 6.44 (m, 1H), 6.25 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 5.40 – 5.04 (m, 1H), 4.20 – 4.03 (m, 1H), 3.99 – 3.40 (m, 3H), 3.21 – 3.00 (m, 2H), 2.68 – 2.44 (m, 1H), 2.25 – 2.04 (m, 1H), 1.95 – 1.65 (m, 1H); m/z = 335.1 & 335.2 [M+H] ⁺
I-0152	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.75 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.36 (t, J = 5.9 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 (d, J = 15.2 Hz, 1H), 5.93 (d, J = 8.7 Hz, 1H), 3.84 (s, 2H), 3.64 (s, 3H), 3.28 (dd, J = 10.2, 7.4 Hz, 1H), 3.25 – 3.18 (m, 1H), 3.09 (dt, J = 9.9, 7.5 Hz, 1H), 2.89 (dd, J = 10.2, 6.9 Hz, 1H), 2.73 – 2.62 (m, 2H), 2.20 – 2.08 (m, 1H), 1.88 – 1.75 (m, 1H), 1.53 – 1.39 (m, 1H); m/z = 403.0 & 403.1 [M+H] ⁺
I-0153	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.73 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 5.9 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 (d, J = 15.4 Hz, 1H), 5.93 (d, J = 8.9 Hz, 1H), 3.71 (s, 2H), 3.28 (dd, J = 10.2, 7.4 Hz, 1H), 3.21 (s, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.72 – 2.63 (m, 2H), 2.54 (s, 3H), 2.20 – 2.08 (m, 1H), 1.88 – 1.75 (m, 1H), 1.53 – 1.39 (m, 1H); m/z = 389.0 & 389.1 [M+H] ⁺
I-0156	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.63 (d, J = 1.6 Hz, 1H), 7.57 (dd, J = 7.9, 1.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 5.9 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 5.96 (d, J = 14.4 Hz, 1H), 5.93 (d, J = 7.8 Hz, 1H), 4.29 – 4.19 (m, 1H), 3.30 – 3.22 (m, 4H), 3.22 – 3.13 (m, 3H), 3.07 (dt, J = 9.8, 7.5 Hz, 1H), 3.03 – 2.93 (m, 2H), 2.92 – 2.84 (m, 1H), 2.74 – 2.59 (m, 2H), 2.21 – 2.08 (m, 1H), 1.87 – 1.75 (m, 1H), 1.53 – 1.38 (m, 1H); m/z = 401.0 & 401.1 [M+H] ⁺
I-0157	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.46 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 5.8 Hz, 1H), 7.26 (dd, J = 7.7, 1.7 Hz, 1H), 7.07 (d, J = 1.6 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 (d, J = 13.4 Hz, 1H), 5.94 (d, J = 6.8 Hz, 1H), 4.63 (t, J = 8.8 Hz, 2H), 3.33 – 3.22 (m, 3H), 3.24 – 3.14 (m, 1H), 3.08 (dt, J = 10.0, 7.5 Hz, 1H), 2.87 (dd, J = 10.3, 6.9 Hz, 1H), 2.75 – 2.58 (m, 2H), 2.22 – 2.06 (m, 1H), 1.88 – 1.75 (m, 1H), 1.53 – 1.39 (m, 1H); m/z = 389.0 & 389.1 [M+H] ⁺
I-0132	¹ H-NMR (400 MHz, CDCl ₃) δ 7.90 – 7.79 (m, 2H), 7.26 – 7.18 (m, 2H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.63 (t, J = 6.4 Hz, 1H), 3.43 – 3.28 (m, 2H), 3.17 (dt, J = 9.9, 7.6 Hz, 1H), 3.04 (dd, J = 10.1, 6.2 Hz, 1H), 2.91 (t, J = 6.8 Hz, 2H), 2.43 – 2.31 (m, 1H), 2.02 – 1.91 (m, 1H), 1.61 (dq, J = 12.9, 7.5 Hz, 1H); m/z = 349.0 & 349.1 [M+H] ⁺
I-0133	¹ H-NMR (400 MHz, CDCl ₃) δ 7.94 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 4.73 (t, J = 6.4 Hz, 1H), 3.45 – 3.36 (m, 2H), 3.21 (dt, J = 9.9, 7.6 Hz, 1H), 3.08 (dd, J = 10.1, 6.4 Hz, 1H), 2.98 – 2.86 (m, 2H), 2.45 – 2.33 (m, 1H), 2.04 – 1.92 (m, 1H), 1.67 – 1.55 (m, 1H); m/z = 356.0 & 356.1 [M+H] ⁺
I-0151	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.70 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 5.4 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 (d, J = 14.7 Hz, 1H), 5.93 (d, J = 8.2 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 3.22 (d, J = 37.0 Hz, 5H), 3.08 (dt, J = 10.0, 7.5 Hz, 1H), 2.96 – 2.83 (m, 3H), 2.74 – 2.58 (m, 2H), 2.20 – 2.07 (m, 1H), 1.87 – 1.74 (m, 1H), 1.52 – 1.38 (m, 1H); m/z = 389.0 & 389.1 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0134	¹ H-NMR (400 MHz, CDCl ₃) δ 7.72 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 4.77 (t, J = 6.4 Hz, 1H), 3.42 – 3.35 (m, 1H), 3.35 – 3.27 (m, 1H), 3.19 – 3.10 (m, 1H), 3.07 – 2.96 (m, 2H), 2.94 – 2.85 (m, 1H), 2.41 – 2.29 (m, 1H), 1.99 – 1.88 (m, 1H), 1.64 – 1.53 (m, 1H), 1.28 (d, J = 6.9 Hz, 6H); m/z = 373.1 [M+H] ⁺
I-0135	¹ H-NMR (400 MHz, CDCl ₃) δ 7.49 – 7.40 (m, 1H), 7.42 – 7.35 (m, 1H), 7.34 – 7.28 (m, 1H), 7.13 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.70 (t, J = 6.4 Hz, 1H), 3.87 (s, 3H), 3.43 – 3.29 (m, 2H), 3.18 (dt, J = 9.9, 7.6 Hz, 1H), 3.04 (dd, J = 10.1, 6.1 Hz, 1H), 2.89 (dd, J = 7.3, 6.4 Hz, 2H), 2.41 – 2.29 (m, 1H), 2.01 – 1.88 (m, 1H), 1.66 – 1.52 (m, 1H); m/z = 361.0 & 361.1 [M+H] ⁺
I-0154	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.83 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 (d, J = 13.1 Hz, 1H), 5.94 (d, J = 6.5 Hz, 1H), 4.21 (s, 2H), 3.29 (dd, J = 10.2, 7.4 Hz, 1H), 3.25 – 3.18 (m, 1H), 3.10 (dt, J = 9.9, 7.5 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.74 – 2.59 (m, 2H), 2.20 – 2.08 (m, 1H), 1.88 – 1.75 (m, 1H), 1.53 – 1.39 (m, 1H); m/z = 370.0 & 370.1 [M+H] ⁺
I-0155	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.46 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 5.8 Hz, 1H), 7.26 (dd, J = 7.7, 1.7 Hz, 1H), 7.07 (d, J = 1.6 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 (d, J = 13.4 Hz, 1H), 5.94 (d, J = 6.8 Hz, 1H), 4.63 (t, J = 8.8 Hz, 2H), 3.33 – 3.22 (m, 3H), 3.24 – 3.14 (m, 1H), 3.08 (dt, J = 10.0, 7.5 Hz, 1H), 2.87 (dd, J = 10.3, 6.9 Hz, 1H), 2.75 – 2.58 (m, 2H), 2.22 – 2.06 (m, 1H), 1.88 – 1.75 (m, 1H), 1.53 – 1.39 (m, 1H); m/z = 373.0 & 373.1 [M+H] ⁺
I-0163	m/z = 388.0 & 388.1 [M+H] ⁺
I-0174	¹ H-NMR (400 MHz, CD ₃ OD) δ 8.07 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H), 6.56 (dd, J = 16.5, 10.0 Hz, 1H), 6.06 (d, J = 16.5 Hz, 1H), 5.92 (d, J = 10.0 Hz, 1H), 3.41 (dd, J = 10.3, 7.3 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.24 (dt, J = 10.0, 7.5 Hz, 1H), 3.03 (dd, J = 10.3, 6.6 Hz, 1H), 2.82 – 2.67 (m, 2H), 2.32 – 2.20 (m, 1H), 1.97 – 1.84 (m, 1H), 1.64 – 1.50 (m, 1H); m/z = 374.0 & 374.1 [M+H] ⁺
I-0184	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 7.80 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 6.60 (dd, J = 16.5, 10.0 Hz, 1H), 6.10 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 10.0 Hz, 1H), 3.95 – 3.87 (m, 2H), 3.87 – 3.78 (m, 2H), 3.42 – 3.35 (m, 1H), 3.26 – 3.16 (m, 1H), 3.13 – 3.04 (m, 1H), 3.04 – 2.98 (m, 1H), 2.80 (d, J = 7.1 Hz, 2H), 2.28 (hept, J = 7.1 Hz, 1H), 1.98 – 1.86 (m, 1H), 1.57 (dq, J = 12.6, 7.8 Hz, 1H); ¹³ C-NMR (101 MHz, Acetone- <i>d</i> ₆) δ 147.4, 136.8, 134.8, 129.2, 127.4, 125.2, 63.4, 51.0, 50.8, 47.1, 44.9, 38.9; m/z = 405.1 [M+H] ⁺
I-0001236	¹ H-NMR (400 MHz, CDCl ₃) δ 7.94 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H), 6.48 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.97 (d, J = 9.9 Hz, 1H), 4.78 (t, J = 6.4 Hz, 1H), 3.45 – 3.35 (m, 2H), 3.20 (dt, J = 9.9, 7.6 Hz, 1H), 3.08 (dd, J = 10.1, 6.5 Hz, 1H), 2.98 – 2.86 (m, 2H), 2.42 – 2.34 (m, 1H), 2.04 – 1.94 (m, 1H), 1.68 – 1.57 (m, 1H); m/z = 356.0 & 356.1 [M+H] ⁺
I-0195	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 8.06 (d, J = 1.8 Hz, 1H), 7.76 (dd, J = 8.4, 1.9 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 6.61 (dd, J = 16.6, 10.0 Hz, 1H), 6.26 (s, 1H), 6.04 (d, J = 16.6 Hz, 1H), 5.93 (d, J = 10.0 Hz, 1H), 3.45 – 3.37 (m, 1H), 3.37 – 3.28 (m, 1H), 3.26 – 3.16 (m, 1H), 3.08 – 2.99 (m, 1H), 2.93 – 2.79 (m, 2H), 2.35 (hept, J = 7.2 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.68 – 1.55 (m, 1H); m/z = 404.0 [M+H] ⁺
I-0196	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 11.49 (s, 1H), 8.25 (s, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.98 (dd, J = 8.6, 2.0 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 6.60 (dd, J = 16.5, 10.0 Hz, 1H), 6.31 – 6.23 (m, 1H), 6.03 (d, J = 16.6 Hz, 1H), 5.92 (d, J = 10.0 Hz, 1H), 3.46 (dd, J = 10.2, 7.3 Hz, 1H), 3.41 – 3.33 (m, 1H), 3.30 – 3.21 (m, 1H), 3.07 (dd, J = 10.2, 6.8 Hz, 1H), 2.91 – 2.85 (m, 2H), 2.37 (hept, J = 7.2 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.69 – 1.56 (m, 1H); m/z = 399.1 [M+H] ⁺
I-0193	¹ H-NMR (400 MHz, CDCl ₃) δ 7.90 – 7.68 (m, 2H), 7.58 – 7.46 (m, 2H), 6.46 (dd, J = 16.4, 9.8 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 10.0 Hz, 1H), 5.78 – 5.64 (m, 1H), 4.73 – 4.62 (m, 1H), 3.53 – 3.43 (m, 1H), 3.39 – 3.27 (m, 3H), 3.27 – 3.13 (m, 2H), 3.08 – 2.97 (m, 1H), 2.97 – 2.77 (m, 2H), 2.47 – 2.11 (m, 2H), 2.09 – 1.71 (m, 2H), 1.61 – 1.30 (m, 3H), 1.03 – 0.83 (m, 1H); m/z = 506.1 & 506.2 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0204	¹ H-NMR (400 MHz, CDCl ₃) δ 7.79 – 7.71 (m, 2H), 7.48 – 7.39 (m, 2H), 7.26 – 7.16 (m, 3H), 7.09 – 6.98 (m, 2H), 6.45 (dd, J = 16.5, 10.6 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 5.67 – 5.54 (m, 1H), 4.58 – 4.45 (m, 1H), 3.57 – 3.45 (m, 2H), 3.45 – 3.29 (m, 3H), 3.26 – 3.13 (m, 1H), 3.08 – 2.98 (m, 1H), 2.94 – 2.70 (m, 4H), 2.46 – 2.12 (m, 2H), 2.01 – 1.69 (m, 2H), 1.56 (m, 1H), 1.46 – 1.19 (m, 2H), 1.01 – 0.80 (m, 1H); m/z = 582.2 [M+H] ⁺
I-0180	¹ H-NMR (400 MHz, CDCl ₃) δ 7.85 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 4.67 (t, J = 6.4 Hz, 1H), 3.44 – 3.29 (m, 2H), 3.16 (dt, J = 9.9, 7.6 Hz, 1H), 3.05 (dd, J = 10.1, 6.3 Hz, 1H), 2.95 – 2.87 (m, 2H), 2.42 – 2.32 (m, 1H), 2.02 – 1.90 (m, 1H), 1.67 – 1.55 (m, 1H); m/z = 439.0 & 439.1 [M+H] ⁺
I-0182	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.46 (t, J = 6.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 (d, J = 12.9 Hz, 1H), 5.94 (d, J = 6.4 Hz, 1H), 4.35 (d, J = 6.0 Hz, 2H), 3.26 (dd, 1H), 3.23 – 3.16 (m, 1H), 3.07 (dt, J = 9.9, 7.5 Hz, 1H), 2.88 (dd, J = 10.2, 6.9 Hz, 1H), 2.73 – 2.61 (m, 2H), 2.18 – 2.09 (m, 1H), 1.90 (s, 3H), 1.85 – 1.74 (m, 1H), 1.51 – 1.39 (m, 1H); m/z = 402.1 [M+H] ⁺
I-0183	¹ H-NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.29 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 6.0 Hz, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 5.93 (d, J = 16.5 Hz, 1H), 5.88 (d, J = 10.0 Hz, 1H), 3.39 – 3.22 (m, 2H), 3.17 (dt, J = 9.9, 7.5 Hz, 1H), 2.95 (dd, J = 10.3, 6.8 Hz, 1H), 2.74 – 2.56 (m, 2H), 2.16 (p, J = 7.2 Hz, 1H), 1.83 (dtd, J = 12.2, 7.2, 4.9 Hz, 1H), 1.48 (dq, J = 12.5, 7.7 Hz, 1H); m/z = 399.1 [M+H] ⁺
I-0001553	m/z = 493.2 & 495.2 [M+H] ⁺
I-0202	¹ H-NMR (400 MHz, CDCl ₃) δ 7.87 – 7.73 (m, 2H), 7.57 – 7.43 (m, 2H), 6.52 – 6.33 (m, 1H), 6.25 – 6.09 (m, 1H), 5.98 – 5.80 (m, 1H), 4.97 – 4.69 (m, 1H), 3.86 – 3.70 (m, 1H), 3.45 – 3.27 (m, 2H), 3.26 – 3.10 (m, 1H), 3.10 – 2.95 (m, 1H), 2.95 – 2.72 (m, 2H), 2.41 – 2.14 (m, 2H), 2.11 – 1.84 (m, 2H), 1.65 – 1.28 (m, 3H), 1.07 – 0.82 (m, 1H); m/z = 497.0 & 497.1 [M+H] ⁺
I-0203	¹ H-NMR (400 MHz, CDCl ₃) δ 7.83 – 7.71 (m, 2H), 7.57 – 7.46 (m, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.20 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 5.84 – 5.66 (m, 1H), 4.73 – 4.57 (m, 1H), 3.56 – 3.44 (m, 1H), 3.41 – 3.26 (m, 2H), 3.26 – 3.12 (m, 1H), 3.09 – 2.96 (m, 1H), 2.96 – 2.82 (m, 2H), 2.82 – 2.69 (m, 3H), 2.54 – 2.14 (m, 2H), 2.10 – 1.72 (m, 2H), 1.72 – 1.27 (m, 3H), 1.04 – 0.79 (m, 1H); m/z = 492.1 [M+H] ⁺
I-0206	¹ H-NMR (400 MHz, CDCl ₃) δ 7.87 – 7.72 (m, 2H), 7.59 – 7.47 (m, 2H), 6.45 (dd, J = 16.6, 9.9 Hz, 1H), 6.25 – 6.15 (m, 1H), 5.95 (d, J = 9.8 Hz, 1H), 5.68 – 5.55 (m, 1H), 5.51 (s, 1H), 4.66 – 4.51 (m, 1H), 3.65 – 3.52 (m, 1H), 3.43 – 3.29 (m, 2H), 3.27 – 3.17 (m, 1H), 3.07 – 2.97 (m, 1H), 2.93 – 2.79 (m, 2H), 2.48 – 2.12 (m, 2H), 2.09 – 1.75 (m, 2H), 1.55 – 1.28 (m, 3H), 1.03 – 0.86 (m, 1H); m/z = 478.1 [M+H] ⁺
I-0213	¹ H-NMR (400 MHz, CD ₃ OD) δ 7.82 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 6.57 (dd, J = 16.5, 10.0 Hz, 1H), 6.07 (d, J = 16.6 Hz, 1H), 5.92 (d, J = 10.0 Hz, 1H), 4.43 (s, 2H), 3.40 – 3.33 (m, 2H), 3.24 – 3.15 (m, 1H), 2.99 (dd, J = 10.2, 6.7 Hz, 1H), 2.76 (d, J = 7.1 Hz, 2H), 2.31 – 2.20 (m, 2H), 1.95 – 1.85 (m, 1H), 1.61 – 1.48 (m, 2H); m/z = 413.1 [M+H] ⁺
I-0235	
I-0236	
I-0238	
I-0201	¹ H-NMR (400 MHz, CDCl ₃) δ 7.89 – 7.66 (m, 2H), 7.53 – 7.43 (m, 2H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.22 (d, J = 16.5 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 4.54 – 4.41 (m, 1H), 4.24 – 4.06 (m, 2H), 3.80 – 3.68 (m, 1H), 3.43 – 3.29 (m, 2H), 3.23 – 3.13 (m, 1H), 3.08 – 2.98 (m, 1H), 2.98 – 2.83 (m, 2H), 2.41 – 2.11 (m, 2H), 2.06 – 1.83 (m, 2H), 1.66 – 1.51 (m, 1H), 1.51 – 1.31 (m, 2H), 1.29 – 1.16 (m, 3H), 1.05 – 0.82 (m, 1H); m/z = 507.1 [M+H] ⁺
I-0210	¹ H-NMR (400 MHz, CD ₃ OD) δ 7.77 (s, 0H), 7.76 – 7.73 (m, 1H), 7.60 – 7.57 (m, 2H), 6.56 (dd, J = 16.5, 10.0 Hz, 1H), 6.05 (d, J = 16.6 Hz, 1H), 5.91 (d, J = 10.0 Hz, 1H), 4.43 (s, 2H), 3.40 – 3.32 (m, 1H), 3.29 – 3.24 (m, 1H), 3.23 – 3.14 (m, 1H), 3.02 – 2.93 (m, 1H), 2.79 – 2.63 (m, 2H), 2.24 (hept, J = 7.1 Hz, 1H), 1.93 – 1.82 (m, 1H), 1.59 – 1.47 (m, 1H); m/z = 413.1 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0211	¹ H-NMR (400 MHz, CD ₃ OD) δ 8.51 (t, J = 1.7 Hz, 1H), 8.41 (s, 1H), 8.32 (dt, J = 7.7, 1.4 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.71 (t, J = 7.8 Hz, 1H), 6.51 (dd, J = 16.5, 10.0 Hz, 1H), 6.01 (d, J = 16.6 Hz, 1H), 5.84 (d, J = 10.0 Hz, 1H), 3.51 – 3.43 (m, 1H), 3.07 (dd, J = 10.4, 6.5 Hz, 1H), 2.81 – 2.67 (m, 2H), 2.34 – 2.21 (m, 1H), 1.99 – 1.86 (m, 2H), 1.65 – 1.53 (m, 2H); m/z = 399.1 [M+H] ⁺
I-0229	
I-0237	
I-0239	
I-0244 & I-0245	
I-0246 & I-0247	
I-0248 & I-0249	
I-0001568	
I-0001572	
I-0001576	
I-0011	
I-0031	
I-0168	
I-0170	
I-0001569	
I-0001574	
I-0001578	
I-0029	
I-0167	
I-0169	
I-0171	
I-0001229	m/z = 353.1 [M+H] ⁺
I-0001567	
I-0001575	
I-0001252	m/z = 347.1 [M+H] ⁺
I-0001570	
I-0175	¹ H-NMR (400 MHz, CDCl ₃) δ 7.74 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.32 – 7.16 (m, 3H), 7.14 – 7.03 (m, 2H), 6.46 (dd, J = 16.6, 9.9 Hz, 1H), 6.18 (d, J = 16.6 Hz, 1H), 5.93 (d, J = 9.9 Hz, 1H), 5.68 (d, J = 5.4 Hz, 1H), 4.87 (t, J = 6.2 Hz, 1H), 3.56 (s, 2H), 3.54 – 3.44 (m, 2H), 3.39 – 3.27 (m, 2H), 3.25 – 3.09 (m, 1H), 3.04 (dd, J = 10.3, 5.9 Hz, 1H), 2.88 – 2.66 (m, 4H), 2.41 – 2.26 (m, 1H), 2.00 – 1.86 (m, 1H), 1.63 – 1.48 (m, 1H); m/z = 492.1 & 492.2 [M+H] ⁺
I-0176	¹ H-NMR (400 MHz, CDCl ₃) δ 7.77 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 6.41 (dd, J = 16.5, 9.9 Hz, 1H), 6.27 (t, J = 5.8 Hz, 1H), 6.14 (d, J = 16.6 Hz, 1H), 5.90 (d, J = 9.9 Hz, 1H), 4.74 (t, J = 6.3 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.68 (s, 2H), 3.38 – 3.26 (m, 2H), 3.26 – 3.15 (m, 1H), 3.03 (dd, J = 10.3, 5.9 Hz, 1H), 2.88 – 2.76 (m, 1H), 2.76 – 2.64 (m, 1H), 2.37 – 2.25 (m, 1H), 1.98 – 1.85 (m, 1H), 1.59 – 1.45 (m, 1H); m/z = 546.1 [M+H] ⁺
I-0177	¹ H-NMR (400 MHz, CDCl ₃) δ 8.30 (s, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 6.78 – 6.70 (m, 1H), 6.70 – 6.65 (m, 1H), 6.47 (dd, J = 16.5, 9.9 Hz, 1H), 6.19 (d, J = 16.6 Hz, 1H), 6.14 – 6.08 (m, 1H), 5.94 (d, J = 9.9 Hz, 1H), 5.82 – 5.72 (m, 1H), 4.62 (t, J = 6.3 Hz, 1H), 4.40 – 4.23 (m, 2H), 3.62 (s, 2H), 3.38 – 3.26 (m, 2H), 3.21 (dt, J = 10.0, 7.4 Hz, 1H), 3.03 (dd, J = 10.4, 5.8 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.73 – 2.63 (m, 1H), 2.38 – 2.25 (m, 1H), 1.98 – 1.85 (m, 1H), 1.59 – 1.47 (m, 1H); m/z = 467.1 [M+H] ⁺
I-0192	¹ H-NMR (400 MHz, Acetone-d ₆) δ 7.78 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.33 – 7.19 (m, 5H), 6.61 (dd, J = 16.6, 10.0 Hz, 1H), 6.25 (s, 1H), 6.05 (d, J = 16.6 Hz, 1H), 5.93 (d, J = 10.0 Hz, 1H), 4.40 (d, J = 5.9 Hz, 2H), 3.71 (s, 2H), 3.42 – 3.35 (m, 1H), 3.35 – 3.26 (m, 1H), 3.23 – 3.14 (m, 1H), 3.06 – 2.99 (m, 1H), 2.87 – 2.75 (m, 7H), 2.33 (hept, J = 7.2 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.66 – 1.52 (m, 2H), 1.29 (s, 5H); m/z = 478.1 [M+H] ⁺

Compound Identifier	Analytical Analysis
I-0197	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 7.78 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 7.7 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 7.7 Hz, 4H), 6.63 (dd, J = 16.6, 10.0 Hz, 1H), 6.29 (s, 1H), 6.07 (d, J = 16.6 Hz, 1H), 5.96 (d, J = 10.0 Hz, 1H), 3.62 (s, 2H), 3.55 – 3.48 (m, 2H), 3.44 – 3.37 (m, 1H), 3.36 – 3.28 (m, 1H), 3.25 – 3.16 (m, 1H), 3.07 – 3.00 (m, 1H), 2.92 (t, J = 7.1 Hz, 3H), 2.41 – 2.28 (m, 1H), 2.01 – 1.89 (m, 2H), 1.67 – 1.55 (m, 1H); m/z = 560.1 [M+H] ⁺
I-0198	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 8.41 (d, J = 6.2 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.39 (s, 1H), 7.17 (d, J = 6.1 Hz, 1H), 6.62 (dd, J = 16.6, 10.0 Hz, 1H), 6.46 (s, 1H), 6.05 (d, J = 16.6 Hz, 1H), 5.94 (d, J = 10.0 Hz, 1H), 3.59 (s, 2H), 3.54 – 3.47 (m, 2H), 3.43 – 3.37 (m, 1H), 3.35 – 3.28 (m, 1H), 3.23 – 3.15 (m, 1H), 3.05 – 2.98 (m, 1H), 2.89 – 2.80 (m, 4H), 2.33 (hept, J = 7.2 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.66 – 1.54 (m, 1H); m/z = 493.2 [M+H] ⁺
I-0199	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 8.52 – 8.46 (m, 1H), 7.83 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.74 – 7.67 (m, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 6.9 Hz, 1H), 7.26 – 7.19 (m, 1H), 6.61 (dd, J = 16.6, 10.0 Hz, 1H), 6.27 (s, 1H), 6.05 (d, J = 16.5 Hz, 1H), 5.93 (d, J = 10.0 Hz, 1H), 4.50 (d, J = 5.7 Hz, 2H), 3.38 (dd, J = 10.2, 7.3 Hz, 1H), 3.35 – 3.26 (m, 1H), 3.23 – 3.13 (m, 1H), 3.02 (dd, J = 10.3, 6.6 Hz, 1H), 2.33 (hept, J = 7.2 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.66 – 1.51 (m, 1H); m/z = 479.1 [M+H] ⁺
I-0200	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 8.46 (d, J = 6.1 Hz, 1H), 7.90 (s, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 6.1 Hz, 1H), 6.61 (dd, J = 16.6, 9.9 Hz, 1H), 6.31 (s, 1H), 6.05 (d, J = 16.6 Hz, 1H), 5.93 (d, J = 9.9 Hz, 1H), 4.44 (d, J = 6.1 Hz, 2H), 3.76 (s, 2H), 3.38 (dd, J = 10.3, 7.3 Hz, 1H), 3.35 – 3.28 (m, 1H), 3.23 – 3.15 (m, 1H), 3.06 – 2.98 (m, 1H), 2.88 – 2.81 (m, 3H), 2.33 (hept, J = 7.3 Hz, 1H), 2.00 – 1.87 (m, 2H), 1.64 – 1.53 (m, 1H); m/z = 479.1 [M+H] ⁺
I-0208	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 8.48 – 8.40 (m, 2H), 7.87 (s, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.32 – 7.26 (m, 1H), 6.61 (dd, J = 16.6, 10.0 Hz, 1H), 6.42 (s, 1H), 6.05 (d, J = 16.6 Hz, 1H), 5.93 (d, J = 10.0 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.71 (s, 2H), 3.43 – 3.35 (m, 1H), 3.35 – 3.26 (m, 1H), 3.23 – 3.14 (m, 1H), 3.01 (dd, J = 10.3, 6.8 Hz, 1H), 2.90 – 2.80 (m, 3H), 2.32 (hept, J = 7.2 Hz, 1H), 2.00 – 1.86 (m, 1H), 1.64 – 1.50 (m, 1H); m/z = 479.1 [M+H] ⁺
I-0209	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 7.77 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 6.62 (dd, J = 16.6, 10.0 Hz, 1H), 6.24 (s, 1H), 6.05 (d, J = 16.6 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 3.38 (dd, J = 10.3, 7.3 Hz, 1H), 3.35 – 3.26 (m, 1H), 3.25 – 3.16 (m, 1H), 3.10 (s, 3H), 3.06 – 2.99 (m, 1H), 2.91 (s, 3H), 2.86 – 2.71 (m, 3H), 2.39 – 2.26 (m, 1H), 1.98 – 1.87 (m, 2H), 1.65 – 1.51 (m, 1H); m/z = 416.1 [M+H] ⁺
I-0221	¹ H-NMR (400 MHz, CD ₃ OD) δ 7.79 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.57 (dd, J = 16.6, 10.0 Hz, 1H), 6.07 (d, J = 16.6 Hz, 1H), 5.92 (d, J = 10.0 Hz, 1H), 4.38 (s, 2H), 3.68 (s, 2H), 3.46 (s, 1H), 3.36 (dd, J = 10.2, 7.3 Hz, 1H), 3.25 – 3.14 (m, 1H), 3.00 (dd, J = 10.2, 6.7 Hz, 1H), 2.77 (d, J = 7.2 Hz, 2H), 2.32 – 2.20 (m, 1H), 1.96 – 1.84 (m, 1H), 1.61 – 1.48 (m, 1H); m/z = 502.2 [M+H] ⁺
I-0222	¹ H-NMR (400 MHz, CD ₃ OD) δ 7.80 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 6.59 (dd, J = 16.5, 10.0 Hz, 1H), 6.09 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 10.0 Hz, 1H), 4.35 (s, 2H), 3.68 (s, 2H), 3.41 – 3.35 (m, 2H), 3.27 – 3.16 (m, 1H), 3.05 – 2.96 (m, 1H), 2.78 (d, J = 7.1 Hz, 2H), 2.27 (hept, J = 7.2 Hz, 1H), 2.13 (s, 3H), 1.98 – 1.85 (m, 1H), 1.64 – 1.50 (m, 1H); m/z = 535.2 [M+H] ⁺
I-0223	¹ H-NMR (400 MHz, Acetone- <i>d</i> ₆) δ 8.55 – 8.42 (m, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.67 (td, J = 7.6, 1.9 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.41 (s, 1H), 7.23 – 7.15 (m, 2H), 6.64 (dd, J = 16.6, 10.0 Hz, 1H), 6.29 (s, 1H), 6.07 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 3.65 – 3.56 (m, 4H), 3.43 – 3.37 (m, 1H), 3.36 – 3.28 (m, 1H), 3.25 – 3.15 (m, 1H), 3.07 – 3.00 (m, 1H), 2.95 (t, J = 6.9 Hz, 2H), 2.89 – 2.77 (m, 5H), 2.35 (hept, J = 7.4 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.67 – 1.54 (m, 1H); m/z = 493.2 [M+H] ⁺
I-0224	¹ H-NMR (400 MHz, CD ₃ OD) δ 7.81 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 6.55 (dd, J = 16.6, 10.0 Hz, 1H), 6.05 (d, J = 16.5 Hz, 1H), 5.90 (d, J = 9.9 Hz, 1H), 3.80 (s, 2H), 3.44 (s, 2H), 3.40 – 3.33 (m, 1H), 3.24 – 3.14 (m, 3H), 3.03 – 2.95 (m, 1H), 2.75 (d, J = 7.2 Hz, 2H), 2.25 (hept, J = 7.2 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.60 – 1.48 (m, 1H), 1.10 (t, J = 7.2 Hz, 3H); m/z = 549.2 [M+H] ⁺
I-0228	
I-0232	

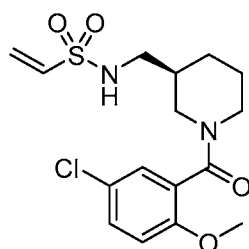
Compound Identifier	Analytical Analysis
I-0233	
I-0234	
I-0240	
I-0241	
I-0242	
I-0243	

Example I-9: Covalent modification analysis using Matrix Assisted Laser

Desorption/Ionization - Time of Flight Mass Spectrometry (MALDI-TOF MS)

[0344] Compounds of the synthesized library were evaluated for covalent modification of K-Ras4b 1-188 protein using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), which confirmed covalent labeling at C185 by many of the synthesized compounds.

[0345] *Reaction:* 20 μ M of K-Ras4b (1-188) protein (Protein Expression Laboratory, FNLCR/Leidos Biomed.) in 20 mM HEPES buffer containing 150 mM NaCl, 1 mM $MgCl_2$, pH 7.3 was prepared freshly before assay. 20 μ l aliquots of protein were dispensed in a 384-well polypropylene plate, then compounds to be tested (0.8 μ l, 10 mM in DMSO) were added to different wells. For each assay, three blank and three control samples were prepared by mixing 20 μ l of protein solution with 0.8 μ l DMSO or 10 mM standard compound (below). The contents of the wells were mixed by aspiration, then the plate was sealed by adhesive cover, centrifuged at 2000 g for 1 minute, and incubated in the dark at room temperature for 24 h.



Standard Compound

[0346] *Target plate pretreatment:* Before each assay, the MALDI target plate (Bruker MTP 384 ground steel BC) was pre-treated by pipetting 1 μ l of saturated sinapinic acid in acetonitrile (ACN) onto each spot. This may improve the uniformity of sample crystallization across the plate, enhancing sensitivity.

[0347] *Sample preparation:* After the 24 h reaction described above, 2 μ l of the reaction mixture was pipetted into 20 μ l of MALDI matrix solution (saturated solution of sinapinic acid in 1:1 ACN:water solution containing 0.75% trifluoroacetic acid (TFA)) and deposited on a 384 well polypropylene MALDI plate. The resulting solution was mixed by aspiration, centrifuged at 2000 *g* for 1 minute, then 2 μ l aliquots were dispensed onto the pre-treated MALDI target plate described above using a Beckman Coulter Biomek FX^P 96/Span-8 Laboratory Automation Workstation. The MALDI target plate was dried under mild vacuum to produce spots with fine crystalline structure.

[0348] *Measurements:* MALDI-TOF measurements were performed on a Bruker Daltonics ultraflex III TOF-TOF mass spectrometer using linear mode and mass range from 5 to 45 kDa. Detector gain was set to $\times 9$ (1734 V), sample rate to 1 GS/s, smart beam parameter set: 3_medium was used, and the laser frequency was 66.7 Hz. Spectra were automatically collected using a custom AutoXecute method. Laser power was auto-adjusted using fuzzy control. The peak selection range was set to be between 20500 and 23000 Da. Peak evaluation used half width parameter set to be smaller than 30 Da. Fuzzy control used Proteins/Oligonucleotides protocol with minimum half width 1/6 times above threshold. Up to 1500 shots were collected in 500 shot steps. Dynamic termination was implemented to finish data collection when peak intensity was reaching value of 1200 [a.u.].

[0349] *Spectra processing:* Spectra were smoothed by SavitzkyGolay algorithm using 12 *m/z* width and six cycles. Centroid peak detection algorithm was used with signal to noise threshold set to 11, relative intensity threshold 5%, minimum intensity threshold 50 [a.u.], peak width 20 *m/z* and TopHat baseline subtraction. Peak intensity and area under the peak were evaluated and recorded for all peaks between 21,460 Da and 23,500 Da.

Table I-4. Percent modification by compounds after 24 h with K-Ras4b(1-188) GDP no TCEP, as evaluated with MALDI.

Compound ID	% labeling	Compound ID	% labeling	Compound ID	% labeling	Compound ID	% labeling
I-0130	47	I-0234	0	I-0001074	71	I-0001245	53
I-0132	59	I-0235	67	I-0001075	64	I-0001246	66
I-0133	60	I-0236	0	I-0001076	26	I-0001247	65
I-0134	52	I-0237	57	I-0001077	70	I-0001248	62
I-0135	60	I-0238	45	I-0001078	64	I-0001250	62
I-0136	56	I-0239	55	I-0001080	66	I-0001251	68
I-0137	71	I-0240	0	I-0001081	65	I-0001253	61

Compound ID	% labeling	Compound ID	% labeling	Compound ID	% labeling	Compound ID	% labeling
I-0152	62	I-0241	56	I-0001086	56	I-0001254	61
I-0157	62	I-0242	33	I-0001092	72	I-0001255	77
I-0163	61	I-0243	11	I-0001095	5	I-0001256	56
I-0174	70	I-0244	8	I-0001096	59	I-0001268	64
I-0175	60	I-0245	13	I-0001097	67	I-0001269	55
I-0176	8	I-0246	24	I-0001098	48	I-0001270	63
I-0177	71	I-0247	17	I-0001099	68	I-0001271	52
I-0180	0	I-0248	4	I-0001100	67	I-0001272	29
I-0182	68	I-0249	27	I-0001101	60	I-0001273	60
I-0183	74	I-0250	62	I-0001102	67	I-0001274	29
I-0184	73	I-0001023	70	I-0001103	67	I-0001277	66
I-0192	32	I-0001024	55	I-0001105	67	I-0001278	49
I-0193	59	I-0001025	66	I-0001106	73	I-0001279	51
I-0195	77	I-0001026	75	I-0001107	77	I-0001281	61
I-0196	66	I-0001027	34	I-0001108	9	I-0001282	77
I-0197	6	I-0001028	55	I-0001109	71	I-0001284	64
I-0198	33	I-0001030	79	I-0001110	71	I-0001285	65
I-0199	46	I-0001031	44	I-0001111	74	I-0001286	74
I-0200	16	I-0001032	75	I-0001112	68	I-0001287	72
I-0201	8	I-0001050	51	I-0001113	75	I-0001288	60
I-0202	57	I-0001051	59	I-0001114	66	I-0001289	65
I-0203	53	I-0001052	69	I-0001212	30	I-0001290	73
I-0204	0	I-0001053	60	I-0001213	29	I-0001292	75
I-0206	65	I-0001054	65	I-0001219	65	I-0001293	68
I-0208	24	I-0001055	56	I-0001220	68	I-0001294	62
I-0209	61	I-0001056	41	I-0001225	71	I-0001295	70
I-0210	57	I-0001057	48	I-0001226	63	I-0001297	15
I-0211	24	I-0001058	0	I-0001228	68	I-0001298	31
I-0213	14	I-0001059	48	I-0001229	62	I-0001299	73
I-0219	8	I-0001060	71	I-0001230	78	I-0001300	72
I-0221	16	I-0001061	71	I-0001232	60	I-0001301	67
I-0222	56	I-0001062	72	I-0001233	41	I-0001317	69
I-0223	51	I-0001063	73	I-0001234	68	I-0001318	74
I-0224	62	I-0001064	72	I-0001236	72	I-0001319	77
I-0225	56	I-0001065	10	I-0001237	66	I-0001320	72
I-0228	6	I-0001066	71	I-0001238	75	I-0001321	71
I-0229	21	I-0001067	47	I-0001239	70	I-0001322	53
I-0232	53	I-0001069	67	I-0001240	70	I-0001323	62
I-0233	19	I-0001073	72	I-0001243	70	I-0001326	65
I-0001329	64	I-0001387	67	I-0001442	36	I-0001547	57
I-0001330	64	I-0001388	75	I-0001443	36	I-0001552	57
I-0001331	70	I-0001389	67	I-0001444	48	I-0001553	35
I-0001348	47	I-0001390	71	I-0001445	27	I-0001554	69
I-0001352	67	I-0001391	66	I-0001447	22	I-0001555	59
I-0001356	65	I-0001396	50	I-0001448	66	I-0001556	46
I-0001358	66	I-0001411	48	I-0001449	68	I-0001557	33
I-0001359	71	I-0001412	59	I-0001465	65	I-0001558	42
I-0001360	63	I-0001413	63	I-0001468	65	I-0001565	82

Compound ID	% labeling	Compound ID	% labeling	Compound ID	% labeling	Compound ID	% labeling
I-0001361	69	I-0001415	66	I-0001475	57	I-0001566	69
I-0001363	68	I-0001416	57	I-0001476	53	I-0001567	85
I-0001364	65	I-0001417	67	I-0001479	58	I-0001568	88
I-0001365	66	I-0001418	69	I-0001481	41	I-0001569	100
I-0001366	64	I-0001419	66	I-0001482	54	I-0001570	100
I-0001367	61	I-0001421	64	I-0001483	54	I-0001572	61
I-0001371	63	I-0001422	0	I-0001488	56	I-0001573	92
I-0001372	6	I-0001423	46	I-0001510	56	I-0001574	86
I-0001374	68	I-0001424	63	I-0001512	59	I-0001575	100
I-0001375	34	I-0001425	71	I-0001516	64	I-0001576	100
I-0001376	35	I-0001426	17	I-0001524	58	I-0001578	70
I-0001377	65	I-0001427	70	I-0001532	64	I-0001579	50
I-0001378	25	I-0001428	67	I-0001538	16	I-0001580	93
I-0001379	66	I-0001429	67	I-0001539	46	I-0001581	42
I-0001380	24	I-0001430	58	I-0001540	69	I-0001582	65
I-0001381	61	I-0001436	62	I-0001541	66	I-0001584	100
I-0001382	60	I-0001437	64	I-0001542	42	I-0001586	70
I-0001383	50	I-0001438	66	I-0001543	55	I-0001587	74
I-0001384	52	I-0001439	61	I-0001544	72	I-0001588	69
I-0001385	71	I-0001440	68	I-0001545	57		
I-0001386	54	I-0001441	63	I-0001546	73		
I-0001591	47	I-0001592	58				

Example I-10: Cell proliferation assays

[0350] Compounds of the synthesized library were also evaluated using cell-based using a mouse embryonic fibroblast (MEF) cell line panel containing single RAS transgene alleles. These MEFs are endogenous *HRAS*, *NRAS* and *KRAS* null, and their growth is completely dependent on exogenous *RAS* or activated *MAPK* pathway genes. By adding back specific isoforms of *RAS* genes or other pathway activators, cell lines were developed which are completely dependent on these genes, but maintain a similar isogenic background. The MEF panel used included all of the major oncogenic mutants of K-Ras4b as well as wild type alleles of the other Ras isoforms (e.g. K-Ras4b G12D, K-Ras4b G12V, K-Ras4b Q61R, H-Ras WT). The control cell line was *KRAS G12D* MEF that carries C185S mutation (preventing post translational modification by farnesyl), and membrane attachment necessary for K-Ras signaling is enabled through N-terminal myristoyl moiety (Myr-K-Ras G12D/C185S). Cell viability in the presence of synthesized compounds was measured using CellTiter-Glo® (Promega).

[0351] Cells were plated in black-walled 384-well plates (Greiner, 781091) at densities in accordance with their doubling time (for MEFs typically 1,000 cells/well in 20 μ L), using the Multidrop Combi Reagent Dispenser (Thermo). They were then incubated overnight at 37°C in a humidified atmosphere of 5% CO₂ prior to drug addition. Compound and DMSO addition to microplates was performed using the AccessTM Laboratory Workstation (Labcyte®) and Echo 555 (Labcyte®) liquid handler. Source plates with compounds and DMSO were prepared, and the Echo 555 was used to transfer 50 nL of compound, DMSO, or combination to the appropriate wells. Five μ L of complete culture medium was added to all wells of the microplate after compound addition. The highest final compound concentration in each assay was 100 μ M or 50 μ M with between seven to 12 dilutions. The final DMSO concentration in all wells was 0.2%.

[0352] Cells were incubated with compounds for 72h. All conditions were done in triplicate and experiments performed at least thrice. Cellular ATP levels (an indicator of cell count) were determined with the CellTiter-Glo (CTG, Promega G7573) luminescence assay, using an EnVision Plate Reader (PerkinElmer).

[0353] Plates were harvested at two time points. At the time of drug addition, one plate for each cell line with no compounds added received 5 μ L of media and were harvested to represent a measurement of the cell population at the time of compound addition (T0). After 72 h incubation, the compound-treated plates were harvested using CTG reagent and the luminescence was read using the EnVision giving control growth (C) and compound treated well (T72) measurements. Growth inhibition was calculated by:

$$\frac{T72 - T0}{C - T0} \times 100$$

[0354] Dose-response curves were generated using Prism 7 software (GraphPad).

[0355] It was observed that compounds with a pyrrolidinyl A ring, SO₂ linker X, and benzene B ring with 4-position substitution (pyrrolidine-sulfonamide compounds substituted at the 4-position of the benzene ring) appeared to have desired biological activity, showing some selectivity towards MEF cell lines expressing *KRAS4b* mutant *versus Myr-KRAS4b* G12D or *HRAS* cells (e.g., compounds I-0001105, I-0001114, I-0001289, and I-0001543).

[0356] Results from cell proliferation assays with selected compounds is tabulated in FIGS. 5A-5D (MEF cells, 72h incubation, IC₅₀ values (μ M)). FIGS. 8A-8C are heat maps

comparing IC₅₀ values for selected compounds. In FIG. 8A, bracketed compounds demonstrated desirable selectivity for MEF cells expressing oncogenic mutant of *KRAS4b* (such as G12V, G12D or Q61R), compared to MEFs expressing HRAS, or control cell line expressing *Myr-KRASG12D/C185S*. In FIG. 8C, bracketed compounds demonstrated higher activity in MEFs expressing *KRAS4b G12V*, compared to *KRAS4a*, *HRAS*, or *Myr-KRAS G12D/C185S* cells.

Example I-11: Comparative Cell Proliferation Assays

[0357] Growth rates of *KRAS4b G12D* MEF line, and the control MEF line *Myr-KRAS G12D/C185S* cells in presence of selected were compared. The control cells expressed KRAS protein bearing a C185S mutation that prevents post translational modification by farnesyl. Membrane attachment of *Myr-K-Ras G12D/C185S* is achieved through N-terminal myristoyl moiety. MAPK signaling in these cells does not differ from other MEF lines, including *KRAS4b G12D*. Since C185 in K-Ras in these cells is not available for covalent modification, any growth arrest after treatment with a compound indicates off target toxicity.

[0358] Cells were treated with an increasing concentration of a compound (1-100 μ M) for 72 h, then cell number was assessed using CTG (Promega). IC₅₀ values were calculated using GraphPad Prism software, and IC₅₀ ratios of K-Ras4b G12D to *Myr-K-Ras G12D/C185* were calculated. An IC₅₀ ratio equal to 1 indicates similar responses of both cell lines to the compound. An IC₅₀ ratio lower than 1 suggests selectivity towards K-Ras4b G12D. These values are listed in FIG. 6.

[0359] Levels of covalent modification to C185 (measured by MALDI-TOF MS) were correlated with calculated IC₅₀ ratios. Compounds I-0001219, I-0001086, I-0001114, I-0001285, I-0001277, I-0001289, I-0001377, I-0001247, I-0001105, I-0001282, I-0001381, I-0001098, I-0001107 demonstrated a desirable level of covalent modification to C185, and IC₅₀ ratios 0.6 or below, suggesting on-target activity (FIG. 7, box within the graph). A number of these compounds are 4-substituted analogues.

Example I-12: Immunoblot analysis

[0360] Certain compounds of the synthesized library were evaluated for effect on localization of K-Ras in cell membranes.

[0361] Cells (MEF *KRAS Q61R*, *KRAS G12D*, and *Myr-KRAS G12D/C185S*) were rinsed trice with ice-cold PBS and then were lysed on ice with ice-cold TNE buffer supplemented with Halt protease and phosphatase inhibitors (Thermo Scientific). This was then centrifuged at 15,000g for 15 minutes to collect whole-cell lysates. Protein concentration was measured with the BCA protein assay (Pierce). Thirty micrograms of total protein per sample was loaded into 4%–12% NuPAGE Bis-Tris gradient gels (Life Technologies) and separated by SDS-PAGE. Proteins were transferred to polyvinylidene difluoride (PVDF) membranes. The following antibodies were used for immunoblotting: mouse monoclonal anti-K-Ras (Sigma WH0003845M1, clone 3B10-2F2), mouse anti-RAS (Thermo 1862335), rabbit anti-pERK1/2 (T202/Y204; Cell Signaling Technology 4370), mouse anti-ERK1/2 (Cell Signaling Technology 4696), rabbit anti-p-MEK1/2 (S217/221; Cell Signaling Technology 9154), mouse anti-MEK1/2 (Cell Signaling Technology 4694), rabbit anti-p-AKT (S473; Cell Signaling Technology 4060), mouse anti-AKT (Cell Signaling Technology 2920). Vinculin (rabbit anti-vinculin, Cell Signaling Technology 4650) was used as a loading control. Primary antibodies were detected with fluorescence-conjugated (LI-COR) secondary antibodies. FIG. 1 depicts an immunoblot demonstrating the effect of compound I-0175 on the level of K-Ras in mouse embryonic fibroblast (MEF) cell lines expressing K-Ras Q61R, K-Ras G12D, or Myr-K-Ras G12D/C185S proteins.

[0362] For the cell fractionation experiments, cells (MEF *KRAS G12D*, *KRAS G12V*, and *KRAS WT*) were seeded at 2×10^5 onto 10-cm Petri dishes and allowed to grow for 24 h. Compounds were added to the medium to a final concentration 10 - 30 μ M for 72h. Cells were rinsed three times with ice-cold PBS, then digitonin [300 μ l of 190 μ g/ml in lysis buffer (PBS containing 75 mM KCl, 250 mM sucrose and Halt protease and phosphatase inhibitors (Thermo))] was added for 10 min on ice. Cells were then scraped gently and centrifuged 10 min at 12,000g at 4 °C. The supernatant (cytosolic fraction) was removed, and the remaining pellet (membrane fraction) was resuspended in 100 μ l of TNE lysis buffer (25 mM HEPES buffer containing 150 mM NaCl, 5 mM $MgCl_2$, 1% SDS, 10% glycerol, 2.5 mM EDTA, supplemented with Halt protease and phosphatase inhibitors) and allowed to incubate for 30 min before processing with standard immunoblot protocol. The following antibodies were used: mouse monoclonal anti-KRAS (Sigma WH0003845M1, clone 3B10-2F2), mouse anti-RAS (Thermo 1862335), mouse anti-MEK1/2 (Cell Signaling Technology 4694) as a loading control for cytosolic fraction, and rabbit anti-Na,K-ATPase (Cell Signaling Technology 3010) as a loading control for membrane fraction. FIG. 2 depicts an immunoblot

demonstrating the effect of compound I-0175 on K-Ras membrane localization in the different MEF cell lines: K-Ras4b G12D, K-Ras4b G12V, and H-Ras wild type (WT). “WCL” refers to whole cell lysate.

[0363] Results from the immunoblot (Western blot) analysis in MEF cells for selected compounds are shown in Table I-5 below.

Table I-5. Western blot analysis, MEFs, DMSO ctrl = 100

Compound ID	K-Ras4b G12V	K-Ras4b G12D	Myr-K-Ras4b G12D/C185S
I-0001026	42	62	76
I-0001030	64	65	92
I-0001031	67	73	92
I-0001032		94	195
I-0001050	91	66	152
I-0001056	98	87	96
I-0001057	93	56	62
I-0001066	81	88	110
I-0001101	47	48	104
I-0001105	55	90	135
I-0001107	44		66
I-0001113	47		76
I-0001114	61		98
I-0001212	48	57	97
I-0001219	62	118	176
I-0001230	68	80	97
I-0001238	52	45	90
I-0001239	115	192	
I-0001243	51	77	141
I-0001255	100	66	120
I-0001287	91	59	140
I-0001319		69	76
I-0001320	87	85	149
I-0001323	58	67	81
I-0001326	85	97	118
I-0001352	109	92	118
I-0001358	89	81	80
I-0001359	108	124	133
I-0001363	91	85	117
I-0001367	51	62	52
I-0001388	29	46	102
I-0001415	68	61	82
I-0001421	55	50	89

Compound ID	K-Ras4b G12V	K-Ras4b G12D	Myr-K-Ras4b G12D/C185S
I-0001423	71	84	104
I-0001436	100	111	148
I-0001447	132	198	172
I-0001482	77	82	84
I-0001538	52	88	148
I-0001539	63	78	93
I-0001542	104	100	106
I-0001543	45	77	98
I-0001554	123	127	123
I-0001556	68	118	129
I-0001565	127	159	147

Example I-13: Confocal visualization of KRAS localization

[0364] HeLa cells expressing tet-inducible *eGFP-KRAS4b G12D* in a lentiviral expression vector were used for confocal imaging. The transgene expression was induced with 200 ng/ml doxycycline, followed immediately with addition of the compound directly to the growth medium, at final concentrations depicted on the image (FIG. 3, numbers on image indicate specific concentrations of compound). Cells were treated with compound for 48 hours (re-dosed at 24 hr). Cells were then fixed with 4% paraformaldehyde (Electron Microscopy Sciences), and counterstained with 1 µg/ml Hoechst (Cell Signaling) and 5 µg/ml of ConcanavainA-Alexa647 (Thermo Fisher Scientific). Images were acquired with a Crestoptics spinning disk confocal on a Nikon Eclipse-TI inverted microscope and a Plan Apo 20x/0.75 N.A. objective. Images were taken after 48h induction of KRAS expression with doxycycline alone, or in the presence of 9 to 30 micromolar compound. (Dox+) represents control cells, showing GFP fluorescence at the plasma membrane, indicating KRAS attachment to the membrane. Treatment with I-0175 has a dose-dependent effect on KRAS4b G12D localization at the plasma membrane. FIG. 4 depicts confocal images of the effect of compound I-0176 on HeLa cells expressing eGFP-KRAS4b G12D in a doxycycline-inducible system.

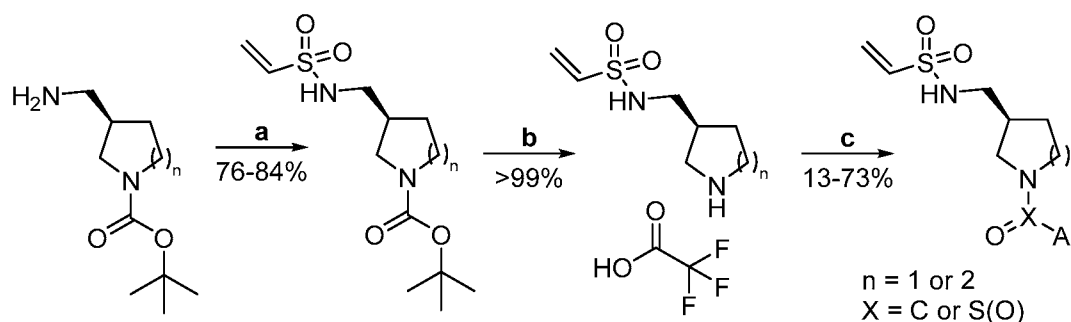
Example I-14: Mouse Xenograft Experiments

[0365] Human pancreas or lung adenocarcinoma cell lines are obtained from the American Type Culture Collection and cultured according to the cell supplier's protocol, for a maximum of four passages before use. Cells are harvested at 70–80% confluence, washed

with phosphate buffered saline, suspended in phosphate buffered saline, and implanted subcutaneously at 5×10^6 cells/0.2 mL into NCr nu/nu athymic mice, obtained from Charles River. Frederick National Laboratory for Cancer Research is accredited by AAALAC International and follows the Public Health Service Policy for the Care and Use of Laboratory Animals. Animal care is provided in accordance with the procedures outlined in the "Guide for Care and Use of Laboratory Animals" (National Research Council, 1996; National Academy Press, Washington, DC). When the tumors reach approximately $3 \text{ mm} \times 3 \text{ mm}$, the mice are distributed randomly into groups of 12 for treatment.

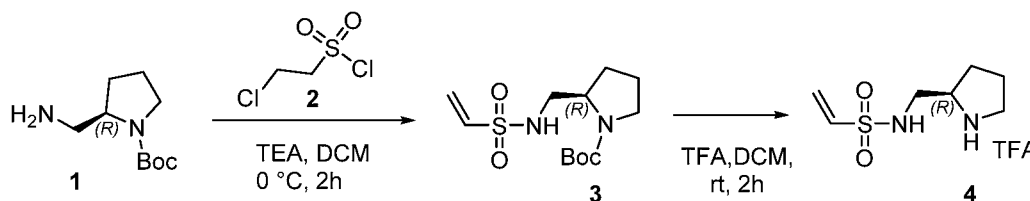
[0366] Compounds are injected into the tail veins of the mice, at $100 \mu\text{mol/kg}$ body weight, 3 times per week for 4 weeks. Control groups are treated with saline. Mice are weighed, and tumors are measured 2 times per week. Tumor volumes in mm^3 are estimated by the formula $(\pi/2 \times \text{length} \times \text{width}^2)$. Mice are euthanized almost immediately after the last treatment. Blood is collected under isoflurane anesthesia. Tumors are removed and frozen immediately for biochemical analysis.

Example II-1: General synthesis of 3-vinyl sulfonamide analogs



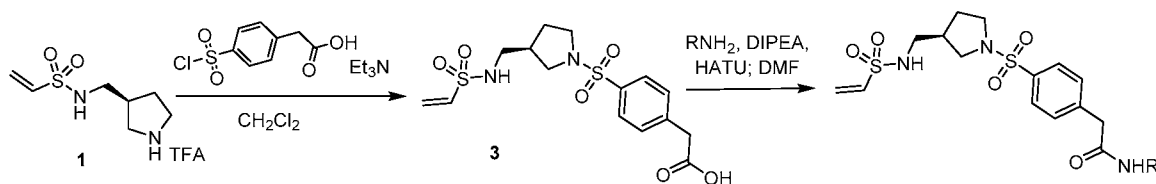
[0367] Provided above is a general synthesis that was used to produce various 3-vinyl sulfonamide compounds described herein. Conditions: (a) 2-chloroethanesulfonyl chloride, Et_3N , DCM, 0°C – RT, 18 h; (b) TFA, DCM, 0°C – RT, 1 h; (c) $\text{R}-\text{C}(\text{O})\text{Cl}$, Et_3N , DCM, RT, 2 h or $\text{R}-\text{S}(\text{O})_2\text{Cl}$, Et_3N , DCM, RT 2h. In step (c), R is Aryl (Ar).

Example II-2: Synthesis of (R)-N-(pyrrolidin-2-ylmethyl)ethenesulfonamide



[0368] The above compound 4 can be treated with various acid chlorides and sulfonyl chlorides under the conditions described in Example II-1 to produce various 2-vinyl sulfonamide compounds described herein.

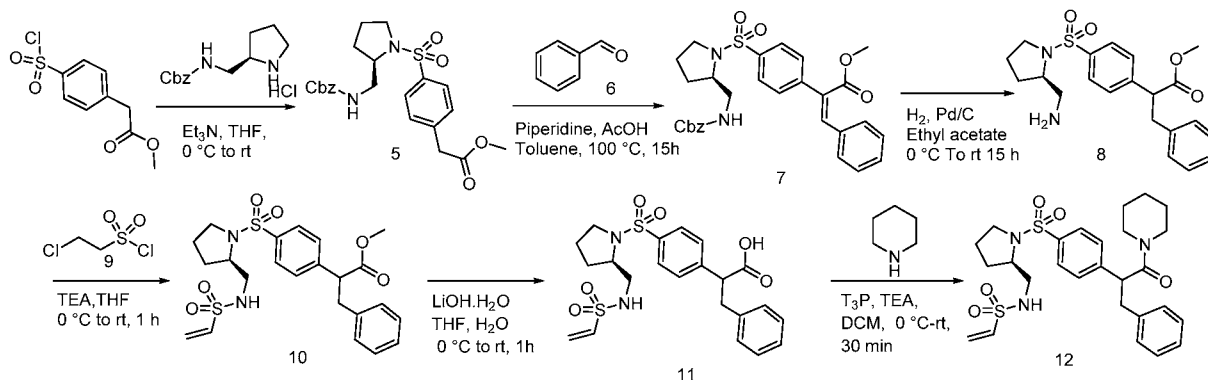
Example II-3: General scheme for (R)-2-(4-((3-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)acetamide analogs



[0369] To a solution of (R)-2-(4-((3-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)acetic acid (80 mg, 0.196 mmol), amine (3.76 mg, 0.235 mmol) and Hunig's Base (103 μ L, 0.587 mmol) in DMF (500 μ L) was added a solution of HATU (89 mg, 0.235 mmol) in DMF (500 μ L) at rt. The plate was placed in the agitator overnight. The reaction mixtures were filtered and purified by preparative HPLC (Waters, Basic (0.1% Ammonium Bicarbonate), Basic, phenomenex evo kinetex Prep-C18, 5 μ m, 21x50 mm column, 2-10% MeCN in Water) to afford the desired product.

