

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] The present application claims the benefit under 35 U.S.C. § 119(e) of the earlier filing date of U.S. Provisional Patent Application No. 63/487,431, filed February 28, 2023, the entire content of which is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[002] The disclosure relates to compounds and methods for modulating RAS-PI3K.

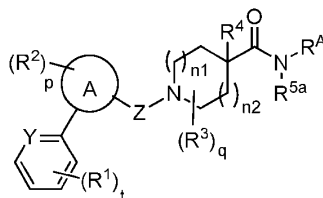
BACKGROUND OF THE DISCLOSURE

[003] There is a need for improved cancer therapeutics and methods of treatment.

SUMMARY

[004] Disclosed herein in some aspects are modulators of RAS-PI3K. Some such aspects relate to a RAS-PI3K agonist. Some aspects relate to a RAS-PI3K inhibitor. The RAS-PI3K modulators may include a compound described herein. The RAS-PI3K modulators may be useful in a method described herein.

[005] In one aspect, described herein is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (I),

wherein,

Z is C(=O) or S(=O)₂;

Ring A is phenyl, 5 to 10-membered heteroaryl, C₃-C₈ cycloalkyl, C₈-C₉ spirocyclyl, or 5 to 8-membered heterocycloalkyl;

Y is N, CH, or CR¹;

each R¹ is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

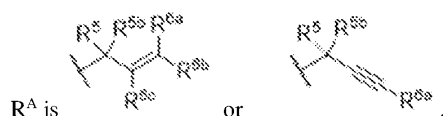
each R² is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, oxo (=O), optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆

deuteroalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkylamino, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R³ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuteroalkyl, or C₁-C₆ haloalkyl;

R⁴ is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;



wherein

R⁵ is H, optionally substituted C₁-C₃ alkyl, optionally substituted C₁-C₃ haloalkyl, or optionally substituted C₁-C₃ hydroxyalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5a} is H; or R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring; or R^{5a} is absent and R^{6c} is bound directly to the nitrogen to which R^A is attached to form a 4-membered heterocyclic ring;

or R^{5a} and R⁵ together with the nitrogen and carbon atoms to which they are attached form a 4-membered heterocyclic ring;

R^{5b} is H or C₁-C₃ alkyl;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuteroalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, a three- to six-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuteroalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and

alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

n₁ and n₂ are each independently 0, 1, 2, or 3;

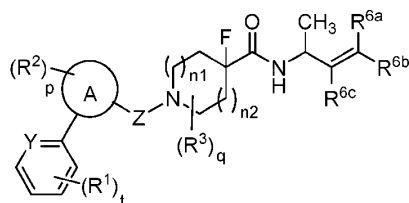
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[006] In some embodiments of Formula (I), R⁴ is halogen. In some embodiments of Formula (I), R^{5a} and R^{5b} are each H. In some embodiments of Formula (I), R⁵ is C₁-C₃ alkyl. In some embodiments of Formula (I), R⁵ is -CH₃ or -CH₂CH₃. In some embodiments of Formula (I), R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine together to form a 4-membered heterocycloalkyl ring.

[007] In some embodiments, the compound of Formula (I) has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (Ia),

wherein,

Z is C(=O) or S(=O)₂;

Ring A is phenyl, 5 to 10-membered heteroaryl, C₃-C₈ cycloalkyl, C₈-C₉ spirocyclyl, or 5 to 8-membered heterocycloalkyl;

Y is CH or CR¹;

each R¹ is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R^2 is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, oxo (=O), optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkylamino, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R^2 together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R^3 is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R^7 is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, a 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

n_1 and n_2 are each independently 0, 1, 2, or 3;

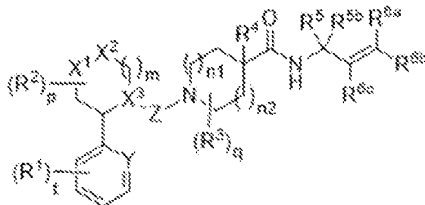
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[008] In some embodiments of Formula (I) or (Ia), ring A is a C₅-C₇ cycloalkyl or 5 to 7-membered heterocycloalkyl.

[009] In some embodiments, the compound of Formula (I) has the structure of Formula (II), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (II),

wherein,

X¹ and X² are each independently CH₂, CHR², CR²R², O, or NR^{2a}; wherein at least one of X¹ or X² is CH₂, CHR², or CR²R²;

X³ is CR⁸ or N, provided that when X³ is N, R⁸ is absent;

Y is N, CH, or CR¹;

Z is C(=O) or S(=O)₂;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl;

R^{2a} is H, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or phenyl;

each R³ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R⁴ is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R⁸ is absent, H, halogen, -OCH₃, or -CH₃;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deutoalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₃C₈ aryl, C₃C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deutoalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

m is 0 or 1;

n₁ and n₂ are each independently 0, 1, 2, or 3;

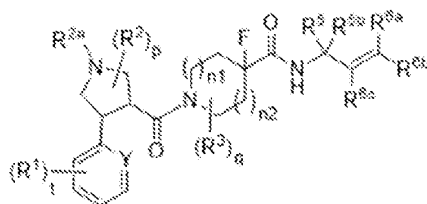
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

[0010] In some embodiments of Formula (II), Z is -C(=O)-. In some embodiments of Formula (II), X³ is CR⁸; and R⁸ is H. In some embodiments of Formula (II), m is 0. In some embodiments of Formula (II), X¹ is NR^{2a}; and X² is CH₂.

[0011] In some embodiments, the compound of Formula (II) has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIb),

wherein,

Y is CH or CR¹;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl;

each R² is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₃-C₆ cycloalkyl;

R^{2a} is H, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted arylalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R³ is independently C₁-C₃ alkyl or C₁-C₃ deuterioalkyl;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl

is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

n1 and n2 are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

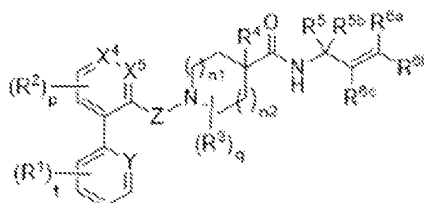
q is 0, 1, or 2; and

t is 1, 2, or 3.

[0012] In some embodiments of Formula (IIb), R^{2a} is -C(=O)R^a, -C(=O)OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₃-C₆ cycloalkyl; wherein each R^a is independently C₁-C₆ alkyl. In some embodiments of Formula (IIb), p is 0. In some embodiments of Formula (IIb), Y is CH or CR¹, each R¹ is halogen, R^{2a} is C₁-C₆ haloalkyl, R⁵ is C₁-C₃ alkyl, R^{5b} is H, R^{6a} and R^{6b} are each independently H or -S(=O)(=NH)R⁷ wherein each R⁷ is independently C₁-C₆ alkyl, or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring, R^{6c} is H, n1 and n2 are each independently 1 or 2, p is 0 or 1, q is 0 or 1, and t is 1 or 2.

[0013] In some embodiments of Formula (I) or (Ia), ring A is phenyl or a 5 to 10-membered heteroaryl. In some embodiments of Formula (I) or (Ia), ring A is phenyl or pyridinyl.

[0014] In some embodiments, the compound of Formula (I) has the structure of Formula (III), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (III),

wherein,

Y is N, CH, or CR¹;

Z is C(=O) or S(=O)₂;

X⁴ is CH, CR², or N;

X⁵ is CH, CR², or N;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R^2 is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R^2 together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R^3 is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R^4 is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;

R^5 is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R^7 is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

n1 and n2 are each independently 0, 1 or 2;

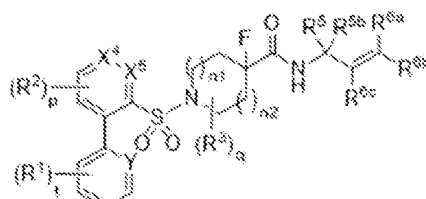
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0015] In some embodiments of Formula (III), Z is $-S(=O)_2-$. In some embodiments of Formula (III), R^4 is halogen.

[0016] In some embodiments, the compound of Formula (III) has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIIa),

wherein,

Y is CH or CR^1 ;

X^4 is CH, CR^2 , or N;

X^5 is CH, CR^2 , or N;

each R^1 is independently halogen, -CN, -OH, $-OR^a$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 deutoalkyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, or optionally substituted C_3 - C_6 cycloalkyl;

each R^2 is independently halogen, -CN, -OH, $-OR^a$, $-N(R^b)_2$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 deutoalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted 4 to 6-membered heterocycloalkyl, or optionally substituted arylalkyl;

each R^3 is independently C_1 - C_3 alkyl or C_1 - C_3 deutoalkyl;

R^5 is H, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, or C_1 - C_3 hydroxyalkyl;

R^{5b} is H or C_1 - C_3 alkyl;

R^{6a} and R^{6b} are each independently H, -CN, $-C(=O)N(R^7)_2$, $-S(=O)_2R^7$, or $-S(=O)(=NH)R^7$; wherein
 each R^7 is independently C_1 - C_3 alkyl, or a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;
 or two R^7 together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;
 or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered

heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

n1 and n2 are each independently 0, 1 or 2;

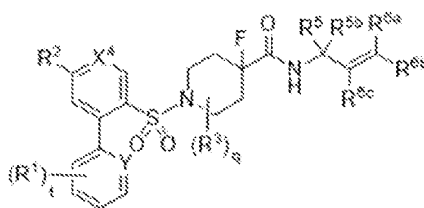
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0017] In some embodiments of Formula (III) or (IIIa), X⁴ is CH or CR²; and X⁵ is CH or CR². In some embodiments of Formula (III) or (IIIa), X⁴ is N; and X⁵ is CH or CR². In some embodiments of Formula (III) or (IIIa), X⁴ is CH or CR²; and X⁵ is N. In some embodiments of Formula (III) or (IIIa), p is 1.

[0018] In some embodiments, the compound of Formula (III) has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIIb),

wherein,

X⁴ is CH or N;

Y is CR¹ or CH;

each R^1 is independently halogen, -CN, -OR^a, optionally substituted C₁-C₄ alkyl, optionally substituted C₁-C₄ deuterioalkyl, C₂-C₄ alkynyl, or C₁-C₃ fluoroalkyl;

R^2 is halogen, -CN, -OH, -OR^a, -N(R^b)₂, -C(=O)R^a, optionally substituted C₁-C₄ alkyl, optionally substituted C₁-C₄ deuterioalkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₃ fluoroalkyl, optionally substituted C₁-C₃ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

Each R^3 is independently -CH₃ or -CD₃;

R^5 is H, -CH₃, or -CH₂CH₃;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)N(R⁷)₂, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein each R^7 is independently C₁-C₃ alkyl, or a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms; or two R^7 together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms; or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

each R^a is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or C₁-C₃ fluoroalkyl;

each R^b is independently H or C₁-C₃ alkyl;

q is 0, 1, or 2; and

t is 0, 1, or 2.

[0019] In some embodiments of Formula (III), (IIIa), or (IIIb), each R^2 is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, -C(=O)R^a, optionally substituted C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₃ fluoroalkyl, optionally substituted C₁-C₃ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (III), (IIIa), or (IIIb), each R^2 is independently Cl, Br, F, -CN, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CF₃, -CH₂CF₃, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -OCF₃, -N(CH₃)₂, azetidine, oxetane, pyrrolidine, piperazine, or morpholine. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^1 is independently halogen, -CN, -OH, -OR^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, or optionally substituted C₁-C₆ haloalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently halogen, -OR^a, or optionally substituted C₁-C₆ alkyl.

[0020] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently Cl, Br, F, -OCH₃, or -CH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is CH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa) or (IIIb), q is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa) or (IIIb), q is 0. In some embodiments of

Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), n_1 is 1; and n_2 is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6a} is $S(=O_2)R^7$; and R^{6b} and R^{6c} are each H. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6b} is $S(=O_2)R^7$; and R^{6a} and R^{6c} are each H. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^7 is independently optionally substituted C_1 - C_6 alkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6a} is $-C(=O)N(R^7)_2$ and R^{6b} and R^{6c} are each H; or R^{6b} is $-C(=O)N(R^7)_2$, and R^{6a} and R^{6c} are each H, wherein two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered ring.

[0021] In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof; and at least one pharmaceutically acceptable excipient.

[0022] In another aspect, provided herein is a method of modulating RAS-PI3K, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof. In some embodiments, the method comprises inhibition of RAS-PI3K. In some embodiments, the method comprises activation of RAS-PI3K.

[0023] In another aspect, provided herein is a method of treating a disease or condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof. In some embodiments, the disease or condition is mediated by the modulation of RAS-PI3K. In some embodiments, the disease is cancer. In some embodiments, the cancer is selected from the group consisting of bladder cancer, uterine cancer, head and neck cancer, esophageal cancer, ovarian cancer, liver cancer, cervical cancer, lung cancer, colorectal cancer, cholangiocarcinoma, gastric cancer, kidney cancer, and pancreatic cancer. In some embodiments, the disease or condition is an immunological disease or condition. In some embodiments, the immunological condition is wound healing.

[0024] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of

other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0025] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION

[0026] RAS proteins are small GTPases known for their involvement in oncogenesis. RAS operates in a complex signaling network with multiple activators and effectors, which allows them to regulate cellular functions such as cell proliferation, differentiation, apoptosis, and senescence.

Phosphatidylinositol 3-kinase (PI3K) is one of the main effector pathways of RAS, regulating cell growth, cell cycle entry, cell survival, cytoskeleton reorganization, and metabolism. It is the involvement of this pathway in human tumors that has attracted most attention. PI3K has proven to be necessary for RAS-induced transformation *in vitro*. Mice with mutations in the PI3K catalytic subunit p110 α that block its ability to interact with RAS are highly resistant to endogenous oncogenic KRAS-induced lung tumorigenesis and HRAS-induced skin carcinogenesis. These animals also have a delayed development of the lymphatic vasculature.

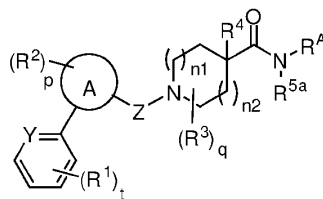
[0027] Disclosed herein are compounds and methods for modulating RAS-PI3K activity. Some embodiments relate to a compound or method of inhibiting RAS-PI3K activity. Some embodiments, relate to a compound or method of activating RAS-PI3K activity. The modulating of RAS-PI3K activity may be *in vitro* or *in vivo*. The compound for modulating RAS-PI3K may be formulated for administration to a subject. The RAS-PI3K modulation may be performed in a subject.

[0028] The compounds disclosed herein may be useful for treatment of diseases where RAS-PI3K activity may be a concern. In some embodiments, the compound is used for wound healing. In some embodiments, the compound is used for treatment of cancer.

Compounds of the Disclosure

[0029] Disclosed herein, in some embodiments are modulators of RAS-PI3K.

[0030] In an aspect, provided herein is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (I),

wherein,

Z is C(=O) or S(=O)₂;

Ring A is phenyl, 5 to 10-membered heteroaryl, C₃-C₈ cycloalkyl, C₈-C₉ spirocyclyl, or 5 to 8-membered heterocycloalkyl;

Y is N, CH, or CR¹;

each R¹ is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -C(=O)R^a, -C(=O)OR^a, -

C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl,

optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-

C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -S(=O)₂R^a, -C(=O)R^a, -

C(=O)OR^a, -C(=O)NR^aR^b, oxo (=O), optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆

deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally

substituted C₁-C₆ alkylamino, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆

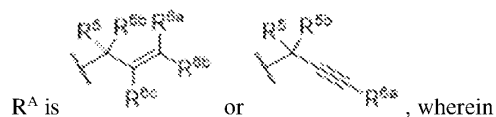
hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally

substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R³ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R⁴ is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;



R⁵ is H, optionally substituted C₁-C₃ alkyl, optionally substituted C₁-C₃ haloalkyl, or optionally substituted C₁-C₃ hydroxyalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5a} is H; or R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring; or R^{5a} is absent and R^{6c} is bound directly to the nitrogen to which R^A is attached to form a 4-membered heterocyclic ring;

or R^{5a} and R⁵ together with the nitrogen and carbon atoms to which they are attached form a 4-membered heterocyclic ring;

R^{5b} is H or C₁-C₃ alkyl;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl), and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

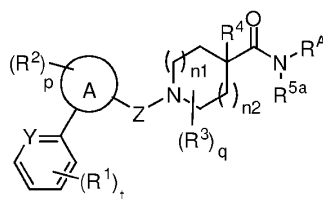
n₁ and n₂ are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0031] In some embodiments, provided herein is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (I),

wherein,

Z is C(=O) or S(=O)₂;

Ring A is phenyl, pyridinyl, or 5 to 6-membered heterocycloalkyl;

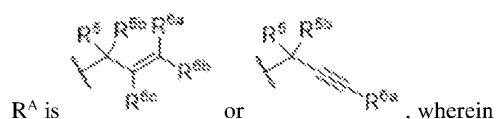
Y is CH or CR¹;

each R¹ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

each R³ is independently C₁-C₃ alkyl or C₁-C₃ deuterioalkyl;

R⁴ is F;



R⁵ is

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{6ᵃ} and R^{6ᵇ} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, or -S(=O)₂R⁷; wherein each R⁷ is independently optionally substituted C₁-C₃ alkyl or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6ᶜ} is H;

or R^{6ᶜ} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5ᵃ} is H; or R^{5ᵃ} and R^{6ᶜ} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5ᵇ} is H or C₁-C₃ alkyl;

n₁ and n₂ are each independently 0, 1 or 2;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, cycloalkyl, heterocycloalkyl, or aryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, or aryl, is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

each R^b is independently H or C₁-C₆ alkyl;

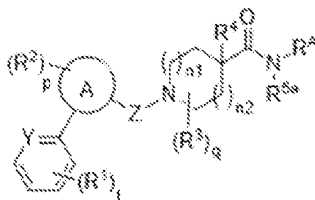
or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

[0032] In some embodiments, provided herein is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (I),

wherein,

Z is C(=O) or S(=O)₂;

Ring A is phenyl, pyridinyl, or 5-membered heterocycloalkyl;

Y is CH or CR¹;

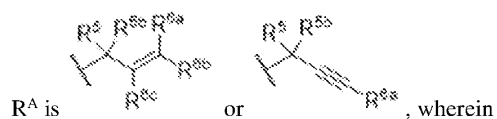
each R^1 is independently Cl, Br, F, -OCH₃, CH₃, or -CD₃;

each R^2 is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,

C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₆ cycloalkyl, or 4 to 6-membered heterocycloalkyl;

each R^3 is independently -CH₃ or -CD₃;

R^4 is F;



R^A is or , wherein

R^5 is H, -CH₃, or -CH₂CH₃;

R^{5a} and R^{5b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, or -S(=O)₂R⁷; wherein

each R^7 is independently optionally substituted C₁-C₃ alkyl or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an

optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5a} is H; or R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5b} is H or C₁-C₃ alkyl;

n₁ and n₂ are each independently 0, 1, or 2;

each R^a is independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

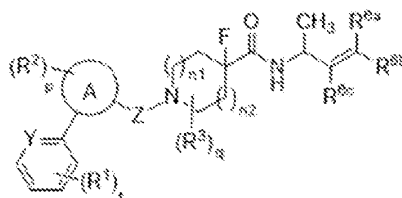
each R^b is independently H or C₁-C₆ alkyl;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

[0033] In some embodiments, the compound of Formula (I) has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (Ia),

wherein,

Z is C(=O) or S(=O)₂;

Ring A is phenyl, 5 to 10-membered heteroaryl, C₃-C₈ cycloalkyl, C₈-C₉ spirocyclyl, or 5 to 8-membered heterocycloalkyl;

Y is CH or CR¹;

each R¹ is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl,

optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, oxo (=O), optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally

substituted C₁-C₆ alkylamino, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R³ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

n1 and n2 are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

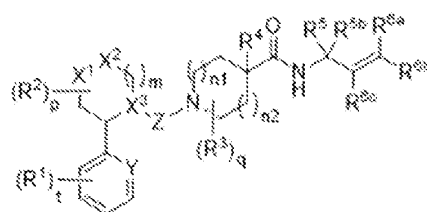
t is 0, 1, 2, or 3.

[0034] In some embodiments of Formula (I) or (Ia), Y is N. In some embodiments of Formula (I) or (Ia), Y is CH or CR¹. In some embodiments of Formula (I) or (Ia), Y is CH. In some embodiments of Formula (I) or (Ia), Y is CR¹.

[0035] In some embodiments of Formula (I) or (Ia), ring A is a C₅-C₇ cycloalkyl or 5 to 7-membered heterocycloalkyl. In some embodiments of Formula (I) or (Ia), ring A is C₃-C₈ cycloalkyl. In some embodiments of Formula (I) or (Ia), ring A is a C₅-C₇ cycloalkyl. In some embodiments of Formula (I) or (Ia), ring a is a cyclopentyl. In some embodiments of Formula (I) or (Ia), ring A is a cyclohexyl. In some embodiments, ring A is a cyclohexene.

[0036] In some embodiments of Formula (I) or (Ia), ring A is a 5 to 8-membered heterocycloalkyl. In some embodiments of Formula (I) or (Ia), ring A is a heterocycloalkyl. In some embodiments of Formula (I) or (Ia), the heterocycloalkyl is monocyclic, bicyclic, or polycyclic. In some embodiments of Formula (I) or (Ia), ring A is a 5 to 7-membered heterocycloalkyl. In some embodiments of Formula (I) or (Ia), ring A is a 5 to 6-membered heterocycloalkyl. In some embodiments of Formula (I) or (Ia), ring A is a 5 membered heterocycloalkyl comprising 1 or 2 heteroatoms selected from O or N. In some embodiments of Formula (I) or (Ia), ring A is a 5 membered heterocycloalkyl comprising 1 heteroatom selected from O or N. In some embodiments, ring A is a 6-membered heterocycloalkyl. In some embodiments of Formula (I) or (Ia), ring A is a 6 membered heterocycloalkyl comprising 1 or 2 heteroatoms selected from O or N. In some embodiments of Formula (I) or (Ia), ring A is a 6 membered heterocycloalkyl comprising 1 heteroatom selected from O or N. In some embodiments of Formula (I) or (Ia), the heterocycloalkyl is piperazine, piperidine, morpholine, tetrahydropyran, pyrrolidine, or tetrahydrofuran. In some embodiments of Formula (I) or (Ia), the heterocycloalkyl is piperazine. In some embodiments of Formula (I) or (Ia), the heterocycloalkyl is piperidine, morpholine. In some embodiments of Formula (I) or (Ia), the heterocycloalkyl is tetrahydropyran. In some embodiments of Formula (I) or (Ia), the heterocycloalkyl is pyrrolidine. In some embodiments of Formula (I) or (Ia), the heterocycloalkyl is tetrahydrofuran.

[0037] In another aspect, provided herein is a compound having the structure of Formula (II), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (II),

wherein,

X¹ and X² are each independently CH₂, CHR², CR²R², O, or NR^{2a}, wherein at least one of X¹ or X² is CH₂, CHR², or CR²R²;

X³ is CR⁸ or N, provided that when X³ is N, R⁸ is absent;

Y is N, CH, or CR¹;

Z is C(=O) or S(=O)₂;

each R^1 is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R^2 is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R^2 together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl;

R^{2a} is H, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or phenyl;

each R^3 is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R^4 is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;

R^5 is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R^7 is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^8 is absent, H, halogen, -OCH₃, or -CH₃;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl:

m is 0 or 1;

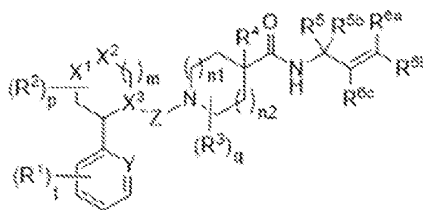
n1 and n2 are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

[0038] In another aspect, provided herein is a compound having the structure of Formula (II), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (II),

wherein,

X^1 and X^2 are each independently CH_2 , CHR^2 , CR^2R^2 , O, or NR^{2a} ; wherein at least one of X^1 or X^2 is CH_2 , CHR^2 , or CR^2R^2 ;

X^3 is $\mathbb{C}R^8$ or N , provided that when X^3 is N , R^8 is absent;

Y is CH or CR¹;

Z is C(=O) or S(=O)₂;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deutoalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl;

R^{2a} is H, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₃-C₆ cycloalkyl;

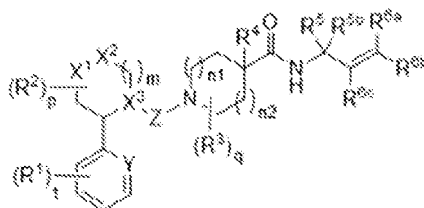
each R³ is independently C₁-C₃ alkyl or C₁-C₃ deuterioalkyl;

R⁴ is H or halogen;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein
 each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;
 or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;
 or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;
 R^{6c} is H or -CN;
 or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;
 R^8 is absent, H, halogen, -OCH₃, or -CH₃;
 each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;
 each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;
 or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;
 m is 0 or 1;
 n₁ and n₂ are each independently 0, 1, or 2;
 p is 0, 1, 2, or 3;
 q is 0, 1, or 2; and
 t is 1, 2, or 3.

[0039] In some embodiments, provided herein is a compound having the structure of Formula (II), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (II),

wherein,

X¹ and X² are each independently CH₂, CHR², CR²R², O, or NR^{2a}, wherein at least one of X¹ or X² is CH₂, CHR², or CR²R²;

 X^3 is $\mathbb{C}R^8$;

Y is CH or CR¹:

Z is C(=O);

each R¹ is independently Cl, Br, F, -OCH₃, CH₃ or -CD₃;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or 4 to 6-membered heterocycloalkyl;

R^{2a} is -C(=O)R^a, -C(=O)OR^a, C₁-C₆ haloalkyl, or C₃-C₆ cycloalkyl.

each R³ is independently -CH₃ or -CD₃;

 $\mathbf{R}^4$ is $\mathbf{F}$;

R⁵ is H, -CH₃, or -CH₂CH₃;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, or -S(=O)₂R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₃ alkyl or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5a} is H; or R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring;

 $\mathbb{R}^8$ is H ;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, cycloalkyl, heterocycloalkyl, or aryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, or aryl, is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

each R^b is independently H or C₁-C₆ alkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

n_1 and n_2 are each independently 0, 1, or 2;

m is 0 or 1;

p is 0, 1, 2, or 3;

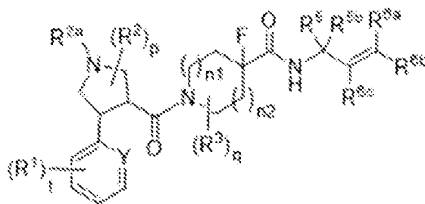
q is 0, 1, or 2; and

t is 1, 2, or 3.

[0040] In some embodiments of Formula (II), X^3 is CR^8 . In some embodiments of Formula (II), X^3 is N.

[0041] In some embodiments of Formula (II), R^8 is H, halogen, OCH_3 , or CH_3 . In some embodiments of Formula (II), R^8 is halogen. In some embodiments of Formula (II), R^8 is F, Cl, or Br. In some embodiments of Formula (II), R^8 is OCH_3 , or CH_3 . In some embodiments of Formula (II), R^8 is H.

[0042] In some embodiments, the compound of Formula (II) has the structure of Formula (IIa), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIa);

wherein,

X^1 or X^2 are each independently CH_2 , CHR^2 , CR^2R^2 , O, or NR^{2a} ; wherein at least one of X^1 or X^2 is CH_2 , CHR^2 , or CR^2R^2 ;

X^3 is CR^8 ;

Y is CH or CR^1 ;

each R^1 is independently halogen, -CN, -OH, -OR^a, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 deutoalkyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, or C_1 - C_6 hydroxyalkyl;

each R^2 is independently optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 deutoalkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_3 - C_6 cycloalkyl;

R^{2a} is H, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted arylalkyl, or optionally substituted C_3 - C_6 cycloalkyl;

each R^3 is independently C_1 - C_3 alkyl or C_1 - C_3 deutoalkyl;

R^5 is H, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, or C_1 - C_3 hydroxyalkyl;

R^{5b} is H or C_1 - C_3 alkyl;

R^{6a} and R^{6b} are each independently H, -CN, $-C(=O)OR^7$, $-C(=O)N(R^7)_2$, $-S(=O)R^7$, $-S(=O)_2R^7$, or $-S(=O)(=NH)R^7$; wherein

each R^7 is independently optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_6 cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^8 is H, halogen, $-OCH_3$, or $-CH_3$;

each R^a is independently H, C_1 - C_6 alkyl, C_1 - C_6 deuterioalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, C_5 - C_8 aryl, C_5 - C_8 heteroaryl, $-C_1$ - C_6 alkyl(aryl), $-C_1$ - C_6 alkyl(heteroaryl), $-C_1$ - C_6 alkyl(cycloalkyl), or $-C_1$ - C_6 alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkoxy;

each R^b is independently H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

$n1$ and $n2$ are each independently 0, 1, 2, or 3;

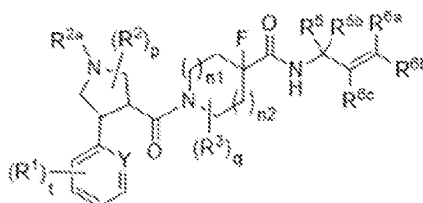
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

[0043] In some embodiments of Formula (II) or (IIa), X^1 is CH_2 , CHR^2 or CR^2R^2 ; and X^2 is CH_2 , CHR^2 , or CR^2R^2 . In some embodiments of Formula (II) or (IIa), X^1 is CH_2 , CHR^2 , or CR^2R^2 ; and X^2 is O or NR^{2a} . In some embodiments of Formula (II) or (IIa), X^1 is CH_2 , CHR^2 , or CR^2R^2 ; and X^2 is O. In some embodiments of Formula (II) or (IIa), X^1 is CH_2 , CHR^2 , or CR^2R^2 ; and X^2 is NR^{2a} . In some embodiments of Formula (II) or (IIa), X^2 is CH_2 , CHR^2 , or CR^2R^2 ; and X^1 is O or NR^{2a} . In some embodiments of Formula (II) or (IIa), X^2 is CH_2 , CHR^2 , or CR^2R^2 ; and X^1 is O. In some embodiments of Formula (II) or (IIa), X^2 is CH_2 , CHR^2 , or CR^2R^2 ; and X^1 is NR^{2a} .

[0044] In some embodiments, the compound of Formula (II) has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIb),

wherein,

Y is CH or CR¹;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deutoalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl;

each R² is independently optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₃-C₆ cycloalkyl;

R^{2a} is H, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted arylalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R³ is independently C₁-C₃ alkyl or C₁-C₃ deutoalkyl;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deutoalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂C₆ alkenyl, C₂C₆ alkynyl, C₃C₆ cycloalkyl, C₃C₆ heterocycloalkyl, C₅C₈ aryl, C₅C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deutoalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and

alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

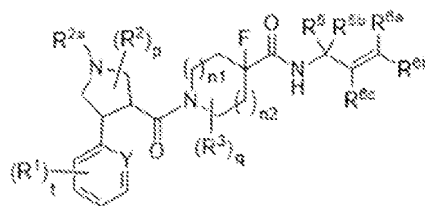
n₁ and n₂ are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (IIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIb),

wherein,

Y is CH or CR¹;

each R¹ is independently Cl, Br, F, -OCH₃, CH₃ or CD₃;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, C₁-C₆ alkyl, C₁-C₆ deutoalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or 4 to 6-membered heterocycloalkyl;

R^{2a} is H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₃-C₆ cycloalkyl;

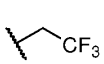
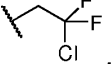
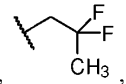
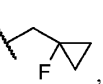
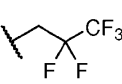
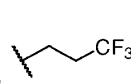
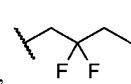
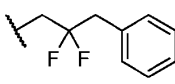
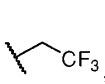
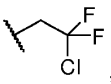
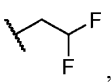
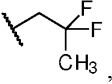
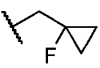
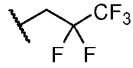
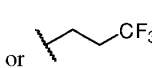
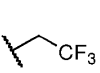
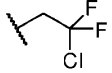
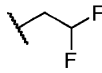
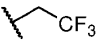
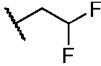
each R³ is independently -CH₃ or -CD₃;

R⁵ is H, -CH₃, or -CH₂CH₃;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, or -S(=O)₂R⁷; wherein

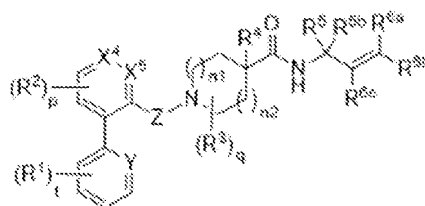
each R⁷ is independently optionally substituted C₁-C₃ alkyl or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

[0048] In some embodiments of Formula (II), (IIa), or (IIb), R^{2a} is , , , , , , , , or . In some embodiments of Formula (II), (IIa), or (IIb), R^{2a} is , , , , , , or . In some embodiments of Formula (II), (IIa), or (IIb), R^{2a} is , , . In some embodiments of Formula (II), (IIa), or (IIb), R^{2a} is , .

[0049] In some embodiments of Formula (I) or (Ia), ring A is phenyl or a 5 to 10-membered heteroaryl. In some embodiments of Formula (I) or (Ia), ring A is a 5 to 8-membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms selected from N, O, and S. In some embodiments of Formula (I) or (Ia), ring A is a 5-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from N or O. In some embodiments of Formula (I) or (Ia), ring A is a 6-membered heteroaryl comprising 1, 2, or 3 heteroatoms selected from N or O. In some embodiments of Formula (I) or (Ia), ring A is phenyl, pyridinyl, pyrimidinyl, pyridin-2-one, furanyl, isoxazolyl, or pyrrolyl. In some embodiments of Formula (I) or (Ia), ring A is phenyl or pyridinyl. In some embodiments of Formula (I) or (Ia), ring A is phenyl. In some embodiments of Formula (I) or (Ia), ring A is pyridinyl.

[0050] In another aspect, provided herein is a compound having the structure of Formula (III), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (III),

wherein,

Y is N, CH, or CR¹;

Z is C(=O) or S(=O)₂;

X^4 is CH, CR², or N;

X^5 is CH, CR^2 , or N;

each R^1 is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R^2 is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R^2 together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R^3 is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R^4 is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;

R^5 is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R^7 is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

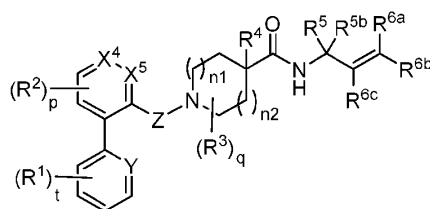
n₁ and n₂ are each independently 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0051] In another aspect, provided herein is a compound having the structure of Formula (III), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (III),

wherein,

Y is CH or CR¹;

Z is C(=O) or S(=O)₂;

X⁴ is CH, CR², or N;

X⁵ is CH, CR², or N;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R³ is independently C₁-C₃ alkyl or C₁-C₃ deuterioalkyl;

R⁴ is halogen;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, or -S(=O)₂R⁷; wherein

each R^7 is independently optionally substituted C_1 - C_3 alkyl or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_1$ - C_6 alkyl(aryl), $-C_1$ - C_6 alkyl(heteroaryl), $-C_1$ - C_6 alkyl(cycloalkyl), or $-C_1$ - C_6 alkyl(heterocycloalkyl); wherein each alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

each R^b is independently H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

n_1 and n_2 are each independently 0, 1, or 2;

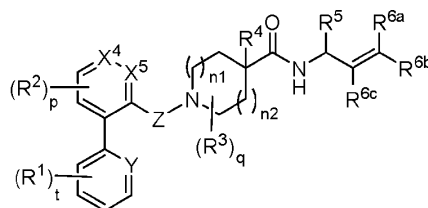
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0052] In some embodiments of Formula (III), Z is $-S(=O)_2-$.

[0053] In another aspect, provided herein is a compound having the structure of Formula (III), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (III),

wherein,

Z is S(=O)₂;

X⁴ is CH, CR², or N;

X⁵ is CH or CR²;

Y is CH or CR¹;

each R¹ is independently halogen, -OR_a, C₁-C₆ alkyl, C₁-C₆ deutoalkyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl;

each R² is independently halogen, -OH, -OR_a, -N(R_b)₂, C₁-C₆ alkyl, C₁-C₆ deutoalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a 5-membered heteroaryl ring;

each R³ is independently -CH₃ or -CD₃;

R⁴ is F;

R⁵ is H, -CH₃, or -CH₂CH₃;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, or -S(=O)₂R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₃ alkyl or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring; R^{5a} is H; or R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R_a is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, cycloalkyl, heterocycloalkyl, or aryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, or aryl, is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

each R_b is independently H or C₁-C₆ alkyl;

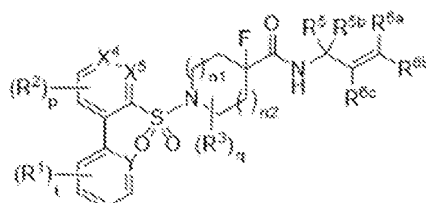
n₁ and n₂ are each independently 1 or 2;

p is 1;

q is 0, 1, or 2; and

t is 1, 2, or 3.

In some embodiments, the compound of Formula (III) has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIIa),

wherein,

Y is CH or CR¹;

X⁴ is CH, CR², or N;

X⁵ is CH, CR², or N;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deutoalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deutoalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

each R³ is independently C₁-C₃ alkyl or C₁-C₃ deutoalkyl;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)N(R⁷)₂, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein each R⁷ is independently C₁-C₃ alkyl, or a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms; or two R⁷ together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms; or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deutoalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deutoalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

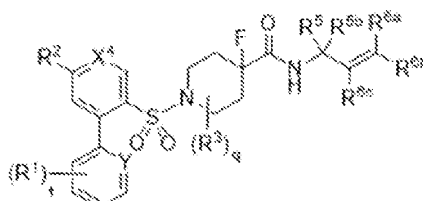
n_1 and n_2 are each independently 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

[0054] In some embodiments, the compound of Formula (III) has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIIb),

wherein,

X^4 is CH or N;

Y is CR¹ or CH;

each R^1 is independently halogen, -CN, -OR^a, optionally substituted C₁-C₄ alkyl, optionally substituted C₁-C₄ deuterioalkyl, C₂-C₄ alkynyl, or C₁-C₃ fluoroalkyl;

R^2 is halogen, -CN, -OH, -OR^a, -N(R^b)₂, -C(=O)R^a, optionally substituted C₁-C₄ alkyl, optionally substituted C₁-C₄ deuterioalkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₃ fluoroalkyl, optionally substituted C₁-C₃ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

Each R^3 is independently -CH₃ or -CD₃;

R^5 is H, -CH₃, or -CH₂CH₃;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)N(R⁷)₂, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein each R^7 is independently C₁-C₃ alkyl, or a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;

or two R^7 together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

each R^a is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or C₁-C₃ fluoroalkyl;

each R^b is independently H or C₁-C₃ alkyl;

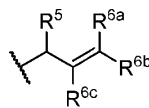
q is 0, 1, or 2; and

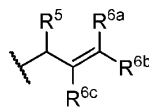
t is 0, 1, or 2.

[0055] In some embodiments of Formula (III) or (IIIa), X⁴ is CH or CR² and X⁵ is CH or CR². In some embodiments of Formula (III) or (IIIa), X⁴ is N and X⁵ is N.

[0056] In some embodiments of Formula (III) or (IIIa), X⁴ is CH or CR². In some embodiments of Formula (III), (IIIa), or (IIIb), X⁴ is CH. In some embodiments of Formula (III), (IIIa), or (IIIb), X⁴ is N.