[0370] Various 2- and 3-substituted analogs were synthesized generally following the synthetic route shown above, including X-0000749, X-0000750, X-0000751, X-0000752, X-0000753, X-0000754, X-0000755, X-0000763, X-0000774, X-0000775, X-0000776, X-0000777, X-0000778, X-0000781, X-0000953, X-0000951, X-0000802, X-0000803, I-0176, X-0000804, X-0000805, X-0000816, X-0000817, X-0000952, X-0000818, X-0000820, X-0001010, X-0001094, X-0001032, X-0001034, X-0001098, X-0001025, X-0001040, X-0001041, X-0001105, and X-0001103

Example II-4: General scheme for synthesis of various alkyl branched analogs



[0371] Various 2-substituted and 3-substituted branched analogs were synthesized generally following the procedure for X-0001302, shown above and described below. These analogs include X-0001131, X-0001132, X-0001133, X-0001289, X-0001290, X-0001291, X-0001348, X-0001305, X-0001424, X-0001425, X-0001426, X-0001360, X-0001359, X-0001358, X-0001423, X-0001365, X-0001364, X-0001436, X-0001443, X-0001427, X-0001361, X-0001618, X-0001362, X-0001363, X-0001393, X-0001427, X-0001394, X-0001439, X-0001440, X-0001494, X-0001520, X-0001521, X-0001526, X-0001527, X-0001546, X-0001545, X-0001468, X-0001527, X-0001470, X-0001529, X-0001582, X-0001583, X-0001575, X-0001576, X-0001352, X-0001304, and X-0001430.

[0372] *Synthesis of methyl (R)-2-(4-((2-(((benzyloxy)carbonyl)amino)methyl)pyrrolidin-1-yl)sulfonyl)phenyl)acetate:* To a stirred solution of benzyl (R)-(pyrrolidin-2-ylmethyl)carbamate HCl salt (0.85 g, 3.14 mmol) and triethylamine (2.26 mL, 15.71 mmol) in tetrahydrofuran (10 mL) at 0°C was added methyl 2-(4-(chlorosulfonyl)phenyl)acetate (1.16 g, 4.71 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 30 % ethyl acetate in hexane as eluent to give the title compound as gummy material. $m/z = 447.2$ $[M + H]^+$; Yield (0.84 g, 60 %).

[0373] *Synthesis of methyl (R,Z)-2-(4-((2-(((benzyloxy)carbonyl)amino)methyl)pyrrolidin-1-yl)sulfonyl)phenyl)-3-phenylacrylate:* To a stirred solution of methyl (R)-2-(4-((2-(((benzyloxy)carbonyl)amino)methyl)pyrrolidin-1-yl)sulfonyl)phenyl)acetate (0.84 g, 1.88 mmol) in toluene (10 mL) in a sealed tube was added benzaldehyde (1.9 mL, 18.18 mmol), piperidine (2.4 mL, 18.18 mmol) and acetic acid (0.5 mL) and the sealed tube was closed and was stirred at 100 °C for 15 h. The reaction mixture was cooled, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography using combiflash purifier with 20 % ethyl acetate in hexane as eluent to give the title compound as yellow liquid. $m/z = 535.2$ $[M + H]^+$; Yield (0.58 g, 58 %).

[0374] *Synthesis of methyl 2-(4-(((R)-2-(aminomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)-3-phenylpropanoate:* To a stirred solution of methyl (R,Z)-2-(4-((2-(((benzyloxy)carbonyl)amino)methyl)pyrrolidin-1-yl)sulfonyl)phenyl)-3-phenylacrylate (0.35 g, 0.65 mmol) in ethyl acetate (10 mL) was added palladium on carbon (0.05 g, 10 % wt) and the reaction mixture was stirred at room temperature under hydrogen bladder pressure for 15 h. The reaction mixture was filtered through Celite ® and the filtrate is evaporated under reduced pressure to give the title compound as gummy material. $m/z = 403.3$ $[M + H]^+$; Yield (0.25 g, crude).

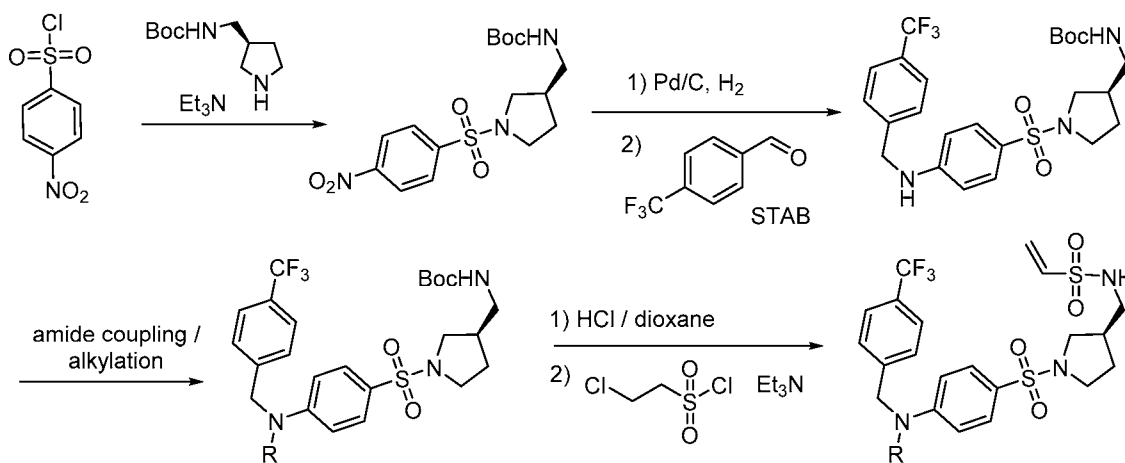
[0375] *Synthesis of methyl 3-phenyl-2-(4-(((R)-2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)propanoate:* To a stirred solution of methyl 2-(4-(((R)-2-(aminomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)-3-phenylpropanoate (0.25 g, 0.62 mmol), and triethylamine (0.43 mL, 3.1 mmol) in tetrahydrofuran (10 mL) at 0 °C was added 2-chloroethane-1-sulfonyl chloride (0.13 mL, 1.24 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (25 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the title compound as brown liquid. $m/z = 493.2$ $[M + H]^+$; Yield (0.29 g, crude).

[0376] *Synthesis of 3-phenyl-2-(4-(((R)-2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)propanoic acid:* To a stirred solution of methyl 3-phenyl-2-(4-(((R)-2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)propanoate (0.29 g, 0.58 mmol) in tetrahydrofuran (5 mL) and water (5 mL) at 0°C was added lithium hydroxide monohydrate (0.24 g, 5.8 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction was cooled and evaporated under reduced pressure. The residue was diluted with cold water (25 mL) and acidified to pH~3 using saturated citric acid solution and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the title compound as yellow gum. $m/z = 479.1$ $[M + H]^+$; Yield (0.22 g, crude).

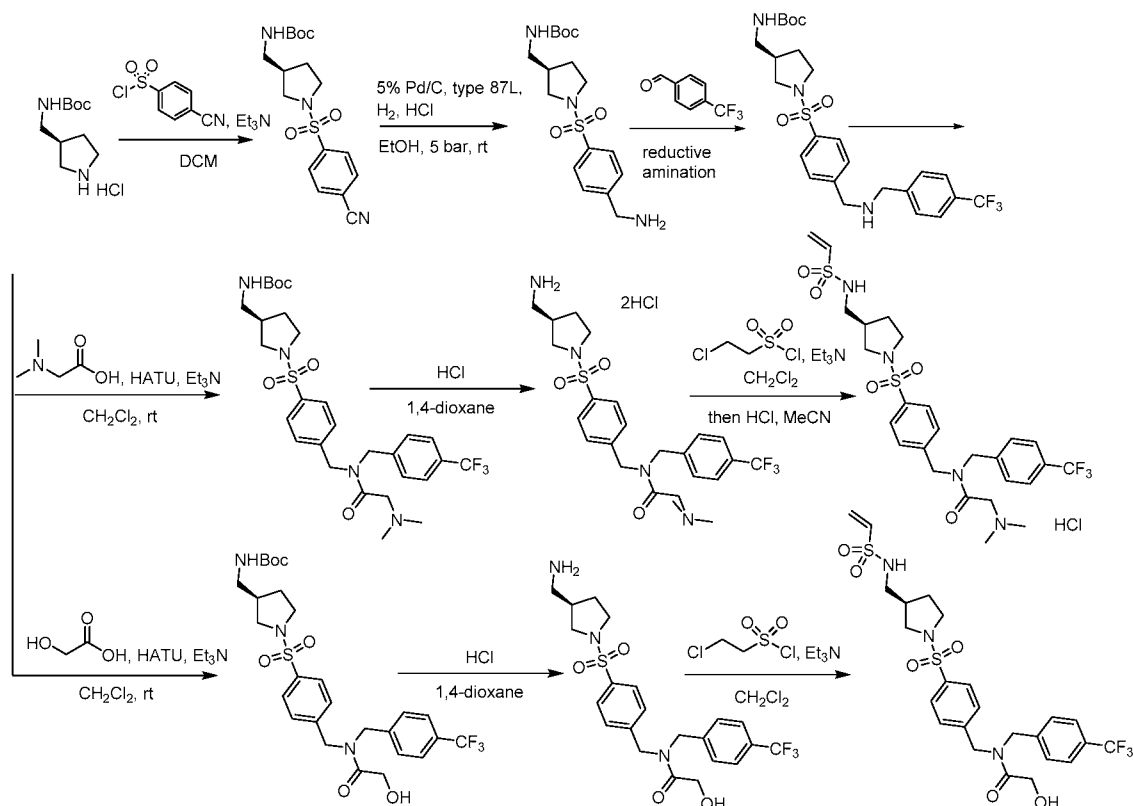
[0377] *Synthesis of N-(((2R)-1-((4-(1-oxo-3-phenyl-1-(piperidin-1-yl)propan-2-yl)phenyl)sulfonyl)pyrrolidin-2-yl)methyl)ethanesulfonamide (X-0001302):* To a stirred solution of 3-phenyl-2-(4-(((R)-2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)propanoic acid (0.22 g, 0.46 mmol), piperidine (0.05 g, 0.46 mmol) and triethylamine (0.33 mL, 2.3 mmol) in dichloromethane (5 mL) at 0 °C was added T₃P (0.44

mL, 0.69 mmol, 50 % solution in ethyl acetate) and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by preparative HPLC using Inertsil ODS 3V (250mm x 4.6mm x 5mic) column with 0.1 % ammonia in water as mobile phase A and acetonitrile as mobile phase B to give the title compound as white solid. Yield (0.02 g, 8 %).

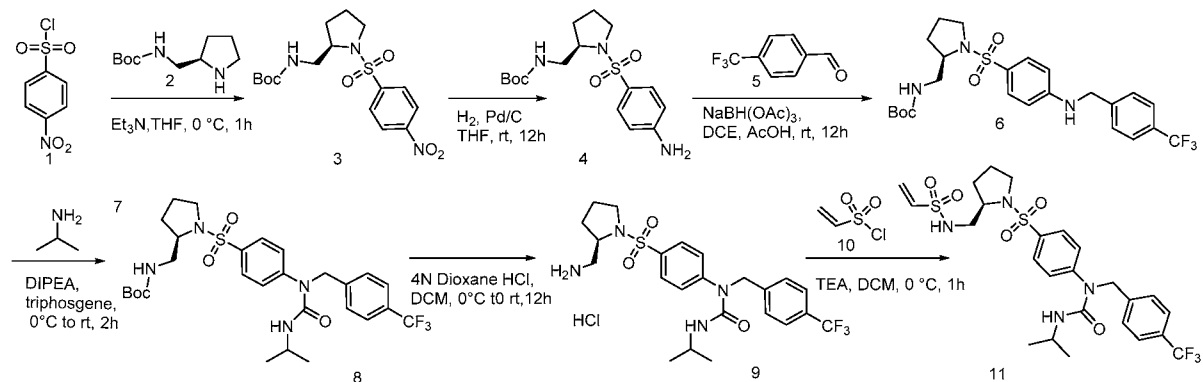
Example II-5: General scheme for synthesis of various aniline analogs



[0378] The general synthetic route shown above was used to synthesize various aniline analogs such as X-0001208, X-0001223, X-0001224, and X-0001225.

Example II-6: General schemes for various benzylamine analogs

[0379] The general synthetic routes shown above were used to synthesized various benzylamine analogs such as X-0000979, X-000098, X-0000986, X-0001044, X-0001045, X-0001046, and X-0001047.

Example II-7: General scheme for urea-linked analogs

[0380] Both 2- and 3-substituted urea-linked analogs were synthesized generally following the procedure for X-0001396, shown above and described below, including compounds X-0001472, X-0001432, X-0001428, and X-0001473.

[0381] *Synthesis of tert-butyl (R)-((1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate:* To a stirred solution of tert-butyl (R)-(pyrrolidin-2-ylmethyl)carbamate (1.8 g, 9.02 mmol) and triethylamine (6.27 mL, 45.1 mmol) in tetrahydrofuran (30 mL) at 0 °C was added 4-nitrobenzenesulfonyl chloride (2.0 g, 9.02 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was washed with n-pentane (100 mL) to give the title compound as off white solid. $m/z = 286.1$ $[M + H]^+$; Yield (3.0 g, 86 %).

[0382] *Synthesis of tert-butyl (R)-((1-((4-aminophenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate:* To a stirred solution of tert-butyl (R)-((1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate (3.0 g, 7.78 mmol) in THF (30 mL) was added palladium on carbon (0.3 g, 10 % w/w) at room temperature and the reaction mixture was hydrogenated under hydrogen bladder for 12 h. The reaction mixture was filtered through Celite® bed and washed with THF (30 mL). The filtrate was evaporated under reduced pressure to get the title compound as gummy compound. $m/z = 356.0$ $[M + H]^+$; Yield (2.70 g, crude).

[0383] *Synthesis of tert-butyl (R)-((1-((4-((4-(trifluoromethyl)benzyl)amino)phenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate:* To a stirred solution of tert-butyl (R)-((1-((4-aminophenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate (2.0 g, 5.62 mmol) in 1,2-dichloroethane (30 mL) at 0 °C were added 4-(trifluoromethyl)benzaldehyde (1.17 g, 6.74 mmol) and acetic acid (2.0 mL). The reaction mixture was stirred at room temperature for 5 h and then cooled to 0 °C, sodium triacetoxyborohydride (2.38 g, 11.24 mmol) was added and stirred at room temperature for 12 h. The reaction mixture was evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 40 % ethyl acetate in hexane as eluent to give the title compound as white solid. $m/z = 514.4$ $[M + H]^+$; Yield (1.8 g, 78 %).

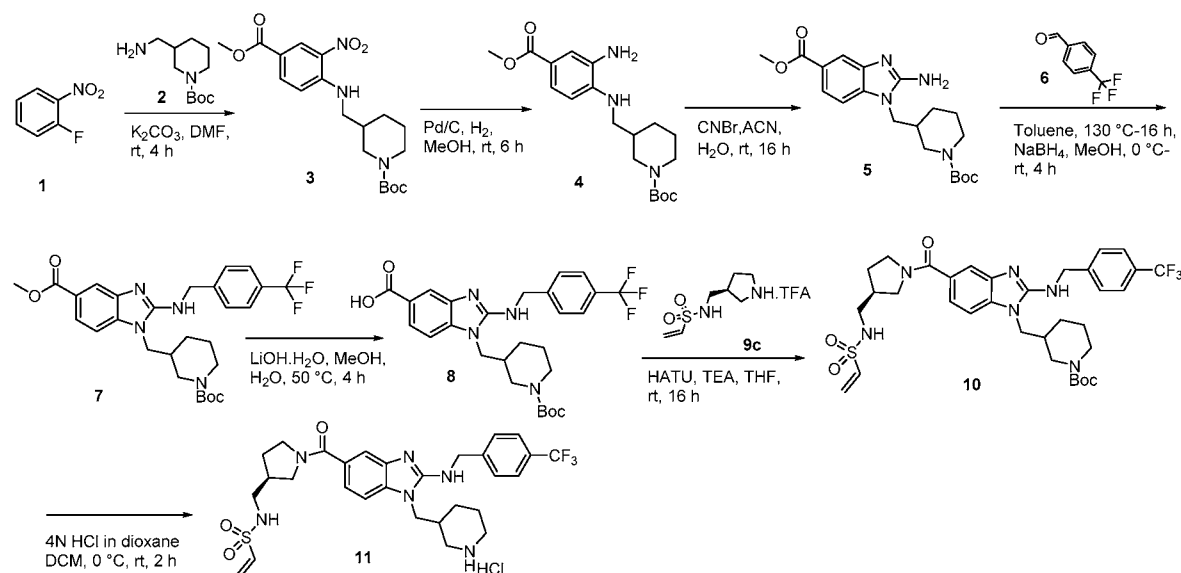
[0384] *Synthesis of tert-butyl (R)-((1-((4-(3-isopropyl-1-(4-(trifluoromethyl)benzyl)ureido)phenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate:* To a stirred solution of tert-butyl (R)-((1-((4-((4-(trifluoromethyl)benzyl)amino)phenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate (0.7 g, 1.36 mmol) in dichloromethane (15 mL) at 0 °C were added triphosgene (0.6 g, 2.02 mmol) and N, N-diisopropylethylamine (1.2 mL, 6.8 mmol) and the

reaction mixture was stirred at 0 °C for 0.5 h, and then isopropyl amine (0.133 mL, 1.63 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 80 % ethyl acetate in hexane as eluent to give the title compound as gummy compound. $m/z = 499.3$ [$M + H$]⁺; Yield (0.6 g, 74 %).

[0385] *Synthesis of (R)-1-(4-((2-(aminomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)-3-isopropyl-1-(4-(trifluoromethyl)benzyl)urea HCl salt*: To a stirred solution of tert-butyl (R)-((1-((4-(3-isopropyl-1-(4-(trifluoromethyl)benzyl)ureido)phenyl)sulfonyl)pyrrolidin-2-yl)methyl)carbamate (0.1 g, 0.167 mmol) in dichloromethane (5 mL) at 0 °C was added hydrochloric acid (1.0 mL, 4N in dioxane) drop wise and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was evaporated under reduced pressure. The residue was washed with diethyl ether and dried to get the title compound as white solid. $m/z = 499.3$ [$M + H$]⁺; Yield (0.09 g, crude).

[0386] *Synthesis of (R)-N-((1-((4-(3-isopropyl-1-(4-(trifluoromethyl)benzyl)ureido)phenyl)sulfonyl)pyrrolidin-2-yl)methyl)ethanesulfonamide (X-0001396)*: To a stirred solution of (R)-1-(4-((2-(aminomethyl)pyrrolidin-1-yl)sulfonyl)phenyl)-3-isopropyl-1-(4-(trifluoromethyl)benzyl)urea HCl salt (0.09 g, 0.168 mmol) and triethylamine (0.12 mL, 0.84 mmol) in dichloromethane (5 mL) at 0 °C was added ethanesulfonyl chloride (0.026 g, 0.21 mmol) and the reaction mixture was stirred at 0 °C for 0.5h and then at room temperature for 0.5 h. The reaction mixture was evaporated under reduced pressure. The crude product was purified by preparative HPLC using Kinetex C18 (100mm X 4.6 mm X 2.6μm) column with 0.1 % trifluoroacetic acid in water as mobile phase A and acetonitrile as mobile phase B to give the title compound as white solid. Yield (0.15 g, 15 %).

Example II-8: Synthesis of N-(((3S)-1-(1-(piperidin-3-ylmethyl)-2-((4-(trifluoromethyl)benzyl)amino)-1H-benzo[d]imidazole-5-carbonyl)pyrrolidin-3-yl)methyl)ethanesulfonamide hydrochloride (HCl salt of X-0001002)



[0387] *Synthesis of tert-butyl 3-(((4-(methoxycarbonyl)-2-nitrophenyl)amino)methyl)piperidine-1-carboxylate:* To a stirred solution of 1-fluoro-2-nitrobenzene (0.1 g, 0.52 mmol) in N,N-dimethylformamide (5 mL) at room temperature was added potassium carbonate (0.14 g, 1.04 mmol) and tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (0.13 g, 0.62 mmol), the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 20 % ethyl acetate in hexane as eluent to give the title compound as yellow solid. $m/z = 392.1$ $[M + H]^+$; Yield (0.15 g, 73 %).

[0388] *Synthesis tert-butyl 3-(((2-amino-4-(methoxycarbonyl)phenyl)amino)methyl)piperidine-1-carboxylate:* To a stirred solution of tert-butyl 3-(((4-(methoxycarbonyl)-2-nitrophenyl)amino)methyl)piperidine-1-carboxylate (1.4 g, 3.56 mmol) in methanol (20 mL) was added palladium on carbon (0.5 g, 10 % wt) and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 6 h. The reaction mixture was filtered through Celite® and washed with methanol, the combined filtrate was evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 5 % methanol in dichloromethane as eluent to give the title compound as pale yellow liquid. $m/z = 364.2$ $[M + H]^+$; Yield (1.1 g, 85 %).

[0389] *Synthesis of methyl 2-amino-1-((1-(tert-butoxycarbonyl)piperidin-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate:* To a stirred solution of tert-butyl 3-(((2-amino-4-(methoxycarbonyl)phenyl)amino)methyl)piperidine-1-carboxylate (1.1 g, 3.03 mmol) in acetonitrile (10 mL) and water (3 mL) at 0°C was added cyanogen bromide (0.34 g, 3.33 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 5 % methanol in dichloromethane as eluent to give the title compound as green liquid. $m/z = 389.1 [M + H]^+$; Yield (0.8 g, 68 %).

[0390] *Synthesis of methyl 1-((1-(tert-butoxycarbonyl)piperidin-3-yl)methyl)-2-((4-(trifluoromethyl)benzyl)amino)-1H-benzo[d]imidazole-5-carboxylate:* To a stirred solution of methyl 2-amino-1-((1-(tert-butoxycarbonyl)piperidin-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (0.8 g, 2.06 mmol) and 4-(trifluoromethyl)benzaldehyde (0.43 g, 2.47 mmol) in toluene (30 mL) was heated at 130°C under dean-stark condenser for 16 h and the solvent was evaporated, the resulting mixture was cooled to 0°C and was added methanol (20 mL) and sodium borohydride (0.12 g, 5.15 mmol) portion wise and the reaction mixture stirred at room temperature for 4 h. The reaction mixture was quenched with water (20 mL) and evaporated the methanol solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 5 % methanol in dichloromethane as eluent to give the title compound as off white solid. $m/z = 547.2 [M + H]^+$; Yield (0.3 g, 26 %).

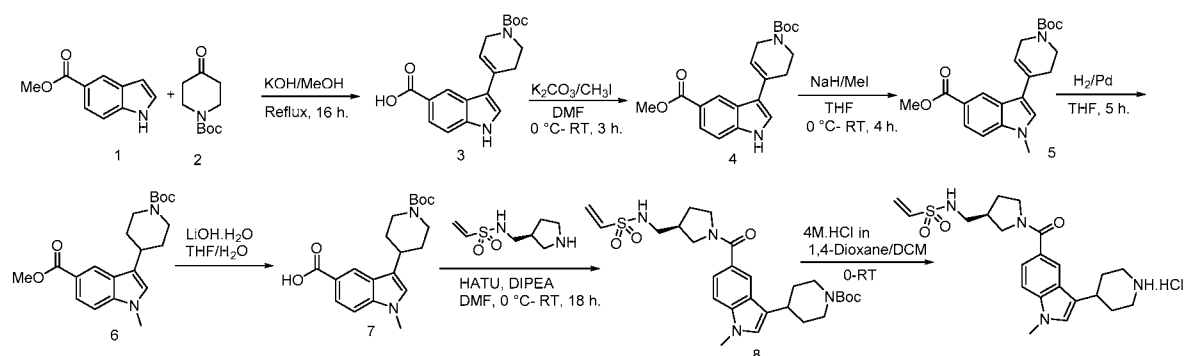
[0391] *Synthesis of 1-((1-(tert-butoxycarbonyl)piperidin-3-yl)methyl)-2-((4-(trifluoromethyl)benzyl)amino)-1H-benzo[d]imidazole-5-carboxylic acid:* To a stirred solution of methyl 1-((1-(tert-butoxycarbonyl)piperidin-3-yl)methyl)-2-((4-(trifluoromethyl)benzyl)amino)-1H-benzo[d]imidazole-5-carboxylate (0.3 g, 5.49 mmol) and in methanol (5 mL), tetrahydrofuran (5 mL) water (2.5 mL) at 0 °C was added lithium hydroxide monohydrate (0.4 g, 54.94 mmol) and the reaction mixture stirred at 50 °C for 4 h. The reaction mixture was cooled, diluted with water (20 mL) and evaporated under reduced

pressure. The residue was diluted with water, acidified to pH~3 using 1N hydrochloric acid and was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the title compound as green solid. $m/z = 533.2$ $[M + H]^+$; Yield (0.28 g, crude).

[0392] *Synthesis of tert-butyl 3-((2-((4-(trifluoromethyl)benzyl)amino)-5-((S)-3-(vinylsulfonamidomethyl)pyrrolidine-1-carbonyl)-1H-benzo[d]imidazol-1-yl)methyl)piperidine-1-carboxylate*: To a stirred solution of 1-((1-(tert-butoxycarbonyl)piperidin-3-yl)methyl)-2-((4-(trifluoromethyl)benzyl)amino)-1H-benzo[d]imidazole-5-carboxylic acid (0.28 g, 0.52 mmol) and N-(((3S)-1-(2,2,2-trifluoroacetyl)-1H-pyrrolidin-3-yl)methyl)ethenesulfonamide (0.22 g, 0.78 mmol) in tetrahydrofuran (15 mL) at 0°C was added triethylamine (0.37 mL, 2.63 mmol) and HATU (0.19 g, 0.52 mmol) and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by preparative HPLC using 0.1 % ammonia in water as mobile phase A and acetonitrile as mobile phase B to give the title compound as green solid. $m/z = 705.2$ $[M + H]^+$; Yield (0.14 g, 72 %).

[0393] *Synthesis of N-(((3S)-1-(1-(piperidin-3-ylmethyl)-2-((4-(trifluoromethyl)benzyl)amino)-1H-benzo[d]imidazole-5-carbonyl)pyrrolidin-3-yl)methyl)ethenesulfonamide hydrochloride (HCl salt of X-0001002)*: To a stirred solution of tert-butyl 3-((2-((4-(trifluoromethyl)benzyl)amino)-5-((S)-3-(vinylsulfonamidomethyl)pyrrolidine-1-carbonyl)-1H-benzo[d]imidazol-1-yl)methyl)piperidine-1-carboxylate (0.14 g, 0.232 mmol) in dichloromethane (10 mL) at 0 °C was added 4N HCl in dioxane (0.4 mL) and the reaction mixture stirred at room temperature for 2 h. The reaction mixture evaporated under reduced pressure to give the title compound as off white gummy liquid. Yield (0.1 g, 85 %).

Example II-9: Synthesis of (*S*)-N-((1-(1-methyl-3-(piperidin-4-yl)-1H-indole-5-carbonyl)pyrrolidin-3-yl) methyl) ethanesulfonamide hydrochloride (HCl salt of X-0001064):



[0394] In addition to compound X-0001064, compounds X-0001067, X-0001068, X-0001115, X-0001171, X-0001172, X-0001253, X-0001256, X-0001257, X-0001121, and X-0001119 were also synthesized generally following the scheme above and procedures described below.

[0395] *Synthesis of 3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-5-carboxylic acid:* To a stirred solution of methyl 1H-indole-5-carboxylate (2.0 g, 11.40 mmol) in methanol (20 mL) were added potassium hydroxide (1.5 g, 34.2 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (4.5 g, 22.8 mmol) at room temperature and the mixture was heated to reflux for 16h. After completion of the reaction, concentrated and diluted with water (20 mL) and acidified using citric acid solution (10 mL, pH~6). The obtained solid was filtered and dried giving the title compound as a pale yellow solid. $m/z = 341.3$ $[M - H]^+$; Yield (1.7 g, 43%).

[0396] *Synthesis of methyl 3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-5-carboxylate:* To a stirred solution of 3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-5-carboxylic acid (1.5 g, 4.38 mmol) in *N,N*-Dimethylformamide (15 mL) were added potassium carbonate (1.2 g, 8.77 mmol) and methyl iodide (0.4 mL, 6.57 mmol) at 0°C and allowed to stir at room temperature for 2h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 x 60 mL). The combined organic layer was washed with water (60 mL), brine (60 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified over silica gel (60-120) using 20% ethyl acetate in hexane as an eluent to give title compound as off white solid. $m/z = 355.2$ $[M - H]^+$; Yield (0.7 g, 47%).

[0397] *Synthesis of methyl 3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-methyl-1H-indole-5-carboxylate:* To a stirred solution of methyl 3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-5-carboxylate (0.5 g, 1.40 mmol) in tetrahydrofuran (10 mL) was added 60% sodium hydride (67 mg, 1.68 mmol) and methyl iodide (0.1 mL, 2.1 mmol) at 0 °C and left it to stir at room temperature for 3h. It was quenched with water (10 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give the title compound as an off white solid. ¹H NMR (400 MHz, CDCl₃): δ ppm 8.61 (s, 1H), 7.95 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 6.20 (s, 1H), 4.15 (d, *J* = 8.2 Hz, 2H), 3.94 (s, 3H), 3.79 (s, 3H), 3.68 (t, *J* = 11.2 Hz, 2H), 2.55 (s, 2H), 1.50 (s, 9H): Yield (0.35 g, 67%).

[0398] *Synthesis of methyl 3-(1-(tert-butoxy carbonyl) piperidin-4-yl)-1-methyl-1H-indole-5-carboxylate:* To a stirred solution of methyl 3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-methyl-1H-indole-5-carboxylate (0.7 g, 1.89 mmol) in tetrahydrofuran (15 mL) was added 10% Palladium on carbon (0.2 g) at room temperature and stirred the mixture under hydrogen balloon pressure for 3 h. The reaction mixture was filtered through a celite bed, washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to give the title compound as an off white solid. *m/z* = 373.2 [*M* + *H*]⁺; Yield (0.55 g, 78%).

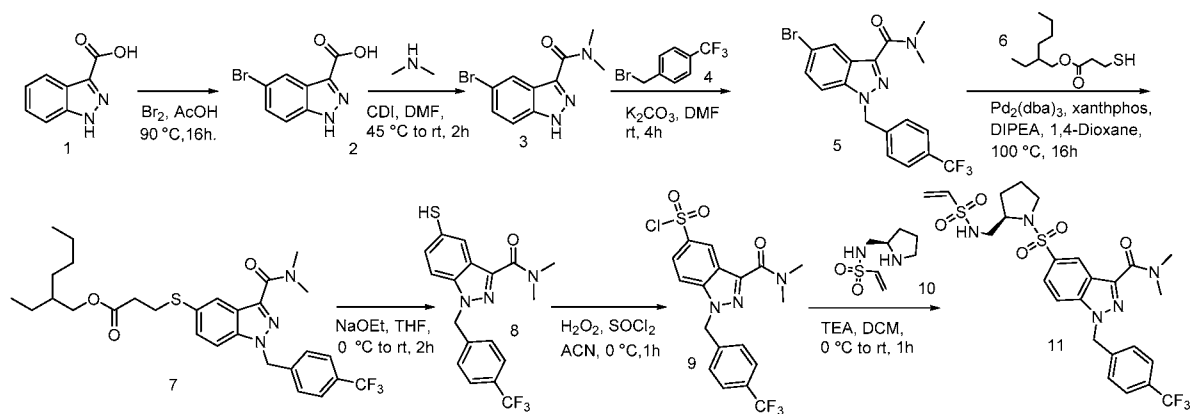
[0399] *Synthesis of 3-(1-(tert-butoxy carbonyl) piperidin-4-yl)-1-methyl-1H-indole-5-carboxylic acid:* To a solution of methyl 3-(1-(tert-butoxy carbonyl) piperidin-4-yl)-1-methyl-1H-indole-5-carboxylate (0.55 g, 1.47 mmol) in (1:1:1) tetrahydrofuran, methanol and water (9 mL) solvent mixture was added lithium hydroxide monohydrate (0.5 g, 11.82 mmol) at 0 °C. The mixture was stirred at room temperature for 20 h. After completion of the reaction, concentrated under reduced pressure to dryness. It was then diluted with water (5 mL) and acidified using citric acid solution (3 mL, *pH*~6) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give the title compound as an off white solid. *m/z* = 357.1 [*M* - *H*]⁺; Yield (0.32 g, 61%).

[0400] *Synthesis of (S)-tert-butyl 4-(1-methyl-5-(3-(vinylsulfonamidomethyl) pyrrolidine-1-carbonyl)-1H-indol-3-yl) piperidine-1-carboxylate:* To a stirred solution of 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1-methyl-1H-indole-5-carboxylic acid (0.22 g, 0.614 mmol)

in *N,N*-dimethylformamide (5 mL) at 0 °C were added (*S*)-*N*-(pyrrolidin-3-ylmethyl)ethanesulfonamide (0.23 g, 1.22 mmol), 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro phosphate (0.46g, 1.22 mmol) and *N*-Ethyl-diisopropylamine (0.25 mL, 1.53 mmol) at 0 °C and allowed to stir at room temperature for 4h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified over silica gel (60-120) using 10 % methanol in ethyl acetate as an eluent to afford the title compound as a colorless semi solid. $m/z = 531.2$ [$M + H$]⁺; Yield (0.25 g, 78%).

[0401] *Synthesis of (S)-N-((1-(1-methyl-3-(piperidin-4-yl)-1*H*-indole-5-carbonyl)pyrrolidin-3-yl) methyl) ethanesulfonamide hydrochloride (HCl salt of X-0001064):* To a stirred solution of *tert*-butyl (S)-4-(1-methyl-5-(3-(vinylsulfonamidomethyl) pyrrolidine-1-carbonyl)-1*H*-indol-3-yl) piperidine-1-carboxylate (0.1 g, 0.188 mmol) in 1,4-dioxane (2 mL) at 0 °C was added 4M HCl in 1,4-dioxane (0.2 mL) drop wise and the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to dryness. The crude product was triturated with diethyl ether to give the title compound as an off white solid. Yield (0.042 g, 48 %).

Example II-10: ((R)-N,N-dimethyl-1-(4-(trifluoromethyl)benzyl)-5-((2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)-1*H*-indazole-3-carboxamide (X-0001433)



[0402] In addition to X-0001433, compound X-0001434 was also synthesized generally following the scheme above, and procedure described below.

[0403] *Synthesis of 5-bromo-1H-indazole-3-carboxylic acid:* A suspension of indazole-3-carboxylic acid (5.0 g, 30.8 mmol) in glacial acetic acid (250 mL) was heated at 120° C to get a clear solution. The solution was cooled to 90 °C and added a solution of bromine (3.17 mL, 61.7 mmol) in glacial acetic acid (50 mL) drop wise and the reaction mixture was heated at 90 °C for 16 h. The reaction mixture was cooled to room temperature, poured into ice water, the precipitated solid was filtered, washed with water and n-pentane and dried in high vacuum to give the title compound as off white solid. m/z 241.0 $[M + H]^+$; Yield (6 g, 81%).

[0404] *Synthesis of 5-bromo-N,N-dimethyl-1H-indazole-3-carboxamide:* A stirred solution of 5-bromo-1H-indazole-3-carboxylic acid (2 g, 8.33 mmol) and 1,1'-carbonyldiimidazol (2.02 g, 12.4 mmol) in N,N-Dimethylformamide (20 mL) was heated at 45 °C for 1 h. The reaction mixture was cooled to room temperature and added dimethyl amine (8.33 mL, 20.8 mmol, 2M in tetrahydrofuran) drop wise and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with water (100 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic layer was washed with water (100 mL), brine (50 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the title compound as off white solid. m/z 270.0 $[M + H]^+$; Yield (1.3 g, 58 %).

[0405] *Synthesis of 5-bromo-N,N-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-indazole-3-carboxamide:* To a stirred 5-bromo-N,N-dimethyl-1H-indazole-3-carboxamide (1.5 g, 5.61mmol) in DMF (20 mL) was added potassium carbonate (1.54 g, 11.22 mmol) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.6 g, 6.74 mmol) and stirred at room temperature for 4 hours. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with water (100 mL), brine (50 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash chromatography using combiflash purifier with 28 % ethyl acetate in hexane as eluent to give the title compound as off white solid. m/z 425.9 $[M + H]^+$; Yield (2.0 g, 84 %).

[0406] *Synthesis of 2-ethylhexyl 3-((3-(dimethylcarbamoyl)-1-(4-(trifluoromethyl)benzyl)-1H-indazol-5-yl)thio)propanoate:* To a stirred solution of 5-bromo-N,N-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-indazole-3-carboxamide (2.0 g, 4.7 mmol) and 2-ethylhexyl 3-mercaptopropanoate (2.05 g, 9.41 mmol) in dioxane (50 mL) in a sealed tube was added diisopropylethylamine (2.5 mL, 14.1 mmol) and xanthphos (0.136 g, 0.23 mmol), then

reaction mixture was degassed with nitrogen for 5 min, added $\text{Pd}_2(\text{dba})_3$ (0.215 g, 0.23 mmol) and the sealed tube was closed and was stirred at 100 °C for 15 h. The reaction mixture was cooled, filtered through Celite® and the filtrate was diluted with water and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography using combiflash purifier with 35 % ethyl acetate in hexane as eluent to give the title compound Yellow liquid. m/z 564.3 $[\text{M} + \text{H}]^+$; Yield (2.5 g, 94 %).

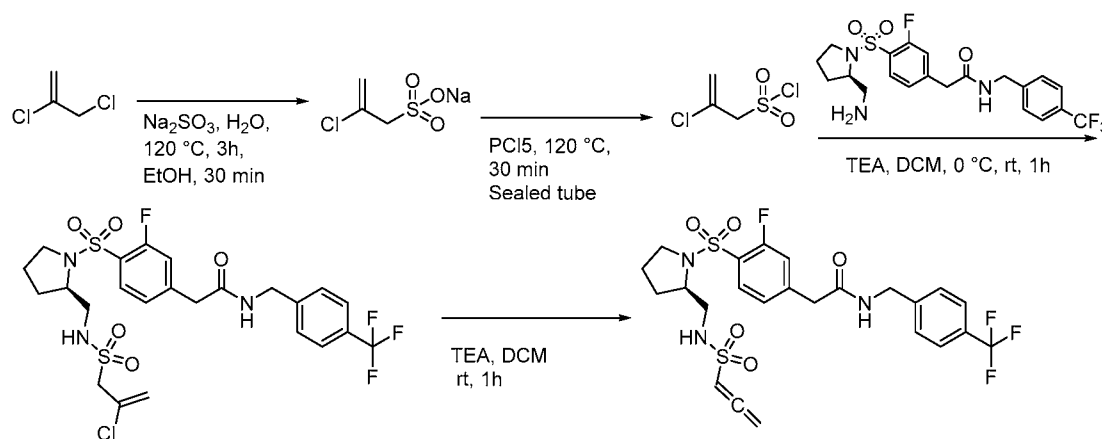
[0407] *Synthesis of 5-mercapto-N,N-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-indazole-3-carboxamide:* To a stirred solution of 2-ethylhexyl 3-((3-(dimethylcarbamoyl)-1-(4-(trifluoromethyl)benzyl)-1H-indazol-5-yl)thio)propanoate (2.5 g, 4.4 mmol) in tetrahydrofuran (30 mL) at 0 °C was added sodium ethoxide (2.85 mL, 8.8 mmol, 21 % solution in ethanol) and the reaction mixture was stirred at room temperature 4 h. The reaction mixture was quenched with 1 N hydrochloric acid (25 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography using combiflash purifier with 40 % ethyl acetate in hexane as eluent to give the title compound as yellow solid. m/z 380.1 $[\text{M} + \text{H}]^+$. Yield (1.5 g, 89 %).

[0408] *Synthesis of 3-(dimethylcarbamoyl)-1-(4-(trifluoromethyl)benzyl)-1H-indazole-5-sulfonyl chloride:* To a stirred solution of 5-mercapto-N,N-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-indazole-3-carboxamide (0.40 g, 1.0 mmol) in acetonitrile (10 mL) was added hydrogen peroxide (0.6 mL, 5.27 mmol, 30 % solution) and the reaction mixture was cooled to 0 °C. Then thionyl chloride (0.35 mL, 4.22 mmol) was added drop wise and the reaction mixture was stirred at room temperature 2 h. The reaction mixture was quenched with water (25 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound as white solid. m/z 446.1 $[\text{M} + \text{H}]^+$. Yield (0.3 g, crude).

Synthesis of ((R)-N,N-dimethyl-1-(4-(trifluoromethyl)benzyl)-5-((2-(vinylsulfonamidomethyl)pyrrolidin-1-yl)sulfonyl)-1H-indazole-3-carboxamide (X-0001433): To a stirred solution of (R)-N-(pyrrolidin-2-ylmethyl)ethanesulfonamide (0.130 g, 0.67

mmol) and triethylamine (0.188 mL, 1.34 mmol) in tetrahydrofuran (5 mL) at 0 °C was added 3-(dimethylcarbamoyl)-1-(4-(trifluoromethyl)benzyl)-1H-indazole-5-sulfonyl chloride (0.20 g, 0.44 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by preparative HPLC to give the title compound as white solid. Yield (0.080 g, 26 %).

Example II-11: Synthesis of X-0001495



[0409] *Synthesis of sodium 2-chloroprop-2-ene-1-sulfonate:* To a stirred solution of sodium sulfite (5.7 g, 26.31 mmol) in water (35 mL) was dropwise added 2,3-dichloroprop-1-ene (5.0 g, 26.31 mmol) and the reaction mixture was stirred at 120 °C for 3h. The reaction mixture was evaporated under reduced pressure, the resulting crude was diluted with ethanol (45 mL) and the reaction mixture was refluxed for 30 min. The reaction mixture was filtered and filtrate was cooled. The crystalline solid precipitated was collected by filtration as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.44 (s, 1H), 5.27 (s, 1H), 3.42 (s, 2H); Yield (4g, crude).

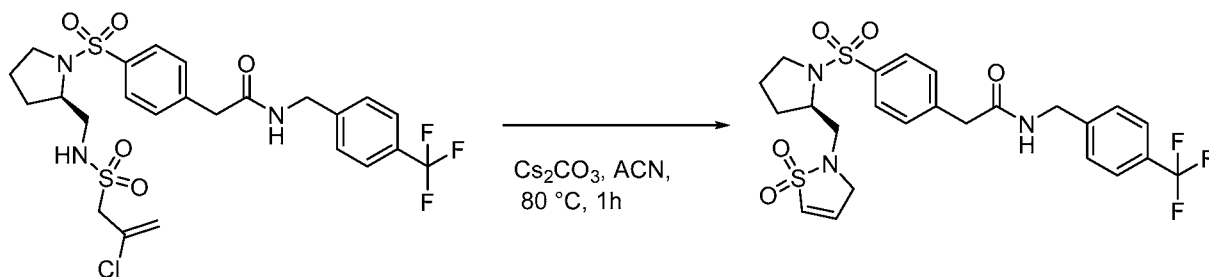
[0410] *Synthesis of 2-chloroprop-2-ene-1-sulfonyl chloride:* A mixture of sodium 2-chloroprop-2-ene-1-sulfonate (0.7 g, 40.00 mmol) and phosphorous pentachloride (0.8 g, 40.00 mmol) was stirred vigorously at 120 °C in sealed tube for 30 min. The reaction mixture was cooled and diluted with dichloromethane (50 mL). The organic phase was washed with 5% sodium bicarbonate solution (2 x 25 mL), water (35 mL), dried over anhydrous sodium sulphate and evaporated under reduced pressure to give the title compound as brown liquid.

¹H NMR (400 MHz, DMSO d₆) δ 5.44 (s, 1H), 5.29 (s, 1H), 3.45 (s, 2H). Yield (0.5 g, crude).

[0411] *Synthesis of (R)-2-(4-((2-(((2-chloroallyl)sulfonamido)methyl)pyrrolidin-1-yl)sulfonyl)-3-fluorophenyl)-N-(4-(trifluoromethyl)benzyl)acetamide*: To a stirred solution of (R)-2-(4-((2-(aminomethyl)pyrrolidin-1-yl)sulfonyl)-3-fluorophenyl)-N-(4-(trifluoromethyl)benzyl)acetamide (0.4 g, 0.845 mmol) in dichloromethane (15 mL) at 0 °C was added triethylamine (0.48 mL, 3.382 mmol) and 2-chloroprop-2-ene-1-sulfonyl chloride (0.17 g, 1.014 mmol) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 70 % ethyl acetate in hexane as eluent to give the title compound as yellow solid. m/z = 574 [M + H]⁺; Yield (0.12 g, crude)

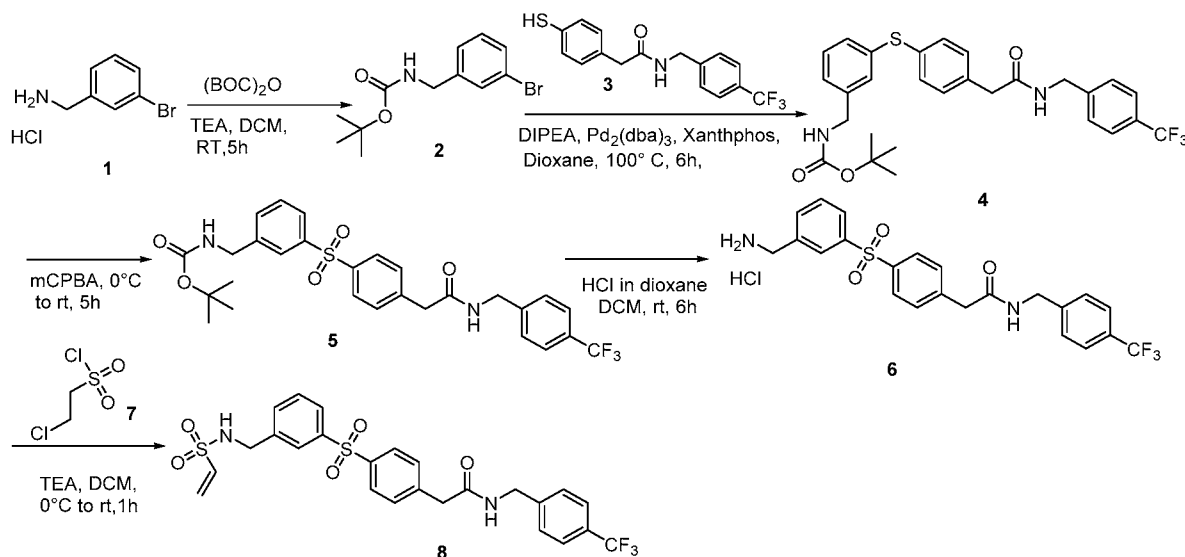
[0412] *Synthesis of (R)-2-(3-fluoro-4-((2-((propa-1,2-dien-1-yl)sulfonamido)methyl)pyrrolidin-1-yl)sulfonyl)phenyl)-N-(4-(trifluoromethyl)benzyl)acetamide (X-0001495)*: To a stirred solution of (R)-2-(4-((2-(((2-chloroallyl)sulfonamido)methyl)pyrrolidin-1-yl)sulfonyl)-3-fluorophenyl)-N-(4-(trifluoromethyl)benzyl)acetamide (0.1 g, 0.16 mmol) in dichloromethane (10 mL) was added triethylamine (0.11 mL, 0.81 mmol) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by preparative HPLC using BEH C18 (50 mm x 2.1 mm x 1.7 mic) column with 0.1 % formic acid in water and acetonitrile as mobile phase to give the title compound as off white solid.

Example II-12: Synthesis of X-0001554



[0413] *Synthesis of (R)-2-(4-((2-((1,1-dioxidoisothiazol-2(3H)-yl)methyl)pyrrolidin-1-yl)sulfonyl)phenyl)-N-(4-(trifluoromethyl)benzyl)acetamide*: To a stirred solution of (R)-2-(4-((2-(((2-chloroallyl)sulfonamido)methyl)pyrrolidin-1-yl)sulfonyl)phenyl)-N-(4-(trifluoromethyl)benzyl)acetamide (0.1 g, 0.41 mmol) in acetonitrile (10 mL) was added cesium carbonate (0.11 g, 0.33 mmol) and the reaction mixture was stirred at 80 °C for 1h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography by using combiflash purifier with 70 % ethyl acetate in hexane as eluent to give the title compound as off white solid.

Example II-13: Synthesis of N-(4-(trifluoromethyl)benzyl)-2-(4-((3-(vinylsulfonamidomethyl)phenyl)sulfonyl)phenyl)acetamide (X-0001579)



[0414] *Synthesis of tert-butyl (3-bromobenzyl)carbamate*: To a stirred solution of (3-bromophenyl)methanamine hydrochloride (2.0 g, 0.089 mol) in dichloromethane was added triethylamine (1.39 mL, 0.010 mol) and stirred for 10 minutes. After 10 minutes Di-tert-butyl dicarbonate (2.35 g, 0.010 mol) was added and stirred for 6h. The reaction mixture was diluted with water and extracted in to dichloromethane. The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by combiflash purifier with 18 % ethyl acetate in hexane as an eluent give the title compound as semi solid. $m/z = 187.9$ $[\text{M} + \text{H}]^+$; Yield: (2.2 g, 76 %).

[0415] *Synthesis of tert-butyl (3-((4-(2-oxo-2-((4-(trifluoromethyl)benzyl)amino)ethyl)phenyl)thio)benzyl)carbamate:* To a stirred solution of 2-(4-mercaptophenyl)-N-(4-(trifluoromethyl)benzyl)acetamide (1.0 g, 3.07 mmol) and tert-butyl (3-bromobenzyl) carbamate (1.05 g, 3.69 mmol) in dioxane (15 mL) in a sealed tube was added diisopropylethylamine (1.07 mL, 6.0 mmol), then reaction mixture was degassed with nitrogen for 5 min, then added xantphos (0.177 g, 0.307 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.14 g, 0.15 mmol) and the sealed tube was closed and was stirred at 100 °C for 6 h. The reaction mixture was cooled, filtered through Celite ® and the filtrate washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by combiflash purifier with 40 % ethyl acetate in hexane as an eluent give the title compound as yellow solid. $m/z = 430.9$ $[\text{M} + \text{H}]^+$; Yield: (0.65 g, 40 %)

[0416] *Synthesis of tert-butyl (3-((4-(2-oxo-2-((4-(trifluoromethyl)benzyl) amino)ethyl) phenyl)sulfonyl)benzyl)carbamate:* To a stirred solution of tert-butyl (3-((4-(2-oxo-2-((4-(trifluoromethyl)benzyl)amino)ethyl)phenyl)thio)benzyl)carbamate (0.65 g, 1.2 mmol) in dichloromethane (10 mL) at 0 °C was added m-chloroperbenzoic acid (0.9 g, 3.67 mmol) portion wise and the reaction mixture was stirred at room temperature for 5h. The reaction mixture was quenched with saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give title compound. $m/z = 506.8$ $[\text{M} + \text{H}]^+$; Yield: (0.35g, crude).

[0417] *Synthesis of 2-(4-((3-(aminomethyl)phenyl)sulfonyl)phenyl)-N-(4-(trifluoromethyl) benzyl)acetamide hydrochloride:* To a stirred solution of tert-butyl (3-((4-(2-oxo-2-((4-(trifluoromethyl)benzyl)amino)ethyl)phenyl)sulfonyl)benzyl)carbamate (0.35 g, 0.62 mmol) in dichloromethane (10 mL) at 0 °C was added 4M HCl in dioxane (3mL) drop wise and the reaction mixture was stirred at room temperature for 6h. The reaction mixture was evaporated under reduced pressure. The residue was washed with diethyl ether and dried to get the title compound (0.2 g, crude) as semi solid. $m/z 462.9$ $[\text{M} + \text{H}]^+$

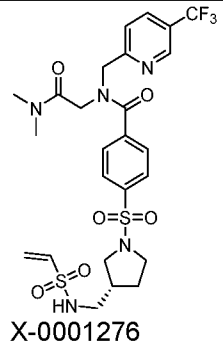
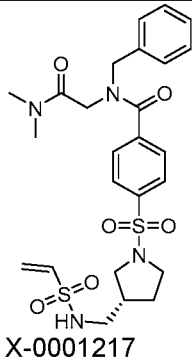
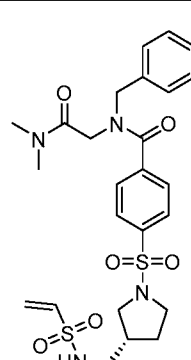
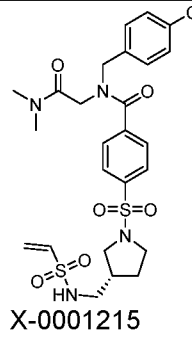
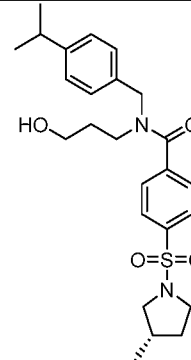
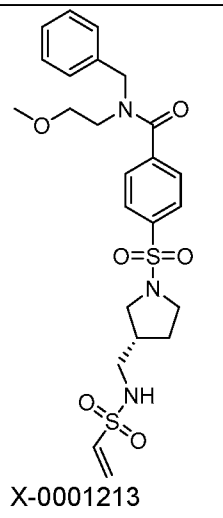
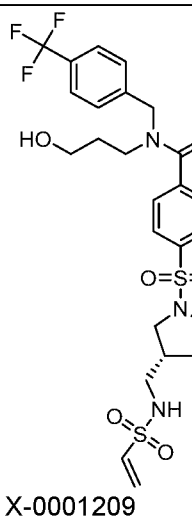
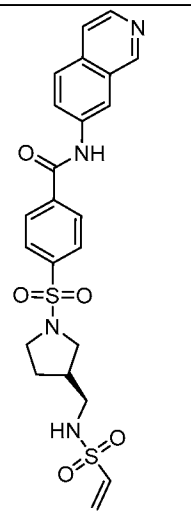
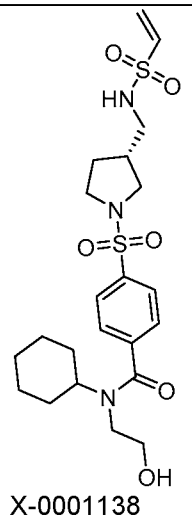
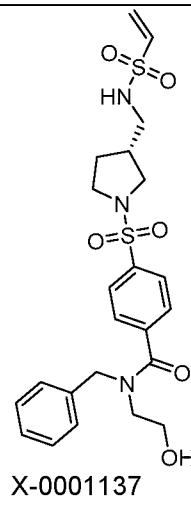
[0418] *Synthesis of N-(4-(trifluoromethyl)benzyl)-2-(4-((3-(vinylsulfonamidomethyl) phenyl) sulfonyl)phenyl)acetamide (X-0001579):* To a stirred solution of 2-(4-((3-(aminomethyl)phenyl) sulfonyl)phenyl)-N-(4-(trifluoromethyl)benzyl)acetamide hydrochloride (0.2 g, 0.4 mmol), triethylamine (0.17mL, 1.2 mmol) in dichloromethane (5 mL) at 0 °C was added 2-chloroethane-1-sulfonyl chloride (0.08 mL, 8.0 mmol) and the

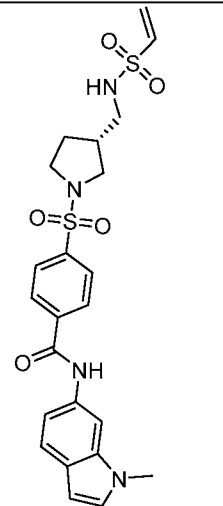
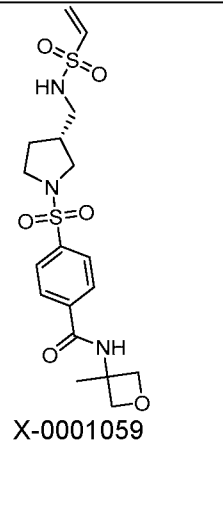
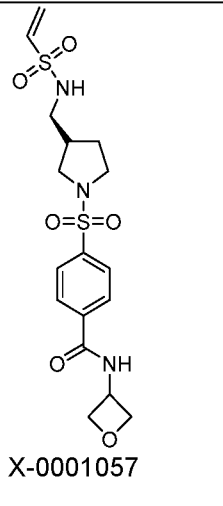
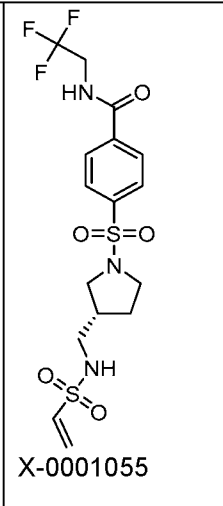
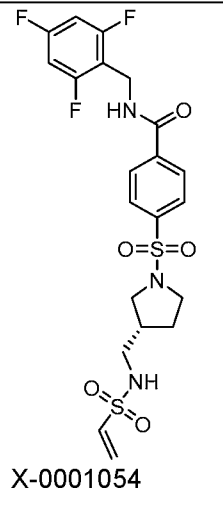
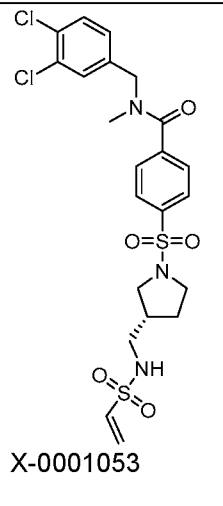
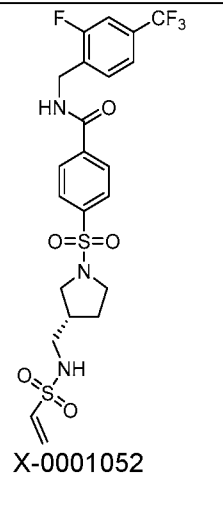
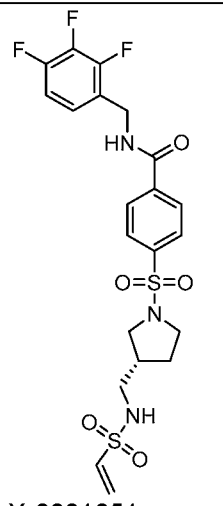
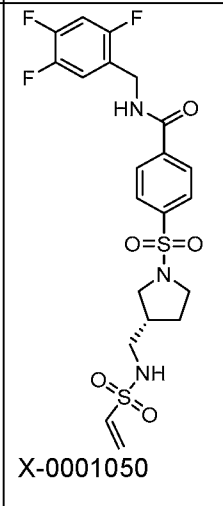
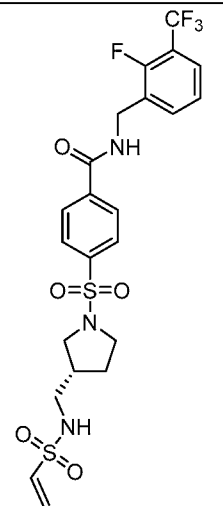
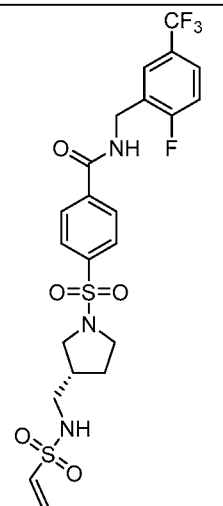
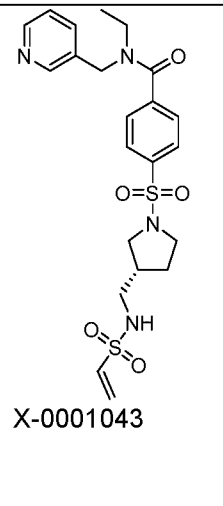
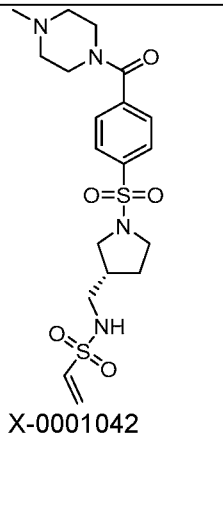
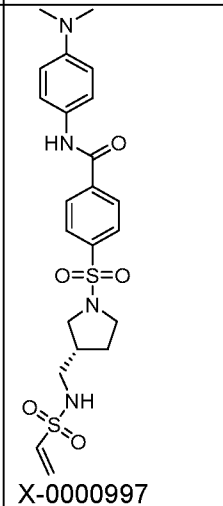
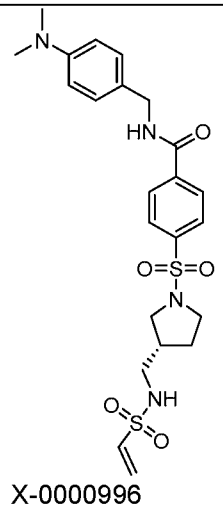
reaction mixture was stirred at 0°C for 0.5 h and room temperature for 0.5h. The reaction mixture was evaporated under reduced pressure. The crude product was purified by preparative HPLC using X bridge (250mm X 4.6mm X 5mic) column with 0.1% Ammonia in water and acetonitrile as mobile phase to give the title compound as white solid. Yield (0.03 g, 14 %).