[0057] In some embodiments of Formula (III) or (IIIa), X⁵ is CH or CR². In some embodiments of Formula (III) or (IIIa), X⁵ is CH. In some embodiments of Formula (III) or (IIIa), X⁵ is N.



[0058] In some embodiments of Formula (I), R^A is , wherein

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷ or -

S(=O)(=NH)R⁷; wherein

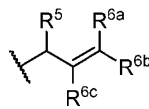
each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

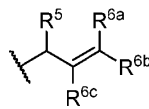
or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring.



[0059] In some embodiments of Formula (I), R^A is , wherein

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂ or -S(=O)₂R⁷; wherein

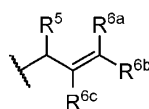
each R⁷ is independently optionally substituted C₁-C₃ alkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

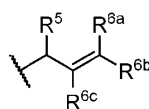
or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring.



[0060] In some embodiments of Formula (I), R^A is , wherein

R⁵ is C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -C(=O)N(R⁷)₂ or -S(=O)₂R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₃ alkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring.

[0061] In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is C₁-C₃ haloalkyl. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is -CF₃ or -CH₂CF₃. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is C₁-C₃ alkyl. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is -CH₃ or -CH₂CH₃. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is -CH₂CH₃. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is -CH₂OCH₃ or -CH₂OCH₂CH₃. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is H, -CH₃, -CH₂CH₃, -CH₂OCF₃, or -CH₂OCH₃. In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R⁵ is H.

[0062] In some embodiments of Formula (I) or (Ia), R^{5a} is H.

[0063] In some embodiments of Formula (I) or (Ia), R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring.

[0064] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6a} is -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂ or -S(=O)₂R⁷; and R^{6b} and R^{6c} are each H. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6a} is -C(=O)N(R⁷)₂ or -S(=O)₂R⁷; and R^{6b} and R^{6c} are each H. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6a} is S(=O)₂R⁷; and R^{6b} and R^{6c} are each H.

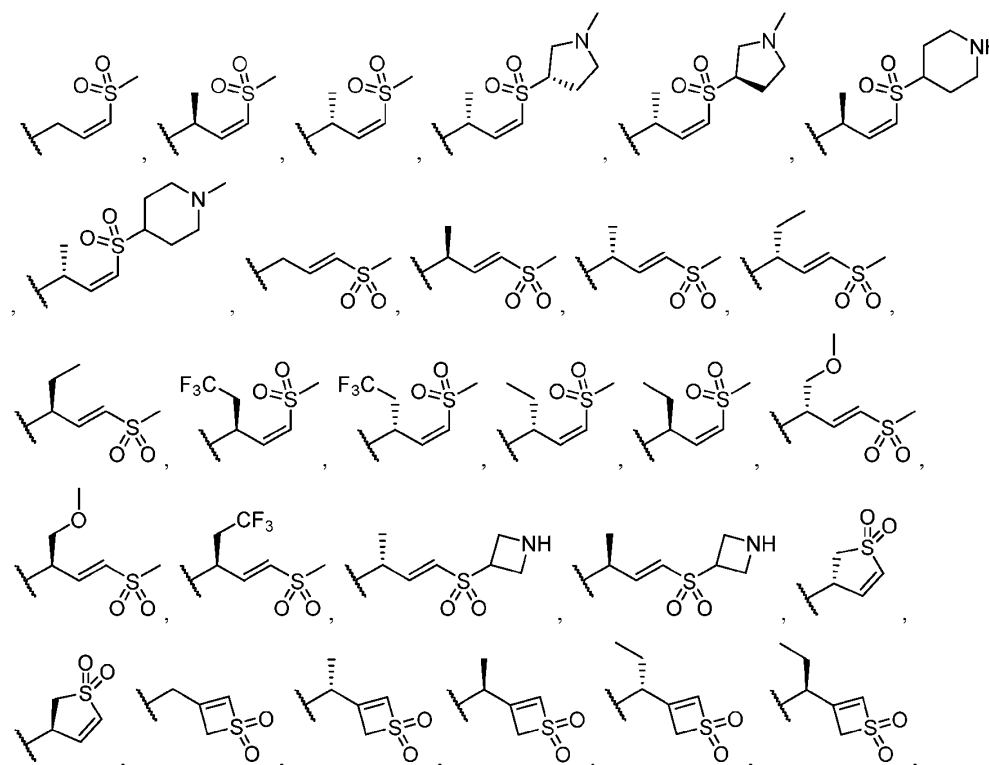
[0065] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6b} is $-\text{CN}$, $-\text{C}(=\text{O})\text{OR}^7$, $-\text{C}(=\text{O})\text{N}(\text{R}^7)_2$ or $-\text{S}(=\text{O})_2\text{R}^7$; and R^{6a} and R^{6c} are each H. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6b} is $-\text{C}(=\text{O})\text{N}(\text{R}^7)_2$ or $-\text{S}(=\text{O})_2\text{R}^7$; and R^{6a} and R^{6c} are each H. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6b} is $\text{S}(=\text{O})_2\text{R}^7$; and R^{6a} and R^{6c} are each H.

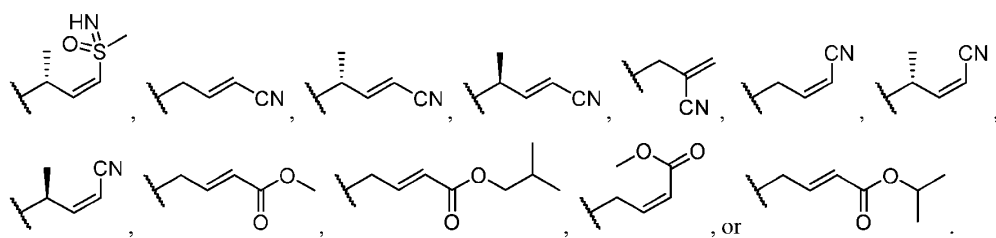
[0066] In some embodiments of Formula (I), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring.

[0067] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring.

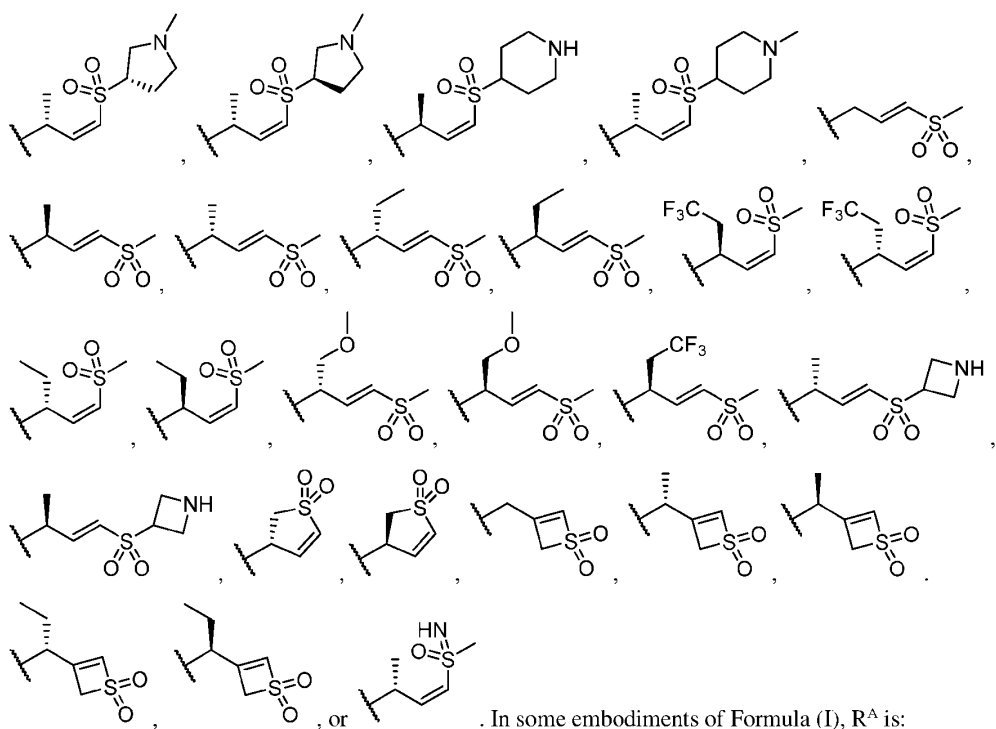
[0068] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^7 is independently optionally substituted C_1 - C_3 alkyl or optionally substituted 4 to 6-membered heterocycloalkyl ring. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^7 is independently C_1 - C_3 alkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^7 is independently a 4 to 6-membered heterocycloalkyl ring.

[0069] In some embodiments of Formula (I), R^A is:

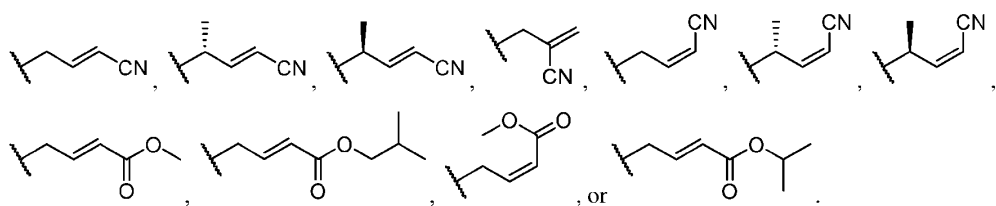


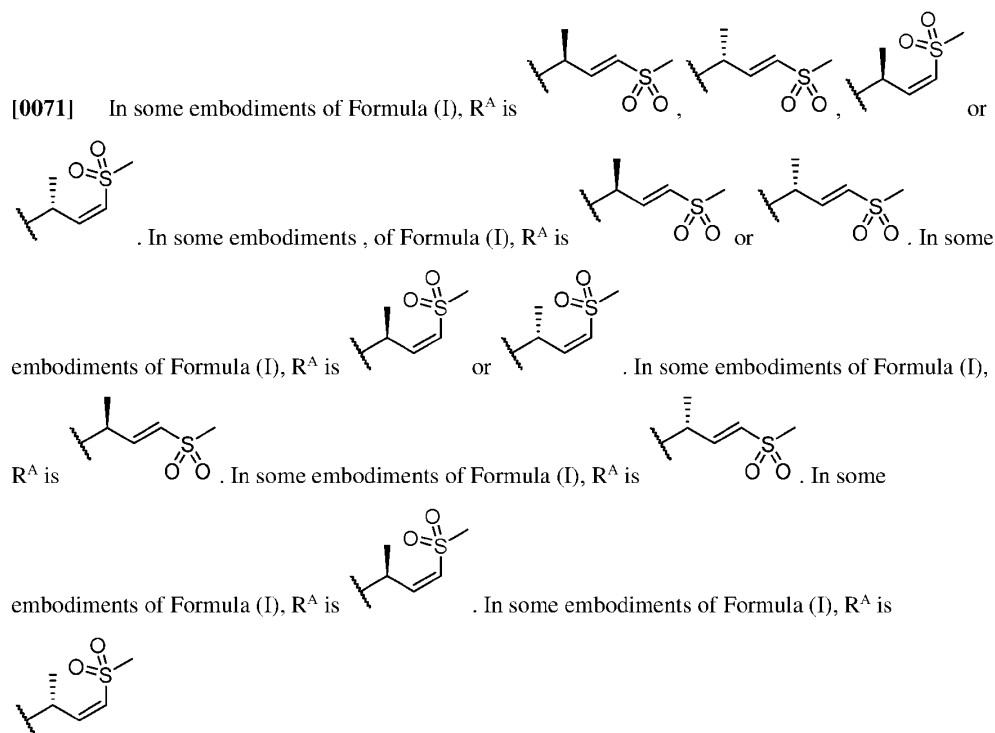


[0070] In some embodiments of Formula (I), R^A is:



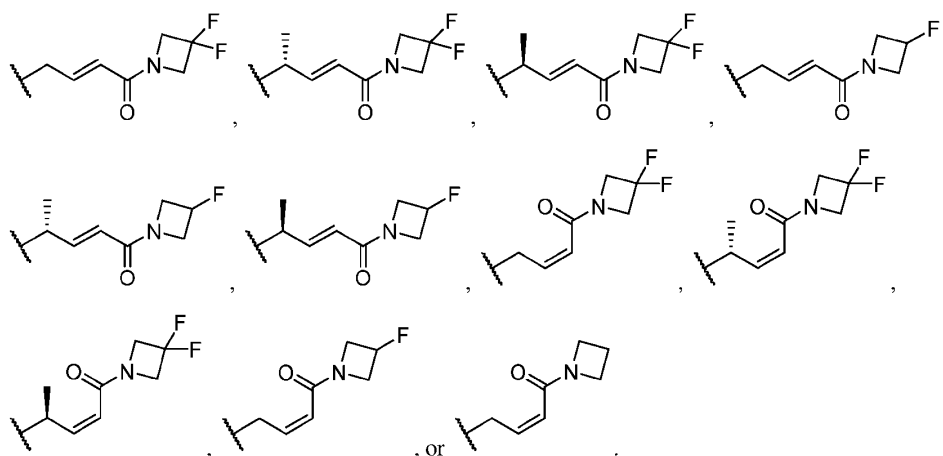
. In some embodiments of Formula (I), R^A is:

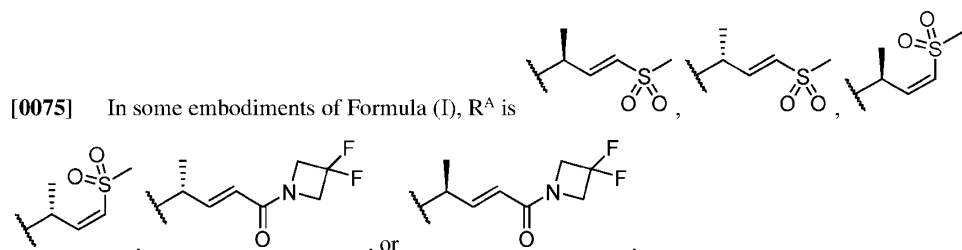
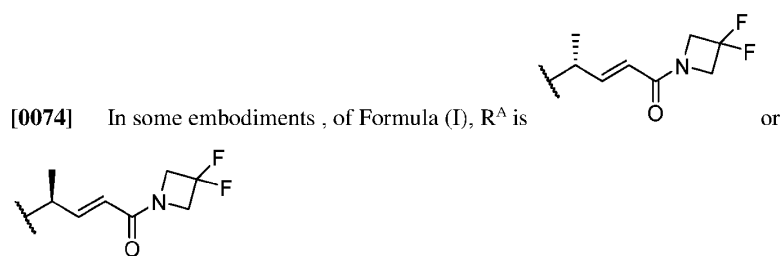




[0072] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6a} is $-C(=O)N(R^7)_2$, and R^{6b} and R^{6c} are each H; or R^{6b} is $-C(=O)N(R^7)_2$, and R^{6a} and R^{6c} are each H, wherein two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered ring. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), R^{6a} is $-C(=O)N(R^7)_2$ and R^{6b} and R^{6c} are each H. In some embodiments, R^{6b} is $-C(=O)N(R^7)_2$ and R^{6a} and R^{6c} are each H.

[0073] In some embodiments of Formula (I), R^A is:





[0076] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently halogen, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or C₁-C₆ hydroxyalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently halogen. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently Br, Cl, or F. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently optionally substituted C₁-C₆ alkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently -CH₃ or -CH₂CH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently -OR^a. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently -O(alkyl), -O(haloalkyl), or -O(cycloalkyl). In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently -OCH₃, -OCH₂CH₃, -OCF₃, -O(cyclopropyl), or -O(cyclobutyl).

[0077] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently Cl, F, -CF₃, -CH₃, -CH₂CH₃, -OCH₃, -O(cyclopropyl), or -O(cyclobutyl). In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently Cl, F, -CH₃, -CH₂CH₃, or -OCH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently Cl, F, or -CH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently Cl or F. In some embodiments of Formula (I), (Ia),

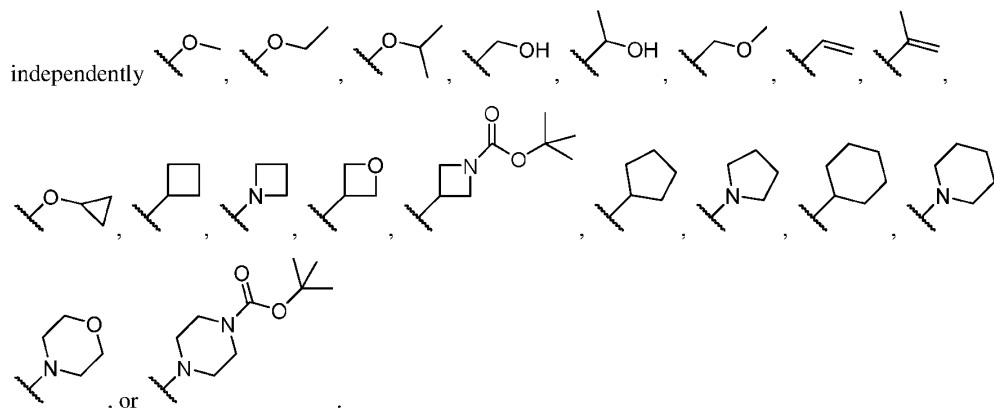
(II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently Cl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^1 is independently F.

[0078] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, oxo (=O), optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkylamino, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl.

[0079] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently halogen. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently Cl, Br, or F. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently -OR^a or -N(R^b)₂. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently -OCH₃, -OCF₃, -OCH₂CH₃, -OCHF₂, -OCH(CH₃)₂, -O(cyclopropyl), or -N(CH₃)₂. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently optionally substituted C₁-C₆ alkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently -CH₃, -CH₂CH₃, -CHCH₂, or -CH(CH₃)₂. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently optionally substituted C₁-C₆ haloalkyl or optionally substituted C₁-C₆ hydroxyalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently -CH₂OH, -CH₂CH₂OH, -CHOHCH₃, -CF₃, -CHF₂, -CH₂CF₃, or -CH₂CHF₂. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently an optionally substituted C₃-C₆ cycloalkyl or optionally substituted 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently azetidine, oxetane, pyrrolidine, piperazine, or morpholine.

[0080] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently Cl, F, Br, -CN, -OH, -OCH₃, -OCF₃, -OCH₂CH₃, -OCHF₂, -OCH(CH₃)₂, -O(cyclopropyl), -N(CH₃)₂, -CH₃, -CH₂CH₃, -CHCH₂, -CH(CH₃)₂, -CH₂OH, -CH₂CH₂OH, -CHOHCH₃, -CF₃, -CHF₂, -CH₂CF₃, -CH₂CHF₂, azetidine, oxetane, pyrrolidine, piperazine, or morpholine or pyrrolidin-2-one. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is independently Cl, F, Br, -OCH₃, -OCF₃, -OCH₂CH₃, -OCHF₂, -OCH(CH₃)₂, -O(cyclopropyl), -N(CH₃)₂, -CH₃, -CH₂CH₃, -CHCH₂, -CH(CH₃)₂, -CH₂OH, -CH₂CH₂OH, -CHOHCH₃, -CF₃, -CHF₂, -CH₂CF₃, or -CH₂CHF₂.

[0081] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^2 is



[0082] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), two R^2 together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or 5-membered heteroaryl ring. In some embodiments, the two R^2 groups are on the same carbon atom or on adjacent atoms. In some embodiments, the two R^2 groups are on the same carbon atom. In some embodiments, the two R^2 groups are on adjacent atoms. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), two R^2 together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl ring. In some embodiments of Formula (I), (Ia), (II), (IIa), or (IIb), two R^2 combine with the carbon atom to which they are attached to form a cyclopropyl or cyclobutyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), two R^2 together with the atom(s) to which they are attached combine to form a 4 to 5-membered heterocycloalkyl ring. In some embodiments of Formula (I), (Ia), (II), (IIa), or (IIb), two R^2 together with the carbon atom to which they are attached form an oxetane.

[0083] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently halogen, -OH, -OR^a, or C₁-C₆ alkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently C₁-C₆ alkyl. In some embodiments, each R^3 is independently C₁-C₃ alkyl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently -CH₃ or -CH₂CH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently -CH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently -CH₂CH₃. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently halogen. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently F, Cl, or Br. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently F. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently Cl. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^3 is independently Br.

[0084] In some embodiments of Formula (I), (Ia), (II), or (III), two R^3 together with the atom(s) to which they are attached combine to form a C₃-C₈ cycloalkyl or 3 to 8-membered heterocycloalkyl ring. In some embodiments of Formula (I), (Ia), (II), or (III), two R^3 together with the atom(s) to which they are attached combine to form a C₃-C₈ cycloalkyl.

[0085] In some embodiments of Formula (I), (II), or (III), R^4 is halogen, -OH, -OR^a, or C₁-C₆ alkyl. In some embodiments of Formula (I), (II), or (III), R^4 is H or halogen. In some embodiments of Formula (I), (II), or (III), R^4 is halogen. In some embodiments of Formula (I), (II), or (III), R^4 is Cl, Br, or F. In some embodiments of Formula (I), (II), or (III), R^4 is F. In some embodiments of Formula (I), (II), or (III), R^4 is -OR^a or C₁-C₆ alkyl. In some embodiments of Formula (I), (II), or (III), R^4 is -OCH₃ or -CH₃. In some embodiments of Formula (I), (II), or (III), R^4 is H.

[0086] In some embodiments of Formula (II), m is 1. In some embodiments of Formula (II), m is 0.

[0087] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), n₁ and n₂ are each independently 0, 1, 2, or 3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), n₁ and n₂ are each independently 0, 1, 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), n₁ and n₂ are each independently 1 or 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), n₁ and n₂ are each independently 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), n₁ is 1 or 2; and n₂ is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), n₁ is 2; and n₂ is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), n₁ is 1; and n₂ is 1.

[0088] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is an integer from 0-8. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is an integer from 0-4. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is an integer from 0-3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 0, 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 0, 1, 2, 3, or 4. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 0, 1, 2, or 3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 0, 1, or 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 1 or 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), p is 0.

[0089] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa) or (IIIb), q is an integer from 0-12. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa) or (IIIb), q is an integer from 0-8. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa) or (IIIb), q is an integer from 0-2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 0, 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 0, 1, 2, 3, or 4. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 0, 1, 2, or 3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 0, 1 or 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 0 or 1. In some embodiments

of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), q is 0.

[0090] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 0, 1, 2, or 3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 0, 1 or 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 0 or 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 3. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 2. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 1. In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), t is 0.

[0091] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, each R^a is independently C₁-C₆ alkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments each R^a is independently C₁-C₆ alkyl or C₁-C₆ heteroalkyl; wherein the alkyl or heteroalkyl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl.

[0092] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, each R^b is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, each R^b is independently H, C₁-C₆ alkyl or C₁-C₆ heteroalkyl; wherein the alkyl or heteroalkyl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, each R^b is hydrogen.

[0093] In some embodiments of Formula (I), (Ia), (II), (IIa), (IIb), (III), or (IIIa), two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered heterocycloalkyl which is optionally substituted with

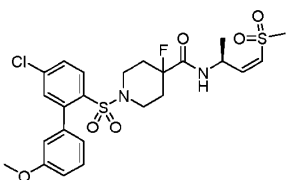
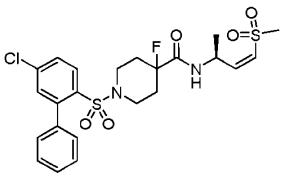
one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form pyrrolidine, piperidine, or morpholine, which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form pyrrolidine, piperidine, or morpholine.

[0094] The compounds of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), and (IIIb) can be present in chiral or achiral form. The form may either be racemic or R or S configuration. The compounds of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), and (IIIb) may be stereoisomers. The compounds may be atropisomers or pharmaceutically acceptable salts of an atropisomer.

[0095] Compounds of the disclosure include, but are not limited to the compound of **Table 1**, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof.

[0096] All stereocenters labeled with (*S*) or (*R*) are known, absolute stereochemistry. In cases where the stereochemistry is pure but unknown, the stereocenter is drawn and defined as (**S*) or (**R*). Stereochemistry that is drawn but not labeled is in the correct cis or trans configuration but are racemic and designated as “*rac*” or *RS*.

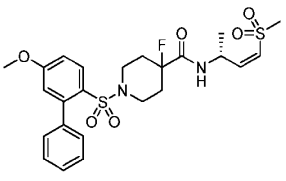
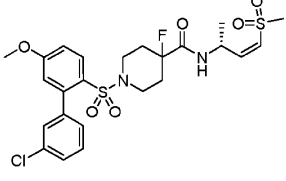
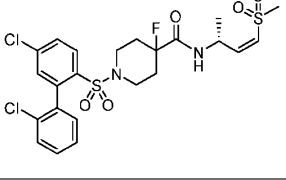
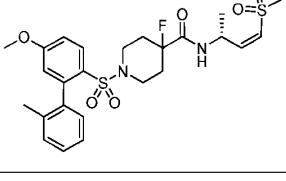
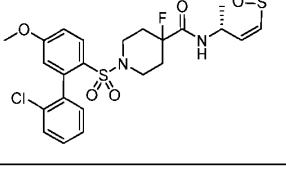
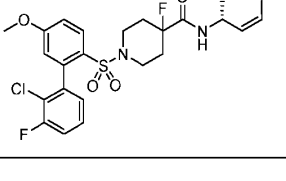
Table 1. Compounds of the Disclosure.

Structure	Cmp. No.	IUPAC
	1	(S,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	2	(S,Z)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

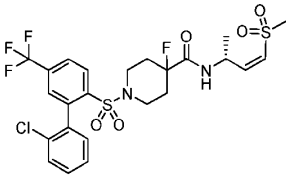
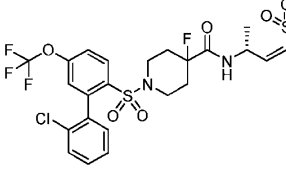
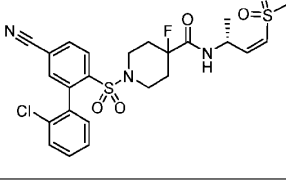
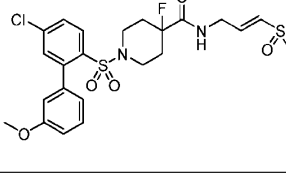
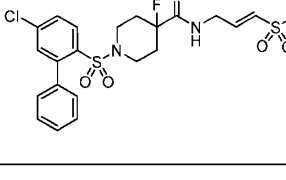
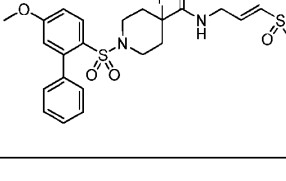
Structure	Cmp. No.	IUPAC
	3	(S,Z)-1-((3',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	4	(S,Z)-4-fluoro-1-((5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	5	(S,Z)-1-((3',5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	6	(S,Z)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	7	(S,Z)-1-((3'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	8	(S,Z)-1-((5-chloro-3'-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

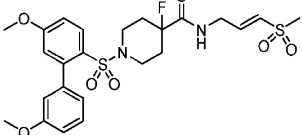
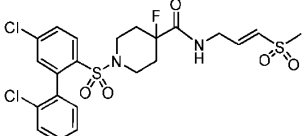
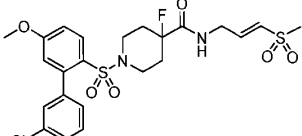
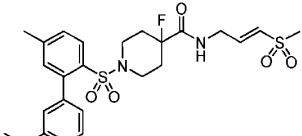
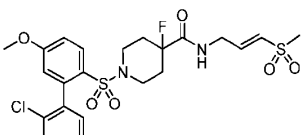
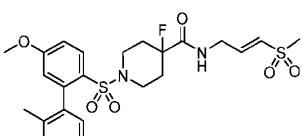
Structure	Cmp. No.	IUPAC
	9	(S,Z)-4-fluoro-1-((5-fluoro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	10	(S,Z)-1-((5-chloro-3'-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	11	(S,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	12	(S,Z)-4-fluoro-1-((5-methoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	13	(S,Z)-1-((3'-butoxy-5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	14	(S,Z)-1-((5-chloro-3'-propoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

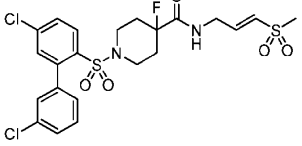
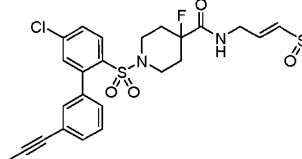
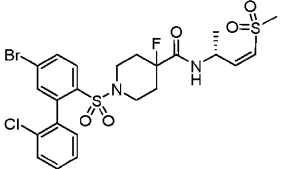
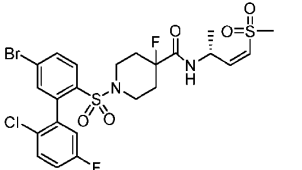
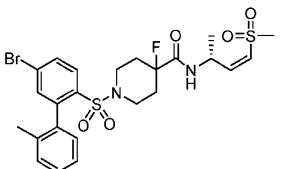
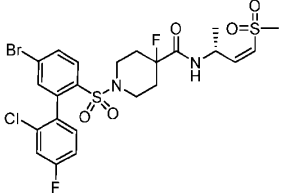
Structure	Cmp. No.	IUPAC
	15	(S,Z)-1-((5-chloro-3'-cyclopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	16	(S,Z)-1-((2',5-dichloro-5'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	17	(S,Z)-1-((5-chloro-3'-(ethoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	18	(S,Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	19	(S,Z)-4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	20	(R,Z)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

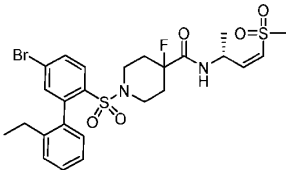
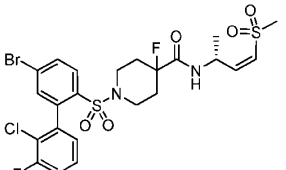
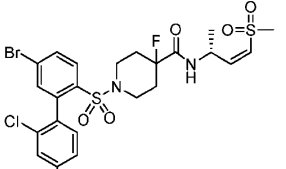
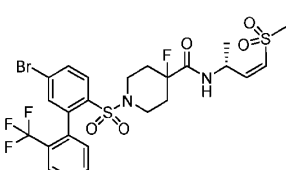
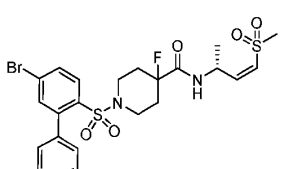
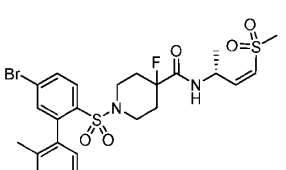
Structure	Cmp. No.	IUPAC
	21	(R,Z)-4-fluoro-1-((5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	22	(R,Z)-1-((3'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	23	(R,Z)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	24	(R,Z)-4-fluoro-1-((5-methoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	25	(R,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	26	(R,Z)-1-((2'-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

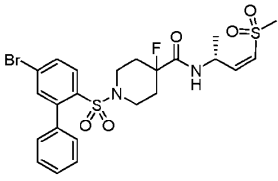
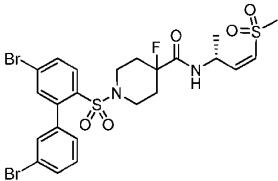
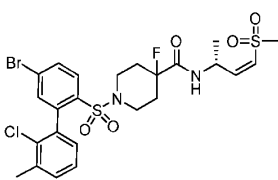
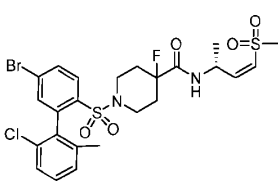
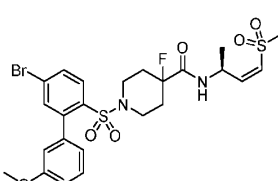
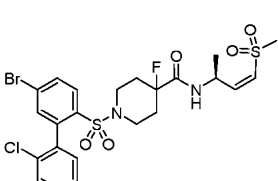
Structure	Cmp. No.	IUPAC
	27	(R,Z)-1-((2'-chloro-4'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	28	(R,Z)-1-((2'-chloro-5'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	29	(R,Z)-1-((2',4-dichloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	30	1-((2'-chloro-6'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	31	(R,Z)-1-((2'-chloro-5-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	32	1-((2',6-dichloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

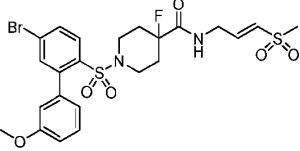
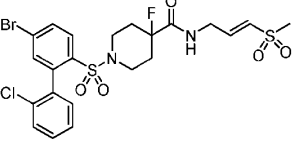
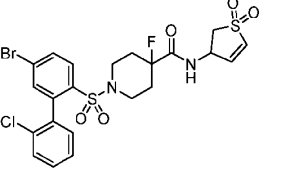
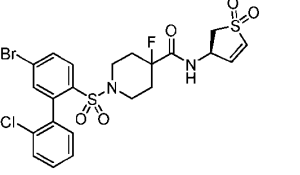
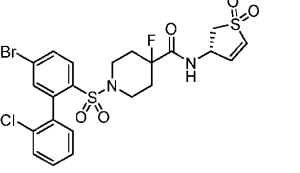
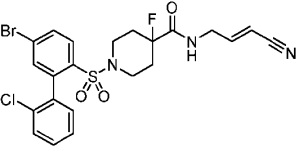
Structure	Cmp. No.	IUPAC
	33	(R,Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	34	(R,Z)-1-((2'-chloro-5-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	35	(R,Z)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	36	(E)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	37	(E)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	38	(E)-4-fluoro-1-((5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	39	(E)-1-((3',5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	40	(E)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	41	(E)-1-((3'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	42	(E)-4-fluoro-1-((3'-methoxy-5-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	43	(E)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	44	(E)-4-fluoro-1-((5-methoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide

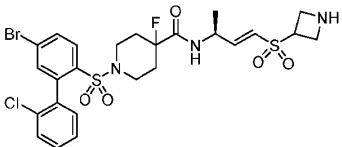
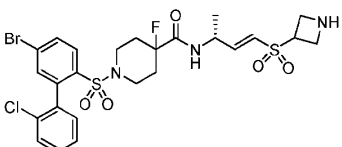
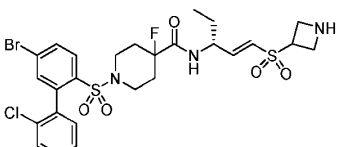
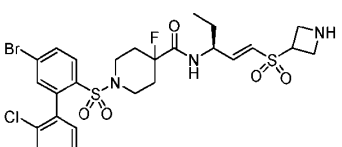
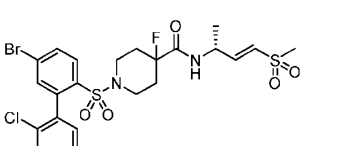
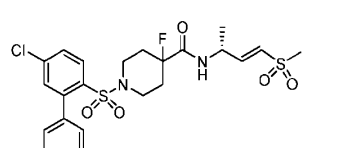
Structure	Cmp. No.	IUPAC
	45	(E)-1-((3',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	46	(E)-1-((5-chloro-3'-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	47	(R,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	48	(R,Z)-1-((5-bromo-2'-chloro-5'-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	49	(R,Z)-1-((5-bromo-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	50	(R,Z)-1-((5-bromo-2'-chloro-4'-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

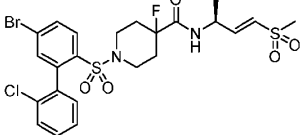
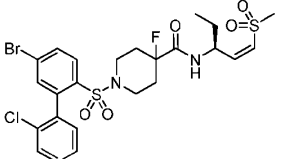
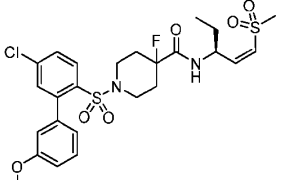
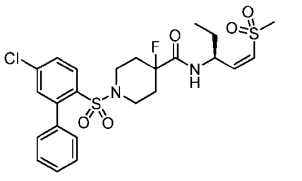
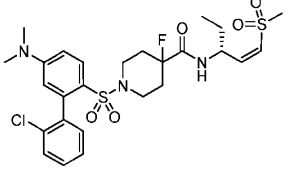
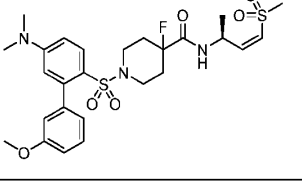
Structure	Cmp. No.	IUPAC
	51	(R,Z)-1-((5-bromo-2'-ethyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	52	(R,Z)-1-((5-bromo-2'-chloro-3'-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	53	(R,Z)-1-((5-bromo-2'-chloro-4'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	54	(R,Z)-1-((5-bromo-2'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	55	(R,Z)-1-((5-bromo-3'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	56	(R,Z)-1-((5-bromo-3'-fluoro-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	57	(R,Z)-1-((5-bromo-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	58	(R,Z)-1-((3',5-dibromo-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	59	(R,Z)-1-((5-bromo-2'-chloro-3'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	60	1-((5-bromo-2'-chloro-6'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	61	(S,Z)-1-((5-bromo-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	62	(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	63	(E)-1-((5-bromo-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	64	(E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	65	<i>rac</i> -1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide
	66	(R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide
	67	(S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide
	68	(E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	69	(E)-N-(3-cyanoallyl)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide
	70	(Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide
	71	(Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide
	72	1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(2-cyanoallyl)-4-fluoropiperidine-4-carboxamide
	73	1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((2R,Z)-4-((RS)-(S-methylsulfonimidoyl)but-3-en-2-yl)piperidine-4-carboxamide
	74	1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-((R)-S-methylsulfonimidoyl)but-3-en-2-yl)piperidine-4-carboxamide

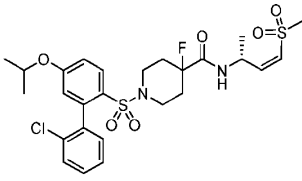
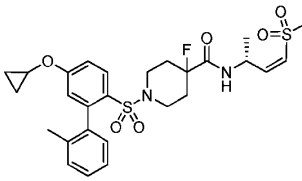
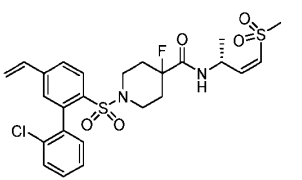
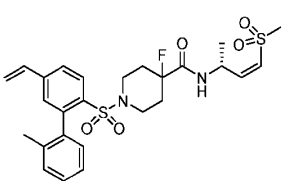
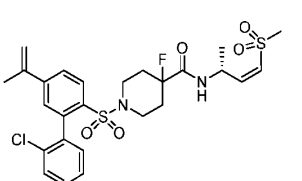
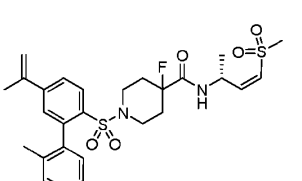
Structure	Cmp. No.	IUPAC
	75	(S,E)-N-(4-(azetidin-3-ylsulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide
	76	(R,E)-N-(4-(azetidin-3-ylsulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide
	77	(R,E)-N-(1-(azetidin-3-ylsulfonyl)pent-1-en-3-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide
	78	(S,E)-N-(1-(azetidin-3-ylsulfonyl)pent-1-en-3-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide
	79	(R,E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	80	(R,E)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