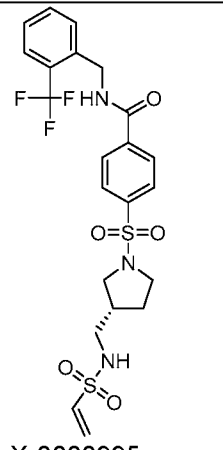
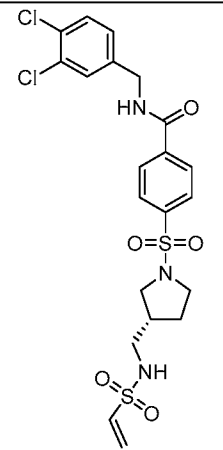
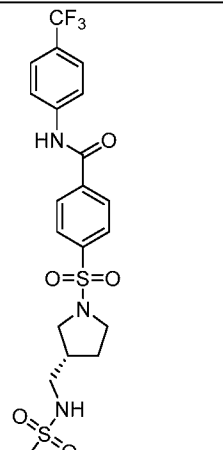
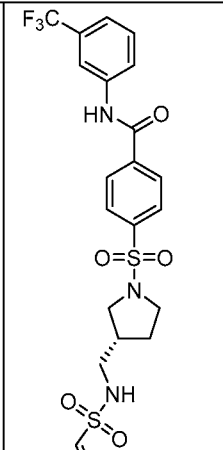
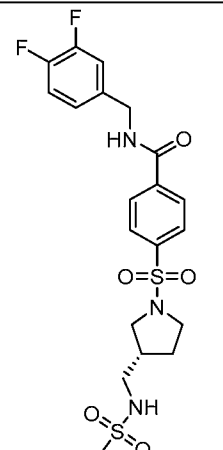
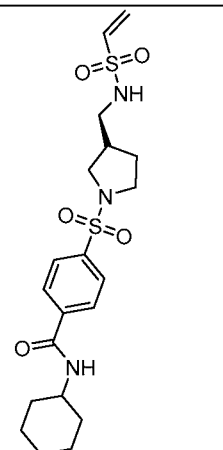
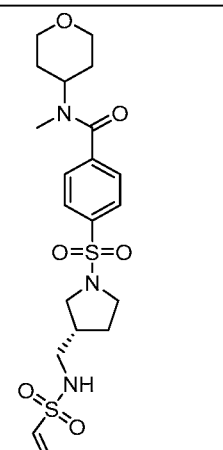
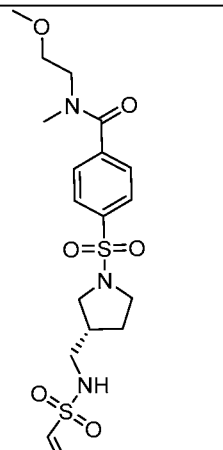
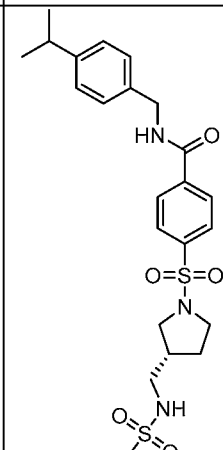
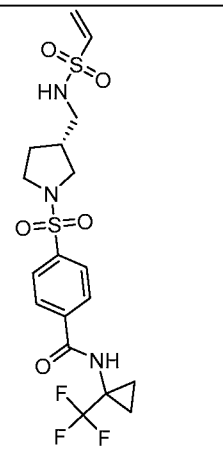
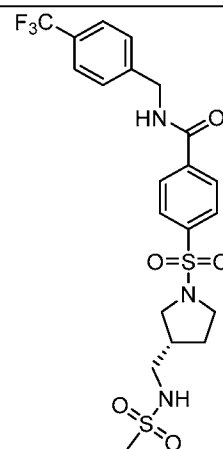
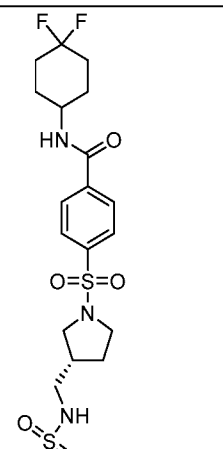
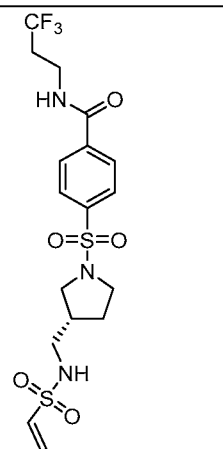
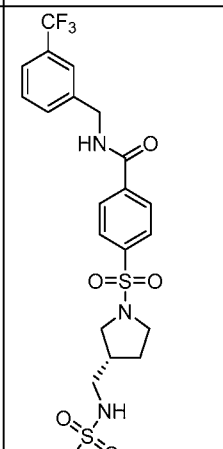
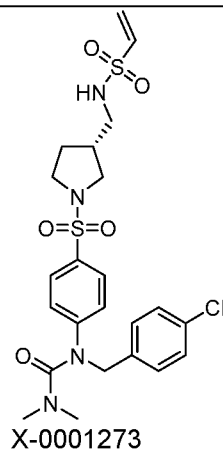
Example II-14: Additional Compounds

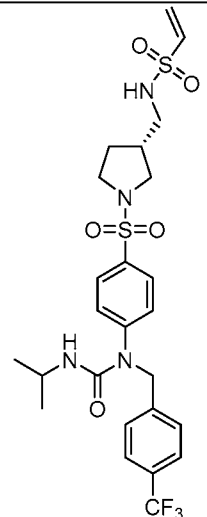
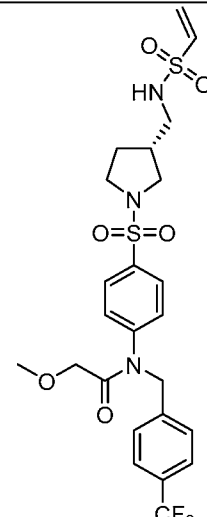
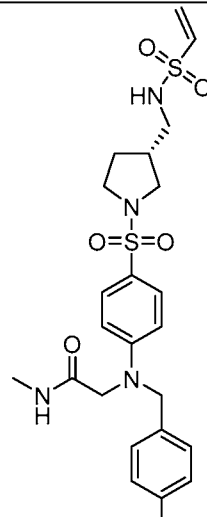
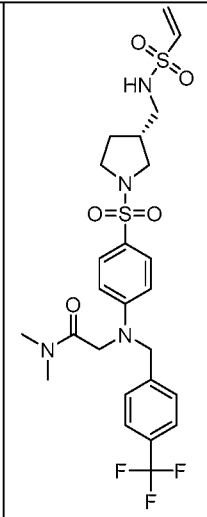
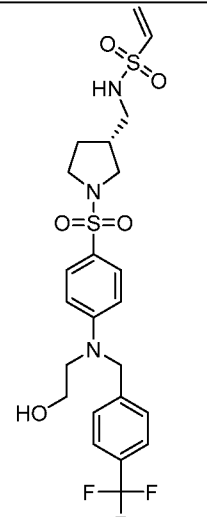
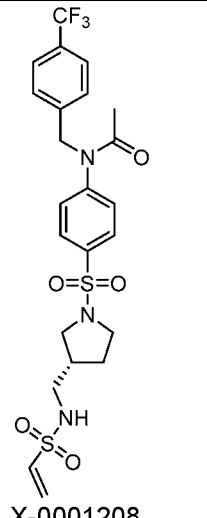
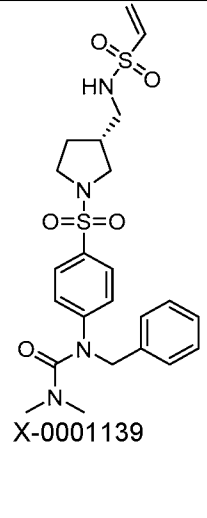
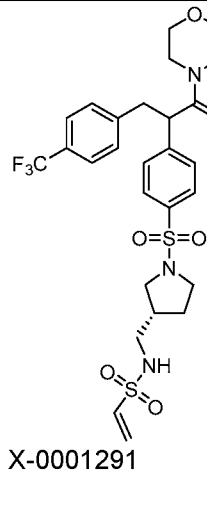
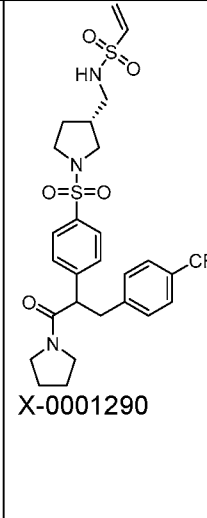
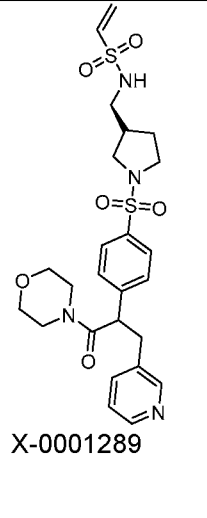
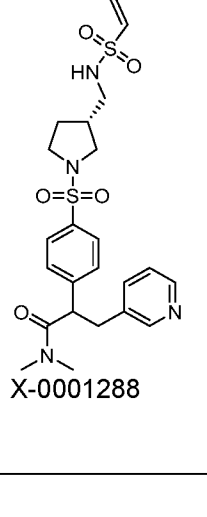
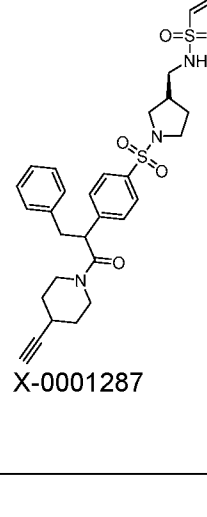
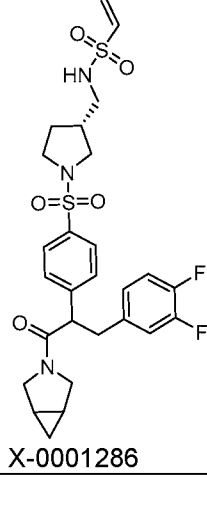
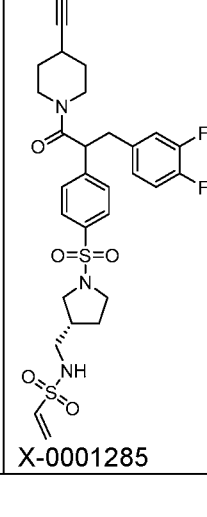
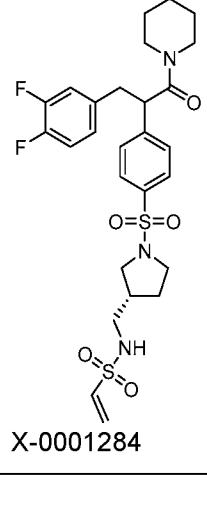
[0419] Additional compounds synthesized using methods similar to those described in the above Examples are provided in Table II-1 below. Characterization of compounds is provided in Table II-2 below.

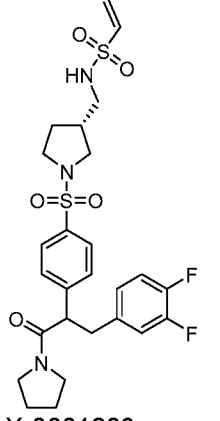
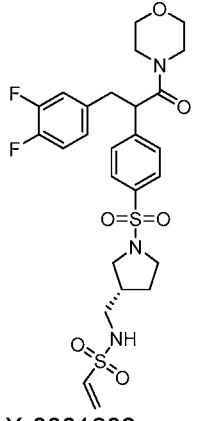
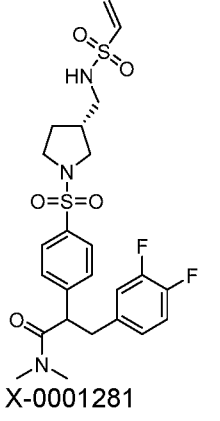
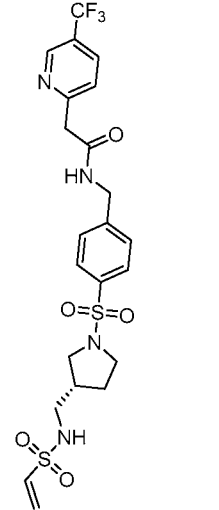
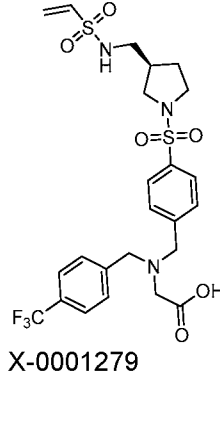
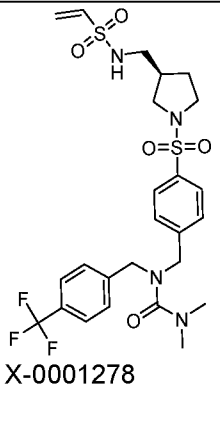
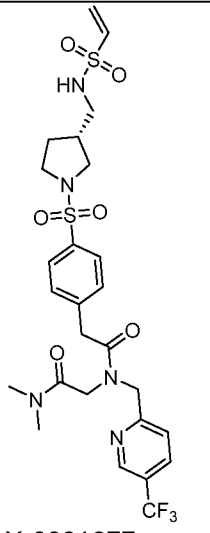
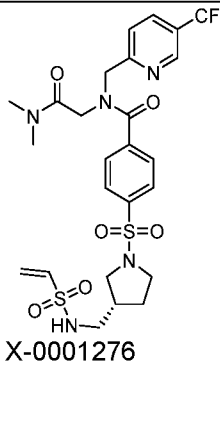
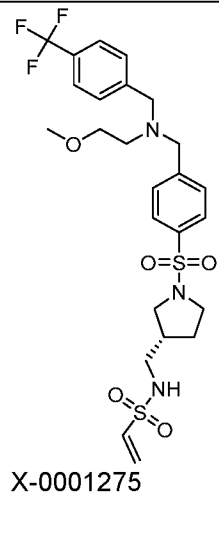
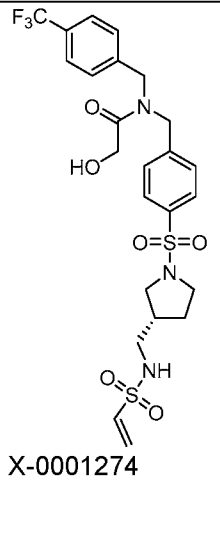
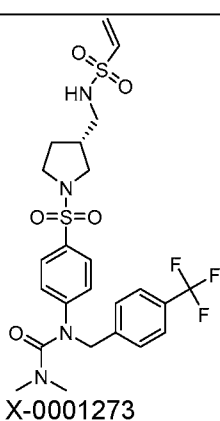
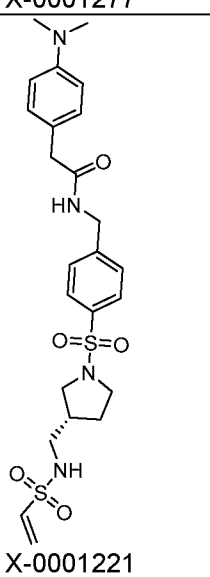
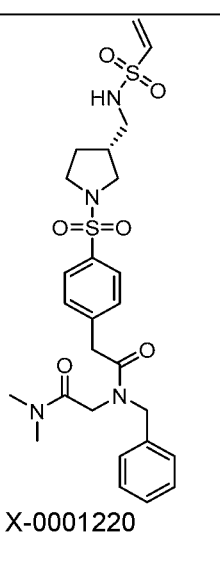
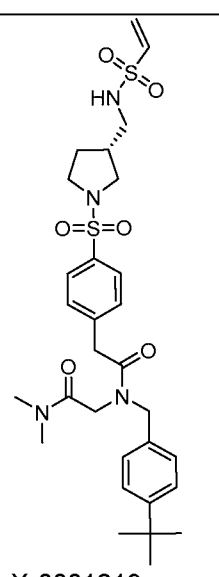
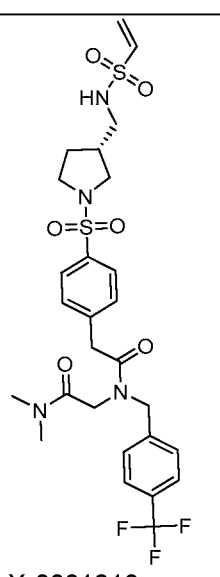
Table II-1. Additional synthesized compounds

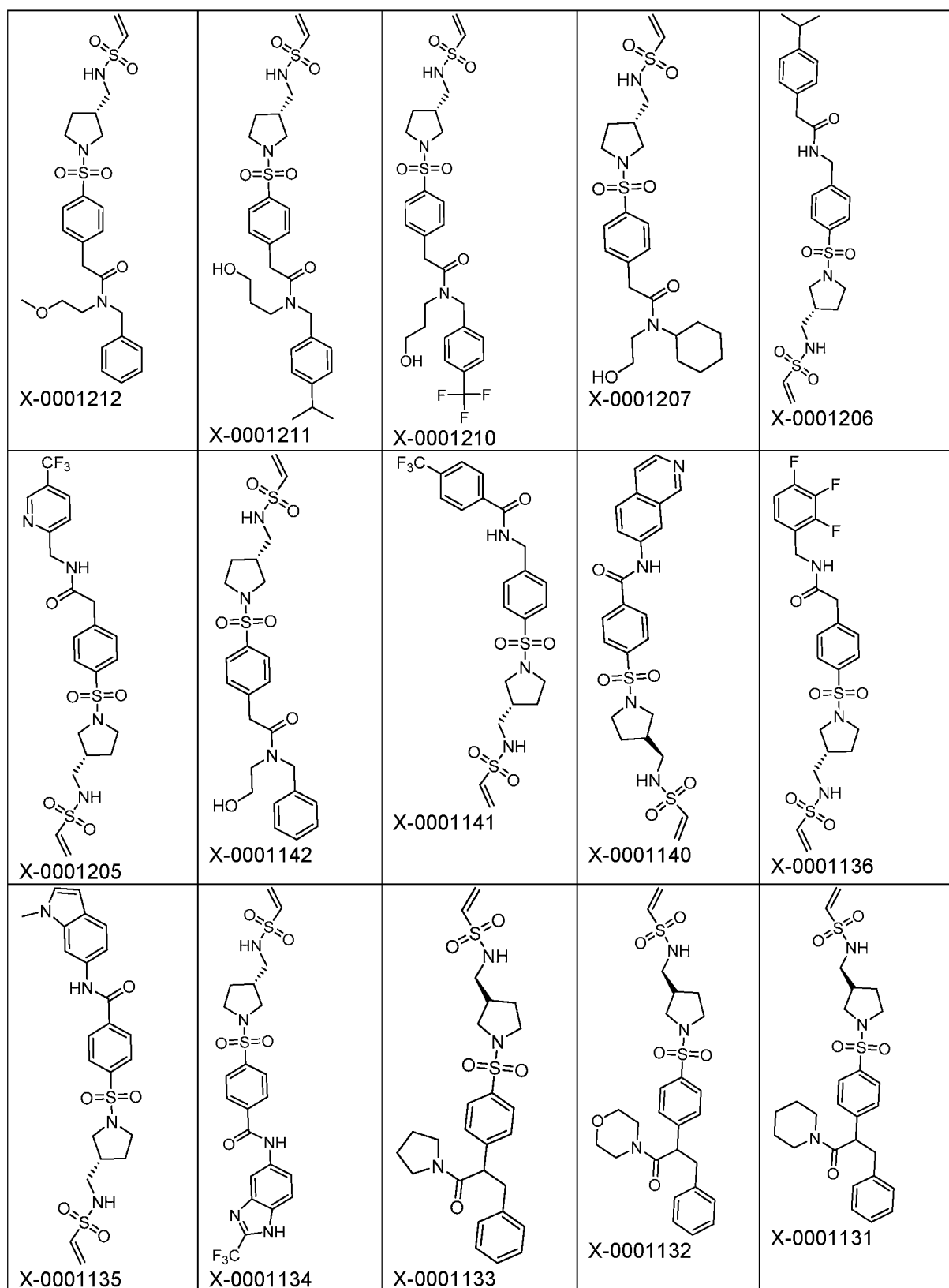
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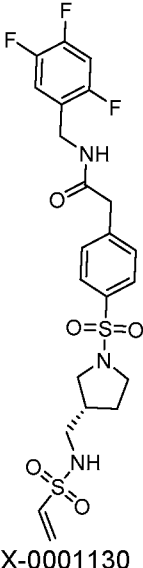
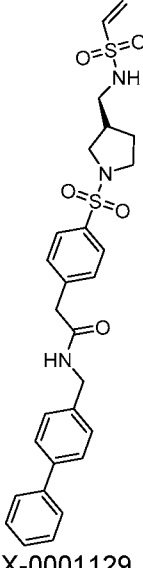
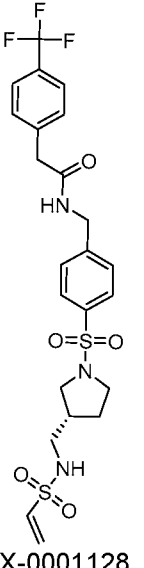
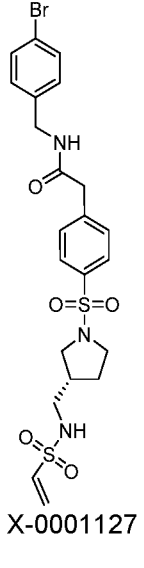
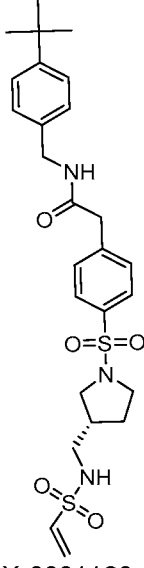
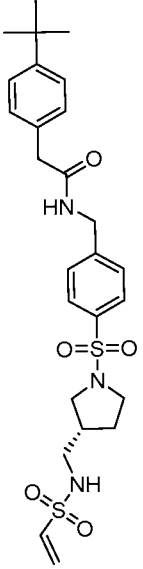
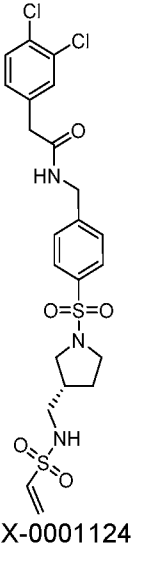
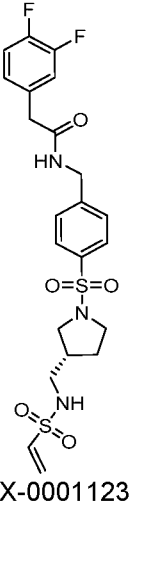
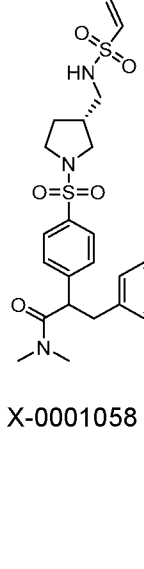
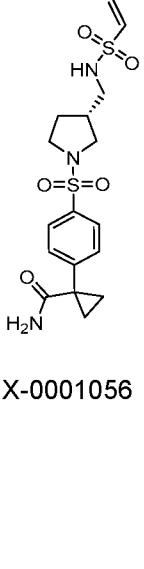
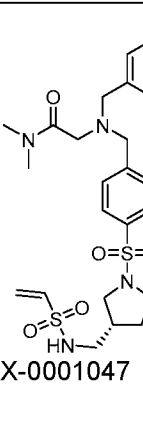
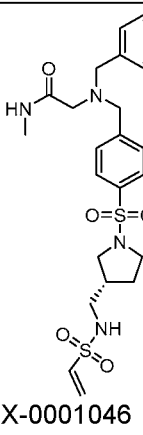
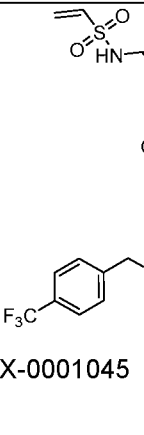
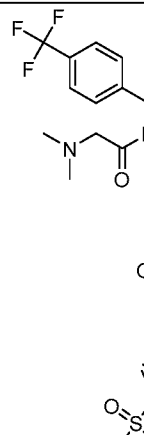
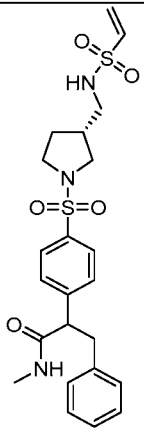
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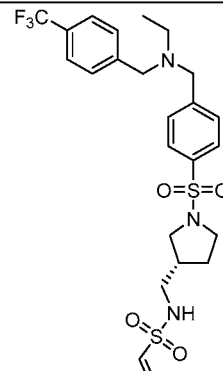
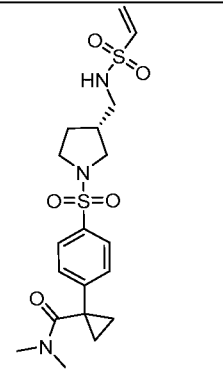
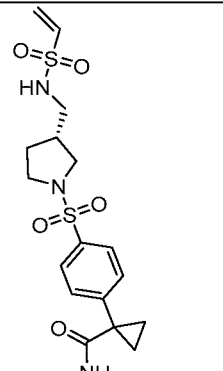
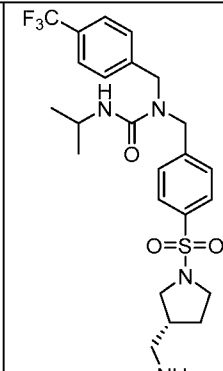
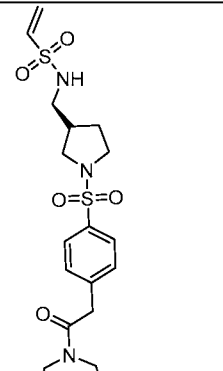
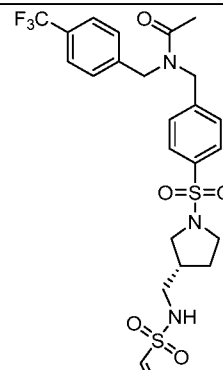
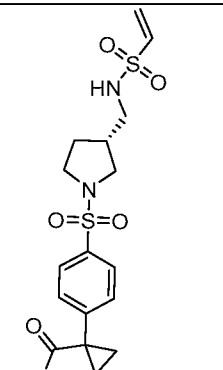
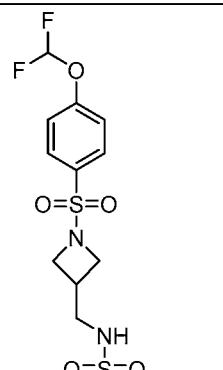
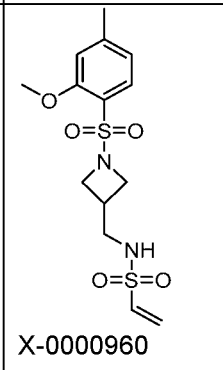
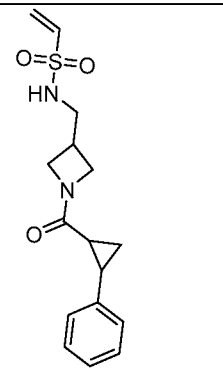
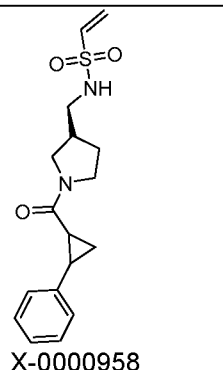
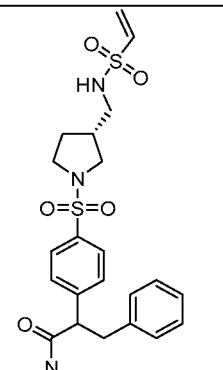
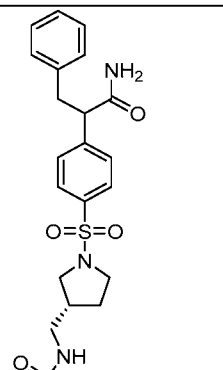
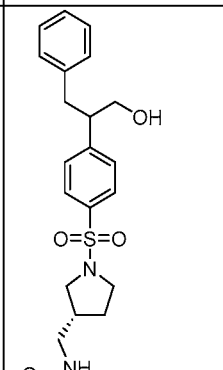
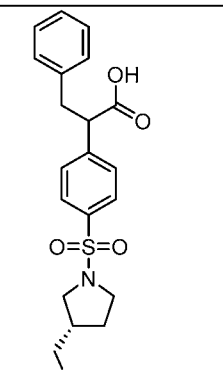
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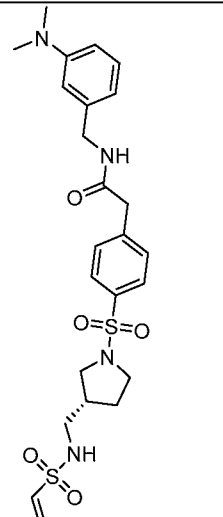
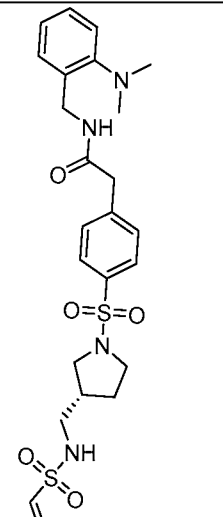
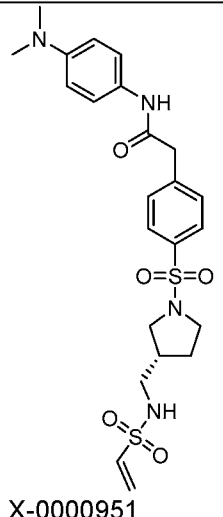
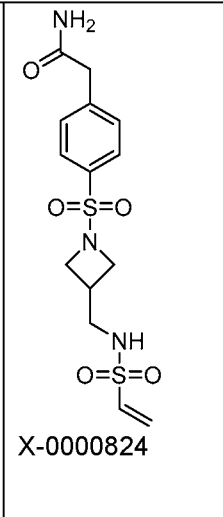
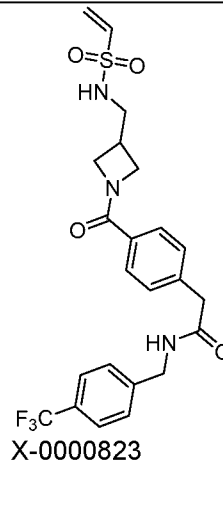
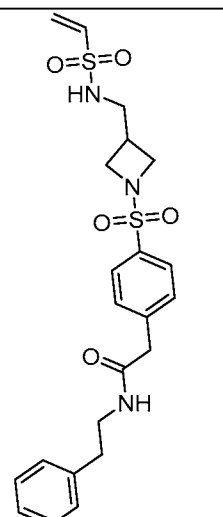
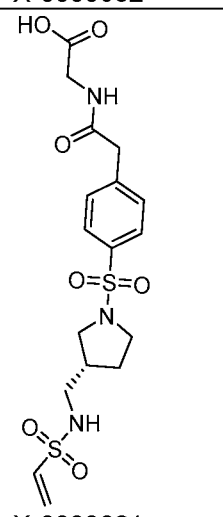
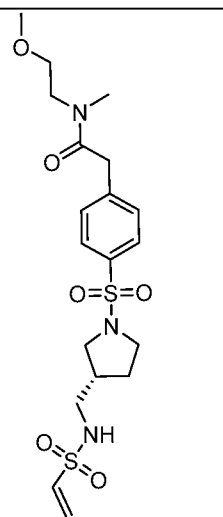
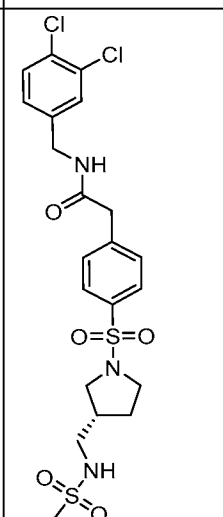
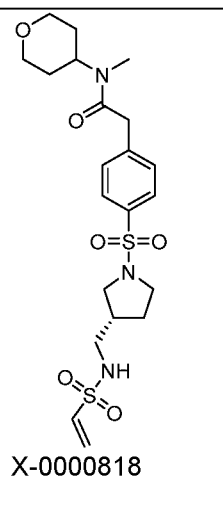
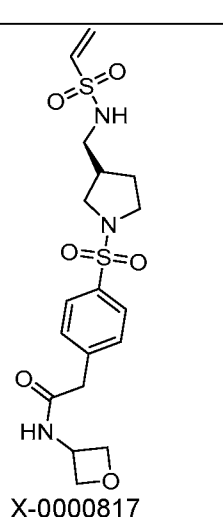
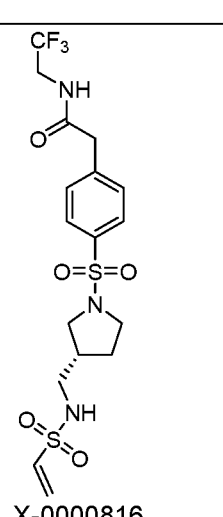
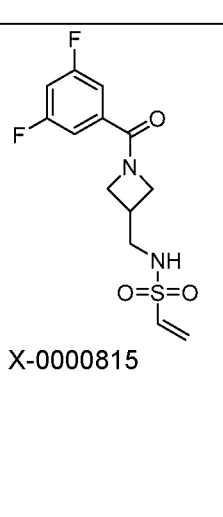
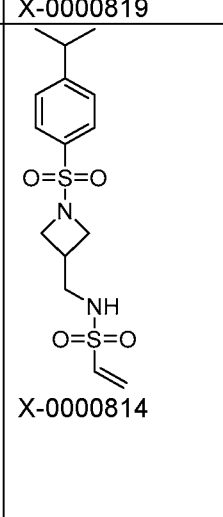
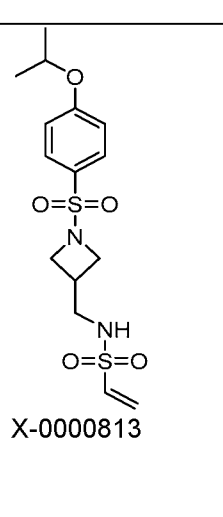
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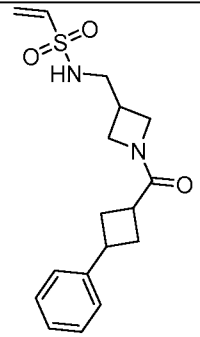
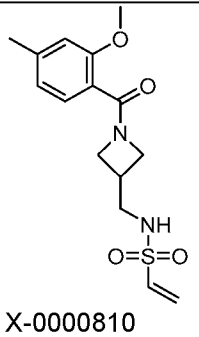
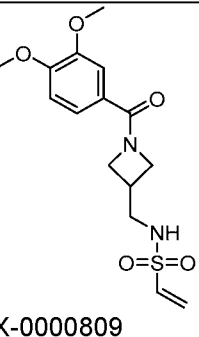
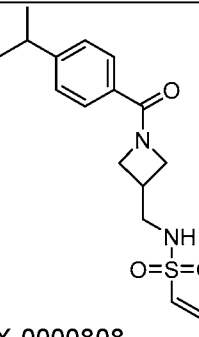
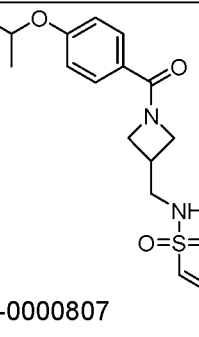
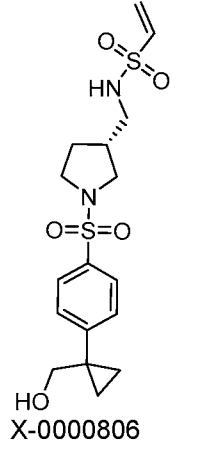
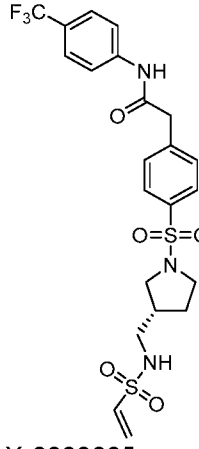
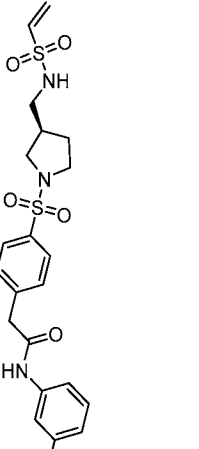
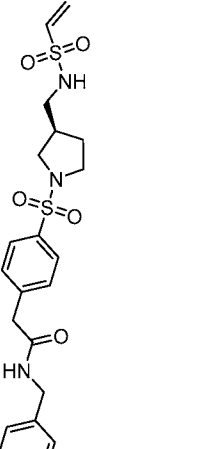
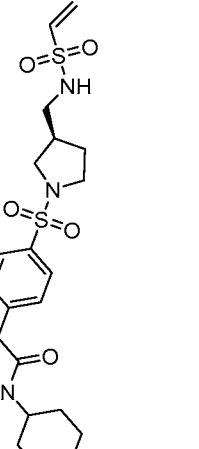
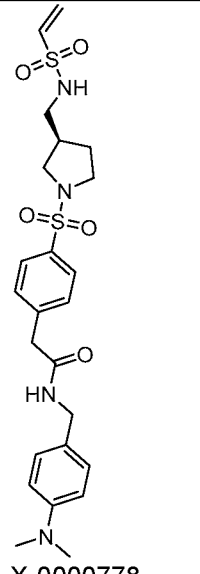
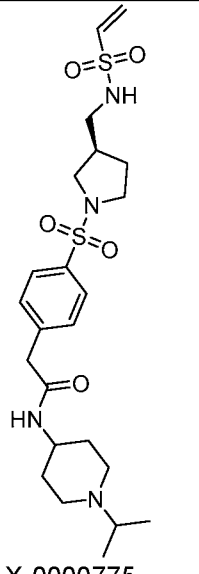
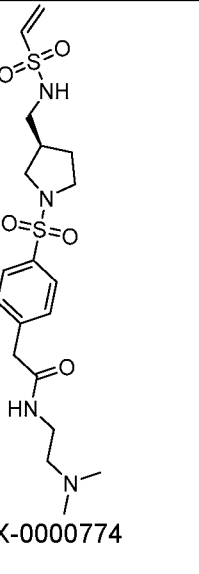
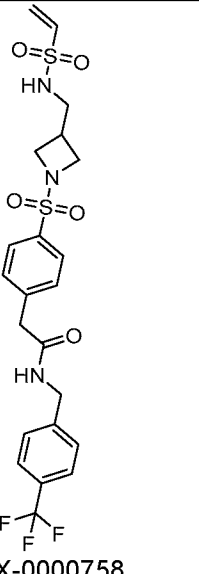
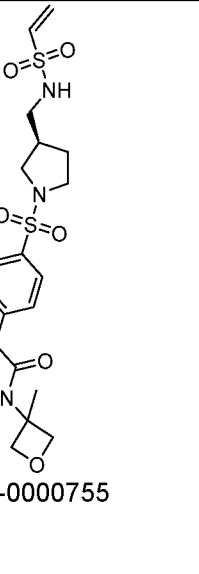
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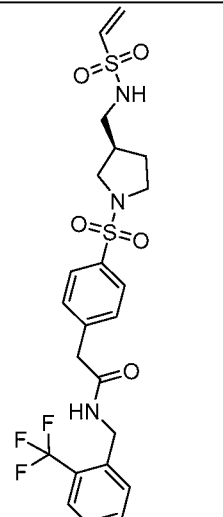
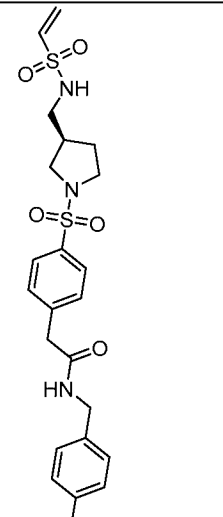
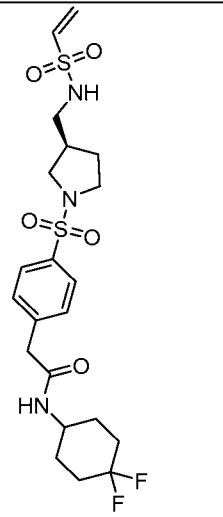
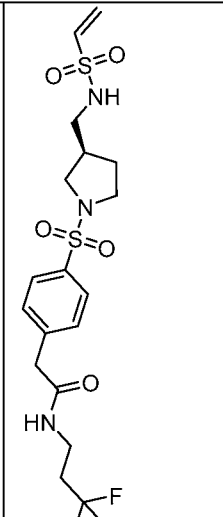
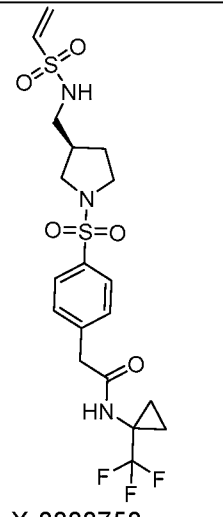
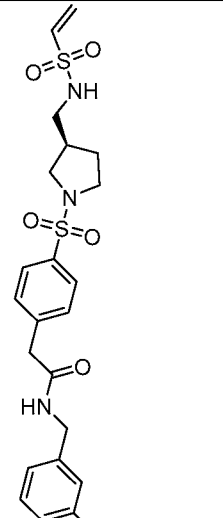
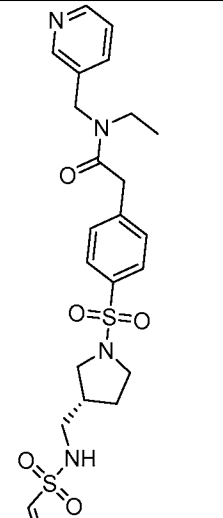
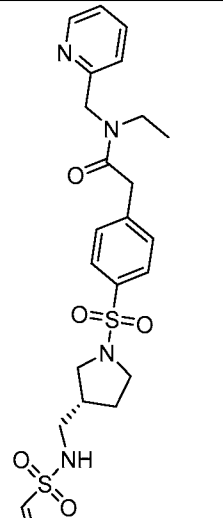
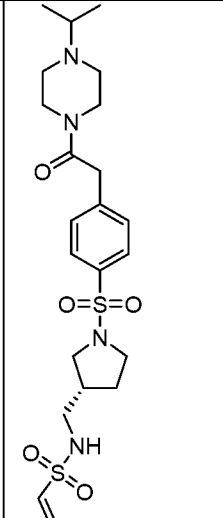
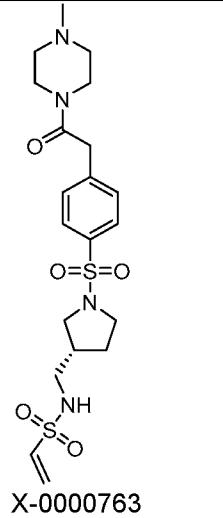
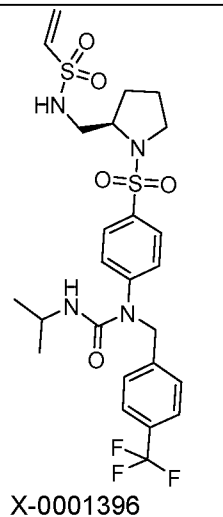
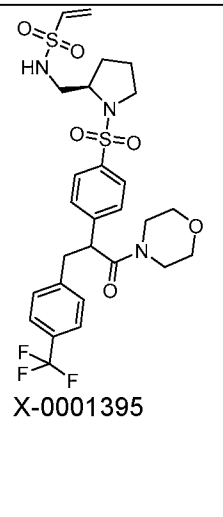
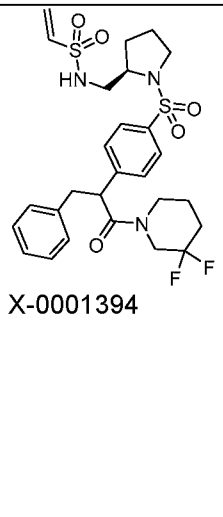
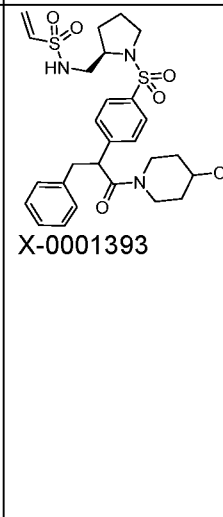
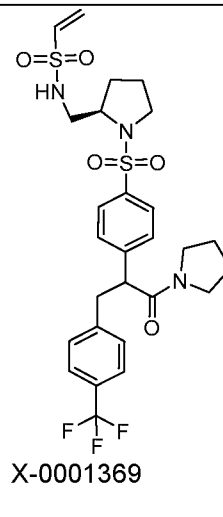