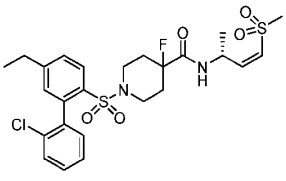
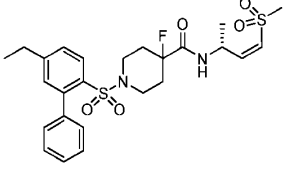
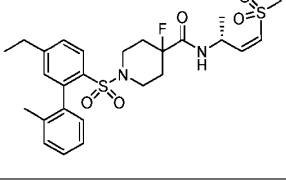
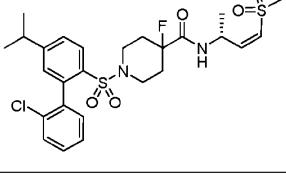
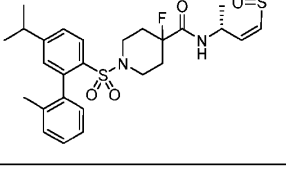
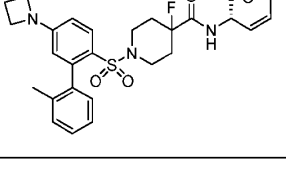
Structure	Cmp. No.	IUPAC
	81	(S,E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	82	(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide
	83	(S,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide
	84	(S,Z)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide
	85	(R,Z)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide
	86	(S,Z)-1-((5-(dimethylamino)-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	87	(S,Z)-1-((2'-chloro-5-(dimethylamino)-5'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	88	(S,Z)-1-((5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	89	(S,Z)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	90	(S,Z)-1-((2'-chloro-5-(dimethylamino)-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	91	(R,Z)-1-((5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	92	(R,Z)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	93	(R,Z)-1-((5-(dimethylamino)-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	94	(E)-1-((5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	95	(E)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	96	(E)-1-((5-(dimethylamino)-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	97	(E)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide
	98	(R,Z)-1-((2'-chloro-5-cyclobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	99	tert-butyl (R,Z)-3-(2'-chloro-6-((4-fluoro-4-((4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidin-1-yl)sulfonyl)-[1,1'-biphenyl]-3-yl)azetidine-1-carboxylate
	100	(S,Z)-1-((5-chloro-3'-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	101	(R,Z)-1-((2'-chloro-5-cyclopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	102	(R,Z)-1-((5-ethoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	103	(R,Z)-4-fluoro-1-((5-isopropoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	104	(R,Z)-1-((2'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	105	(R,Z)-1-((2'-chloro-5-isopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	106	(R,Z)-1-((5-cyclopropoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	107	(R,Z)-1-((2'-chloro-5-vinyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	108	(R,Z)-4-fluoro-1-((2'-methyl-5-vinyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	109	(R,Z)-1-((2'-chloro-5-(prop-1-en-2-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	110	(R,Z)-4-fluoro-1-((2'-methyl-5-(prop-1-en-2-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

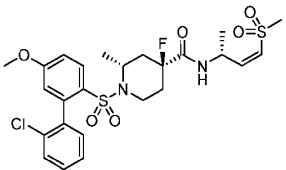
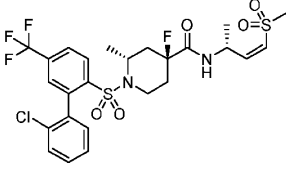
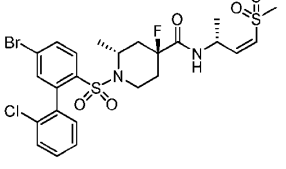
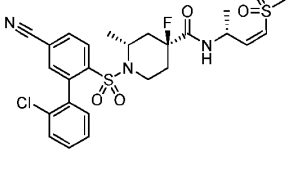
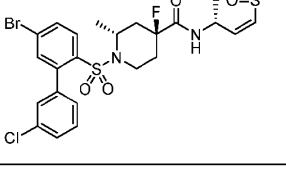
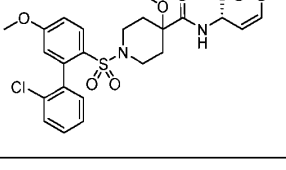
Structure	Cmp. No.	IUPAC
	111	(R,Z)-1-((2'-chloro-5-ethyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	112	(R,Z)-1-((5-ethyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	113	(R,Z)-1-((5-ethyl-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	114	(R,Z)-1-((2'-chloro-5-isopropyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	115	(R,Z)-4-fluoro-1-((5-isopropyl-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	116	(R,Z)-1-((5-(azetidin-1-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	117	(R,Z)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)-1-((5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxamide
	118	tert-butyl (R,Z)-4-(2'-chloro-6-((4-fluoro-4-((4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidin-1-yl)sulfonyl)-[1,1'-biphenyl]-3-yl)piperazine-1-carboxylate
	119	(R,Z)-1-((2'-chloro-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	120	(R,Z)-4-fluoro-1-((2'-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	121	(R,Z)-1-((2'-chloro-5-morpholino-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	122	(R,Z)-4-fluoro-1-((2'-methyl-5-morpholino-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	123	(R,Z)-1-((2'-chloro-4'-fluoro-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	124	(R,Z)-1-((5-(azetidin-1-yl)-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	125	(S,Z)-1-((5-chloro-3'-(2-methoxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	126	(S,Z)-1-((5-chloro-3'-(methoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	127	1-((5-chloro-3'-((E)-(methoxyimino)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((S,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	128	(R,Z)-1-((2'-chloro-5-(2-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	129	1-((2'-chloro-5-(1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	130	(R,Z)-1-((2'-chloro-5-(hydroxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	131	(R,Z)-1-((2'-chloro-5-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	132	(R,Z)-1-((2'-chloro-5-(oxetan-3-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	133	(R,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methoxy-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	134	(R,E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	135	(R,E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	136	(R,E)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	137	(R,E)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	138	(R,E)-1-((5-acetyl-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	139	(R,Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methoxy-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	140	1-((2'-chloro-5-(1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	141	(2R,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	142	(2R,4S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	143	(2R,4S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	144	(2R,4S)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	145	(2R,4S)-1-((5-bromo-3'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	146	(R,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methoxy-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	147	(2*R,4*R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	148	(2*S,4*S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	149	(2R,4S)-1-((2'-chloro-5-(methoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	150	(*R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2,2-dimethyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	151	(2R,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	152	(2R,4S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	153	(2R,4S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	154	(2R,4S)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	155	(2R,4S)-1-((5-bromo-3'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	156	(2R,4S)-1-((2'-chloro-5-(methoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	157	(R,Z)-1-((5-(2-chlorophenyl)benzo[b]thiophen-6-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	158	tert-butyl cis-(3RS,4RS)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate

Structure	Cmp. No.	IUPAC
	159	isopropyl (3R,4R)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate
	160	ethyl (3R,4R)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate
	161	1-((3R,4R)-4-(2-chlorophenyl)-1-pivaloylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	162	1-((3R,4R)-1-benzoyl-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	163	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	164	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	165	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	166	(R)-1-((3R,4R)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	167	(R)-1-((3R,4R)-4-(2-chloro-4-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	168	(R)-1-((3R,4R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	169	(R)-1-((3R,4R)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	170	(R)-1-((3R,4R)-4-(2-chloro-5-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	171	(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	172	(R)-1-((3R,4R)-4-(2-chloro-3-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	173	(R)-1-((3R,4R)-4-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	174	(2S,4S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	175	(2S,4S)-1-((3R,4R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	176	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoroazepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	177	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	178	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	179	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	180	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	181	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoro-2-phenylethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	182	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,3,3,3-pentafluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	183	(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	184	(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(1-fluorocyclopropyl)methyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	185	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(1-fluorocyclopropyl)methyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	186	(R,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	187	(S,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	188	(E)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	189	(E)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	190	(S,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	191	(E)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide
	192	(S,Z)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	193	(R,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	194	(Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	195	(R)-1-((3R,4R)-1-(2-chloro-2,2-difluoroethyl)-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	196	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	197	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	198	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-1-(methylsulfonyl)pent-1-en-3-yl)azepane-4-carboxamide
	199	isopropyl (3S,4S)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate
	200	(S,Z)-1-((5-chloro-3-(3-methoxyphenyl)pyridin-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	201	(S,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	202	(R,Z)-1-((2'-chloro-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	203	(R,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	204	(R,Z)-1-((4-bromo-2-(3-chloropyridin-2-yl)phenyl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	205	(R,Z)-1-((2'-chloro-5-(2-oxopyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	206	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	207	(R,Z)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	208	(S,Z)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	209	(R,Z)-1-((4-(2-chloro-3-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	210	(S,Z)-1-((4-(2-chloro-3-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	211	(R,Z)-1-((4-(2-chloro-4-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	212	(S,Z)-1-((4-(2-chloro-4-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	213	(R,E)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	214	(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	215	(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	216	(R,E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5-(3-fluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)piperidine-4-carboxamide
	217	(R,Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	218	(R,Z)-1-((5-bromo-3-(2-chlorophenyl)pyridin-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	219	(S,Z)-1-((2',5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	220	(S,Z)-1-((5-chloro-3'-(2-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	221	(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	222	(R)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	223	(R)-4-fluoro-1-((3*R,4*R)-4-(2-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	224	(R)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)-1-((3*R,4*R)-4-(o-tolyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)azepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	225	(2*S,4*S)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	226	(R)-1-((3*S,4*S)-4-(2-chloro-3,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	227	(R)-1-((3*S,4*S)-4-(2-chloro-4,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	228	(E)-4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-((1-methylpiperidin-4-yl)sulfonyl)allyl)piperidine-4-carboxamide
	229	(R,E)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-cyanobut-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	230	(Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidin-4-yl(3-(2-(methylsulfonyl)vinyl)azetidin-1-yl)methanone

Structure	Cmp. No.	IUPAC
	231	(R,Z)-1-((6-chloro-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	232	(E)-1-((6-chloro-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide
	233	1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((1,1-dioxido-2H-thiet-3-yl)methyl)-4-fluoropiperidine-4-carboxamide
	234	(*R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide
	235	(R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide
	236	(R)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	237	1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(((R)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	238	1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(((S)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	239	(*S,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide
	240	(*S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide
	241	(R)-1-(5-bromo-2'-chloro-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	242	(R)-1-(2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	243	(R)-1-(5-bromo-2'-chloro-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide
	244	(R)-1-(2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide
	245	(4R)-1-(2'-chloro-6'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide
	246	(R,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	247	(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	248	(R,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	249	(E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-2-methyl-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	250	(2R,4S)-1-((2'-chloro-5-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	251	(2R,4S)-1-((2'-chloro-5-(difluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	252	(2R,4S)-1-((2'-chloro-5-((R,S)-1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	253	(2R,4S)-1-((2'-chloro-5-(difluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	254	(R)-1-((3R,4R)-4-(2-chlorophenyl)-3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	255	1-((1*S,2*S)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	256	1-((3*R,4*S)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2H-pyran-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	257	1-((6*R,7*R)-6-(2-chlorophenyl)spiro[3.5]nonane-7-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	258	tert-butyl 5-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)-3,4-dihydropyridine-1(2H)-carboxylate
	259	tert-butyl (3*R,4*S)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)piperidine-1-carboxylate
	260	(S,Z)-1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	261	(S,Z)-1-((5-chloro-3'-((3-methoxybenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	262	(S,Z)-1-((5-chloro-3'-(pentyloxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	263	(S,Z)-1-((5-chloro-3'-cyclobutoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	264	(S,Z)-1-((3'-(but-2-yn-1-yloxy)-5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	265	(S,Z)-1-((5-chloro-3'-((2-chlorobenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	266	(S,Z)-1-((5-chloro-3'-((3-chlorobenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	267	(S,Z)-1-((5-chloro-3'-phenoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	268	(S,Z)-1-((3'-(benzyloxy)-5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	269	(S,Z)-1-((5-chloro-3'-(pyridin-2-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	270	(S,Z)-1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	271	(S,Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	272	(*R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azocane-4-carboxamide

Structure	Cmp. No.	IUPAC
	273	(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidin-4-yl)(3-((methylsulfonyl)methylene)azetidin-1-yl)methanone
	274	(R,Z)-1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	275	(R,Z)-1-((5-(2-chlorophenyl)-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	276	(R,Z)-1-((4-(2-chlorophenyl)-6-hydroxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	277	(R,Z)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	278	(E)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide

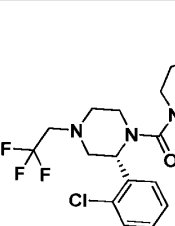
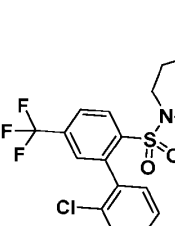
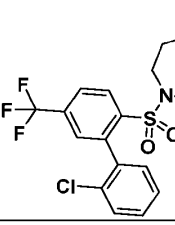
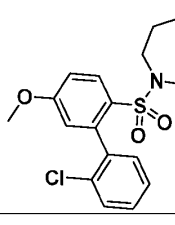
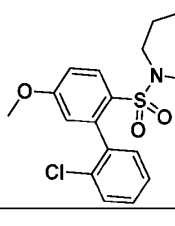
Structure	Cmp. No.	IUPAC
	279	(S,Z)-1-((5-chloro-3'-(propylcarbamoyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	280	(R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(dimethylamino)-5-oxopent-3-yn-2-yl)-4-fluoropiperidine-4-carboxamide
	281	(S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(dimethylamino)-5-oxopent-3-yn-2-yl)-4-fluoropiperidine-4-carboxamide
	282	(E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide
	283	(E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide
	284	(Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide

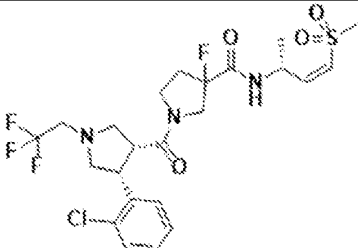
Structure	Cmp. No.	IUPAC
	285	(Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide
	286	(Z)-N-(4-(azetidin-1-yl)-4-oxobut-2-en-1-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide
	287	(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide
	288	(2R,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	289	(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	290	(2R,4S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	291	(2R,4S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	292	(2R,4S)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	293	(2*R,4*S)-1-((3*R,4*S)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2H-pyran-3-carbonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	294	(R)-1-(2'-chloro-5-methoxy-[1,1'-biphenyl]-2-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoroazepane-4-carboxamide
	295	(R)-1-(2'-chloro-5-methoxy-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	296	(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	297	(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((S,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	298	(2R,4S)-1-((2'-chloro-5-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	299	(2R,4S)-1-((2'-chloro-5-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	300	(2R,4S)-1-((2'-chloro-5-(methoxy-d3)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide
	301	(2R,4S)-1-((2'-chloro-5-(methoxy-d3)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	302	(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide

Structure	Cmp. No.	IUPAC
	303	(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	304	1-((3R,4R)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	305	(R)-1-((3*R,4*R)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	306	(R)-1-((3*R,4*R)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	307	1-((3*S,4*S)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide
	308	(R)-1-((3*R,4*S)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	309	(R)-1-((R)-2-(2-chlorophenyl)-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	310	(R)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	311	(S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	312	(R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide
	313	(S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide

Structure	Cmp. No.	IUPAC
	314	1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-3-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)pyrrolidine-3-carboxamide

Any combination of the groups described above for the various variables is contemplated herein.

Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

Further Forms of Compounds

[0097] In some aspects, a compound disclosed herein possesses one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Furthermore, the compounds may exist as atropisomers. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981. In one aspect, stereoisomers are obtained by stereoselective synthesis.

[0098] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid

group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically, or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically, or therapeutically active form of the compound.

[0099] In one aspect, prodrugs are designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug, or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacokinetic, pharmacodynamic processes, and drug metabolism *in vivo*, once a pharmaceutically active compound is known, the design of prodrugs of the compound is possible. (See, for example, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, Inc., San Diego, pages 352-401, Rooseboom *et al.*, *Pharmacological Reviews*, 56:53-102, 2004; Aesop Cho, "Recent Advances in Oral Prodrug Discovery", *Annual Reports in Medicinal Chemistry*, Vol. 41, 395-407, 2006; T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series).

[00100] In some embodiments, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00101] In some embodiments, sites on the aromatic ring portion of compounds described herein are susceptible to various metabolic reactions. Therefore incorporation of appropriate substituents on the aromatic ring structures will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00102] In another embodiment, the compounds described herein are labeled isotopically (e.g., with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00103] The compounds disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of ^2H , ^3H , ^{11}C , ^{13}C and/or ^{14}C . In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

[00104] Unless otherwise stated, compounds described herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of the present disclosure.

[00105] The compounds of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium (^2H), tritium (^3H), iodine-125 (^{125}I) or carbon-14

(¹⁴C). Isotopic substitution with ²H, ¹¹C, ¹³C, ¹⁴C, ¹⁵C, ¹²N, ¹³N, ¹⁵N, ¹⁶N, ¹⁶O, ¹⁷O, ¹⁴F, ¹⁵F, ¹⁶F, ¹⁷F, ¹⁸F, ³³S, ³⁴S, ³⁵S, ³⁶S, ³⁵Cl, ³⁷Cl, ⁷⁹Br, ⁸¹Br, and ¹²⁵I are all contemplated. All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[00106] In some embodiments of a compound disclosed herein, one or more of R¹, R², R³, R⁴, R⁵, R^{5a}, R^{6a}, R^{6b}, R^{6c}, R⁷, and R⁸ groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

[00107] In some embodiments of a compound disclosed herein, one or more hydrogens are replaced with one or more deuteriums in one or more of the following groups R¹, R², R³, R⁴, R⁵, R^{5a}, R^{6a}, R^{6b}, R^{6c}, R⁷, and R⁸.

[00108] In some embodiments of a compound disclosed herein, the abundance of deuterium in each of R¹, R², R³, R⁴, R⁵, R^{5a}, R^{6a}, R^{6b}, R^{6c}, R⁷, and R⁸ is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of a total number of hydrogen and deuterium.

[00109] In certain embodiments, the compounds disclosed herein have some or all of the ¹H atoms replaced with ²H atoms. The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the following synthetic methods.

[00110] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

[00111] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

[00112] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00113] "Pharmaceutically acceptable" as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00114] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, pharmaceutically acceptable

salts are obtained by reacting a compound disclosed herein with acids. Pharmaceutically acceptable salts are also obtained by reacting a compound disclosed herein with a base to form a salt.

[00115] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g., lithium, sodium, potassium), an alkaline earth ion (e.g., magnesium, or calcium), or an aluminum ion. In some cases, compounds described herein may coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein may form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00116] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms, particularly solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Pharmaceutical Compositions

[00117] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a

pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in the manufacture of a medicament.

[00118] In one aspect, the compounds described herein (e.g., compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or pharmaceutically acceptable salts thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof) are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[00119] A pharmaceutical composition, as used herein, refers to a mixture of a compound disclosed herein with other chemical components (i.e., pharmaceutically acceptable inactive ingredients), such as carriers, excipients, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to an organism.

[00120] Pharmaceutical formulations described herein are administrable to a subject in a variety of ways by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intralymphatic, intranasal injections), intranasal, buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00121] In some embodiments, the compounds disclosed herein are administered orally.

[00122] In some embodiments, the compounds disclosed herein are administered topically. In such embodiments, the compound disclosed herein is formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. In one aspect, the compounds disclosed herein are administered topically to the skin.

[00123] In another aspect, the compounds disclosed herein are administered by inhalation.

[00124] In another aspect, the compounds disclosed herein are formulated for intranasal administration. Such formulations include nasal sprays, nasal mists, and the like.

[00125] In another aspect, the compounds disclosed herein are formulated as eye drops.

[00126] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound disclosed herein is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by inhalation to the mammal; and/or (e) administered by nasal administration to the mammal; or and/or (f) administered by injection to the mammal; and/or (g) administered topically to the mammal; and/or (h) administered by ophthalmic administration; and/or (i) administered rectally to the mammal; and/or (j) administered non-systemically or locally to the mammal.

[00127] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound disclosed herein, including further embodiments in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) the compound is administered continually; or (iv) the compound is administered continuously.

[00128] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound disclosed herein, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound disclosed herein is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00129] In certain embodiments, the compound disclosed herein is administered in a local rather than systemic manner.

[00130] In some embodiments, the compound disclosed herein is administered topically. In some embodiments, the compound disclosed herein is administered systemically.

[00131] In some embodiments, the pharmaceutical formulation is in the form of a tablet. In other embodiments, pharmaceutical formulations of the compounds disclosed herein are in the form of a capsule.

[00132] In one aspect, liquid formulation dosage forms for oral administration are in the form of aqueous suspensions or solutions selected from the group including, but not limited to, aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups.

[00133] For administration by inhalation, a compound disclosed herein is formulated for use as an aerosol, a mist, or a powder.

[00134] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner.

[00135] In some embodiments, compounds disclosed herein are prepared as transdermal dosage forms.

[00136] In one aspect, a compound disclosed herein is formulated into a pharmaceutical composition suitable for intramuscular, subcutaneous, or intravenous injection.

[00137] In some embodiments, the compound disclosed herein is be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, or ointments.

[00138] In some embodiments, the compounds disclosed herein are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas.

Methods of Treatment

[00139] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in a method of modulating RAS-PI3K. In some embodiments, the method comprises inhibiting RAS-PI3K. In some embodiments, the method comprises activating RAS-PI3K.

[00140] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in a method of treating a disease or condition. In some embodiments, provided herein is a method of treating a disease or condition, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof. In some embodiments, the disease or condition is mediated by RAS-PI3K. In some embodiments, the disease is cancer.

[00141] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in the manufacture of a medicament for modulating RAS-PI3K.

[00142] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a

pharmaceutically acceptable salt of an atropisomer thereof, for use in treating cancer in a subject in need thereof.

[00143] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in the manufacture of a medicament for treating a cancer in a subject in need thereof.

[00144] In some embodiments, the disease mediated by RAS-PI3K is a cancer. In some embodiments, the cancer is selected from the group consisting of bladder cancer, uterine cancer, head and neck cancer, esophageal cancer, ovarian cancer, liver cancer, lung cancer, colorectal cancer, cervical cancer, cholangiocarcinoma, gastric cancer, kidney cancer, and pancreatic cancer.

[00145] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in a method of treating an immunological disease or condition.

[00146] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in the manufacture of a medicament for treating an immunological disease or condition in a subject in need thereof.

[00147] In some embodiments, the immunological disease or condition is selected from Psoriasis, Psoriatic Arthritis, Crohn's disease, Ulcerative colitis, Lupus (including Systemic Lupus Erythematosus, Cutaneous lupus, Lupus nephritis), Rheumatoid arthritis, Juvenile Idiopathic arthritis, Still's disease, Spondyloarthritis, and Scleroderma, acute cytokine release syndrome associated with viral infections such as COVID, with cell therapies such as CAR-T and with gene therapy.

[00148] In another aspect, provided herein is a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, for use in a method of treating a disease or condition.

[00149] In some embodiments, administration of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof, promotes wound healing.

[00150] In another aspect, provided herein is a use of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (III), (IIIa), or (IIIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a

pharmaceutically acceptable salt of an atropisomer thereof, for the treatment of an immunological disease or condition or cancer.

Dosing and Treatment Regimens

[00151] In one aspect, the compounds disclosed herein are used in the preparation of medicaments for the treatment of diseases or conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound disclosed herein or a pharmaceutically acceptable salt, active metabolite, prodrug, or solvate thereof, in therapeutically effective amounts to said subject.

[00152] In some embodiments, the compositions containing the compound disclosed herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient or subject already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00153] In prophylactic applications, compositions containing the compounds disclosed herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition.

[00154] In some embodiments, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). Doses employed for adult human treatment are typically in the range of 0.01mg-5000 mg per day or from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses.

Combination Treatments

[00155] In certain instances, it is appropriate to administer at least one compound disclosed herein in combination with another therapeutic agent.

[00156] In one specific embodiment, a compound disclosed herein is co-administered with a second therapeutic agent, wherein the compound disclosed herein and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

[00157] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug(s) employed, on the specific drug(s) employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with one or more other therapeutic agents, the compound provided herein is administered either simultaneously with the one or more other therapeutic agents, or sequentially.

[00158] If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms.

Definitions

[00159] As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[00160] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[00161] “Oxo” refers to the =O substituent.

[00162] “Alkyl” refers to a straight or branched hydrocarbon chain radical, having from one to twenty carbon atoms, and which is attached to the rest of the molecule by a single bond. An alkyl comprising up to 10 carbon atoms is referred to as a C₁-C₁₀ alkyl, likewise, for example, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl. Alkyls (and other moieties defined herein) comprising other numbers of carbon atoms are represented similarly. Alkyl groups include, but are not limited to, C₁-C₁₀ alkyl, C₁-C₉ alkyl, C₁-C₈ alkyl, C₁-C₇ alkyl, C₁-C₆ alkyl, C₁-C₅ alkyl, C₁-C₄ alkyl, C₁-C₃ alkyl, C₁-C₂ alkyl, C₂-C₈ alkyl, C₃-C₈ alkyl and C₄-C₈ alkyl. Representative alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*i*-propyl), *n*-butyl, *i*-butyl, *s*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, 1-ethyl-propyl, and the like. In some embodiments, the alkyl is methyl or ethyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted as described below.

[00163] “Alkylene” refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group. In some embodiments, the alkylene is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{CH}_2-$. In some embodiments, the alkylene is $-\text{CH}_2-$. In some embodiments, the alkylene is $-\text{CH}_2\text{CH}_2-$. In some embodiments, the alkylene is $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

[00164] “Alkoxy” refers to a radical of the formula -OR where R is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted as described below. Representative alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy. In some embodiments, the alkoxy is methoxy. In some embodiments, the alkoxy is ethoxy.

[00165] “Heteroalkyl” refers to an alkyl radical as described above where one or more carbon atoms of the alkyl is replaced with a O, N (i.e., NH, N-alkyl) or S atom. “Heteroalkylene” refers to a straight or branched divalent heteroalkyl chain linking the rest of the molecule to a radical group. Unless stated otherwise specifically in the specification, the heteroalkyl or heteroalkylene group may be optionally substituted as described below. Representative heteroalkyl groups include, but are not limited to -OCH₂OMe, -OCH₂CH₂OMe, or -OCH₂CH₂OCH₂CH₂NH₂. Representative heteroalkylene groups

from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, bicyclo[1.1.1]pentyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.2]decane, norbornyl, decalinyl and adamantyl. In some embodiments, the cycloalkyl is monocyclic. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In some embodiments, the monocyclic cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, the cycloalkyl is bicyclic. Bicyclic cycloalkyl groups include fused bicyclic cycloalkyl groups, spiro bicyclic cycloalkyl groups, and bridged bicyclic cycloalkyl groups. In some embodiments, cycloalkyl groups are selected from among spiro[2.2]pentyl, bicyclo[1.1.1]pentyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.2]decane, norbornyl, 3,4-dihydronaphthalen-1(2H)-one and decalinyl. In some embodiments, the cycloalkyl is polycyclic. Polycyclic radicals include, for example, adamantyl. In some embodiments, the polycyclic cycloalkyl is adamantyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

[00171] “Fused” refers to any ring structure described herein which is fused to an existing ring structure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with a nitrogen atom.

[00172] “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo.

[00173] “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

[00174] “Haloalkoxy” refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethoxy, difluoromethoxy, fluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 1,2-difluoroethoxy, 3-bromo-2-fluoropropoxy, 1,2-dibromoethoxy, and the like. Unless stated otherwise specifically in the specification, a haloalkoxy group may be optionally substituted.

[00175] “Heterocycloalkyl” or “heterocyclyl” or “heterocyclic ring” refers to a stable 3- to 14-membered non-aromatic ring radical comprising 2 to 10 carbon atoms and from one to 4 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic ring (which may include a fused bicyclic heterocycloalkyl (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), bridged heterocycloalkyl or spiro heterocycloalkyl), or polycyclic. In some embodiments, the heterocycloalkyl is monocyclic or bicyclic. In some embodiments, the heterocycloalkyl is monocyclic. In some embodiments, the heterocycloalkyl is bicyclic. The nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized. The nitrogen atom may be

optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranlyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl. The term heterocycloalkyl also includes all ring forms of carbohydrates, including but not limited to monosaccharides, disaccharides and oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 8 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 8 carbons in the ring and 1 or 2 N atoms. In some embodiments, heterocycloalkyls have from 2 to 10 carbons, 0-2 N atoms, 0-2 O atoms, and 0-1 S atoms in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons, 1-2 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e., skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl group may be optionally substituted.

[00176] “Heteroaryl” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. The heteroaryl is monocyclic or bicyclic. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, furazanyl, indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Illustrative examples of bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, heteroaryl is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, thiadiazolyl or furyl. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C₁-C₉heteroaryl. In some embodiments, monocyclic heteroaryl is a C₁-C₅heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, a bicyclic heteroaryl is a C₆-C₉heteroaryl.

effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a “therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An “activity decreasing amount,” as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A “function disrupting amount,” as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[00181] The term “pharmaceutical combination” as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g., a compound of Formula (I) and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g., a compound of Formula (I) and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g., the administration of three or more active ingredients.

[00182] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, humans. In one embodiment, the mammal is a human.

[00183] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

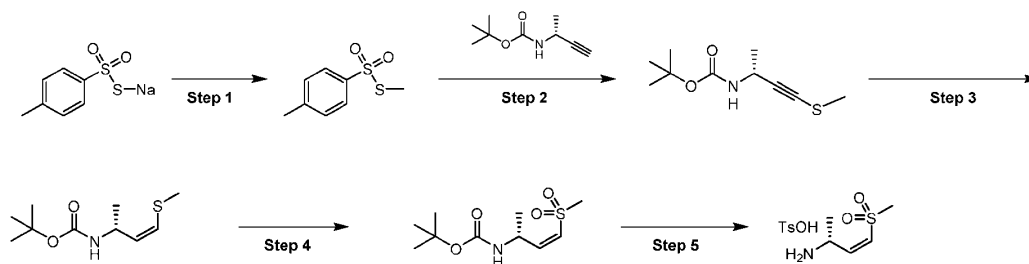
Table 2. Abbreviations.

Acronym	Term
¹ H NMR	Proton nuclear magnetic resonance
ACN, MeCN	Acetonitrile
aq.	Aqueous
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
Boc	<i>tert</i> -Butyloxycarbonyl
DAST	Diethylaminosulfur trifluoride
DCE	Dichloroethane
DCM	Dichloromethane
DEA	Diethylamine
Deoxo-Fluor®	Bis(2-methoxyethyl)aminosulfur trifluoride
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EA, EtOAc	Ethyl acetate
ESI	Electrospray ionization
FCC	Normal phase silica gel column chromatography
h, hr(s)	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
HPLC	High performance liquid chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
KOtBu	Potassium <i>tert</i> -butoxide
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
<i>m</i> -CPBA	meta-Chloroperoxybenzoic acid
min	Minutes
MTBE	Methyl <i>tert</i> -butyl ether
<i>m/z</i>	Mass-to-charge ratio
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NFSI	<i>N</i> -Fluorobenzenesulfonimide
NMP	<i>N</i> -Methyl-2-pyrrolidone
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PE	Petroleum ether
ppm	Parts per million
psi	Pounds per square inch
PTFE	Polytetrafluoroethylene
quant.	Quantitative
RP-HPLC	Reverse phase high performance liquid chromatography
R _t	Retention time
rt	Room temperature
RuPhos Pd G4	[Dicyclohexyl(2',6'-diisopropoxy-2-biphenyl)phosphine-κ <i>P</i>](methanesulfonato-κ <i>O</i>)[2'-(methylamino-κ <i>N</i>)-2-biphenyl-κ <i>C</i> ²]palladium
sat.	Saturated
Selectfluor®	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SFC	Supercritical fluid chromatography

Acronym	Term
SPhos Pd G4	(<i>SP</i> -4-3)-[Dicyclohexyl(2',6'-dimethoxy[1,1'-biphenyl]-2-yl)phosphine- κ P](methanesulfonato- κ O)[2'-(methylamino- κ N)[1,1'-biphenyl]-2-yl- κ C]palladium
T ₃ P®	2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TsOH	<i>p</i> -Toluenesulfonic acid
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	Dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane

Example 1. Synthesis of the Compounds of the Disclosure

Scheme 1. Synthesis of Intermediate (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine



[00184] **Step 1.** To a solution of sodium 4-methylbenzenesulfonothioate (30 g, 143 mmol, 1.0 eq) in DMF (100 mL, 1.4 M) was added iodomethane (8.9 mL, 143 mmol, 1.0 eq). The reaction was stirred for 24 h at 25°C under N₂. The reaction mixture was quenched with water (300 mL) and extracted with EtOAc (300 mL × 2). The combined organic layers were washed with brine (300 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 50:1) to give *S*-methyl 4-methylbenzenesulfonothioate (27 g, 133 mmol, 94% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.81 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 2.50 (s, 3H), 2.46 (s, 3H).

[00185] **Step 2.** *n*-Butyllithium (39.7 mL, 99.3 mmol, 2.1 eq) was added dropwise to a stirred solution of *tert*-butyl (*R*)-but-3-yn-2-ylcarbamate (8.0 g, 47.3 mmol, 1.0 eq) and *N,N,N',N'*-tetramethylethylenediamine (5.5 g, 47.3 mmol, 1.0 eq) in anhydrous THF (30 mL, 0.24 M) at 0°C under N₂ atmosphere. After 30 minutes, *S*-methyl 4-methylbenzenesulfonothioate (10 g, 49.6 mmol, 1.1 eq) in THF (80 mL, 0.60 M) was added. The reaction was stirred at 0°C for 2 h before being quenched by sat. aq. NH₄Cl (200 mL) at 0°C and extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 5:1) to afford *tert*-butyl (*R*)-4-(methylthio)but-3-yn-2-ylcarbamate (9.0 g, 41.8 mmol, 88% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.65 - 4.76 (m, 1H), 4.50 - 4.63 (m, 1H), 2.37 (s, 3H), 1.46 (s, 9H), 1.39 (d, *J* = 6.88 Hz, 3H).

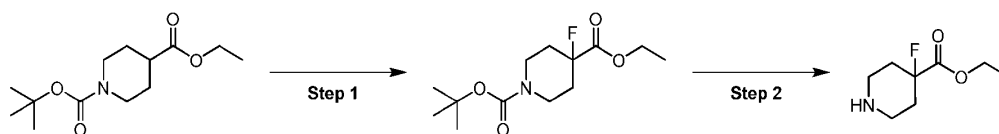
[00186] **Step 3.** *tert*-Butyl (*R*)-(4-(methylthio)but-3-en-2-yl)carbamate (3.0 g, 13.9 mmol, 1.0 eq), Lindlar catalyst (900 mg), and hexene (6 mL) were taken up in methanol (30 mL, 0.46 M). The reaction was stirred under H₂ (30 psi) at 25°C for 3 h. The mixture was filtered concentrated under vacuum. The resulting residue was purified by FCC (PE:EtOAc = 3:1) to afford *tert*-butyl (*R,Z*)-(4-(methylthio)but-3-en-2-yl)carbamate (2.6 g, 12.0 mmol, 86% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.96 (d, *J* = 9.6 Hz, 1H), 5.43 (dd, *J* = 8.0, 9.5 Hz, 1H), 4.63 - 4.34 (m, 2H), 2.28 (s, 3H), 1.45 (s, 9H), 1.22 (d, *J* = 6.4 Hz, 3H).

[00187] **Step 4.** To a solution of *tert*-butyl (*R,Z*)-(4-(methylthio)but-3-en-2-yl)carbamate (2.6 g, 12.0 mmol, 1.0 eq) in DCM (10 mL, 1.2 M) was added 3-chloroperbenzoic acid (6.2 g, 35.9 mmol, 3.0 eq) in portions over 5 min. The reaction was stirred at 25°C for 2 h before being diluted with sat. aq. Na₂SO₃ (100 mL × 2) and extracted with DCM (200 mL). The extract was washed with sat. aq. NaHCO₃ (100 mL × 2) then washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:1) to afford *tert*-butyl (*R,Z*)-(4-(methylsulfonyl)but-3-en-2-yl)carbamate (2.4 g, 9.47 mmol, 79% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.31 - 6.22 (m, 1H), 6.21 - 6.11 (m, 1H), 4.63 (s, 1H), 3.19 (s, 3H), 1.42 (s, 9H), 1.31 (d, *J* = 6.8 Hz, 3H).

[00188] **Step 5.** *tert*-Butyl (*R,Z*)-(4-(methylsulfonyl)but-3-en-2-yl)carbamate (2.4 g, 9.47 mmol, 1.0 eq) and *p*-toluenesulfonic acid monohydrate (1.8 g, 9.47 mmol, 1.0 eq) were taken up in MeCN (30 mL, 0.32 M). The reaction was stirred at 40 °C for 16 h. The mixture was concentrated under vacuum to afford (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine (TsOH salt, 3.0 g, 9.33 mmol, 99% yield) as a white solid, which was used in the next step directly. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.13 (br s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 11.2 Hz, 1H), 6.37 (dd, *J* = 9.6, 11.2 Hz, 1H), 5.09 (br s, 2H), 4.95 - 4.75 (m, 1H), 3.12 (s, 3H), 2.29 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 3H).

[00189] **Intermediate (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine, 4-methylbenzenesulfonic acid salt** was synthesized in an analogous manner to (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine starting with *tert*-butyl (*S*)-but-3-en-2-ylcarbamate.

Scheme 2. Synthesis of Intermediate ethyl 4-fluoropiperidine-4-carboxylate



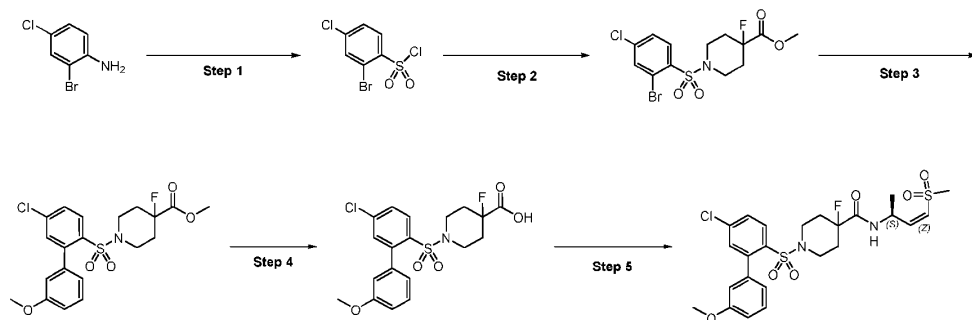
[00190] **Step 1.** To a solution of 1-*tert*-butyl 4-ethyl piperidine-1,4-dicarboxylate (54 g, 209.9 mmol, 1 eq) in THF (500 mL) was added 2 M LDA (157 mL, 315 mmol, 1.5 eq) dropwise at -45°C and the mixture was stirred at -45°C for 0.5 hour. Then to the mixture was added NFSI (82.7 g, 262 mmol, 1.3 eq) in THF (500 mL) dropwise and the resulting solution was stirred at -45°C for 1 hr and at -45~15°C for 1 hr. The reaction was quenched with sat. aq. NH₄Cl (1 L) and extracted with EtOAc (1 L × 2). The combined organic phases were washed with brine (1 L × 2), dried over Na₂SO₄, filtered, concentrated and

purified by FCC (PE:EtOAc = 9:1) to give 1-*tert*-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate as a light yellow oil (47.3 g, 172 mmol, 82% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.26 (q, *J* = 7.2 Hz, 2H), 4.09 - 3.94 (m, 2H), 3.11 (br s, 2H), 2.05 (s, 1H), 1.99 - 1.88 (m, 3H), 1.48 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H).

[00191] Step 2. A mixture of 1-*tert*-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (30 g, 109 mmol, 1 eq) in HCl/EtOAc (4 M, 350 mL) was stirred at 25°C for 1 hr. The reaction was concentrated to give a crude product as a pink solid. The crude product was washed with a mixture solvent MTBE/PE (1:1, 100 mL × 3) to give ethyl 4-fluoropiperidine-4-carboxylate as a light pink solid (22.3 g, 106 mmol, 97%). ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 4.28 (q, *J* = 7.1 Hz, 2H), 3.48 - 3.39 (m, 2H), 3.30 - 3.20 (m, 2H), 2.42 - 2.18 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H).

[00192] Intermediate methyl 4-fluoropiperidine-4-carboxylate was prepared from 1-*tert*-butyl 4-methyl 4-fluoropiperidine-1,4-dicarboxylate in a manner analogous to Step 2 of the synthesis of ethyl 4-fluoropiperidine-4-carboxylate.

Scheme 3. Synthesis of (*S,Z*)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 1)



[00193] Step 1. 2-Bromo-4-chloroaniline (1.5 g, 7.26 mmol, 1.0 eq) was added in one portion to a mixture of concentrated hydrochloric acid (3 mL) and glacial acetic acid (1 mL) in a beaker equipped with a mechanical stirrer. The thick pink hydrochloride salt was cooled in an ice bath to 0°C. A solution of sodium nitrite (553 mg, 8.0 mmol, 1.1 eq) in water (1.5 mL) was added dropwise at a rate such that the temperature did not exceed 0°C. This mixture was stirred for 45 min at 0°C. In a separate beaker, sulfur dioxide gas was bubbled through 5 mL of glacial acetic acid under vigorous stirring for 30 minutes. Copper(I) chloride (274 mg) was added to this solution and bubbling of sulfur dioxide gas was continued until the yellow-green suspension became blue-green and most of the solids dissolved (about 30 minutes). This mixture was cooled to 0°C in an ice bath with stirring and to it was added the diazotization mixture in portions over 30 minutes, after which period the ice bath was removed and the mixture was allowed to warm to rt. The mixture was stirred for an additional 30 minutes. The reaction was poured into ice water (10 mL) and the precipitated gummy solid was extracted with MTBE (20 mL × 3). The combined extracts were washed with sat. aq. sodium bicarbonate (30 mL) until neutral and washed with water (30 mL × 2), dried over Na₂SO₄, filtered, and concentrated under vacuum to yield 2-bromo-4-

chloro-benzenesulfonyl chloride as a dark green solid (1.4 g, 4.72 mmol, 65%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.14 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.0 Hz, 1H).

[00194] Step 2. To a solution of methyl 4-fluoropiperidine-4-carboxylate (300 mg, 1.52 mmol, 1 eq) in DCM (5 mL, 0.3 M) was added TEA (307 mg, 3.04 mmol, 2 eq) and 2-bromo-4-chloro-benzenesulfonyl chloride (572 mg, 1.97 mmol, 1.3 eq) at 0°C. The reaction was stirred at 25°C for 2 hrs. The reaction mixture was poured into water (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica (PE:EtOAc = 8:2) to provide methyl 1-(2-bromo-4-chloro-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (600 mg, 1.45 mmol, 95% yield) as a yellow oil. [M+H] calculated for C₁₃H₁₄BrClFNO₄S, 415; found 416.

[00195] Step 3. To a solution of methyl 1-(2-bromo-4-chloro-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (200 mg, 0.48 mmol, 1.0 eq) and 3-methoxyphenylboronic acid (80.6 mg, 0.53 mmol, 1.1 eq) in toluene (9 mL, 0.04 M) and water (3 mL, 0.04 M) was added Na₂CO₃ (153 mg, 1.45 mmol, 3.0 eq) and Pd(PPh₃)₄ (55.7 mg, 0.05 mmol, 0.1 eq) at 25°C under N₂. The mixture was stirred at 80°C for 18 h. After cooling to rt, the reaction mixture was poured into water (15 mL) and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (PE:EtOAc = 80:20) to provide methyl 1-[4-chloro-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (160 mg, 0.36 mmol, 75% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.02 (d, *J* = 8.7 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.23 - 7.31 (m, 2H), 6.84 - 6.95 (m, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 3.12 (br d, *J* = 13.1 Hz, 2H), 2.50 - 2.60 (m, 2H), 1.65 - 1.81 (m, 4H). [M+H] calculated for C₂₀H₂₁ClFNO₅S, 441; found 442.

[00196] Step 4. To a solution of methyl 1-[4-chloro-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (160 mg, 0.36 mmol, 1.0 eq) in THF (6 mL, 0.05 M) and water (2 mL, 0.05 M) was added LiOH (43.4 mg, 1.81 mmol, 5.0 eq). The mixture was stirred at 50°C for 3 hrs. After cooling to rt, the mixture was acidified with 1N HCl to pH = 4-5, poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Compound 1-[4-chloro-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid was obtained as a yellow oil (140 mg, 0.33 mmol, 90%).

[00197] Step 5. To a solution of 1-[4-chloro-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (50 mg, 0.12 mmol, 1 eq) in DCM (3 mL, 0.04 M) was added (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine (TsOH salt, 41 mg, 0.13 mmol, 1.1 eq), HATU (67 mg, 0.18 mmol, 1.5 eq) and DIPEA (38 mg, 0.29 mmol, 2.5 eq) at 0 °C. The mixture was stirred at 25°C for 2 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM:MeOH = 20:1) to give (*S,Z*)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-

yl)piperidine-4-carboxamide (**Compound 1**) (35 mg, 0.06 mmol, 53%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.36 (br d, $J = 7.9$ Hz, 1H), 8.04 (d, $J = 8.5$ Hz, 1H), 7.70 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.47 (d, $J = 2.3$ Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 6.93 - 7.03 (m, 3H), 6.45 (d, $J = 11.2$ Hz, 1H), 6.26 (dd, $J = 11.1, 9.6$ Hz, 1H), 5.25 - 5.41 (m, 1H), 3.78 (s, 3H), 3.12 (s, 5H), 2.52 - 2.56 (m, 2H), 1.58 - 1.84 (m, 4H), 1.20 (d, $J = 6.78$ Hz, 3H). $[\text{M}+\text{H}]$ calculated for $\text{C}_{24}\text{H}_{28}\text{ClFN}_2\text{O}_6\text{S}_2$, 558.1; found 559.1.

[00198] **Compounds 2-18, Compounds 219-220, and Compounds 267-268** were synthesized in a manner analogous to **Compound 1** starting with the appropriate aniline in Step 1 and the appropriate boronic acid in Step 3. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00199] **Compound 19** and **Compound 200** were synthesized from the appropriate sulfonyl chloride in a manner analogous to Steps 2-5 of **Compound 1**.

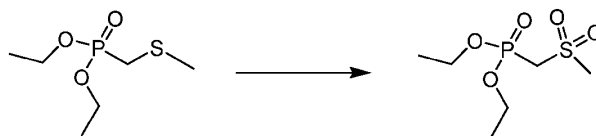
[00200] **Intermediates 4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxylic acid** and **1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid** were synthesized from the appropriate sulfonyl chloride and boronic acid in a manner analogous to Steps 2-4 of **Compound 1**.

[00201] **Compound 201** was synthesized in a manner analogous to **Compound 1** using ethyl 4-methyl-4-piperidinecarboxylate hydrochloride in Step 2.

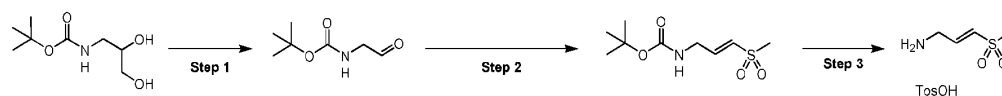
[00202] **Compound 203** was synthesized in a manner analogous to **Compound 201** using (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine, TsOH salt in Step 5.

[00203] **Intermediate ethyl 1-((5-chloro-3'-hydroxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate** was prepared in a manner analogous to **Compound 1**, Steps 1-3, using 3-hydroxyphenylboronic acid in Step 3.

Scheme 4. Synthesis of Intermediate 1-[ethoxy(methylsulfonylmethyl)phosphoryl]oxyethane



[00204] To a mixture of diethyl (methylthiomethyl)phosphonate (20 g, 101 mmol, 1 eq) in MeCN (160 mL, 0.42 M) and water (80 mL, 0.42 M) was added oxone (185 g, 303 mmol, 3 eq) in portions at 0-5°C. The mixture was stirred at 25°C for 2 h. The reaction mixture was filtered and the filtrate was quenched with sat. aq. Na_2SO_3 (200 mL) at 0-5°C, then the mixture was concentrated under reduced pressure to remove MeCN. The residue was extracted with DCM (100 mL $\times$ 2). The combined organic layers were washed with brine (100 mL $\times$ 1), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give 1-[ethoxy(methylsulfonylmethyl)phosphoryl]oxyethane (21 g, 91.2 mmol, 90%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.20 - 4.32 (m, 4H), 3.59 (d, $J = 16.4$ Hz, 2H), 3.21 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 6H).

Scheme 5. Synthesis of Intermediate (*E*)-3-(methylsulfonyl)prop-2-en-1-amine

[00205] **Step 1.** To a suspension of *tert*-butyl *N*-(2,3-dihydroxypropyl)carbamate (2.5 g, 13.1 mmol, 1 eq) in water (20 mL, 0.65 M) was added NaIO₄ (3.1 g, 14.4 mmol, 1.1 eq) at 0°C. The flask was covered in foil to protect NaIO₄ from light. The mixture was stirred for 4 h at 0°C under N₂. The mixture was extracted with DCM (10 mL × 5). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *tert*-butyl *N*-(2-oxoethyl)carbamate (1.6 g, 9.80 mmol, 75%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.65 (s, 1H), 5.21 (br s, 1H), 4.07 (br d, *J* = 4.5 Hz, 2H), 1.45 (s, 9H).

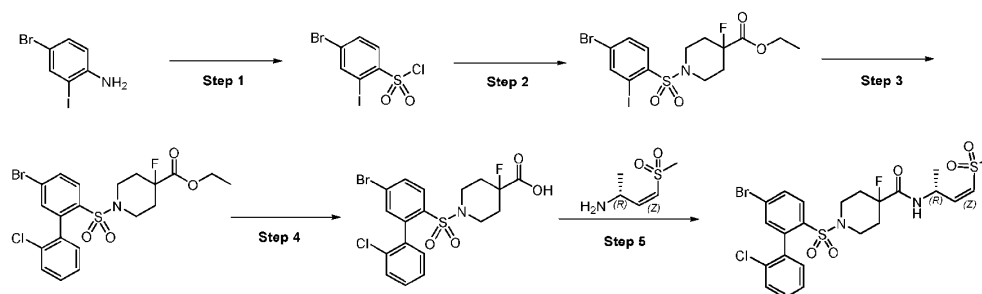
[00206] **Step 2.** To a suspension of 1-[ethoxy(methylsulfonylmethyl)phosphoryl]oxyethane (13.6 g, 59.07 mmol, 1 eq) and potassium carbonate (24.5 g, 177 mmol, 3 eq) in THF (140 mL, 0.42 M) was added *tert*-butyl *N*-(2-oxoethyl)carbamate (8.5 g, 53.2 mmol, 0.9 eq) at 25°C under N₂. The mixture was stirred at 50°C for 8 h. After cooling to rt, the mixture was diluted with water (150 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by FCC (PE:EtOAc = 4:1 to 1:1) to give *tert*-butyl *N*-[(*E*)-3-methylsulfonylallyl]carbamate (8.5 g, 36.1 mmol, 61%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.89 - 6.96 (m, 1H), 6.46 - 6.55 (m, 1H), 4.77 - 4.91 (m, 1H), 3.93 - 4.05 (m, 2H), 1.46 (s, 9H), 2.95 (s, 3H).

[00207] **Step 3.** To a solution of *tert*-butyl *N*-[(*E*)-3-methylsulfonylallyl]carbamate (8.5 g, 36.3 mmol, 1 eq) in MeCN (85 mL, 0.43 M) was added *p*-toluenesulfonic acid monohydrate (8.3 g, 43.5 mmol, 1.2 eq). The mixture was stirred at 60°C for 12 h. Then the reaction was filtered and concentrated under reduced pressure to give 4-methylbenzenesulfonate; (*E*)-3-methylsulfonylprop-2-en-1-amine (6.7 g, 21.9 mmol, 60%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.04 (br s, 3H), 7.45 - 7.52 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.97 (dt, *J* = 15.48, 1.6 Hz, 1H), 6.73 (dt, *J* = 15.42, 5.6 Hz, 1H), 3.74 (dd, *J* = 5.57, 1.6 Hz, 2H), 3.05 (s, 3H), 2.28 (s, 3H).

[00208] **Compounds 36-45** were synthesized in a manner analogous to **Compound 1** starting with the appropriate aniline in Step 1, the appropriate boronic acid in Step 3 and using (*E*)-3-methylsulfonylprop-2-en-1-amine in Step 5. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00209] **Intermediate 3-((methylsulfonyl)methylene)azetidine** was synthesized in a manner analogous to (*E*)-3-(methylsulfonyl)prop-2-en-1-amine, Steps 2-3, starting with *tert*-butyl 3-oxoazetidine-1-carboxylate in Step 2.

Scheme 6. Synthesis of 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (Compound 47)



[00210] Step 1. To a solution of 4-bromo-2-iodo-aniline (1 g, 3.36 mmol, 1 eq) in concentrated HCl (15 mL)/acetic acid (5 mL, 0.09 M) was added NaNO₂ (254 mg, 3.70 mmol, 1.1 eq) at 0°C. This **mixture 1** was stirred at 0°C for 1 hour. In a separate flask, SO₂ was bubbled through acetic acid (33 mL, 0.09 M) for about 10 min at 0°C before CuCl (99 mg, 1.01 mmol, 0.3 eq) was added. SO₂ was bubbled through **mixture 2** for about 10 min. **Mixture 1** was added to the **mixture 2** at 0°C. The resulting mixture was stirred at 0°C~20°C for 1 hour. The reaction mixture was quenched with water (30 mL) and extracted with MTBE (30 mL × 2). The combined organic layers were washed with sat. aq. sodium bicarbonate (30 mL × 2) and 30 mL brine. The organic layer was then separated and dried (Na₂SO₄) before evaporation *in vacuo*. The crude material was purified by FCC (PE:EtOAc 50:1) to give 4-bromo-2-iodo-benzenesulfonyl chloride (4 g, 10.5 mmol, 62% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.72 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.37 (d, *J* = 1.9 Hz, 1H).

[00211] Step 2. To a solution of 4-bromo-2-iodo-benzenesulfonyl chloride (3.6 g, 9.44 mmol, 1 eq) and ethyl 4-fluoropiperidine-4-carboxylate hydrochloride (2.0 g, 9.44 mmol, 1 eq) in DCM (10 mL, 0.9 M) was added triethylamine (2.9 g, 28.3 mmol, 3 eq) dropwise at 0°C. The resulting mixture was stirred at 20°C for 1 hour. The reaction mixture was quenched with water (15 mL) and extracted with DCM (15 mL × 2). The combined organic layers were washed with 20 mL brine. The organic layer was then separated and dried (Na₂SO₄) before evaporation *in vacuo*. The crude material was then purified by FCC to give ethyl 1-(4-bromo-2-iodo-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (4.3 g, 8.3 mmol, 87% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.28 (d, *J* = 1.88 Hz, 1H), 7.99 (d, *J* = 8.50 Hz, 1H), 7.64 (dd, *J* = 8.44, 1.94 Hz, 1H), 4.27 (q, *J* = 7.13 Hz, 2H), 3.75 (dt, *J* = 13.01, 2.56 Hz, 2H), 3.18 (td, *J* = 12.76, 2.75 Hz, 2H), 2.12 - 2.31 (m, 2H), 1.99 - 2.08 (m, 2H), 1.32 (t, *J* = 7.13 Hz, 3H).

[00212] Step 3. To a solution of ethyl 1-(4-bromo-2-iodo-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (878 mg, 1.69 mmol, 1 eq) in 1,4-dioxane (9 mL, 0.2 M) and 1 M aq. K₃PO₄ (2.7 mL) was added 2-chlorophenylboronic acid (290 mg, 1.86 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (195 mg, 0.169 mmol, 0.1 eq). The mixture was stirred at 80°C under nitrogen for 16 hrs. The mixture was diluted with water (100 mL) and extracted with EtOAc (150 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EtOAc 3:1) to give ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (400 mg,

0.79 mmol, 47% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.01 (d, $J = 8.5$ Hz, 1H), 7.67 (dd, $J = 1.9, 8.5$ Hz, 1H), 7.55 - 7.44 (m, 2H), 7.43 - 7.27 (m, 3H), 4.22 (q, $J = 7.0$ Hz, 2H), 3.24 (br d, $J = 13.4$ Hz, 1H), 3.07 (br d, $J = 13.3$ Hz, 1H), 2.98 - 2.85 (m, 1H), 2.72 - 2.58 (m, 1H), 2.04 - 1.79 (m, 4H), 1.34 - 1.27 (m, 3H). [M+H] calculated for $\text{C}_{20}\text{H}_{20}\text{BrClFNO}_4\text{S}$, 505; found 506.

[00213] **Step 4.** Ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (460 mg, 0.911 mmol, 1 eq) and lithium hydroxide monohydrate (115 mg, 2.73 mmol, 3 eq) were taken up in THF (6 mL, 0.11 M) and water (2 mL, 0.11 M). The mixture was stirred at 25°C for 2 h. The mixture was concentrated to remove organic solvent and acidified with 6 M HCl to adjust pH to 2-4. The precipitate was filtered to afford 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (400 mg, 0.84 mmol, 92% yield) as a white solid.

[00214] **Step 5.** 1-[4-Bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (500 mg, 1.05 mmol, 1 eq), (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine (TsOH salt, 438 mg, 1.36 mmol, 1.3 eq), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (1.7 g, 2.62 mmol, 2.5 eq) and DIPEA (407 mg, 3.15 mmol, 3 eq) were combined in DCM (5 mL, 0.21 M). The mixture was stirred at 25°C for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL). The extract was washed with brine (20 mL), dried over Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (PE:EtOAc 10:1~1:1) to afford 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (**Compound 47**) as a white solid (428 mg, 0.70 mmol, 66.5% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.37 (br d, $J = 6.0$ Hz, 1H), 7.99 - 7.92 (m, 1H), 7.92 - 7.86 (m, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.58 - 7.51 (m, 1H), 7.49 - 7.41 (m, 1H), 7.39 (d, $J = 4.1$ Hz, 2H), 6.45 (d, $J = 11.3$ Hz, 1H), 6.28 (dd, $J = 9.5, 11.1$ Hz, 1H), 5.44 - 5.27 (m, 1H), 3.21 - 3.05 (m, 5H), 2.79 - 2.69 (m, 1H), 2.65 - 2.56 (m, 1H), 2.02 - 1.61 (m, 4H), 1.20 (d, $J = 6.9$ Hz, 3H). [M+H] calculated for $\text{C}_{23}\text{H}_{25}\text{BrClFN}_2\text{O}_5\text{S}_2$, 606; found 607.

[00215] **Compounds 20-35** were synthesized in a manner analogous to **Compound 47** using the appropriate aniline in Step 1 and the appropriate boronic acid in Step 3. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00216] **Compounds 48-58** were synthesized in a manner analogous to **Compound 47** using the appropriate boronic acid in Step 3. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00217] **Compounds 59-60** were synthesized in a manner analogous to **Compound 47** using the appropriate pinacol boronate ester in Step 3 in the place of the boronic acid. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00218] **Compounds 61-62** were synthesized in a manner analogous to **Compound 47** using the appropriate boronic acid in Step 3 and (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine, TsOH salt in Step 5. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00219] **Compounds 63-64** were synthesized in a manner analogous to **Compound 47** using the appropriate boronic acid in Step 3 and (*E*)-3-(methylsulfonyl)prop-2-en-1-amine, TsOH salt in Step 5. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00220] **Compound 65** was synthesized in a manner analogous to **Compound 47** using 3-amino-2,3-dihydrothiophene 1,1-dioxide in Step 5.

[00221] **Compound 66** was synthesized in a manner analogous to **Compound 47** using (*R*)-3-amino-2,3-dihydrothiophene 1,1-dioxide in Step 5.

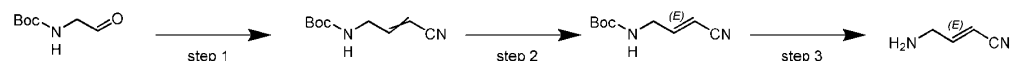
[00222] **Compound 67** was synthesized in a manner analogous to **Compound 47** using (*S*)-3-amino-2,3-dihydrothiophene 1,1-dioxide in Step 5.

[00223] **Compound 202** was synthesized in a manner analogous to **Compound 47** starting with 2-bromo-4,5-dimethoxybenzenesulfonyl chloride in Step 2.

[00224] **Compound 204** was synthesized in a manner analogous to **Compound 47** using 3-chloro-2-(tributylstannyl)pyridine in Step 3 and reacting under microwave irradiation at 140°C for 1 h.

[00225] **Compound 273** was synthesized in a manner analogous to **Compound 47** using 3-((methylsulfonyl)methylene)azetidine in Step 5.

Scheme 7. Synthesis of Intermediate (*E*)-4-aminobut-2-enenitrile



[00226] **Step 1.** To a solution of *N*-*tert*-butyl 2-aminoacetaldehyde (11 g, 69.1 mmol, 1.0 eq) in THF (130 mL, 0.53 M) was added diethyl cyanomethylphosphonate (12.2 g, 69.1 mmol, 1 eq) and K_2CO_3 (19.1 g, 138 mmol, 2 eq) at 0°C. The mixture was stirred at 25°C for 12 h. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined organic phase was washed with brine (80 mL), dried over by Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give *tert*-butyl (3-cyanoallyl)carbamate (8 g, 43.9 mmol, 63%) as a yellow oil.

[00227] **Step 2.** Crude *tert*-butyl *N*-(3-cyanoallyl)carbamate (4 g, 22 mmol, 1 eq) was purified by prep-HPLC to give *tert*-butyl *N*-[(*E*)-3-cyanoallyl]carbamate (1 g, 5.5 mmol, 25%) and *tert*-butyl *N*-[(*Z*)-3-cyanoallyl]carbamate (300 mg, 1.64 mmol, 7.5%).

[00228] **Step 3.** To a solution of *tert*-butyl *N*-[(*E*)-3-cyanoallyl]carbamate (100 mg, 0.55 mmol, 1 eq) in DCM (3 mL, 0.15 M) was added TFA (0.5 mL) under N_2 . The reaction was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give (*E*)-4-aminobut-2-enenitrile; 2,2,2-trifluoroacetic acid (80 mg, 0.408 mmol, 74%) as a yellow oil. 1H NMR (400 MHz, Methanol- d_4) δ ppm 6.77 (dt, J = 16.4, 6.2 Hz, 1H), 5.92 (d, J = 16.4 Hz, 1H), 3.77 (d, J = 6.1 Hz, 2H).

[00229] **Intermediate (*Z*)-4-aminobut-2-enenitrile** was synthesized in an analogous manner as (*E*)-4-aminobut-2-enenitrile, Step 3, using *tert*-butyl *N*-[(*Z*)-3-cyanoallyl]carbamate.

[00230] **Compound 68** was synthesized in a manner analogous to **Compound 47** using (*E*)-4-aminobut-2-enitrile in Step 5.

[00231] **Compound 69** was synthesized in a manner analogous to **Compound 68** starting with the appropriate aniline in Step 1.

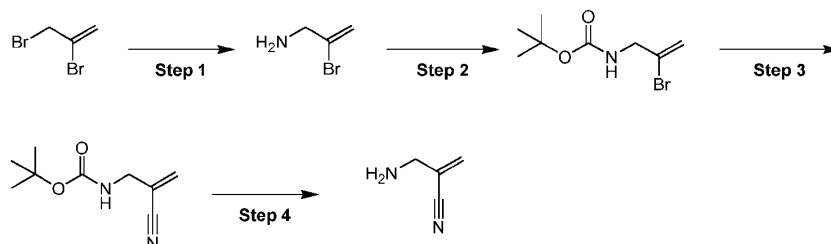
[00232] **Compound 70** was synthesized in a manner analogous to **Compound 47** using (*Z*)-4-aminobut-2-enitrile in Step 5.

[00233] **Compound 71** was synthesized in a manner analogous to **Compound 1** using (*Z*)-4-aminobut-2-enitrile in Step 5.

[00234] **Intermediate (*R,E*)-4-aminopent-2-enitrile** was synthesized in a manner analogous to (*E*)-4-aminobut-2-enitrile starting from 1,1-dimethylethyl *N*-[(1*R*)-1-methyl-2-oxoethyl]carbamate in Step 1.

[00235] **Compound 229** was synthesized in a manner analogous to **Compound 1**, Step 5, using (*R,E*)-4-aminopent-2-enitrile and 1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid in Step 5.

Scheme 8. Synthesis of Intermediate 2-(aminomethyl)acrylonitrile



[00236] **Step 1.** To a solution of hexamethylenetetramine (7 g, 49.9 mmol, 1 eq) in chloroform (50 mL, 1.0 M) was added 2,3-dibromopropene (10.2 g, 50.9 mmol, 1.02 eq) at 70°C. The mixture was stirred at 70°C for 3 hrs. The mixture was cooled in an ice batch and the salt was collected by filtration to give the crude solid. The solid was dissolved in a warm solution of 40 mL of water, 200 mL of EtOH and 45 mL of conc. HCl. A white precipitate of NH₄Cl formed and the reaction mixture was allowed to stand at 25°C for 16 h. The white solid was removed again by filtration and the mother liquid was concentrated and dried to give 2-bromoprop-2-en-1-amine; hydrochloride (13.5 g, 78.3 mmol) as a white solid.

[00237] **Step 2.** 2-Bromoprop-2-en-1-amine; hydrochloride (1 g, 5.80 mmol, 1 eq) and di-*tert*-butyl dicarbonate (1.5 g, 6.95 mmol, 1.2 eq) were taken up in DCM (20 mL, 0.29 M). The mixture was stirred at 20°C for 10 h. The mixture was diluted with H₂O (15 mL) and extracted with DCM (80 mL). The extract was washed with brine (30 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated in *vacuo* and purified by column chromatography to afford *tert*-butyl *N*-(2-bromoallyl)carbamate (600 mg, 2.54 mmol, 44% yield) as a white solid.

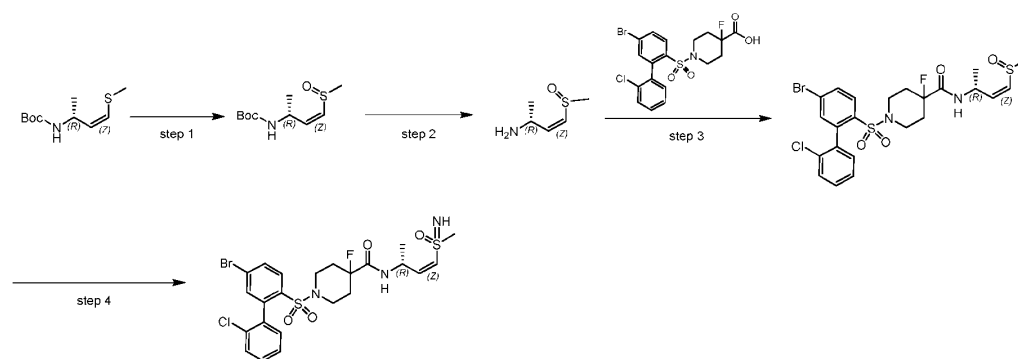
[00238] **Step 3.** To a mixture of *tert*-butyl *N*-(2-bromoallyl)carbamate (200 mg, 0.85 mmol, 1 eq) in DMF (2 mL, 0.42 M) was added Zn(CN)₂ (149 mg, 1.27 mmol, 1.5 eq) and Pd(PPh₃)₄ (98 mg, 0.085

mmol, 0.1 eq). The mixture was stirred at 110°C for 12 hrs. After cooling to rt, the reaction mixture was poured into water (5 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford *tert*-butyl *N*-(2-cyanoallyl)carbamate (80 mg, 0.44 mmol, 52% yield) as a white solid.

[00239] Step 4. To a solution of *tert*-butyl *N*-(2-cyanoallyl)carbamate (80 mg, 0.44 mmol, 1 eq) in DCM (0.3 mL, 1.5 M) was added TFA (0.1 mL). The mixture was stirred at 20°C for 2 hrs. Solvent was removed by vacuum to afford 2-(aminomethyl)prop-2-enitrile (23 mg, 0.28 mmol, 64% yield) as a yellow oil, which was used in the next step directly. ¹H NMR (400 MHz, MeOD-*d*₄) δ ppm 6.37 (s, 1H), 6.28 (s, 1H), 3.82 (s, 2H).

[00240] Compound 72 was synthesized in a manner analogous to **Compound 47** using 2-(aminomethyl)prop-2-enitrile in Step 5.

Scheme 9. Synthesis of 1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((2*R*,*Z*)-4-(*S*-methylsulfonylimidoyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 73)



[00241] Step 1. To a solution of *tert*-butyl (*R*,*Z*)-4-(methylthio)but-3-en-2-ylcarbamate (0.8 g, 3.68 mmol, 1 eq) in EtOAc (10 mL, 0.37 M) was added *m*-CPBA (667 mg, 3.68 mmol, 1 eq) at 0°C and the reaction was stirred at 20°C for 4 h. The solution was diluted with aq. Na₂SO₃ (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 0:1) to give *tert*-butyl ((2*R*,*Z*)-4-(methylsulfinyl)but-3-en-2-yl)carbamate (0.65 g, 2.8 mmol, 76%).

[00242] Step 2. To a solution of *tert*-butyl ((2*R*,*Z*)-4-(methylsulfinyl)but-3-en-2-yl)carbamate (300 mg, 1.29 mmol, 1 eq) in MeCN (3 mL, 0.43 M) was added 4-methylbenzenesulfonic acid (332 mg, 1.93 mmol, 1.5 eq) at 15°C and the reaction was stirred at 50°C for 18 h. The solution was evaporated to get the crude (2*R*,*Z*)-4-(methylsulfinyl)but-3-en-2-amine (350 mg, 1.1 mmol, 89%).

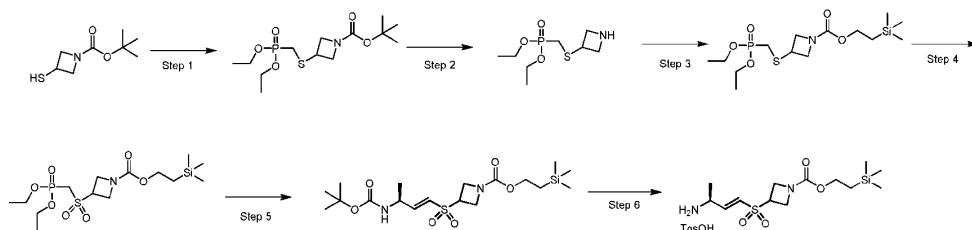
[00243] Step 3. To a solution of 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (100 mg, 0.21 mmol, 1 eq) and (2*R*,*Z*)-4-(methylsulfinyl)but-3-en-2-amine (28 mg, 0.21 mmol, 1 eq) in DCM (3 mL, 0.07 M) was added DIPEA (81.3 mg, 0.63 mmol, 3 eq) and T₃P (0.2 mL,

1.5 eq, 60%) at 15°C. The reaction was stirred at 15°C for 1 h. The solution was diluted with H₂O (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM:MeOH = 10:1). The product 1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((2*R*,*Z*)-4-(methylsulfinyl)but-3-en-2-yl)piperidine-4-carboxamide (60 mg, 0.11 mmol, 48%) was obtained as a yellow oil.

[00244] Step 4. To a solution of 1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((2*R*,*Z*)-4-(methylsulfinyl)but-3-en-2-yl)piperidine-4-carboxamide (60 mg, 0.10 mmol, 1 eq) in methanol (3 mL, 0.03 M) was added PhI(OAc)₂ (163 mg, 0.30 mmol, 3 eq) and NH₄COONH₂ (131 mg, 1.00 mmol, 10 eq). The reaction was stirred at 15°C for 16 h. The mixture was filtrated, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to give 1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((2*R*,*Z*)-4-(*S*-methylsulfonylimidoyl)but-3-en-2-yl)piperidine-4-carboxamide (**Compound 73**) (32.6 mg, 0.05 mmol, 53%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.56 (br t, *J* = 6.7 Hz, 1H), 8.01 - 7.92 (m, 1H), 7.92 - 7.86 (m, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.39 (d, *J* = 4.4 Hz, 2H), 6.85 - 6.62 (m, 2H), 5.39 - 5.20 (m, 1H), 3.79 - 3.61 (m, 3H), 3.15 (br s, 2H), 2.76 - 2.56 (m, 4H), 2.01 - 1.63 (m, 4H), 1.25 (d, *J* = 6.8 Hz, 3H). [M+H]⁺ calculated for C₂₃H₂₆BrClFN₃O₄S₂, 605; found 606.

[00245] Compound 74 was synthesized in an analogous manner to **Compound 73** starting with the chiral sulfoxide in Step 3.

Scheme 10. Synthesis of Intermediate 2-trimethylsilyl ethyl 3-[(*E*,3*S*)-3-aminobut-1-enyl]sulfonylazetidine-1-carboxylate



[00246] Step 1. To a solution of *tert*-butyl 3-sulfanylazetidine-1-carboxylate (6 g, 31.7 mmol, 1 eq) in THF (60 mL) at 0°C was added NaH (1.4 g, 34.87 mmol, 1.1 eq). The mixture was stirred at 0°C for 1 h. Diethyl iodomethylphosphonate (9.7 g, 34.9 mmol, 1.1 eq) was added and the reaction was stirred at 25°C for 1 hr. The reaction mixture was poured into aq. sat. NH₄Cl (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude *tert*-butyl 3-(diethoxyphosphorylmethylsulfanyl)azetidine-1-carboxylate (11.1 g, 32.7 mmol) was obtained as a yellow oil, which was used in the next step without further purification.

[00247] Step 2. To *tert*-butyl 3-(diethoxyphosphorylmethylsulfanyl)azetidine-1-carboxylate (11.1 g, 32.7 mmol, 1 eq) in DCM (30 mL, 0.55 M) was added TFA (30 mL, 0.55 M). The mixture was stirred at

20°C for 8 hrs. The mixture was concentrated under vacuum to obtain 3-(diethoxyphosphorylmethylsulfanyl) azetidin-1-ium; 2,2,2-trifluoroacetate (11.6 g, 34.0 mmol, 100%) as a yellow oil, which was used in the next step without further purification.

[00248] Step 3. To a solution of 3-(diethoxyphosphorylmethylsulfanyl) azetidin-1-ium; 2,2,2-trifluoroacetate (11.6 g, 34.0 mmol, 1.0 eq) in methanol (50 mL) and DCM (50 mL) was added (2,5-dioxopyrrolidin-1-yl) 2-trimethylsilylethyl carbonate (9.7 g, 37.5 mmol, 1.1 eq) and triethylamine (10.3 g, 102 mmol, 3 eq). The mixture was stirred at 30°C for 5 h. The reaction mixture was poured into water (45 mL) and extracted with EtOAc (45 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude 2-trimethylsilylethyl 3-(diethoxyphosphorylmethylsulfanyl) azetidine-1-carboxylate (12.7 g, 33.11 mmol, 97%) was obtained as a yellow oil, which was used in the next step without further purification.

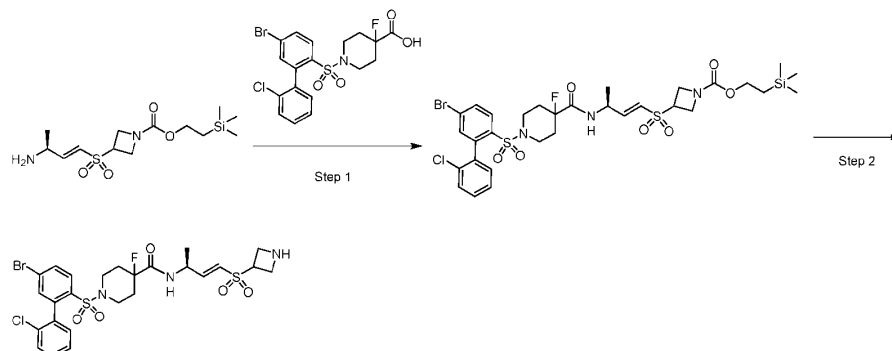
[00249] Step 4. To a solution of 2-trimethylsilylethyl 3-(diethoxyphosphorylmethylsulfanyl) azetidine-1-carboxylate (16.7 g, 43.5 mmol, 1 eq) in DCM (100 mL, 0.44 M) was added 3-chloroperbenzoic acid (19.4 g, 95.8 mmol, 2.2 eq) at 0°C. The mixture was stirred at 20 °C for 12 hrs. The reaction mixture was poured into sat. aq. Na₂SO₃ (100 mL) and extracted with DCM (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography to give 2-trimethylsilylethyl 3-(diethoxyphosphorylmethylsulfonyl) azetidine-1-carboxylate (7.7 g, 18.5 mmol, 43%).

[00250] Step 5. A solution of 2-trimethylsilylethyl 3-(diethoxyphosphorylmethylsulfonyl) azetidine-1-carboxylate (1 g, 2.41 mmol, 1 eq) in THF (20 mL, 0.12 M) was cooled to -78°C. Then lithium bis(trimethylsilyl)amide (2.6 mL, 2.64 mmol, 1.1 eq) was added. The mixture was stirred at -78°C for 1 hr. *tert*-Butyl (*S*)-(1-oxopropan-2-yl)carbamate (458 mg, 2.65 mmol, 1.1 eq) was added. After 10 min, the mixture was heated to 20°C and stirred for 1 hr. The reaction mixture was poured into sat. aq. NH₄Cl (100 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography to give 2-trimethylsilylethyl 3-[(*E*,3*S*)-3-(*tert*-butoxycarbonylamino)but-1-enyl] sulfonylazetidine-1-carboxylate (0.8 g, 1.84 mmol, 76%) as a yellow oil.

[00251] Step 6. To 2-trimethylsilylethyl 3-[(*E*,3*S*)-3-(*tert*-butoxycarbonylamino)but-1-enyl] sulfonylazetidine-1-carboxylate (0.8 g, 1.84 mmol, 1 eq) in MeCN (5 mL, 0.37 M) was added *p*-toluenesulfonic acid monohydrate (350 mg, 1.84 mmol, 1 eq). The mixture was stirred at 20°C for 2 hrs. The mixture was filtered to give 4-methylbenzenesulfonate; 2-trimethylsilylethyl 3-[(*E*,3*S*)-3-aminobut-1-enyl]sulfonylazetidine-1-carboxylate (500 mg, 0.99 mmol, 54%) as a white solid.

[00252] Intermediates 2-trimethylsilylethyl 3-[(*E*,3*R*)-3-aminobut-1-enyl]sulfonylazetidine-1-carboxylate, 2-(trimethylsilyl)ethyl (*S*,*E*)-3-((3-aminopent-1-en-1-yl)sulfonyl)azetidine-1-carboxylate, and 2-(trimethylsilyl)ethyl (*R*,*E*)-3-((3-aminopent-1-en-1-yl)sulfonyl)azetidine-1-carboxylate were synthesized in a manner analogous to 2-trimethylsilylethyl 3-[(*E*,3*S*)-3-aminobut-1-enyl]sulfonylazetidine-1-carboxylate starting with the appropriate aldehyde in Step 5.