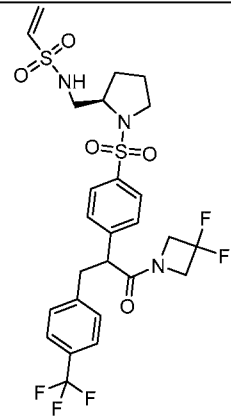
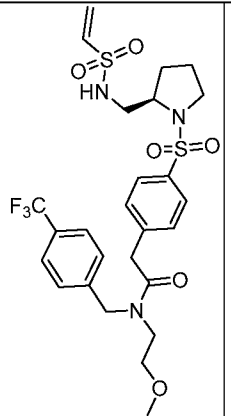
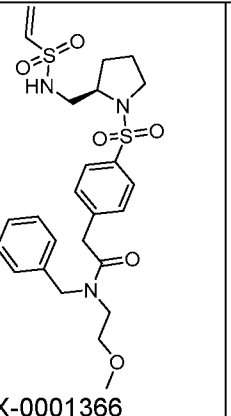
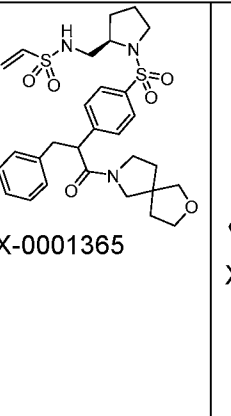
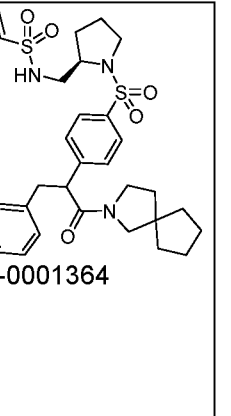
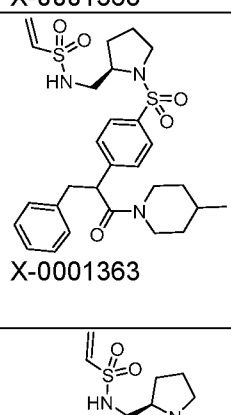
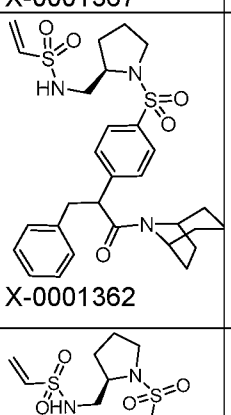
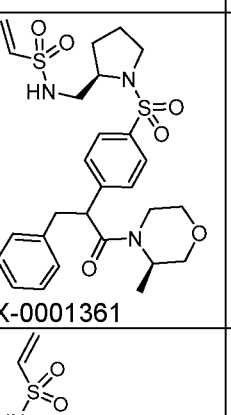
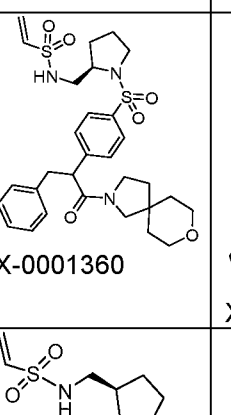
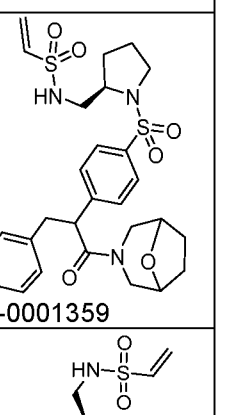
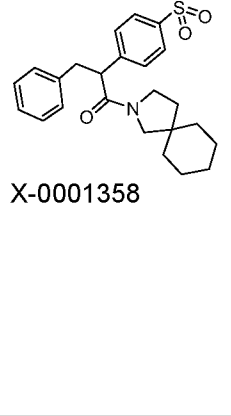
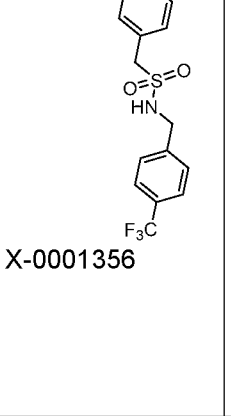
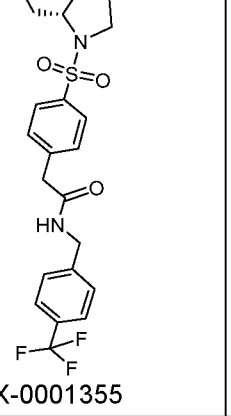
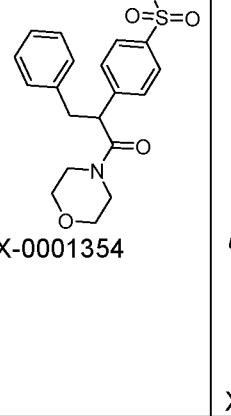
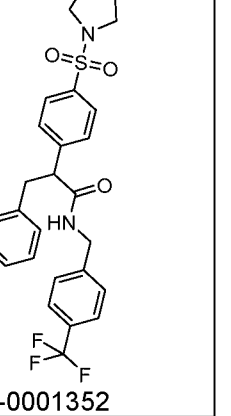
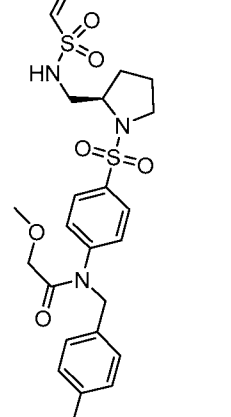
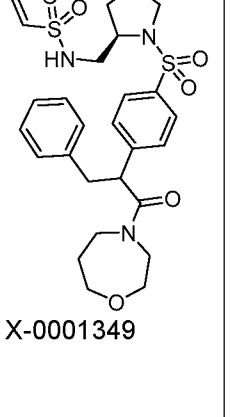
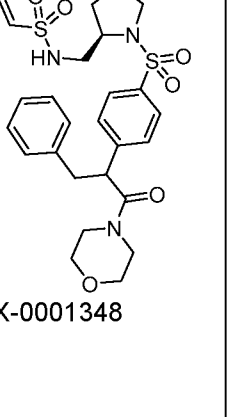
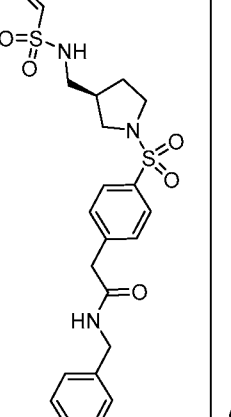
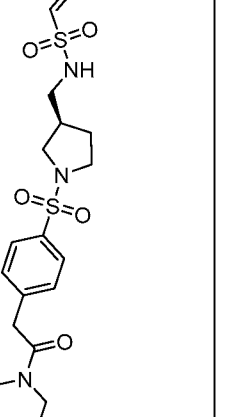
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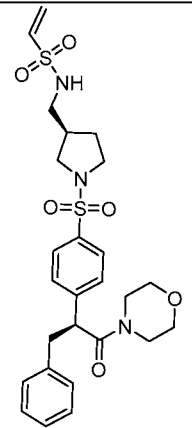
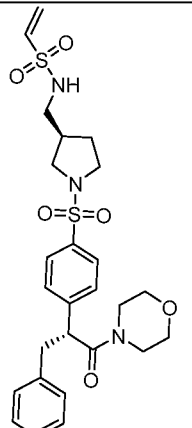
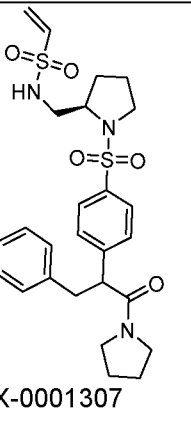
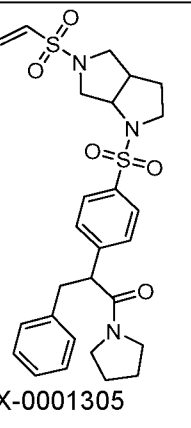
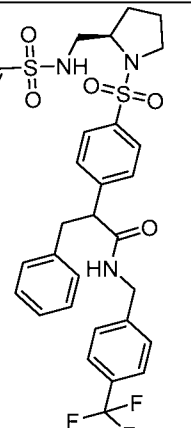
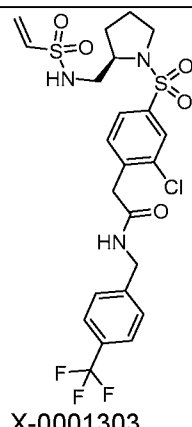
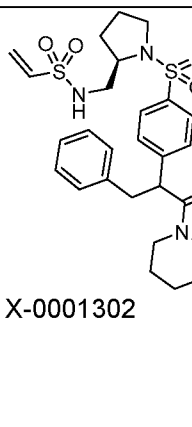
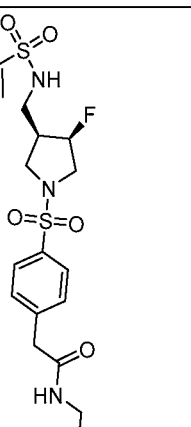
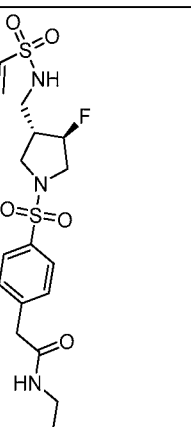
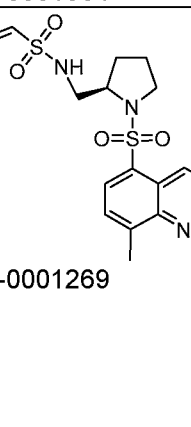
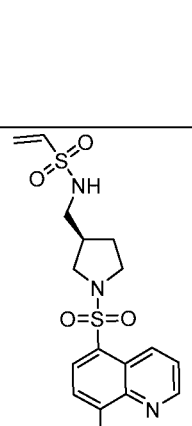
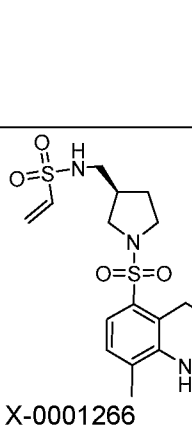
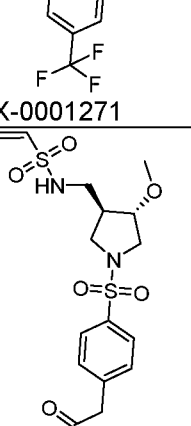
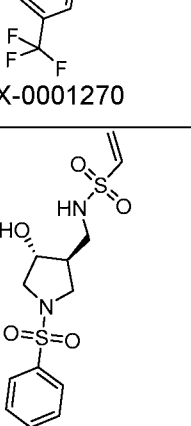
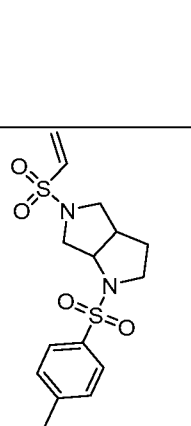
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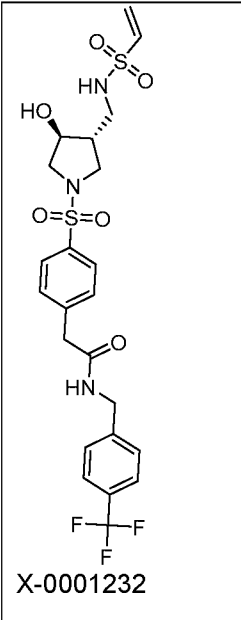
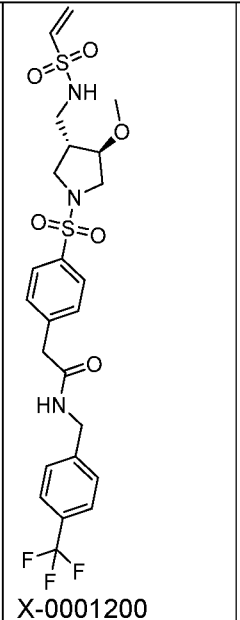
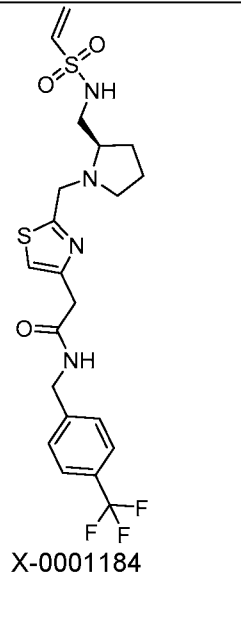
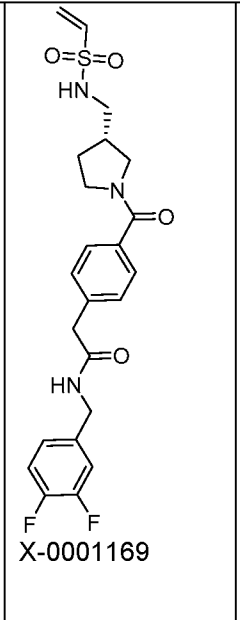
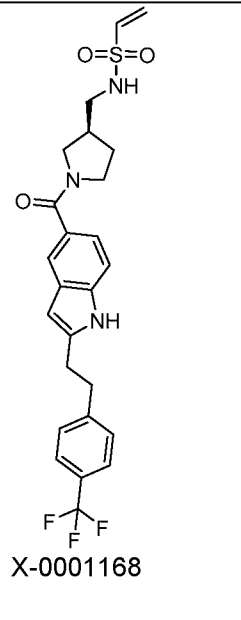
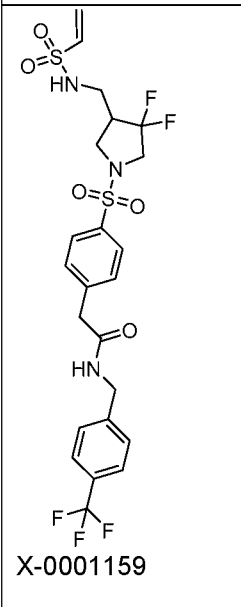
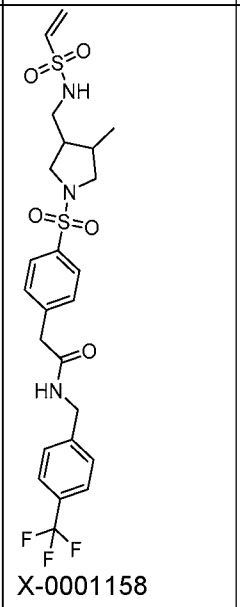
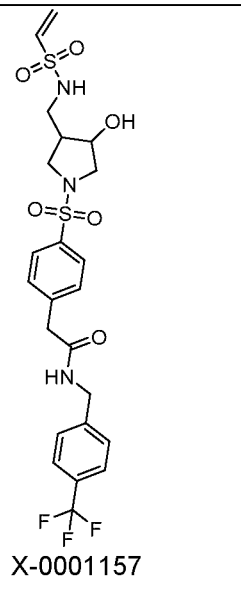
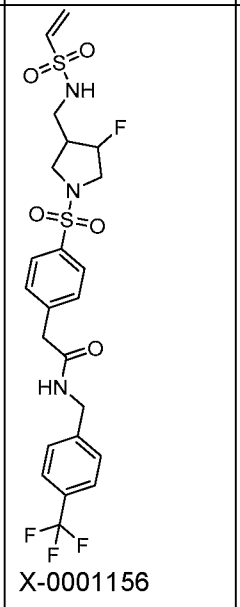
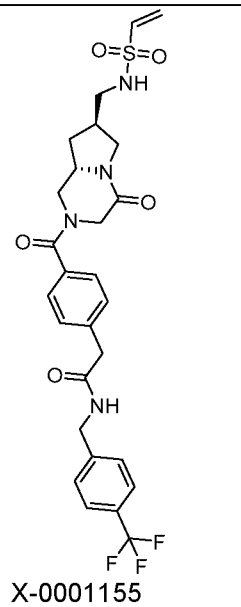
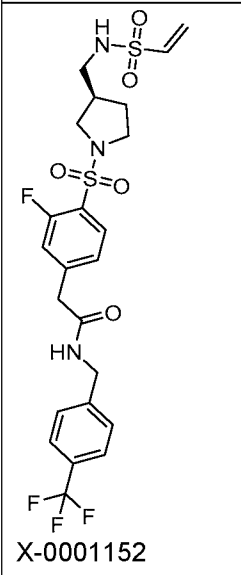
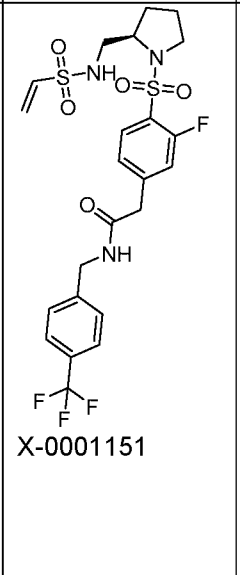
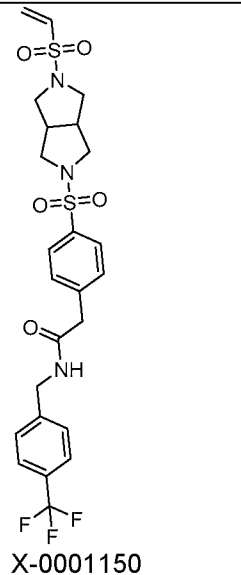
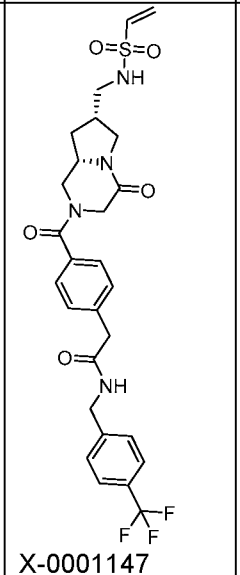
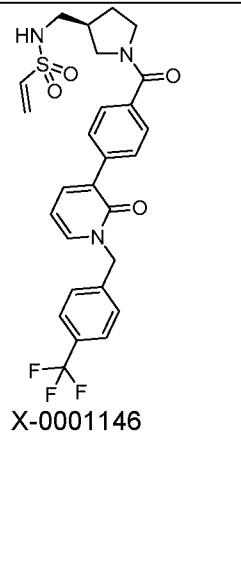
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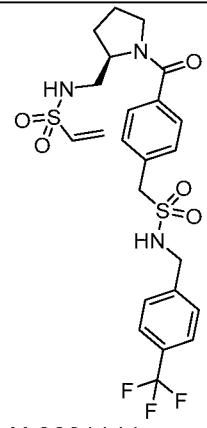
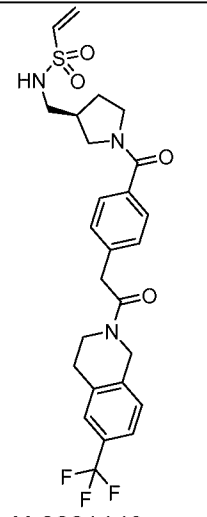
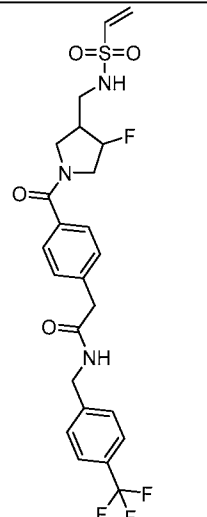
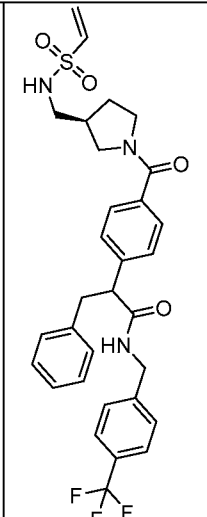
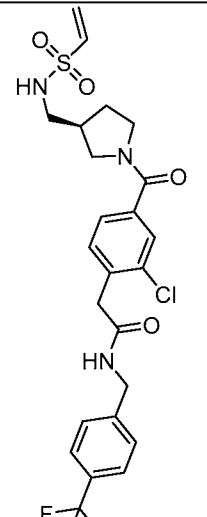
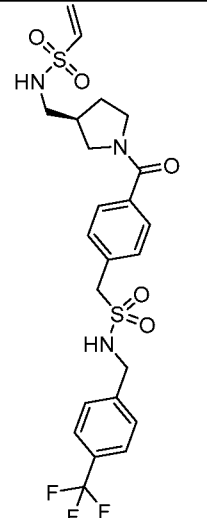
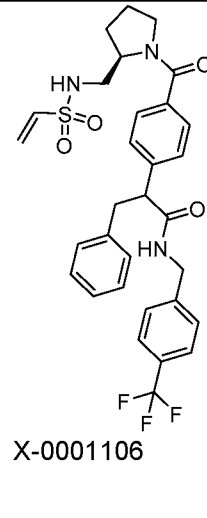
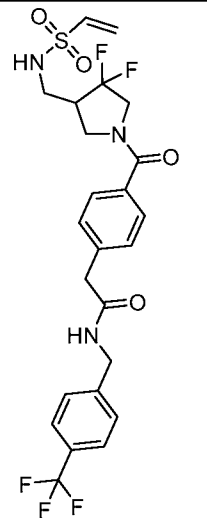
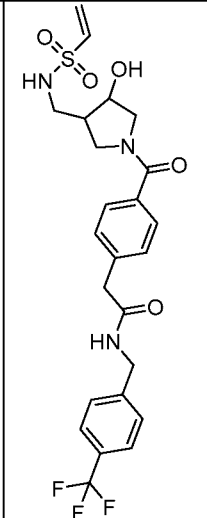
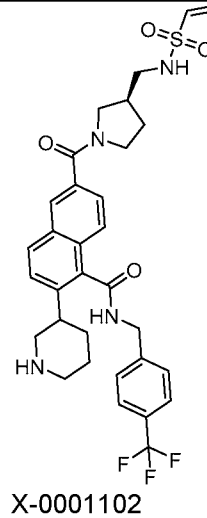
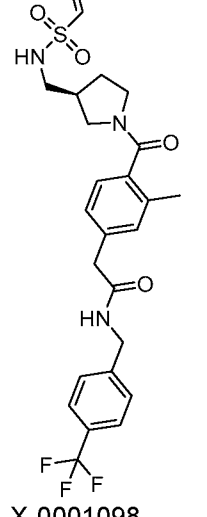
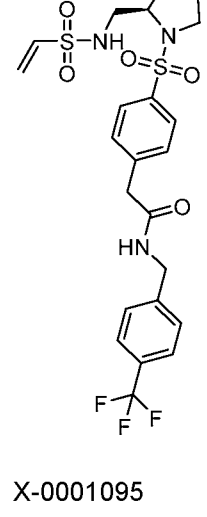
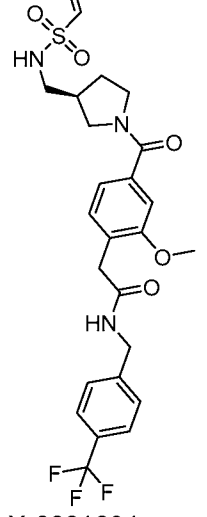
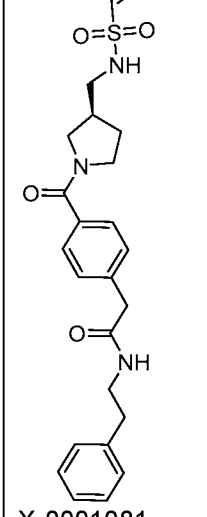
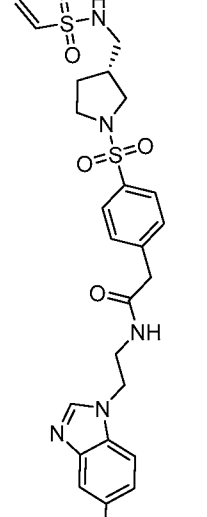
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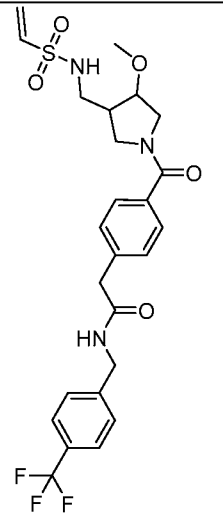
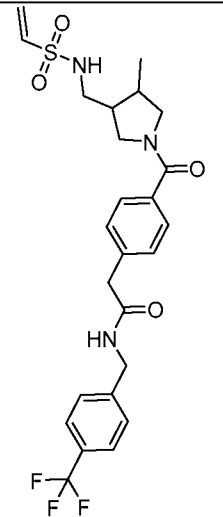
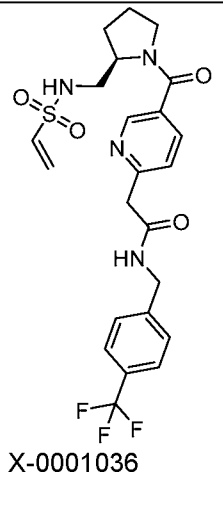
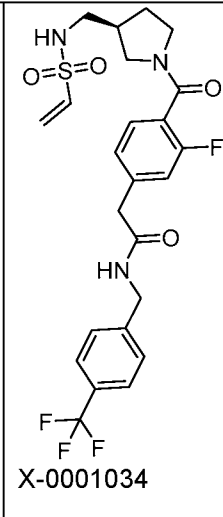
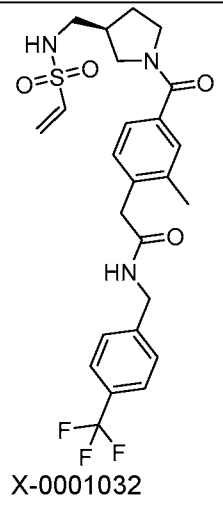
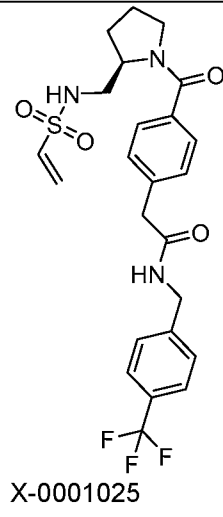
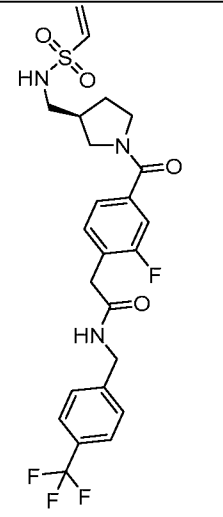
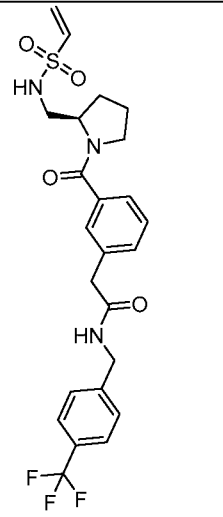
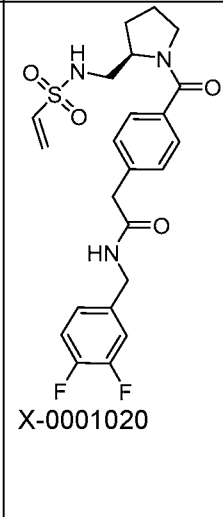
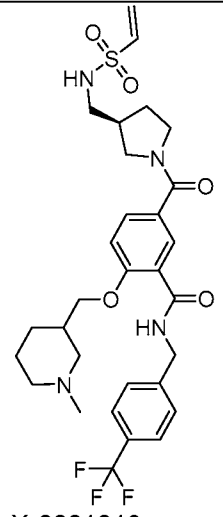
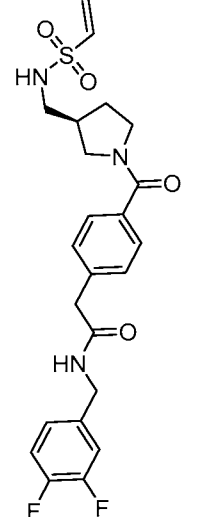
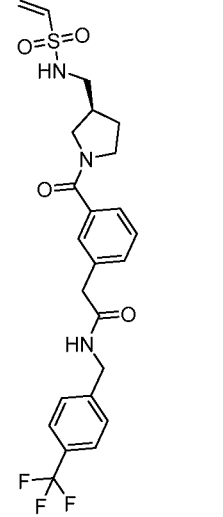
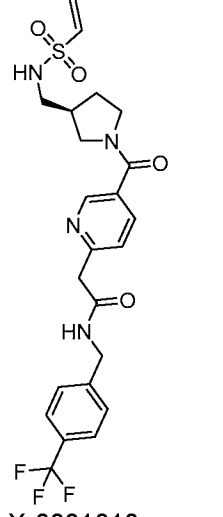
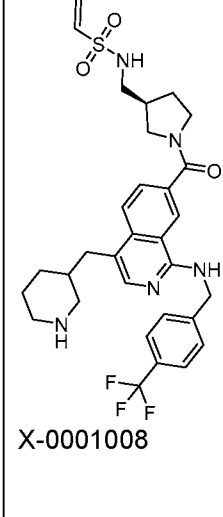
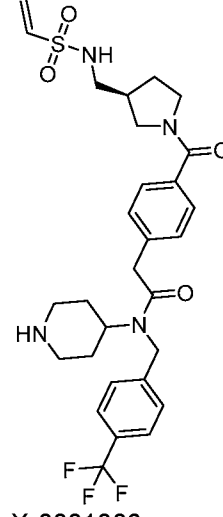
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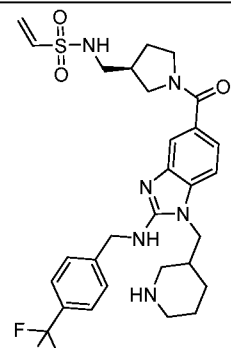
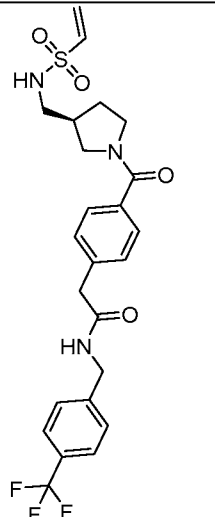
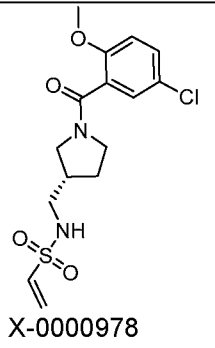
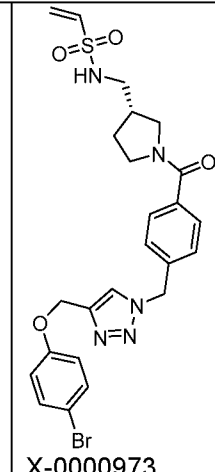
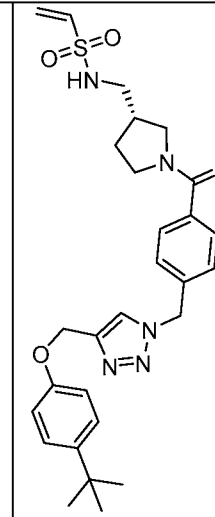
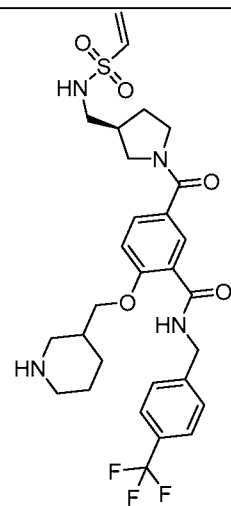
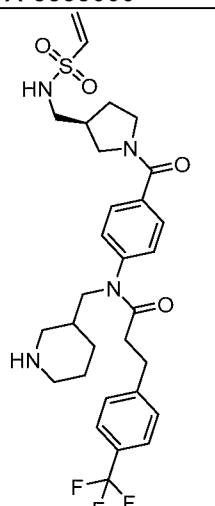
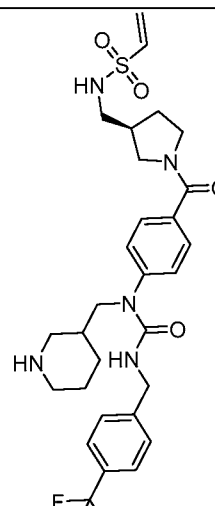
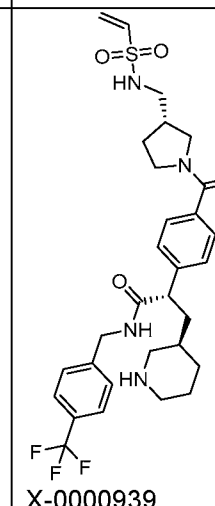
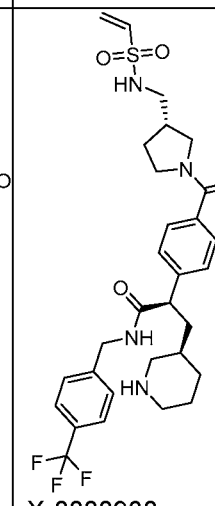
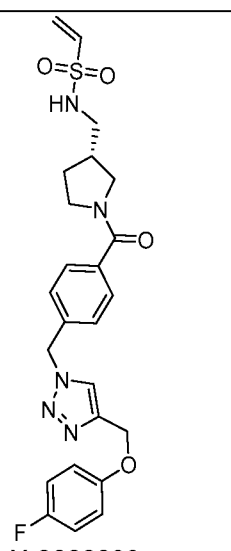
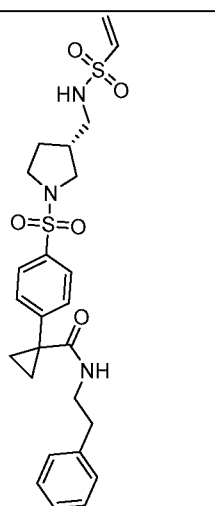
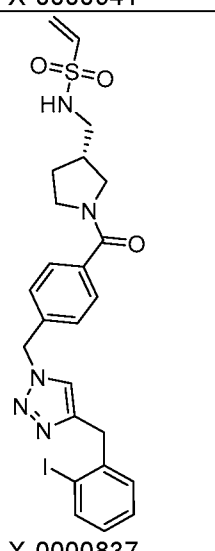
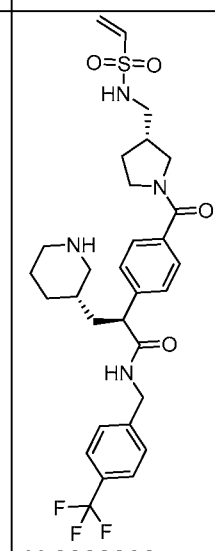
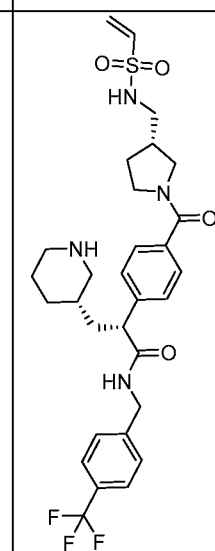
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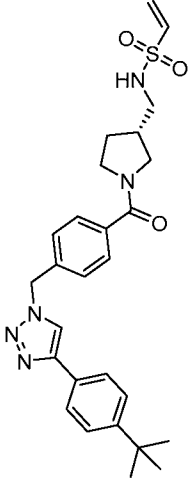
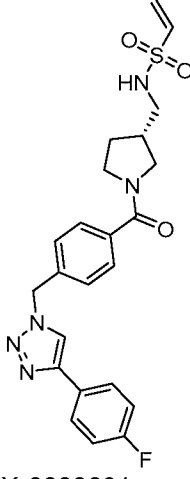
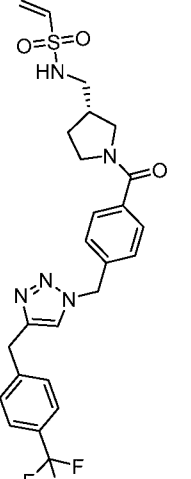
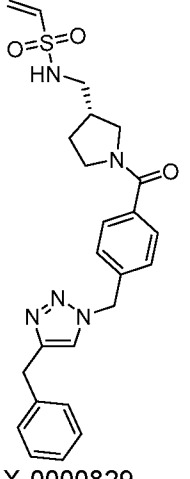
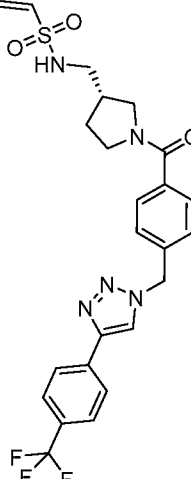
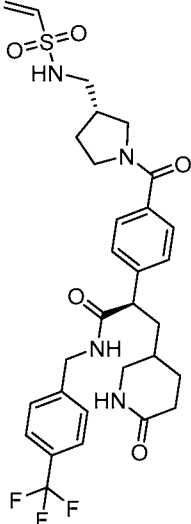
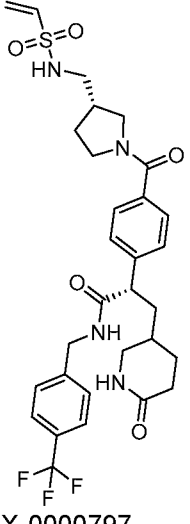
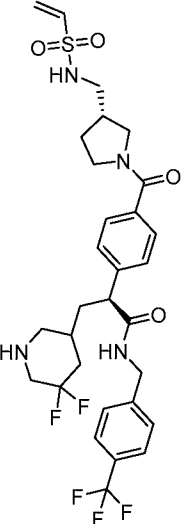
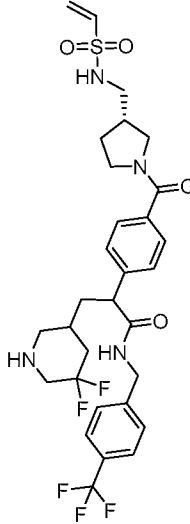
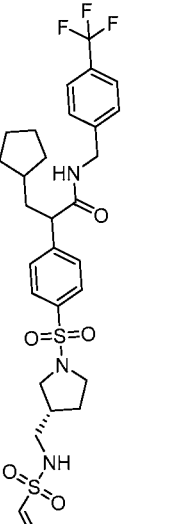
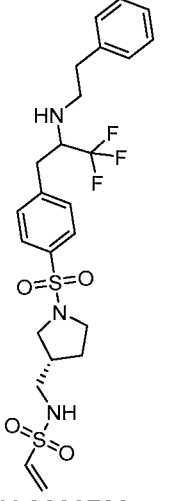
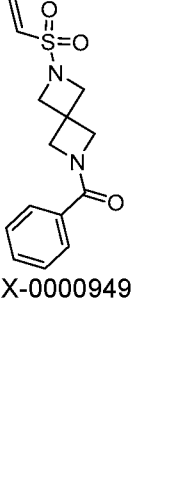
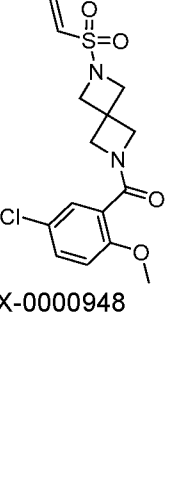
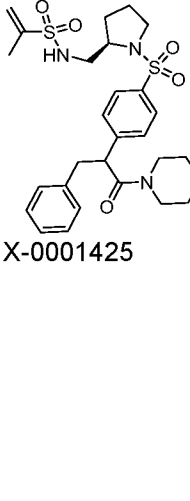
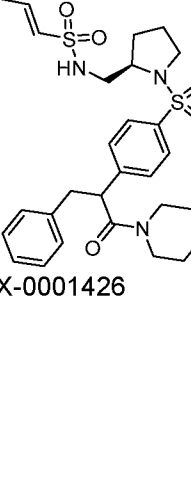
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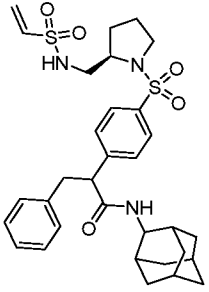
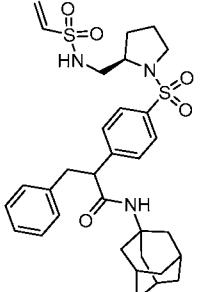
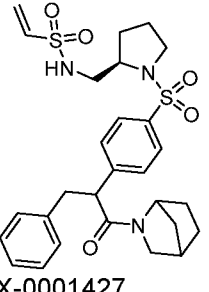
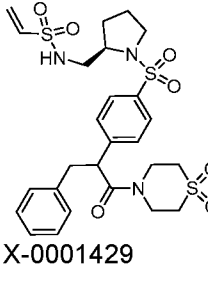
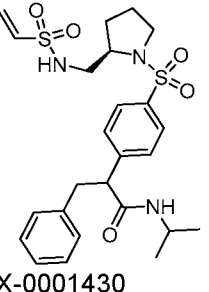
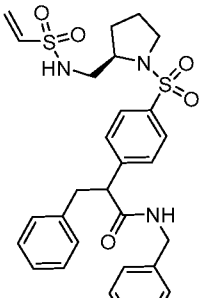
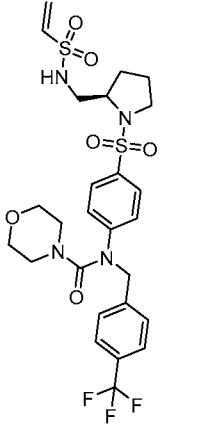
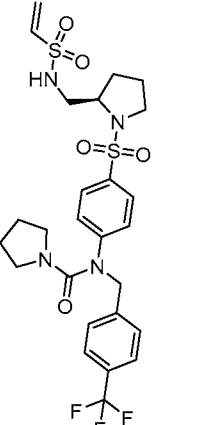
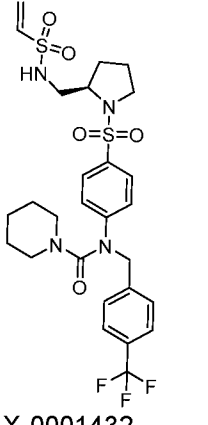
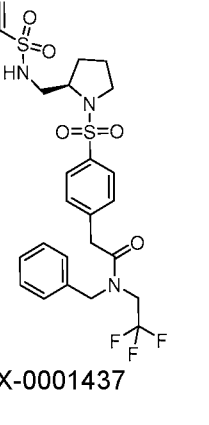
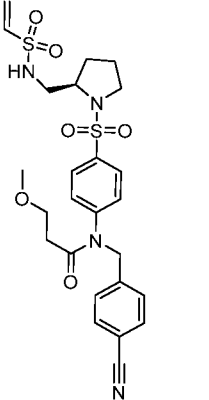
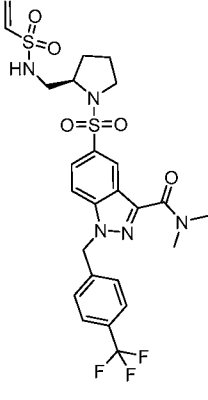
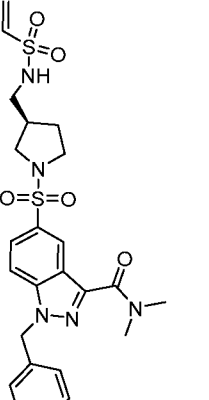
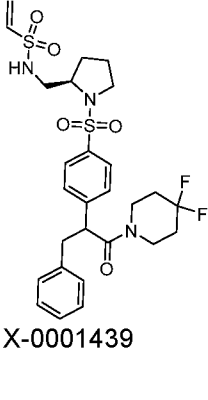
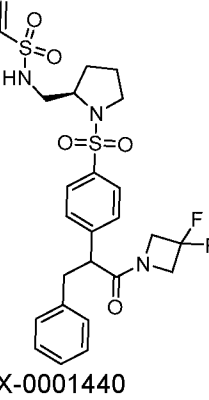
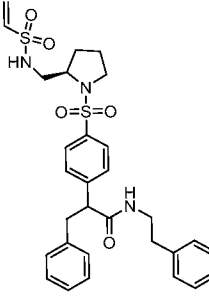
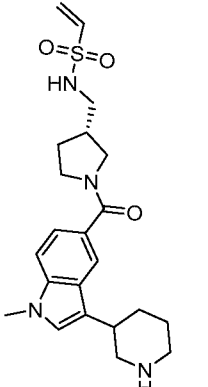
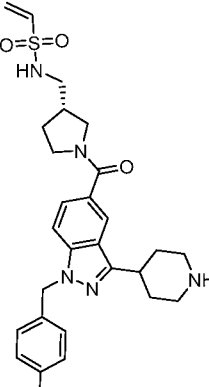
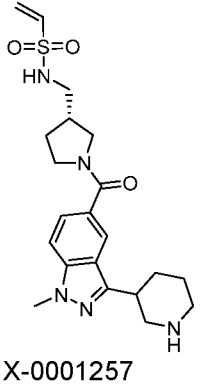
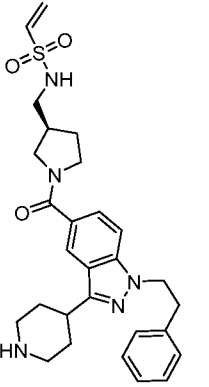
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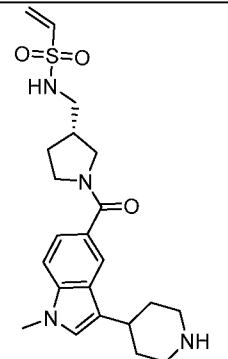
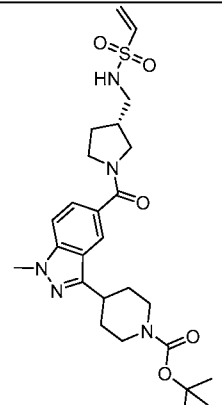
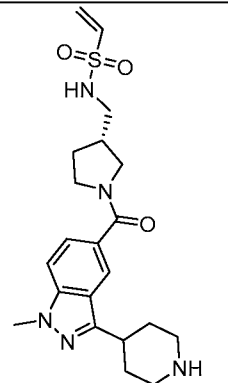
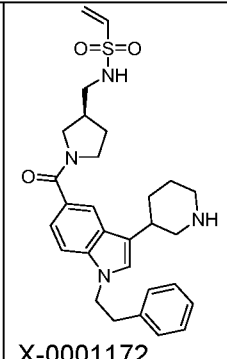
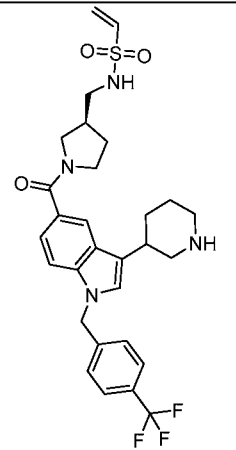
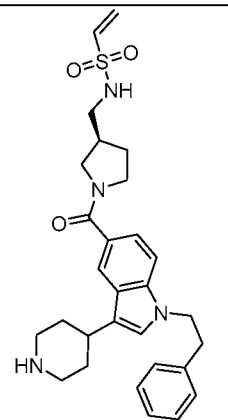
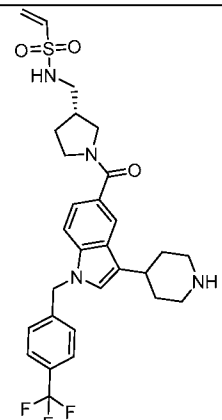
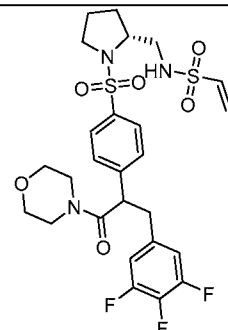
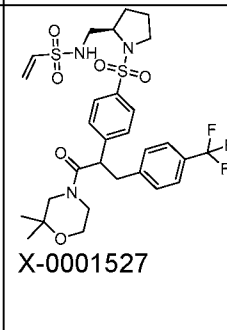
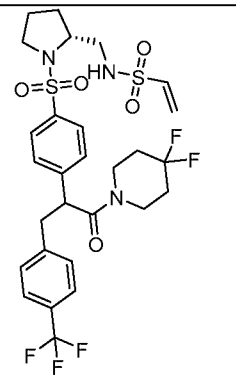
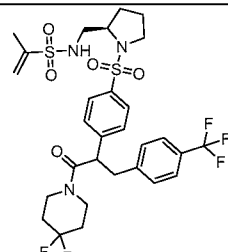
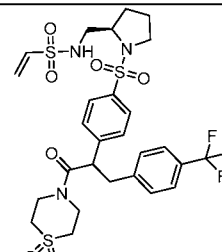
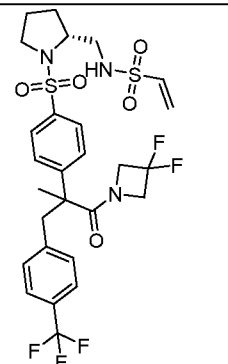
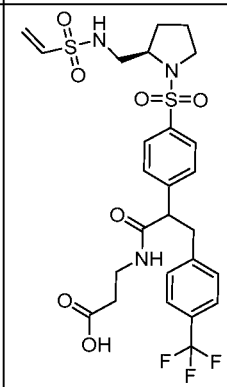
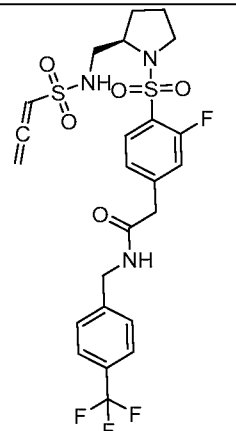
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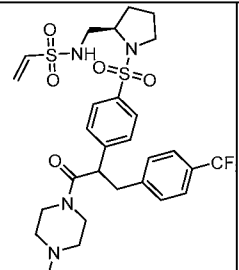
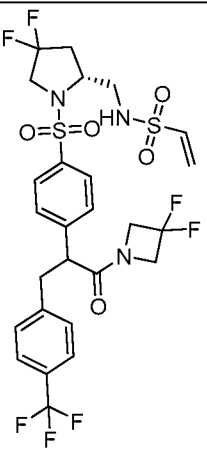
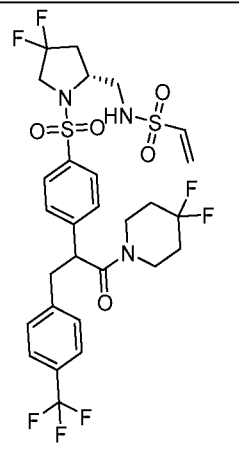
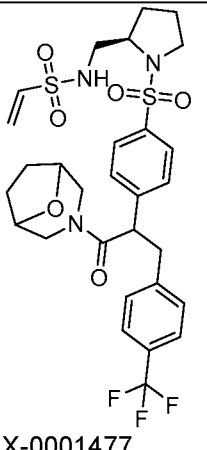
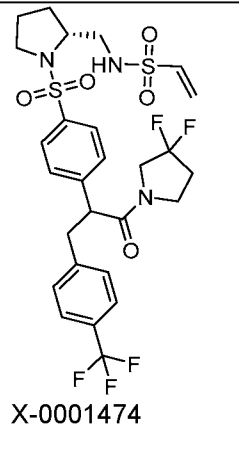
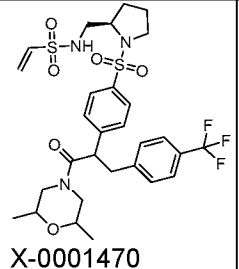
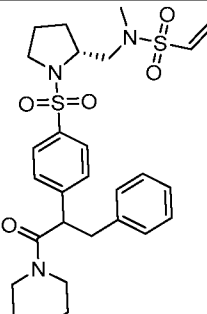
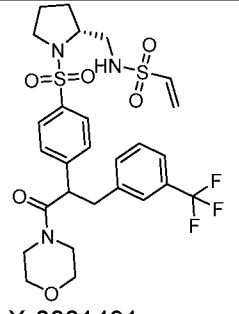
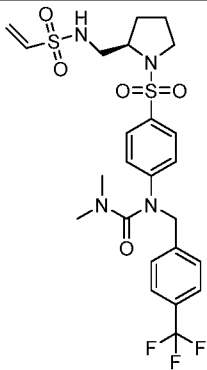
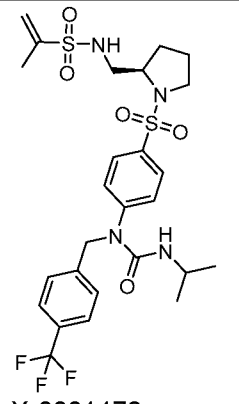
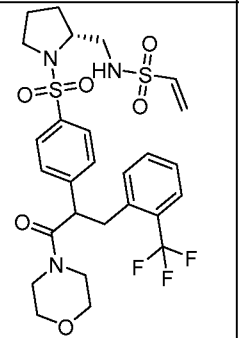
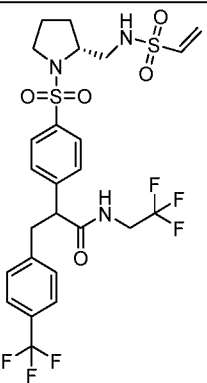
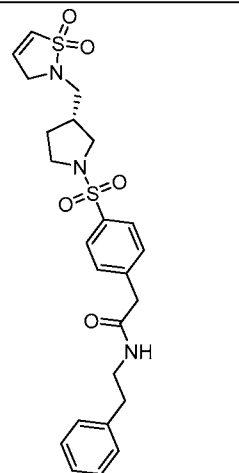
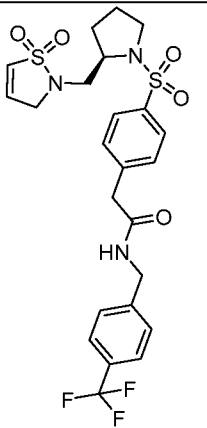
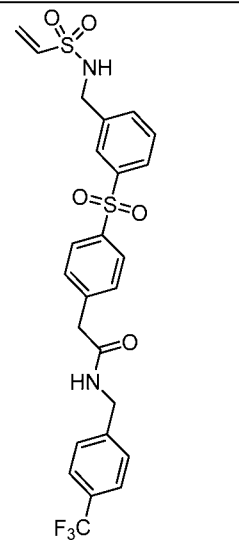
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 X-0001002	 X-0000999	 X-0000978	 X-0000973	 X-0000972
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 X-0001423	 X-0001424	 X-0001427	 X-0001429	 X-0001430
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 X-0001422	 X-0001433	 X-0001434	 X-0001439	 X-0001440
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 X-0001068	 X-0001067	 X-0001529	 X-0001527	 X-0001526
 X-0001521	 X-0001520	 X-0001497	 X-0001496	 X-0001495

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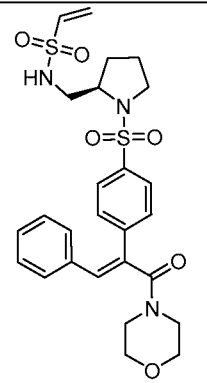
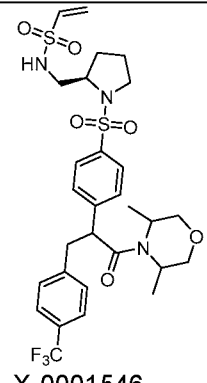
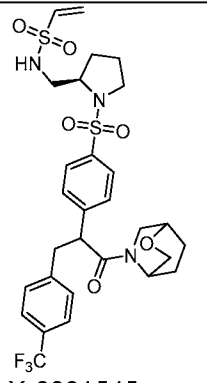
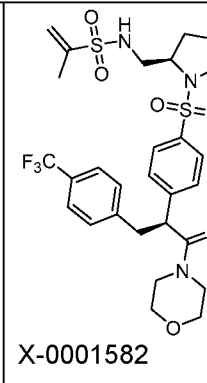
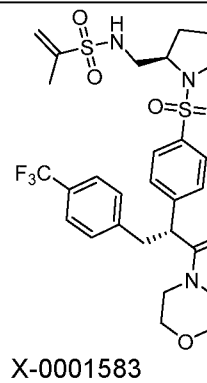
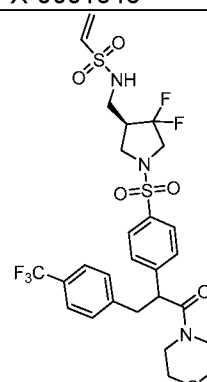
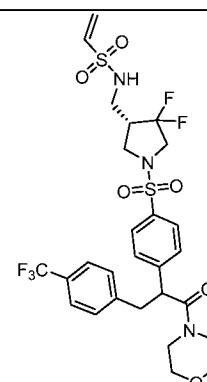
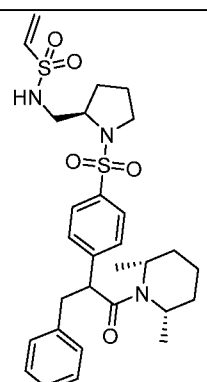
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Table II-2. Characterization of synthesized compounds

I-0250	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.43 (app. q, J = 6.1 Hz, 1H), 7.30 (app. t, J = 7.6 Hz, 2H), 7.26 - 7.10 (m, 3H), 6.72 (ddd, J = 16.5, 9.9, 8.8 Hz, 1H), 6.09 - 5.89 (m, 2H), 3.59 - 3.35 (m, 4H), 3.29 - 3.12 and 3.01 - 2.97 (2 x m, 3H), 2.89 - 2.79 (m, 2H), 2.50 - 2.44 (m, 1H), 2.39 - 2.31 and 2.29 - 2.13 (2 x m, 3H), 2.07 - 1.78 (m, 1H), 1.69 - 1.51 (m, 1H).; m/z = 349.4 [M+H] ⁺
X-0000749	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.76 (t, J = 6.0 Hz, 1H), 7.76-7.71 (m, 2H), 7.63-7.49 (m, 6H), 7.36 (br m, 1H), 6.64 (dd, J = 16.6, 10.0 Hz, 1H), 5.99-5.90 (m, 2H), 4.37 (d, J = 5.9 Hz, 2H), 3.64 (s, 2H), 3.29-3.24 (m, 1H), 3.23-3.19 (m, 1H), 3.10-3.05 (m, 1H), 2.89 (dd, J = 10.2, 6.9 Hz, 1H), 2.71-2.65 (br m, 2H), 2.17-2.11 (m, 1H), 1.85-1.77 (m, 1H), 1.50-1.42 (m, 1H).; m/z = 546.3 [M+H] ⁺
X-0000750	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.95 (s, 1H), 7.78-7.68 (m, 2H), 7.51-7.42 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.90 (m, 2H), 3.56 (s, 2H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.11-3.06 (m, 1H), 2.88 (dd, J = 10.3, 6.9 Hz, 1H), 2.72-2.61 (m, 2H), 2.18-2.10 (m, 1H), 1.84-1.77 (m, 1H), 1.48-1.41 (m, 1H), 1.28-1.18 (m, 2H), 1.06-0.98 (br m, 2H).; m/z = 496.2 [M+H] ⁺
X-0000751	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.36 (t, J = 5.7 Hz, 1H), 7.76-7.68 (m, 2H), 7.54-7.44 (m, 2H), 7.36 (br m, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.90 (m, 2H), 3.55 (s, 2H), 3.29-3.24 (m, 2H), 3.23-3.18 (m, 1H), 3.10-3.05 (m, 1H), 2.88 (dd, J = 10.2, 6.9 Hz, 1H), 2.70-2.62 (m, 2H), 2.46-2.36 (m, 3H), 2.17-2.11 (m, 1H), 1.84-1.77 (m, 1H), 1.49-1.42 (m, 1H). m/z = 484.2 [M+H] ⁺ ; m/z = 484.2 [M+H] ⁺
X-0000752	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17 (d, J = 7.6 Hz, 1H), 7.76-7.69 (m, 2H), 7.53-7.46 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.90 (m, 2H), 3.79-3.69 (br m, 1H), 3.53 (s, 2H), 3.29-3.24 (m, 1H), 3.23-3.18 (m, 1H), 3.11-3.06 (m, 1H), 2.88 (dd, J = 10.2, 6.9 Hz, 1H), 2.73-2.60 (m, 2H), 2.18-2.10 (m, 1H), 2.06-1.75 (m, 7H), 1.56-1.38 (m, 3H).; m/z = 506.3 [M+H] ⁺

X-0000753	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.59 (t, J = 5.8 Hz, 1H), 7.77-7.70 (m, 2H), 7.55-7.49 (m, 2H), 7.36 (s, 1H), 7.21-7.11 (m, 4H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 5.99-5.90 (m, 2H), 4.23 (d, J = 5.8 Hz, 2H), 3.60 (s, 2H), 3.29-3.25 (m, 1H), 3.24-3.19 (m, 1H), 3.11-3.06 (m, 1H), 2.93-2.81 (m, 2H), 2.72-2.62 (m, 2H), 2.17-2.12 (m, 1H), 1.86-1.76 (m, 1H), 1.50-1.43 (m, 1H), 1.18 (d, J = 6.9 Hz, 6H).; m/z = 520.4 [M+H] ⁺
X-0000754	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.72 (t, J = 5.8 Hz, 1H), 7.79-7.68 (m, 3H), 7.63 (t, J = 7.7 Hz, 1H), 7.59-7.51 (m, 2H), 7.49-7.46 (br m, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.89 (m, 2H), 4.46 (d, J = 5.7 Hz, 2H), 3.68 (s, 2H), 3.29-3.25 (m, 1H), 3.24-3.19 (m, 1H), 3.11-3.06 (m, 1H), 2.89 (dd, J = 10.2, 6.9 Hz, 1H), 2.74-2.61 (m, 2H), 2.19-2.10 (m, 1H), 1.84-1.78 (m, 1H), 1.50-1.42 (m, 1H).; m/z = 546.3 [M+H] ⁺
X-0000755	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.65 (s, 1H), 7.81-7.66 (m, 2H), 7.57-7.43 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.6, 10.0 Hz, 1H), 6.01-5.90 (m, 2H), 4.56 (d, J = 6.1 Hz, 2H), 4.29 (d, J = 6.3 Hz, 2H), 3.55 (s, 2H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.11-3.06 (m, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.71-2.63 (m, 2H), 2.19-2.10 (m, 1H), 1.84-1.78 (m, 1H), 1.49 (s, 3H), 1.48-1.38 (m, 1H).; m/z = 458.3 [M+H] ⁺
X-0000758	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.76 (t, J = 6.0 Hz, 1H), 7.79 - 7.72 (m, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.62 - 7.56 (m, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.02 - 5.86 (m, 2H), 4.38 (d, J = 5.6 Hz, 2H), 3.71 (t, J = 8.5 Hz, 2H), 3.67 (s, 2H), 3.42 (dd, J = 8.5, 5.6 Hz, 2H), 2.76 (d, J = 7.2 Hz, 2H), 2.48 - 2.40 (m, 1H).; m/z = 531.6 [M+H] ⁺
X-0000763	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.76-7.70 (m, 2H), 7.50-7.44 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.06-5.85 (m, 2H), 3.84 (s, 2H), 3.49-3.45 (m, 4H), 3.30-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.88 (dd, J = 10.3, 6.9 Hz, 1H), 2.70-2.62 (m, 2H), 2.22 (dt, J = 12.8, 5.0 Hz, 4H), 2.16-2.09 (m, 4H), 1.83-1.77 (m, 1H), 1.48-1.41 (m, 1H).; m/z = 471.4 [M+H] ⁺
X-0000774	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.08 (t, J = 5.4 Hz, 1H), 7.76-7.69 (m, 2H), 7.53-7.48 (m, 2H), 7.36 (br s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.02-5.87 (m, 2H), 3.54 (s, 2H), 3.28-3.24 (m, 1H), 3.23-3.18 (m, 1H), 3.16-3.13 (m, 2H), 3.10-3.05 (m, 1H), 2.88 (dd, J = 10.2, 6.9 Hz, 1H), 2.72-2.62 (br m, 2H), 2.27 (t, J = 6.6 Hz, 2H), 2.18-2.11 (m, 7H), 1.86-1.76 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 459.4 [M+H] ⁺
X-0000775	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.10 (br s, 1H), 7.77-7.68 (m, 2H), 7.53-7.46 (m, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.89 (m, 2H), 3.52 (br m, 3H), 3.29-3.24 (m, 1H), 3.23-3.18 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.97-2.56 (br m, 6H), 2.30-1.92 (br m, 3H), 1.86-1.67 (br m, 3H), 1.51-1.27 (br m, 3H), 1.08-0.84 (br m, 6H).; m/z = 513.4 [M+H] ⁺
X-0000776	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.75-7.70 (m, 2H), 7.49-7.44 (m, 2H), 7.36 (t, J = 6.1 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.91 (m, 2H), 3.84 (s, 2H), 3.49-3.43 (br m, 4H), 3.29-3.25 (m, 1H), 3.24-3.18 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.70-2.61 (m, 3H), 2.40-2.31 (m, 4H), 2.17-2.11 (m, 1H), 1.83-1.77 (m, 1H), 1.48-1.41 (m, 1H), 0.94 (d, J = 6.5 Hz, 6H).; m/z = 499.4 [M+H] ⁺
X-0000777	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.60-8.47 (m, 1H), 7.82-7.67 (m, 3H), 7.57-7.50 (m, 1H), 7.47-7.40 (m, 1H), 7.39-7.29 (m, 2H), 7.29-7.18 (m, 1H), 6.67-6.61 (m, 1H), 6.01-5.89 (m, 2H), 4.66 (d, J = 68.0 Hz, 2H), 3.92 (d, J = 35.9 Hz, 2H), 3.48 (q, J = 7.1 Hz, 1H), 3.36-3.33 (m, 1H), 3.31-3.17 (m, 2H), 3.13-3.04 (m, 1H), 2.89 (dd, J = 10.4, 6.9 Hz, 1H), 2.69-2.64 (br m, 2H), 2.20-2.09 (br m, 1H), 1.84-1.77 (m, 1H), 1.51-1.40 (m, 1H), 1.03 (dt, J = 42.6, 7.1 Hz, 3H).; m/z = 507.4 [M+H] ⁺

X-0000778	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.48 (t, J = 5.7 Hz, 1H), 7.77-7.68 (m, 2H), 7.54-7.48 (m, 2H), 7.36 (t, J = 6.0 Hz, 1H), 7.10-7.02 (m, 2H), 6.70-6.60 (m, 3H), 6.00-5.89 (m, 2H), 4.15 (d, J = 5.7 Hz, 2H), 3.57 (s, 2H), 3.29-3.24 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.85 (s, 6H), 2.72-2.62 (m, 2H), 2.17-2.12 (m, 1H), 1.84-1.78 (m, 1H), 1.50-1.42 (dq, J = 12.7, 7.8 Hz, 1H).; m/z = 521.3 [M+H] ⁺
X-0000801	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.51-8.40 (m, 2H), 7.75-7.69 (m, 2H), 7.65-7.61 (br m, 1H), 7.49 (dd, J = 31.9, 8.0 Hz, 2H), 7.41-7.31 (m, 2H), 6.67-6.62 (m, 1H), 6.00-5.90 (m, 2H), 4.62 (d, J = 79.0 Hz, 2H), 3.91 (d, J = 32.5 Hz, 2H), 3.43-3.39 (m, 1.5H), 3.31-3.17 (m, 2.5H), 3.11-3.05 (m, 1H), 2.74-2.62 (br m, 1H), 2.74-2.62 (m, 2H), 2.18-2.11 (m, 1H), 1.84-1.77 (m, 1H), 1.48-1.42 (m, 1H), 1.09-0.98 (m, 3H).; m/z = 507.4 [M+H] ⁺
X-0000802	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.03 (d, J = 7.8 Hz, 1H), 7.76-7.67 (m, 2H), 7.50-7.48 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.89 (m, 2H), 3.55-3.45 (m, 3H), 3.29-3.25 (m, 1H), 3.23-3.18 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.88 (dd, J = 10.2, 6.9 Hz, 1H), 2.72-2.61 (m, 2H), 2.18-2.09 (m, 1H), 1.84-1.77 (m, 1H), 1.76-1.62 (m, 4H), 1.58-1.50 (m, 1H), 1.49-1.42 (m, 1H), 1.29-1.20 (m, 2H), 1.20-1.08 (m, 3H).; m/z = 470.4 [M+H] ⁺
X-0000803	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.69 (t, J = 6.0 Hz, 1H), 7.75-7.73 (m, 2H), 7.53-7.52 (m, 2H), 7.40-7.34 (m, 2H), 7.28-7.23 (m, 1H), 7.12-7.06 (br m, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.89 (m, 2H), 4.26 (d, J = 5.8 Hz, 2H), 3.63 (s, 2H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.2, 6.9 Hz, 1H), 2.72-2.62 (m, 2H), 2.19-2.11 (m, 1H), 1.84-1.78 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 514.3 [M+H] ⁺
X-0000804	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.60 (s, 1H), 8.11-8.10 (m, 1H), 7.81-7.72 (m, 3H), 7.60-7.54 (m, 3H), 7.41 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 5.7 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.88 (m, 2H), 3.83 (s, 2H), 3.29-3.25 (m, 1H), 3.24-3.19 (m, 1H), 3.09 (dt, J = 9.8, 7.6 Hz, 1H), 2.90 (dd, J = 10.2, 6.9 Hz, 1H), 2.72-2.63 (m, 2H), 2.18-2.12 (m, 1H), 1.85-1.78 (m, 1H), 1.50-1.43 (m, 1H).; m/z = 532.3 [M+H] ⁺
X-0000805	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.62 (s, 1H), 7.84-7.74 (m, 4H), 7.69-7.67 (m, 2H), 7.62-7.55 (m, 2H), 7.36 (t, J = 5.9 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.89 (m, 2H), 3.84 (s, 2H), 3.30-3.26 (m, 1H), 3.24-3.19 (m, 1H), 3.09 (dt, J = 9.8, 7.6 Hz, 1H), 2.90 (dd, J = 10.2, 6.9 Hz, 1H), 2.72-2.63 (m, 2H), 2.17-2.12 (m, 1H), 1.85-1.78 (m, 1H), 1.50-1.43 (m, 1H).; m/z = 532.3 [M+H] ⁺
X-0000806	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.72 - 7.62 (m, 2H), 7.56 - 7.45 (m, 2H), 7.35 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00 - 5.89 (m, 2H), 4.80 (t, J = 5.6 Hz, 1H), 3.59 (d, J = 5.4 Hz, 2H), 3.31 - 3.14 (m, 2H), 3.09 - 3.04 (m, 1H), 2.88 (dd, J = 10.2, 6.8 Hz, 1H), 2.73 - 2.59 (m, 2H), 2.14 (app. hept, J = 7.2 Hz, 1H), 1.84 - 1.78 (m, 1H), 1.49 - 1.42 (m, 1H), 0.96 - 0.90 (m, 2H), 0.89 - 0.80 (m, 2H).; m/z = 401.3 [M+H] ⁺
X-0000807	¹ H NMR in DMSO-d ₆ 2102-42-A1 was consistent with product structure at >95% purity. ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.57 - 7.53 (m, 2H), 7.49 (s, 1H), 6.98 - 6.91 (m, 2H), 6.73 (dd, J = 16.5, 10.0 Hz, 1H), 6.10 - 5.94 (m, 2H), 4.68 (app. hept, J = 6.0 Hz, 1H), 4.34 (br. s, 1H), 4.10 - 3.94 (m, 2H), 3.73 (d, J = 8.3 Hz, 1H), 3.05 (d, J = 7.0 Hz, 2H), 2.74 (p, J = 6.6 Hz, 1H), 1.27 (d, J = 6.0 Hz, 6H).; m/z = 339.3 [M+H] ⁺
X-0000808	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.54 (d, J = 8.0 Hz, 2H), 7.52 - 7.46 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.73 (dd, J = 16.5, 10.0 Hz, 1H), 6.07 - 5.92 (m, 2H), 4.33 (app. t, J = 8.5 Hz, 1H), 4.13 - 3.87 (m, 2H), 3.74 (dd, J = 10.2, 5.6 Hz, 1H), 3.12 - 2.99 (m, 2H), 2.93 (p, J = 6.9 Hz, 1H), 2.78 - 2.70 (m, 1H), 1.21 (d, J = 6.9 Hz, 6H).; m/z = 323.3 [M+H] ⁺

X-0000809	1H NMR (500 MHz, DMSO-d6) δ 7.50 (t, J = 6.0 Hz, 1H), 7.27 - 7.08 (m, 2H), 6.99 (d, J = 8.1 Hz, 1H), 6.73 (dd, J = 16.5, 10.0 Hz, 1H), 6.13 - 5.85 (m, 2H), 4.35 (app. t, J = 8.5 Hz, 1H), 4.05 - 3.99 (m, 2H), 3.79 (d, J = 9.7 Hz, 6H), 3.77 - 3.69 (m, 1H), 3.06 (app. t, J = 6.5 Hz, 2H), 2.80 - 2.69 (m, 1H).; m/z = 341.3 [M+H] ⁺
X-0000810	1H NMR in DMSO-d6 2102-42-A5 was consistent with product structure at >95% purity (2 weight% EtOAc). 1H NMR (500 MHz, DMSO-d6) δ 7.48 (t, J = 6.1 Hz, 1H), 7.13 (dd, J = 7.6, 1.2 Hz, 1H), 6.89 (s, 1H), 6.81 - 6.76 (m, 1H), 6.72 (ddd, J = 16.5, 10.0, 1.2 Hz, 1H), 6.05 - 5.91 (m, 2H), 3.97 (app. t, J = 9.2 Hz, 1H), 3.86 (app. t, J = 8.6 Hz, 1H), 3.79 (d, J = 1.2 Hz, 3H), 3.66 (dd, J = 10.1, 5.3 Hz, 1H), 3.56 (dd, J = 9.0, 5.2 Hz, 1H), 3.02 (app. t, J = 6.5 Hz, 2H), 2.71 - 2.63 (m, 1H), 2.32 (s, 3H).; m/z = 325.3 [M+H] ⁺
X-0000811	1H NMR in DMSO-d6 2102- was consistent with product structure at >95% purity. 1H NMR (500 MHz, DMSO-d6) δ 7.49 (br. s, 1H), 7.37 - 7.25 (m, 2H), 7.25 - 7.13 (m, 3H), 6.73 (ddd, J = 16.4, 10.0, 1.4 Hz, 1H), 6.14 - 5.89 (m, 2H), 4.11 (app. t, J = 8.4 Hz, 1H), 3.84 (app. t, J = 9.0 Hz, 1H), 3.77 (dd, J = 8.5, 5.3 Hz, 1H), 3.54 (dd, J = 9.8, 5.3 Hz, 1H), 3.40 (p, J = 9.2 Hz, 1H), 3.03 - 3.00 (m, 3H), 2.73 - 2.65 (m, 1H), 2.47 - 2.33 (m, 2H), 2.23 - 2.07 (m, 2H).; m/z = 335.3 [M+H] ⁺
X-0000813	1H NMR in DMSO-d6 2102-42-A10 was consistent with product structure at >95% purity. 1H NMR (500 MHz, DMSO-d6) δ 7.73 - 7.61 (m, 2H), 7.36 (t, J = 5.9 Hz, 1H), 7.20 - 7.10 (m, 2H), 6.62 (ddd, J = 17.0, 10.7, 1.8 Hz, 1H), 5.99 - 5.89 (m, 2H), 4.77 (p, J = 6.0 Hz, 1H), 3.69 (app. t, J = 8.4 Hz, 2H), 3.37 (dd, J = 8.4, 5.6 Hz, 2H), 2.73 (app. t, J = 6.6 Hz, 2H), 2.47 - 2.38 (m, 1H), 1.36 - 1.21 (m, 6H).; m/z = 375.3 [M+H] ⁺
X-0000814	1H NMR in DMSO-d6 2102-42-A11 was consistent with product structure at >95% purity. 1H NMR (500 MHz, DMSO-d6) δ 7.77 - 7.67 (m, 2H), 7.62 - 7.47 (m, 2H), 7.35 (br. s, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 5.97 - 5.92 (m, 2H), 3.71 (t, J = 8.4 Hz, 2H), 3.40 (dd, J = 8.5, 5.6 Hz, 2H), 3.03 (p, J = 6.9 Hz, 1H), 2.72 (d, J = 7.2 Hz, 2H), 2.49 - 2.40 (m, 1H), 1.25 (d, J = 6.9 Hz, 6H).; m/z = 359.3 [M+H] ⁺
X-0000815	1H NMR in DMSO-d6 2102-42-A6 was consistent with product structure at >95% purity. 1H NMR (400 MHz, DMSO-d6) δ 7.49 (t, J = 5.8 Hz, 1H), 7.42 (td, J = 9.3, 2.4 Hz, 1H), 7.34 - 7.21 (m, 2H), 6.73 (ddd, J = 16.5, 10.0, 1.1 Hz, 1H), 6.13 - 5.93 (m, 2H), 4.35 (app. t, J = 8.6 Hz, 1H), 4.06 (app. t, J = 9.3 Hz, 1H), 3.99 (dd, J = 8.9, 5.4 Hz, 1H), 3.76 (dd, J = 10.3, 5.4 Hz, 1H), 3.07 (app. t, J = 6.3 Hz, 2H), 2.82 - 2.63 (m, 1H).; m/z = 317.3 [M+H] ⁺
X-0000816	1H NMR (500 MHz, DMSO-d6) δ 8.84 (t, J = 6.3 Hz, 1H), 7.77-7.71 (m, 2H), 7.54-7.47 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.90 (m, 2H), 3.97-3.89 (m, 2H), 3.66 (s, 2H), 3.29-3.26 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.72-2.62 (m, 2H), 2.18-2.10 (m, 1H), 1.84-1.77 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 470.3 [M+H] ⁺
X-0000817	1H NMR (500 MHz, DMSO-d6) δ 8.94 (d, J = 6.6 Hz, 1H), 7.77-7.68 (m, 2H), 7.54-7.46 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.89 (m, 2H), 4.81-4.73 (m, 1H), 4.71 (dd, J = 7.5, 5.9 Hz, 2H), 4.41 (t, J = 6.3 Hz, 2H), 3.57 (s, 2H), 3.29-3.25 (m, 1H), 3.24-3.15 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.88 (dd, J = 10.3, 6.9 Hz, 1H), 2.72-2.62 (m, 2H), 2.17-2.11 (m, 1H), 1.84-1.78 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 444.3 [M+H] ⁺
X-0000818	1H NMR (500 MHz, DMSO-d6) δ : 7.76-7.69 (m, 2H), 7.51-7.45 (m, 2H), 7.36 (s, 1H), 6.67-6.62 (m, 1H), 6.01-5.91 (m, 2H), 4.52-4.46 (m, 0.5H), 4.01-3.80 (m, 4.5H), 3.37-3.17 (m, 4H), 3.13-3.02 (m, 1H), 2.91-2.61 (m, 6H), 2.16-2.09 (m, 1H), 1.85-1.63 (m, 3H), 1.48-1.39 (m, 2H), 1.33-1.31 (br m, 1H).; m/z = 486.4 [M+H] ⁺

X-0000819	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.71 (t, J = 6.0 Hz, 1H), 7.79-7.69 (m, 2H), 7.57 (d, J = 8.2 Hz, 1H), 7.55-7.50 (m, 2H), 7.45 (d, J = 2.0 Hz, 1H), 7.36 (s, 1H), 7.23 (dd, J = 8.3, 2.1 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.89 (m, 2H), 4.28 (d, J = 5.9 Hz, 2H), 3.63 (s, 2H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.71-2.63 (m, 2H), 2.19-2.10 (m, 1H), 1.84-1.78 (m, 1H), 1.50-1.42 (m, 1H).; m/z = 546.2 [M+H] ⁺
X-0000820	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.75-7.69 (m, 2H), 7.47-7.44 (m, 2H), 7.36 (t, J = 5.7 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.02-5.90 (m, 2H), 3.84 (d, J = 5.6 Hz, 2H), 3.55 (t, J = 5.3 Hz, 1H), 3.47-3.45 (m, 2H), 3.44-3.40 (m, 1H), 3.29-3.19 (m, 5H), 3.11-3.06 (m, 1H), 3.04 (s, 2H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.85 (s, 1H), 2.72-2.61 (m, 2H), 2.19-2.10 (m, 1H), 1.84-1.78 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 460.3 [M+H] ⁺
X-0000821	¹ H NMR (500 MHz, DMSO-d ₆) δ 12.67 (br s, 1H), 8.43-8.36 (br m, 1H), 7.76-7.70 (m, 2H), 7.56-7.49 (m, 2H), 7.39 (t, J = 6.0 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.90 (m, 2H), 3.74 (d, J = 5.7 Hz, 2H), 3.62 (s, 2H), 3.29-3.26 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.88 (dd, J = 10.3, 6.9 Hz, 1H), 2.72-2.61 (m, 2H), 2.18-2.09 (m, 1H), 1.86-1.76 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 446.3 [M+H] ⁺
X-0000822	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.21 (t, J = 5.7 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.38 (t, J = 5.8 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.23 - 7.14 (m, 3H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 5.99 - 5.91 (m, 2H), 3.71 (t, J = 8.4 Hz, 2H), 3.54 (s, 2H), 3.42 (dd, J = 8.5, 5.5 Hz, 2H), 3.33 - 3.26 (m, 2H), 2.76 (t, J = 6.5 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.47 - 2.39 (m, 1H).; m/z = 478.3 [M+H] ⁺
X-0000823	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.71 (t, J = 6.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.62 - 7.54 (m, 2H), 7.51 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.40 - 7.31 (m, 2H), 6.73 (dd, J = 16.5, 10.0 Hz, 1H), 6.12 - 5.94 (m, 2H), 4.40 - 4.28 (m, 3H), 4.05 (t, J = 9.2 Hz, 1H), 3.98 (dd, J = 8.9, 5.4 Hz, 1H), 3.76 (dd, J = 10.1, 5.4 Hz, 1H), 3.56 (s, 2H), 3.07 (dd, J = 6.9, 1.4 Hz, 2H), 2.81 - 2.70 (m, 1H).; m/z = 496.4 [M+H] ⁺
X-0000824	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.76 - 7.71 (m, 2H), 7.57 (dd, J = 6.7, 4.8 Hz, 3H), 7.38 (s, 1H), 7.01 (s, 1H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 5.99 - 5.92 (m, 2H), 3.71 (t, J = 8.4 Hz, 2H), 3.54 (s, 2H), 3.42 (dd, J = 8.5, 5.5 Hz, 2H), 2.75 (d, J = 7.3 Hz, 2H), 2.48 - 2.38 (m, 1H).; m/z = 374.3 [M+H] ⁺
X-0000948	¹ H NMR (400 MHz, DMSO d ₆) δ 7.43 (d, J = 9.2 Hz, 1H), 7.27 (s, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.97 - 6.90 (m, 1H), 6.26 (d, J = 9.6 Hz, 1H), 6.15 (d, J = 16.4 Hz, 1H), 4.10 (s, 2H), 3.99 - 3.78 (m, 6H), 3.78 (s, 3H); m/z = 357.0 [M + H] ⁺
X-0000949	¹ H NMR (400 MHz, DMSO d ₆) δ 7.57 (d, J = 7.2 Hz, 2H), 7.48 - 7.40 (m, 3H), 6.98 - 6.89 (m, 1H), 6.27 (d, J = 10 Hz, 1H), 6.13 (d, J = 16.8 Hz, 1H), 4.40 (s, 2H), 4.16 (d, J = 18.8 Hz, 2H), 3.97-3.81 (m, 4H); m/z = 293.1 [M + H] ⁺
X-0000951	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.95 (s, 1H), 7.79-7.71 (m, 2H), 7.60-7.54 (m, 2H), 7.41-7.38 (m, 2H), 7.36 (s, 1H), 6.71-6.59 (m, 3H), 6.00-5.89 (m, 2H), 3.71 (s, 2H), 3.29-3.24 (m, 1H), 3.23-3.19 (m, 1H), 3.11-3.06 (m, 1H), 2.92-2.87 (m, 1H), 2.83 (s, 6H), 2.72-2.62 (m, 2H), 2.19-2.11 (m, 1H), 1.86-1.77 (m, 1H), 1.50-1.43 (m, 1H).; m/z = 507.4 [M+H] ⁺
X-0000952	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.53 (t, J = 5.8 Hz, 1H), 7.77-7.70 (m, 2H), 7.57-7.51 (m, 2H), 7.36 (s, 1H), 7.22-7.18 (m, 1H), 7.17-7.15 (m, 1H), 7.10-7.09 (m, 1H), 7.00-6.97 (m, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.90 (m, 2H), 4.35 (d, J = 5.7 Hz, 2H), 3.63 (s, 2H), 3.28 (dd, J = 10.2, 7.4 Hz, 1H), 3.24-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.2, 6.9 Hz, 1H), 2.73-2.62 (m, 2H), 2.60 (s, 6H), 2.19-2.10 (m, 1H), 1.84-1.78 (m, 1H), 1.50-1.42 (m, 1H).; m/z = 521.4 [M+H] ⁺

X-0000953	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.59 (t, J = 5.9 Hz, 1H), 7.74-7.72 (m, 2H), 7.55-7.53 (m, 2H), 7.36 (s, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.60-6.58 (m, 1H), 6.56-6.49 (m, 2H), 6.04-5.85 (m, 2H), 4.22 (d, J = 5.7 Hz, 2H), 3.60 (s, 2H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.10-3.05 (m, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.83 (s, 6H), 2.73-2.62 (m, 2H), 2.17-2.12 (m, 1H), 1.84-1.78 (m, 1H), 1.46 (dq, J = 12.5, 7.8 Hz, 1H).; m/z = 521.4 [M+H] ⁺
X-0000954	¹ H NMR (500 MHz, DMSO-d ₆) δ 12.67 (br. s, 1H), 7.79 - 7.64 (m, 2H), 7.59 - 7.53 (m, 2H), 7.38 (t, J = 6.0 Hz, 1H), 7.22 - 7.21 (m, 2H), 7.17 - 7.10 (m, 3H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.04 - 5.86 (m, 2H), 4.01 (t, J = 7.8 Hz, 1H), 3.26 (ddd, J = 10.3, 7.5, 4.0 Hz, 2H), 3.21 - 3.17 (m, 1H), 3.08 - 3.02 (m, 1H), 2.97 (dd, J = 13.7, 7.5 Hz, 1H), 2.89 - 2.84 (m, 1H), 2.71 - 2.66 (m, 2H), 2.13 (p, J = 7.3 Hz, 1H), 1.78 (dt, J = 12.3, 7.2, 4.9 Hz, 1H), 1.41 (dq, J = 12.5, 7.9 Hz, 1H).; m/z = 479.2 [M+H] ⁺
X-0000955	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.64 (app. d, J = 8.3 Hz, 2H), 7.44 - 7.40 (m, 2H), 7.37 (app. d, J = 5.4 Hz, 1H), 7.17 (dd, J = 8.1, 6.8 Hz, 2H), 7.12 - 7.06 (m, 1H), 7.06 - 7.01 (m, 2H), 6.66 (dd, J = 16.5, 10.0 Hz, 1H), 6.04 - 5.90 (m, 2H), 4.76 (app. t, J = 5.1 Hz, 1H), 3.62 (app. t, J = 5.5 Hz, 2H), 3.24 (ddd, J = 10.3, 7.5, 5.9 Hz, 1H), 3.20 - 3.13 (m, 1H), 3.13 - 2.97 (m, 3H), 2.93 - 2.75 (m, 2H), 2.69 - 2.66 (m, 2H), 2.11 (app. h, J = 7.4 Hz, 1H), 1.85 - 1.69 (m, 1H), 1.39 (dq, J = 12.6, 7.9 Hz, 1H).; m/z = 465.3 [M+H] ⁺
X-0000956	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.78 - 7.69 (m, 2H), 7.62 - 7.56 (m, 2H), 7.54 (d, J = 2.5 Hz, 1H), 7.38 (t, J = 6.0 Hz, 1H), 7.28 - 7.19 (m, 2H), 7.19 - 7.13 (m, 3H), 6.92 (d, J = 2.4 Hz, 1H), 6.66 (dd, J = 16.5, 10.0 Hz, 1H), 6.02 - 5.92 (m, 2H), 3.89 (dd, J = 8.9, 6.5 Hz, 1H), 3.32 - 3.24 (m, 2H), 3.23 - 3.13 (m, 1H), 3.09 - 3.04 (m, 1H), 2.94 - 2.82 (m, 2H), 2.71 - 2.68 (m, 2H), 2.14 (p, J = 7.3 Hz, 1H), 1.84 - 1.77 (m, 1H), 1.47-1.40 (m, 1H).; m/z = 478.3 [M+H] ⁺
X-0000957	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.70 (app. d, J = 8.3 Hz, 2H), 7.57 - 7.49 (m, 2H), 7.38 (t, J = 5.6 Hz, 1H), 7.23 - 7.09 (m, 5H), 6.66 (dd, J = 16.5, 9.9 Hz, 1H), 6.08 - 5.88 (m, 2H), 4.41 (t, J = 7.5 Hz, 1H), 3.30 - 3.22 (m, 2H), 3.20 - 3.16 (m, 1H), 3.11 - 3.02 (m, 1H), 2.92 - 2.85 (m, 2H), 2.84 (s, 3H), 2.77 (s, 3H), 2.67 (app. t, J = 6.4 Hz, 2H), 2.12 (h, J = 7.4 Hz, 1H), 1.82 - 1.76 (m, 1H), 1.44 - 1.35 (dq, J = 12.9, 7.9 Hz, 1H).; m/z = 506.3 [M+H] ⁺
X-0000958	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.42 (s, 1H), 7.28 - 7.25 (m, 2H), 7.19 - 7.16 (m, 3H), 6.77 - 6.63 (m, 1H), 6.06 - 5.90 (m, 2H), 3.81 - 3.35 (m, 3H), 3.29 - 3.20 and 3.04 - 3.00 (2 x m, 1H), 2.86 - 2.83 (m, 2H), 2.43 - 2.24 (m, 2H), 2.08 - 1.83 (m, 2H), 1.73 - 1.50 (m, 1H), 1.42 - 1.35 (m, 1H), 1.26 - 1.15 (m, 1H).; m/z = 335.3 [M+H] ⁺
X-0000959	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.48 (s, 1H), 7.31 - 7.21 (m, 2H), 7.21 - 7.13 (m, 3H), 6.72 (ddd, J = 16.4, 13.5, 10.0 Hz, 1H), 6.09 - 5.92 (m, 2H), 4.26 and 4.18 (2 x t, J = 8.4 Hz, 1H), 3.94 - 3.80 (m, 2H), 3.57 (dd, J = 9.7, 5.4 Hz, 1H), 3.05 - 2.99 (m, 2H), 2.76 - 2.69 (m, 1H), 2.27 - 2.18 (m, 1H), 1.81 - 1.76 (m, 1H), 1.35 - 1.30 (m, 1H), 1.23 - 1.18 (m, 1H).; m/z = 321.3 [M+H] ⁺
X-0000960	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.58 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.12 (s, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.67 (dd, J = 16.5, 10.0 Hz, 1H), 6.05 - 5.91 (m, 2H), 3.89 (s, 3H), 3.81 (app. t, J = 8.2 Hz, 2H), 3.53 (dd, J = 8.2, 5.7 Hz, 2H), 2.88 (app. t, J = 5.9 Hz, 2H), 2.59 - 2.50 (m, 1H), 2.39 (s, 3H).; m/z = 361.3 [M+H] ⁺
X-0000961	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.92 - 7.82 (m, 2H), 7.61 - 7.24 (m, 4H), 6.63 (ddd, J = 16.5, 10.0, 1.4 Hz, 1H), 5.99 - 5.89 (m, 2H), 3.73 (t, J = 8.3 Hz, 2H), 3.43 (dd, J = 8.5, 5.6 Hz, 2H), 2.75 (t, J = 6.2 Hz, 2H), 2.48 - 2.44 (m, 1H).; m/z = 383.2 [M+H] ⁺

X-0000962	¹ H NMR (500 MHz, DMSO-d ₆) δ 12.52 (s, 1H), 7.79 - 7.65 (m, 2H), 7.63 - 7.54 (m, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.10 - 5.83 (m, 2H), 3.30 - 3.26 (m, 1H), 3.22 (ddd, J = 9.8, 8.0, 4.7 Hz, 1H), 3.12 - 3.05 (m, 1H), 2.91 (dd, J = 10.2, 6.8 Hz, 1H), 2.76 - 2.62 (m, 2H), 2.16 (p, J = 7.2 Hz, 1H), 1.87 - 1.78 (m, 1H), 1.54 - 1.39 (m, 3H), 1.21 (q, J = 4.0 Hz, 2H).; m/z = 415.3 [M+H] ⁺
X-0000963	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.39 (t, J = 6.0 Hz, 1H), 8.15 - 8.09 (m, 2H), 7.94 - 7.89 (m, 2H), 7.70 (s, 1H), 7.69 - 7.55 (m, 4H), 7.35 (t, J = 6.0 Hz, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 5.98 - 5.87 (m, 2H), 4.60 (d, J = 5.9 Hz, 2H), 3.32 (dd, J = 10.3, 7.4 Hz, 1H), 3.24 (ddd, J = 9.9, 8.0, 4.9 Hz, 1H), 3.14 (dt, J = 9.9, 7.5 Hz, 1H), 2.93 (dd, J = 10.3, 6.9 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.21 - 2.08 (m, 1H), 1.87 - 1.77 (m, 1H), 1.53 - 1.42 (m, 1H). ; m/z = 532.1 [M+H] ⁺
X-0000964	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.94 (t, J = 5.6 Hz, 1H), 8.07 - 8.01 (m, 2H), 7.93 - 7.87 (m, 2H), 7.35 (t, J = 6.0 Hz, 1H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 5.98 - 5.89 (m, 2H), 3.52 (td, J = 6.9, 5.5 Hz, 2H), 3.31 (dd, J = 10.3, 7.4 Hz, 1H), 3.23 (ddd, J = 9.9, 8.0, 4.8 Hz, 1H), 3.13 (dt, J = 9.9, 7.5 Hz, 1H), 2.95 - 2.87 (m, 1H), 2.71 - 2.53 (m, 4H), 2.20 - 2.07 (m, 1H), 1.86 - 1.76 (m, 1H), 1.51 - 1.40 (m, 1H).; m/z = 470.2 [M+H] ⁺
X-0000965	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.57 (d, J = 7.7 Hz, 1H), 8.10 - 8.04 (m, 2H), 7.91 - 7.85 (m, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 5.99 - 5.90 (m, 2H), 4.08 - 3.96 (m, 1H), 3.30 (dd, J = 6.6, 3.6 Hz, 1H), 3.24 (ddd, J = 9.9, 8.0, 4.8 Hz, 1H), 3.13 (dt, J = 9.9, 7.5 Hz, 1H), 2.91 (dd, J = 10.3, 6.9 Hz, 1H), 2.72 - 2.58 (m, 2H), 2.19 - 1.86 (m, 7H), 1.86 - 1.76 (m, 1H), 1.65 (dq, J = 16.3, 6.9, 4.4 Hz, 2H), 1.46 (dq, J = 12.6, 7.8 Hz, 1H).; m/z = 492.4 [M+H] ⁺
X-0000966	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.40 (t, J = 6.0 Hz, 1H), 8.15 - 8.09 (m, 2H), 7.94 - 7.88 (m, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 6.0 Hz, 1H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 5.98 - 5.87 (m, 2H), 4.58 (d, J = 5.9 Hz, 2H), 3.34 - 3.28 (m, 1H), 3.24 (ddd, J = 10.0, 8.0, 4.8 Hz, 1H), 3.13 (dt, J = 10.0, 7.6 Hz, 1H), 2.92 (dd, J = 10.4, 6.9 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.20 - 2.08 (m, 1H), 1.86 - 1.76 (m, 1H), 1.46 (dq, J = 12.6, 7.8 Hz, 1H).; m/z = 532.3 [M+H] ⁺
X-0000979	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.79 - 7.67 (m, 4H), 7.47 - 7.43 (m, 4H), 7.36 (br s, 1H), 6.65 (ddd, J = 16.5, 10.0, 1.4 Hz, 1H), 6.00 - 5.91 (m, 2H), 4.69 (s, 2H), 4.60 (d, J = 5.5 Hz, 2H), 3.29 - 3.25 (m, 1H), 3.23 - 3.18 (m, 1H), 3.08 (dq, J = 9.8, 7.4 Hz, 1H), 2.92 - 2.88 (m, 1H), 2.71 - 2.61 (br m, 2H), 2.19 - 2.08 (m, 4H), 1.85 - 1.76 (m, 1H), 1.51 - 1.41 (m, 1H).; m/z = 560.3 [M+H] ⁺
X-0000980	¹ H NMR in DMSO-d ₆ 2102-83-A1 was consistent with product structure at <95% purity. ¹ H NMR (500 MHz, DMSO-d ₆) δ 9.43 (s, 1H), 8.14 - 8.02 (m, 2H), 7.92 - 7.86 (m, 2H), 7.35 (t, J = 6.0 Hz, 1H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 6.02 - 5.83 (m, 2H), 3.31 - 3.27 (m, 1H), 3.23 (ddd, J = 10.0, 8.0, 4.8 Hz, 1H), 3.12 (app. dt, J = 10.0, 7.5 Hz, 1H), 2.90 (dd, J = 10.3, 6.9 Hz, 1H), 2.69 - 2.58 (m, 2H), 2.13 (h, J = 7.2 Hz, 1H), 1.80 (app. dtd, J = 12.2, 7.3, 4.8 Hz, 1H), 1.49 - 1.42 (m, 1H), 1.37 - 1.31 (m, 2H), 1.17 (d, J = 6.7 Hz, 2H); m/z = 482.2 [M+H] ⁺
X-0000981	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.25 (t, J = 5.9 Hz, 1H), 8.15 - 8.05 (m, 2H), 7.94 - 7.85 (m, 2H), 7.34 (s, 1H), 7.27 - 7.23 (m, 2H), 7.21 - 7.17 (m, 2H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.09 - 5.84 (m, 2H), 4.45 (d, J = 5.9 Hz, 2H), 3.31 - 3.28 (m, 1H), 3.23 (ddd, J = 10.1, 8.0, 4.9 Hz, 1H), 3.12 (app. dt, J = 10.1, 7.5 Hz, 1H), 2.96 - 2.81 (m, 2H), 2.70 - 2.57 (m, 2H), 2.13 (hept, J = 7.2 Hz, 1H), 1.81 (app. dtd, J = 12.4, 7.3, 4.9 Hz, 1H), 1.52 - 1.37 (m, 1H), 1.18 (d, J = 6.9 Hz, 6H); m/z = 506.5 [M+H] ⁺

X-0000982	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.77-7.70 (m, 2H), 7.50-7.48 (m, 2H), 7.36 (s, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.01-5.91 (m, 2H), 4.28 (dd, J = 26.0, 6.6 Hz, 2H), 3.98-3.83 (m, 2H), 3.79-3.55 (m, 2H), 3.29-3.15 (m, 3H), 3.12-3.05 (m, 1H), 2.90-2.86 (m, 1H), 2.80-2.77 (br m, 1H), 2.69-2.65 (br m, 2H), 2.16-2.11 (m, 1H), 1.87-1.63 (m, 3H), 1.53-1.35 (m, 3H).; m/z = 484.3 [M+H] ⁺
X-0000983	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.76-7.68 (m, 4H), 7.45-7.34 (m, 5H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.38 (d, J = 7.7 Hz, 1H), 6.01-5.91 (m, 2H), 4.53 (s, 4H), 3.89-3.82 (m, 1H), 3.29-3.25 (m, 1H), 3.22-3.18 (m, 1H), 3.07 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.72-2.63 (m, 2H), 2.19-2.10 (m, 1H), 1.84-1.76 (m, 1H), 1.49-1.41 (m, 1H), 1.05 (d, J = 6.6 Hz, 6H).; m/z = 603.4 [M+H] ⁺
X-0000984	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.78 - 7.68 (m, 2H), 7.60 - 7.49 (m, 2H), 7.41 (s, 1H), 6.92 (d, J = 5.0 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.02 - 5.85 (m, 2H), 3.31 - 3.24 (m, 1H), 3.22 (ddd, J = 9.8, 7.9, 4.9 Hz, 1H), 3.10 (d, J = 9.8 Hz, 1H), 2.91 (dd, J = 10.2, 6.7 Hz, 1H), 2.73 - 2.61 (m, 2H), 2.53 (d, J = 4.5 Hz, 3H), 2.22 - 2.13 (m, 1H), 1.88 - 1.78 (m, 1H), 1.48 (dd, J = 12.6, 7.7 Hz, 1H), 1.37 (dd, J = 3.9 Hz, 2H), 1.01 (dd, J = 3.9 Hz, 2H); m/z = 428.2 [M+H] ⁺
X-0000985	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.72 (app. d, J = 8.4 Hz, 2H), 7.44 (dd, J = 6.5, 3.6 Hz, 1H), 7.36 - 7.26 (m, 2H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 6.09 - 5.89 (m, 2H), 3.26 (dd, J = 10.3, 7.4 Hz, 1H), 3.18 (ddd, J = 10.1, 7.9, 4.9 Hz, 1H), 3.08 (app. dt, J = 10.1, 7.5 Hz, 1H), 2.93 - 2.72 (m, 6H), 2.69 - 2.55 (m, 3H), 2.14 (h, J = 7.3 Hz, 1H), 1.82 - 1.76 (m, 1H), 1.50 - 1.40 (m, 1H), 1.40 - 1.34 (m, 2H), 1.29 - 1.27 (m, 2H); m/z = 442.3 [M+H] ⁺
X-0000986	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.75-7.68 (m, 4H), 7.62-7.58 (m, 4H), 7.34 (t, J = 5.7 Hz, 1H), 6.61 (dd, J = 16.5, 10.0 Hz, 1H), 5.97-5.87 (m, 2H), 3.68-3.64 (m, 4H), 3.28-3.25 (m, 1H), 3.22-3.17 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.88 (dd, J = 10.3, 6.8 Hz, 1H), 2.68-2.59 (m, 2H), 2.45 (q, J = 7.0 Hz, 2H), 2.15-2.09 (m, 1H), 1.82-1.75 (m, 1H), 1.46-1.39 (m, 1H), 1.02 (t, J = 7.0 Hz, 3H).; m/z = 546.4 [M+H] ⁺
X-0000987	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.23 (d, J = 5.0 Hz, 1H), 7.72 - 7.65 (m, 2H), 7.62 - 7.54 (m, 2H), 7.46 (t, J = 6.0 Hz, 1H), 7.20 (t, J = 7.4 Hz, 2H), 7.17 - 7.09 (m, 3H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.01 - 5.88 (m, 2H), 3.93 (t, J = 7.7 Hz, 1H), 3.32 - 3.22 (m, 2H), 3.19 (dddd, J = 10.5, 7.7, 4.5, 2.7 Hz, 1H), 3.08 - 3.02 (m, 1H), 2.95 - 2.82 (m, 2H), 2.70 - 2.66 (m, 2H), 2.48 (s, 3H), 2.18 - 2.09 (m, 1H), 1.82 - 1.76 (m, 1H), 1.46 - 1.39 (m, 1H); m/z = 492.3 [M+H] ⁺
X-0000988	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.84 (t, J = 8.2 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00 - 5.86 (m, 2H), 3.69 - 3.49 (m, 4H), 3.41 (t, J = 5.3 Hz, 1H), 3.37 - 3.27 (m, 3H), 3.24 (ddd, J = 14.9, 8.8, 4.6 Hz, 1H), 3.19 - 3.09 (m, 1H), 3.03 - 2.86 (m, 4H), 2.18 - 2.13 (m, 2H), 2.16 (hept, J = 7.2 Hz, 1H), 1.82 (app. dtd, J = 12.3, 7.3, 4.9 Hz, 1H), 1.50 - 1.43 (m, 1H); m/z = 446.6 [M+H] ⁺
X-0000989	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.96 - 7.74 (m, 2H), 7.63 (app. d, J = 7.8 Hz, 2H), 7.38 (br. s, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.05 - 5.87 (m, 2H), 4.56 (brs, 1H), 4.00 - 3.89 (m, 1H), 3.87 - 3.76 (m, 1H), 3.36 - 3.29 (m, 1H), 3.28 - 3.19 (m, 1H), 3.17 - 3.12 (m, 1H), 3.05 (br. s, 1H), 2.94 - 2.87 (m, 3H), 2.81 - 2.59 (m, 4H), 2.17 (p, J = 7.2 Hz, 1H), 1.86 - 1.80 (m, 3H), 1.67 - 1.38 (m, 3H).; m/z = 472.7 [M+H] ⁺
X-0000990	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.47 (d, J = 7.9 Hz, 1H), 8.12 - 7.97 (m, 2H), 7.91 - 7.79 (m, 2H), 7.36 (t, J = 6.0 Hz, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.06 - 5.85 (m, 2H), 3.78 (d, J = 9.4 Hz, 1H), 3.31 (dd, J = 10.3, 7.4 Hz, 1H), 3.23 (ddd, J = 10.1, 8.0, 4.8 Hz, 1H), 3.12 (app. dt, J = 10.1, 7.5 Hz, 1H), 2.91 (dd, J = 10.3, 6.9 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.13 (hept, J = 7.1 Hz, 1H), 1.85 - 1.68 (m, 5H), 1.68 - 1.59 (m, 1H), 1.46 (dq, J = 12.6, 7.8 Hz, 1H), 1.39 - 1.24 (m, 4H), 1.22 - 1.07 (m, 1H); m/z = 456.7 [M+H] ⁺

X-0000991	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.33 (t, J = 5.9 Hz, 1H), 8.18 - 8.06 (m, 2H), 8.00 - 7.81 (m, 2H), 7.47 - 7.30 (m, 3H), 7.27 - 7.09 (m, 1H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 6.09 - 5.82 (m, 2H), 4.49 (d, J = 6.0 Hz, 2H), 3.37 - 3.28 (m, 1H), 3.24 (ddd, J = 10.1, 8.0, 4.9 Hz, 1H), 3.19 - 3.13 (m, 1H), 2.92 (dd, J = 10.3, 6.9 Hz, 1H), 2.73 - 2.57 (m, 2H), 2.17 - 2.12 (m, 1H), 1.85 - 1.79 (m, 1H), 1.50 - 1.43 (m, 1H); m/z = 500.2 [M+H] ⁺
X-0000992	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.79 (s, 1H), 8.25 (d, J = 2.0 Hz, 1H), 8.24 - 8.19 (m, 2H), 8.06 (dd, J = 8.2, 1.7 Hz, 1H), 8.01 - 7.94 (m, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.38 (t, J = 5.7 Hz, 1H), 6.66 (dd, J = 16.5, 10.0 Hz, 1H), 6.02 - 5.86 (m, 2H), 3.38 - 3.33 (m, 1H), 3.31 - 3.23 (m, 1H), 3.16 (app. dt, J = 10.0, 7.5 Hz, 1H), 2.95 (dd, J = 10.3, 7.0 Hz, 1H), 2.77 - 2.60 (m, 2H), 2.17 (p, J = 7.3 Hz, 1H), 1.87 - 1.81 (m, 1H), 1.53 - 1.45 (m, 1H); m/z = 518.3 [M+H] ⁺
X-0000993	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.81 (s, 1H), 8.22 - 8.12 (m, 2H), 8.07 - 7.87 (m, 4H), 7.76 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 5.9 Hz, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.18 - 5.81 (m, 2H), 3.37 - 3.33 (m, 1H), 3.27 (ddd, J = 10.0, 7.9, 4.6 Hz, 1H), 3.15 (app. dt, J = 10.0, 7.6 Hz, 1H), 2.94 (dd, J = 10.3, 7.0 Hz, 1H), 2.73 - 2.65 (m, 2H), 2.16 (p, J = 7.2 Hz, 1H), 1.92 - 1.73 (m, 1H), 1.52 - 1.44 (m, 1H); m/z = 518.3 [M+H] ⁺
X-0000994	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.35 (s, 1H), 8.16 - 8.04 (m, 2H), 7.95 - 7.83 (m, 2H), 7.65 - 7.55 (m, 2H), 7.43 - 7.22 (m, 2H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.02 - 5.85 (m, 2H), 4.49 (d, J = 5.9 Hz, 2H), 3.32 - 3.27 (m, 1H), 3.24 (ddd, J = 9.9, 8.0, 4.8 Hz, 1H), 3.13 (dt, J = 10.0, 7.5 Hz, 1H), 2.92 (dd, J = 10.3, 6.9 Hz, 1H), 2.72 - 2.55 (m, 2H), 2.14 (p, J = 7.2 Hz, 1H), 1.81 (dtd, J = 12.2, 7.2, 4.8 Hz, 1H), 1.46 (dq, J = 12.5, 7.8 Hz, 1H); m/z = 532.2 [M+H] ⁺
X-0000995	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.35 (s, 1H), 8.15 - 7.97 (m, 2H), 7.97 - 7.74 (m, 2H), 7.71 - 7.15 (m, 5H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.24 - 5.77 (m, 2H), 4.48 (d, J = 5.8 Hz, 2H), 3.31 (dd, J = 10.3, 7.3 Hz, 1H), 3.23 (ddd, J = 10.0, 8.0, 4.8 Hz, 1H), 3.13 (dt, J = 10.0, 7.6 Hz, 1H), 3.05 (br. s, 6H), 2.91 (dd, J = 10.3, 6.8 Hz, 1H), 2.63 (ddq, J = 19.5, 13.0, 6.5 Hz, 2H), 2.54 - 2.52 (m, 1H), 2.13 (p, J = 7.2 Hz, 1H), 1.90 - 1.67 (m, 1H), 1.53 - 1.39 (m, 1H); m/z = 507.3 [M+H] ⁺
X-0000996	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.35 (s, 1H), 8.15 - 7.97 (m, 2H), 7.97 - 7.74 (m, 2H), 7.71 - 7.15 (m, 5H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.24 - 5.77 (m, 2H), 4.48 (d, J = 5.8 Hz, 2H), 3.31 (dd, J = 10.3, 7.3 Hz, 1H), 3.23 (ddd, J = 10.0, 8.0, 4.8 Hz, 1H), 3.13 (dt, J = 10.0, 7.6 Hz, 1H), 3.05 (br. s, 6H), 2.91 (dd, J = 10.3, 6.8 Hz, 1H), 2.63 (ddq, J = 19.5, 13.0, 6.5 Hz, 2H), 2.54 - 2.52 (m, 1H), 2.13 (p, J = 7.2 Hz, 1H), 1.90 - 1.67 (m, 1H), 1.53 - 1.39 (m, 1H); m/z = 507.3 [M+H] ⁺
X-0000997	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.24 (s, 1H), 8.28 - 8.03 (m, 2H), 8.03 - 7.84 (m, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.37 (t, J = 6.0 Hz, 1H), 6.77 (br. s, 2H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.08 - 5.80 (m, 2H), 3.34 (dt, J = 10.4, 4.8 Hz, 1H), 3.27 (ddd, J = 10.0, 8.0, 4.8 Hz, 1H), 3.21 - 3.11 (m, 1H), 3.00 - 2.80 (m, 7H), 2.74 - 2.60 (m, 2H), 2.21 - 2.12 (m, 1H), 1.88 - 1.77 (m, 1H), 1.48 (dd, J = 12.6, 7.8 Hz, 1H); m/z = 493.2 [M+H] ⁺
X-0001002	¹ H NMR (400 MHz, DMSO-d ₆) δ 13.83 (bs, 1H), 10.14 (s, 1H), 9.06 (s, 1H), 8.72 (bs, 1H), 7.73 (s, 3H), 7.62 - 7.06 (m, 1H), 7.48 - 7.44 (m, 2H), 7.33 (s, 1H), 6.73 - 6.59 (m, 1H), 6.03 - 5.91 (m, 1H), 4.74 (s, 2H), 4.14 - 4.12 (m, 2H), 3.54 - 3.35 (m, 4H), 3.31 - 3.18 (m, 3H), 2.88 - 2.64 (m, 4H), 2.37 - 2.30 (m, 3H), 1.97 - 1.88 (m, 3H), 1.58 - 1.52 (m, 2H), 1.36 - 1.30 (m, 1H); m/z = 605.5 [M + H] ⁺
X-0001010	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.70 (bs, 1H), 8.61 (s, 1H), 7.85 (bs, 1H), 7.67 - 7.53 (m, 2H), 7.48 - 7.46 (m, 2H), 7.40 - 7.39 (m, 2H), 6.74 - 6.60 (m, 1H), 6.04 - 5.89 (m, 2H), 4.36 (d, J = 5.6 Hz, 2H), 3.45 - 3.41 (m, 2H), 3.21 - 3.16 (m, 1H), 3.04 (s, 4H), 2.88 (bs, 2H), 2.36 - 2.30 (m, 2H), 1.98 - 1.89 (m, 1H), 1.67 - 1.58 (m, 1H); m/z = 511.2 [M + H] ⁺

X-0001025	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.63 (s, 1H), 7.65 - 7.62 (d, J = 8.0 Hz, 1H), 7.44 - 7.29 (m, 6H), 6.74 - 6.67 (m, 1H), 6.02 - 5.92 (m, 2H), 4.34 - 4.32 (d, J = 6.0 Hz, 2H), 4.16 (s, 1H), 3.52 (s, 2H), 3.45 - 3.35 (m, 1H), 3.15 - 3.01 (m, 2H), 1.96 - 1.84 (m, 3H), 1.66 - 1.62 (m, 1H); m/z = 510.1 [M + H] ⁺
X-0001032	¹ H NMR (400 MHz, DMSO d ₆) δ 8.59 (bs, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.45 - 7.37 (m, 3H), 7.26 - 7.22 (m, 3H), 6.73 - 6.59 (m, 1H), 6.04 - 5.89 (m, 2H), 4.34 (d, J = 5.6 Hz, 2H), 3.60 - 3.40 (m, 5H), 3.18 - 3.13 (m, 1H), 2.90 - 2.88 (m, 1H), 2.79 - 2.76 (m, 1H), 2.34 - 2.30 (m, 4H), 1.95 - 1.89 (m, 1H), 1.63 - 1.60 (m, 1H); m/z = 524.2 [M + H] ⁺
X-0001034	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.67 - 8.65 (d, J = 5.2 Hz, 1H), 7.66 - 7.63 (m, 2H), 7.45 - 7.31 (m, 4H), 1.17 - 7.13 (m, 2H), 6.73 - 6.59 (m, 1H), 6.04 - 5.89 (m, 2H), 4.34 (s, 2H), 3.71 - 3.37 (m, 4H), 3.32 - 3.10 (m, 2H), 2.99 - 2.64 (m, 2H), 2.47 - 2.33 (m, 1H), 2.00 - 1.67 (m, 1H), 1.67 - 1.55 (m, 1H); m/z = 528.1 [M + H] ⁺
X-0001040	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 8.4 (s, 1H), 7.66 - 7.62 (d, J = 8.04 Hz, 2H), 7.48 - 7.42 (m, 4H), 7.35 - 7.31 (d, J = 7.8 Hz, 2H), 7.1 (bs, 1H), 6.6 (bs, 1H), 6.05 - 5.91 (m, 2H), 4.39 - 4.36 (m, 2H), 3.64 - 3.56 (m, 4H), 3.3 (bs, 1H), 3.21 (bs, 1H), 3.05 - 2.98 (m, 1H), 2.80 (bs, 1H), 2.38 - 2.31 (m, 2H), 1.06 - 0.91 (m, 3H); m/z = 524.42 [M + H] ⁺
X-0001041	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.71 (bs, 1H), 7.68 (d, J = 5.60 Hz, 2H), 7.52 (bs, 1H), 7.46 - 7.45 (m, 4H), 7.34 (d, J = 7.60 Hz, 2H), 6.78 - 6.63 (m, 1H), 6.08 - 5.92 (m, 2H), 4.43 (d, J = 5.64 Hz, 2H), 3.80 (bs, 1H), 3.71 - 3.55 (m, 2H), 3.51 (s, 3H), 3.48 - 3.40 (m, 1H), 3.27 (s, 2H), 3.16 (s, 1H), 2.91 - 2.88 (m, 1H), 2.82 - 2.71 (m, 1H), 2.32 (bs, 1H); m/z = 540.39 [M + H] ⁺
X-0001042	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.99 - 7.76 (m, 2H), 7.75 - 7.63 (m, 2H), 7.10 (s, 1H), 6.63 (dd, J = 16.6, 10.0 Hz, 1H), 6.17 - 5.77 (m, 2H), 3.74 (br. s, 5H), 3.38 (dd, J = 10.2, 7.4 Hz, 1H), 3.34 - 3.15 (m, 5H), 2.99 (dd, J = 10.3, 6.8 Hz, 1H), 2.84 (s, 3H), 2.76 (app. t, J = 6.3 Hz, 2H), 2.27 (hept, J = 7.2 Hz, 1H), 1.93 - 1.87 (m, 1H), 1.58 - 1.51 (m, 1H); m/z = 457.3 [M+H] ⁺
X-0001043	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.62 (d, J = 4.7 Hz, 1H), 7.97 (s, 1H), 7.85 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.60 - 7.41 (m, 2H), 7.13 (br. s, 1H), 6.63 (dd, J = 16.6, 10.0 Hz, 1H), 6.06 - 5.79 (m, 2H), 4.76 (br. s, 2H), 3.46 - 3.33 (m, 3H), 3.28 (ddd, J = 9.9, 8.1, 4.9 Hz, 1H), 3.19 (app. dt, J = 9.9, 7.5 Hz, 1H), 2.97 (dd, J = 10.3, 6.9 Hz, 1H), 2.77 (d, J = 7.1 Hz, 2H), 2.25 (hept, J = 7.2 Hz, 1H), 1.91 - 1.85 (m, 1H), 1.56 - 1.49 (m, 1H), 1.11 (t, J = 7.1 Hz, 3H); m/z = 493.2 [M+H] ⁺
X-0001044	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.73 (br s, 1H), 7.83-7.66 (m, 4H), 7.55-7.45 (m, 4H), 7.43-7.40 (m, 1H), 6.69-6.63 (m, 1H), 6.03-5.90 (m, 2H), 4.67-4.64 (m, 4H), 4.40 (s, 2H), 3.30-3.16 (m, 2H), 3.12-3.05 (m, 1H), 2.95-2.87 (m, 1H), 2.86-2.80 (br m, 6H), 2.70-2.64 (m, 2H), 2.19-2.12 (m, 1H), 1.87-1.77 (m, 1H), 1.52-1.40 (m, 1H).; m/z = 603.4 [M+H] ⁺
X-0001045	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.77-7.61 (m, 8H), 7.43-7.01 (m, 3H), 6.61 (dd, J = 16.5, 10.0 Hz, 1H), 5.97-5.85 (m, 2H), 3.76-3.75 (m, 4H), 3.29-3.23 (m, 1H), 3.22-3.18 (m, 1H), 3.08 (dt, J = 9.9, 7.5 Hz, 1H), 2.99 (s, 2H), 2.88 (dd, J = 10.3, 6.8 Hz, 1H), 2.69-2.57 (m, 2H), 2.16-2.10 (m, 1H), 1.82 (m, 1H), 1.47-1.38 (m, 1H).; m/z = 575.7 [M+H] ⁺
X-0001046	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.77-7.62 (m, 9H), 7.34 (s, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 5.98-5.85 (m, 2H), 3.75-3.74 (m, 4H), 3.29-3.25 (m, 1H), 3.22-3.18 (m, 1H), 3.08 (dt, J = 9.8, 7.5 Hz, 1H), 3.01 (s, 2H), 2.88 (dd, J = 10.3, 6.8 Hz, 1H), 2.67-2.60 (m, 2H), 2.57 (d, J = 4.7 Hz, 3H), 2.16-2.10 (m, 1H), 1.82-1.76 (m, 1H), 1.49-1.39 (m, 1H).; m/z = 589 [M+H] ⁺

X-0001047	1H NMR (500 MHz, DMSO-d6) δ 7.75-7.68 (m, 4H), 7.60-7.57 (m, 4H), 7.34 (s, 1H), 6.62 (dd, J = 16.5, 9.9 Hz, 1H), 5.97-5.86 (m, 2H), 3.81-3.80 (m, 4H), 3.29-3.25 (m, 1H), 3.21-3.17 (m, 1H), 3.08 (dt, J = 10.0, 7.6 Hz, 1H), 2.90-2.71 (m, 9H), 2.68-2.58 (m, 2H), 2.15-2.09 (m, 1H), 1.81-1.75 (m, 1H), 1.47-1.37 (m, 1H); m/z = 603.1 [M+H] ⁺
X-0001048	1H NMR (500 MHz, DMSO-d6) δ 9.34 (t, J = 5.7 Hz, 1H), 8.19 - 7.93 (m, 2H), 7.96 - 7.85 (m, 2H), 7.79 (dd, J = 6.8, 2.4 Hz, 1H), 7.74 (dt, J = 7.8, 3.7 Hz, 1H), 7.46 (t, J = 9.1 Hz, 1H), 7.34 (s, 1H), 6.61 (dd, J = 16.5, 10.0 Hz, 1H), 6.00 - 5.85 (m, 2H), 4.60 (d, J = 5.6 Hz, 2H), 3.32 - 3.28 (m, 1H), 3.23 (ddd, J = 10.0, 8.0, 4.9 Hz, 1H), 3.13 (dt, J = 10.0, 7.5 Hz, 1H), 2.92 (dd, J = 10.3, 6.8 Hz, 1H), 2.71 - 2.57 (m, 2H), 2.14 (p, J = 7.2 Hz, 1H), 1.80 (ddd, J = 14.6, 7.3, 5.1 Hz, 1H), 1.54 - 1.36 (m, 1H); m/z = 550.3 [M+H] ⁺
X-0001049	1H NMR (500 MHz, DMSO-d6) δ 9.38 (t, J = 5.7 Hz, 1H), 8.14 - 8.08 (m, 2H), 7.93 - 7.87 (m, 2H), 7.76 - 7.68 (m, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.34 (s, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.05 - 5.88 (m, 2H), 4.60 (d, J = 5.6 Hz, 2H), 3.30 (d, J = 7.2 Hz, 1H), 3.23 (ddd, J = 9.9, 8.0, 4.9 Hz, 1H), 3.13 (dt, J = 10.0, 7.5 Hz, 1H), 2.92 (dd, J = 10.3, 6.8 Hz, 1H), 2.71 - 2.55 (m, 2H), 2.14 (hept, J = 7.2 Hz, 1H), 1.84 - 1.78 (m, 1H), 1.50 - 1.43 (m, 1H); m/z = 550.3 [M+H] ⁺
X-0001050	1H NMR (500 MHz, DMSO-d6) δ 9.28 (t, J = 5.7 Hz, 1H), 8.14 - 8.05 (m, 2H), 7.96 - 7.80 (m, 2H), 7.55 (ddd, J = 10.9, 9.7, 6.7 Hz, 1H), 7.48 (ddd, J = 11.1, 9.1, 6.8 Hz, 1H), 7.34 (t, J = 5.9 Hz, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.00 - 5.86 (m, 2H), 4.49 (d, J = 5.6 Hz, 2H), 3.30 (d, J = 7.3 Hz, 1H), 3.23 (ddd, J = 9.9, 8.0, 4.9 Hz, 1H), 3.13 (dt, J = 10.0, 7.5 Hz, 1H), 2.92 (dd, J = 10.3, 6.8 Hz, 1H), 2.75 - 2.54 (m, 2H), 2.14 (p, J = 7.2 Hz, 1H), 1.82 (ddd, J = 12.3, 7.3, 5.0 Hz, 1H), 1.50 - 1.42 (m, 1H); m/z = 518.3 [M+H] ⁺
X-0001051	1H NMR (500 MHz, DMSO-d6) δ 9.33 (t, J = 5.7 Hz, 1H), 8.18 - 8.00 (m, 2H), 7.95 - 7.73 (m, 2H), 7.39 - 7.21 (m, 3H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 6.07 - 5.85 (m, 2H), 4.54 (d, J = 5.6 Hz, 2H), 3.33 - 3.29 (m, 1H), 3.24 (ddd, J = 9.9, 8.0, 4.8 Hz, 1H), 3.13 (app. dt, J = 10.0, 7.5 Hz, 1H), 2.92 (dd, J = 10.3, 6.9 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.15 (h, J = 7.2 Hz, 1H), 1.81 (dtd, J = 12.2, 7.3, 4.8 Hz, 1H), 1.47 (dd, J = 12.6, 7.8 Hz, 1H); m/z = 518.3 [M+H] ⁺
X-0001052	1H NMR (500 MHz, DMSO-d6) δ 9.39 (t, J = 5.8 Hz, 1H), 8.18 - 8.05 (m, 2H), 7.99 - 7.86 (m, 2H), 7.71 - 7.53 (m, 3H), 7.36 (s, 1H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 5.99 - 5.85 (m, 2H), 4.61 (d, J = 5.7 Hz, 2H), 3.31 (d, J = 7.3 Hz, 1H), 3.25 (ddd, J = 9.9, 8.0, 4.8 Hz, 1H), 3.14 (dt, J = 9.9, 7.5 Hz, 1H), 2.93 (dd, J = 10.3, 6.9 Hz, 1H), 2.65 (app. qd, J = 13.1, 7.5 Hz, 2H), 2.15 (p, J = 7.2 Hz, 1H), 1.85 - 1.79 (m, 1H), 1.51 - 1.43 (m, 1H); m/z = 550.3 [M+H] ⁺
X-0001053	1H NMR (500 MHz, DMSO-d6) δ 7.85 (app. dd, J = 20.2, 7.9 Hz, 2H), 7.77 - 7.10 (m, 6H), 6.63 (dd, J = 16.4, 9.9 Hz, 1H), 6.06 - 5.87 (m, 2H), 4.69 and 4.45 (2 x s, 2H, rotamers), 3.30 (br. s, 1H), 3.23 (br. s, 1H), 3.19 - 3.08 (m, 1H), 3.00 - 2.90 (m, 2H), 2.85 (br. s, 2H), 2.71 - 2.64 (m, 2H), 2.16 (p, J = 7.2 Hz, 1H), 1.82 (dd, J = 12.5, 6.3 Hz, 1H), 1.47 (dd, J = 12.9, 7.4 Hz, 1H); m/z = 546.6 [M+H] ⁺
X-0001054	1H NMR (500 MHz, DMSO-d6) δ 9.15 (t, J = 5.2 Hz, 1H), 8.08 - 7.99 (m, 2H), 7.93 - 7.85 (m, 2H), 7.35 (t, J = 6.0 Hz, 1H), 7.20 (dd, J = 9.3, 8.0 Hz, 2H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.04 - 5.71 (m, 2H), 4.50 (d, J = 5.1 Hz, 2H), 3.32 - 3.27 (m, 1H), 3.22 (ddd, J = 9.8, 8.0, 4.8 Hz, 1H), 3.12 (app. dt, J = 9.9, 7.5 Hz, 1H), 2.91 (dd, J = 10.3, 6.8 Hz, 1H), 2.71 - 2.57 (m, 2H), 2.13 (hept, J = 7.3 Hz, 1H), 1.81 (ddd, J = 12.5, 7.4, 5.1 Hz, 1H), 1.46 (app. dq, J = 12.6, 7.8 Hz, 1H); m/z = 518.3 [M+H] ⁺
X-0001055	1H NMR (500 MHz, DMSO-d6) δ 9.37 (t, J = 6.2 Hz, 1H), 8.14 - 8.08 (m, 2H), 7.96 - 7.90 (m, 2H), 7.36 (s, 1H), 6.63 (dd, J = 16.5, 10.0 Hz, 1H), 5.99 - 5.89 (m, 2H), 4.19 - 4.08 (m, 2H), 3.37 - 3.29 (m, 1H), 3.28 - 3.20 (m, 1H), 3.19 - 3.10 (m, 1H), 2.93 (dd, J = 10.3, 6.8 Hz, 1H), 2.72 - 2.57 (m, 2H), 2.21 - 2.08 (m, 1H), 1.87 - 1.77 (m, 1H), 1.53 - 1.42 (m, 1H); m/z = 456.2 [M+H] ⁺

X-0001057	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14 - 8.04 (m, 2H), 7.93 - 7.86 (m, 2H), 7.35 (s, 1H), 6.63 (dd, J = 16.5, 9.9 Hz, 1H), 6.05 - 5.83 (m, 2H), 4.90 - 4.80 (m, 1H), 4.53 - 4.44 (m, 1H), 4.40 - 4.28 (m, 2H), 3.60 (dd, J = 9.7, 5.4 Hz, 1H), 3.52 (app. dt, J = 10.3, 4.7 Hz, 1H), 3.31 (dd, J = 7.7, 2.8 Hz, 1H), 3.23 (ddd, J = 10.0, 8.0, 4.9 Hz, 1H), 3.13 (app. dt, J = 10.0, 7.5 Hz, 1H), 2.91 (dd, J = 10.4, 6.8 Hz, 1H), 2.73 - 2.56 (m, 2H), 2.14 (hept, J = 7.0 Hz, 1H), 1.84 - 1.78 (m, 1H), 1.50 - 1.43 (m, 1H); m/z = 430.2 [M+H] ⁺
X-0001058	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.76 - 7.67 (m, 2H), 7.61 - 7.52 (m, 4H), 7.41 - 7.34 (m, 3H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.04 - 5.87 (m, 2H), 4.50 (t, J = 7.5 Hz, 1H), 3.36 (dd, J = 13.6, 8.2 Hz, 1H), 3.26 (ddd, J = 10.4, 7.5, 4.2 Hz, 1H), 3.22 - 3.14 (m, 1H), 3.11 - 3.02 (m, 1H), 2.98 (dd, J = 13.6, 6.8 Hz, 1H), 2.91 - 2.85 (m, 1H), 2.85 (s, 3H), 2.78 (s, 3H), 2.71 - 2.63 (m, 2H), 2.17 - 2.07 (m, 1H), 1.86 - 1.70 (m, 1H), 1.47 - 1.32 (m, 1H); m/z = 574.6 [M+H] ⁺
X-0001059	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14 - 8.01 (m, 2H), 7.90 - 7.83 (m, 2H), 7.34 (s, 1H), 6.62 (dd, J = 16.5, 10.0 Hz, 1H), 6.01 - 5.89 (m, 2H), 4.93 (t, J = 5.7 Hz, 1H), 4.44 (d, J = 8.2 Hz, 1H), 4.04 (d, J = 8.1 Hz, 1H), 3.48 - 3.34 (m, 2H), 3.31 - 3.27 (m, 1H), 3.25 - 3.18 (m, 1H), 3.12 (app. dt, J = 10.1, 7.5 Hz, 1H), 2.90 (ddd, J = 10.0, 6.9, 2.6 Hz, 1H), 2.69 - 2.55 (m, 2H), 2.19 - 2.05 (m, J = 6.7 Hz, 1H), 1.80 (dtd, J = 12.3, 7.2, 4.9 Hz, 1H), 1.46 (dq, J = 12.8, 7.8, 2.1 Hz, 1H), 1.24 (s, 3H); m/z = 444.3 [M+H] ⁺
X-0001064	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.82 (bs, 2H), 7.85 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.21 (s, 1H), 6.77 - 6.62 (m, 1H), 6.07 - 5.92 (m, 2H), 3.57 - 3.49 (m, 3H), 3.39 - 3.31 (m, 3H), 3.16 - 3.07 (m, 3H), 2.95 - 2.90 (m, 2H), 2.85 - 2.74 (m, 1H), 2.70 (s, 3H), 2.43 - 2.31 (m, 1H), 2.28 - 2.08 (m, 2H), 1.93 - 1.89 (m, 2H), 1.86 - 1.60 (m, 1H); m/z = 431.3 [M + H] ⁺
X-0001067	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.84 (bs, 2H), 7.88 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.45 (dd, J = 6 Hz, 22 Hz, 2H), 7.27 (d, J = 8.4 Hz, 1H), 6.73 - 6.61 (m, 1H), 6.06 - 5.90 (m, 2H), 5.52 (s, 2H), 3.5 (s, 1H), 3.42 - 3.37 (m, 3H), 3.31 - 3.27 (m, 2H), 3.16 - 3.11 (m, 2H), 3.08 - 3.05 (m, 2H), 2.79 - 2.73 (m, 3H), 2.40 - 2.28 (m, 2H), 2.14 - 2.10 (m, 2H), 1.93 - 1.87 (m, 2H), 1.67 - 1.59 (m, 1H); m/z = 575.4 [M + H] ⁺
X-0001068	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.80 (bs, 1H), 8.66 (bs, 1H), 7.83 (s, 1H), 7.50 - 7.44 (m, 1H), 7.29 - 7.16 (m, 7H), 6.73 - 6.62 (m, 1H), 6.07 - 5.91 (m, 2H), 4.39 - 4.35 (m, 2H), 3.67 - 3.51 (m, 4H), 3.37 - 3.24 (m, 3H), 3.12 - 3.03 (m, 5H), 2.94 - 2.84 (m, 2H), 2.43 - 2.30 (m, 2H), 2.07 - 1.95 (m, 3H), 1.86 - 1.77 (m, 1H); m/z = 521.4 [M + H] ⁺
X-0001094	¹ H NMR (400 MHz, DMSO d ₆) δ 8.44 (bs, 1H), 7.67 - 7.65 (m, 2H), 7.55 - 7.38 (m, 3H), 7.21 (d, J = 7.2 Hz, 1H), 7.03 - 6.98 (m, 2H), 6.73 - 6.59 (m, 1H), 6.04 - 5.88 (m, 2H), 4.34 (d, J = 5.6 Hz, 2H), 3.76 (s, 2H), 3.61 - 3.42 (m, 4H), 3.18 (bs, 1H), 2.90 (d, J = 6.8 Hz, 1H), 2.85 - 2.77 (m, 2H), 2.37 - 2.27 (m, 2H), 1.95 - 1.89 (m, 1H), 1.67 - 1.60 (m, 1H); m/z = 540.0 [M + H] ⁺
X-0001098	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.62 - 8.61 (m, 1H), 7.64 (t, J = 10.2 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.40 - 7.39 (m, 1H), 7.12 - 7.10 (m, 3H), 6.73 - 6.59 (m, 1H), 6.03 - 5.89 (m, 2H), 4.34 - 4.32 (d, J = 4.8 Hz, 2H), 3.61 - 3.37 (m, 3H), 3.21 - 3.16 (m, 2H), 3.04 (t, J = 6.8 Hz, 1H), 2.88 - 2.64 (m, 2H), 2.28 - 2.23 (m, 1H), 2.16 (s, 1H), 2.04 - 1.65 (m, 1H), 1.67 - 1.540 (m, 1H); m/z = 524.1 [M + H] ⁺
X-0001103	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.70 (bs, 1H), 7.68 (d, J = 7.64 Hz, 2H), 7.46 - 7.44 (m, 5H), 7.34 (d, J = 6.36 Hz, 2H), 6.76 - 6.60 (m, 1H), 6.07 - 5.92 (m, 2H), 5.22 (dd, J = 35.56 Hz, J = 4.24 Hz, 1H), 4.36 (d, J = 5.68 Hz, 2H), 4.03 - 3.95 (m, 1H), 3.71 - 3.58 (m, 2H), 3.55 (s, 2H), 3.26 - 3.18 (m, 2H), 3.00 - 2.95 (m, 1H), 2.98 - 2.78 (m, 1H), 2.18 - 2.08 (bs, 1H); m/z = 526.34 [M + H] ⁺