Scheme 11. Synthesis of (*S,E*)-*N*-(4-(azetidin-3-ylsulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide (Compound 75)

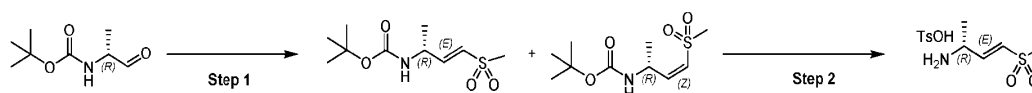


[00253] Step 1. To a solution of 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (150 mg, 0.315 mmol, 1 eq) and 4-methylbenzenesulfonate; 2-(trimethylsilyl)ethyl 3-[(*E*,3*S*)-3-aminobut-1-enyl]sulfonylazetidine-1-carboxylate (239 mg, 0.472 mmol, 1.5 eq) in MeCN (1 mL, 0.31 M) was added 1-methylimidazole (77.5 mg, 0.94 mmol, 3 eq) and *N*-[chloro(dimethylamino)methylidene]-*N*-methylmethanaminium hexafluorophosphate (132 mg, 0.472 mmol, 1.5 eq). The mixture was stirred at 25°C for 1 hour. The mixture was purified by column chromatography to give 2-(trimethylsilyl)ethyl (*S,E*)-3-((3-(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamido)but-1-en-1-yl)sulfonyl)azetidine-1-carboxylate (200 mg, 0.25 mmol, 80%).

[00254] Step 2. To 2-(trimethylsilyl)ethyl (*S,E*)-3-((3-(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamido)but-1-en-1-yl)sulfonyl)azetidine-1-carboxylate (200 mg, 0.252 mmol, 1 eq) in DCM (1 mL) was added TFA (0.3 mL). The mixture was stirred at 20°C for 1 hour. The mixture was concentrated under vacuum and purified by prep-HPLC to give (*S,E*)-*N*-(4-(azetidin-3-ylsulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide (**Compound 75**) (117.9 mg, 0.18 mmol, 72%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.18 - 8.98 (m, 2H), 8.52 - 8.42 (m, 1H), 7.97 - 7.85 (m, 2H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.48 - 7.35 (m, 3H), 6.85 (dd, *J* = 5.0, 15.2 Hz, 1H), 6.65 (dd, *J* = 1.2, 15.3 Hz, 1H), 4.65 - 4.54 (m, 1H), 4.49 - 4.37 (m, 1H), 4.29 - 4.18 (m, 2H), 4.12 - 4.00 (m, 2H), 3.19 - 3.09 (m, 2H), 2.78 - 2.67 (m, 1H), 2.63 - 2.52 (m, 1H), 1.97 - 1.67 (m, 4H), 1.22 (d, *J* = 7.0 Hz, 3H). [M+H]⁺ calculated for C₂₅H₂₈BrClFN₃O₅S₂, 647; found 648.

[00255] Compounds 76-78 were synthesized from the appropriate intermediate in a manner analogous to **Compound 75**.

Scheme 12. Synthesis of Intermediate (*R,E*)-4-methylsulfonylbut-3-en-2-amine



[00256] **Step 1.** To a solution of diethyl ((methylsulfonyl)methyl)phosphonate (2.7 g, 11.5 mmol, 1.0 eq) in THF (60 mL) was added NaH (462 mg, 1 eq, 11.5 mmol, 60%) at 0°C. The mixture was stirred at 0°C for 0.5 h before (*R*)-*tert*-butyl (1-oxopropan-2-yl)carbamate (2 g, 11.5 mmol, 1.0 eq) in THF (10 mL) was added to the mixture. The reaction was stirred at 0°C for 1 h. The reaction was quenched with water (50 mL) and extracted with EtOAc (30 mL × 3). The organic layers were combined and dried over Na₂SO₄, filtered, and concentrated to give a crude mixture. The residue was purified by prep-HPLC to give the *tert*-butyl (*R,E*)-(4-(methylsulfonyl)but-3-en-2-yl)carbamate (950 mg, 3.81 mmol, 33%) as a white solid and *tert*-butyl (*R,Z*)-(4-(methylsulfonyl)but-3-en-2-yl)carbamate (160 mg, 0.64 mmol, 5.6%) as a white solid.

[00257] **Step 2.** To a solution of *tert*-butyl (*R,E*)-(4-(methylsulfonyl)but-3-en-2-yl)carbamate (200 mg, 0.8 mmol, 1 eq) in MeCN (3 mL) was added 4-methylbenzenesulfonic acid (138 mg, 0.8 mmol, 1 eq). The mixture was stirred at 60°C for 12 h. The reaction was concentrated to give 4-methylbenzenesulfonic acid; (*R,E*)-4-methylsulfonylbut-3-en-2-amine (200 mg, 0.62 mmol, 78%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 7.71 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8 Hz, 2H), 6.92 - 7.01 (m, 1H), 6.81 - 6.89 (m, 1H), 4.18 (q, *J* = 6.5 Hz, 1H), 3.02 (s, 3H), 2.37 (s, 3H), 1.47 (d, *J* = 6.8 Hz, 3H).

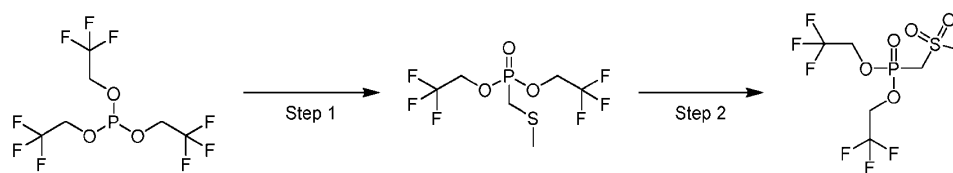
[00258] **Intermediate (*S,E*)-4-methylsulfonylbut-3-en-2-amine** was synthesized in a manner analogous to (*R,E*)-4-methylsulfonylbut-3-en-2-amine.

[00259] **Compound 79** was synthesized in a manner analogous to **Compound 47** using (*R,E*)-4-methylsulfonylbut-3-en-2-amine in Step 5.

[00260] **Compound 80** was synthesized in a manner analogous to **Compound 1** using (*R,E*)-4-methylsulfonylbut-3-en-2-amine in Step 5.

[00261] **Compound 81** was synthesized in a manner analogous to **Compound 47** using (*S,E*)-4-methylsulfonylbut-3-en-2-amine in Step 5.

Scheme 13. Synthesis of Intermediate bis(2,2,2-trifluoroethyl) ((methylsulfonyl)methyl)phosphonate

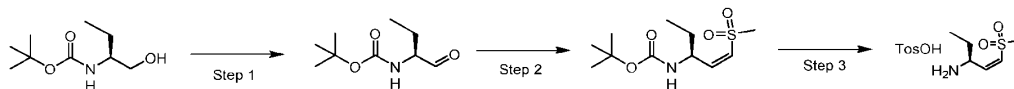


[00262] **Step 1.** A mixture of chloromethyl methyl sulfide (1.5 mg, 15.2 mmol, 1 eq) and tris (2,2,2-trifluoroethyl)phosphite (5 g, 15.2 mmol, 1 eq) was heated at 160°C for 7 h and then 140°C for 16 h. The reaction was concentrated directly to give 1,1,1-trifluoro-2-[methylsulfonylmethyl(2,2,2-trifluoroethoxy)phosphoryl]oxy-ethane (4 g, 13.1 mmol, 86%) as a colorless oil, which was used directly in the next step.

[00263] **Step 2.** To a solution of 1,1,1-trifluoro-2-[methylsulfonylmethyl(2,2,2-trifluoroethoxy)phosphoryl]oxy-ethane (4 g, 13.1 mmol, 1 eq) in DCM (100 mL, 0.13 M) was added *m*-

CPBA (6.6 g, 32.7 mmol, 2.2 eq) in portions at 0°C, then the mixture was stirred at 20°C for 15 h. The reaction was quenched with 10% aq. Na₂S₂O₃ (100 mL) and sat. aq. NaHCO₃ (100 mL). Then the mixture was extracted with DCM (100 mL × 2). The organic layers were combined, dried over Na₂SO₄ and concentrated to give a crude product, which was purified by column chromatography to give bis(2,2,2-trifluoroethyl) ((methylsulfonyl)methyl)phosphonate (3.5 g, 10.3 mmol, 79%) as a white solid.

Scheme 14. Synthesis of Intermediate (S,Z)-1-(methylsulfonyl)pent-1-en-3-amine



[00264] Step 1. To a solution of *tert*-butyl *N*-[(1*S*)-1-(hydroxymethyl)propyl]carbamate (0.5 g, 2.64 mmol, 1 eq) in DCM (10 mL, 0.26 M) was added Dess-Martin periodinane (1.2 g, 2.77 mmol, 1.1 eq) at 0°C and the mixture was stirred for 10 mins. Then the mixture was warmed up 20°C and stirred for 16 h. The reaction mixture was quenched by 10% aq. Na₂S₂O₄ (20 mL). The organic layer was washed with sat. aq. NaHCO₃ (20 mL), dried over Na₂SO₄, filtered, and concentrated to dryness. The crude was then purified by column chromatography to give the product *tert*-butyl *N*-[(1*S*)-1-formylpropyl]carbamate (360 mg, 1.92 mmol, 73%) as a colorless oil.

[00265] Step 2. To a solution of bis(2,2,2-trifluoroethyl) ((methylsulfonyl)methyl)phosphonate (650 mg, 1.92 mmol, 1 eq) in THF (8 mL, 0.16 M) was added NaH (76.9 mg, 1.92 mmol, 1 eq) in portions at 0°C and this was stirred for 0.5 h. Then *tert*-butyl *N*-[(1*S*)-1-formylpropyl]carbamate (360 mg, 1.92 mmol, 1 eq) in THF (4 mL, 0.16 M) was added dropwise at 0°C and stirred for 2 h. The reaction mixture was quenched by addition of aq. sat. NH₄Cl (10 mL) at 0°C, and then extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give *tert*-butyl *N*-[(*Z*,1*S*)-1-ethyl-3-methylsulfonyl-allyl]carbamate (210 mg, 0.80 mmol, 41%) as a yellow oil and *tert*-butyl *N*-[(*E*,1*S*)-1-ethyl-3-methylsulfonyl-allyl]carbamate (190 mg, 0.72 mmol, 37%) as a yellow oil.

[00266] Step 3. To a solution of *tert*-butyl *N*-[(*Z*,1*S*)-1-ethyl-3-methylsulfonyl-allyl]carbamate (210 mg, 0.80 mmol, 1 eq) in MeCN (6 mL, 0.13 M) was added *p*-toluenesulfonic acid monohydrate (152 mg, 0.80 mmol, 1 eq). The mixture was stirred at 65°C for 16 h. The reaction mixture was concentrated to give the product 4-methylbenzenesulfonic acid; (*S*,*Z*)-1-(methylsulfonyl)pent-1-en-3-amine (267 mg, 0.80 mmol, 100%) as a yellow solid.

[00267] Intermediate (*R*,*Z*)-1-(methylsulfonyl)pent-1-en-3-amine was synthesized in a manner analogous to (*S*,*Z*)-1-(methylsulfonyl)pent-1-en-3-amine.

[00268] Compound 82 was synthesized in a manner analogous to **Compound 47** using (*S*,*Z*)-1-(methylsulfonyl)pent-1-en-3-amine in Step 5.

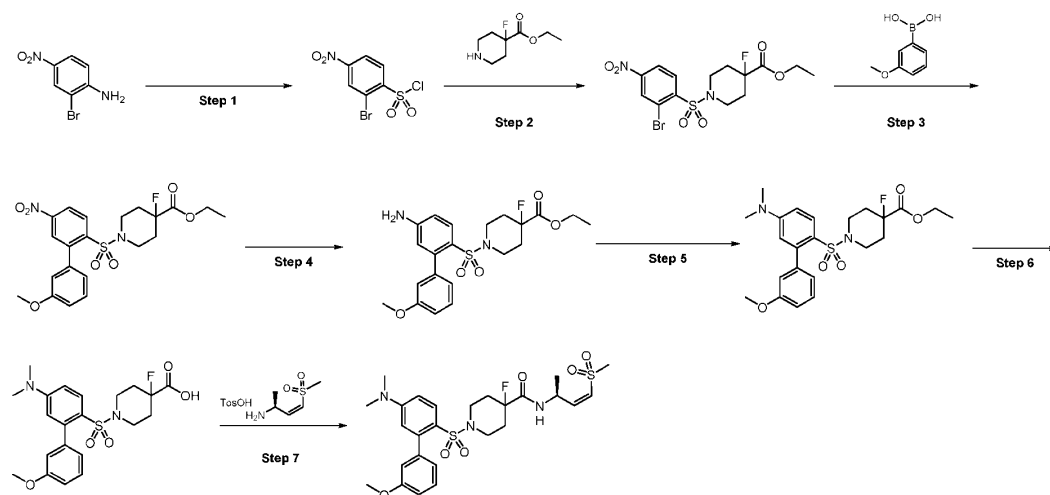
[00269] Compound 83 was synthesized in a manner analogous to **Compound 1** using (*S*,*Z*)-1-(methylsulfonyl)pent-1-en-3-amine in Step 5.

[00270] **Compound 84** was synthesized in a manner analogous to **Compound 83** using the appropriate boronic acid in Step 3.

[00271] **Intermediate (Z)-3-(2-(methylsulfonyl)vinyl)azetidine** was synthesized in a manner analogous to (S,Z)-1-(methylsulfonyl)pent-1-en-3-amine starting with tert-butyl 3-formylazetidine-1-carboxylate in Step 2.

[00272] **Compound 230** was synthesized in a manner analogous to **Compound 1**, Step 5, using (Z)-3-(2-(methylsulfonyl)vinyl)azetidine and 1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid in Step 5.

Scheme 15. Synthesis of 1-[4-(dimethylamino)-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-N-[rac-(Z,1S)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (Compound 86)



[00273] **Step 1.** 2-Bromo-4-nitro-aniline (1 g, 4.61 mmol, 1.0 eq) was added to the mixture of HCl (2.4 mL) and acetic acid (0.7 mL, 0.47 M). Once a white solid precipitated, the beaker was placed in ice-ethanol bath. At -10°C, a solution of NaNO₂ (350 mg, 5.07 mmol, 1.1 eq) in water (1 mL, 0.47 M) was added. This mixture was stirred at -10°C for another 1 hr. At the same time, SO₂ was bubbled through acetic acid (8 mL, 0.47 M) separately and CuCl (150 mg, 1.52 mmol, 0.3 eq) was added. SO₂ was continued to bubble until the color of the suspension changed from yellow-green to blue-green. The whole process took about 30 min for completion. When the temperature reached 10°C, the above diazotization reaction mixture was added over 30 min carefully. The mixture was poured into ice water. EtOAc (50 mL) was used for extraction. The organic layer was washed with NaHCO₃ (60 mL), dried over Na₂SO₄, filtered and concentrated. 2-Bromo-4-nitro-benzenesulfonyl chloride was obtained as a yellow oil (1 g, 3.32 mmol, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.71 (d, *J* = 1.5 Hz, 1H), 8.42 - 8.38 (m, 2H).

[00274] **Step 2.** At 0°C, 2-bromo-4-nitro-benzenesulfonyl chloride (772 mg, 2.57 mmol, 1.7 eq) was added to a mixture of ethyl 4-fluoropiperidine-4-carboxylate hydrochloride (320 mg, 1.51 mmol, 1 eq)

and TEA (306 mg, 3.02 mmol, 2 eq) in DCM (5 mL, 0.30 M). The resulting mixture was stirred at 25°C for 2 hrs. The reaction mixture was poured into water (15 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 10:0 - 8:2). Ethyl 1-(2-bromo-4-nitro-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate was obtained as a yellow oil (450 mg, 1.02 mmol, 68% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.60 (d, *J* = 1.6 Hz, 1H), 8.35 – 8.25 (m, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.91 – 3.79 (m, 2H), 3.23 (dt, *J* = 2.7, 12.8 Hz, 2H), 2.31 – 2.01 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H).

[00275] **Step 3.** A solution of ethyl 1-(2-bromo-4-nitro-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (400 mg, 0.91 mmol, 1.0 eq), 3-methoxyphenylboronic acid (415 mg, 2.73 mmol, 3.0 eq) and K₂CO₃ (483 mg, 4.55 mmol, 5 eq) in toluene (9 mL, 0.08 M) and water (3 mL, 0.08 M) was placed under N₂. Pd(PPh₃)₄ (105 mg, 0.09 mmol, 0.1 eq) was added and the mixture was stirred at 80°C for 16 hrs. The reaction was quenched with water (30 mL) and extracted with EtOAc (30 mL × 3). The organic layers were combined and washed with brine (50 mL). The organic layer was dried over Na₂SO₄, filtered, and the filtrate was concentrated to give the crude product. The residue was purified by column chromatography (PE:EtOAc = 10:0 - 7:3). Ethyl 4-fluoro-1-[2-(3-methoxyphenyl)-4-nitro-phenyl]sulfonyl-piperidine-4-carboxylate was obtained as a colorless oil (320 mg, 0.69 mmol, 75%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.39 - 8.28 (m, 2H), 8.20 (d, *J* = 2.1 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.04 - 6.97 (m, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.22 (br d, *J* = 13.1 Hz, 2H), 2.70 - 2.57 (m, 2H), 1.98 - 1.75 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H). [M+H] calculated for C₂₁H₂₃FN₂O₇S, 466; found 467.

[00276] **Step 4.** Fe (240 mg, 4.29 mmol, 5 eq) was added to a mixture of ethyl 4-fluoro-1-[2-(3-methoxyphenyl)-4-nitro-phenyl] sulfonyl-piperidine-4-carboxylate (400 mg, 0.86 mmol, 1 eq) and NH₄Cl (229 mg, 4.29 mmol, 5 eq) in ethanol (10 mL, 0.07 M) and water (2 mL, 0.07 M). The resulting mixture was stirred at 80°C for 3 hrs. After filtration, the filtrate was concentrated. The residue was purified by column chromatography (PE:EtOAc = 10:0 - 7:3). Ethyl 1-[4-amino-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate was obtained as a yellow oil (320 mg, 0.73 mmol, 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.92 (d, *J* = 8.7 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.05 - 7.00 (m, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.91 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.67 (dd, *J* = 2.5, 8.6 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 3.84 (s, 3H), 3.19 (br d, *J* = 12.6 Hz, 2H), 2.65 - 2.53 (m, 2H), 1.89 - 1.70 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H). [M+H] calculated for C₂₁H₂₅FN₂O₅S, 436; found 437.

[00277] **Step 5.** NaBH₃CN (63 mg, 1.01 mmol, 2.2 eq) was added to a mixture of ethyl 1-[4-amino-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (200 mg, 0.46 mmol, 1 eq) and paraformaldehyde (27.5 mg, 0.92 mmol, 2 eq) in acetic acid (1.8 mL, 0.25 M). The resulting mixture was stirred at 25°C for 0.5 hr, then the mixture was heated to 65°C and stirred for 2 hrs. The pH was adjusted to around 10 with NaOH aq. (5 M), and then diluted with EtOAc (80 mL). The layers were separated and the aqueous layer was extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (50 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue

was purified by column chromatography (PE:EtOAc = 100:0 - 85:15). Ethyl 1-[4-(dimethylamino)-2-(3-methoxyphenyl) phenyl] sulfonyl-4-fluoro-piperidine-4-carboxylate was obtained as a yellow solid (170 mg, 0.37 mmol, 79%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.97 (d, *J* = 9.0 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.92 (dd, *J* = 1.8, 8.3 Hz, 1H), 6.66 (dd, *J* = 2.8, 9.0 Hz, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.20 (br d, *J* = 13.0 Hz, 2H), 3.06 (s, 6H), 2.67 - 2.53 (m, 2H), 1.91 - 1.69 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H).

[00278] Step 6. To a solution of ethyl 1-[4-(dimethylamino)-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (170 mg, 0.37 mmol, 1.0 eq) in THF (6 mL, 0.05 M) and water (2 mL, 0.05 M) was added LiOH.H₂O (123 mg, 2.93 mmol, 8 eq). The mixture was stirred at 50°C for 3 hrs. The mixture was acidified with 1N HCl to pH = 4, poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 1-[4-(dimethylamino)-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid as a yellow oil (160 mg, 0.37 mmol, 100%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.97 (d, *J* = 9.0 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.07 - 7.00 (m, 2H), 6.92 (dd, *J* = 2.1, 8.3 Hz, 1H), 6.67 (dd, *J* = 2.6, 9.0 Hz, 1H), 6.53 (d, *J* = 2.6 Hz, 1H), 3.84 (s, 3H), 3.22 (br d, *J* = 12.9 Hz, 2H), 3.06 (s, 6H), 2.69 - 2.58 (m, 2H), 1.90 - 1.72 (m, 4H).

[00279] Step 7. HATU (78 mg, 0.21 mmol, 1.5 eq) was added to a mixture of 1-[4-(dimethylamino)-2-(3-methoxyphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (60 mg, 0.14 mmol, 1 eq), (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine (44 mg, 0.14 mmol, 1 eq) and DIPEA (44 mg, 0.34 mmol, 2.5 eq) in DCM (3 mL, 0.05 M). The resulting mixture was stirred at 25°C for 2 hrs. The reaction mixture was poured into H₂O (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC. 1-[4-(Dimethylamino)-2-(3-methoxyphenyl)phenyl] sulfonyl-4-fluoro-*N*-[*rac*-(*Z*, 1*S*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (**Compound 86**) was obtained as a white solid (21.6 mg, 0.04 mmol, 27% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.32 (br d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.96 - 6.89 (m, 3H), 6.78 (dd, *J* = 2.8, 9.2 Hz, 1H), 6.50 - 6.41 (m, 2H), 6.26 (dd, *J* = 9.6, 11.1 Hz, 1H), 5.40 - 5.26 (m, 1H), 3.77 (s, 3H), 3.12 (s, 3H), 3.06 (br d, *J* = 12.7 Hz, 2H), 3.01 (s, 6H), 2.43 (br d, *J* = 12.7 Hz, 2H), 1.75 - 1.56 (m, 4H), 1.19 (d, *J* = 6.9 Hz, 3H). [M+H] calculated for C₂₆H₃₄N₃O₆S₂, 567; found 568.

[00280] Compounds 87-90 were synthesized in a manner analogous to **Compound 86** using the appropriate boronic acid in Step 3. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

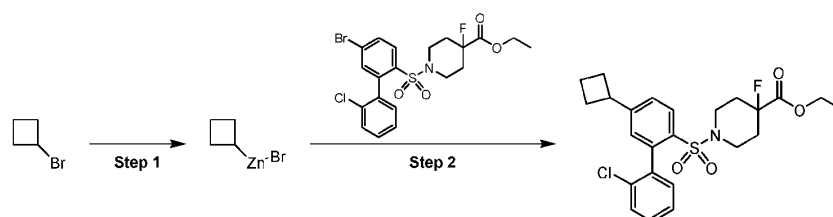
[00281] Compound 85 was synthesized in a manner analogous to **Compound 86** using the appropriate boronic acid in Step 3 and (*R,Z*)-1-(methylsulfonyl)pent-1-en-3-amine in Step 7.

[00282] Compounds 91-93 were synthesized in a manner analogous to **Compound 86** using the appropriate boronic acid in Step 3 and (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine in Step 7. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00283] **Compounds 94-96** were synthesized in a manner analogous to **Compound 86** using the appropriate boronic acid in Step 3 and (*E*)-3-methylsulfonylprop-2-en-1-amine in Step 7. Either methyl 4-fluoropiperidine-4-carboxylate or ethyl 4-fluoropiperidine-4-carboxylate was used in Step 2.

[00284] **Compound 97** was synthesized in a manner analogous to **Compound 86** using the appropriate boronic acid in Step 3 and (*E*)-4-aminobut-2-enitrile in Step 7.

Scheme 16. Synthesis of Intermediate ethyl 1-[2-(2-chlorophenyl)-4-cyclobutyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate

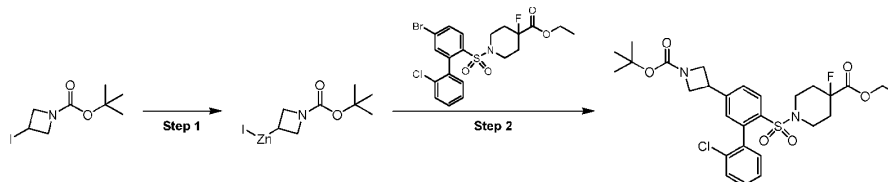


[00285] **Step 1.** To a solution of magnesium (88 mg, 3.33 mmol, 1.5 eq) in THF (10 mL, 0.22 M) was added bromocyclobutane (300 mg, 2.22 mmol, 1 eq). The reaction mixture was stirred for 1 h at 25°C. To the reaction mixture was added dichlorozinc (909 mg, 6.67 mmol, 3 eq) and this was stirred for another 1 h. The zinc reagent was used for the next step directly without purification.

[00286] **Step 2.** To a solution of bromo(cyclobutyl)zinc (300 mg, 1.5 mmol, 1 eq) in THF (10 mL) was added ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (100 mg, 0.20 mmol, 0.13 eq), CuI (100 mg), and Pd(dppf)Cl₂ (100 mg) under N₂. The reaction mixture was stirred for 16 h at 25°C. The reaction was quenched with 20 mL of sat. aq. NH₄Cl and extracted with EtOAc (20 mL). The crude product was purified by prep-TLC (PE:EtOAc = 3:1) to give ethyl 1-[2-(2-chlorophenyl)-4-cyclobutyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (40 mg, 0.08 mmol, 40% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.05 (d, *J* = 8.3 Hz, 1H), 7.40 - 7.53 (m, 2H), 7.28 - 7.36 (m, 3H), 7.13 (s, 1H), 4.14 - 4.29 (m, 2H), 3.62 (q, *J* = 8.8 Hz, 1H), 3.26 (br d, *J* = 13.2 Hz, 1H), 3.12 (br d, *J* = 15.8 Hz, 1H), 2.84 - 2.96 (m, 1H), 2.58 - 2.70 (m, 1H), 2.31 - 2.44 (m, 3H), 1.95 - 2.24 (m, 7H), 1.76 - 1.91 (m, 4H), 1.24 - 1.31 (m, 4H).

[00287] Ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate was converted to **Compound 98** in a manner analogous to Steps 4 and 5 of **Compound 47**.

Scheme 17. Synthesis of Intermediate ethyl 1-[4-(1-*tert*-butoxycarbonylazetidin-3-yl)-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate

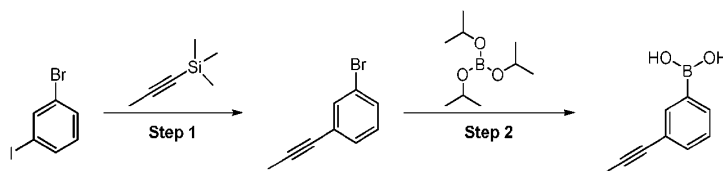


[00288] **Step 1.** To a solution of Zn (289 mg, 6.62 mmol, 2.5 eq) in DMA (8 mL, 0.33 M) was added 1,2-dibromoethane (299 mg, 1.59 mmol, 0.6 eq) and TMSCl (0.14 mL, 1.06 mmol, 0.4 eq) at 50°C and the reaction was stirred at 50°C for 30 min. Then 1-boc-3-iodoazetidine (750 mg, 2.65 mmol, 1 eq) was added at 50°C and this was stirred at 50°C for 30 min. The reaction mixture of (1-*tert*-butoxycarbonylazetidin-3-yl)-iodo-zinc (923 mg, 2.65 mmol, 100%) was used for the next step directly.

[00289] **Step 2.** To a solution of ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (400 mg, 0.79 mmol, 1 eq) in DMA (5 mL, 0.16 M) was added CuI (15 mg, 0.047 mmol, 0.06 eq), Pd(dppf)Cl₂ (78 mg, 0.039 mmol, 0.05 eq) and (1-*tert*-butoxycarbonylazetidin-3-yl)-iodo-zinc (828 mg, 2.38 mmol, 3 eq, in DMA) at 15°C. The mixture was stirred at 80°C for 2 h under N₂. The solution was diluted with water (15 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (PE:EtOAc = 1:0 to 10:1) to give ethyl 1-[4-(1-*tert*-butoxycarbonylazetidin-3-yl)-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (500 mg, 0.8 mmol, 100%) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.13 (d, *J* = 8.3 Hz, 1H), 7.52 - 7.42 (m, 3H), 7.39 - 7.32 (m, 2H), 7.26 (d, *J* = 1.8 Hz, 1H), 4.37 (dt, *J* = 2.4, 8.7 Hz, 2H), 4.18 - 4.09 (m, 1H), 4.04 - 3.95 (m, 2H), 3.87 - 3.70 (m, 1H), 3.32 - 3.07 (m, 2H), 2.94 - 2.86 (m, 1H), 2.66 (dt, *J* = 2.7, 12.9 Hz, 1H), 2.04 - 1.76 (m, 4H), 1.46 (s, 9H), 1.33 - 1.28 (m, 3H).

[00290] Ethyl 1-[4-(1-*tert*-butoxycarbonylazetidin-3-yl)-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate was converted to **Compound 99** in a manner analogous to Steps 4 and 5 of **Compound 47**.

Scheme 18. Synthesis of Intermediate (3-prop-1-ynylphenyl)boronic acid



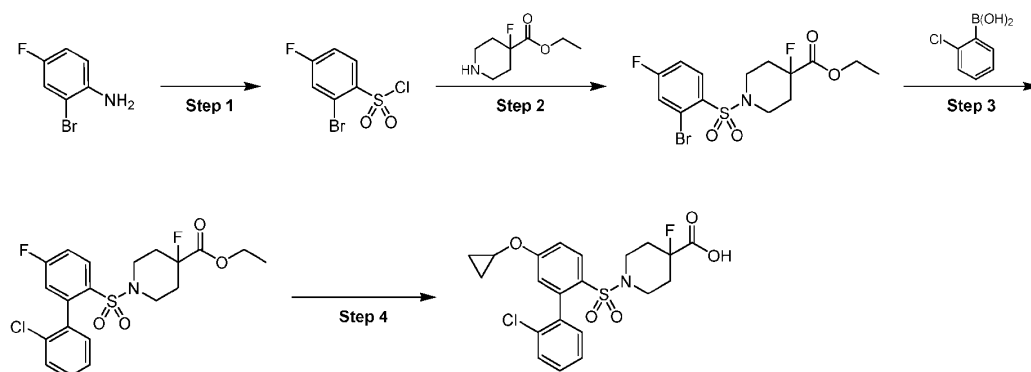
[00291] **Step 1.** To a solution of 1-bromo-3-iodobenzene (3 g, 10.6 mmol, 1 eq) in toluene (30 mL, 0.35 M) was added CuI (604 mg, 3.18 mmol, 0.3 eq) and Pd(PPh₃)₄ (300 mg). This was stirred for 5 min. Then to the mixture was added 1-(trimethylsilyl)-1-propyne (1.2 g, 10.6 mmol, 1 eq), TEA (3.5 g, 35.0 mmol, 3.3 eq) and TBAF (1 M, 10.6 mL, 1.0 eq) at rt. The resulting mixture was stirred at 20°C for 5 h. The reaction mixture was quenched with water (50 mL), extracted with MTBE (20 mL × 3) and the organic layers were combined. The organic phase was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to give the crude product. The crude product was purified by column chromatography (PE = 100%) to give 1-bromo-3-prop-1-ynylbenzene (2 g, 10.2 mmol, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.54 (t, *J* = 1.6 Hz, 1H), 7.40 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.08 - 7.19 (m, 1H), 2.05 (s, 3H).

[00292] **Step 2.** To a solution of 1-bromo-3-(prop-1-yn-1-yl)benzene (500 mg, 2.56 mmol, 1 eq) and triisopropyl borate (530 mg, 2.82 mmol, 1.1 eq) in THF (3 mL, 0.85 M) and toluene (9 mL) was added *n*-BuLi (1.1 mL, 1.1 eq, 1M) at -78°C. The reaction was stirred at -78°C for 30 min. The mixture was warmed to 15°C and stirred at 15°C for 1 h. The reaction mixture was cooled to -78°C and 3 M HCl was added to adjust pH to 2 and this was stirred at 15°C for 15 min. Potassium hydroxide was added to adjust the pH to 8. 2-Methyl-tetrahydrofuran was added and the solution was filtered. The product (3-prop-1-ynylphenyl)boronic acid (350 mg, 2.18 mmol, 85%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.55 - 7.82 (m, 2H), 6.95 - 7.23 (m, 2H), 2.01 (s, 3H).

[00293] **Compound 100** was synthesized in a manner analogous to **Compound 1** using (3-prop-1-ynylphenyl)boronic acid in Step 3.

[00294] **Compound 46** was synthesized in a manner analogous to **Compound 100** using (*E*)-3-(methylsulfonyl)prop-2-en-1-amine in Step 5.

Scheme 19. Synthesis of Intermediate 1-((2'-chloro-5-cyclopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid



[00295] **Step 1.** To a solution of 2-bromo-4-fluoroaniline (15 g, 78.9 mmol, 1 eq) in HCl/acetic acid (v/v 3:1, 44 mL, 1.3 M) was added NaNO₂ (6 g, 86.8 mmol, 1.1 eq) at 0°C. This **mixture 1** was stirred at 0°C for 1 h. In a separate flask, SO₂ was bubbled through acetic acid (50 mL, 1.3 M) for about 10 min at 0°C before CuCl (2.3 g, 23.7 mmol, 0.3 eq) was added. SO₂ was bubbled through **mixture 2** for about 10 min. **Mixture 1** was added to **mixture 2** at 0°C. The resulting mixture was stirred at 0~20°C for 1 h. The reaction mixture was quenched by water (300 mL) and extracted with MTBE (300 mL × 2). The organic layers were washed with sat. aq. sodium bicarbonate (300 mL × 2) and 300 mL of brine. The organic layer was then separated, dried over Na₂SO₄, filtered, and concentrated to dryness. The crude was then purified by column chromatography (PE:EtOAc = 50:1) to give 2-bromo-4-fluorobenzenesulfonyl chloride (10 g, 36.6 mmol, 46%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.24 (dd, *J* = 9.1, 5.4 Hz, 1H), 7.61 (dd, *J* = 7.8, 2.6 Hz, 1H), 7.27 (s, 1H).

[00296] **Step 2.** To a solution of 2-bromo-4-fluorobenzenesulfonyl chloride (5 g, 18.3 mmol, 1 eq) and ethyl 4-fluoropiperidine-4-carboxylate hydrochloride (3.9 g, 18.3 mmol, 1 eq) in DCM (100 mL, 0.18 M)

was added TEA (5.5 g, 54.8 mmol, 3 eq) dropwise at 0°C. The resulting mixture was stirred at 0°C for 1 h. The mixture was quenched with H₂O (80 mL) and extracted with DCM (100 mL × 2). The organic layers were washed with 120 mL of brine. The organic layer was then separated, dried over Na₂SO₄, filtered, and concentrated to dryness. The crude product was then purified by column chromatography (PE:EtOAc = 3:1) to give the product ethyl 1-(2-bromo-4-fluoro-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.14 (dd, *J* = 8.9, 5.8 Hz, 1H), 7.51 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.17 (ddd, *J* = 8.9, 7.4, 2.6 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.80 (dt, *J* = 12.9, 2.6 Hz, 2H), 3.16 (td, *J* = 12.7, 2.8 Hz, 2H), 2.10 - 2.29 (m, 2H), 2.06 (br s, 1H), 1.99 - 2.05 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H).

[00297] Step 3. To a solution of ethyl 1-(2-bromo-4-fluoro-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (1.5 g, 3.64 mmol, 1 eq) in 1,4-dioxane/water (v/v 10:1, 22 mL, 0.18 M) was added 2-chlorophenylboronic acid (1.1 g, 7.28 mmol, 2 eq) and K₂CO₃ (1 g, 7.28 mmol, 2.0 eq). The mixture was placed under N₂ and Pd(dppf)Cl₂ (500 mg) was added. The resulting mixture was stirred at 90°C for 12 h. After cooling to rt, the reaction mixture was quenched by H₂O (30 mL) and extracted with EtOAc (20 mL × 2). The organic layers were washed with 30 mL of brine. The organic was then separated, dried over Na₂SO₄, filtered, and concentrated to dryness. The crude was then purified by column chromatography to give the product ethyl 1-[2-(2-chlorophenyl)-4-fluoro-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (1 g, 2.25 mmol, 62%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.18 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.46 - 7.41 (m, 1H), 7.40 - 7.31 (m, 2H), 7.25 - 7.19 (m, 1H), 7.04 (dd, *J* = 2.6, 8.8 Hz, 1H), 4.28 - 4.16 (m, 2H), 3.25 (br dd, *J* = 2.1, 13.4 Hz, 1H), 3.08 (td, *J* = 2.3, 13.3 Hz, 1H), 2.98 - 2.87 (m, 1H), 2.73 - 2.58 (m, 1H), 2.16 - 1.76 (m, 5H), 1.31 - 1.27 (m, 3H).

[00298] Step 4. To a solution of ethyl 1-[2-(2-chlorophenyl)-4-fluoro-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (150 mg, 0.34 mmol, 1 eq) in DMF (2 mL, 0.17 M) was added NaH (27 mg, 0.68 mmol, 2.0 eq, 60%) at 0°C. The reaction mixture was stirred for 30 mins, then cyclopropanol (196 mg, 3.38 mmol, 10 eq) was added dropwise at 0°C. The resulting mixture was stirred at 25°C for 1 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with MTBE (10 mL). The aqueous phase was adjusted with aq. HCl until pH = 4 and extracted with EtOAc (5 mL × 2). The combined organic layers were washed with 10 mL of brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated to give 1-((2'-chloro-5-cyclopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (100 mg, 0.22 mmol, 65% yield) as a yellow oil.

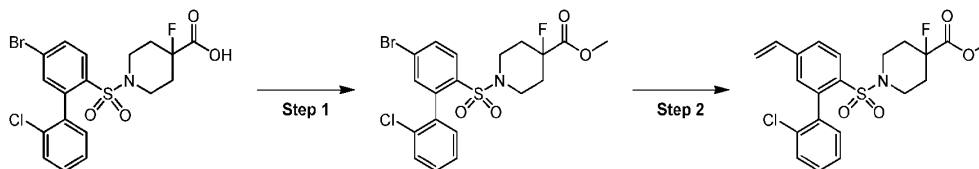
[00299] Compound 101 was synthesized from 1-((2'-chloro-5-cyclopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid in a manner analogous to Step 5 of **Compound 47**.

[00300] Compounds 102-103 were synthesized in a manner analogous to **Compound 101** using the appropriate boronic acid in Step 3 and the appropriate alcohol in Step 4.

[00301] Compounds 104-105 was synthesized in a manner analogous to **Compound 101** using the appropriate alcohol in Step 4.

[00302] Compound 106 was synthesized in a manner analogous to **Compound 101** using the appropriate boronic acid in Step 3.

Scheme 20. Synthesis of Intermediate methyl 1-[2-(2-chlorophenyl)-4-vinyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate



[00303] Step 1. To a solution of 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (200 mg, 0.42 mmol, 1 eq) in methanol (6 mL, 0.07 M) was added SOCl_2 (0.1 mL, 0.84 mmol, 2 eq) at 0°C. The mixture was stirred at 60°C for 3 h. After cooling to rt, the reaction mixture was poured into ice water (15 mL) and extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure.

The crude product was purified by column chromatography (PE: EtOAc = 1:0 to 10:1) and methyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (140 mg, 0.29 mmol, 68%) was obtained as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.98 - 8.04 (m, 1H), 7.62 - 7.70 (m, 1H), 7.47 - 7.51 (m, 2H), 7.40 - 7.43 (m, 1H), 7.31 - 7.39 (m, 2H), 3.79 (s, 3H), 3.26 (dt, J = 13.5, 2.4 Hz, 1H), 3.04 - 3.12 (m, 1H), 2.93 (td, J = 12.8, 3.1 Hz, 1H), 2.59 - 2.69 (m, 1H), 1.75 - 2.10 (m, 4H).