X-0001105	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.43 (bs, 1H), 7.66 - 7.62 (d, <i>J</i> = 16 Hz, 2H), 7.5 - 7.44 (m, 4H), 7.39 - 7.35 (m, 2H), 7.3 (bs, 1H), 6.73 - 6.65 (m, 1H), 6.07 - 5.95 (m, 2H), 4.37 (d, <i>J</i> = 8.0 Hz, 2H), 4.03 - 3.85 (m, 3H), 3.58 (s, 2H), 3.53 - 3.46 (m, 1H), 3.22 - 3.1 (m, 1H), 3.02 - 2.96 (m, 1H), 2.8 (bs, 1H); <i>m/z</i> = 546.34 [M + H] ⁺
X-0001115	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (bs, 1H), 8.57 (bs, 1H), 7.81 (s, 1H), 7.47 (d, <i>J</i> = 16.4 Hz, 1H), 7.30 (d, <i>J</i> = 17.2 Hz, 1H), 7.28 (s, 1H), 6.73 - 6.62 (m, 1H), 6.07 - 5.92 (m, 2H), 3.77 - 3.67 (m, 4H), 3.57 - 3.17 (m, 9H), 2.95 (s, 3H), 2.76 - 2.7 (m, 1H), 2.09 - 1.60 (m, 4H); <i>m/z</i> = 431.5 [M + H] ⁺
X-0001119	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.72-8.64 (m, 1H), 8.59 brs, 1H), 8.05 (s, 1H), 7.62 (d, <i>J</i> = 8.4 Hz, 1H), 7.58- 7.48 (s, 1H), 6.68 - 6.60 (m, 1H), 6.10 - 5.90 (m, 2H), 4.00 (s, 3H), 3.70 - 3.60 (m, 1H), 3.52 (s, 1H), 3.52 - 3.46 (m, 3H), 3.07 (d, <i>J</i> = 10.0 Hz, 2H), 2.94 (brs, 3H), 2.90 - 2.70 (m, 1H), 2.40 - 2.32 (m, 1H), 2.12 - 2.00 (m, 5H), 1.72 - 1.56 (m, 1H) <i>m/z</i> = 432.3 [M + H] ⁺
X-0001121	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 7.94 (s, 1H), 7.54 (d, <i>J</i> = 8.0 Hz, 1H), 7.34 (d, <i>J</i> = 4.4 Hz, 1H), 6.60 - 6.40 (m, 1H), 6.32 - 6.20 (m, 1H), 6.00 - 5.90 (m, 1H), 4.62 (brs, 1H), 4.32 - 4.18 (m, 2H), 4.01 (s, 3H), 3.90 - 3.50 (m, 3H), 3.48 - 3.30 (m, 1H), 3.28 - 3.00 (m, 3H), 2.98 - 2.82 (m, 2H), 2.54 - 2.46 (m, 1H), 2.20 (brs, 1H), 2.11 (brs, 3H), 2.00 - 1.84 (m, 1H), 1.45 (brs, 9H), 1.80 - 1.68 (m, 1H); <i>m/z</i> = 532.4 [M + H] ⁺
X-0001123	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.66 (t, <i>J</i> = 6.0 Hz, 1H), 7.77-7.70 (m, 2H), 7.48-7.46 (m, 2H), 7.40-7.30 (m, 3H), 7.13-7.10 (br m, 1H), 6.64 (dd, <i>J</i> = 16.5, 9.9 Hz, 1H), 6.02-5.87 (m, 2H), 4.38 (d, <i>J</i> = 5.9 Hz, 2H), 3.53 (s, 2H), 3.30-3.23 (m, 1H), 3.22-3.18 (m, 1H), 3.07 (dt, <i>J</i> = 9.9, 7.6 Hz, 1H), 2.88 (dd, <i>J</i> = 10.2, 7.0 Hz, 1H), 2.72-2.62 (m, 2H), 2.16-2.10 (m, 1H), 1.83-1.77 (m, 1H), 1.48-1.41 (m, 1H).; <i>m/z</i> = 514.4 [M+H] ⁺
X-0001124	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.69 (t, <i>J</i> = 6.0 Hz, 1H), 7.80-7.67 (m, 2H), 7.62-7.52 (m, 2H), 7.52-7.43 (m, 2H), 7.36 (s, 1H), 7.28 (dd, <i>J</i> = 8.3, 2.1 Hz, 1H), 6.64 (dd, <i>J</i> = 16.5, 10.0 Hz, 1H), 6.02-5.89 (m, 2H), 4.38 (d, <i>J</i> = 5.9 Hz, 2H), 3.55 (s, 2H), 3.30-3.23 (m, 1H), 3.23-3.18 (m, 1H), 3.07 (dt, <i>J</i> = 9.9, 7.6 Hz, 1H), 2.88 (dd, <i>J</i> = 10.2, 6.9 Hz, 1H), 2.73-2.61 (m, 2H), 2.16-2.10 (m, 1H), 1.83-1.77 (m, 1H), 1.49-1.41 (m, 1H).; <i>m/z</i> = 546.4/548.8 [M+H] ⁺
X-0001125	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.63 (t, <i>J</i> = 6.0 Hz, 1H), 7.75-7.70 (m, 2H), 7.46-7.45 (m, 2H), 7.36 - 7.31 (m, 3H), 7.24-7.17 (m, 2H), 6.64 (dd, <i>J</i> = 16.5, 10.0 Hz, 1H), 6.00-5.88 (m, 2H), 4.36 (d, <i>J</i> = 6.0 Hz, 2H), 3.46 (s, 2H), 3.28-3.24 (m, 1H), 3.22-3.18 (m, 1H), 3.07 (dt, <i>J</i> = 9.9, 7.6 Hz, 1H), 2.88 (dd, <i>J</i> = 10.3, 6.9 Hz, 1H), 2.72-2.62 (m, 2H), 2.16-2.10 (m, 1H), 1.85-1.75 (m, 1H), 1.49-1.41 (m, 1H), 1.27 (s, 9H).; <i>m/z</i> = 534.5 [M+H] ⁺
X-0001126	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.59 (t, <i>J</i> = 5.7 Hz, 1H), 7.77-7.71 (m, 2H), 7.53-7.51 (m, 2H), 7.43-7.25 (m, 3H), 7.20-7.12 (m, 2H), 6.63 (dd, <i>J</i> = 16.5, 10.0 Hz, 1H), 6.05-5.82 (m, 2H), 4.24-4.22 (m, 2H), 3.60 (s, 2H), 3.29-3.24 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, <i>J</i> = 9.8, 7.6 Hz, 1H), 2.89 (dd, <i>J</i> = 10.2, 6.9 Hz, 1H), 2.73-2.62 (m, 2H), 2.17-2.12 (m, 1H), 1.84-1.78 (m, 1H), 1.51-1.41 (m, 1H), 1.26-1.25 (m, 9H).; <i>m/z</i> = 534.4 [M+H] ⁺
X-0001127	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.68 (t, <i>J</i> = 6.0 Hz, 1H), 7.76-7.71 (m, 2H), 7.55-7.47 (m, 4H), 7.36 (s, 1H), 7.22-7.17 (m, 2H), 6.64 (dd, <i>J</i> = 16.5, 10.0 Hz, 1H), 6.00-5.90 (m, 2H), 4.25 (d, <i>J</i> = 5.9 Hz, 2H), 3.62 (s, 2H), 3.29-3.26 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, <i>J</i> = 9.9, 7.6 Hz, 1H), 2.89 (dd, <i>J</i> = 10.3, 6.9 Hz, 1H), 2.71-2.64 (m, 2H), 2.17-2.12 (m, 1H), 1.86-1.77 (m, 1H), 1.50-1.43 (m, 1H).; <i>m/z</i> = 556.2/558.2 [M+H] ⁺

X-0001128	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.75 (t, J = 6.0 Hz, 1H), 7.78-7.65 (m, 4H), 7.55-7.44 (m, 4H), 7.36 (s, 1H), 6.69-6.61 (m, 1H), 6.01-5.90 (m, 2H), 4.39 (d, J = 5.9 Hz, 2H), 3.65 (s, 2H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 10.0, 7.6 Hz, 1H), 2.89 (dd, J = 10.2, 7.0 Hz, 1H), 2.72-2.63 (m, 2H), 2.17-2.11 (m, 1H), 1.84-1.78 (m, 1H), 1.51-1.40 (m, 1H).; m/z = 546.3 [M+H] ⁺
X-0001129	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.69 (t, J = 5.9 Hz, 1H), 7.77-7.71 (m, 2H), 7.66-7.59 (m, 4H), 7.57-7.52 (m, 2H), 7.47-7.44 (m, 2H), 7.39-7.31 (m, 4H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.89 (m, 2H), 4.32 (d, J = 5.8 Hz, 2H), 3.64 (s, 2H), 3.30-3.25 (m, 1H), 3.24-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.93-2.86 (m, 1H), 2.72-2.61 (m, 2H), 2.17 (m, 1H), 1.86-1.75 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 554.7 [M+H] ⁺
X-0001130	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.67 (t, J = 5.7 Hz, 1H), 7.77-7.69 (m, 2H), 7.57-7.49 (m, 3H), 7.39-7.27 (m, 2H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.00-5.90 (m, 2H), 4.27 (d, J = 5.6 Hz, 2H), 3.62 (s, 2H), 3.29-3.25 (m, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.89 (dd, J = 10.2, 6.9 Hz, 1H), 2.72-2.61 (m, 2H), 2.17-2.11 (m, 1H), 1.84-1.77 (m, 1H), 1.51-1.41 (m, 1H).; m/z = 532.3 [M+H] ⁺
X-0001131	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.75-7.66 (m, 2H), 7.58-7.50 (m, 2H), 7.40-7.37 (br m, 1H), 7.22-7.19 (m, 2H), 7.17-7.10 (m, 3H), 6.66 (dd, J = 16.5, 10.0 Hz, 1H), 6.03-5.90 (m, 2H), 4.45 (t, J = 7.5 Hz, 1H), 3.49-3.44 (m, 1H), 3.36-3.32 (m, 3H), 3.31-3.23 (m, 2H), 3.22-3.16 (m, 1H), 3.11-3.00 (m, 1H), 2.90-2.79 (m, 2H), 2.71-2.63 (m, 2H), 2.14-2.08 (m, 1H), 1.82-1.72 (m, 1H), 1.42-1.33 (m, 3H), 1.32-1.18 (m, 2H), 1.08-0.98 (m, 1H), 0.79-0.70 (m, 1H).; m/z = 546.5 [M+H] ⁺
X-0001132	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.76 - 7.66 (m, 2H), 7.58 - 7.48 (m, 2H), 7.38 (br. s, 1H), 7.22 (dd, J = 8.0, 6.6 Hz, 2H), 7.19 - 7.11 (m, 3H), 6.66 (dd, J = 16.5, 10.0 Hz, 1H), 6.05 - 5.83 (m, 2H), 4.49 (dd, J = 8.3, 6.8 Hz, 1H), 3.49 - 3.47 (m, 2H), 3.42 - 3.34 (m, 3H), 3.32 - 3.23 (m, 3H), 3.22 - 3.11 (m, 2H), 3.09 - 3.04 (m, 2H), 2.91 (dd, J = 13.4, 6.7 Hz, 1H), 2.85 (app. dt, J = 10.4, 7.5 Hz, 1H), 2.68 (q, J = 5.6, 4.3 Hz, 2H), 2.19 - 2.04 (m, 1H), 1.81 - 1.74 (m, 1H), 1.47 - 1.34 (m, 1H); m/z = 548.5 [M+H] ⁺
X-0001133	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.70 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.38 (br. s, 1H), 7.19 (app. t, J = 7.3 Hz, 2H), 7.16 - 7.07 (m, 3H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.01 - 5.91 (m, 2H), 4.19 (t, J = 7.6 Hz, 1H), 3.39 - 3.34 (m, 1H), 3.30 - 3.24 (m, 3H), 3.24 - 3.16 (m, 2H), 3.13 (app. dt, J = 10.1, 6.7 Hz, 1H), 3.06 (app. dq, J = 9.9, 7.8 Hz, 1H), 2.91 (dd, J = 13.4, 7.2 Hz, 1H), 2.88 - 2.82 (m, 1H), 2.67 (d, J = 7.1 Hz, 2H), 2.17 - 2.06 (m, 1H), 1.82 - 1.75 (m, 1H), 1.70 (app. dq, J = 12.6, 6.0 Hz, 2H), 1.64 (app. p, J = 6.6 Hz, 2H), 1.44 - 1.36 (m, 1H); m/z = 532.1 [M+H] ⁺
X-0001134	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.71 (s, 1H), 8.37-8.32 (br m, 1H), 8.27-8.16 (m, 2H), 7.96-7.94 (m, 2H), 7.77-7.64 (m, 2H), 7.41 (br t, J = 6.0 Hz, 1H), 6.67-6.62 (m, 1H), 6.02-5.87 (m, 2H), 3.36-3.32 (m, 1H), 3.30-3.25 (m, 1H), 3.16 (dt, J = 10.2, 7.6 Hz, 1H), 2.95 (dd, J = 10.3, 6.9 Hz, 1H), 2.72-2.63 (m, 2H), 2.19-2.14 (m, 1H), 1.86-1.80 (m, 1H), 1.52-1.45 (m, 1H).; m/z = 558.4 [M+H] ⁺
X-0001135	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.46 (s, 1H), 8.21-8.19 (m, 2H), 8.03 (s, 1H), 7.99-7.92 (m, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.43-7.26 (m, 3H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.39 (d, J = 3.0 Hz, 1H), 6.02-5.89 (m, 2H), 3.77 (s, 3H), 3.37-3.33 (m, 1H), 3.28-3.23 (m, 1H), 3.16 (dt, J = 10.0, 7.6 Hz, 1H), 2.95 (dd, J = 10.4, 6.9 Hz, 1H), 2.72-2.64 (m, 2H), 2.20-2.14 (m, 1H), 1.87-1.81 (m, 1H), 1.54-1.42 (m, 1H).; m/z = 503.3 [M+H] ⁺

X-0001136	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.71 (t, J = 5.8 Hz, 1H), 7.74-7.72 (m, 2H), 7.51-7.49 (m, 2H), 7.36 (s, 1H), 7.32-7.24 (m, 1H), 7.19-7.14 (m, 1H), 6.64 (dd, J = 16.5, 9.9 Hz, 1H), 5.99-5.91 (m, 2H), 4.32 (d, J = 5.7 Hz, 2H), 3.61 (s, 2H), 3.30-3.24 (m, 1H), 3.23-3.16 (m, 1H), 3.08 (dt, J = 9.8, 7.6 Hz, 1H), 2.89 (dd, J = 10.3, 6.9 Hz, 1H), 2.72-2.62 (m, 2H), 2.17-2.11 (m, 1H), 1.84-1.77 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 532.6 [M+H] ⁺
X-0001137	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.87 - 7.81 (m, 2H), 7.72 - 7.63 (m, 2H), 7.41 - 7.15 (m, 6H), 6.65 (dd, J = 16.6, 9.6 Hz, 1H), 6.04 - 5.85 (m, 2H), 4.84 (d, J = 5.4 Hz, 1H), 4.77 and 4.52 (2 x s, 2H), 3.62 (d, J = 6.5 Hz, 1H), 3.47 - 3.44 (m, 2H), 3.33 - 3.06 (m, 4H), 2.99 - 2.86 (m, 1H), 2.68 (br. s, 2H), 2.18 (dd, J = 15.0, 8.0 Hz, 1H), 1.86 - 1.81 (m, 1H), 1.52 - 1.45 (m, 1H); m/z = 508.8 [M+H] ⁺
X-0001138	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.86 (app. d, J = 8.0 Hz, 2H), 7.59 (app. d, J = 8.0 Hz, 2H), 7.38 (br. s, 1H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.00 - 5.90 (m, 2H), 4.76 (t, J = 5.9 Hz, 1H), 4.68 and 4.06 (2 x br. s, 1H), 3.58 - 3.55 (m, 1H), 3.40 (app. t, J = 7.0 Hz, 1H), 3.30 (br. s, 1H), 3.25 (ddd, J = 9.9, 8.0, 4.7 Hz, 1H), 3.18 - 3.11 (m, 2H), 2.92 - 2.89 (m, 1H), 2.68 (d, J = 7.0 Hz, 2H), 2.17 (q, J = 7.2 Hz, 1H), 1.88 - 1.72 (m, 2H), 1.71 - 1.39 (m, 7H), 1.38 - 0.77 (m, 4H); m/z = 500.4 [M+H] ⁺
X-0001139	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.71 - 7.62 (m, 2H), 7.39 - 7.26 (m, 5H), 7.23 - 7.19 (m, 1H), 7.17 - 7.13 (m, 2H), 6.65 (dd, J = 16.5, 10.0 Hz, 1H), 6.01 - 5.90 (m, 2H), 4.89 (s, 2H), 3.23 (dd, J = 10.4, 7.5 Hz, 1H), 3.19 - 3.11 (m, 1H), 3.05 (dt, J = 10.1, 7.5 Hz, 1H), 2.82 (dd, J = 10.4, 6.9 Hz, 1H), 2.74 (s, 6H), 2.67 - 2.58 (m, 2H), 2.16 - 2.05 (m, 1H), 1.79 - 1.70 (m, 1H), 1.43 - 1.31 (m, 1H); m/z = 507.4 [M+H] ⁺
X-0001140	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.89 (s, 1H), 9.23 (s, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.46 (d, J = 5.7 Hz, 1H), 8.28 - 8.20 (m, 2H), 8.14 (d, J = 8.9 Hz, 1H), 8.04 - 7.93 (m, 3H), 7.81 (d, J = 5.8 Hz, 1H), 7.39 (s, 1H), 6.66 (dd, J = 16.5, 10.0 Hz, 1H), 6.03 - 5.90 (m, 2H), 3.41 - 3.24 (m, 2H), 3.17 (dt, J = 10.0, 7.6 Hz, 1H), 2.97 (dd, J = 10.4, 7.0 Hz, 1H), 2.68 (q, J = 12.9, 10.5 Hz, 2H), 2.18 (p, J = 7.2 Hz, 1H), 1.91 - 1.79 (m, 1H), 1.50 (dq, J = 12.5, 7.8 Hz, 1H).; m/z = 501.4 [M+H] ⁺
X-0001141	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.39 (t, J = 6.0 Hz, 1H), 8.12-8.10 (m, 2H), 7.89-7.88 (m, 2H), 7.81-7.72 (m, 2H), 7.58-7.56 (m, 2H), 7.36 (s, 1H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.02-5.87 (m, 2H), 4.61 (d, J = 5.8 Hz, 2H), 3.27 (dd, J = 10.2, 7.4 Hz, 1H), 3.23-3.19 (m, 1H), 3.08 (dt, J = 9.9, 7.6 Hz, 1H), 2.88 (dd, J = 10.2, 6.9 Hz, 1H), 2.74-2.61 (m, 2H), 2.17-2.11 (m, 1H), 1.84-1.77 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 532.3 [M+H] ⁺
X-0001142	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.75-7.68 (m, 2H), 7.55-7.39 (m, 2H), 7.39-7.18 (m, 6H), 6.64 (dd, J = 16.5, 10.0 Hz, 1H), 6.03-5.87 (m, 2H), 4.99-4.91 (br m, 0.6H), 4.69-4.67 (br m, 0.4H), 4.73 (s, 0.6H), 4.58 (s, 1.4H), 4.00 (s, 1.3H), 3.84-3.81 (br m, 0.7H), 3.64-3.33 (m, 4H), 3.30-3.15 (m, 2H), 3.12-3.02 (m, 1H), 2.91-2.87 (m, 1H), 2.73-2.62 (m, 2H), 2.17-2.12 (m, 1H), 1.84-1.78 (m, 1H), 1.49-1.42 (m, 1H).; m/z = 522.4 [M+H] ⁺
X-0001171	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.89 (bs, 1H), 8.61 (bs, 1H), 7.85 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 6.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.29 (s, 1H), 6.73 - 6.62 (m, 1H), 5.99 - 5.90 (m, 2H), 3.56 - 3.33 (m, 5H), 2.94 - 2.88 (m, 3H), 2.68 - 2.65 (m, 4H), 2.08 - 1.99 (m, 1H), 1.90 - 1.75 (m, 5H), 1.63 - 1.59 (m, 2H); m/z = 575.4 [M + H] ⁺
X-0001172	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.81 (bs, 1H), 8.50 (bs, 1H), 7.79 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.25 - 7.20 (m, 7H), 6.71 - 6.65 (m, 1H), 6.07 - 5.91 (m, 2H), 4.37 (t, J = 14.0 Hz, 2H), 3.43 - 3.23 (m, 2H), 3.12 - 3.08 (m, 6H), 3.04 - 2.99 (m, 2H), 2.94 - 2.69 (m, 5H), 2.01 - 1.90 (m, 3H), 1.72 - 1.66 (m, 2H); m/z = 521.4 [M + H] ⁺

X-0001253	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.73 (bs, 2H), 8.13 - 8.09 (m, 1H), 7.73 - 7.68 (m, 2H), 7.55 - 7.49 (m, 1H), 7.40 - 7.38 (m, 2H), 6.77 - 6.62 (m, 1H), 6.07 - 5.93 (m, 2H), 5.75 - 5.54 (m, 1H), 3.56 - 3.42 (m, 5H), 3.40 - 3.27 (m, 4H), 3.09 - 3.04 (m, 2H), 2.94 - 2.92 (m, 1H), 2.67 - 2.65 (m, 1H), 2.09 - 2.03 (m, 4H), 2.02 - 1.90 (m, 2H), 1.66 - 1.60 (m, 1H); m/z = 576.6 [M + H] ⁺
X-0001256	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.01 (bs, 2H), 8.03 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.23 - 7.15 (m, 5H), 6.75 - 6.62 (m, 1H), 6.07 - 5.91 (m, 2H), 3.26 - 3.12 (m, 5H), 3.10 - 3.04 (m, 5H), 2.94 - 2.83 (m, 1H), 2.81 - 2.79 (m, 1H), 2.68 - 2.66 (m, 1H), 2.40 - 2.32 (m, 2H), 2.30 - 1.92 (m, 6H), 1.69 - 1.64 (m, 1H); m/z = 522.4 [M + H] ⁺
X-0001257	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.87 (bs, 1H), 8.70 (bs, 1H), 8.04 (s, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.56 - 7.50 (m, 1H), 6.77 - 6.62 (m, 1H), 6.07 - 5.92 (m, 2H), 4.01 (s, 3H), 3.53 - 3.51 (m, 4H), 3.34 - 3.26 (m, 4H), 3.02 - 2.93 (m, 2H), 2.78 - 2.69 (m, 2H), 2.35 - 2.30 (m, 2H), 2.15 - 2.02 (m, 2H), 1.91 - 1.68 (m, 2H); m/z = 432.5 [M + H] ⁺
X-0001302	¹ H NMR (400 MHz, DMSO <i>d</i> ₆) δ 7.70 - 7.68 (m, 1H), 7.51 - 7.45 (m, 3H), 7.17 - 7.10 (m, 5H), 6.73 - 6.67 (m, 1H), 6.05 - 5.96 (m, 2H), 4.41 (bs, 1H), 3.48 - 3.20 (m, 6H merged with DMSO peak), 3.11 - 2.99 (m, 3H), 2.87 - 2.83 (m, 3H), 1.70 (bs, 2H), 1.37 - 1.20 (m, 6H), 1.02 (bs, 1H), 0.67 (bs, 1H); m/z = 546.4 [M + H] ⁺
X-0001304	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.70 (t, J = 8.2 Hz, 1H), 7.75 (d, J = 7.92 Hz, 2H), 7.63 (d, J = 7.8 Hz, 2H), 7.52 - 7.45 (m, 3H), 7.24 - 7.18 (m, 5H), 7.09 (d, J = 7.52 Hz, 2H), 6.75 - 6.68 (m, 1H), 6.06 - 5.98 (m, 2H), 4.38 - 4.30 (m, 1H), 4.18 - 4.15 (m, 1H), 4.01 (t, J = 6.76 Hz, 2H), 3.53 - 3.50 (m, 3H), 3.15 - 3.12 (m, 1H), 3.04 - 2.94 (m, 3H), 1.73 (s, 2H), 1.37 (s, 2H), 1.2 - 1.16 (m, 2H); m/z = 518.46 [M + H] ⁺
X-0001305	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (d, J = 7.88 Hz, 2H), 7.56 (d, J = 7.96 Hz, 2H), 7.29 - 7.20 (m, 5H), 6.89 - 6.81 (m, 1H), 6.20 - 6.12 (m, 2H), 4.21 - 4.17 (m, 1H), 3.95 (bs, 1H), 3.43 - 2.74 (m, 12H), 1.71 - 1.57 (m, 7H); m/z = 544.39 [M + H] ⁺
X-0001348	¹ H NMR (400 MHz, DMSO <i>d</i> ₆) δ 7.69 (d, J = 7.6 Hz, 2H), 7.52 - 7.45 (m, 3H), 7.20 - 7.08 (m, 5H), 6.73 - 6.67 (m, 1H), 6.06 - 5.96 (m, 2H), 4.45 (t, J = 6.8 Hz, 1H), 3.48 - 3.32 (m, 8H merged with DMSO peak), 3.17 - 3.09 (m, 3H), 3.01 (bs, 1H), 2.92 - 2.87 (m, 1H), 2.87-2.81 (m, 1H), 1.71 (bs, 2H), 1.33 (bs, 2H); m/z = 548.3 [M + H] ⁺
X-0001352	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 (t, J = 5.9 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.39 (s, 1H), 7.27 - 7.18 (m, 5H), 7.08 (d, J = 8.0 Hz, 2H), 6.7 (dd, J = 9.96 Hz, J = 9.96 Hz, 1H), 5.99 (dd, J = 16.5 Hz, J = 9.92 Hz, 2H), 4.40 - 4.38 (dd, J = 6.0 Hz, J = 6.2 Hz, 1H), 4.13 - 4.08 (m, 1H), 4.03 - 3.99 (m, 1H), 3.37 - 3.29 (m, 1H), 3.26 - 3.18 (m, 2H), 3.09 - 3.03 (m, 1H), 2.97 - 2.86 (m, 2H), 2.70 (d, J = 6.2 Hz, 1H), 2.17 - 2.10 (m, 1H), 1.80 - 1.78 (m, 1H), 1.48 - 1.39 (m, 1H); m/z = 536.28 [M + H] ⁺
X-0001358	¹ H NMR (400 MHz, DMSO <i>d</i> ₆) δ 7.69 (d, J = 7.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (bs, 1H), 7.16 - 7.10 (m, 5H), 6.74 - 6.66 (m, 1H), 6.05 - 5.96 (m, 2H), 4.20 - 4.14 (m, 1H), 3.47 - 3.45 (m, 1H), 3.45 - 3.18 (m, 4H), 3.12 - 3.07 (m, 2H), 3.00 - 2.99 (m, 2H), 2.91 - 2.83 (m, 2H), 1.71 - 1.70 (m, 2H), 1.55 - 1.48 (m, 2H), 1.31 - 1.00 (m, 12H); m/z = 600.4 [M + H] ⁺
X-0001359	¹ H NMR (400 MHz, DMSO <i>d</i> ₆) δ 7.70 (d, J = 8.0 Hz, 2H), 7.54 - 7.45 (m, 3H), 7.28 - 7.10 (m, 4H), 7.03 - 7.01 (m, 1H), 6.74 - 6.67 (m, 1H), 6.06 - 5.96 (m, 2H), 4.51 (bs, 1H), 4.22 - 4.11 (m, 1H), 4.05 - 3.79 (m, 3H), 3.54 - 3.48 (m, 2H), 3.30 - 3.22 (m, 1H merged with DMSO peak), 3.13 - 2.94 (m, 3H), 2.85 - 2.60 (m, 3H), 1.71 (bs, 2H), 2.55 - 1.52 (m, 2H), 1.36 - 1.0 (m, 4H); m/z = 572.2 [M + H] ⁺

X-0001360	¹ H NMR (400 MHz, DMSO d ₆) δ 7.70 - 7.68 (m, 2H), 7.57 - 7.55 (m, 2H), 7.45 (bs, 1H), 7.2 - 7.1 (m, 5H), 6.74 - 6.66 (m, 1H), 6.05 - 5.96 (m, 2H), 4.21 - 4.15 (m, 1H), 3.52 - 3.45 (m, 2H merged with DMSO peak), 3.35 - 3.00 (m, 11H), 2.92 - 2.81 (m, 2H), 1.7 - 1.55 (m, 4H), 1.33 - 1.07 (m, 6H); m/z = 602.3 [M + H] ⁺
X-0001361	¹ H NMR (400 MHz, DMSO d ₆) δ 7.72 - 7.57 (m, 2H), 7.55 - 7.48 (m, 1H), 7.45 - 7.40 (m, 2H), 7.17 - 7.07 (m, 4H), 6.74 - 6.67 (m, 1H), 6.06 - 5.96 (m, 2H), 4.46 (s, 1H), 4.37 - 4.33 (m, 1H), 4.06 - 4.03 (m, 1H), 3.73 - 3.35 (m, 5H), 3.11 - 3.02 (m, 3H), 3.00 - 2.91 (m, 3H), 2.67 - 2.65 (m, 3H), 1.32 - 1.21 (m, 2H), 1.70 (bs, 1H), 1.03 - 0.89 (m, 2H); m/z = 562.3 [M + H] ⁺
X-0001362	¹ H NMR (400 MHz, DMSO d ₆) δ 7.70 - 7.68 (m, 2H), 7.60 - 7.53 (m, 2H), 7.74 (s, 1H), 7.22 - 7.05 (m, 5H), 6.92 - 6.67 (m, 1H), 6.05 - 5.96 (m, 2H), 4.42 - 4.18 (m, 4H), 3.48 - 3.45 (m, 2H), 3.12 - 3.09 (m, 1H), 2.93 - 2.83 (m, 4H), 1.75 - 1.70 (m, 2H), 1.55 (t, J = 8.4 Hz, 3H), 1.41 - 1.31 (m, 7H), 0.84 (bs, 1H); m/z = 571.75 [M + H] ⁺
X-0001363	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.2 Hz, 1H), 7.45 (s, 2H), 7.20 - 7.06 (m, 4H), 6.74 - 6.67 (m, 1H), 6.06 - 5.96 (m, 2H), 4.45 - 4.34 (m, 2H), 4.29 - 4.26 (m, 1H), 3.96 - 3.85 (m, 2H), 3.28 (bs, 3H), 3.12 - 3.09 (m, 1H), 3.03 - 2.97 (m, 2H), 2.82 - 2.80 (m, 3H), 2.40 - 2.37 (m, 1H), 1.73 - 1.70 (m, 2H), 1.46 - 1.28 (m, 4H), 1.80 - 1.12 (m, 1H), 0.73 - 0.72 (m, 1H), 0.62 (t, J = 6.0 Hz, 2H); m/z = 559.74 [M + H] ⁺
X-0001364	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 (d, J = 8 Hz, 2H), 7.54 - 7.52 (m, 2H), 7.44 (s, 2H), 7.19 - 7.09 (m, 4H), 6.74 - 6.69 (m, 1H), 6.06 - 5.96 (m, 2H), 4.16 (q, J = 7.6 Hz, 1H), 3.35 - 3.49 (bs, 1H), 3.30 - 3.25 (m, 3H), 3.23 - 3.17 (m, 2H), 3.15 - 3.01 (m, 2H), 2.99 - 2.65 (m, 4H), 1.71 - 1.60 (m, 2H), 1.58 - 1.42 (m, 5H), 1.32 - 1.22 (m, 6H), 1.05 - 1.04 (bs, 1H); m/z = 586.3 [M + H] ⁺
X-0001365	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 (d, J = 8 Hz, 2H), 7.56 - 7.52 (m, Hz, 2H), 7.45 - 7.44 (m, 1H), 7.20 - 7.09 (m, 5H), 6.74 - 6.67 (m, 1H), 6.06 - 5.96 (m, 2H), 4.18 (q, J = 7.6 Hz, 1H), 3.36 - 3.50 (m, 3H), 3.35 - 2.65 (m, 12H), 2.48 - 1.59 (m, 5H), 1.57 - 1.21 (m, 3H); m/z = 588.4 [M + H] ⁺
X-0001393	¹ H NMR (400 MHz, DMSO d ₆) δ 7.70 (t, J = 8.0 Hz, 2H), 7.53 - 7.44 (m, 3H), 7.19 - 7.04 (m, 5H), 6.70 - 6.79 (m, 1H), 6.05 - 5.96 (m, 2H), 4.44 (s, 1H), 3.94 - 3.86 (m, 1H), 3.80 - 3.71 (m, 2H), 3.71 - 3.61 (m, 2H), 3.07 - 3.08 (m, 3H), 3.01 - 2.83 (m, 5H), 1.70 (bs, 3H), 1.33 (bs, 3H), 1.10 - 1.0 (m, 1H); m/z = 570.72 [M + H] ⁺
X-0001394	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 - 7.65 (m, 2H), 7.53 (d, J = 7.6 Hz, 1H), 7.47 - 7.44 (m, 2H), 7.17 - 7.06 (m, 4H), 6.73 - 6.66 (m, 1H), 6.05 - 5.95 (m, 2H), 4.51 - 4.49 (m, 1H), 3.98 - 3.93 (m, 1H), 3.82 - 3.68 (m, 1H), 3.52 - 3.48 (m, 3H), 3.35 - 3.25 (m, 3H), 3.10 - 3.07 (m, 1H), 3.00 - 2.98 (m, 1H), 2.92 - 2.84 (m, 2H), 1.89 - 1.84 (m, 2H), 1.70 (bs, 1H), 1.60 - 1.50 (m, 1H), 1.31 - 1.21 (m, 3H), 0.80 (bs, 1H); m/z = 581.69 [M + H] ⁺
X-0001396	¹ H NMR (400 MHz, DMSO d ₆) δ 7.65 - 7.62 (m, 4H), 7.41 - 7.35 (m, 4H), 6.72 - 6.65 (m, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.04 - 5.95 (m, 2H), 5.03 (s, 2H), 3.86 - 3.79 (m, 1H), 3.47 (bs, 1H), 3.25 (s, 1H), 3.10 - 3.06 (m, 1H), 3.00 - 2.96 (m, 1H), 2.81 - 2.75 (m, 1H), 1.67 (bs, 2H), 1.29 - 1.21 (m, 2H), 1.03 (d, J = 6.4 Hz, 6H); m/z = 589.1 [M + H] ⁺
X-0001423	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 (d, J = 8.0 Hz, 1H), 7.56 - 7.44 (m, 4H), 7.20 - 7.10 (m, 5H), 6.74 - 6.67 (m, 1H), 6.05 - 5.97 (m, 2H), 3.85 (t, J = 7.6 Hz, 1H), 3.51 - 3.50 (m, 1H), 3.26 - 3.21 (m, 3H), 3.12 - 2.99 (m, 2H), 2.85 - 2.80 (m, 2H), 1.91 (bs, 2H), 1.74 - 1.70 (m, 8H), 1.56 - 1.53 (m, 6H), 1.34 (bs, 2H); m/z = 612.4 [M + H] ⁺

X-0001424	¹ H NMR (400 MHz, DMSO d ₆) δ 7.81 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.45 - 7.43 (m, 1H), 7.20 - 7.12 (m, 5H), 6.74 - 6.67 (m, 1H), 6.05 - 5.97 (m, 2H), 4.13 (t, J = 6.4 Hz, 1H), 3.68 (bs, 1H), 3.49 (bs, 1H), 3.13 - 3.09 (m, 1H), 3.03 - 2.98 (m, 2H), 2.91 - 2.77 (m, 3H), 1.72 - 1.59 (m, 15H), 1.32 - 1.21 (m, 4H); m/z = 612.4 [M + H] ⁺
X-0001425	¹ H NMR (400 MHz, DMSO d ₆) δ 7.68 (d, J = 7.2 Hz, 2H), 7.52 - 7.49 (m, 3H), 7.19 - 7.08 (m, 5H), 5.81 (s, 1H), 5.72 - 5.71 (m, 1H), 4.45 - 4.34 (m, 1H), 3.38 - 3.23 (m, 6H), 3.17 - 3.01 (m, 6H), 2.92 - 2.87 (m, 2H), 2.76 - 2.74 (m, 1H), 1.97 - 1.96 (m, 3H), 1.71 (m, 2H), 1.32 - 1.30 (m, 2H); m/z = 562.4 [M + H] ⁺
X-0001426	¹ H NMR (400 MHz, DMSO d ₆ , major rotamer) δ 7.69 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 3H), 7.28 (bs, 1H), 7.19 - 7.08 (m, 5H), 6.59 - 6.54 (m, 1H), 6.41 - 6.37 (m, 1H), 4.45 (bs, 1H), 3.48 - 3.14 (m, 8H, merged with DMSO peak), 3.16 - 3.00 (m, 5H), 2.92 - 2.87 (m, 1H), 2.80 - 2.77 (m, 1H), 1.85 (bs, 3H), 1.70 (bs, 2H), 1.32 (bs, 2H); m/z = 562.3 [M + H] ⁺
X-0001427	¹ H NMR (400 MHz, DMSO d ₆) δ 7.80 - 7.68 (m, 2H), 7.61 - 7.51 (m, 1H), 7.49 - 7.47 (m, 2H), 7.21 - 7.18 (m, 2H), 7.08 - 7.03 (m, 2H), 6.56 - 6.54 (m, 1H), 6.55 (d, J = 10 Hz, 1H), 5.98 (d, J = 10 Hz, 1H), 5.09 (bs, 1H), 4.12 - 3.98 (m, 1H), 3.90 - 3.80 (m, 1H), 3.79 - 3.70 (m, 1H), 3.69 - 3.63 (m, 1H), 3.58 - 3.40 (m, 2H), 3.30 - 3.28 (m, 1H), 3.25 - 3.11 (m, 2H), 3.10 - 2.90 (m, 2H), 2.72 - 2.62 (m, 1H), 2.50 (s, 1H), 1.81 (bs, 2H), 1.50 - 1.32 (m, 3H), 1.30 - 1.25 (m, 2H), 0.98 - 0.80 (m, 2H); m/z = 557.72 [M + H] ⁺
X-0001428	¹ H NMR (400 MHz, DMSO d ₆) δ 7.67 - 7.61 (m, 4H), 7.45 - 7.42 (m, 3H), 7.30 (d, J = 8.8 Hz, 2H), 6.72 - 6.06 (m, 1H), 6.04 - 5.96 (m, 2H), 4.99 (s, 2H), 3.43 (s, 4H), 3.18 (s, 4H), 3.09 - 3.05 (m, 1H), 2.98 - 2.94 (m, 2H), 2.82 - 2.76 (m, 2H), 1.65 (bs, 2H), 1.21 (bs, 2H); m/z = 616.67 [M + H] ⁺
X-0001430	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.6 Hz, 2H), 7.45 - 7.44 (m, 1H), 7.20 - 7.10 (m, 5H), 6.74 - 6.67 (m, 1H), 6.06 - 5.96 (m, 2H), 3.81 - 3.73 (m, 2H), 3.59 - 3.49 (m, 1H), 3.26 - 3.23 (m, 2H), 3.19 - 2.98 (m, 2H), 2.89 - 2.65 (m, 2H), 1.72 - 1.70 (m, 2H), 1.34 - 1.30 (m, 2H), 0.87 - 0.86 (m, 6H); m/z 520.3 [M + H] ⁺
X-0001432	¹ H NMR (400 MHz, DMSO d ₆) δ 7.66 - 7.62 (m, 4H), 7.50 (d, J = 8.0 Hz, 2H), 7.45 - 7.42 (m, 1H), 7.25 - 7.23 (m, 2H), 6.72 - 6.65 (m, 1H), 6.04 - 5.96 (m, 2H), 4.96 (s, 2H), 3.66 - 3.44 (m, 2H), 3.32 - 3.25 (m, 1H), 3.22 (s, 4H), 3.10 - 3.05 (m, 1H), 2.98 - 2.94 (m, 1H), 2.81 - 2.74 (m, 1H), 1.75 - 1.65 (m, 2H), 1.45 (s, 2H), 1.32 (s, 3H), 1.22 (d, J = 7.6 Hz, 2H); m/z = 615.3 [M + H] ⁺
X-0001433	¹ H NMR (400 MHz, DMSO) δ = 8.47 (s, 1H), 8.08 - 8.06 (d, J = 8.8 Hz, 2H), 7.85 - 7.82 (m, 1H), 7.71 - 7.69 (d, J = 8.4 Hz, 1H), 7.48 - 7.46 (d, J = 8.4 Hz, 1H), 6.74 - 6.68 (m, 1H), 6.06 - 5.98 (m, 2H), 5.91 (s, 2H), 3.57 (bs, 1H), 3.33 - 3.31 (m, 3H), 3.16 - 3.13 (m, 2H), 3.06 - 3.00 (m, 4H), 2.86 - 2.79 (m, 2H), 1.73 - 1.69 (m, 2H), 1.42 - 1.37 (m, 2H); m/z 600.3 [M + H] ⁺
X-0001434	¹ H NMR (400 MHz, CDCl ₃) δ 8.69 (s, 1H), 7.87 - 7.85 (d, J = 8.8 Hz, 1H), 7.85 - 7.61 - 7.59 (d, J = 8 Hz, 2H), 7.51 - 7.46 (d, 1H), 7.44 - 7.25 (m, 2H), 6.46 - 6.40 (m, 1H), 6.17 - 6.15 (m, 1H), 5.89 - 5.87 (m, 1H), 5.70 (m, 2H), 5.12 (bs, 1H), 3.44 (s, 3H), 3.25 - 3.21 (m, 5H), 2.91 - 1.91 (m, 1H), 1.32 - 1.25 (m, 1H), 0.83 (m, 1H); m/z 600.2 [M + H] ⁺
X-0001436	¹ H NMR (400 MHz, DMSO d ₆) δ 8.56 (t, J = 5.2 Hz, 1H), 7.72 (d, 7.6 Hz, 2H), 7.62 - 7.60 (d, J = 6.8 Hz, 2H), 7.64 (m, 1H), 7.21 - 7.14 (m, 7H), 6.92 - 6.87 (bs, 3H), 6.71 (q, 10 Hz, 1H), 6.06 - 5.97 (m, 2H), 4.29 - 4.23 (m, 1H), 4.10 - 4.05 (m, 1H), 3.98 - 3.95 (m, 1H), 3.23 - 3.51 (bs, 1H), 3.10 - 2.95 (m, 3H), 2.94 - 2.91 (m, 1H), 2.85 - 2.65 (m, 1H), 1.96 (bs, 1H), 1.71 (bs, 2H), 1.37-1.35 (m, 2H); m/z = 568.2 [M + H] ⁺

X-0001439	¹ H NMR (400 MHz, DMSO d ₆) δ 7.70 (d, J = 7.2 Hz, 2H), 7.63 (s, 1H), 7.54 - 7.53 (m, 2H), 7.46 (m, 1H), 7.18 - 7.12 (m, 4H), 6.74 - 6.68 (m, 1H), 6.06 - 5.96 (m, 2H), 4.58 - 4.52 (m, 1H), 3.51 (bs, 5H), 3.09 (bs, 1H), 2.98 (bs, 1H), 2.90 - 2.81 (m, 2H), 1.70 (s, 4H), 1.32 - 1.23 (m, 4H), 1.21 (bs, 1H), 0.83 - 0.82 (m, 1H); m/z = 581 [M + H] ⁺
X-0001440	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.46 (bs, 1H), 7.18 - 7.07 (m, 4H), 6.74 - 6.68 (m, 1H), 6.06 - 5.98 (m, 2H), 4.34 - 4.10 (m, 4H), 4.01 (t, J = 7.6 Hz, 1H), 3.47 (bs, 1H), 3.31 (bs, 2H), 3.09 (bs, 1H), 2.99 - 2.92 (m, 2H), 2.81 (bs, 2H), 1.70 (bs, 2H), 1.31 (bs, 2H); m/z = 553.64 [M + H] ⁺
X-0001443	¹ H NMR (400 MHz, DMSO d ₆) δ 8.13 (s, 1H), 7.69 (d, 6.4 Hz, 2H), 7.61-7.54 (m, 2H), 7.46 - 7.39 (m, 1H), 7.19 - 7.13 (m, 7H), 6.92 (bs, 3H), 6.74 - 6.67 (m, 1H), 6.06 - 6.01 (m, 2H), 3.83 (bs, 1H), 3.50 (bs, 1H), 3.32 - 3.00 (m, 5H), 2.91 - 2.81 (m, 3H), 1.70 (bs, 2H), 1.35 (bs, 2H); m/z = 582.4 [M + H] ⁺
X-0001468	¹ H NMR (400 MHz, DMSO d ₆) δ 8.76 (s, 1H), 8.71 (d, J = 7.6 Hz, 2H), 7.58 - 7.53 (m, 4H), 7.46 - 7.46 (m, 1H), 7.35 (d, J = 7.2 Hz, 2H), 6.73 - 6.67 (m, 1H), 6.06 - 6.96 (m, 2H), 4.03 (t, J = 7.6 Hz, 1H), 3.86 - 3.78 (m, 2H), 3.48 - 3.35 (m, 3H), 3.09 - 3.05 (m, 2H), 3.00 - 2.82 (m, 2H), 1.69 - 1.59 (m, 2H), 1.27-1.21 (m, 2H); m/z = 628.1 [M + H] ⁺
X-0001470	¹ H NMR (400 MHz, DMSO d ₆) δ 7.72 - 7.08 (m, 2H), 7.62 - 7.38 (m, 4H), 7.35 (d J = 8.0 Hz, 26.74 - 6.71 (m, 1H), 6.06 - 5.97 (m, 2H), 4.51 - 4.50 (s, 24.26 - 4.23 (m, 1H), 3.96 - 3.84 (m, 2H), 3.08 - 3.01 (m, 4H), 2.83 - 2.65 (m, 2H), 2.31 - 2.24 (m, 2H), 1.70 (bs, 2H), 1.29 - 1.27 (m, 1H), 1.01 - 0.98 (m, 3H), 0.82 (s, 1H); m/z = 644.3 [M + H] ⁺
X-0001472	¹ H NMR (400 MHz, DMSO d ₆) δ 7.63 (d, J = 8.0 Hz, 3H), 7.50 (s, 1H), 7.41 - 7.35 (m, 3H), 6.60 (d, J = 7.6 Hz, 1H), 5.80 (s, 1H), 7.40 (s, 1H), 5.03 (s, 2H), 3.86 - 3.81 (m, 1H), 3.44 (bs, 1H), 3.30 (s, 2H), 3.06 - 2.97 (m, 2H), 2.79 - 2.68 (m, 1H), 1.96 (s, 3H), 1.68 (bs, 2H), 1.29 (bs, 2H), 1.21 (s, 1H), 1.04 - 0.98 (m, 5H), 0.83 (bs, 1H); m/z = 602.68 [M + H] ⁺
X-0001473	¹ H NMR (400 MHz, DMSO d ₆) δ 7.63 (t, J = 8.4 Hz, 4H), 7.51 (d, J = 8.0 Hz, 2H), 7.44 (bs, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.72 - 6.66 (m, 1H), 6.06 - 5.96 (m, 2H), 4.97 (s, 2H), 3.44 (s, 1H), 3.22 - 3.18 (m, 2H), 3.08 - 3.05 (m, 1H), 2.98 - 2.95 (m, 2H), 2.77 - 2.65 (m, 3H), 1.64 (bs, 2H), 1.21 (bs, 3H), 0.83 (bs, 1H); m/z = 574.63 [M + H] ⁺
X-0001494	¹ H NMR (400 MHz, DMSO d ₆) δ 8.79 (bs, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.55 - 7.47 (m, 4H), 7.36 - 7.30 (m, 2H), 6.75 - 6.70 (m, 1H), 6.06 - 5.96 (m, 2H), 4.63 (bs, 1H), 4.63 - 4.26 (m, 2H), 3.45 - 3.34 (m, 2H), 3.39 - 3.10 (m, 5H), 3.04 - 2.99 (m, 2H), 2.97 - 2.68 (m, 8H), 1.70 (d, J = 4.6 Hz, 2H), 1.28 - 1.22 (m, 2H), m/z = 629.2 [M + H] ⁺
X-0001495	¹ H NMR (400 MHz, DMSO d ₆) δ 8.73 (s, 1H), 8.30 (t, J = 5.6 Hz, 1H), 7.75 - 7.65 (m, 4H), 7.45 - 7.37 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 6.54 (t, J = 6.0 Hz, 1H), 5.52 (d, J = 6.0 Hz, 2H), 4.35 (m, 2H), 4.12 (s, 2H), 3.73 (s, 1H), 3.64 (m, 2H), 3.21 - 2.84 (m, 4H), 1.83 (bs, 2H), 1.59 (bs, 2H); m/z = 593.7 [M + H] ⁺
X-0001520	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 (d, J = 7.2 Hz, 2H), 7.64 (s, 1H), 7.55 - 7.44 (m, 3H), 7.35 - 7.30 (m, 2H), 6.62 - 6.50 (m, 1H), 6.06 - 5.98 (m, 2H), 4.59 (s, 1H), 3.83 (s, 1H), 3.73 (s, 4H), 3.26 - 3.05 (m, 7H), 3.05 - 2.79 (m, 6H), 2.65 (s, 3H), 2.16 (s, 2H), 1.68 (s, 2H), 1.20 (s, 5H); m/z = 664.2 [M + H] ⁺
X-0001521	¹ H NMR (400 MHz, DMSO d ₆) δ 7.70 (d, J = 16.8 Hz, 2H), 7.55 - 7.47 (m, 4H), 7.36 - 7.30 (m, 2H), 6.75 - 6.70 (m, 1H), 6.06 - 5.96 (m, 2H), 4.63 (bs, 1H), 4.63 - 4.26 (m, 2H), 3.56 - 3.35 (m, 4H), 3.04 - 2.96 (m, 5H), 2.77 (s, 2H), 1.97 (d, J = 10.2 Hz, 3H), 1.71 (m, 5H), 1.49 (m, 2H), 3.32 - 3.45 (m, 3H); m/z = 664.2 [M + H] ⁺

X-0001526	¹ H NMR (400 MHz, DMSO d ₆) δ 7.71 (d, J = 7.2 Hz, 2H), 7.54 (d, J = 6.4 Hz, 4H), 7.44 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 2H), 6.73 - 6.65 (m, 1H), 6.05 - 5.95 (m, 2H), 4.60 (d, J = 6.8 Hz, 1H), 3.53 (s, 2H), 3.47 (s, 4H), 3.08 - 2.97 (m, 4H), 2.79 (bs, 2H), 3.04 - 2.96 (m, 5H), 2.77 (s, 1H), 1.69 (bs, 5H), 1.47 (m, 1H), 1.25 (s, 3H); m/z = 650.2 [M + H] ⁺
X-0001527	¹ H NMR (400 MHz, DMSO d ₆) δ 7.38 (d, J = 8.4 Hz, 2H), 7.64 - 7.45 (m, 4H), 7.39 - 7.33 (m, 3H), 6.74 - 6.68 (m, 1H), 6.06 - 5.97 (m, 2H), 4.61 (bs, 1H), 4.44 (s, 1H), 3.46 (s, 5H), 3.12 - 2.98 (m, 6H), 2.82 (s, 2H), 1.70 (m, 5H), 1.27 (s, 1H), 0.95 - 0.70 (m, 5H); m/z = 644.1 [M + H] ⁺
X-0001529	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.70 (d, J = 7.6 Hz, 2H), 7.45 (d, J = 7.6 Hz, 3H), 7.05 (t, J = 8.0 Hz, 2H), 6.73 - 6.66 (m, 1H), 6.05 - 5.96 (m, 2H), 4.48 (t, J = 7.6 Hz, 1H), 3.48 - 3.37 (m, 4H), 3.31 - 3.09 (m, 3H), 3.08 - 2.80 (m, 6H), 1.71 - 1.69 (m, 2H), 1.30 - 1.20 (m, 4H); m/z = 602.2 [M + H] ⁺
X-0001545	¹ H NMR (400 MHz, DMSO d ₆) δ 7.76 - 7.67 (m, 1H), 7.65 - 7.45 (m, 4H), 7.40 - 7.31 (m, 3H), 6.74 - 6.66 (m, 1H), 6.06 - 5.96 (m, 2H), 4.50 (bs, 1H), 4.30 (d, J = 8.4 Hz, 1H), 4.03 (m, 1H), 3.85 - 3.58 (m, 2H), 3.42 - 3.03 (m, 4H), 2.82 - 2.65 (m, 4H), 1.86 - 1.71 (s, 4H), 1.48 (s, 1H), 1.30 - 1.22 (m, 3H); m/z = 642.2 [M + H] ⁺
X-0001546	¹ H NMR (400 MHz, DMSO d ₆) δ 7.74 - 7.64 (m, 3H), 7.59 - 7.52 (m, 3H), 7.42 - 7.32 (m, 3H), 6.75 - 6.66 (m, 1H), 6.07 - 5.96 (m, 2H), 4.60 - 4.52 (m, 1H), 4.43 - 4.26 (s, 1H), 3.87 (s, 2H), 3.58 (s, 1H), 3.55 - 3.49 (m, 2H), 3.20 - 3.81 (m, 4H), 2.78 (s, 1H), 1.70 (s, 2H), 1.30 - 1.16 (m, 2H), 1.14 - 1.02 (m, 2H), 0.91 (bs, 2H); m/z = 644.2 [M + H] ⁺
X-0001548	¹ H NMR (400 MHz, DMSO-d ₆) 7.76 (d, J = 8.4 Hz, 2H), 7.54 - 7.45 (m, 3H), 7.20 - 7.17 (m, 3H), 7.03 - 7.01 (m, 2H), 6.87 (s, 1H), 6.74 - 6.49 (m, 1H), 6.06 - 5.96 (m, 2H), 3.57 (bs, 9H), 3.19 - 3.06 (m, 3H), 2.87 - 2.80 (m, 1H), 1.75 (bs, 2H), 1.42 - 1.32 (m, 2H); m/z = 546.3 [M + H] ⁺
X-0001554	¹ H NMR (400 MHz, DMSO d ₆) δ 8.72 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 5.52 (s, 1H), 5.42 (s, 1H), 4.58 (d, J = 14.8 Hz, 1H), 4.36 - 4.29 (m, 3H), 3.63 (s, 4H), 3.54 (s, 1H), 3.10 (s, 1H), 1.74 (s, 2H), 1.38 (bs, 2H), 1.22 (s, 1H); m/z = 558.2 [M + H] ⁺
X-0001575	¹ H NMR (400 MHz, CDCl ₃) δ 7.76 (d, J = 7.6 Hz, 2H), 7.49-7.41 (m, 4H), 7.18 (d, J = 7.6, 2H), 6.52-6.45 (m, 1H), 6.26 (d, J = 16.4 Hz, 1H), 5.99 (d, J = 9.6 Hz, 1H), 4.48-4.42(m, 1H), 4.07-4.03 (m, 1H), 3.71 - 3.65 (m, 3H), 3.55 - 3.42 (m, 4H), 3.32-3.31 (m, 2H), 3.24-3.04 (m, 5H), 2.81-2.07 (m, 2 H); m/z = 652.3[M + H] ⁺
X-0001576	¹ H NMR (400 MHz, DMSO d ₆) δ 7.77 (d, J = 8 Hz, 2H), 7.56-7.49 (m, 4H), 7.35 (d, J = 7.6 Hz, 2H), 6.72-6.66 (m, 1H), 6.03-5.96 (m, 2H), 4.50-4.59 (m, 1H), 3.69-3.55 (m, 2 H), 3.51-3.39 (m, 5H), 3.34-3.21 (m, 4H), 3.07-2.82 (m, 4H), 2.81-2.65 (m, 2H); m/z = 651.1 [M + H] ⁺
X-0001579	¹ H NMR (400 MHz, DMSO d ₆) δ 8.70 (t, J = 5.6Hz, 1H), 7.94 - 7.82 (m, 5H), 7.64 - 7.54 (m, 4H), 7.49 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.66 - 6.55 (m, 1H), 5.99 - 5.84 (m, 2H), 4.31 (d, J = 5.6 Hz, 2H), 4.14 (d, J = 6.0 Hz, 2H), 3.59 (s, 2H); m/z = 553.1 [M + H] ⁺
X-0001582	¹ H NMR (400 MHz, DMSO d ₆) δ 7.71 - 7.69 (d, J = 8.0 Hz, 2H), 7.55 - 7.51 (m, 5H), 7.36 - 7.34 (d, J = 8.0 Hz, 2H), 5.82 - 5.73 (m, 2H), 4.57 - 4.53 (t, J = 8 Hz, 1H), 3.52 - 3.19 (m, 10H), 3.08 - 3.00 (m, 3H), 2.79 - 2.72 (m, 1H), 1.98 (s, 3H), 1.74 - 1.63 (m, 2H), 1.36 - 1.21 (m, 2H); m/z 630.2 [M + H] ⁺
X-0001583	¹ H NMR (400 MHz, DMSO d ₆) δ 7.70 - 7.68 (d, J = 8.0 Hz, 2H), 7.55 - 7.51 (m, 5H), 7.36 - 7.34 (d, J = 8.0 Hz, 2H), 5.81 - 5.72 (m, 2H), 4.5 (bs, 1H), 3.52 - 3.15 (m, 10H), 3.05 - 2.97 (m, 3H), 2.75 - 2.65 (m, 1H), 1.97 (s, 3H), 1.70 (bs, 2H), 1.32 - 1.22 (m, 2H); m/z 630.2 [M + H] ⁺

X-0001618	¹ H NMR (400 MHz, DMSO d ₆) δ 7.69 - 7.57 (m, 2H), 7.55 - 7.40 (m, 3H), 6.74 - 6.67 (m, 5H), 6.59 - 6.39 (m, 1H), 6.05 - 5.96 (m, 2H), 4.52 - 4.31 (m, 2H), 4.06 - 4.03 (m, 3H), 3.73 - 3.40 (m, 4H), 3.29 - 3.18 (m, 3H), 3.18 - 2.61 (m, 7H), 1.70 (bs, 2H), 1.32 - 1.21 (m, 3H), 0.97 - 0.89 (m, 2H); m/z = 573.7 [M + H] ⁺
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[0420] Compounds were evaluated using cell-based proliferation assays, using a mouse embryonic fibroblast (MEF) cell line panel generally following the procedure laid out in Example I-10 above. Results of the evaluation are shown in Tables II-3 through II-6 below, as IC₅₀ values.

Table II-3. Evaluation of selected compounds using cell-based proliferation assays (n=1; IC₅₀ units are μM).

Compound	IC50 HRas WT	IC50 Myr-KRas4b G12D/C185S	IC50 KRas4b Q61R	IC50 KRas4b G12D	IC50 KRas4b G12V	IC50 Myr-KRas4b G12V/C185S	IC50 NRas WT
X-0001554		40		40			
X-0001437	13	14.8		13	4.01	12	
X-0001430	13	12.3		7.1	1.99	10	
X-0001478	9.9			5.1	2.72	8.6	6.3
X-0001477	10			3.9	2.25	10	7.9
X-0001474	11			4.5	2.44	10	7.8
X-0001470	13			4.7	2.37	13	10
X-0001473	11			4	2.55	12	8.3
X-0001472	40			2	0.84	40	51
X-0001471	12			3.9	2.54	11	8
X-0001468	10			69	3.95	10	7.2
X-0001443	7.5			5.9	3.32	8	
X-0001440	2.3			6.5	1.09	11	
X-0001439	15			3.8	1.26	13	
X-0001436	9.3			7.7	3.22	11	
X-0001434	6.9			6.1	2.29	8.1	
X-0001426	40			16	1.63	40	
X-0001424	8.9			5.4	2.13	6.7	
X-0001423	6			4.6	1.95	6.3	
X-0001422	51			19	4.87	39	
X-0001396	14			5.5	0.55	13	4.4
X-0001395	14			5	0.77	11	3.8
X-0001369	13			4.4	0.74	10	4.4
X-0001359	5.3			3.8	0.58	8	2.6
X-0001307	15	15.4		8.3	3.01	14	
X-0001252		16.3		11.1			
X-0001251		100		100			
X-0001232		100		100			
X-0001225		16.1		2.2			
X-0001224		39.3		9.6			
X-0001223		22.5		5.9			
X-0001222		10.3		4.4			
X-0001221		43		28			
X-0001220		102.1		26.9			
X-0001219		14.2		3			
X-0001218		44		10.1			
X-0001217		100		71.4			

Compound	IC50 HRas WT	IC50 Myr- KRas4b G12D/C185S	IC50 KRas4b Q61R	IC50 KRas4b G12D	IC50 KRas4b G12V	IC50 Myr- KRas4b G12V/C185S	IC50 NRas WT
X-0001216		13.6		6.5			
X-0001215		45.3		17.4			
X-0001214		17.7		7			
X-0001213		37.2		7.3			
X-0001212		24.5		4.3			
X-0001211		15.6		4.1			
X-0001210		25.9		7.7			
X-0001209		33.4		14.6			
X-0001208		12.5		4.1			
X-0001207		96.3		26			
X-0001206		28.1		16.9			
X-0001205		61		28.1			
X-0001200		21.2		11.4	9.4		
X-0001184		48.5		28.6	27.1		
X-0001169		100		100	83.8		
X-0001168		22.8		22.8	13.5		
X-0001159		8		5.9	4.8		
X-0001158		11.1		8	6.9		
X-0001157		102.7		81.1	57.2		
X-0001156		28		14.6	15		
X-0001155		100		100	100		
X-0001152		13.2		7.1	6.3		
X-0001151		12.6		8.4	7		
X-0001150		11.1		5.6	7.1		
X-0001147		100		100	100		
X-0001146		24.6		22.2	21		
X-0001144		36.8		20.9	12.8		
X-0001143		35.8		25.9	21		
X-0001142		81.8		34	21.6		
X-0001141		15.8		8.5	6.7		
X-0001140		22.7		17.1	19		
X-0001139		25.2		8.2	7.8		
X-0001138		144.9		32.6	21.4		
X-0001137		108.6		44.9	27.9		
X-0001136		24.6		9.5	8		
X-0001135		13.7		6	3.1		
X-0001134		100		85.8	52.4		
X-0001133		21.5		3.8	2		
X-0001132		24.6		4.5	3.7		
X-0001131		15.4		3.5	2		
X-0001130		26.9		12.7	8.6		
X-0001129		1.6		1.6	1.4		
X-0001128		15		10.5	8.3		
X-0001127		11.2		7.9	5.6		
X-0001126		33.6		27.4	21.1		
X-0001125		11.3		10.4	8.4		
X-0001124		11		7.5	6.1		
X-0001123		21.6		10.2	8.9		
X-0001114		87		63.5	38.5		
X-0001113		15.9		14	9.9		
X-0001111		43.4		30.8	19.2		
X-0001107		64		39.3	23.3		
X-0001106		16.7		16.3	11.7		
X-0001105		38.8		27.9	18.4		
X-0001103		100		100	100		

Compound	IC50 HRas WT	IC50 Myr- KRas4b G12D/C185S	IC50 KRas4b Q61R	IC50 KRas4b G12D	IC50 KRas4b G12V	IC50 Myr- KRas4b G12V/C185S	IC50 NRas WT
X-0001102		100		100	100		
X-0001099		31.3		20.7	13.4		
X-0001098		94		75	41.7		
X-0001095		11.4		8.2	5.6		
X-0001094		82.5		62.7	36.5		
X-0001081	100	100	100	100	100		
X-0001072	100	100	76.6	83.2	42.6		
X-0001059	100	84.6	62.8	54.2	33.3		
X-0001058	11.2	11.2	9	7.1	4.3		
X-0001057	100	100	118	89.8	45.9		
X-0001056	100	120.2	101.2	85.6	53.8		
X-0001055	142.4	60.8	43.6	41	22		
X-0001054	72.3	24.1	19.8	19	11.7		
X-0001053	12	10.5	8.5	6.6	4.7		
X-0001052	27.4	21.7	15.6	13.5	9.9		
X-0001051	47.1	24.2	16.7	15.2	10.8		
X-0001050	47.6	25.2	18.1	15.2	10.7		
X-0001049	23.7	16.7	12.4	12.1	8.9		
X-0001048	21.9	15	10.3	10	6.9		
X-0001047	15.8	14.4	13.3	9.6	6.1		
X-0001046	30.3	16.3	13.5	10.6	7		
X-0001045	30.8	15	14.4	10	6.3		
X-0001044	35.5	12.7	10.4	10.5	7.3		
X-0001043	100	76.9	56.1	49.6	36.1		
X-0001042	100	100	100	100	116.1		
X-0001041	100	121.2	79.2	90.8	68.6		
X-0001040	100	54.8	42.8	28	37		
X-0001036	100	46.9	36.5	45.9	37.6		
X-0001034	100	56.1	40.2	43	32.4		
X-0001032	146.6	52.8	39.6	46.3	33.8		
X-0001025	78.4	15	10.9	13.3	9.6		
X-0001022	100	52.5	36.4	45.1	32		
X-0001021	108.5	49.2	35.9	38	30.5		
X-0001020	123	26.4	19.3	24.3	15.7		
X-0001019	100	100	100	100	100		
X-0001014	100	100	103.1	100	82.7		
X-0001013	133.8	68.9	33.4	46.4	30.7		
X-0001010	100	100	100	100	104.1		
X-0001008	104.3	50.6	29.6	72.6	30.2		
X-0001006	100	100	100	100	100		
X-0001002	100	100	100	100	100		
X-0000999	100	84.8	45.1	67.4	39.2		
X-0000997	32.6	16.6	9.7	10.2	5.5		
X-0000996	61	25.2	15.9	17.5	9.5		
X-0000995	32.5	23	13.5	16.6	10.3		
X-0000994	19.5	14.6	9.5	10.5	6.4		
X-0000993	21.9	22	19	20.2	12.3		
X-0000992	30.9	30	26.8	29.3	18.5		
X-0000991	42.5	24	12	14.6	7.7		
X-0000990	39.6	25.9	14.8	17.6	9.6		
X-0000989	100	100	89.9	104.2	51.8		
X-0000988	100	100	124.7	131.9	66.4		
X-0000987	100	50.4	27.2	32.6	18		
X-0000986	21	23.7	17.3	20.6	10.9		
X-0000985	100	129.9	66.8	75.1	34.1		

Compound	IC50 HRas WT	IC50 Myr- KRas4b G12D/C185S	IC50 KRas4b Q61R	IC50 KRas4b G12D	IC50 KRas4b G12V	IC50 Myr- KRas4b G12V/C185S	IC50 NRas WT
X-0000984	108.1	93.6	51.9	76.4	42.1		
X-0000983	16.7	13.7	7	7.1	2.8		
X-0000982	100	100	98.6	123.6	67.3		
X-0000981	25.1	19.1	12.3	14.9	8.8		
X-0000980	100	72	38.8	47.4	20.4		
X-0000979	17.6	16.7	7.5	8.2	4.1		
X-0000973	28.4	10	8.3	9.9	4.3		
X-0000972	40.5	25.5	20.7	22.4	15.5		
X-0000949	30.5	41.7	25	28.1	18.1		
X-0000946	100	100	100	100	100		
X-0000944	100	100	20.6	105.2	21.1		
X-0000941	100	100	93.5	100	94.9		
X-0000839	77.3	32	18	23.1	17.3		
X-0000838	19.8	26	15.7	15.5	10.2		
X-0000837	44.3	27.8	20.2	22.1	12.4		
X-0000833	47.2	15.8	14.8	18.1	14.4		
X-0000831	84.6	22	12	20.3	10.3		
X-0000830	46.8	24.7	10.5	18.6	9.5		
X-0000829	100	60.5	36	45	25.1		
X-0000827	47.1	15	8.9	13.1	7.4		
X-0000824	100	100	98.6	122.5	80.2		
X-0000823	106	67.2	46.5	75.8	37.6		
X-0000822	100	35.8	20.2	26.7	16.6		
X-0000821	100	100	100	100	100		
X-0000820	100	111.1	57.4	76.7	35.3		
X-0000819	32.4	12.1	8	9	5.6		
X-0000818	100	100	65	91.9	30.7		
X-0000817	100	100	100	100	100		
X-0000816	100	66.8	33.7	37.7	17.4		
X-0000815	54.2	56.2	40.6	43	35.7		
X-0000814	43.6	41	30.6	39	28.2		
X-0000813	47.3	38.6	25	34.6	21.1		
X-0000811	19.8	20	20	19.6	19.6		
X-0000810	91.8	89.1	49.6	71.5	44		
X-0000809	118.4	48.4	24.7	31.8	24.7		
X-0000808	25.6	17.7	11.9	23.4	16.6		
X-0000807	42.1	25.4	18.7	26.8	21.5		
X-0000806	68.2	44.2	21.4	22	9.4		
X-0000805	10.8	10	6.6	8	4		
X-0000804	18	10.8	6.9	7.9	5.3		
X-0000801	100	100	95.6	122.6	62.6		
X-0000798	100	100	100	100	100		
X-0000797	100	100	100	100	100		
X-0000794	100	100	100	100	100		
X-0000793	100	100	100	100	100		
X-0000781	31	25	19.8	21.4	11.3		
X-0000780	42.1	50.8	33.4	30.1	11		
I-0249	100	100	100	100	100		
I-0001289	41.8	58.4	44.7	50.3	32.3		

Table II-4. Evaluation of selected compounds using cell-based proliferation assays. SD = standard deviation, ($\pm$); n = number of replicates; IC50 is average in μ M.

	IC50 HRas WT			IC50 Myr-KRas4b G12V/C118S			IC50 KRas4b Q61R			IC50 KRas4b G12D			KRas4b G12V		
Cmpd.	Avg	SD	n	Avg	SD	n	Avg	SD	n	Avg	SD	n	Avg	SD	n
X-0001432	10	1.5	2							1.8	0.16	2	0.485	0.431	2
X-0001431	12	1.5	2							2.2	0.11	2	0.565	0.53	2
X-0001425	49	13	2							10	2.7	2	3.56	4.43	2
X-0001327	28	--	1							10	10	2	4.23	1.68	2
X-0001326	15	--	1							6.6	8	2	4.19	2.4	2
X-0001272	16	0.46	3							6.3	4.4	4	1.86	2.22	4
X-0000966	25	3.6	4	18	0.241	4	11.3	1.55	4	11	3.5	4	7.7	0.411	4
X-0000965	100	26	4	37.5	5.16	4	22.1	2.85	4	23	7	4	13.8	1.33	4
X-0000964	83	24	2	57.5	2.41	2	32.9	8.37	2	25	13	2	14.9	3.62	2
X-0000963	26	5	2	16.4	0.136	2	10.4	1.52	2	8.8	1.8	2	7.94	1.37	2
X-0000962	> 100	0	2	> 100	0	2	> 100	0	2	> 100	0	2	> 100	0	2
X-0000961	71	17	2	107	6.18	2	64.7	3.99	2	84	4.6	2	62.9	6.8	2
X-0000960	29	5.9	2	26.3	1.29	2	18.9	1.97	2	22	1.7	2	17	3.36	2
X-0000959	31	12	2	39.6	0.904	2	24.8	3.68	2	29	4.9	2	20.9	5.92	2
X-0000958	36	12	2	42.7	0.435	2	31.1	2.09	2	36	0.84	2	23.5	4.24	2
X-0000957	24	3.6	2	20.5	2.01	2	9.83	5.7	2	6.9	6.9	2	3.38	2.9	2
X-0000956	> 100	0	2	67.2	8.38	2	43.1	5.25	2	37	20	2	23.4	3.88	2
X-0000955	58	4	2	33.4	0.0954	2	21.2	3.78	2	16	11	2	12.1	2.99	2
X-0000954	> 100	0	2	> 100	0	2	> 100	0	2	> 100	0	2	> 100	0	2
X-0000953	99	10	2	23.8	1.04	2	14.5	3.16	2	12	7.3	2	8.78	3.65	2
X-0000952	56	2.7	2	22.3	0.52	2	14.1	1.71	2	10	6.7	2	8.2	2.62	2
X-0000951	77	19	2	24.1	0.407	2	16.5	3.16	2	17	2.4	2	12.1	2.29	2
X-0000803	67	1.1	2	21.9	1.15	2	8.79	0.399	2	11	1.4	2	6.61	1.78	2
X-0000802	96	8.5	2	33.6	2.06	2	15.8	0.832	2	18	3.8	2	10.4	3.31	2
X-0000778	130	6.2	2	36.2	0.636	2	20.4	1.77	2	23	0.44	2	15.2	0.219	2
X-0000777	100	0	2	60	2.65	2	30.7	1.28	2	30	2.6	2	17.8	3.76	2
X-0000776	100	0	2	92.1	1.52	2	50.3	3.2	2	63	6.4	2	30.9	2.53	2
X-0000775	100	0	2	100	0	2	100	0	2	100	0	2	100	0	2
X-0000774	100	0	2	100	0	2	100	0	2	100	0	2	100	0	2
X-0000763	100	0	2	115	21.3	2	90.4	13.5	2	100	0	2	108	11	2
X-0000758	77	7.1	2	26.2	0.113	2	12.3	1.05	2	16	1.8	2	12.5	0.792	2
X-0000755	100	5.6	2	100	0	2	100	0	2	100	0	2	119	27.2	2
X-0000754	37	4.6	2	20.2	1.55	2	10.5	0.99	2	11	0.57	2	7.21	1.09	2
X-0000753	23	4.3	2	11.1	0.679	2	5.3	0.099	2	8.8	0.69	2	3.82	0.205	2
X-0000752	100	0	2	53.9	5.69	2	28.9	5.37	2	31	3.3	2	18.8	5.55	2
X-0000751	100	0	2	69.3	22.9	2	44	9.26	2	46	0.11	2	25.6	5.2	2
X-0000750	110	10	2	60.4	41.5	2	46.2	12.3	2	45	3	2	24	9.48	2
X-0000749	55	1.2	2	14.2	12.3	2	12.8	1.46	2	12	0.99	2	7.18	3.9	2
I-0250	23	13	3	25.6	12.4	3	20.7	7.02	3	20	7.5	3	14.6	6.74	3
I-0176	42	6.3	4	18.8	2.12	5	10.6	2.3	4	13	1.5	5	9.37	1.63	5
I-0175	100	12	5	32.2	4.89	6	19	3.86	5	21	1.8	6	13.1	2.57	6

Table II-5. Evaluation of selected compounds using cell-based proliferation assays. SD = standard deviation, ($\pm$); n = number of replicates; IC50 is average in μ M.

Cmpd.	IC50 Myr-KRas4b G12D/C118S (μM)			IC50 Myr-KRas4b G12V/C185S (μM)			IC50 NRas WT (μM)		
	Avg	SD	n	Avg	SD	n	Avg	SD	n
X-0001433				7.9	--	1			
X-0001429				23	--	1			
X-0001427				9.3	--	1			
X-0001432	8.25	0.877	2	8.8	1.2	2	6.4	--	1
X-0001431	9.85	0.544	2	11	2.8	2	7.7	--	1
X-0001425	45.4	7.7	2	40	0.28	2	40	--	1
X-0001396	6.23	--	1	13	--	1	4.4	--	1
X-0001395	4.94	--	1	11	--	1	3.8	--	1
X-0001369	5.21	--	1	10	--	1	4.4	--	1
X-0001359	3.63	--	1	8	--	1	2.6	--	1
X-0001327	22.7	6.95	2						
X-0001326	21	7.53	2						
X-0001272	13.4	3.64	4				6.3	1.6	2
X-0001478	8.13	--	1						
X-0001477	10.2	--	1						
X-0001474	9.43	--	1						
X-0001470	13	--	1						
X-0001478	11.1	--	1	8.6	--	1	6.3	--	1
X-0001477	40	--	1	10	--	1	7.9	--	1
X-0001474	14	--	1	10	--	1	7.8	--	1
X-0001470	9.83	--	1	13	--	1	10	--	1
X-0001473	7.4	--	1	12	--	1	8.3	--	1
X-0001472	9.7	--	1	40	--	1	51	--	1
X-0001471	11.7	--	1	11	--	1	8	--	1
X-0001468	11.2	--	1	10	--	1	7.2	--	1
X-0001443	8.74	--	1	8	--	1			
X-0001440	40	--	1	11	--	1			
X-0001439	6.8	--	1	13	--	1			
X-0001436	6.2	--	1	11	--	1			
X-0001434	48.8	--	1	8.1	--	1			

Table II-6. Evaluation of selected compounds using cell-based proliferation assays. SD = standard deviation, (±); n = number of replicates; IC50 is average in μM.

	IC50 HRAS WT (μM)			KRas4b G12D (μM)			KRas4b G12V (μM) (n=1)	Myr-KRas4b G12D/C185S (μM)		
	Avg	SD	n	Avg	SD	n		Avg	SD	n
X-0001433	8.5	--	1	7.1	1.7	2	1.87	9.65	1.34	2
X-0001429	22	--	1	15	--	1	4.03	28.9		1
X-0001427	13	--	1	5.7	2.1	2	1.35	10.9		1

[0421] A heat map comparing cell-based proliferation data across selected compounds is presented in FIG. 9, with a table summarizing the heat map data in FIG. 10.

[0422] Selected compounds were also evaluated for protein labeling using MALDI, generally following the procedure laid out in Example I-9 above. Results are presented in Table II-7 below.

Table II-7. Labeling of K-Ras4b(1-188) GDP as evaluated by MALDI (20:1, 24 h).
SD = standard deviation, ($\pm$); n = number of replicates

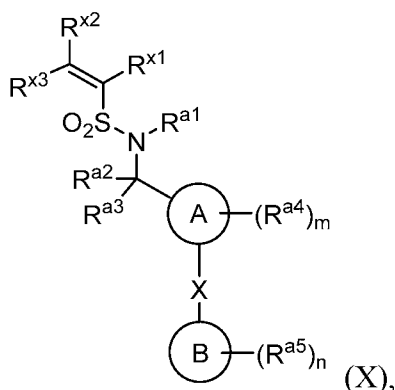
Compound	(%)	SD	n	Compound	(%)	SD	n
X-0001437	4	2	3	X-0001124	5	1	3
X-0001430	23	2	3	X-0001123	52	1	3
X-0001429	19	2	3	X-0001121	81	5	3
X-0001427	7	1	3	X-0001119	78	1	3
X-0001327	43	10	3	X-0001115	48	1	3
X-0001326	55	1	3	X-0001067	56	2	2
X-0001291	4	1	3	X-0001064	64	1	3
X-0001289	27	3	3	X-0001059	73	1	3
X-0001288	26	4	3	X-0001058	4	1	3
X-0001283	5	1	3	X-0001056	70	5	3
X-0001282	18	4	3	X-0001055	72	3	3
X-0001281	18	2	3	X-0001054	43	5	3
X-0001280	2	1	3	X-0001053	3	1	3
X-0001279	55	2	3	X-0001052	2	1	3
X-0001278	2	0	3	X-0001051	30	1	3
X-0001277	40	2	3	X-0001050	28	3	3
X-0001276	34	6	3	X-0001049	6	1	3
X-0001275	0	0	3	X-0001048	9	6	3
X-0001274	28	1	3	X-0001046	6	1	3
X-0001273	2	2	3	X-0001045	8	1	3
X-0001225	20	1	3	X-0001044	50	3	3
X-0001224	16	3	3	X-0001043	68	2	3
X-0001223	4	1	3	X-0001042	54	1	3
X-0001222	7	1	3	X-0000997	46	4	3
X-0001221	16	5	3	X-0000996	43	3	3
X-0001220	65	9	3	X-0000995	11	3	3
X-0001219	10	7	3	X-0000994	3	1	3
X-0001218	3	1	3	X-0000992	6	3	2
X-0001217	71	3	3	X-0000991	38	3	3
X-0001216	9	2	3	X-0000990	75	2	3
X-0001215	34	5	3	X-0000989	71	1	3
X-0001214	22	3	3	X-0000988	65	4	3
X-0001213	67	1	3	X-0000987	59	1	3
X-0001212	58	2	3	X-0000985	56	3	3
X-0001211	15	1	3	X-0000984	54	3	3
X-0001210	39	4	3	X-0000982	54	1	3
X-0001209	42	3	3	X-0000980	74	2	3
X-0001208	11	2	3	X-0000979	8	1	3
X-0001207	64	8	3	X-0000966	1	2	6
X-0001205	56	3	3	X-0000965	76	3	6
X-0001171	58	10	3	X-0000964	74	0	3
X-0001142	69	2	3	X-0000963	9	2	3

X-0001139	64	2	3	X-0000962	80	4	3
X-0001138	61	1	3	X-0000961	36	4	3
X-0001137	70	4	3	X-0000960	96	2	3
X-0001136	44	2	3	X-0000959	87	7	3
X-0001135	5	1	3	X-0000958	84	2	3
X-0001134	3	0	3	X-0000957	64	3	3
X-0001133	26	4	2	X-0000956	67	5	3
X-0001132	52	6	8	X-0000955	74	4	3
X-0001131	7	2	3	X-0000954	82	3	3
X-0001130	49	2	3	X-0000953	61	3	3
X-0001127	12	3	3	X-0000952	59	2	3
X-0001126	1	1	3	X-0000951	46	1	3

CLAIMS

What is claimed is:

1. A compound of Formula (X):



or a pharmaceutically acceptable salt thereof, wherein:

R^{x1} , R^{x2} , and R^{x3} are independently hydrogen, -CN, or alkyl; or R^{x2} and R^{x3} together form alkenyl; or R^{x1} and R^{x2} together with the carbon atoms to which they are attached form heteroaryl, heterocycloalkenyl, or cycloalkenyl; or R^{a1} and R^{x2} together with the atoms to which they are attached form heterocycloalkenyl; wherein each alkyl, alkenyl, heteroaryl, heterocycloalkenyl, and cycloalkenyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo and -OR^{x4}, wherein each R^{x4} is independently H, alkyl, or haloalkyl;

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, -C(S)-, -C(O)-, or -C(R^{a6})₂-, wherein when A is piperidinyl and B is phenyl, X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, -C(S)-, or -C(R^{a6})₂-;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and =O;

R^{a1} is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when R^{a1} is alkyl or haloalkyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(O)-$;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$, wherein when A is phenyl, R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, cycloalkyl, heterocycloalkyl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, and $-SO_2R^{a10}$; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-NO_2$, $-CN$, $-SO_2NH_2$, $-NR^{a7}R^{a8}$, $-OR^{a9}$, $=O$, $-SR^{a47}$, and $-SO_2R^{a10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or, when X is $-\text{C}(\text{O})-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a spirocycle with ring A, wherein the spirocycle is unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{\text{a48}}\text{R}^{\text{a49}}$, $-\text{NR}^{\text{a11}}\text{R}^{\text{a12}}$, $-\text{OR}^{\text{a13}}$, $-\text{SO}_2\text{R}^{\text{a14}}$, $=\text{O}$, and $-\text{SR}^{\text{a15}}$,

wherein each alkenyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a16}}$, $=\text{O}$, $-\text{NR}^{\text{a17}}\text{R}^{\text{a18}}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a50}}\text{R}^{\text{a51}}$, $-\text{SR}^{\text{a52}}$, $-\text{SO}_2\text{R}^{\text{a53}}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a19}}$, $=\text{O}$, $-\text{NR}^{\text{a20}}\text{R}^{\text{a21}}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a54}}\text{R}^{\text{a55}}$, $-\text{SR}^{\text{a56}}$, $-\text{SO}_2\text{R}^{\text{a57}}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a35} , R^{a54} , and R^{a55} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $=\text{O}$, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{\text{a22}}\text{R}^{\text{a23}}$, $-\text{OR}^{\text{a24}}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting

of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, $=\text{O}$, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, $-\text{NR}^{\text{a}38}\text{C}(\text{O})\text{R}^{\text{a}39}$, $-\text{OR}^{\text{a}40}$, and $\text{R}^{\text{a}59}$, wherein each $\text{R}^{\text{a}59}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each $\text{R}^{\text{a}59}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $=\text{O}$, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

each $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, $\text{R}^{\text{a}24}$, $\text{R}^{\text{a}36}$, $\text{R}^{\text{a}37}$, $\text{R}^{\text{a}38}$, and $\text{R}^{\text{a}39}$ is independently hydrogen, alkyl, or haloalkyl;

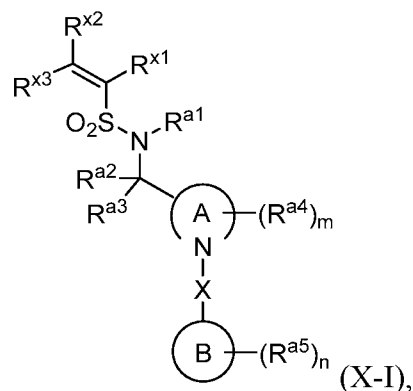
wherein each alkyl or haloalkyl or $\text{R}^{\text{a}22}$ and $\text{R}^{\text{a}23}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

each $\text{R}^{\text{a}40}$ is independently hydrogen, alkyl, haloalkyl, aryl, or heteroaryl, wherein each aryl or heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl;

m is an integer from 0 to 13; and

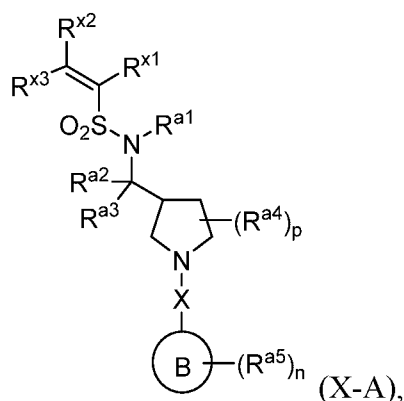
n is an integer from 0 to 11.

2. The compound of claim 1, wherein the compound is of Formula (X-I):



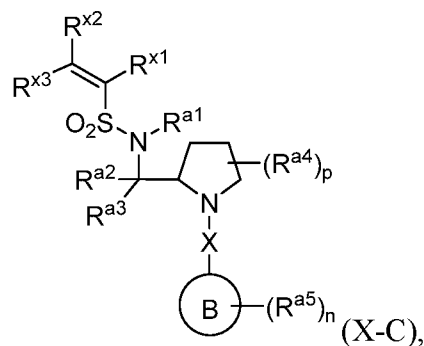
or a pharmaceutically acceptable salt thereof, wherein A is 4- to 10-membered heterocycloalkyl, and B , X , R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , m , and n are as defined for Formula (X).

3. The compound of claim 1 or 2, wherein the compound is of Formula (X-A):



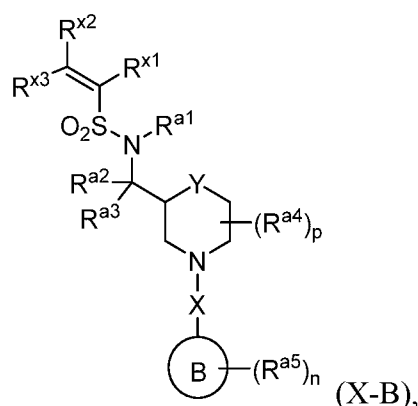
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B , X , R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , and n are as defined for Formula (X).

4. The compound of claim 1 or 2, wherein the compound is of Formula (X-C):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , and n are as defined for Formula (X).

5. The compound of claim 1 or 2, wherein the compound is of Formula (X-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-C(R^{a45})_2-$, $-S(O)_r-$, $-O-$, or $-N(R^{a45})-$, wherein each R^{a45} is independently hydrogen or R^{a4} ;

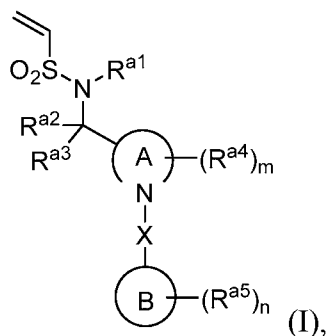
X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, $-C(O)-$, or $-C(R^{a6})_2-$, wherein when Y is $-CH_2-$ and B is phenyl, X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, $-C(S)-$, or $-C(R^{a6})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

and B, R^{x1} , R^{x2} , R^{x3} , R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} , R^{a46} , and n are as defined for Formula (X).

6. The compound of claim 1, wherein the compound is of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$, wherein when A is piperidiny and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$;

each $\text{R}^{\text{a}6}$ is independently hydrogen, halo, alkyl, or haloalkyl;

$\text{R}^{\text{a}46}$ is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $=\text{O}$;

$\text{R}^{\text{a}1}$ is hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl, wherein when $\text{R}^{\text{a}1}$ is alkyl or haloalkyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{O})-$;

$\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}3}$ are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each $\text{R}^{\text{a}4}$ is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{\text{a}7}\text{R}^{\text{a}8}$, $-\text{OR}^{\text{a}9}$, $=\text{O}$, $-\text{SR}^{\text{a}47}$, and $-\text{SO}_2\text{R}^{\text{a}10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each $\text{R}^{\text{a}7}$, $\text{R}^{\text{a}8}$, $\text{R}^{\text{a}9}$, $\text{R}^{\text{a}10}$, and $\text{R}^{\text{a}47}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, or haloheterocycloalkyl;

or two to four $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or $\text{R}^{\text{a}2}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or $\text{R}^{\text{a}3}$ and one $\text{R}^{\text{a}4}$, together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

or, when X is $-S(O)-$, $-S(O)_2-$, $-S(O)NR^{a46}-$, or $-C(S)-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl, unsubstituted or substituted with one or more halo;

each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-NO_2$, $-CN$, $-SO_2NR^{a48}R^{a49}$, $-NR^{a11}R^{a12}$, $-OR^{a13}$, $-SO_2R^{a14}$, $=O$, and $-SR^{a15}$, wherein each cycloalkyl, aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a16}$, $=O$, $-NR^{a17}R^{a18}$, $-CN$, $-SF_5$, $-SO_2NR^{a50}R^{a51}$, $-SR^{a52}$, $-SO_2R^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-OR^{a19}$, $=O$, $-NR^{a20}R^{a21}$, $-CN$, $-SF_5$, $-SO_2NR^{a54}R^{a55}$, $-SR^{a56}$, $-SO_2R^{a57}$, and R^{a58} , wherein each R^{a58} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{a11} , R^{a12} , R^{a13} , R^{a14} , R^{a15} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , R^{a48} , R^{a49} , R^{a50} , R^{a51} , R^{a52} , R^{a53} , R^{a54} , R^{a55} , R^{a56} , and R^{a57} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, or haloalkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a11} , R^{a12} , R^{a13} , R^{a16} , R^{a17} , R^{a18} , R^{a19} , R^{a20} , R^{a21} , and R^{a35} , and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo,

=O, -CN, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, -NR^{a22}R^{a23}, -OR^{a24}, and -SF₅;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, -CN, -SF₅, =O, -NR^{a36}R^{a37}, -NR^{a38}C(O)R^{a39}, -OR^{a40}, and R^{a59}, wherein each R^{a59} is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each R^{a59} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, -NH₂, -SF₅, -OH, -O-alkyl, -O-haloalkyl, halo, alkyl, and haloalkyl;

each R^{a22}, R^{a23}, R^{a24}, R^{a36}, R^{a37}, R^{a38}, R^{a39}, and R^{a40} is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

n is an integer from 0 to 11.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein:

A is 4- to 8-membered heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, -C(S)-, -C(O)-, or -C(R^{a6})₂-, wherein when A is piperidiny and B is phenyl, X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, -C(S)-, or -C(R^{a6})₂-;

each R^{a6} is independently hydrogen, halo, alkyl, or haloalkyl;

R^{a46} is hydrogen or alkyl, wherein the alkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and =O;

R^{a1} is hydrogen, alkyl, or cycloalkyl, wherein when R^{a1} is alkyl, X is -S(O)-, -S(O)₂-, -S(O)NR^{a46}-, -C(S)-, or -C(O)-;

R^{a2} and R^{a3} are independently selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, heterocycloalkyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{a7}\text{R}^{a8}$, $-\text{OR}^{a9}$, and $-\text{SO}_2\text{R}^{a10}$, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently unsubstituted or substituted with one or more halo;

each R^{a4} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NH}_2$, $-\text{NR}^{a7}\text{R}^{a8}$, $-\text{OR}^{a9}$, $=\text{O}$, $-\text{SR}^{a47}$, and $-\text{SO}_2\text{R}^{a10}$, wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more halo;

each R^{a7} , R^{a8} , R^{a9} , R^{a10} , and R^{a47} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

or two to four R^{a4} , together with the atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

or R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or R^{a3} and one R^{a4} , together with the atoms to which they are attached, form a cycloalkyl or heterocycloalkyl;

or R^{a1} and R^{a2} , together with the atoms to which they are attached, form a heterocycloalkyl;

or R^{a2} and R^{a3} , together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl;

or, when X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{a46}-$, or $-\text{C}(\text{S})-$, R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a heterocycloalkyl;

each R^{a5} is independently selected from the group consisting of halo, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkynyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_2\text{NR}^{a48}\text{R}^{a49}$, $-\text{NR}^{a11}\text{R}^{a12}$, $-\text{OR}^{a13}$, $-\text{SO}_2\text{R}^{a14}$, $=\text{O}$, and $-\text{SR}^{a15}$,

wherein each cycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{a16}$, $=\text{O}$, $-\text{NR}^{a17}\text{R}^{a18}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{a50}\text{R}^{a51}$, $-\text{SR}^{a52}$, $-\text{SO}_2\text{R}^{a53}$, and R^{a35} , wherein each R^{a35} is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each aryl, heteroaryl, and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, $-\text{SF}_5$, and $\text{R}^{\text{a}35}$, wherein $\text{R}^{\text{a}35}$ is independently alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, $-\text{OR}^{\text{a}19}$, =O, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, $-\text{CN}$, $-\text{SF}_5$, $-\text{SO}_2\text{NR}^{\text{a}54}\text{R}^{\text{a}55}$, $-\text{SR}^{\text{a}56}$, $-\text{SO}_2\text{R}^{\text{a}57}$, and $\text{R}^{\text{a}58}$, wherein each $\text{R}^{\text{a}58}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each $\text{R}^{\text{a}14}$, $\text{R}^{\text{a}15}$, $\text{R}^{\text{a}16}$, $\text{R}^{\text{a}17}$, $\text{R}^{\text{a}18}$, $\text{R}^{\text{a}48}$, $\text{R}^{\text{a}49}$, $\text{R}^{\text{a}50}$, $\text{R}^{\text{a}51}$, $\text{R}^{\text{a}52}$, $\text{R}^{\text{a}53}$, $\text{R}^{\text{a}54}$, $\text{R}^{\text{a}55}$, $\text{R}^{\text{a}56}$, and $\text{R}^{\text{a}57}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl;

each $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, and $\text{R}^{\text{a}21}$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

each $\text{R}^{\text{a}13}$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or alkynyl;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}11}$, $\text{R}^{\text{a}12}$, $\text{R}^{\text{a}13}$, $\text{R}^{\text{a}19}$, $\text{R}^{\text{a}20}$, $\text{R}^{\text{a}21}$, and $\text{R}^{\text{a}35}$, and each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of $\text{R}^{\text{a}58}$ is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, $-\text{CN}$, aryl, heteroaryl, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, $-\text{NR}^{\text{a}22}\text{R}^{\text{a}23}$, $-\text{OR}^{\text{a}24}$, and $-\text{SF}_5$;

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, $-\text{CN}$, $-\text{SF}_5$, =O, $-\text{NR}^{\text{a}36}\text{R}^{\text{a}37}$, $-\text{NR}^{\text{a}38}\text{C}(\text{O})\text{R}^{\text{a}39}$, $-\text{OR}^{\text{a}40}$, and $\text{R}^{\text{a}59}$, wherein each $\text{R}^{\text{a}59}$ is independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, and wherein each $\text{R}^{\text{a}59}$ is independently unsubstituted or substituted with one or more substituents independently

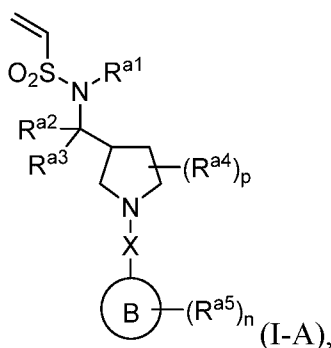
selected from the group consisting of =O, $-\text{NH}_2$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-alkyl}$, $-\text{O-haloalkyl}$, halo, alkyl, and haloalkyl

each $\text{R}^{\text{a}22}$, $\text{R}^{\text{a}23}$, $\text{R}^{\text{a}24}$, $\text{R}^{\text{a}36}$, $\text{R}^{\text{a}37}$, $\text{R}^{\text{a}38}$, $\text{R}^{\text{a}39}$, and $\text{R}^{\text{a}40}$ is independently hydrogen, alkyl, or haloalkyl;

m is an integer from 0 to 13; and

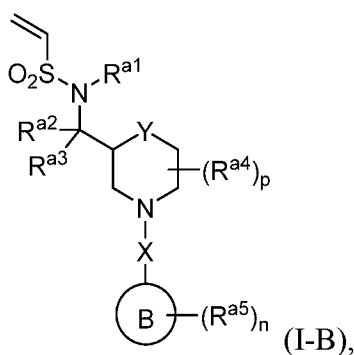
n is an integer from 0 to 11.

8. The compound of claim 6 or 7, wherein the compound is of Formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7, and B, X, $\text{R}^{\text{a}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}4}$, $\text{R}^{\text{a}5}$, and n are as defined for Formula (I).

9. The compound of claim 6 or 7, wherein the compound is of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{C}(\text{R}^{\text{a}45})_2-$, $-\text{S}(\text{O})_r-$, $-\text{O}-$, or $-\text{N}(\text{R}^{\text{a}45})-$, wherein each $\text{R}^{\text{a}45}$ is independently hydrogen or $\text{R}^{\text{a}4}$,

X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$, wherein when Y is $-\text{CH}_2-$ and B is phenyl, X is $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})\text{NR}^{\text{a}46}-$, $-\text{C}(\text{S})-$, or $-\text{C}(\text{R}^{\text{a}6})_2-$;

r is 0, 1, or 2;

p is an integer from 0 to 7;

and B, R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6}, R^{a46}, and n are as defined for Formula (I).

10. The compound of claim 5 or 9, or a pharmaceutically acceptable salt thereof, wherein Y is -CH₂-.
11. The compound of any one of claims 1, 2, 6, or 7, or a pharmaceutically acceptable salt thereof, wherein A is 5- or 6-membered heterocycloalkyl.
12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is 5- or 6-membered heteroaryl.
13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein B is heteroaryl, cycloalkyl, or heterocycloalkyl.
14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein B is 5- or 6-membered heterocycloalkyl or 5- or 6-membered heteroaryl, and wherein the heterocycloalkyl or heteroaryl comprises one to three ring heteroatoms independently selected from the group consisting of O, N, and S.
15. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein B is 9- or 10-membered bicyclic heteroaryl comprising one to three ring heteroatoms independently selected from the group consisting of O, N, and S.
16. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein B is (C₉-C₁₀)bicyclic aryl.
17. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein B is (C₅-C₁₀)cycloalkyl.
18. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein B is phenyl.
19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is:

unsubstituted or substituted alkyl, wherein the alkyl is branched;

-NR^{a11}R^{a12}, wherein at least one of R^{a11} and R^{a12} is not hydrogen; or

(C₁-C₂)alkyl substituted with one or more substituents independently selected from the group consisting of =O, -NR^{a20}R^{a21}, and R^{a58}, wherein R^{a58} is heterocycloalkyl and at least one of R^{a20} and R^{a21} is not hydrogen.

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein both R^{a11} and R^{a12} are not hydrogen.
21. The compound of claim 19 or 20, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{a11} and R^{a12} is substituted alkyl.
22. The compound of any one of claims 19 to 21, or a pharmaceutically acceptable salt thereof, wherein R^{a11} is alkyl substituted with aryl, wherein the aryl is unsubstituted or substituted.
23. The compound of any one of claims 19 to 22, or a pharmaceutically acceptable salt thereof, wherein R^{a12} is alkyl substituted with one or more substituents independently selected from the group consisting of =O, -NR^{a22}R^{a23}, -OR^{a24}, and heterocycloalkyl, wherein the heterocycloalkyl is independently unsubstituted or substituted.
24. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is C₁-alkyl substituted with -NR^{a20}R^{a21}, wherein at least one of R^{a20} and R^{a21} is not hydrogen.
25. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is C₂-alkyl substituted with =O and -NR^{a20}R^{a21}, wherein at least one of R^{a20} and R^{a21} is not hydrogen.
26. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is substituted alkyl, wherein the alkyl is isopropyl, wherein the isopropyl is substituted with two or more substituents independently selected from the group consisting of =O, -NR^{a20}R^{a21}, -OR^{a19}, and R^{a58},

wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkynyl, -CN, and =O, and wherein each alkyl is independently unsubstituted or substituted with one or more halo.

w is 0 or 1;

R^{a20} and R^{a21} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl,

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, =O, $-NR^{a22}R^{a23}$, $-OR^{a24}$, alkyl, aryl, and heteroaryl;

wherein each alkyl is independently unsubstituted or substituted with one or more halo; and each aryl and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, and haloalkyl.

31. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein one or more R^{a5} is alkyl, wherein the alkyl is isopropyl, wherein each terminal methyl of the isopropyl is independently substituted with one or more substituents independently selected from the group consisting of =O, $-NR^{a20}R^{a21}$, $-OR^{a19}$, and R^{a58} ;

wherein each aryl, heteroaryl, cycloalkyl, and heterocycloalkyl of R^{a58} is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, $-CN$, alkynyl, halo, and alkyl, and wherein each alkyl is independently unsubstituted or substituted with one or more halo.

32. The compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein one terminal methyl of the isopropyl is substituted with phenyl, wherein the phenyl is unsubstituted or substituted with one to three substituents independently selected from the group consisting of halo and haloalkyl.

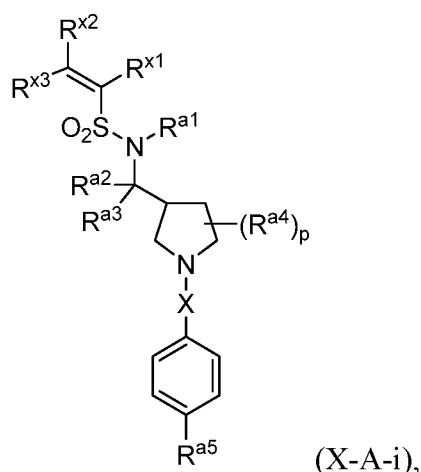
33. The compound of claim 31 or 32, or a pharmaceutically acceptable salt thereof, wherein one terminal methyl of the isopropyl is substituted with =O and $-NR^{a20}R^{a21}$ or =O and R^{a58} , wherein R^{a58} is heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted.

34. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein one or more R^{a5} are independently selected from the group consisting of halo;

$-O-(C_1-C_4)$ alkyl unsubstituted or substituted with one or more fluoro or chloro; phenyl;

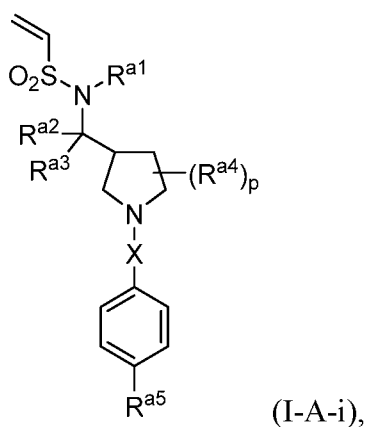
heteroaryl; heterocycloalkyl; $-\text{SO}_2\text{NH}_2$; $-\text{NO}_2$; $-\text{CN}$; $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ unsubstituted or substituted with one or more fluoro or chloro; and $(\text{C}_1\text{-C}_6)\text{alkyl}$ unsubstituted or substituted with one or more substituents independently selected from the group consisting of $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_6)\text{heterocycloalkyl}$, aryl, heteroaryl, halo, $-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_4)\text{alkyl}$, $=\text{O}$, $-\text{NR}^{\text{a}20}\text{R}^{\text{a}21}$, and $-\text{CN}$.

35. The compound of any one of claims 1 to 3 or 19 to 34, wherein the compound is of Formula (X-A-i):



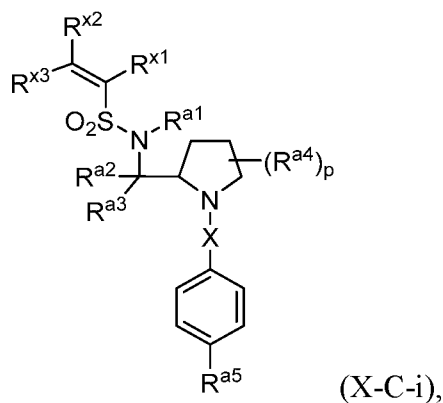
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X, $\text{R}^{\text{x}1}$, $\text{R}^{\text{x}2}$, $\text{R}^{\text{x}3}$, $\text{R}^{\text{a}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}4}$, and $\text{R}^{\text{a}5}$ are as defined in Formula (X).

36. The compound of any one of claims 6 to 8 or 19 to 34, wherein the compound is of Formula (I-A-i):



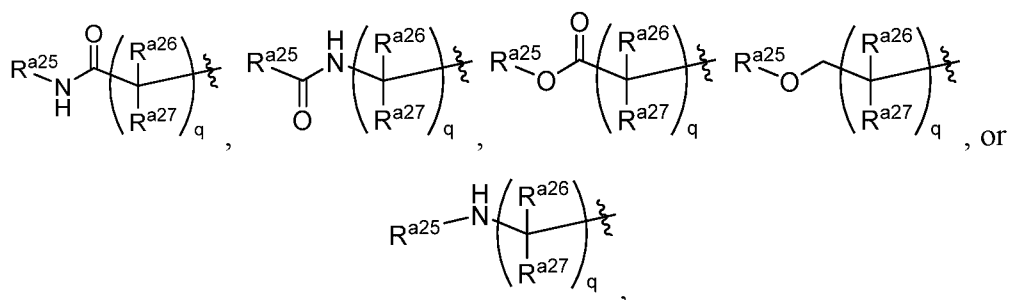
or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7.

37. The compound of any one of claims 1, 2, 4, or 19 to 34, wherein the compound is of Formula (X-C-i):



or a pharmaceutically acceptable salt thereof, wherein p is an integer from 0 to 7 and X, R^{x1}, R^{x2}, R^{x3}, R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are as defined in Formula (X).

38. The compound of any one of claims 1 to 18 or 34 to 37, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{a5} is:



wherein:

R^{a25} is hydrogen, alkyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl;

wherein the alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, =O, -OR^{a28}, -SF₅, and -NR^{a29}R^{a30},

wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of alkyl, haloalkyl, alkynyl, halo, -SF₅, =O, -OR^{a31}, -NR^{a41}R^{a42}, -NR^{a43}C(O)R^{a44}, cycloalkyl, and heterocycloalkyl, wherein each cycloalkyl and heterocycloalkyl is independently unsubstituted or substituted with one or more substituents

independently selected from the group consisting of =O, halo, –OH, and –SF₅;

each R^{a26} and R^{a27} is independently hydrogen, halo, or alkyl;

wherein each alkyl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, –OR^{a32}, and –NR^{a33}R^{a34},

wherein each cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, haloalkyl, alkyl, –OH, =O, and –SF₅;

or one R^{a26} and one R^{a27} attached to the same atom, together with the atom to which they are attached, form a cycloalkyl or heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with one or more halo;

each R^{a28}, R^{a29}, R^{a30}, R^{a31}, R^{a32}, R^{a33}, R^{a34}, R^{a41}, R^{a42}, R^{a43}, and R^{a44} is independently hydrogen, alkyl, or haloalkyl;

and q is 1 or 2.

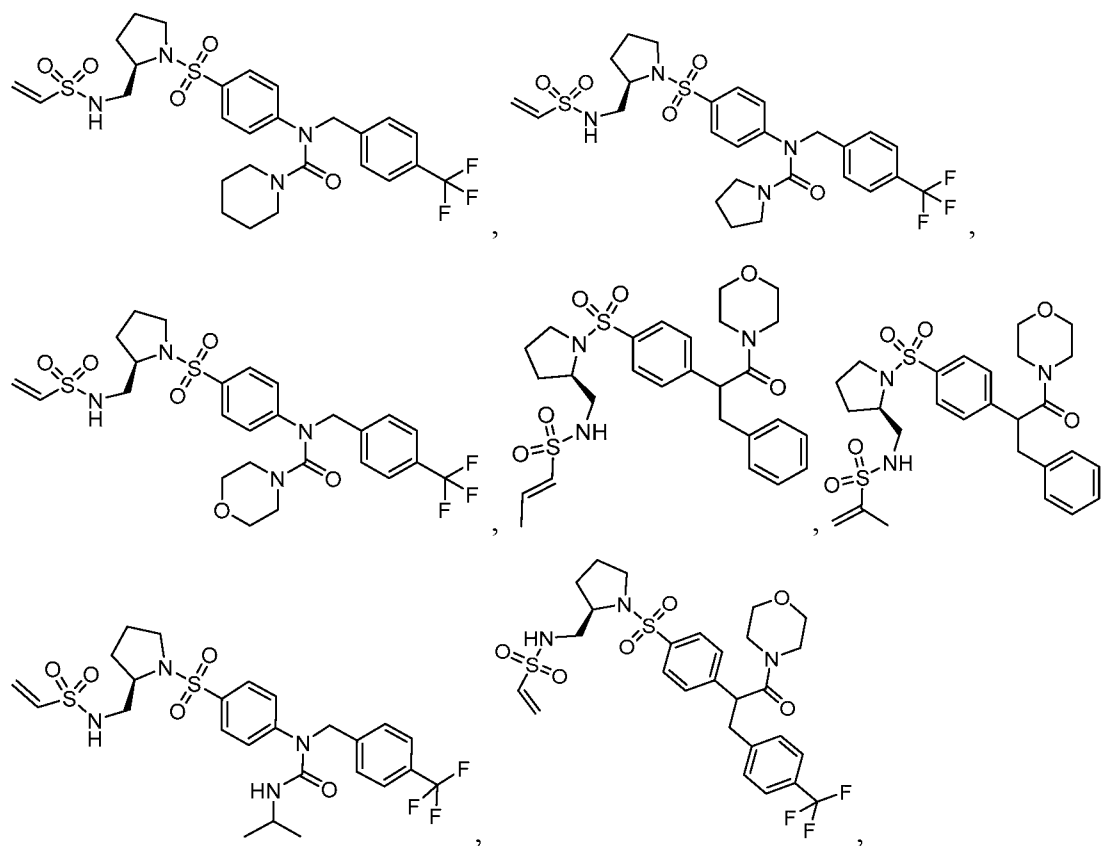
39. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein q is 1 and R^{a26} is hydrogen.

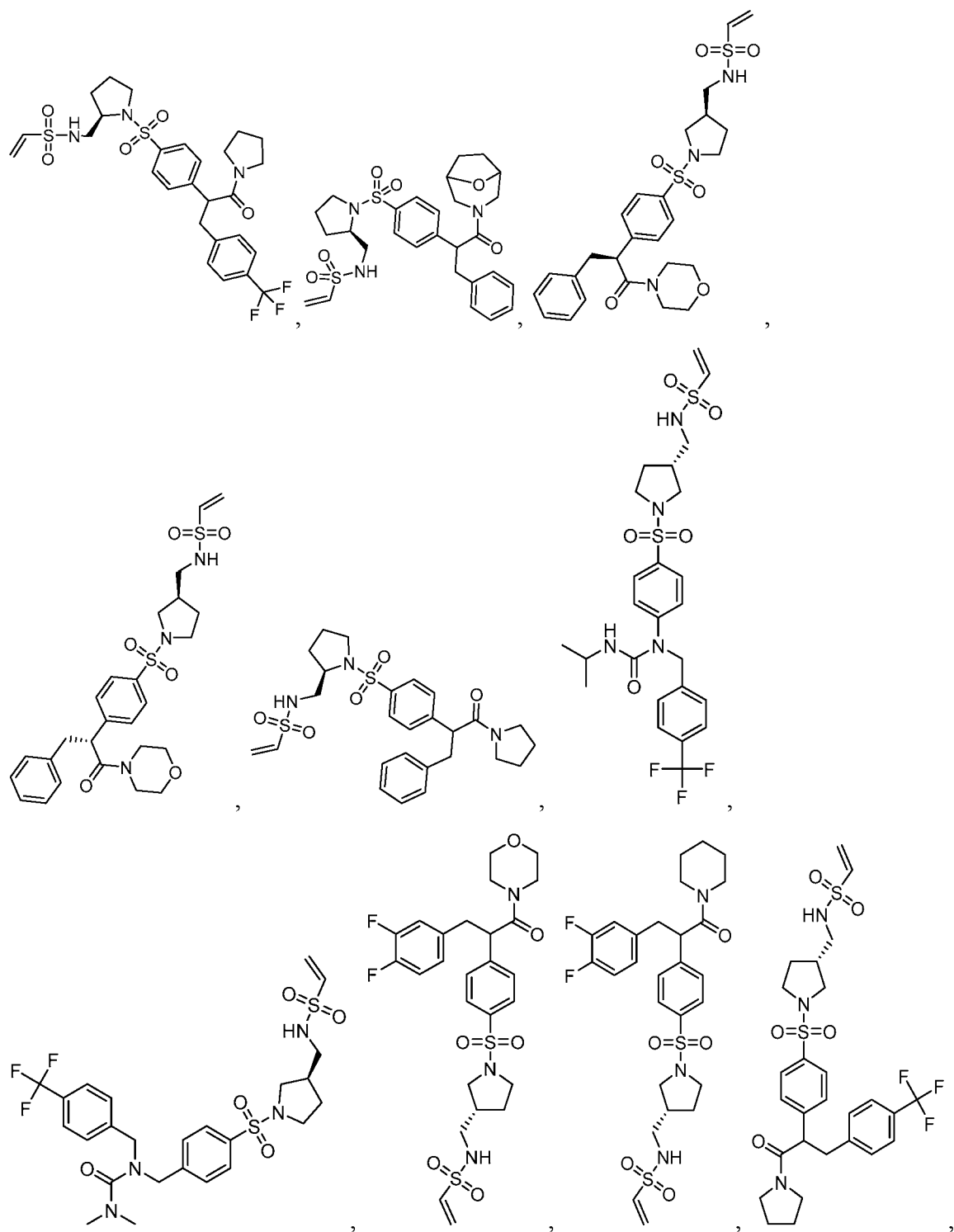
40. The compound of any one of claims 1 to 18 or 34 to 39, or a pharmaceutically acceptable salt thereof, wherein at least one R^{a5} is heteroaryl or heterocycloalkyl, wherein the heteroaryl or heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of =O, –SF₅, and R^{a35}.

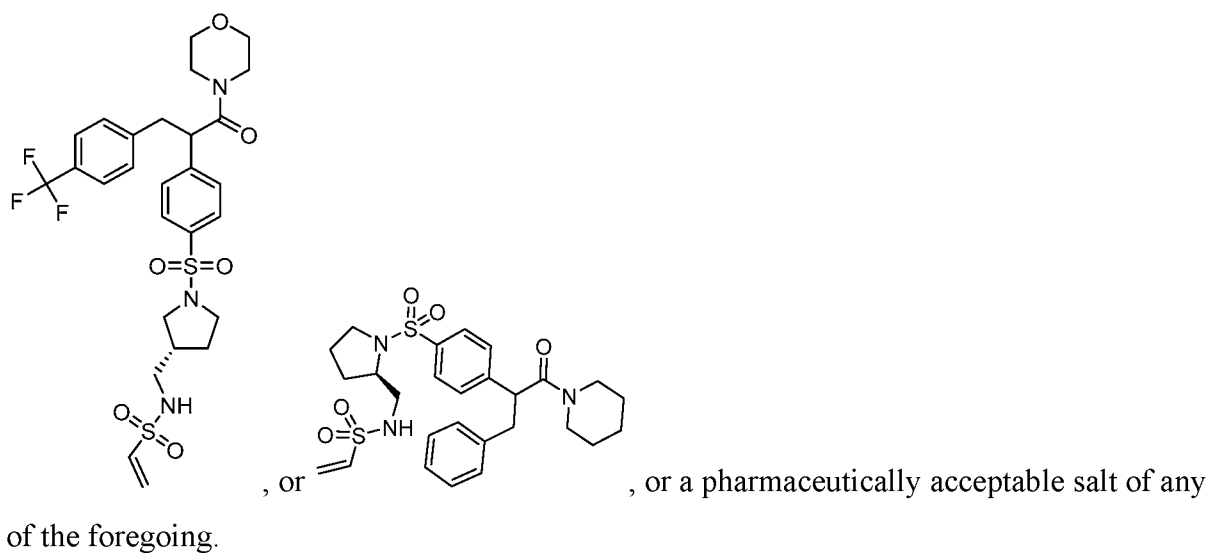
41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein R^{a35} is alkyl substituted with aryl or heteroaryl, wherein the aryl or heteroaryl is unsubstituted or substituted with haloalkyl or –SF₅.

42. The compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and R^{a3} , together with the atom to which they are attached, form a (C₃-C₅)cycloalkyl or a 3- to 5-membered heterocycloalkyl.
43. The compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, wherein X is $-S(O)_2-$, and R^{a1} and one R^{a4} , together with the atoms to which they are attached, form a 3- to 6-membered heterocycloalkyl.
44. The compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and one R^{a4} , together with the atoms to which they are attached, form a (C₃-C₆)cycloalkyl or a 3- to 6-membered heterocycloalkyl.
45. The compound of any one of claims 1 to 41, or 43, or a pharmaceutically acceptable salt thereof, wherein R^{a2} and R^{a3} are each hydrogen.
46. The compound of any one of claims 1 to 42, 44, or 45, or a pharmaceutically acceptable salt thereof, wherein X is $-S(O)_2-$.
47. The compound of any one of claims 1 to 42, 44, or 45, or a pharmaceutically acceptable salt thereof, wherein X is $-C(O)-$.
48. The compound of any one of claims 1 to 42, 44, or 45, or a pharmaceutically acceptable salt thereof, wherein X is $-CH_2-$.
49. The compound of any one of claims 1 to 34 or 38 to 48, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.
50. The compound of any one of claims 1, 2, 6, 7, 11 to 34, or 38 to 49, or a pharmaceutically acceptable salt thereof, wherein m is 0.
51. The compound of any one of claims 3 to 5, 8 to 10, or 13 to 49, or a pharmaceutically acceptable salt thereof, wherein p is 0.
52. The compound of any one of claims 1 to 12, 19 to 34, 38 to 48, 50, or 51, or a pharmaceutically acceptable salt thereof, wherein B is phenyl and n is an integer from 0 to 5.