[00304] Step 2. To a solution of methyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (100 mg, 0.21 mmol, 1 eq) in ethanol (5 mL, 0.04 M) was added potassium vinyltrifluoroborate (33 mg, 0.25 mmol, 1.2 eq) and TEA (41 mg, 0.41 mmol, 2 eq). The mixture was stirred at 20°C for 10 min. Then $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (50 mg, 0.021 mmol, 0.1 eq) was added to the mixture. The mixture was stirred at 85°C for 12 h. After cooling to rt, the mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EtOAc = 3:1, R_f (product) = 0.6). Methyl 1-[2-(2-chlorophenyl)-4-vinyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (75 mg, 0.17 mmol, 84%) was obtained as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.10 (d, J = 8.3 Hz, 1H), 7.52 - 7.63 (m, 1H), 7.41 - 7.51 (m, 2H), 7.30 - 7.38 (m, 3H), 6.76 (dd, J = 17.5, 10.9 Hz, 1H), 5.86 - 5.95 (m, 1H), 5.86 - 5.95 (m, 1H), 5.42 - 5.50 (m, 1H), 3.64 - 3.83 (m, 3H), 3.28 (br d, J = 14.9 Hz, 1H), 3.12 (br d, J = 10.8 Hz, 1H), 2.83 - 2.98 (m, 2H), 2.60 - 2.73 (m, 1H), 2.60 - 2.73 (m, 1H), 1.91 - 2.04 (m, 2H), 1.75 - 1.90 (m, 2H). $[\text{M}+\text{H}]$ calculated for $\text{C}_{21}\text{H}_{21}\text{ClFNO}_4\text{S}$, 437, found 438.

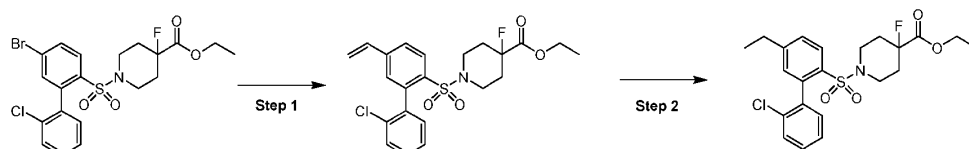
[00305] Compound 107 was synthesized in a manner analogous to **Compound 47**, Steps 4-5, using methyl 1-[2-(2-chlorophenyl)-4-vinyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate.

[00306] Intermediate methyl 4-fluoro-1-((2'-methyl-5-vinyl-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxylate was prepared in a manner analogous to methyl 1-[2-(2-chlorophenyl)-4-vinyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate starting from 1-((5-bromo-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid.

[00307] **Compound 108** was synthesized in a manner analogous to **Compound 47**, Steps 4-5, using methyl 4-fluoro-1-((2'-methyl-5-vinyl-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxylate.

[00308] **Compounds 109-110** were synthesized in a manner analogous to **Compound 107** using the appropriate carboxylic acid in Step 1 and potassium trifluoro(isopropenyl)borate in Step 2.

Scheme 21. Synthesis of Intermediate ethyl 1-[2-(2-chlorophenyl)-4-ethyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate



[00309] **Step 1.** To a solution of ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (100 mg, 0.19 mmol, 1 eq) in ethanol (5 mL, 0.04 M) was added potassium vinyltrifluoroborate (32 mg, 0.24 mmol, 1.2 eq) and TEA (40 mg, 0.40 mmol, 2 eq). The mixture was stirred at 20°C for 10 min. Then Pd(dppf)Cl₂·CH₂Cl₂ (50 mg, 0.019 mol, 0.1 eq) was added to the mixture. The mixture was stirred at 85°C for 12 h. After cooling to rt, the mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EtOAc = 3:1). Ethyl 1-[2-(2-chlorophenyl)-4-vinyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (70 mg, 0.15 mmol, 79%) was obtained as a colorless oil. ¹H NMR (400MHz, CDCl₃) δ ppm 8.09 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.50 - 7.46 (m, 1H), 7.45 - 7.42 (m, 1H), 7.38 - 7.30 (m, 3H), 6.75 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.89 (d, *J* = 17.6 Hz, 1H), 5.47 - 5.42 (m, 1H), 4.26 - 4.17 (m, 2H), 3.27 (td, *J* = 2.2, 13.3 Hz, 1H), 3.12 (td, *J* = 2.2, 13.3 Hz, 1H), 2.91 (dt, *J* = 2.9, 12.7 Hz, 1H), 2.66 (dt, *J* = 2.8, 12.8 Hz, 1H), 2.14 - 1.77 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H).

[00310] **Step 2.** To a solution of ethyl 1-[2-(2-chlorophenyl)-4-vinyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (60 mg, 0.13 mmol, 1 eq) in methanol (5 mL, 0.03 M) was added Pd/C (100 mg, 5%, wetted with ca. 55% water). The mixture was stirred at 20°C under H₂ for 30 min. The mixture was filtered and concentrated under reduced pressure to give ethyl 1-[2-(2-chlorophenyl)-4-ethyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (50 mg, 0.11 mmol, 83%) as a colorless oil.

[00311] **Compound 111** was synthesized in a manner analogous to **Compound 47**, Steps 4-5, using ethyl 1-[2-(2-chlorophenyl)-4-ethyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate.

[00312] **Intermediates ethyl 1-((5-ethyl-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate** and **ethyl 1-((5-ethyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate** were prepared in a manner analogous to ethyl 1-[2-(2-chlorophenyl)-4-ethyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate starting from the appropriately substituted biphenyl sulfonamide.

[00313] **Compounds 112-113** were synthesized in a manner analogous to **Compound 111** using the appropriate intermediate in Step 1.

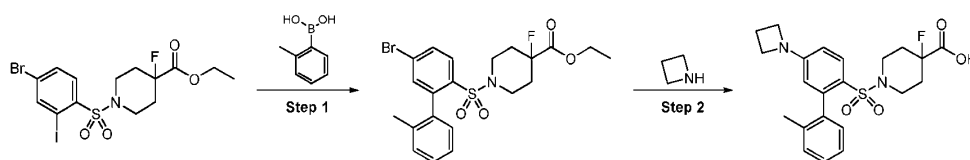
[00314] **Intermediate ethyl 1-((2'-chloro-5-isopropyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate** was prepared in a manner analogous to ethyl 1-[2-(2-chlorophenyl)-4-ethyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate using potassium trifluoro(isopropenyl)borate in Step 1.

[00315] **Compound 114** was synthesized in a manner analogous to **Compound 47**, Steps 4-5, using ethyl 1-((2'-chloro-5-isopropyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate.

[00316] **Intermediate ethyl 4-fluoro-1-((5-isopropyl-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxylate** was prepared in a manner analogous to ethyl 1-((2'-chloro-5-isopropyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate using the appropriately substituted biphenyl sulfonamide.

[00317] **Compound 115** was synthesized in a manner analogous to **Compound 47**, Steps 4-5, using ethyl 4-fluoro-1-((5-isopropyl-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxylate.

Scheme 22. Synthesis of Intermediate 1-[4-(azetidin-1-yl)-2-(*o*-tolyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid



[00318] **Step 1.** To a solution of ethyl 1-(4-bromo-2-iodo-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (200 mg, 0.38 mmol, 1 eq) in 1,4-dioxane (3 mL, 0.12 M) was added *o*-tolylboronic acid (78 mg, 0.58 mmol, 1.5 eq), Na₂CO₃ (140 mg, 0.96 mmol, 2.5 eq) in water (0.38 mL, 0.17 M), and Pd(dppf)Cl₂ (0.15 eq, 0.058 mmol, 59 mg). The reaction was heated to 90°C and stirred for 16 h. After cooling to rt, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL × 2). The organic phase was dried over Na₂SO₄, filtered, and evaporated under vacuum. The crude product was purified by prep-TLC (PE: EtOAc = 3:1) to give ethyl 1-[4-bromo-2-(*o*-tolyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (154 mg, 0.32 mmol, 83%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.00 (d, *J* = 8.6 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.40 - 7.50 (m, 1H), 7.28 (br d, *J* = 3.1 Hz, 2H), 7.19 - 7.25 (m, 2H), 4.19 - 4.25 (m, 2H), 3.16 (br d, *J* = 12.5 Hz, 2H), 2.61 - 2.75 (m, 2H), 2.07 - 2.12 (m, 3H), 1.82 - 2.05 (m, 4H), 1.25 - 1.30 (m, 3H).

[00319] **Step 2.** To a solution of ethyl 1-[4-bromo-2-(*o*-tolyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (154 mg, 0.32 mmol, 1 eq) in 1,4-dioxane (3 mL, 0.1 M) was added azetidine (22 mg, 0.38 mmol, 1.2 eq), *t*-BuONa (91 mg, 0.95 mmol, 3 eq), Pd₂(dba)₃ (14 mg, 0.016 mmol, 0.05 eq) and XantPhos (18 mg, 0.03 mmol, 0.1 eq). The reaction was heated to 100°C and stirred for 16 h. After cooling to rt, the mixture was quenched with water (10 mL) and adjusted to pH 3 with 1N HCl. The aqueous phase was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 1-[4-(azetidin-1-yl)-2-(*o*-tolyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (120 mg, 0.27 mmol,

87%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.84 (d, $J = 8.7$ Hz, 1H), 7.31 - 7.58 (m, 4H), 7.06 - 7.13 (m, 2H), 3.90 (br t, $J = 7.3$ Hz, 4H), 3.06 - 3.23 (m, 4H), 2.46 - 2.74 (m, 4H), 2.31 - 2.41 (m, 2H), 2.05 (s, 3H). [M+H] calculated for $\text{C}_{22}\text{H}_{25}\text{FN}_2\text{O}_4\text{S}$ 432, found 433.

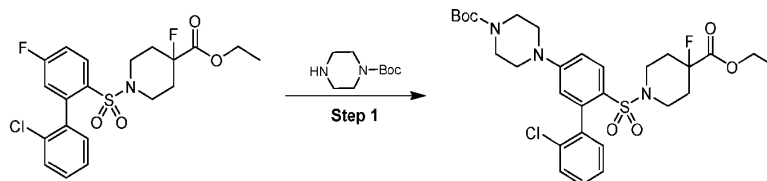
[00320] **Compound 116** was synthesized in a manner analogous to **Compound 47**, Step 5, using 1-[4-(azetidin-1-yl)-2-(*o*-tolyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid.

[00321] **Compound 117** was synthesized in a manner analogous to **Compound 116** starting from methyl 1-(4-bromo-2-phenyl-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate and using pyrrolidine and BINAP instead of XantPhos as a reagent.

[00322] **Intermediate ethyl 1-((2'-chloro-5-(2-oxopyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate** was synthesized in a manner analogous to 1-[4-(azetidin-1-yl)-2-(*o*-tolyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid using 2-chlorophenylboronic acid in Step 1 and 2-pyrrolidone in Step 2.

[00323] **Compound 205** was synthesized in a manner analogous to **Compound 47**, Steps 4-5, from ethyl 1-((2'-chloro-5-(2-oxopyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate.

Scheme 23. Synthesis of Intermediate *tert*-butyl 4-[3-(2-chlorophenyl)-4-[(4-ethoxycarbonyl-4-fluoro-1-piperidyl)sulfonyl]phenyl] piperazine-1-carboxylate



[00324] **Step 1.** To a solution of ethyl 1-[2-(2-chlorophenyl)-4-fluoro-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (100 mg, 0.23 mmol, 1 eq) in MeCN (2 mL, 0.11 M) was added *tert*-butyl piperazine-1-carboxylate (50 mg, 0.27 mmol, 1.2 eq) and DIPEA (58 mg, 0.46 mmol, 2 eq) at rt. The reaction was slowly heated to 100°C and stirred for 36 h. Then the mixture was heated at 130°C for 16 h. When the reaction was complete and cooled to rt, the reaction was quenched with water (10 mL), and the aqueous solution was extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude product was purified by prep-TLC to give *tert*-butyl 4-[3-(2-chlorophenyl)-4-[(4-ethoxycarbonyl-4-fluoro-1-piperidyl)sulfonyl]phenyl] piperazine-1-carboxylate (50 mg, 0.08 mmol, 36%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.99 (d, $J = 8.9$ Hz, 1H), 7.40 - 7.51 (m, 2H), 7.30 - 7.35 (m, 2H), 6.90 (dd, $J = 9.0, 2.6$ Hz, 1H), 6.70 (d, $J = 2.5$ Hz, 1H), 4.23 (q, $J = 7.1$ Hz, 2H), 3.58 (br d, $J = 5.3$ Hz, 4H), 3.34 (br d, $J = 5.1$ Hz, 4H), 3.25 (br d, $J = 13.0$ Hz, 1H), 3.13 (br d, $J = 11.5$ Hz, 1H), 2.82 - 2.94 (m, 1H), 2.62 - 2.71 (m, 1H), 1.76 - 2.03 (m, 4H), 1.56 - 1.58 (m, 9H), 1.29 - 1.32 (m, 3H).

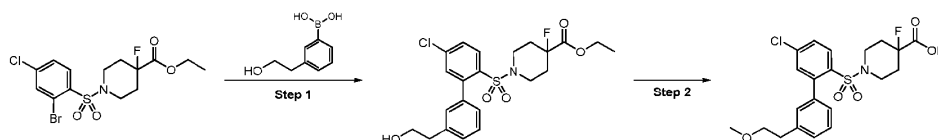
[00325] **Compound 118** was synthesized in a manner analogous to **Compound 47**, Steps 4-5, using *tert*-butyl 4-[3-(2-chlorophenyl)-4-[(4-ethoxycarbonyl-4-fluoro-1-piperidyl)sulfonyl]phenyl] piperazine-1-carboxylate.

[00326] **Compounds 119** and **121** were synthesized in a manner analogous to **Compound 118** using the appropriate amine in Step 4.

[00327] **Compounds 120, 122, and 123** were synthesized in a manner analogous to **Compound 118** using the appropriate boronic acid in Step 3 and amine in Step 4.

[00328] **Compound 124** was synthesized by combining ethyl 1-(2-bromo-4-fluoro-phenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate and azetidine in a manner analogous to Step 4 of *tert*-butyl 4-[3-(2-chlorophenyl)-4-[(4-ethoxycarbonyl-4-fluoro-1-piperidyl)sulfonyl]phenyl]piperazine-1-carboxylate followed by a coupling with 2-chlorophenylboronic acid in a manner analogous to Step 3 of *tert*-butyl 4-[3-(2-chlorophenyl)-4-[(4-ethoxycarbonyl-4-fluoro-1-piperidyl)sulfonyl]phenyl] piperazine-1-carboxylate followed by hydrolysis and coupling with (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine.

Scheme 24. Synthesis of Intermediate 1-[4-chloro-2-[3-(2-methoxyethyl)phenyl]phenyl] sulfonyl-4-fluoro-piperidine-4-carboxylic acid



[00329] **Step 1.** To a solution of ethyl 1-(2-bromo-4-chlorophenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (150 mg, 0.35 mmol, 1 eq) in 1,4-dioxane (2 mL, 0.16 M) was added [3-(2-hydroxyethyl)phenyl]boronic acid (70 mg, 0.420 mmol, 1.2 eq), K_2CO_3 (96 mg, 0.70 mmol, 2 eq) in water (0.2 mL, 0.16 M), and $Pd(dppf)Cl_2$ (45 mg, 0.035 mmol, 0.1 eq). The reaction mixture was heated to 90°C and stirred for 2 h. After cooling to rt, the mixture was quenched with the water (5 mL) and extracted with EtOAc (5 mL $\times$ 3). The organic phase was dried over Na_2SO_4 , filtered and evaporated under vacuum. The crude product was purified by prep-TLC to give ethyl 1-[4-chloro-2-[3-(2-hydroxyethyl)phenyl]phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (100 mg, 0.21 mmol, 61%) as a yellow oil. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (d, J = 8.6 Hz, 1H), 7.48 (dd, J = 8.6, 2.2 Hz, 1H), 7.37 - 7.42 (m, 1H), 7.35 - 7.37 (m, 1H), 7.33 (s, 1H), 7.29 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.15 (br d, J = 12.9 Hz, 2H), 2.93 (t, J = 6.2 Hz, 2H), 2.52 - 2.63 (m, 2H), 1.74 - 1.94 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H).

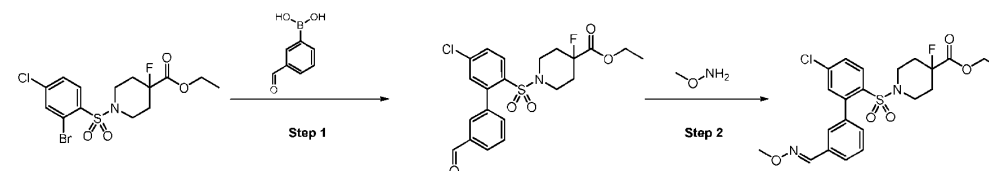
[00330] **Step 2.** Ethyl 1-[4-chloro-2-[3-(2-hydroxyethyl)phenyl]phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (100 mg, 0.21 mmol, 1 eq) was taken up in THF (2 mL, 1.2 M) and placed under N_2 . NaH (10 mg, 0.43 mmol, 2.0 eq) was added in portions at 0°C. After 5 min, CH_3I (90 mg, 0.64 mmol, 3 eq) was added and the resulting solution was stirred for 1 h at 0°C. The reaction mixture was warmed to rt. The reaction was then quenched by the addition of water (5 mL) and acidified with 1N HCl until pH = 3. The aqueous phase was extracted with ethyl acetate (5 mL $\times$ 3). The separated organic phase was dried

over Na₂SO₄, filtered, and evaporated to dryness to give 1-[4-chloro-2-[3-(2-methoxyethyl)phenyl]phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (100 mg, 0.22 mmol, 100%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.11 (d, *J* = 8.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.33 - 7.40 (m, 2H), 7.29 (s, 3H), 3.69 (t, *J* = 6.7 Hz, 2H), 3.38 (s, 3H), 3.10 (br d, *J* = 12.9 Hz, 2H), 2.95 (t, *J* = 6.7 Hz, 2H), 2.54 - 2.66 (m, 2H), 1.73 - 1.93 (m, 5H). [M+H]⁺ calculated for C₂₁H₂₃ClFNO₅S, 455, found 456.

[00331] **Compound 125** was synthesized from 1-[4-chloro-2-[3-(2-methoxyethyl)phenyl]phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid in a manner analogous to Step 5 of **Compound 1**.

[00332] **Compound 126** was synthesized in a manner analogous to **Compound 125** starting with [3-(hydroxymethyl)phenyl]boronic acid.

Scheme 25. Synthesis of Intermediate ethyl 1-[4-chloro-2-[3-(*E*)-methoxyiminomethyl]phenyl]phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate



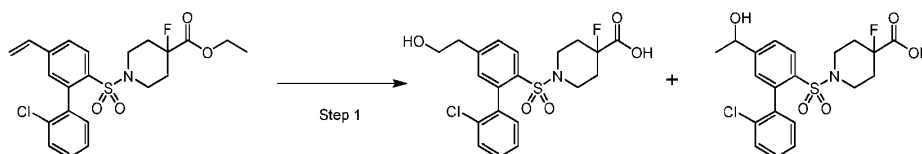
[00333] **Step 1.** To a solution of ethyl 1-(2-bromo-4-chlorophenyl)sulfonyl-4-fluoro-piperidine-4-carboxylate (0.1 g, 0.23 mmol, 1 eq) in 1,4-dioxane/water (v/v 3:1, 2.0 mL, 0.15 M) was added 3-formylphenylboronic acid (0.04 g, 0.30 mmol, 1.3 eq), K₂CO₃ (1.9 g, 0.69 mmol, 3 eq), and Pd(dppf)Cl₂ (500 mg, 0.023 mmol, 0.1 eq). The reaction was stirred for 16 h at 90°C under N₂. After cooling to rt, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL × 3). The combined aqueous layer was acidified with 1N HCl to pH = 5 then concentrated. Ethyl 1-[4-chloro-2-[3-(3-formylphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (0.1 g, 0.26 mmol) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 10.08 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.89 - 7.99 (m, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.59 - 7.65 (m, 1H), 7.54 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.18 (br d, *J* = 13.3 Hz, 2H), 2.59 - 2.73 (m, 2H), 1.70 - 1.91 (m, 4H), 1.28 - 1.31 (m, 2H).

[00334] **Step 2.** To a solution of ethyl 1-[4-chloro-2-[3-(3-formylphenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (50 mg, 0.11 mmol, 1 eq) and *O*-methylhydroxylamine hydrochloride (11 mg, 0.13 mmol, 1.2 eq) in methanol/DCM (v/v 1:1, 2 mL, 0.05 M) was added Na₂CO₃ (11 mg, 0.11 mmol, 1 eq) until pH 7~8. To the solution was added AcOH (one drop) and the mixture was stirred at 20°C for 15 min. The reaction mixture was quenched with water (5 mL) and extracted with DCM (5 mL × 3). The combined organic layers were washed with brine (12 mL), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC (PE: EtOAc = 3:1) to give ethyl 1-[4-chloro-2-[3-(*E*)-methoxyiminomethyl]phenyl]phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (36 mg, 0.07 mmol, 68%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.07 - 8.11 (m, 2H), 7.60 - 7.65 (m, 2H), 7.49

(dd, $J = 8.5, 2.0$ Hz, 1H), 7.42 - 7.45 (m, 2H), 7.36 (d, $J = 2.1$ Hz, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.98 (s, 3H), 3.18 (br d, $J = 12.9$ Hz, 2H), 2.59 - 2.70 (m, 2H), 1.74 - 1.93 (m, 4H), 1.29 (t, $J = 7.2$ Hz, 3H).

[00335] **Compound 127** was synthesized from ethyl 1-[4-chloro-2-[3-[(*E*)-methoxyiminomethyl]phenyl]phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate in a manner analogous to Steps 4 and 5 of **Compound 1**.

Scheme 26. Synthesis of Intermediates 1-[2-(2-chlorophenyl)-4-(2-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid and 1-[2-(2-chlorophenyl)-4-(1-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid

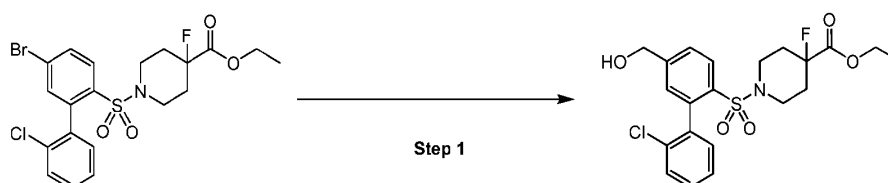


[00336] **Step 1.** To a solution of $\text{BH}_3 \cdot \text{THF}$ (0.93 mL, 0.93 mmol, 1 M, 1.5 eq) was added a solution of ethyl 1-[2-(2-chlorophenyl)-4-vinyl-phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (280 mg, 0.62 mmol, 1.0 eq) in THF (5 mL, 0.12 M) dropwise at 0°C . The mixture was stirred at 25°C for 1 h. A solution of NaOH (1 M, 4 mL) was added to the mixture at 0°C followed by H_2O_2 (0.53 mL, 6.2 mmol, 10 eq). The mixture was stirred at 0°C for 30 min then 25°C for 30 min. The mixture was diluted with aq. Na_2SO_3 (40 mL) and extracted with DCM (20 mL). The organic phase was washed with sat. aq. NaHCO_3 (20 mL $\times$ 2), then washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated. Purification by prep-HPLC afforded 1-[2-(2-chlorophenyl)-4-(2-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (50 mg, 0.12 mmol, 18%) as a white solid and 1-[2-(2-chlorophenyl)-4-(1-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (25 mg, 0.06 mmol, 9%) as a white solid.

[00337] **Compound 128** was synthesized from 1-[2-(2-chlorophenyl)-4-(2-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid in a manner analogous to Step 5 of **Compound 47**.

[00338] **Compound 129** was synthesized from 1-[2-(2-chlorophenyl)-4-(1-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid in a manner analogous to Step 5 of **Compound 47**.

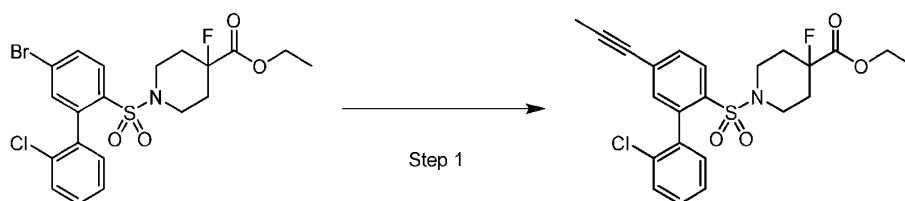
Scheme 27. Synthesis of Intermediate ethyl 1-[2-(2-chlorophenyl)-4-(hydroxymethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate



[00339] **Step 1.** To a solution of ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (50 mg, 0.099 mmol, 1 eq) in DMF (5 mL, 0.12 M) was added Pd(PPh₃)₄ (69 mg, 0.059 mmol, 0.1 eq) and tributylstannylmethanol (191 mg, 0.59 mmol, 1 eq). The solution was purged with N₂ and stirred at 100°C for 12 h. After cooling to rt, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by prep-TLC (PE:EtOAc = 3:1) to give ethyl 1-[2-(2-chlorophenyl)-4-(hydroxymethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (70 mg, 0.15 mmol, 26%) as a colorless oil.

[00340] **Compound 130** was synthesized from ethyl 1-[2-(2-chlorophenyl)-4-(hydroxymethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate in a manner analogous to Steps 4 and 5 of **Compound 47**.

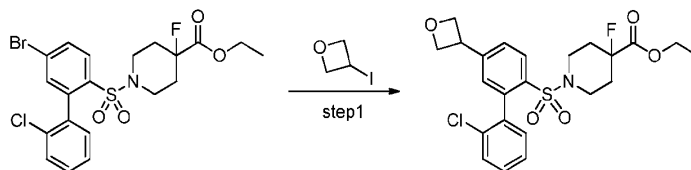
Scheme 28. Synthesis of Intermediate ethyl 1-((2'-chloro-5-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate



[00341] **Step 1.** To a solution of ethyl 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (150 mg, 0.30 mmol, 1 eq) and propargyltrimethylsilane (67 mg, 0.59 mmol, 2 eq) in TEA (1 mL) was added Pd(PPh₃)₂Cl₂ (21 mg, 0.03 mmol, 0.1 eq). The mixture was stirred at 70°C for 16 h. After cooling to rt, the reaction mixture was concentrated. The residue was quenched with NH₄Cl (10 mL) and extracted with EtOAc (3 mL × 2). The combined organic layers were washed with 10 mL of brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by prep-HPLC (neutral conditions) to give ethyl 1-((2'-chloro-5-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (60 mg, 0.11 mmol, 95% yield) as a white solid.

[00342] **Compound 131** was synthesized from ethyl 1-((2'-chloro-5-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate in a manner analogous to Steps 4 and 5 of **Compound 47**.

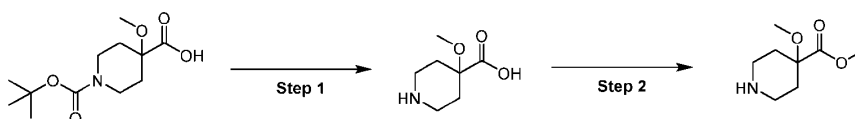
Scheme 29. Synthesis of Intermediate ethyl 1-((2'-chloro-5-(oxetan-3-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate



[00343] Step 1. A mixture of ethyl 1-(4-bromo-2-(2-chlorophenyl)phenyl)sulfonyl-4-fluoropiperidine-4-carboxylate (200 mg, 0.39 mmol, 1 eq), 3-iodooxetane (146 mg, 0.79 mmol, 2 eq), (4,4'-di-*tert*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]iridium(III) hexafluorophosphate (4.4 mg, 0.004 mmol, 0.01 eq), dichloro(dimethoxyethane)nickel (0.4 mg, 0.002 mmol, 0.005 eq), sodium carbonate (84 mg, 0.79 mmol, 2 eq), tris(trimethylsilyl)silane (98 mg, 0.39 mmol, 1 eq) and 4,4-di-*tert*-butyl-2,2'-dipyridyl (0.5 mg, 0.002 mmol, 0.005 eq) in dimethoxyethane (10 mL, 0.04 M) was stirred at 25°C under 34 watt blue LED irradiation for 16 h. The reaction was quenched with water (30 mL) and extracted with EtOAc (20 mL $\times$ 2). The combined organic phases were washed with brine (40 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography (PE:EtOAc = 5:1 to 3:1) to give ethyl 1-(2'-chloro-5-(oxetan-3-yl)-[1,1'-biphenyl]-2-yl)sulfonyl-4-fluoropiperidine-4-carboxylate (125 mg, 0.42 mmol, 52% yield) as a colorless oil. ¹H NMR (400MHz, CDCl₃) δ ppm 8.07 (d, *J* = 8.2 Hz, 1H), 7.48 (dd, *J* = 1.8, 8.2 Hz, 1H), 7.44 - 7.40 (m, 1H), 7.39 - 7.35 (m, 1H), 7.29 - 7.27 (m, 2H), 7.19 (s, 1H), 5.05 (ddd, *J* = 2.3, 6.1, 8.3 Hz, 2H), 4.70 (dt, *J* = 1.9, 6.3 Hz, 2H), 4.26 - 4.12 (m, 3H), 3.20 (td, *J* = 2.2, 13.2 Hz, 1H), 3.04 (td, *J* = 2.3, 13.3 Hz, 1H), 2.85 (s, 1H), 2.59 (dt, *J* = 2.8, 12.8 Hz, 1H), 1.96 - 1.67 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H).

[00344] Compound 132 was synthesized from ethyl 1-(2'-chloro-5-(oxetan-3-yl)-[1,1'-biphenyl]-2-yl)sulfonyl-4-fluoropiperidine-4-carboxylate in a manner analogous to Steps 4 and 5 of **Compound 47**.

Scheme 30. Synthesis of Intermediate methyl 4-methoxypiperidine-4-carboxylate

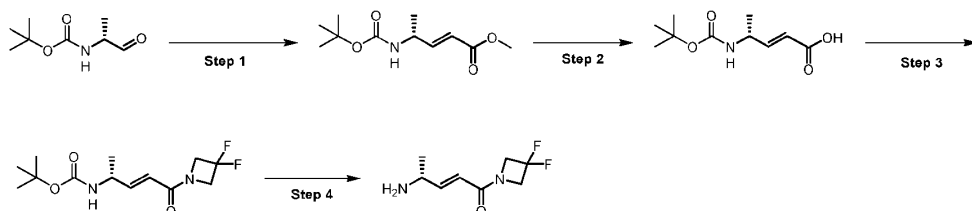


[00345] Step 1. To a solution of 1-*tert*-butoxycarbonyl-4-methoxy-piperidine-4-carboxylic acid (500 mg, 1.93 mmol, 1 eq) was added HCl/1,4-dioxane (4 M, 5 mL) and the reaction was stirred at 25°C for 2 hours. The reaction solution was concentrated *in vacuo* to give 4-methoxypiperidine-4-carboxylic acid (300 mg, 98% yield) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 2.96 (s, 3H), 2.95 (br s, 4H), 1.70 - 1.94 (m, 4H).

[00346] Step 2. To a solution of 4-methoxypiperidine-4-carboxylic acid (300 mg, 1.88 mmol, 1 eq) in methanol (3 mL, 0.6 M) was added thionyl chloride (404 mg, 3.39 mmol) and the reaction was stirred at 25°C for 2 h. The solvent was evaporated to give methyl 4-methoxypiperidine-4-carboxylate (310 mg, 1.79 mmol, 95%) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 2.05 - 2.25 (m, 4H), 3.09 - 3.28 (m, 4H), 3.28 (s, 3H), 3.79 (s, 3H).

[00347] **Compound 133** was synthesized analogous to **Compound 47** using methyl 4-methoxypiperidine-4-carboxylate instead of ethyl 4-fluoropiperidine-4-carboxylate in Step 2.

Scheme 31. Synthesis of Intermediate (*E,4R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one



[00348] **Step 1.** To a solution of trimethyl phosphonoacetate (18.9 g, 104 mmol, 1.2 eq) in THF (40 mL, 2.2 M) was added LiHMDS (40 mL, 1.4 eq, 1 M) at -70°C and this was stirred at -70°C for 1 h. To this mixture was added *tert*-butyl (*R*)-(1-oxopropan-2-yl)carbamate (15 g, 86.6 mmol, 1.0 eq) in THF (20 mL) and the reaction was stirred at -70°C for 1 h. The reaction mixture was quenched with sat. aq. NH₄Cl (80 mL) and extracted with EtOAc (50 mL × 3). Then organic layers were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by FCC on silica (PE:EtOAc = 1:0 - 5:1) then prep-HPLC to give methyl (*E,4R*)-4-(*tert*-butoxycarbonylamino)pent-2-enoate (2.5 g, 10.9 mmol, 13%). ¹H NMR (400 MHz, CDCl₃) δ ppm 6.88 (dd, *J* = 5.0, 15.7 Hz, 1H), 5.91 (dd, *J* = 1.6, 15.7 Hz, 1H), 4.61 - 4.33 (m, 2H), 3.74 (s, 3H), 1.44 (s, 9H), 1.27 (d, *J* = 7.0 Hz, 3H).

[00349] **Step 2.** To a solution of methyl (*E,4R*)-4-(*tert*-butoxycarbonylamino)pent-2-enoate (200 mg, 0.87 mmol, 1.0 eq) in THF (3 mL, 0.22 M) and water (1 mL, 0.22 M) was added lithium hydroxide hydrate (110 mg, 2.62 mmol, 3.0 eq). The reaction solution was stirred at 25°C for 12 h. The reaction solution was adjusted to pH 4 and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated to give (*E,4R*)-4-(*tert*-butoxycarbonylamino)pent-2-enoic acid (190 mg, 0.88 mmol, quant. yield) as a colorless oil, which was used in the next step directly without purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.98 (br dd, *J* = 4.4, 15.8 Hz, 1H), 5.92 (dd, *J* = 1.4, 15.7 Hz, 1H), 4.64 - 4.37 (m, 1H), 1.46 (s, 9H), 1.29 (d, *J* = 6.9 Hz, 3H).

[00350] **Step 3.** To a solution of (*E,4R*)-4-(*tert*-butoxycarbonylamino)pent-2-enoic acid (1.5 g, 6.97 mmol, 1 eq), 3,3-difluoroazetidine HCl (1.1 g, 8.36 mmol, 1.2 eq), and T₃P (3.3 g, 10.4 mmol, 1.5 eq) in DCM (5 mL, 1.4 M) was added DIPEA (2.3 g, 17.4 mmol, 2.5 eq). The reaction solution was stirred at 25°C for 2 h. The reaction mixture was purified by column chromatography (PE:EtOAc = 5:1) to give *tert*-butyl *N*-[(*E,1R*)-4-(3,3-difluoroazetidin-1-yl)-1-methyl-4-oxo-but-2-enyl]carbamate (1.4 g, 4.82 mmol, 69%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.82 (br dd, *J* = 5.4, 15.1 Hz, 1H), 5.93 (dd, *J* = 1.2, 15.3 Hz, 1H), 4.59 - 4.30 (m, 6H), 1.45 (s, 9H), 1.28 (d, *J* = 6.9 Hz, 3H). [M+H]⁺ calculated for C₁₃H₂₀F₂N₂O₃, 290, found 291.

[00351] **Step 4.** To a solution of *tert*-butyl *N*-[(*E,1R*)-4-(3,3-difluoroazetidin-1-yl)-1-methyl-4-oxo-but-2-enyl]carbamate (300 mg, 1.03 mmol, 1 eq) in MeCN (5 mL, 0.21 M) was added 4-

methylbenzenesulfonic acid (890 mg, 5.17 mmol, 5.0 eq). The reaction solution was stirred at 65°C for 12 h. The reaction solution was concentrated to give the 4-methylbenzenesulfonic acid salt of (*E*,4*R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one (300 mg, 0.83 mmol, 80%).

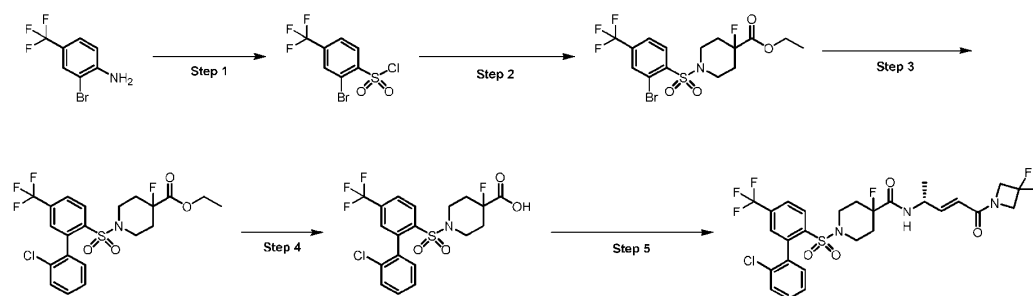
[00352] **Intermediate (*R,E*)-4-amino-1-(3-fluoroazetidin-1-yl)pent-2-en-1-one** was synthesized in a manner analogous to (*E*,4*R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one using 3-fluoroazetidine HCl in Step 3.

[00353] **Intermediate (*E*)-4-amino-1-(3,3-difluoroazetidin-1-yl)-4-methylpent-2-en-1-one** was synthesized in a manner analogous to (*E*,4*R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one using 1,1-dimethylethyl *N*-(1,1-dimethyl-2-oxoethyl)carbamate in Step 1.

[00354] **Intermediate (*E*)-4-amino-1-(3,3-difluoroazetidin-1-yl)but-2-en-1-one** was synthesized in a manner analogous to (*E*,4*R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one using *tert*-butyl (2-oxoethyl)carbamate in Step 1.

[00355] **Compound 282** was synthesized in a manner analogous to **Compound 47** using (*E*)-4-amino-1-(3,3-difluoroazetidin-1-yl)but-2-en-1-one in Step 5.

Scheme 32. Synthesis of 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-*N*-[(*E*,1*R*)-4-(3,3-difluoroazetidin-1-yl)-1-methyl-4-oxo-but-2-enyl]piperidine-4-carboxamide (Compound 134)



[00356] **Step 1.** To a solution of 2-bromo-4-(trifluoromethyl) aniline (10 g, 41.7 mmol, 1 eq) in HCl/acetic acid (v/v 3:1, 20 mL, 0.48 M) was added sodium nitrite (3.2 g, 45.8 mmol, 1.1 eq) at 0°C. **Mixture 1** was stirred at 0°C for 1 h. SO₂ was bubbled through acetic acid (60 mL, 0.69 M) for 10 min at 0°C before cuprous chloride (1.2 g, 12.5 mmol, 0.3 eq) was added. SO₂ was bubbled through **mixture 2** for 10 min. Then, **mixture 1** was added to the **mixture 2** at 0°C. The resulting mixture was stirred at 0-20°C for 1 h. The reaction mixture was quenched with H₂O (100 mL) and extracted with MTBE (60 mL × 3). The organic layers were washed with NaHCO₃ (50 mL × 2) and brine (30 mL). The combined organic layers were separated, dried over Na₂SO₄, filtered, and concentrated to dryness. The residue was purified by column chromatography (PE) to give 2-bromo-4-(trifluoromethyl)benzenesulfonyl chloride (3.8 g, 11.7 mmol, 28%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.07 - 8.11 (m, 1H), 7.90 (s, 1H), 7.70 - 7.75 (m, 1H).