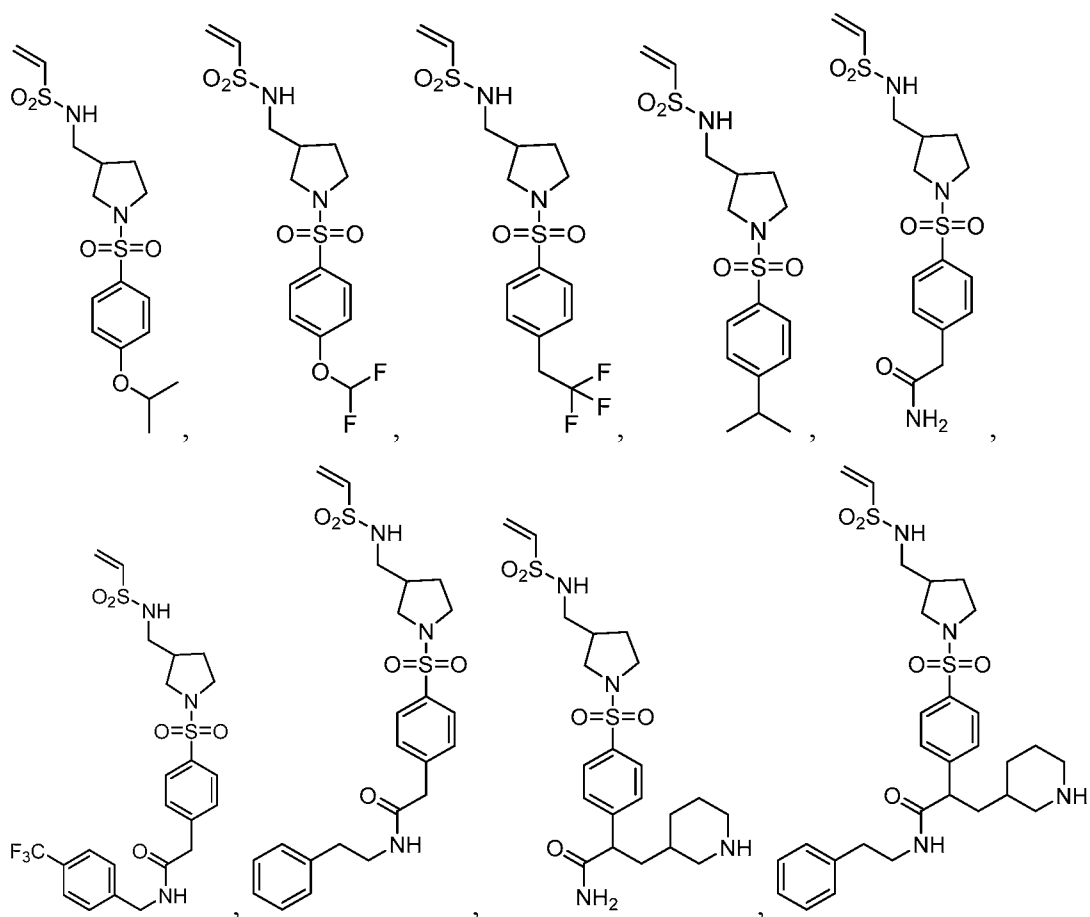
53. The compound of any one of claims 1, 2, 6, 7, 19 to 34, or 38 to 41, or a pharmaceutically acceptable salt thereof, wherein A is a 6-membered heterocycloalkyl, B is phenyl, and n is an integer from 0 to 5.
54. The compound of any one of claims 1 to 5, 10 to 35, or 37 to 53, or a pharmaceutically acceptable salt thereof, wherein R^{x1} is hydrogen.
55. The compound of any one of claims 1 to 5, 10 to 35, 37 to 54, or a pharmaceutically acceptable salt thereof, wherein R^{x2} and R^{x3} are hydrogen.
56. The compound of any one of claims 1 to 5, 10 to 35, or 37 to 55, or a pharmaceutically acceptable salt thereof, wherein one of R^{x1} , R^{x2} , and R^{x3} is unsubstituted or substituted alkyl.
57. The compound of claim 1, wherein the compound is:

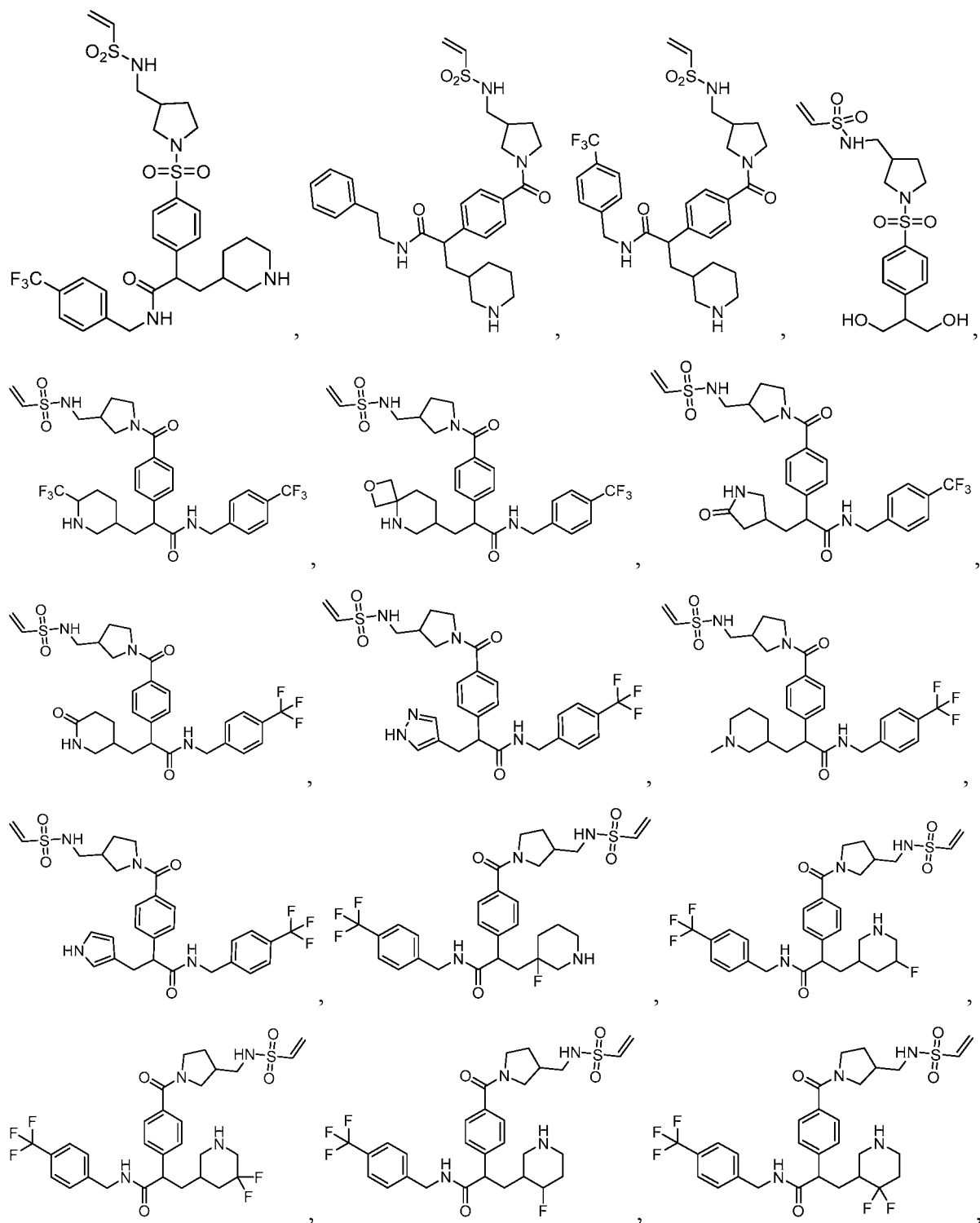


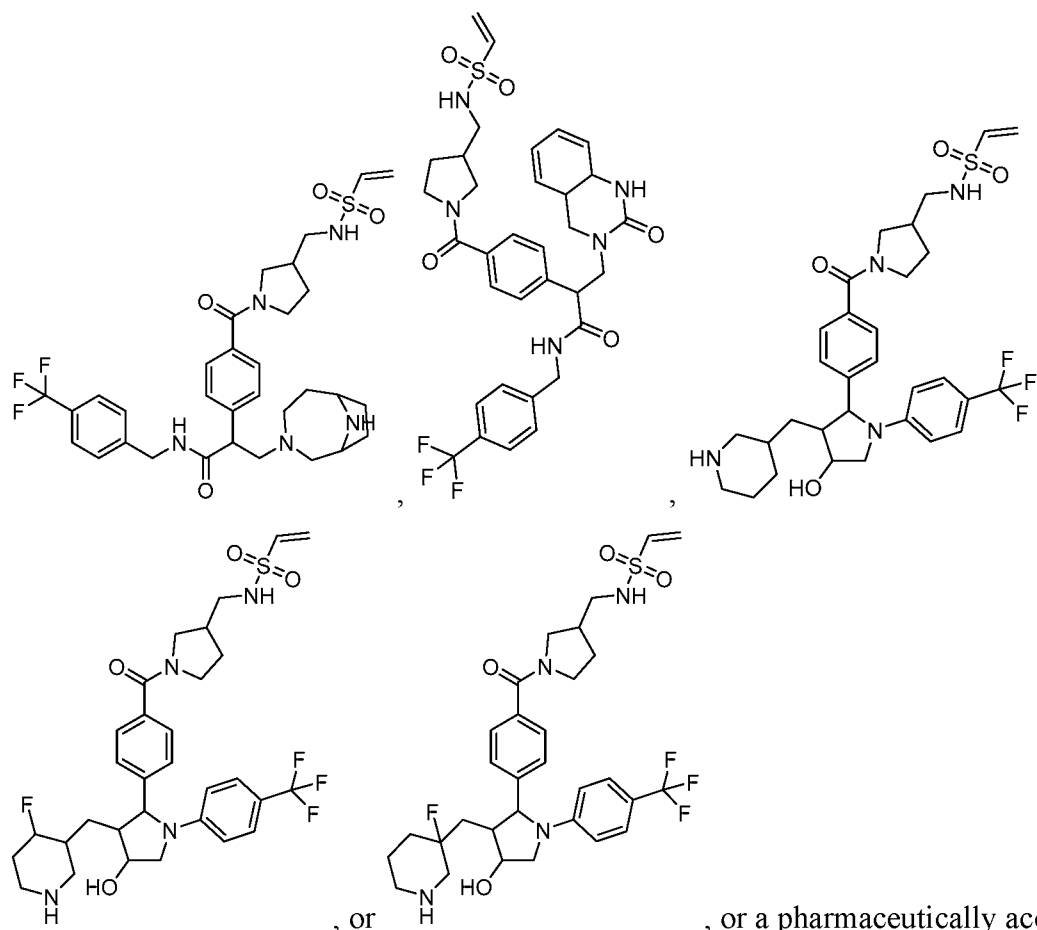




58. A compound of claim 1 or 6, wherein the compound is:

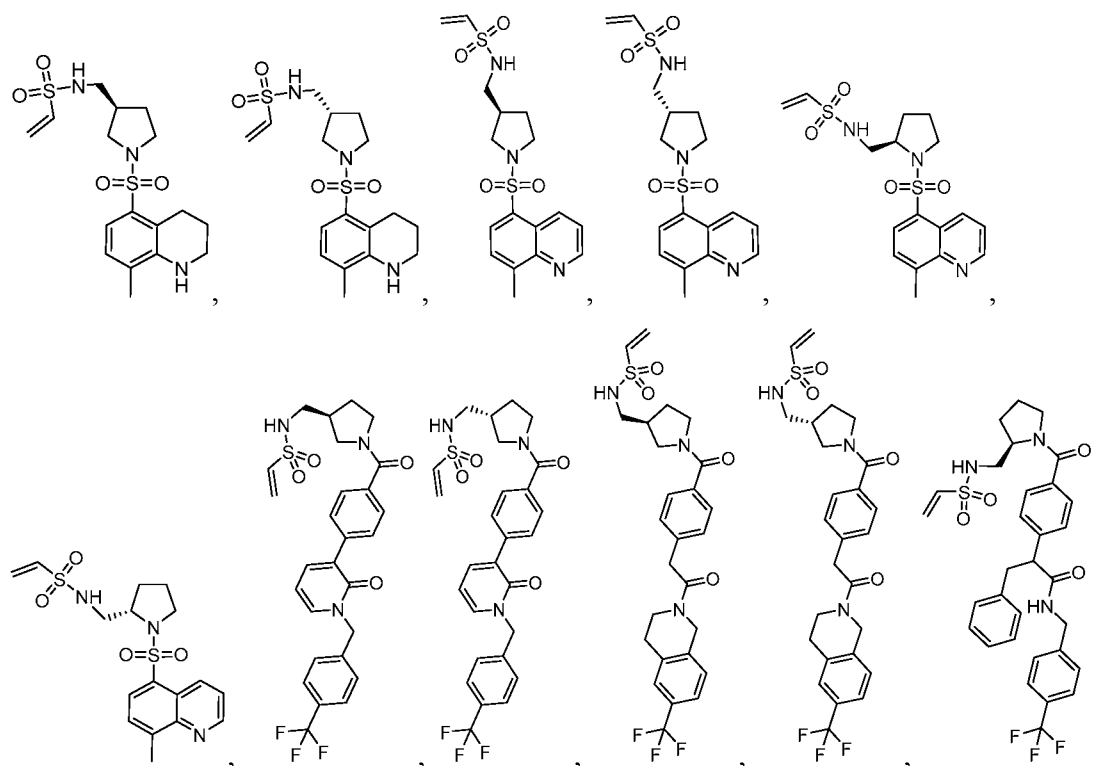


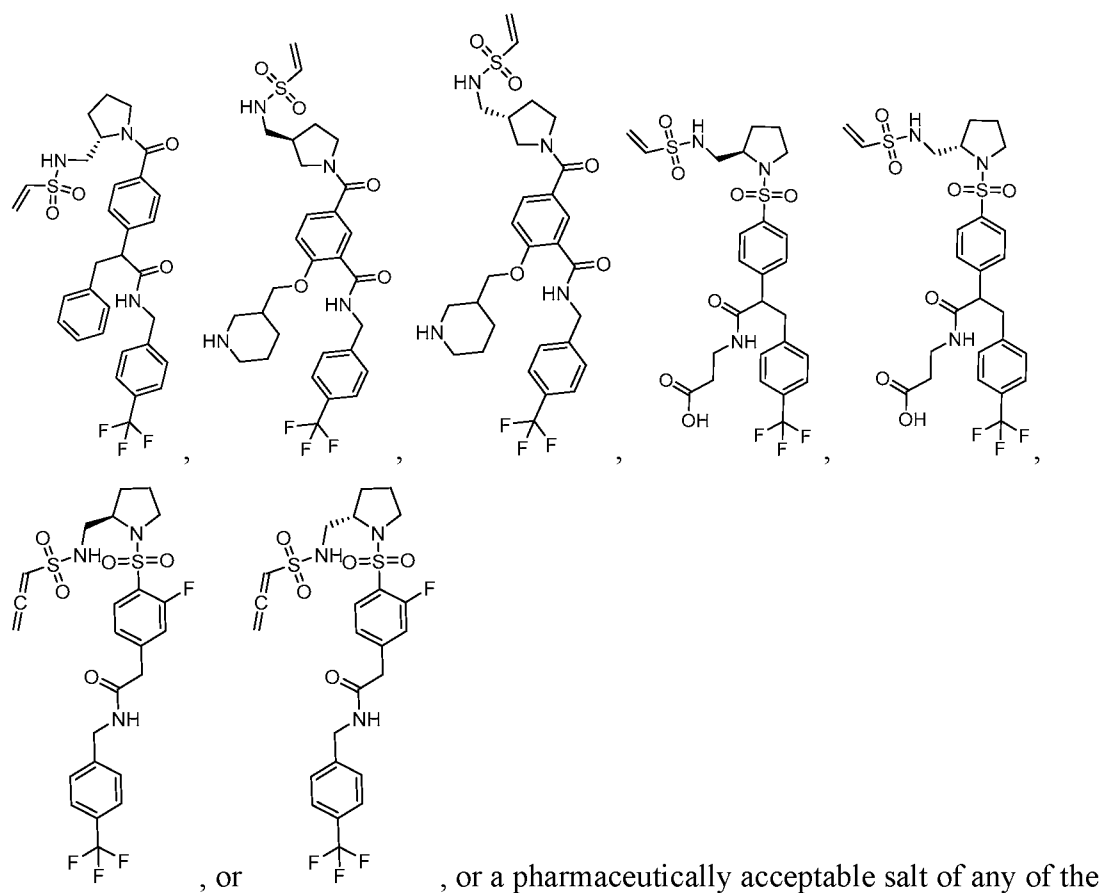




of any of the foregoing.

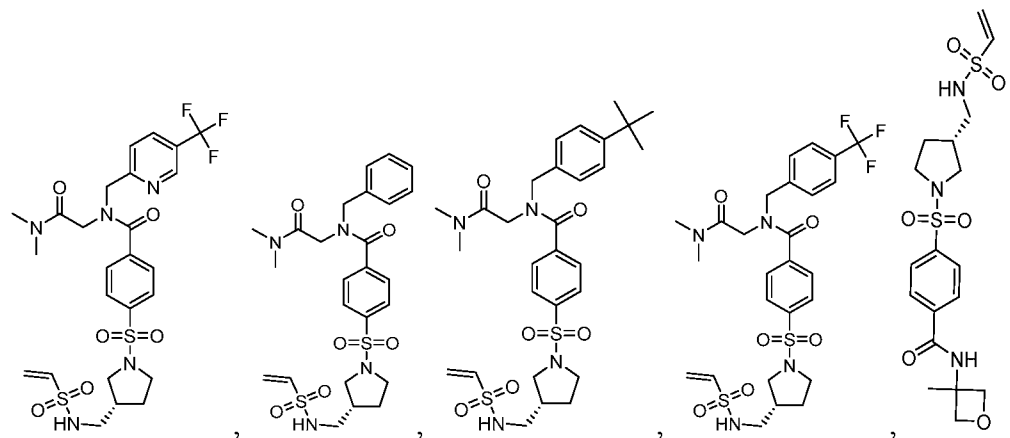
59. The compound of claim 1 or 6, wherein the compound is:

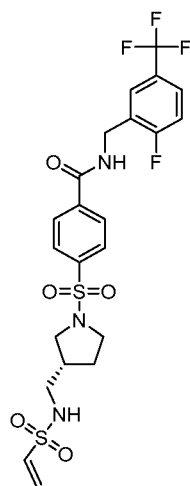
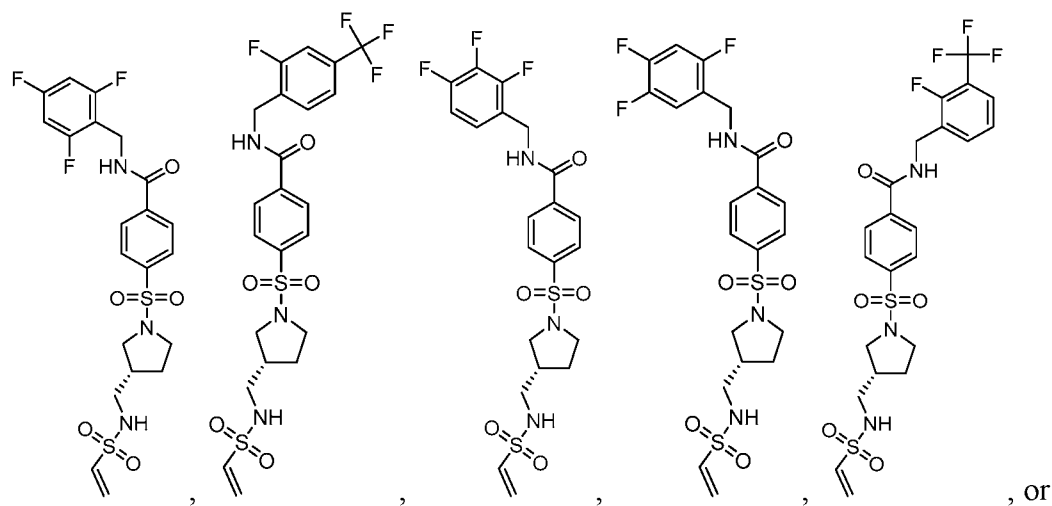
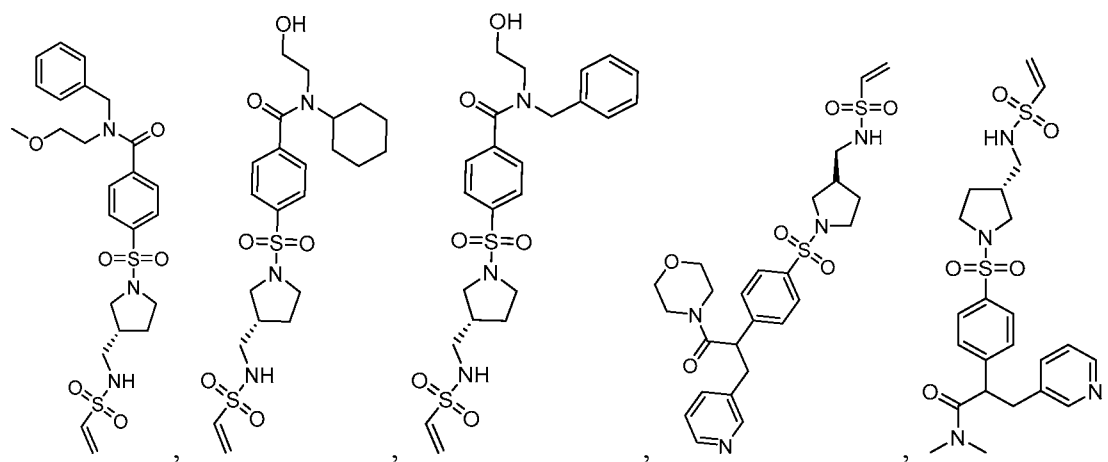




foregoing.

60. The compound of claim 1, wherein the compound is:





, or a pharmaceutically acceptable salt of any of the foregoing.

61. A pharmaceutical composition comprising a compound according to any one of claims 1 to 60, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

62. A method of reducing the level of a K-Ras protein in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 60, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
63. The method of claim 62, wherein the K-Ras protein is human K-Ras4b.
64. A method of treating a disorder in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 60, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
65. The method of claim 64, wherein the disorder is cancer.
66. The method of claim 65, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.
67. The method of claim 64, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.
68. The method of any one of claims 64 to 67, wherein the disorder is associated with a mutation of K-Ras.
69. Use of a compound of any one of claims 1 to 60, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of a K-Ras protein in a subject in need thereof.
70. The use of claim 69, wherein the K-Ras protein is human K-Ras4b.
71. Use of a compound of any one of claims 1 to 60, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof.
72. The use of claim 71, wherein the disorder is cancer.

73. The use of claim 72, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.
74. The use of claim 71, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.
75. The use of any one of claims 71 to 74, wherein the disorder is associated with a mutation of K-Ras.
76. A compound according to any one of claims 1 to 60, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of a K-Ras protein in a subject in need thereof.
77. The compound for use of claim 76, wherein the K-Ras protein is human K-Ras4b.
78. A compound according to any one of claims 1 to 60, or a pharmaceutically acceptable salt thereof, for use in a method of treating a disorder in a subject in need thereof.
79. The compound for use in claim 78, wherein the disorder is cancer.
80. The compound for use of claim 79, wherein the cancer is pancreatic cancer, lung cancer, colorectal cancer, optic pathway glioma, rhabdomyosarcoma, neuroblastoma, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, somatostatinomas, pheochromocytomas, or breast cancer.
81. The compound for use of claim 78, wherein the disorder is neurofibromatosis type 1, Noonan syndrome, cardio-facio-cutaneous syndrome, or Legius syndrome.
82. The compound for use of any one of claims 78 to 81, wherein the disorder is associated with a mutation of K-Ras.

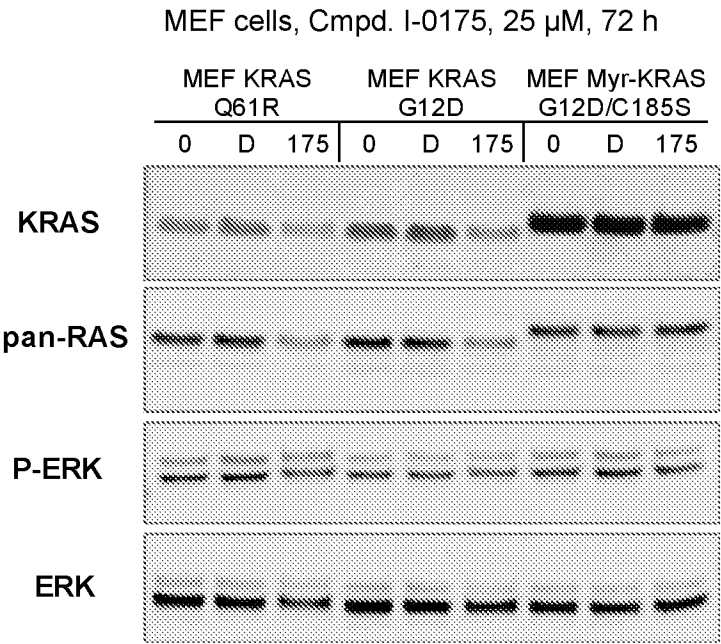


FIG. 1

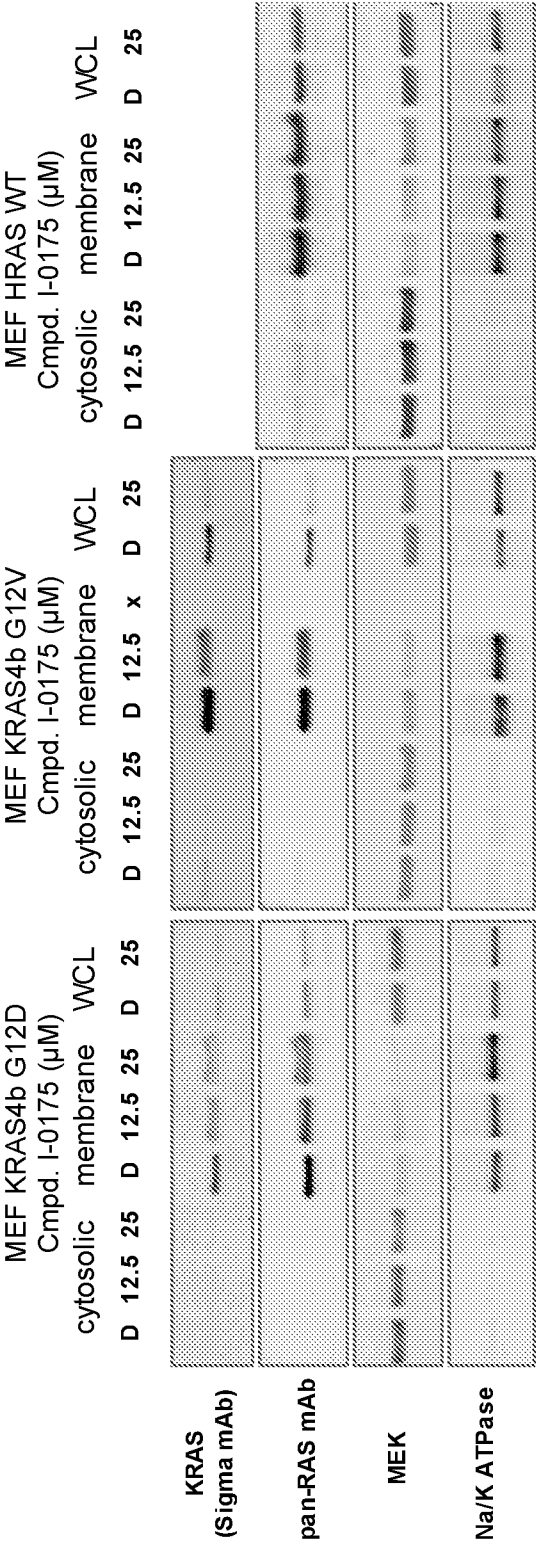
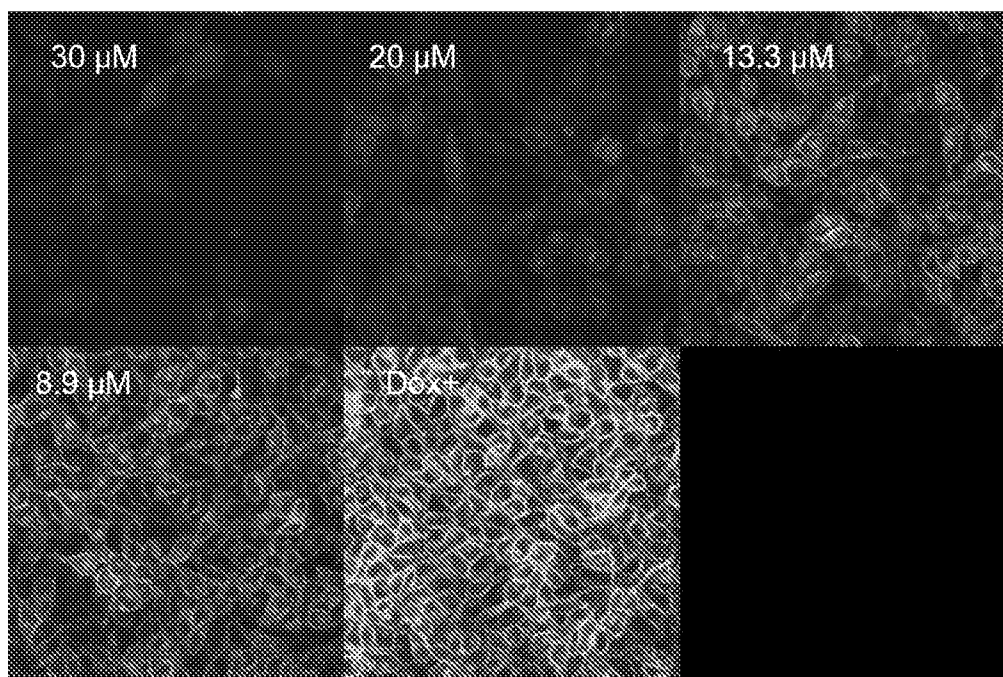
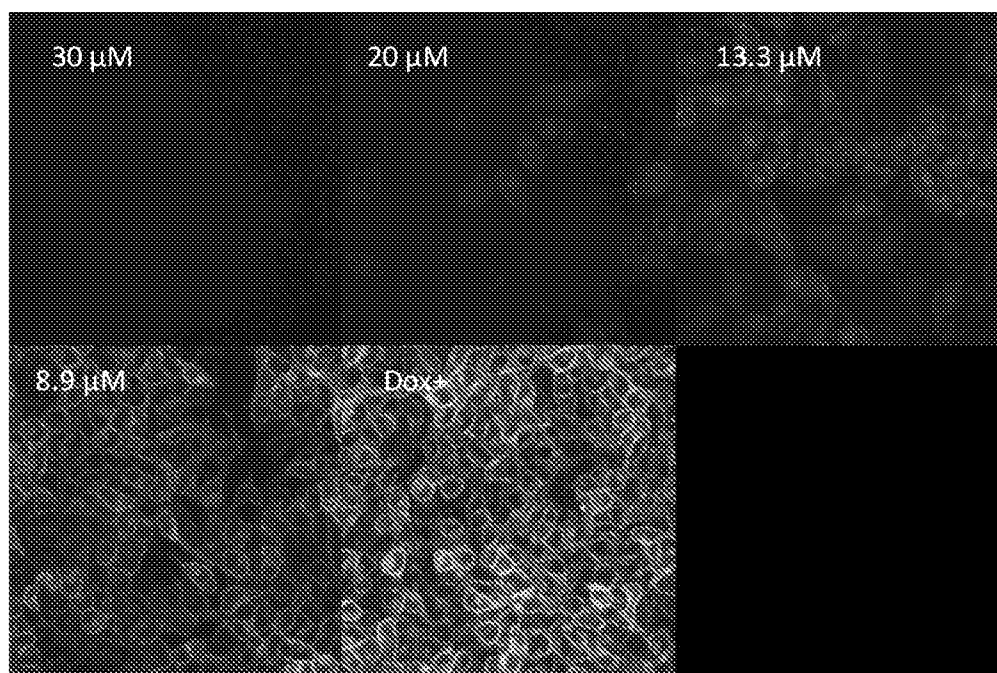


FIG. 2

3/14

**FIG. 3****FIG. 4**

4/14

Compound ID	KRAS4b G12V clone 895	KRAS4b G12V clone 425	KRAS4b G12V clone 603	KRAS4b G12V clone 648	KRAS4b Q61R	KRAS4b G12D	KRAS4b Wild Type	KRAS4a Wild Type	Myr-KRAS4b G12D/C185S	HRAS WT	HRAS WT p53-/-
I-0163	>100	73			>100	>100			>100	>100	>100
I-0174	70	41			71	>100			>100	>100	>100
I-0175	24	20			22	31			37	>100	52
I-0176	17	15	16	19	15	17	18	23	41	>100	47
I-0177	12	11			12	18			21	49	18
I-0180	11	10	11	15	10	14	11	13	22	54	20
I-0182	27	22			36	52			50	>100	29
I-0183	27	20	37	36	29	39	23	30	54	>100	43
I-0192	15	14			16	25			25	21	38
I-0193	99	45			77	>100			>100	>100	>100
I-0195	>100	>100			>100	>100			>100	>100	>100
I-0196	34	32			40	52			54	165	31
I-0197	52	37			35	64			77	>100	
I-0198	67	50			59	85			>100	87	>100
I-0199	55	44			69	107			>100	>100	
I-0200	>100	>100			>100	>100			>100	>100	
I-0201	17	14			15	20			27	60	35
I-0202	>100	>100				>100					
I-0202	102	73			98	>100			>100		
I-0202	>100	>100			>100	>100			>100	>100	>100
I-0202	13	16			9	20			26	28	50

FIG. 5A

5/14

Compound ID	KRAS4b G12V clone 895	KRAS4b G12V clone 425	KRAS4b G12V clone 603	KRAS4b G12V clone 648	KRAS4 b Q61R	KRAS4b G12D	KRAS4b Wild Type	KRAS4 a Wild Type	Myr-KRAS4b G12D/C185S	HRAS WT	HRAS WT p53-/-
I-0203						0				>100	
I-0204	104	62			69	0			>100	>100	
I-0206	9	9			8	12			18	23	23
I-0208	78	55			44	51			37		62
I-0209	68	42			60	>100			98	>100	>100
I-0210	>100	>100			>100	>100			>100	>100	>100
I-0211											59
I-0213	>100	>100			>100	>100			>100	>100	
I-0219	11	15			16	20			21	24	45
I-0221	4	4			5	7			8	31	5
I-0222	>100	>100			>100	>100			>100		
I-0223	>100	92			>100	>100			>100		
I-0224	>100	>100			>100	>100			>100	>100	>100
I-0225	20	11			16	16			18	19	32
I-0001030	18	15			15	20			21	21	34
I-0001031	18	12			13	18			18	16	28
I-0001056	49	35			37	52			53	46	93
I-0001057	27	16			21	32			33	26	66
I-0001062	24	12	21	21	20	24	34	27	34	36	70
		14						29	53		83
I-0001098	11							24	24		45
I-0001101	14	12			19	22			28	23	41

FIG. 5B

6/14

Compound ID	KRAS4b G12V clone 895	KRAS4b G12V clone 425	KRAS4b G12V clone 603	KRAS4b G12V clone 648	KRAS4 b Q61R	KRAS4b G12D	KRAS4b Wild Type	KRAS4a Wild Type	Myr-KRAS4b G12D/C185S	HRAS WT	HRAS WT p53/-
I-0001105	19	18			15	28			31	33	54
	15	11	8	17	13	24	31	38	36	33	70
		17						45	55		70
I-0001107	17	16			21	26			34	34	52
I-0001109	17	14			20	29			36	32	58
		16						26	51		70
I-0001114	25	15	10	19	19	29	36	36	41	37	82
		18						51	73		93
I-0001230	21	18			22	25			35	28	42
I-0001243	20	14			13	26			24	29	27
I-0001255	22	17			21	23			27	24	28
I-0001282	10	7			13	16			18	15	30
I-0001286		13						15	35		36
I-0001288	19							35	56		84
I-0001289	26	27			24	36			34	42	60
	22	19	10	24	19	29	34	40	41	40	83
		26						46	62		47
I-0001292		11						16	30		37
I-0001295											
I-0001298	13							22	36		50
I-0001319	9	7			11	12			11	13	18
I-0001323	12	9			12	18			15	14	34
I-0001326	58	37			49	61			62	84	108
I-0001358	23	19			24	33			27	61	71
I-0001359	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
I-0001363	34	23			26	38			42	48	79

FIG. 5C

7/14

Compound ID	KRAS4b G12V clone 895	KRAS4b G12V clone 425	KRAS4b G12V clone 603	KRAS4b G12V clone 648	KRAS4 b Q61R	KRAS4b G12D	KRAS4b Wild Type	KRAS4a Wild Type	Myr-KRAS4b G12D/C185S	HRAS WT	HRAS WT p53-/-
I-0001367	14	12			12	18			14	19	35
I-0001388	14	11			19	21			30	22	39
I-0001421	25	15			18	21			27	22	46
I-0001422											
I-0001423	25	16			20	32			25	27	54
I-0001436	63	36			67	68			71	79	102
I-0001465	13							21	41		58
I-0001482	22	22			23	28			25	30	46
I-0001539	18							29	52		54
I-0001541	27							38	55		45
I-0001542	27	33			26	39			37	43	61
	20	18	7	20	21	35	39	43	45	43	64
		30						50	61		51
I-0001543	15	11	7	15	13	24	26	32	31	30	60
		14						38	51		52
I-0001554	42	33			34	56			56	102	76
I-0001556	21	17			19	29			24	25	43
I-0001558	11							20	27		38
I-0001565	38	28			30	42			30	49	65
I-0001567	20							26	33		49
I-0001568	19							27	49		36
I-0001580	23							33	43		51

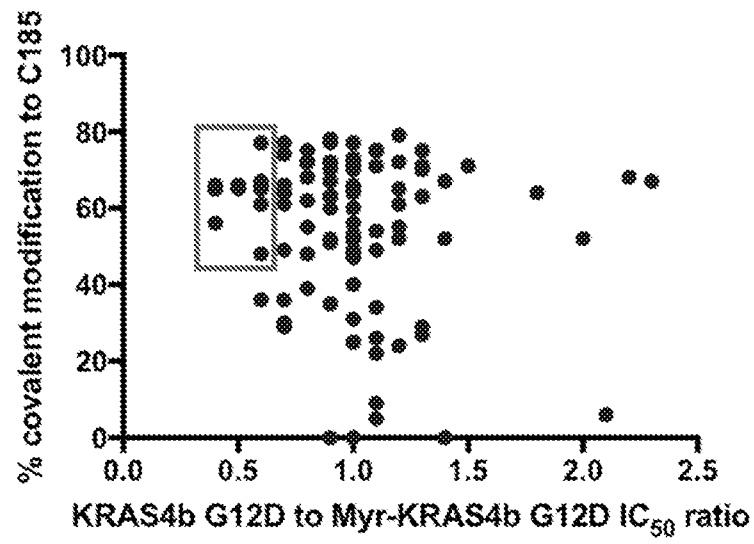
FIG. 5D

8/14

Compound ID	IC50 ratio G12D vs Myr-G12D	Compound ID	IC50 ratio G12D vs Myr-G12D	Compound ID	IC50 ratio G12D vs Myr-G12D
I-0001023	0.9	I-0001111	0.7	I-0001285	0.4
I-0001026	1.1	I-0001113	0.8	I-0001287	0.8
I-0001027	1.1	I-0001114	0.4	I-0001289	0.5
I-0001030	1.2	I-0001212	0.7	I-0001292	1.3
I-0001032	1.1	I-0001213	0.7	I-0001295	1.0
I-0001058	0.9	I-0001214	0.7	I-0001298	1.0
I-0001059	0.8	I-0001219	0.4	I-0001299	1.0
I-0001060	1.1	I-0001220	0.8	I-0001300	0.9
I-0001061	1.5	I-0001230	0.9	I-0001319	1.0
I-0001062	0.8	I-0001236	0.9	I-0001320	0.8
I-0001069	0.9	I-0001237	0.7	I-0001367	1.2
I-0001073	1.0	I-0001239	1.3	I-0001372	2.1
I-0001074	1.0	I-0001247	0.6	I-0001376	0.9
I-0001075	0.7	I-0001248	0.8	I-0001377	0.5
I-0001076	1.1	I-0001255	0.9	I-0001378	1.0
I-0001078	0.6	I-0001268	0.7	I-0001380	1.2
I-0001081	1.0	I-0001269	0.8	I-0001381	0.6
I-0001086	0.4	I-0001270	0.9	I-0001382	1.0
I-0001092	1.2	I-0001271	1.4	I-0001386	1.1
I-0001095	1.1	I-0001272	1.3	I-0001421	1.8
I-0001097	1.4	I-0001273	0.9	I-0001422	1.0
I-0001098	0.7	I-0001274	0.7	I-0001441	1.3
I-0001099	2.2	I-0001277	0.5	I-0001442	0.6
I-0001100	2.3	I-0001278	1.1	I-0001443	0.7
I-0001105	0.6	I-0001279	0.9	I-0001444	1.0
I-0001107	0.7	I-0001281	0.7	I-0001445	1.3
I-0001108	1.1	I-0001282	0.6	I-0001447	1.1
I-0001109	1.3	I-0001284	0.7		

FIG. 6

9/14

**FIG. 7**

10/14

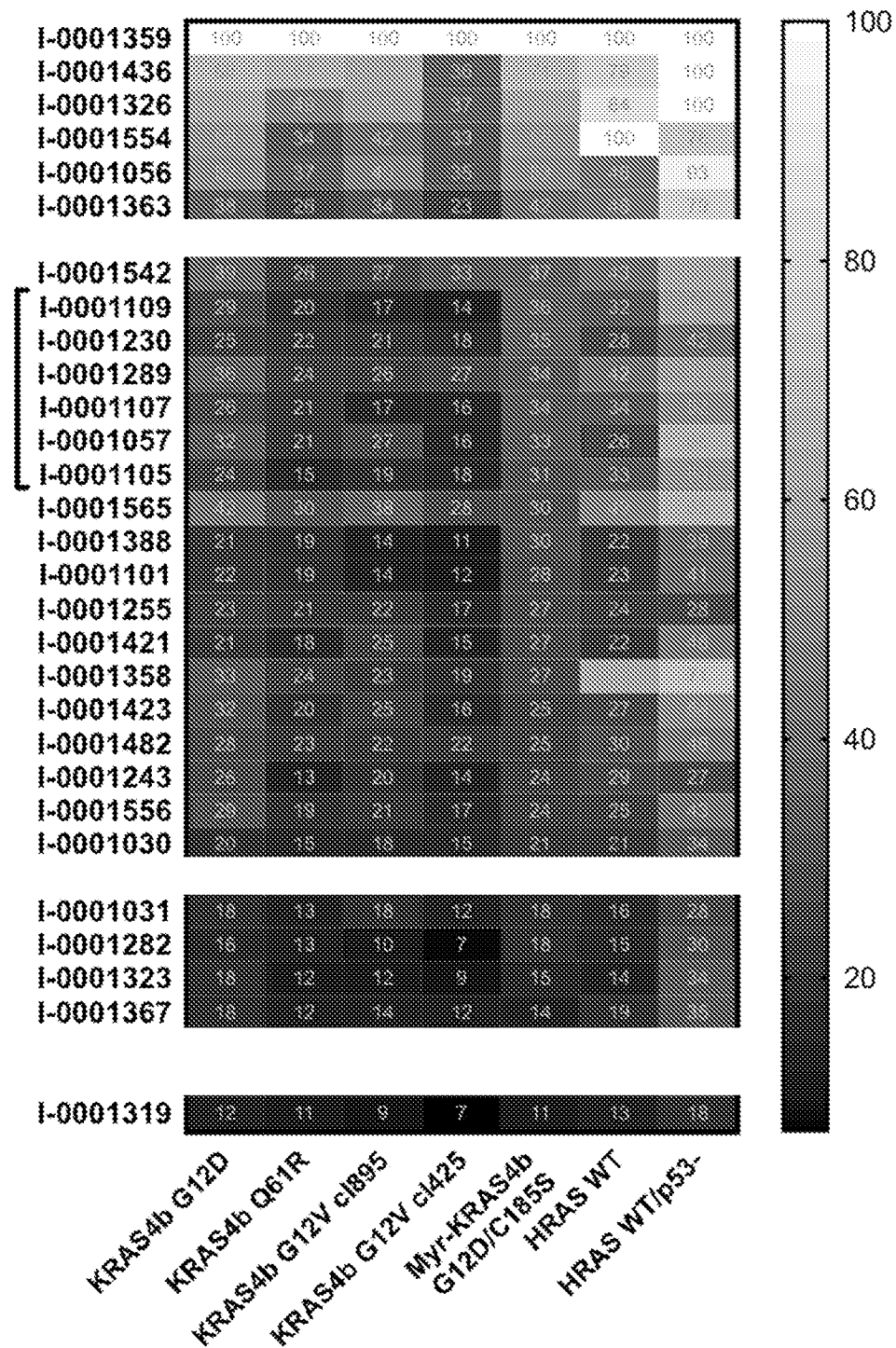


FIG. 8A

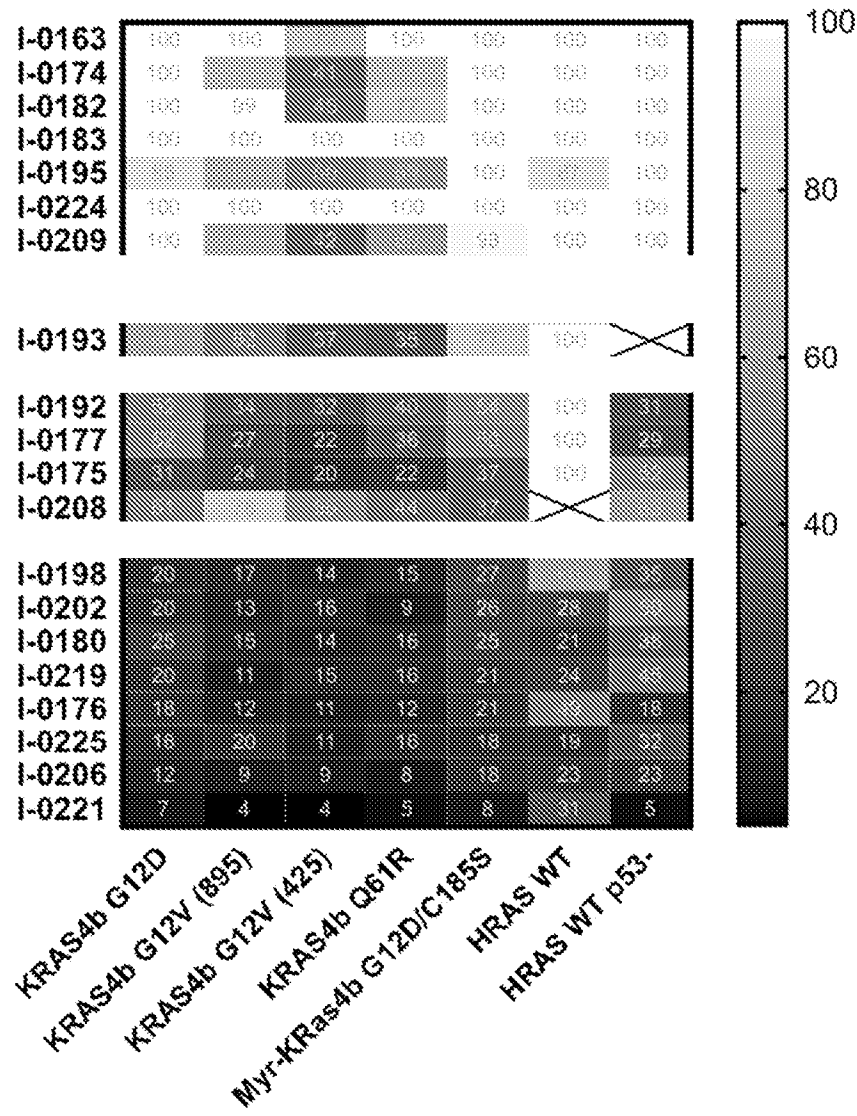


FIG. 8B

12/14

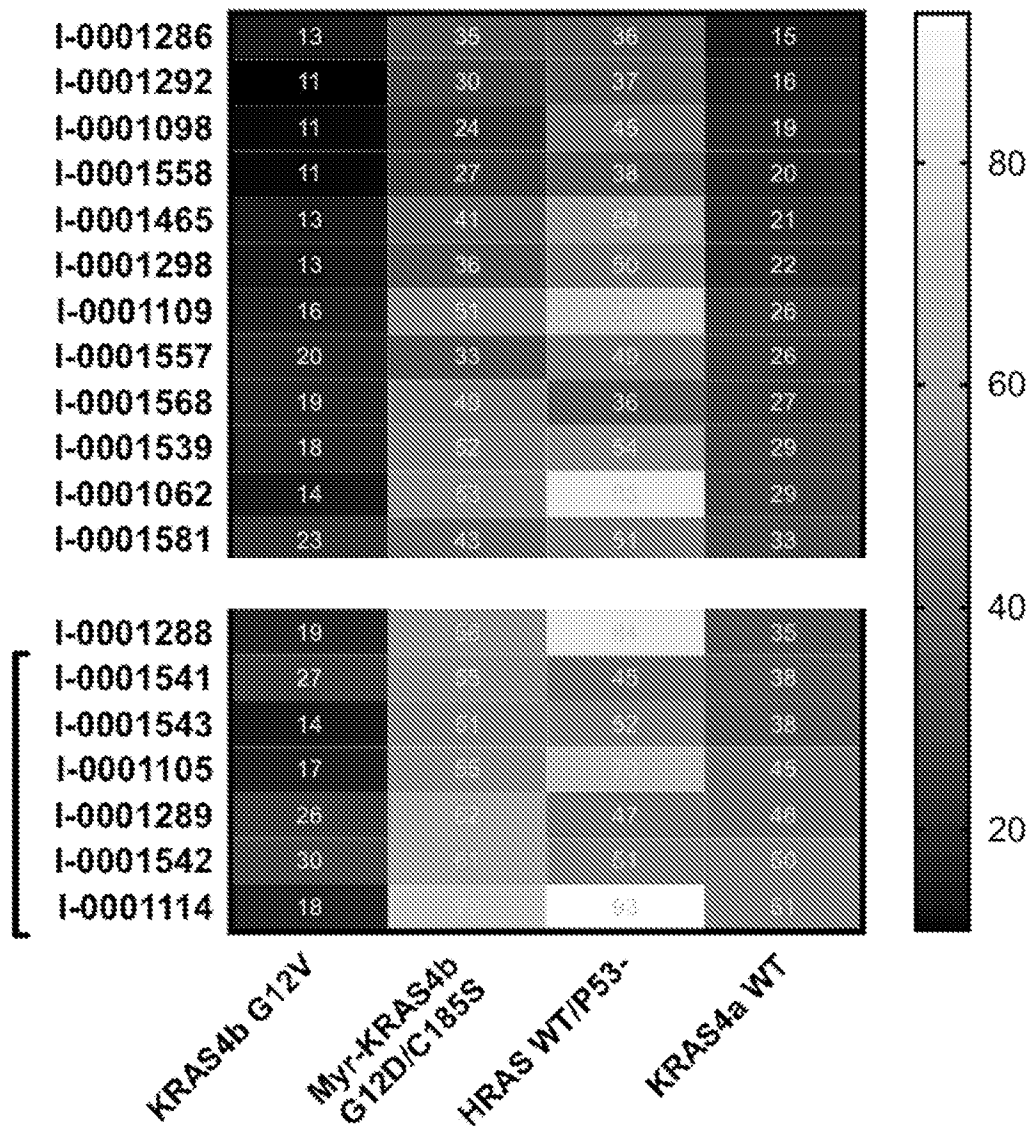


FIG. 8C

13/14

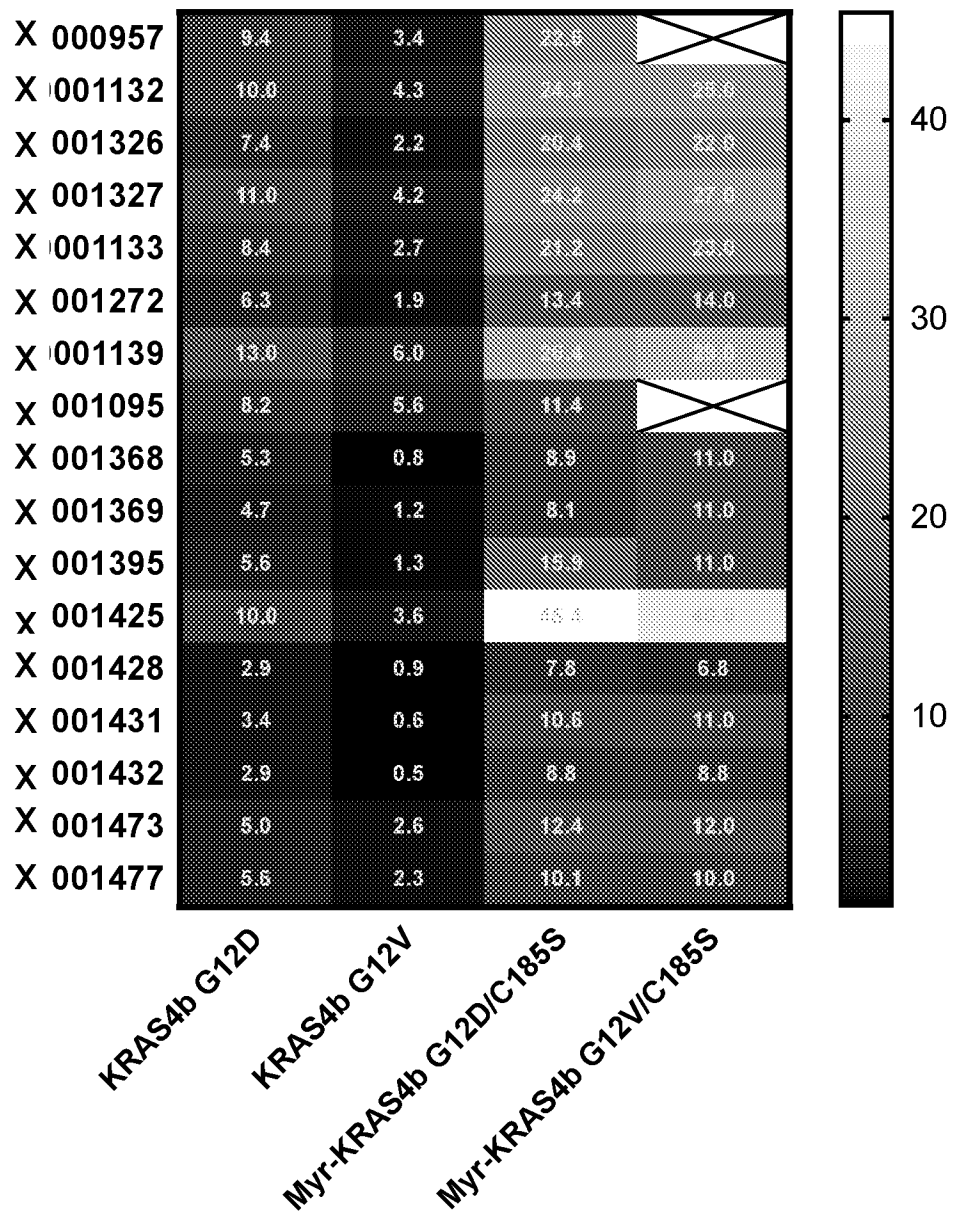


FIG. 9

14/14

	K-Ras4b G12D (μM)	K-Ras4b G12V (μM)	Myr-K-Ras G12D/C185S (μM)	Myr-K-Ras G12V/C185S (μM)
X-0000957	9.4 $\pm$ 6.5 (n=3)	3.38 $\pm$ 2.90 (n=2)	22.6 $\pm$ 3.93 (n=3)	N/A
X-0001132	10 $\pm$ 5.5 (n=6)	4.33 $\pm$ 2.17 (n=5)	24.3 $\pm$ 5.93 (n=6)	25 $\pm$ 2.0 (n=3)
X-0001326	7.4 $\pm$ 5.9 (n=3)	2.19 $\pm$ 2.40 (n=2)	20.4 $\pm$ 5.42 (n=3)	22 (n=1)
X-0001327	11 $\pm$ 7.4 (n=3)	4.23 $\pm$ 1.68 (n=2)	24.2 $\pm$ 5.53 (n=3)	27 (n=1)
X-0001133	8.4 $\pm$ 5.3 (n=5)	2.74 $\pm$ 1.66 (n=4)	21.2 $\pm$ 5.60 (n=5)	23 $\pm$ 3.1 (n=2)
X-0001272	6.3 $\pm$ 4.4 (n=4)	1.86 $\pm$ 2.22 (n=4)	13.4 $\pm$ 3.64 (n=4)	14 $\pm$ 1.2 (n=3)
X-0001139	13 $\pm$ 6.1 (n=5)	6.04 $\pm$ 2.77 (n=4)	26.4 $\pm$ 4.39 (n=5)	29 $\pm$ 2.1 (n=2)
X-0001095	8.2 (n=1)	5.55 (n=1)	11.4 (n=1)	N/A
X-0001368	5.3 $\pm$ 1.5 (n=3)	0.810 $\pm$ 0.509 (n=2)	8.86 $\pm$ 2.76 (n=3)	11 $\pm$ 0.53 (n=2)
X-0001369	4.7 $\pm$ 1.4 (n=3)	1.21 $\pm$ 0.665 (n=2)	8.14 $\pm$ 2.59 (n=3)	11 $\pm$ 0.53 (n=2)
X-0001395	5.6 $\pm$ 1.9 (n=4)	1.33 $\pm$ 0.792 (n=2)	15.9 $\pm$ 13.1 (n=4)	11 $\pm$ 1.2 (n=2)
X-0001425	10 $\pm$ 2.7 (n=2)	3.56 $\pm$ 4.43 (n=2)	45.4 $\pm$ 7.70 (n=2)	40 $\pm$ 0.28 (n=2)
X-0001428	2.9 $\pm$ 1.2 (n=3)	0.880 $\pm$ 0.962 (n=2)	7.79 $\pm$ 1.21 (n=3)	6.8 $\pm$ 0.40 (n=2)
X-0001431	3.4 $\pm$ 2.1 (n=3)	0.565 $\pm$ 0.530 (n=2)	10.6 $\pm$ 1.42 (n=3)	11 $\pm$ 2.8 (n=2)
X-0001432	2.9 $\pm$ 1.8 (n=3)	0.485 $\pm$ 0.431 (n=2)	8.77 $\pm$ 1.09 (n=3)	8.8 $\pm$ 1.2 (n=2)
X-0001473	5.0 $\pm$ 1.4 (n=2)	2.55 (n=1)	12.4 $\pm$ 1.79 (n=2)	12 (n=1)
X-0001477	5.6 $\pm$ 2.4 (n=2)	2.25 (n=1)	10.1 $\pm$ 0.120 (n=2)	10 (n=1)
	IC50 (μM) +/- SD, (n = # repeats)			

FIG. 10