[00357] Step 2. To a solution of ethyl 4-fluoropiperidine-4-carboxylate hydrochloride (2.2 g, 10.5 mmol, 1 eq) in DCM (40 mL, 0.26 M) was added TEA (3.2 g, 31.5 mmol, 3 eq) and 2-bromo-4-(trifluoromethyl)benzenesulfonyl chloride (3.4 g, 10.5 mmol, 1 eq). The mixture was stirred at 20°C for 2 h. The reaction mixture was poured into sat. aq. NH₄Cl (20 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 1:0 - 3:1) to give ethyl 1-[2-bromo-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (4.8 g, 10.4 mmol, 99%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.21 - 8.27 (m, 1H), 7.99 - 8.04 (m, 1H), 7.72 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.24 - 4.30 (m, 2H), 3.80 - 3.87 (m, 2H), 3.21 (td, *J* = 12.8, 2.8 Hz, 2H), 2.12 - 2.30 (m, 2H), 2.07 - 2.10 (m, 1H), 2.02 (br s, 1H), 1.32 (t, *J* = 7.1 Hz, 3H).

[00358] Step 3. To a solution of ethyl 1-[2-bromo-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (3.5 g, 7.57 mmol, 1 eq) in 1,4-dioxane/water (v/v 10:1, 44 mL, 0.17 M) was added 2-chlorophenylboronic acid (1.8 g, 11.4 mmol, 1.5 eq), sodium carbonate (2 g, 18.9 mmol, 2.5 eq) and tetrakis(triphenylphosphine)palladium(0) (0.88 g, 0.76 mmol, 0.1 eq) under N₂. The mixture was stirred at 90°C for 16 h. After cooling to rt, the reaction mixture was poured into sat. aq. NH₄Cl (30 mL) and extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 10:0 - 9:1) to give ethyl 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.30 (d, *J* = 8.3 Hz, 1H), 7.80 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.59 (d, *J* = 1.3 Hz, 1H), 7.50 - 7.54 (m, 1H), 7.43 - 7.47 (m, 1H), 7.34 - 7.42 (m, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.22 - 3.35 (m, 1H), 3.03 - 3.15 (m, 1H), 2.96 (td, *J* = 12.8, 2.9 Hz, 1H), 2.59 - 2.72 (m, 1H), 1.93 - 2.13 (m, 2H), 1.78 - 1.91 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H). [M+H]⁺ calculated for C₂₁H₂₀ClF₄NO₄S, 493, found 494.

[00359] Step 4. To a solution of ethyl 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylate (3.5 g, 6.51 mmol, 1 eq) in THF/water (v/v 3:1, 40 mL, 0.16 M) was added LiOH.H₂O (820 mg, 19.5 mmol, 3 eq). The mixture was stirred at 20°C for 3 h. The pH was adjusted to around 4 with HCl. The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (3 g, 6.44 mmol, 99%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.26 (d, *J* = 8.4 Hz, 1H), 8.06 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.74 (d, *J* = 1.1 Hz, 1H), 7.54 - 7.61 (m, 1H), 7.38 - 7.51 (m, 3H), 3.16 (br dd, *J* = 12.2, 1.8 Hz, 2H), 2.59 - 2.83 (m, 2H), 1.75 - 1.97 (m, 4H).

[00360] Step 5. To a solution of 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (100 mg, 0.21 mmol, 1 eq) in DCM (2 mL, 0.11 M) was added 4-methylbenzenesulfonic acid salt of (*E*,4*R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one (156 mg, 0.43 mmol, 2 eq), T₃P (205 mg, 0.32 mmol, 1.5 eq), and DIPEA (69 mg, 0.54 mmol, 2.5 eq). The mixture was stirred at 25°C for 1 h. The reaction was purified by prep-TLC (PE:EtOAc = 1:2) to give 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-*N*-[(*E*,1*R*)-4-(3,3-difluoroazetidin-1-yl)-

1-methyl-4-oxo-but-2-enyl]piperidine-4-carboxamide (**Compound 134**) (27 mg, 0.04 mmol, 19%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.34 (dd, $J = 1.7, 8.2$ Hz, 1H), 8.26 (d, $J = 8.4$ Hz, 1H), 8.06 (dd, $J = 1.4, 8.4$ Hz, 1H), 7.74 (s, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.52 - 7.39 (m, 3H), 6.66 (dd, $J = 5.9, 15.5$ Hz, 1H), 5.93 (dd, $J = 1.2, 15.4$ Hz, 1H), 4.62 (br t, $J = 10.9$ Hz, 2H), 4.56 - 4.48 (m, 1H), 4.31 (br t, $J = 11.4$ Hz, 2H), 3.24 - 3.18 (m, 2H), 2.78 (dt, $J = 2.6, 12.6$ Hz, 1H), 2.69 - 2.58 (m, 1H), 2.06 - 1.75 (m, 4H), 1.19 (d, $J = 7.0$ Hz, 3H). $[\text{M}+\text{H}]$ calculated for $\text{C}_{27}\text{H}_{26}\text{ClF}_6\text{N}_3\text{O}_4\text{S}$, 637; found 638.

[00361] **Compounds 135-138** were synthesized analogous to **Compound 134** using the appropriate starting aniline.

[00362] **Compound 139** was synthesized analogous to **Compound 134** using methyl 4-methoxypiperidine-4-carboxylate instead of ethyl 4-fluoropiperidine-4-carboxylate in Step 2 and using (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine in Step 5.

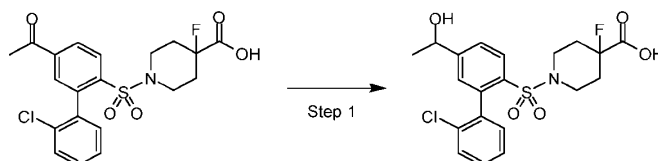
[00363] **Compound 216** was synthesized analogous to **Compound 134** using (*R,E*)-4-amino-1-(3-fluoroazetidin-1-yl)pent-2-en-1-one in Step 5.

[00364] **Compound 249** was synthesized analogous to **Compound 134** using (*E*)-4-amino-1-(3,3-difluoroazetidin-1-yl)-4-methylpent-2-en-1-one in Step 5.

[00365] **Compound 283** was synthesized in a manner analogous to **Compound 134** using (*E*)-4-amino-1-(3,3-difluoroazetidin-1-yl)but-2-en-1-one in Step 5.

[00366] **Intermediate 1-[4-acetyl-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid** was synthesized analogous to 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid.

Scheme 33. Synthesis of Intermediate 1-[2-(2-chlorophenyl)-4-(1-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid



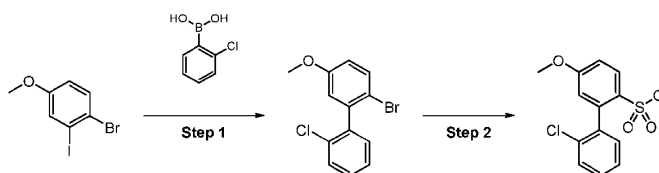
[00367] **Step 1.** To a solution of 1-[4-acetyl-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (120 mg, 0.27 mmol, 1 eq) in methanol (2 mL, 0.14 M) was added sodium borohydride (50 mg, 1.32 mmol, 4.8 eq) and this was stirred at 25°C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 1-[2-(2-chlorophenyl)-4-(1-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid (70 mg, 0.16 mmol, 58%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.94 (d, $J = 8.3$ Hz, 1H), 7.61 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.31 - 7.46 (m, 3H), 7.26 (d, $J = 1.5$ Hz, 1H), 5.33 - 5.53 (m, 1H), 4.76 - 4.89 (m, 1H), 3.99 - 4.22 (m, 1H), 3.03 - 3.13 (m, 2H), 2.61 - 2.72 (m, 1H), 2.53 - 2.59 (m, 1H), 1.59 - 1.99 (m, 4H), 1.35 (dd, $J = 6.5, 2.1$ Hz, 3H).

[00368] **Compound 140** was synthesized analogous to **Compound 134**, Step 5, using 1-[2-(2-chlorophenyl)-4-(1-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid.

[00369] **Intermediate (2*R*,4*S*)-1-((2'-chloro-5-(1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid** was synthesized in a manner analogous to 1-[2-(2-chlorophenyl)-4-(1-hydroxyethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid using (2*R*,4*S*)-1-((5-acetyl-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid.

[00370] **Compound 252** was synthesized in a manner analogous to **Compound 134**, Step 5, using (2*R*,4*S*)-1-((2'-chloro-5-(1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid.

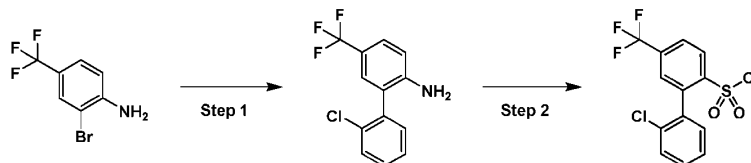
Scheme 34. Synthesis of Intermediate 2'-chloro-5-methoxy-[1,1'-biphenyl]-2-sulfonyl chloride



[00371] **Step 1.** To a mixture of 1-bromo-2-iodo-4-methoxybenzene (45 g, 144 mmol, 1 eq) in 1,4-dioxane/water (v/v 10:1, 550 mL, 0.26 M) was added 2-chlorophenylboronic acid (2.7 g, 173 mmol, 1.2 eq), K_2CO_3 (50 g, 364 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (3.6 g, 12.2 mmol, 0.08 eq). The mixture was stirred at 90°C for 12 h under N_2 . After cooling to rt, the reaction mixture was diluted with water (300 mL) and extracted with EtOAc (300 mL $\times$ 2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 1:0 - 10:1) to give 1-bromo-2-(2-chlorophenyl)-4-methoxybenzene (40 g, 269 mmol, 94%) as a yellow oil.

[00372] **Step 2.** To a solution of 1-bromo-2-(2-chlorophenyl)-4-methoxybenzene (40 g, 134 mmol, 1.0 eq) in THF (400 mL, 0.34 M) at -78°C was added *n*-BuLi (100 mL, 252 mmol, 1.9 eq) and this was stirred for 30 min. To the solution was added a solution of SO_2 in THF (sat. 400 mL). The reaction was stirred at 25°C for 16 h. The reaction mixture was concentrated to remove solvent. *n*-Hexane was added to the residue and the mixture was stirred for 10 min. The mixture was filtered and the filter cake was dissolved in AcOH (150 mL) before NCS (20 g, 151 mmol, 1.2 eq) was added. The resulting reaction was stirred at 25°C for 1 h. The reaction mixture was poured into water (600 mL) and extracted with EtOAc (600 mL $\times$ 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 1:0 - 95:5). 2'-Chloro-5-methoxy-[1,1'-biphenyl]-2-sulfonyl chloride (35 g, 110.34 mmol, 41% yield) was obtained as a yellow oil.

Scheme 35. Synthesis of Intermediate 2-(2-chlorophenyl)-4-(trifluoromethyl)benzenesulfonyl chloride

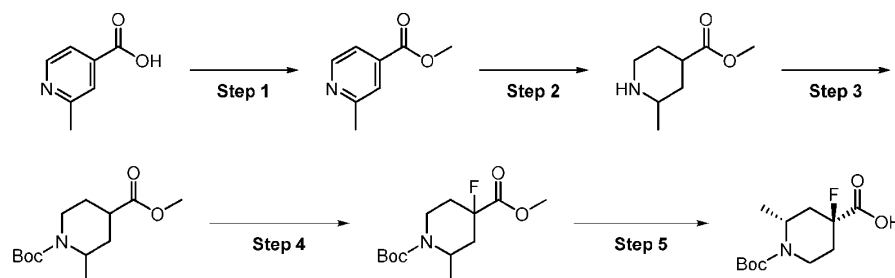


[00373] **Step 1.** To a solution of 2-bromo-4-(trifluoromethyl) aniline (1.0 g, 4.17 mmol, 1.0 eq) in dimethoxyethane/water (v/v 1:1, 20 mL, 0.21 M) was added 2-chlorophenylboronic acid (0.80 g, 4.99 mmol, 1.2 eq), sodium carbonate (1.3 g, 12.5 mmol, 3.0 eq), and Pd(PPh₃)₄ (481 mg, 0.417 mmol, 0.1 eq). The reaction was placed under N₂ and stirred at 80°C for 16 h. After cooling to rt, the reaction was quenched with water (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 to 10:1) to give 2-(2-chlorophenyl)-4-(trifluoromethyl)aniline (670 mg, 2.47 mmol, 59% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 - 7.50 (m, 1H), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.40 - 7.30 (m, 4H), 6.81 (d, *J* = 8.4 Hz, 1H).

[00374] **Step 2.** To a solution of 2-(2-chlorophenyl)-4-(trifluoromethyl) aniline (300 mg, 1.10 mmol, 1.0 eq) in HCl/acetic acid (v/v 3:1, 1.3 mL, 2.8 M) was added a solution of sodium nitrite (84 mg, 1.21 mmol, 1.1 eq) in water (0.10 mL, 2.8 M) dropwise at 0°C. This mixture 1 was stirred for 1 h at 0°C. In a separate beaker, sulfur dioxide gas was bubbled through glacial acetic acid (3.0 mL) under vigorous stirring for 20 minutes. Cuprous chloride (32.8 mg, 0.331 mmol, 0.3 eq) was added and bubbling of sulfur dioxide gas was continued until the yellow-green suspension became close to black and most of the solids dissolved (about 30 minutes). Mixture 1 was added to this solution and the reaction was allowed to warm to 20°C. The reaction was stirred for 2 h before being poured into water (20 mL) and extracted with MTBE (10 mL × 2). The combined organic phases were washed with sat. aq. NaHCO₃ (50 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to give 2-(2-chlorophenyl)-4-(trifluoromethyl)benzenesulfonyl chloride (200 mg, 0.563 mmol, 51% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.39 (d, *J* = 8.4 Hz, 1H), 7.93 (dd, *J* = 1.4, 8.5 Hz, 1H), 7.76 - 7.66 (m, 2H), 7.61 - 7.50 (m, 3H).

[00375] **Intermediates 2-(2-chlorophenyl)-4-cyano-benzenesulfonyl chloride, 5-bromo-2'-chloro-[1,1'-biphenyl]-2-sulfonyl chloride, and 5-bromo-3'-chloro-[1,1'-biphenyl]-2-sulfonyl chloride** were synthesized in a manner analogous to 2-(2-chlorophenyl)-4-(trifluoromethyl)benzenesulfonyl chloride using the appropriate aniline and boronic acid in Step 1.

Scheme 36. Synthesis of Intermediate *rac*-(2*R*,4*S*)-1-*tert*-butoxycarbonyl-4-fluoro-2-methyl-piperidine-4-carboxylic acid



[00376] **Step 1.** To a solution of 2-methylpyridine-4-carboxylic acid (50 g, 365 mmol, 1.0 eq) in methanol (500 mL, 0.73 M) was added SOCl_2 (50 mL) at 0°C . The reaction solution was stirred at 60°C for 6 h. The reaction solution was concentrated to give methyl 2-methylpyridine-4-carboxylate (55 g, 364 mmol, 100%) as a white solid. The crude material was used directly in the next step.

[00377] **Step 2.** To a solution of methyl 2-methylpyridine-4-carboxylate (50 g, 331 mmol, 1 eq) in methanol (400 mL, 0.83 M) was added di-*tert*-butyl dicarbonate (145 g, 663 mmol, 2.0 eq) and PtO_2 (3.5 g) under Ar. The reaction solution was stirred at 25°C for 12 h under H_2 (45 psi). The reaction solution was filtered and the filtrate was concentrated to give methyl 2-methylpiperidine-4-carboxylate (50 g, 318 mmol, 96%) as a white solid.

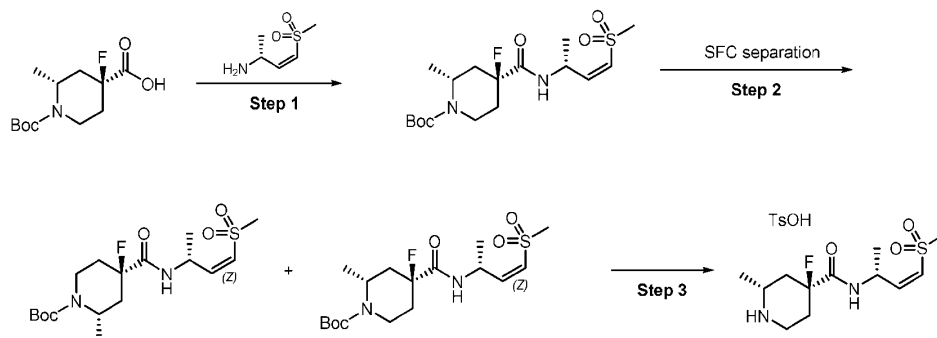
[00378] **Step 3.** To a solution of methyl 2-methylpiperidine-4-carboxylate (50 g, 318 mmol, 1 eq) in THF (300 mL, 1.1 M) was added di-*tert*-butyl dicarbonate (69 g, 318 mmol, 1.0 eq) and TEA (133 mL, 954 mmol, 3 eq) at 0°C . The reaction solution was stirred at 0 - 25°C for 12 h. The reaction solution was concentrated. The crude product was purified by column chromatography (PE:EtOAc = 1:0 - 5:1) to give 1-(*tert*-butyl) 4-methyl 2-methylpiperidine-1,4-dicarboxylate (52 g, 202 mmol, 64%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3 , 298 K) δ ppm 4.21 - 4.15 (m, 1H), 3.87 - 3.79 (m, 1H), 3.71 (s, 3H), 3.10 (ddd, J = 4.1, 12.0, 13.9 Hz, 1H), 2.59 (t, J = 5.7 Hz, 1H), 2.03 - 1.87 (m, 3H), 1.81 - 1.69 (m, 1H), 1.46 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H).

[00379] **Step 4.** To a solution of 1-(*tert*-butyl) 4-methyl 2-methylpiperidine-1,4-dicarboxylate (10 g, 38.9 mmol, 1 eq) in THF (300 mL) was added LDA (39 mL, 77.7 mmol, 2 eq) dropwise at -30°C and the mixture was stirred at -30°C for 1.5 h. To the mixture was added *N*-fluorobenzenesulfonimide (18.4 g, 58.3 mmol, 1.5 eq) in THF (10 mL) dropwise at -30°C and the resulting solution was stirred at -30 - 15°C for 2 h. The reaction was quenched with aq. sat. NH_4Cl (200 mL) and extracted with EtOAc (200 mL $\times$ 2). The combined organic phases were washed with brine (40 mL $\times$ 2), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography (PE:EtOAc = 1:0 - 3:1) then prep-HPLC to give 1-(*tert*-butyl) 4-methyl 4-fluoro-2-methylpiperidine-1,4-dicarboxylate (8 g, 29.10 mmol, 75% yield) as a white solid.

[00380] **Step 5.** A solution of 1-(*tert*-butyl) 4-methyl 4-fluoro-2-methylpiperidine-1,4-dicarboxylate (20 g, 72.6 mmol, 1.0 eq) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (9.1 g, 218 mmol, 3.0 eq) in THF (200 mL, 0.27 M) and water (70 mL, 0.27 M) was stirred at 25°C for 2 h. The mixture was extracted with EtOAc (20 mL). The aqueous phase was adjusted to pH 2 by 1M HCl, diluted with water (50 mL), and extracted with EtOAc (70 mL $\times$ 4). The combined organic phases were concentrated to give *rac*-(2*R*,4*S*)-1-*tert*-butoxycarbonyl-4-fluoro-

2-methyl-piperidine-4-carboxylic acid (19 g, 72.7 mmol, 100%) as a colorless oil, which was used for next step directly. ¹H NMR (400 MHz, CDCl₃, 298 K) δ ppm 4.26 - 4.17 (m, 1H), 4.01 - 3.91 (m, 1H), 3.24 - 3.14 (m, 1H), 2.33 - 2.21 (m, 1H), 2.16 - 2.13 (m, 1H), 2.04 - 1.88 (m, 2H), 1.47 (s, 9H), 1.20 (d, J = 6.8 Hz, 3H).

Scheme 37. Synthesis of Intermediate (2*R*,4*S*)-4-fluoro-2-methyl-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide



[00381] Step 1. To a solution of *rac*-(2*R*,4*S*)-1-*tert*-butoxycarbonyl-4-fluoro-2-methyl-piperidine-4-carboxylic acid (42 g, 161 mmol, 1.0 eq) and (*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-amine, TsOH salt (56.8 g, 177 mmol, 1.1 eq) in DMF (420 mL, 0.38 M) was added HATU (73.3 g, 193 mmol, 1.2 eq) and DIPEA (62.3 g, 482 mmol, 3 eq) dropwise at 25°C. The reaction solution was stirred at 25°C for 0.5 h. The reaction solution was quenched with water (500 mL) and extracted with EtOAc (100 mLx4). The combined organic phases were washed with brine (300 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography to give *tert*-butyl (*rac*-2*R*,4*S*)-4-fluoro-2-methyl-4-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoylpiperidine-1-carboxylate (75 g).

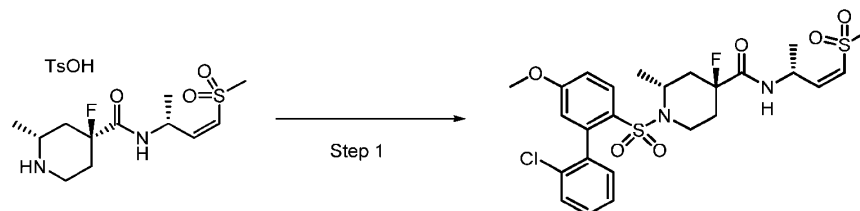
[00382] Step 2. *tert*-Butyl (*rac*-2*R*,4*S*)-4-fluoro-2-methyl-4-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoylpiperidine-1-carboxylate was separated by SFC (Stationary phase: IC (25x5cm); Mobile phase: 35% *i*PrOH/CO₂ with 0.1% NH₄OH) to give *tert*-butyl (2*S*,4*R*)-4-fluoro-2-methyl-4-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]carbamoylpiperidine-1-carboxylate (R_t = 8.85 min, 33 g, 84.1 mmol) as a colorless oil and *tert*-butyl (2*R*,4*S*)-4-fluoro-2-methyl-4-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]carbamoylpiperidine-1-carboxylate (R_t = 9.95 min, 33 g, 84.1 mmol) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.43 (dd, J = 1.9, 7.7 Hz, 1H), 6.47 (d, J = 11.1 Hz, 1H), 6.30 (dd, J = 9.6, 11.1 Hz, 1H), 5.45 - 5.30 (m, 1H), 3.97 (td, J = 6.5, 9.2 Hz, 1H), 3.80 - 3.66 (m, 1H), 3.16 - 3.05 (m, 4H), 2.21 - 2.05 (m, 1H), 2.02 - 1.94 (m, 1H), 1.89 - 1.69 (m, 2H), 1.23 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.5 Hz, 3H).

[00383] Step 3. To a solution of *tert*-butyl (2*R*,4*S*)-4-fluoro-2-methyl-4-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]carbamoylpiperidine-1-carboxylate (33 g, 84.1 mmol, 1 eq) in MeCN (330 mL, 0.25 M) was added *p*-toluenesulfonic acid monohydrate (17.6 g, 92.5 mmol, 1.1 eq) and this was stirred at 60°C for 12 h. The mixture was concentrated to give crude 4-methylbenzenesulfonic acid salt of

(2*R*,4*S*)-4-fluoro-2-methyl-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (35.5 g, 76.4 mmol, 91% yield) as a colorless oil, which was used in the next step directly.

[00384] Intermediate (2*R*,4*S*)-*N*-((*R*,*E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide was synthesized in a manner analogous to (2*R*,4*S*)-4-fluoro-2-methyl-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide starting with the separation of *rac*-(2*R*,4*S*)-1-*tert*-butoxycarbonyl-4-fluoro-2-methyl-piperidine-4-carboxylic acid by chiral SFC to give (2*R*,4*S*)-1-*tert*-butoxycarbonyl-4-fluoro-2-methyl-piperidine-4-carboxylic acid and (2*S*,4*R*)-1-*tert*-butoxycarbonyl-4-fluoro-2-methyl-piperidine-4-carboxylic acid. Coupling with (*E*,4*R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one and removal of the *tert*-butyl carbamate provided the title compound.

Scheme 38. Synthesis of (2*R*,4*S*)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 141)

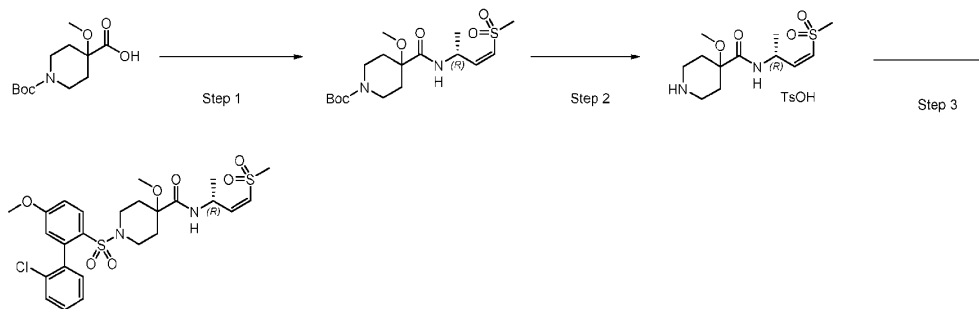


[00385] **Step 1.** To a solution of 4-methylbenzenesulfonic acid salt of (2*R*,4*S*)-4-fluoro-2-methyl-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (35.5 g, 76.4 mmol, 1 eq) in DCM (500 mL, 0.15 M) was added DIPEA (29.6 g, 229 mmol, 3 eq). A solution of 2-(2-chlorophenyl)-4-methoxy-benzenesulfonyl chloride (29 g, 91.7 mmol, 1.2 eq) in DCM (15 mL) was added dropwise at 0°C. The mixture was stirred at 30°C for 12 h. The reaction mixture was poured into water (300 mL) and extracted with DCM (100 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 10:0 - 3:7) then slurried with MTBE (60 mL) to give (2*R*,4*S*)-1-[(2-chlorophenyl)-4-methoxy-phenyl]sulfonyl-4-fluoro-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (**Compound 141**) (20.9 g, 36.1 mmol, 47%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 298 K) δ ppm 8.41 - 8.30 (m, 1H), 7.98 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.61 - 7.51 (m, 1H), 7.45 - 7.30 (m, 3H), 7.16 (td, *J* = 3.2, 8.9 Hz, 1H), 6.88 - 6.80 (m, 1H), 6.44 (d, *J* = 11.1 Hz, 1H), 6.26 (dd, *J* = 9.6, 11.0 Hz, 1H), 5.34 (td, *J* = 7.8, 15.7 Hz, 1H), 3.85 (s, 3H), 3.43 - 3.33 (m, 1H), 3.12 (d, *J* = 2.5 Hz, 3H), 2.96 - 2.74 (m, 1H), 2.66 - 2.58 (m, 1H), 2.36 - 2.23 (m, 1H), 2.13 - 1.52 (m, 4H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.09 - 0.99 (m, 3H). [M+H]⁺ calculated for C₂₅H₃₀ClFN₂O₆S₂, 572; found 573.

[00386] Compounds 142-145 were synthesized in a manner analogous to **Compound 141** starting with the appropriate sulfonyl chloride.

[00387] **Compounds 151-155** were synthesized from (2*R*,4*S*)-*N*-((*R,E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide and the appropriate sulfonyl chloride in a manner analogous to **Compound 141**.

Scheme 39. Synthesis of 1-[2-(2-chlorophenyl)-4-methoxy-phenyl]sulfonyl-4-methoxy-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (Compound 146)



[00388] **Step 1.** To a solution of 1-*tert*-butoxycarbonyl-4-methoxy-piperidine-4-carboxylic acid (400 mg, 1.54 mmol, 1 eq) and (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine, TsOH salt (545 mg, 1.7 mmol, 1.1 eq) in DCM (2 mL, 0.77 M) was added DIPEA (598 mg, 4.6 mmol, 3 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (1.5 g, 2.3 mmol, 1.5 eq). The mixture was stirred at 25°C for 2 h. The reaction mixture was diluted with water (5 mL) and extracted with DCM (5 mL × 2), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 1:0 - 1:1) to give *tert*-butyl 4-methoxy-4-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]carbamoylpiperidine-1-carboxylate (420 mg, 1.1 mmol, 70% yield) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.16 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 11.4 Hz, 1H), 6.29 (dd, *J* = 9.5, 11.1 Hz, 1H), 5.42 - 5.30 (m, 1H), 3.69 (br d, *J* = 9.3 Hz, 2H), 3.11 (d, *J* = 6.0 Hz, 3H), 3.04 - 2.90 (m, 2H), 1.99 (s, 3H), 1.75 - 1.62 (m, 4H), 1.39 (s, 9H), 1.22 - 1.19 (m, 3H).

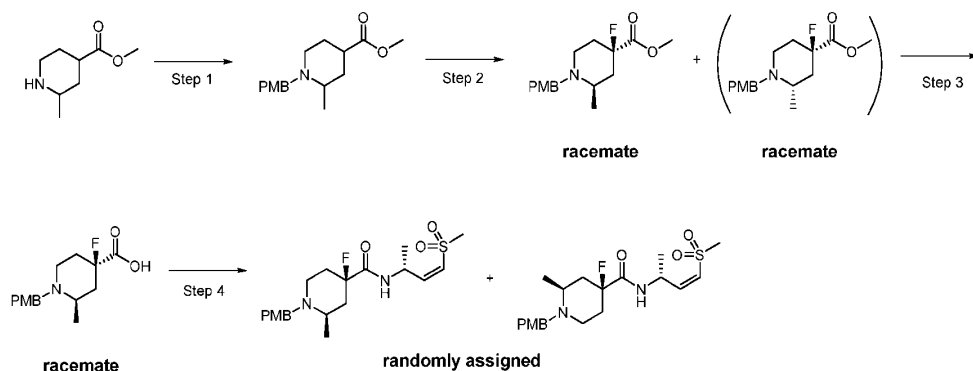
[00389] **Step 2.** To a solution of *tert*-butyl 4-methoxy-4-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]carbamoylpiperidine-1-carboxylate (420 mg, 1.1 mmol, 1 eq) in MeCN (5 mL, 0.22 M) was added *p*-toluenesulfonic acid monohydrate (225 mg, 1.2 mmol, 1.1 eq). The mixture was stirred at 65°C for 4 h. The reaction mixture was concentrated under reduced pressure to give 4-methoxy-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide 4-methylbenzenesulfonic acid salt (180 mg, 1.04 mmol, 96% yield) as a yellow solid.

[00390] **Step 3.** To a solution of 4-methoxy-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide, 4-methylbenzenesulfonic acid (200 mg, 0.43 mmol, 1 eq) in DCM (1 mL, 0.43 M) was added 2-(2-chlorophenyl)-4-methoxy-benzenesulfonyl chloride (205 mg, 0.65 mmol, 1.5 eq) and DIPEA (167 mg, 1.3 mmol, 3 eq). The mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give 1-[2-(2-chlorophenyl)-4-methoxy-phenyl]sulfonyl-4-methoxy-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (**Compound 146**) (47 mg, 0.08 mmol, 19% yield) as a white solid. ¹H

NMR (400 MHz, DMSO- d_6) δ ppm 8.11 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.44 - 7.31 (m, 3H), 7.18 (dd, J = 2.7, 9.0 Hz, 1H), 6.83 (d, J = 2.6 Hz, 1H), 6.43 (d, J = 11.2 Hz, 1H), 6.30 - 6.23 (m, 1H), 5.40 - 5.28 (m, 1H), 3.85 (s, 3H), 3.11 (s, 3H), 3.02 (s, 3H), 3.00 - 2.92 (m, 2H), 2.65 - 2.52 (m, 2H), 1.74 - 1.56 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). [M+H] calculated for $C_{25}H_{31}ClN_2O_7S_2$, 570; found 571.

[00391] Intermediate 4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide, 4-methylbenzenesulfonic acid salt was synthesized in a manner analogous to 4-methoxy-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide, 4-methylbenzenesulfonic acid salt.

Scheme 40. Synthesis of Intermediates (2R*,4**R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide and (2**S*,4**S*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide**



[00392] Step 1. To a solution of methyl 2-methylpiperidine-4-carboxylate (2.6 g, 13.4 mmol, 1 eq) in DMF (260 mL, 0.06 M) was added K_2CO_3 (5.6 g, 40.3 mmol, 3 eq) and 4-methoxybenzyl chloride (2.5 g, 16.1 mmol, 1.2 eq). The reaction mixture was stirred at 25°C for 12 h. The mixture was poured into H_2O (100 mL) and extracted with EtOAc (70 mL $\times$ 3). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated. The crude was purified by column chromatography to give methyl 1-[(4-methoxyphenyl)methyl]-2-methyl-piperidine-4-carboxylate (3.5 g, 12.6 mmol, 94% yield) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 - 7.19 (m, 2H), 6.88 - 6.82 (m, 2H), 4.04 (d, J = 13.3 Hz, 1H), 3.82 - 3.79 (m, 3H), 3.71 - 3.64 (m, 3H), 3.08 (d, J = 13.3 Hz, 1H), 2.91 - 2.80 (m, 1H), 2.66 - 2.48 (m, 1H), 2.40 - 2.18 (m, 2H), 1.93 - 1.73 (m, 2H), 1.71 - 1.47 (m, 2H), 1.32 - 1.18 (m, 3H).

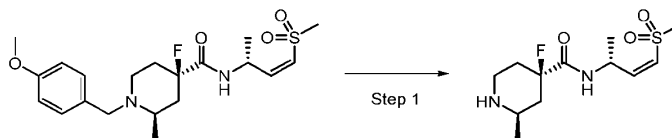
[00393] Step 2. To a solution of methyl 1-[(4-methoxyphenyl)methyl]-2-methyl-piperidine-4-carboxylate (1.5 g, 5.41 mmol, 1 eq) in THF (15 mL) was added LiHMDS (4.1 mL, 8.11 mmol, 1.5 eq) dropwise at -45°C and the mixture was stirred at -45°C for 0.5 h. Then a solution of *N*-fluorobenzenesulfonimide (2.1 g, 6.76 mmol, 1.3 eq) in THF (15 mL) was added dropwise and the resulting solution was stirred at -45°C for 0.5 h and -45 to 15°C for 1 h. The reaction was quenched with

sat. aq. NH_4Cl (30 mL) and extracted with EtOAc (80 mL $\times$ 2). The combined organic phases were washed with brine (50 mL $\times$ 2), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography (PE:EtOAc = 9:1 - 7:3) to give methyl *rac*-(2*R*,4*R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-piperidine-4-carboxylate as a light yellow oil and methyl *rac*-(2*S*,4*R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-piperidine-4-carboxylate as a brown oil.

[00394] Step 3. A solution of methyl *rac*-(2*R*,4*R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-piperidine-4-carboxylate (1.7 g, 5.76 mmol, 1 eq) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (724 mg, 17.3 mmol, 3 eq) in THF (18 mL, 0.24 M) and H_2O (6 mL, 0.24 M) was stirred at 25°C for 2 h. The mixture was extracted with EtOAc (20 mL). The aqueous phase was adjusted with HCl (1 M) to pH = 2. The resulting aqueous phase was extracted with EtOAc (30 mL $\times$ 2). The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated. The crude product was purified by prep-HPLC to give *rac*-(2*R*,4*R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-piperidine-4-carboxylic acid (830 mg, 2.95 mmol, 51%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.70 - 9.39 (m, 1H), 7.55 - 7.36 (m, 2H), 7.03 (d, J = 8.6 Hz, 2H), 4.66 - 4.47 (m, 1H), 4.36 - 4.08 (m, 2H), 3.83 - 3.58 (m, 4H), 3.08 - 2.88 (m, 1H), 2.43 - 2.34 (m, 1H), 2.32 - 1.86 (m, 3H), 1.57 - 1.29 (m, 3H). $[\text{M}+\text{H}]$ calculated for $\text{C}_{15}\text{H}_{20}\text{FNO}_3$, 281; found 282.

[00395] Step 4. To a solution of *rac*-(2*R*,4*R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-piperidine-4-carboxylic acid (830 mg, 2.95 mmol, 1 eq) and (Z,2*R*)-4-methylsulfonylbut-3-en-2-amine, 4-methylbenzenesulfonate (1.0 g, 3.25 mmol, 1.1 eq) in DCM (10 mL, 0.3 M) was added DIPEA (1.1 g, 8.85 mmol, 3 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (4.7 mg, 7.38 mmol, 2.5 eq). The mixture was stirred at 25°C for 2 h. The reaction was poured into H_2O (10 mL) and extracted with DCM (10 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give a crude product, which was separated by SFC to give (2**R*,4**R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-*N*-[(Z,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (410 mg, 0.99 mmol, 34%) as a colorless oil ^1H NMR (400 MHz, CDCl_3) δ ppm 7.77 (br d, J = 7.9 Hz, 1H), 7.41 (br s, 1H), 7.22 - 7.19 (m, 1H), 6.85 (br d, J = 8.5 Hz, 1H), 6.33 - 6.07 (m, 2H), 5.51 - 5.25 (m, 1H), 3.80 (s, 3H), 3.76 - 3.67 (m, 1H), 3.34 - 3.18 (m, 2H), 3.10 (br s, 3H), 2.41 - 2.35 (m, 3H), 2.22 (br s, 4H), 1.72 - 1.42 (m, 3H), 1.40 - 1.28 (m, 3H) and (2**S*,4**S*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-*N*-[(Z,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (430 mg, 1.04 mmol, 35%) as a colorless oil ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.47 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.52 - 6.43 (m, 1H), 6.31 (br t, J = 10.3 Hz, 1H), 5.46 - 5.32 (m, 1H), 4.69 - 3.99 (m, 2H), 3.79 - 3.74 (m, 3H), 3.69 - 3.52 (m, 1H), 3.14 - 3.07 (m, 3H), 2.29 (s, 3H), 2.12 - 2.03 (m, 3H), 1.65 - 1.28 (m, 4H), 1.25 - 1.19 (m, 3H). $[\text{M}+\text{H}]$ calculated for $\text{C}_{20}\text{H}_{29}\text{FN}_2\text{O}_4\text{S}$, 412; found 413.

Scheme 41. Synthesis of Intermediate (2R*,4**R*)-4-fluoro-2-methyl-*N*-[(Z,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide**



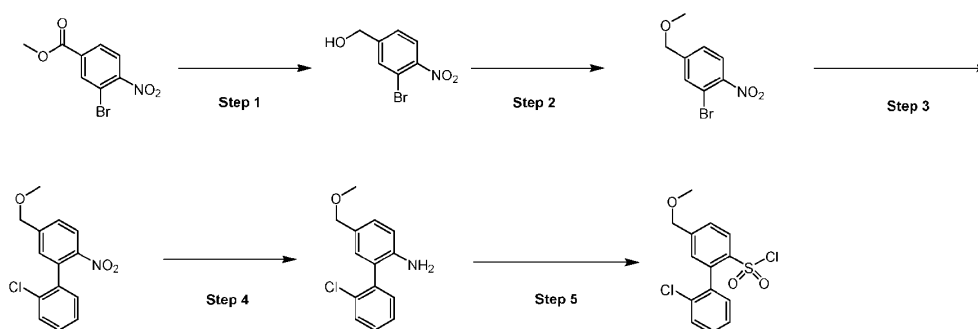
[00396] **Step 1.** Ammonium cerium(IV) nitrate (817 mg, 1.75 mmol, 3 eq) was added to a solution of (2^{*}*R*,4^{*}*R*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (240 mg, 0.58 mmol, 1 eq) in MeCN/water (v/v 3:1, 3.2 mL, 0.18 M) at 0°C and the mixture was stirred at 25°C for 2 h. The reaction mixture was purified directly by prep-HPLC to give (2^{*}*R*,4^{*}*R*)-4-fluoro-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (120 mg, 0.41 mmol, 70%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.66 - 8.52 (m, 1H), 8.50 - 8.33 (m, 1H), 6.49 (d, *J* = 11.3 Hz, 1H), 6.33 (dd, *J* = 9.4, 11.1 Hz, 1H), 5.49 - 5.32 (m, 1H), 3.67 - 3.53 (m, 1H), 3.34 - 3.15 (m, 2H), 3.11 (s, 3H), 2.33 - 2.24 (m, 5H), 2.00 - 1.86 (m, 1H), 1.83 - 1.70 (m, 1H), 1.24 (s, 3H). [M+H]⁺ calculated for C₁₂H₂₁FN₂O₃S, 292; found 293.

[00397] **Intermediate (2^{*}*S*,4^{*}*S*)-4-fluoro-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide** was synthesized in an analogous manner using (2^{*}*S*,4^{*}*S*)-4-fluoro-1-[(4-methoxyphenyl)methyl]-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide.

[00398] **Compound 147** was synthesized from (2^{*}*R*,4^{*}*R*)-4-fluoro-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide in a manner analogous to **Compound 141**.

[00399] **Compound 148** was synthesized from (2^{*}*S*,4^{*}*S*)-4-fluoro-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide in a manner analogous to **Compound 141**.

Scheme 42. Synthesis of Intermediate 2-(2-chlorophenyl)-4-(methoxymethyl)benzenesulfonyl chloride



[00400] **Step 1.** To a solution of methyl 3-bromo-4-nitrobenzoate (5 g, 19.2 mmol, 1.0 eq) in methanol (80 mL, 0.24 M) was added sodium borohydride (7.5 g, 198 mmol, 10 eq) at 0°C. The mixture was stirred at 25°C for 6 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (PE:EtOAc = 100:1 to 0:1) to give (3-bromo-4-nitro-phenyl)methanol (3.8 g,

16.4 mmol, 85%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.87 (d, $J = 8.4$ Hz, 1H), 7.78 (d, $J = 0.8$ Hz, 1H), 7.44 (dt, $J = 8.3, 0.8$ Hz, 1H), 4.80 (s, 2H).

[00401] **Step 2.** To a solution of (3-bromo-4-nitro-phenyl)methanol (2.6 g, 11.2 mmol, 1.0 eq) in DMSO (20 mL, 0.6 M) was added iodomethane (6.4 g, 44.8 mmol, 4 eq) at 0°C and the mixture was stirred for 1 h. Potassium hydroxide (2.5 g, 44.8 mmol, 4 eq) was added and the mixture was stirred at 20°C for 2 h. The reaction mixture was quenched with water (200 mL) and extracted with EtOAc (100 mL $\times$ 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (PE:EtOAc = 100:1 to 1:1) to give 2-bromo-4-(methoxymethyl)-1-nitro-benzene (2.1 g, 8.5 mmol, 76%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.86 (d, $J = 8.3$ Hz, 1H), 7.74 (s, 1H), 7.41 (d, $J = 8.3$ Hz, 1H), 4.51 (s, 2H), 3.45 (s, 3H).

[00402] **Step 3.** To a solution of methyl 2-bromo-4-(methoxymethyl)-1-nitro-benzene (2.1 g, 8.5 mmol, 1 eq), 2-chlorophenylboronic acid (2 g, 12.8 mmol, 1.5 eq) and potassium carbonate (2.4 g, 17 mmol, 2 eq) in toluene/water/ethanol (v/v/v 3:1:1, 40 mL, 0.2 M) was added tetrakis(triphenylphosphine)palladium(0) (986 mg, 0.85 mmol, 0.1 eq) at 25°C . The suspension was purged with N_2 and stirred at 115°C for 16 h. After cooling to rt, the reaction mixture was quenched with water (50 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (PE:EtOAc = 100:1 to 5:1) to give 2-(2-chlorophenyl)-4-(methoxymethyl)-1-nitro-benzene (2.20 g, 7.92 mmol, 93%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.11 (d, $J = 8.5$ Hz, 1H), 7.52 (dd, $J = 8.4, 1.3$ Hz, 1H), 7.43 - 7.49 (m, 1H), 7.32 - 7.39 (m, 3H), 7.28 - 7.31 (m, 1H), 4.58 (s, 2H), 3.47 (s, 3H).

[00403] **Step 4.** To a solution of 2-(2-chlorophenyl)-4-(methoxymethyl)-1-nitro-benzene (2.2 g, 7.9 mmol, 1 eq) in ethanol/water (v/v 3:1, 40 mL, 0.2 M) was added ammonium chloride (2.1 g, 39.6 mmol, 5 eq) and iron powder (2.2 g, 39.6 mmol, 5 eq). The suspension was purged with N_2 and stirred at 80°C for 2 h. After cooling to rt, the mixture reaction was filtered and the filtrate was concentrated under reduced pressure to remove EtOH. The crude was extracted with EtOAc (30 mL $\times$ 3) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (PE:EtOAc = 100:1 to 1:1) to give 2-(2-chlorophenyl)-4-(methoxymethyl)aniline (2 g, 7.27 mmol, 92%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.48 - 7.53 (m, 1H), 7.30 - 7.36 (m, 3H), 7.20 (dd, $J = 8.1, 1.8$ Hz, 1H), 7.05 (d, $J = 2.0$ Hz, 1H), 6.79 (d, $J = 8.1$ Hz, 1H), 4.38 (s, 2H), 3.38 (s, 3H).

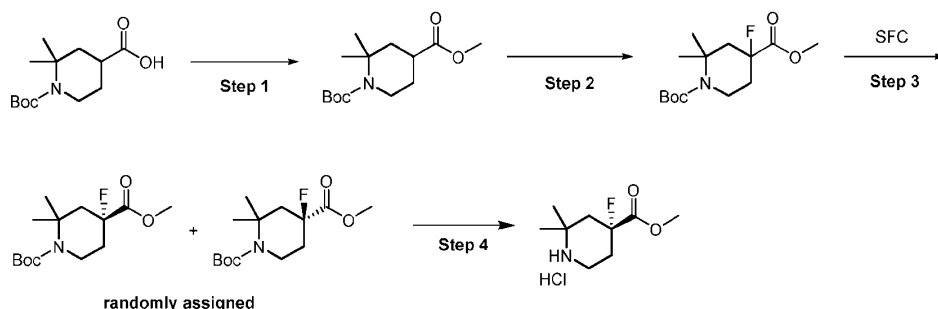
[00404] **Step 5.** To a mixture of 2-(2-chlorophenyl)-4-(methoxymethyl)aniline (320 mg, 1.29 mmol, 1.0 eq) in HCl (6 N, 4 mL) and acetic acid (8 mL, 0.15 M) at 0°C was added a solution of sodium nitrite (107 mg, 1.5 mmol, 1.2 eq) in water (0.5 mL, 0.15 M) dropwise at 0°C . The reaction mixture (mixture 1) was stirred for 1.5 h at 0°C . In a separate beaker (mixture 2), sulfur dioxide gas was bubbled through 10 mL of glacial acetic acid under vigorous stirring for 30 min. CuCl (76.7 mg, 0.77 mmol, 0.6 eq) was added and bubbling of sulfur dioxide gas was continued until the yellow-green suspension turned blue-green

and most of the solids dissolved (about 1 h). Mixture 1 was added to mixture 2 at 0°C and the reaction mixture was warmed to 20°C and stirred for 1 h. The reaction was poured into ice-water (50 mL) and the precipitated gummy solid was extracted with MTBE (3 × 30 mL). The combined organic phase was washed with water (50 mL × 3) and sat. NaHCO₃ (80 mL), dried over Na₂SO₄, filtered and concentrated to give crude product, which was purified by prep-TLC (PE:EtOAc = 5:1) to give 2-(2-chlorophenyl)-4-(methoxymethyl)benzenesulfonyl chloride (25 mg, 0.075 mmol, 5.8%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.22 (d, *J* = 8.2 Hz, 1H), 7.58 - 7.63 (m, 1H), 7.47 - 7.52 (m, 1H), 7.33 - 7.42 (m, 4H), 4.60 (s, 2H), 3.47 (s, 3H).

[00405] **Compound 149** was synthesized from 2-(2-chlorophenyl)-4-(methoxymethyl)benzenesulfonyl chloride in a manner analogous to **Compound 141**.

[00406] **Compound 156** was synthesized from 2-(2-chlorophenyl)-4-(methoxymethyl)benzenesulfonyl chloride and (2*R*,4*S*)-*N*-((*R,E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide in a manner analogous to **Compound 141**.

Scheme 43. Synthesis of Intermediate methyl (4R*)-4-fluoro-2,2-dimethyl-piperidine-4-carboxylate hydrochloride**



[00407] **Step 1.** To a solution of 1-(*tert*-butoxycarbonyl)-2,2-dimethyl-piperidine-4-carboxylic acid (150 mg, 0.58 mmol, 1 eq) in DCM (2 mL, 0.29 M) was added potassium carbonate (161 mg, 1.17 mmol, 2 eq) and iodomethane (165 mg, 1.17 mmol, 2 eq) and the mixture was stirred at 25°C for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EA = 5:1) to give 1-(*tert*-butyl) 4-methyl 2,2-dimethylpiperidine-1,4-dicarboxylate (60 mg, 0.22 mmol, 38%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.70 (s, 3H), 3.63 - 3.69 (m, 1H), 3.30 (ddd, *J* = 13.5, 8.9, 4.2 Hz, 1H), 2.58 - 2.69 (m, 1H), 1.90 - 2.00 (m, 1H), 1.66 - 1.85 (m, 3H), 1.51 (s, 3H), 1.43 - 1.49 (m, 9H), 1.34 (s, 3H).

[00408] **Step 2.** To a solution of 1-(*tert*-butyl) 4-methyl 2,2-dimethylpiperidine-1,4-dicarboxylate (100 mg, 0.37 mmol, 1 eq) in THF (1.5 mL, 0.25 M) was added LDA (2 M, 0.4 mL, 0.74 mmol, 2.0 eq) at -30°C and this was stirred at -30°C for 1.5 hours. To the mixture was added *N*-fluorobenzenesulfonylimide (174 mg, 0.55 mmol, 1.5 eq) in THF (0.1 mL) dropwise at -30°C and the reaction was stirred at 15°C for 2 hours. The solution was diluted with sat. aq. NH₄Cl (1 mL) and extracted with EtOAc (1 mL × 3). The combined organic layers were washed with brine (1 mL × 3), dried over Na₂SO₄, filtered, and

concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EtOAc = 5:1) to give 1-(*tert*-butyl) 4-methyl 4-fluoro-2,2-dimethylpiperidine-1,4-dicarboxylate (20 mg, 0.07 mmol, 19%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.61 - 3.76 (m, 3H), 3.35 - 3.54 (m, 2H), 1.80 - 2.24 (m, 4H), 1.34 - 1.40 (m, 15H).

[00409] **Step 3.** 1-(*tert*-Butyl) 4-methyl 4-fluoro-2,2-dimethylpiperidine-1,4-dicarboxylate (800 mg, 2.76 mmol) was separated by chiral SFC to give 1-*tert*-butyl 4-methyl (4**R*)-4-fluoro-2,2-dimethylpiperidine-1,4-dicarboxylate (400 mg, 1.38 mmol, 40% yield) as a yellow oil and 1-*tert*-butyl 4-methyl (4**S*)-4-fluoro-2,2-dimethylpiperidine-1,4-dicarboxylate (250 mg, 0.86 mmol, 25% yield) as a yellow oil.

[00410] **Step 4.** To a solution of 1-*tert*-butyl 4-methyl (4**R*)-4-fluoro-2,2-dimethylpiperidine-1,4-dicarboxylate (250 mg, 0.86 mmol, 1 eq) in methanol (2.5 mL, 0.35 M) was added HCl/MeOH (4 M, 1 mL) and the reaction was stirred at 25°C for 2 hours. The reaction was concentrated under reduced pressure to give methyl (4**R*)-4-fluoro-2,2-dimethylpiperidine-4-carboxylate hydrochloride (190 mg, 0.84 mmol, 97%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.48 (br s, 2H), 3.75 (s, 3H), 3.28 - 3.18 (m, 2H), 2.42 - 2.08 (m, 4H), 1.38 (d, *J* = 2.6 Hz, 6H).

[00411] **Compound 150** was synthesized by coupling 2'-chloro-5-methoxy-[1,1'-biphenyl]-2-sulfonyl chloride and methyl (4**R*)-4-fluoro-2,2-dimethylpiperidine-4-carboxylate hydrochloride in a manner analogous to Step 2, 4, and 5 of the synthesis of **Compound 47**.

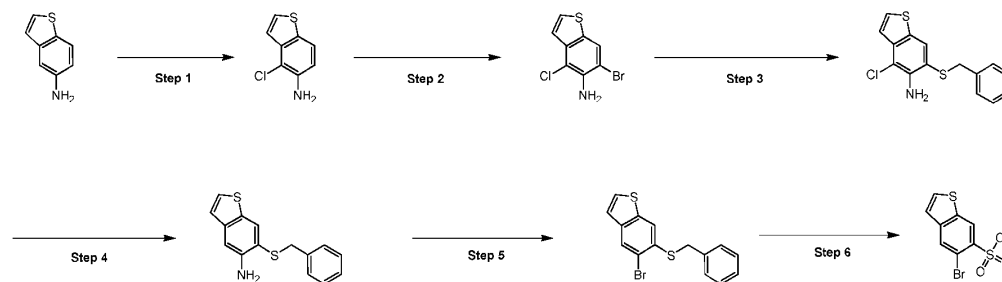
[00412] **Intermediate methyl (2*R*,4*S*)-4-fluoro-2-methylpiperidine-4-carboxylate** was synthesized in a manner analogous to methyl (4**R*)-4-fluoro-2,2-dimethylpiperidine-4-carboxylate hydrochloride starting with 1-*tert*-butyl 4-methyl 4-fluoro-2-methylpiperidine-1,4-dicarboxylate in Step 3.

[00413] **Compound 250** was synthesized in a manner analogous to **Compound 47** starting from methyl (2*R*,4*S*)-4-fluoro-2-methylpiperidine-4-carboxylate and 2-bromo-4-(trifluoromethoxy)benzenesulfonyl chloride in Step 2.

[00414] **Compound 251** was synthesized in a manner analogous to **Compound 134** starting from 2-bromo-4-(difluoromethoxy)benzenamine in Step 1 and using methyl (2*R*,4*S*)-4-fluoro-2-methylpiperidine-4-carboxylate in Step 2.

[00415] **Intermediate (2*R*,4*S*)-1-((5-acetyl-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid** was synthesized in a manner analogous to 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid starting from 1-(4-amino-3-bromophenyl)ethanone in Step 1 and using methyl (2*R*,4*S*)-4-fluoro-2-methylpiperidine-4-carboxylate in Step 2.

[00416] **Intermediate (2*R*,4*S*)-1-((2'-chloro-5-formyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid** was synthesized in a manner analogous to 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid, Steps 1-3, starting from 4-amino-3-bromobenzaldehyde in Step 1 and using methyl (2*R*,4*S*)-4-fluoro-2-methylpiperidine-4-carboxylate in Step 2.

Scheme 44. Synthesis of Intermediate 5-bromobenzo[b]thiophene-6-sulfonyl chloride

[00417] Step 1. A solution of benzo[b]thiophen-5-amine (11 g, 73.7 mmol, 1 eq) and NCS (9.8 g, 73.7 mmol, 1 eq) in acetonitrile (110 mL, 0.67 M) was stirred at 25°C for 16 h. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (20 mL × 3). The extract was washed with brine (20 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (PE:EtOAc = 10:1 - 1:1) to afford 4-chlorobenzo[b]thiophen-5-amine (6.3 g, 34.3 mmol, 46%) as a yellow oil.

[00418] Step 2. A solution of 4-chlorobenzo[b]thiophen-5-amine (6.3 g, 34.3 mmol, 1 eq) and NBS (6.1 g, 34.3 mmol, 1 eq) in ACN (70 mL, 0.49 M) was stirred at 20°C for 16 h under N₂. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (20 mL). The extract was washed with brine (20 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (PE:EtOAc = 1:1) to afford 6-bromo-4-chloro-benzo[b]thiophen-5-amine (5.8 g, 22.1 mmol, 64%) as a yellow oil.

[00419] Step 3. A solution of 6-bromo-4-chloro-benzo[b]thiophen-5-amine (5.8 g, 22.1 mmol, 1 eq), benzyl mercaptan (3.6 g, 28.7 mmol, 1.3 eq), DIPEA (5.7 g, 44.2 mmol, 2 eq), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (1.3 g, 2.21 mmol, 0.1 eq) and tris(dibenzylideneacetone)dipalladium (1 g, 1.1 mmol, 0.05 eq) in toluene (60 mL, 0.37 M) was stirred at 130°C for 16 h under N₂. After cooling to rt, the reaction mixture was poured into water (500 mL) and extracted with EtOAc (500 mL × 3). The combined organic layers were washed with brine (200 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 10:1) to afford 6-benzylsulfanyl-4-chloro-benzo[b]thiophen-5-amine (6.6 g, 21.6 mmol, 98%) as a yellow oil.

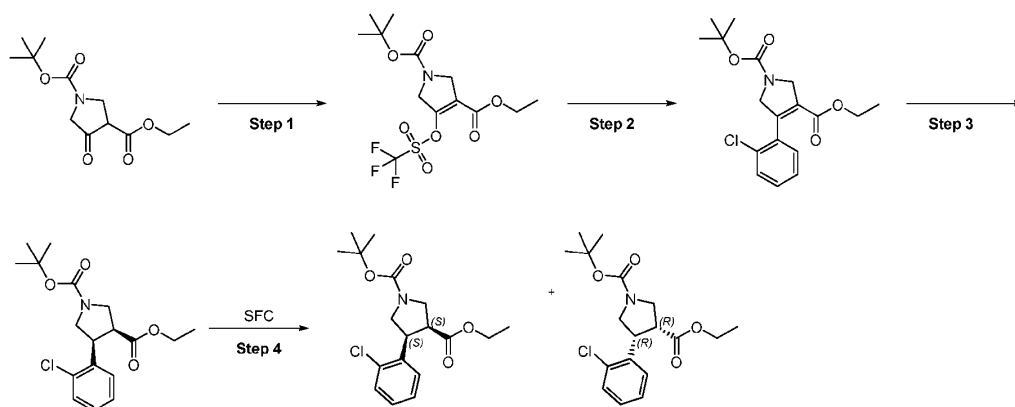
[00420] Step 4. To a solution of 6-benzylsulfanyl-4-chloro-benzo[b]thiophen-5-amine (4 g, 13.1 mmol, 1 eq) in 1,4-dioxane (40 mL, 0.33 M) was added triethylamine (2.6 g, 26.2 mmol, 2 eq), triethylsilane (7.6 g, 65.4 mmol, 5 eq), Pd₂(dba)₃ (0.6 g, 0.654 mmol, 0.05 eq) and XPhos (0.6 g, 1.31 mmol, 0.1 eq) under N₂. The reaction was stirred at 100°C for 16 h under N₂. After cooling to rt, the reaction mixture was poured into water (300 mL) and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (200 mL × 2), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 3:1) to give 6-benzylsulfanylbzenzo[b]thiophen-5-amine (3 g, 11.1 mmol, 84%) as a yellow solid.

[00421] **Step 5.** A solution of 6-benzylsulfanylbenzothiophen-5-amine (1.5 g, 5.53 mmol, 1 eq), *tert*-butyl nitrite (855 mg, 8.29 mmol, 1.5 eq) and cuprous bromide (951 mg, 6.63 mmol, 1.2 eq) in ACN (30 mL, 0.18 M) was stirred at 65°C for 2 h under N₂. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (20 mL). The extract was washed with brine (20 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by prep-TLC (PE:EtOAc = 10:1) to afford 6-benzylsulfanyl-5-bromo-benzothiophene (120 mg, 0.36 mmol, 6.5%) as a yellow solid.

[00422] **Step 6.** To 6-benzylsulfanyl-5-bromo-benzothiophene (30 mg, 0.09 mmol, 1 eq) in acetic acid (1 mL) and water (0.3 mL) was added *N*-chlorosuccinimide (48 mg, 0.36 mmol, 4 eq). The mixture was stirred at 25°C for 1 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL). The extract was washed with brine (20 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* to afford crude 5-bromobenzo[*b*]thiophene-6-sulfonyl chloride (20 mg, 0.064 mmol, 72% yield).

[00423] **Compound 157** was synthesized in a manner analogous to **Compound 47**, Steps 2-5, using 5-bromobenzo[*b*]thiophene-6-sulfonyl chloride in Step 2.

Scheme 45. Synthesis of Intermediate 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate



[00424] **Step 1.** To a solution of 1-(*tert*-butyl) 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (100 g, 389 mmol, 1 eq) in toluene (2 L, 0.19 M) was added DIPEA (75.4 g, 583 mmol, 1.5 eq) and trifluoromethanesulfonyl anhydride (132 g, 466 mmol, 1.2 eq) at 0°C. The reaction was stirred at 20°C for 16 h. The solution was evaporated to get the crude product 1-(*tert*-butyl) 3-ethyl 4-(trifluoromethylsulfonyloxy)-2,5-dihydropyrrole-1,3-dicarboxylate (150 g, 385 mmol, 99%) as a brown oil.

[00425] **Step 2.** To a solution of 1-(*tert*-butyl) 3-ethyl 4-(trifluoromethylsulfonyloxy)-2,5-dihydropyrrole-1,3-dicarboxylate (22 g, 56.5 mmol, 1 eq) in THF (360 mL, 0.16 M) was added 2-chlorophenylboronic acid (9.7 g, 62.2 mmol, 1.1 eq), potassium phosphate tribasic (164 g, 771 mmol, 2 eq) and tetrakis(triphenylphosphine)palladium(0) (22.3 g, 19.3 mmol, 0.05 eq). The reaction was stirred at 70°C for 12 h under N₂. After cooling to rt, the solution was diluted with water (350 mL) and extracted

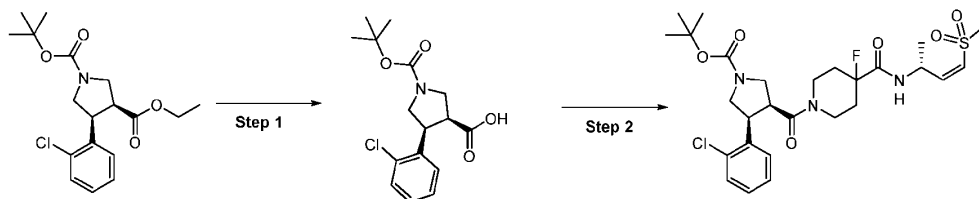
with EtOAc (400 mL $\times$ 3). The combined organic phases were washed with brine (150 mL $\times$ 3), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (PE:EtOAc = 1:0 - 1:1) to give 1-(*tert*-butyl) 3-ethyl 4-(2-chlorophenyl)-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (105 g, 298 mmol, 77%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.40 - 7.44 (m, 1H), 7.27 - 7.32 (m, 2H), 7.19 (br s, 1H), 4.43 - 4.62 (m, 4H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.51 (br d, *J* = 11.3 Hz, 9H), 0.99 - 1.08 (m, 3H).

[00426] **Step 3.** To a solution of 1-(*tert*-butyl) 3-ethyl 4-(2-chlorophenyl)-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (25 g, 71.1 mmol, 1.0 eq) in ethanol (80 mL, 0.04 M) and ethyl acetate (240 mL, 0.04 M) was added PtO₂ (5 g, 35.5 mmol, 0.5 eq) and this was stirred at 20°C for 16 h under H₂ (15 psi). The solution was filtered and evaporated. The residue was purified by prep-HPLC to give *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (7 g, 42.4 mmol, 30%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 - 7.42 (m, 1H), 7.18 - 7.25 (m, 3H), 3.54 - 3.90 (m, 8H), 1.50 (s, 9H), 0.89 (t, *J* = 7.1 Hz, 3H).

[00427] **Step 4.** *Rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (17 g, 48.0 mmol, 1 eq) was separated by SFC to give 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (8 g, 22.6 mmol, 47%) as a white solid ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 - 7.41 (m, 1H), 7.18 - 7.24 (m, 3H), 3.56 - 3.88 (m, 8H), 1.51 (s, 9H), 0.89 (t, *J* = 7.1 Hz, 3H) and 1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (8 g, 22.6 mmol, 47%) as a white solid ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 - 7.41 (m, 1H), 7.16 - 7.24 (m, 3H), 4.04 - 4.19 (m, 1H), 3.58 - 3.87 (m, 7H), 1.50 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H).

[00428] Intermediates *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-6-fluorophenyl)pyrrolidine-1,3-dicarboxylate, *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluorophenyl)pyrrolidine-1,3-dicarboxylate, *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-4-fluorophenyl)pyrrolidine-1,3-dicarboxylate, *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-3-fluorophenyl)pyrrolidine-1,3-dicarboxylate, *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-5-methylphenyl)pyrrolidine-1,3-dicarboxylate, *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-4-methylphenyl)pyrrolidine-1,3-dicarboxylate, *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-3-methylphenyl)pyrrolidine-1,3-dicarboxylate, and *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-fluoro-3-fluorophenyl)pyrrolidine-1,3-dicarboxylate were synthesized in a manner similar to *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate.

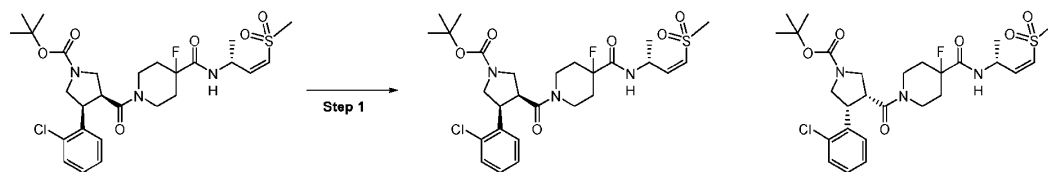
Scheme 46. Synthesis of *tert*-butyl *cis*-(3*RS*,4*RS*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate (Compound 158)



[00429] **Step 1.** To a solution of *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (250 mg, 0.71 mmol, 1 eq) in DCE (20 mL) was added trimethyltin hydroxide (650 mg, 2.13 mmol, 3 eq). The reaction was stirred at 70°C for 72 h. The solution was filtered, diluted with water (20 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give *rac*-(3*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid (230 mg, 0.71 mmol, 100% yield).

[00430] **Step 2.** To a solution of *rac*-(3*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid (230 mg, 0.71 mmol, 1 eq) in DMF (5 mL, 0.14 M) was added HATU (350 mg, 1.06 mmol, 1.5 eq), DIPEA (0.3 mL, 2.13 mmol, 3 eq) and 4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonylallyl]piperidine-4-carboxamide 4-methylbenzenesulfonic acid salt (318 mg, 0.71 mmol, 1 eq). The reaction was stirred at 20°C for 2 h. The solution was diluted with water (10 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give *tert*-butyl (3*RS*,4*RS*)-3-(2-chlorophenyl)-4-(4-fluoro-4-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carboxylate (**Compound 158**) (23 mg, 0.039 mmol, 5.6% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.39 - 8.17 (m, 1H), 7.50 - 7.40 (m, 1H), 7.20 - 7.14 (m, 1H), 7.36 - 7.13 (m, 2H), 6.50 - 6.40 (m, 1H), 6.31 - 6.20 (m, 1H), 5.32 (br d, *J* = 8.5 Hz, 1H), 4.14 - 3.95 (m, 2H), 3.90 (br s, 1H), 3.74 - 3.45 (m, 5H), 3.29 (br s, 1H), 3.18 - 3.03 (m, 3H), 2.69 - 2.56 (m, 1H), 2.42 - 2.30 (m, 1H), 2.03 - 1.72 (m, 2H), 1.70 - 1.49 (m, 2H), 1.47 - 1.38 (m, 9H), 1.26 - 1.14 (m, 3H). [M+H]⁺ calculated for C₂₇H₃₇ClFN₃O₆S, 585.2; found 586.3.

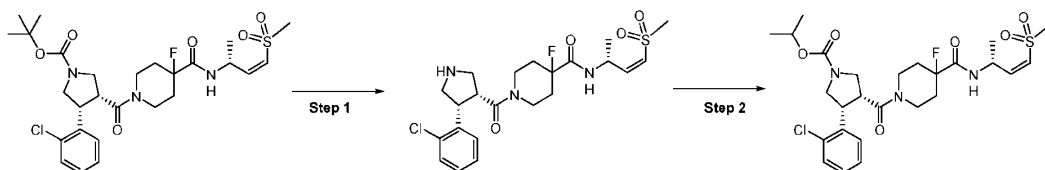
Scheme 47. Synthesis of Intermediates *tert*-butyl (3S*,4**S*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carboxylate and *tert*-butyl (3**R*,4**R*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carboxylate**



[00431] **Step 1.** *tert*-Butyl (3*RS*,4*RS*)-3-(2-chlorophenyl)-4-(4-fluoro-4-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carboxylate was separated by chiral SFC to

give *tert*-butyl (3*S*,4*S*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate and *tert*-butyl (3*R*,4*R*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate.

Scheme 48. Synthesis of isopropyl (3*R*,4*R*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate (Compound 159)



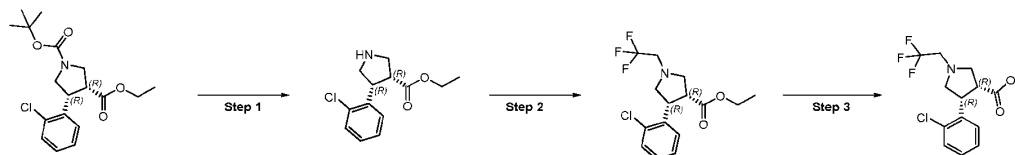
[00432] Step 1. To a solution of *tert*-butyl (3*R*,4*R*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate (600 mg, 1.02 mmol, 1 eq) in DCM (5 mL) was added TFA (3 mL). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give 1-((3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (480 mg, 0.988 mmol, 96% yield).

[00433] Step 2. To a solution of 1-((3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (120 mg, 0.25 mmol, 1 eq) in DCM (5 mL) was added isopropyl chloroformate (36 mg, 0.3 mmol, 1.2 eq) at 0°C. After 10 mins, DIPEA (96 mg, 0.74 mmol, 3 eq) was added. The reaction was stirred at 25°C for 1 hour. The mixture was concentrated and purified by prep-HPLC to give isopropyl (3*R*,4*R*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate (**Compound 159**) (88 mg, 0.15 mmol, 62% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.37 - 8.20 (m, 1H), 7.45 (br d, *J* = 7.2 Hz, 1H), 7.34 - 7.13 (m, 3H), 6.45 (d, *J* = 11.2 Hz, 1H), 6.31 - 6.21 (m, 1H), 5.33 (br s, 1H), 4.85 - 4.74 (m, 1H), 4.15 - 3.99 (m, 3H), 3.78 - 3.59 (m, 4H), 3.58 - 3.53 (m, 1H), 3.12 (d, *J* = 17.9 Hz, 3H), 2.69 - 2.54 (m, 1H), 2.40 - 2.31 (m, 1H), 2.01 - 1.72 (m, 1H), 1.69 - 1.44 (m, 2H), 1.28 - 1.23 (m, 1H), 1.20 (t, *J* = 7.3 Hz, 9H). [M+H]⁺ calculated for C₂₆H₃₅ClFN₃O₆S, 571; found 572.

[00434] Compounds 160-162 were synthesized in an analogous manner to **Compound 159** using the appropriate chloroformate or acid chloride in the final step.

[00435] Compound 199 was synthesized in an analogous manner to **Compound 159** using *tert*-butyl (3*S*,4*S*)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate in Step 1.

Scheme 49. Synthesis of Intermediate (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid



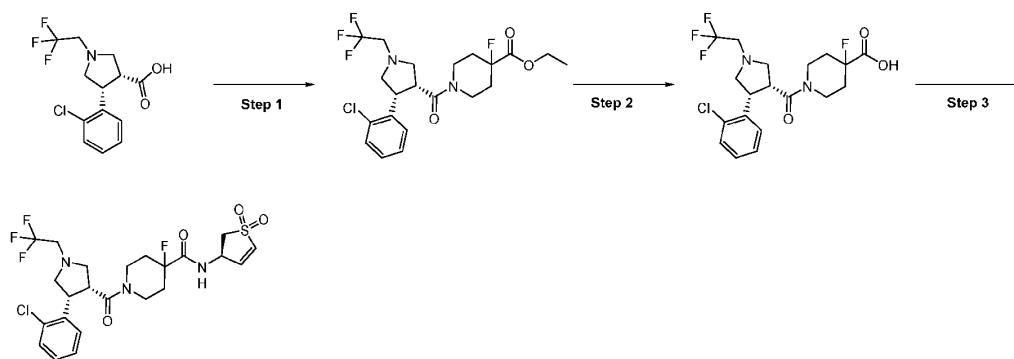
[00436] Step 1. To a solution of 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (7 g, 19.8 mmol, 1 eq) in DCM (70 mL, 0.28 M) was added TFA (20 mL) and the reaction was stirred at 25°C for 3 h. The solution was quenched with sat. aq. sodium bicarbonate (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic phases were washed with brine (5 mL × 3), dried over Na₂SO₄, and filtered. The filtrate was evaporated to get the crude product ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (5 g, 19.7 mmol, 100%) as a yellow oil, which was used in the next step directly.

[00437] Step 2. To a solution of ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (10 g, 39.4 mmol, 1 eq) in toluene (100 mL, 0.39 M) was added DIPEA (12 g, 118 mmol, 3 eq). The mixture was stirred at 20°C for 5 min, cooled to 0 °C, and 2,2,2-trifluoroethyl trifluoromethanesulfonate (18.3 g, 78.8 mmol, 2 eq) was added. The mixture was stirred at 0°C for 0.5 h, then stirred at 80°C for 16 h. After cooling to rt, the mixture was partitioned between EtOAc (30 mL) and water (30 mL). The organic layer was concentrated under vacuum. The residue was purified by column chromatography (PE:EtOAc = 1:0 - 5:1) to give ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (10 g, 29.8 mmol, 76%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.27 - 7.31 (m, 1H), 7.21 - 7.24 (m, 1H), 7.02 - 7.16 (m, 2H), 4.15 (td, *J* = 9.5, 6.5 Hz, 1H), 3.62 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.44 - 3.56 (m, 2H), 3.31 (br t, *J* = 8.9 Hz, 1H), 2.99 - 3.25 (m, 5H), 0.71 (t, *J* = 7.1 Hz, 3H).

[00438] Step 3. Ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (2.3 g, 7.0 mmol, 1 eq) and trimethyltin hydroxide (6.3 g, 35.0 mmol, 5 eq) was combined in DCE (30 mL, 0.23 M). The mixture was heated to 110°C for 24 h. After cooling to rt, the mixture was filtered and filtrate was concentrated *in vacuo* to afford crude product. Purification by prep-HPLC afforded (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (2.1 g, 6.82 mmol, 97% yield).

[00439] Compound 163 was synthesized in a manner analogous to Step 2 of **Compound 158** using (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid.

Scheme 50. Synthesis of 1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-*N*-((*R*)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide (Compound 164)



[00440] Step 1. To a solution of (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (300 mg, 0.975 mmol, 1 eq) and ethyl 4-fluoropiperidine-4-carboxylate (171 mg, 0.975 mmol, 1 eq) in DCM (5 mL, 0.2 M) was added DIPEA (504 mg, 3.9 mmol, 4 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (775 mg, 2.43 mmol, 2.5 eq). The reaction was stirred at 25°C for 2 h. The reaction mixture was poured into water (5 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The compound was purified by prep-TLC to give the product ethyl 1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoropiperidine-4-carboxylate (150 mg, 0.323 mmol, 33% yield).

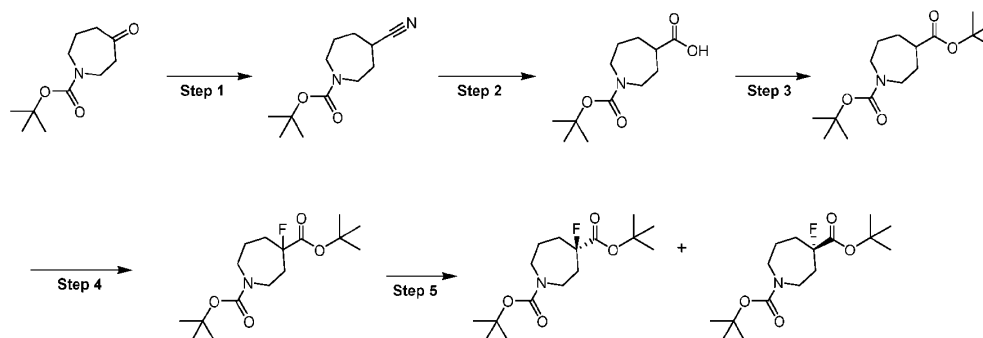
[00441] Step 2. To a solution of ethyl 1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoropiperidine-4-carboxylate (150 mg, 0.323 mmol, 1 eq) in DCE (4 mL, 0.08 M) was added hydroxy(trimethyl)stannane (233 mg, 1.29 mmol, 4 eq). The reaction was stirred at 110°C for 48 h. After cooling to rt, the reaction mixture was poured into water (1 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoropiperidine-4-carboxylic acid (330 mg, 0.302 mmol, 94% yield).

[00442] Step 3. To a solution of 1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoropiperidine-4-carboxylic acid (90 mg, 0.206 mmol, 1 eq) in DCM (3 mL, 0.07 M) was added (*R*)-3-amino-2,3-dihydrothiophene 1,1-dioxide (33 mg, 0.25 mmol, 1.2 eq), DIPEA (80 mg, 0.618 mmol, 3 eq), and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (131 mg, 0.412 mmol, 2 eq). The reaction was stirred at 25°C for 2 h. The solution was diluted with water (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na₂SO₄, and filtered. The solution was evaporated to get the crude product which was purified by prep-HPLC to give 1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-*N*-((*R*)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide (**Compound 164**) (40 mg, 0.072 mmol, 35% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.68 - 8.88 (m, 1H), 7.38 - 7.44 (m, 1H), 7.29 - 7.34 (m, 1H), 7.22 - 7.28 (m, 2H), 7.18 (dt, *J* = 6.7, 2.3 Hz, 1H), 6.76 (td, *J* = 6.4, 2.5 Hz, 1H), 5.05 - 5.22 (m, 1H), 3.96 - 4.24 (m, 2H), 3.53 - 3.93 (m, 3H), 3.41 (q, *J* = 10.0 Hz, 2H), 3.06

- 3.25 (m, 4H), 2.80 - 2.98 (m, 1H), 2.56 - 2.66 (m, 1H), 2.12 - 2.25 (m, 1H), 1.67 - 2.07 (m, 1H), 1.49 - 1.64 (m, 2H), 0.98 - 1.17 (m, 1H). [M+H] calculated for C₂₃H₂₆ClF₄N₃O₄S, 551.1; found 552.1.

[00443] **Compound 314** was synthesized in a manner analogous to **Compound 164** using methyl 3-fluoro-3-pyrrolidinecarboxylate hydrochloride in Step 1 and (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine TsOH in Step 3.

Scheme 51. Synthesis of Intermediate di-*tert*-butyl (*R*)-4-fluoroazepane-1,4-dicarboxylate



[00444] **Step 1.** To a solution of *tert*-butyl 4-oxoazepane-1-carboxylate (5.0 g, 23.4 mmol, 1.0 eq, available from a commercial source) in DME (60 mL, 0.39 M) was added 1-(isocyanomethane)sulfonyl-4-methylbenzene (5.7 g, 29.3 mmol, 1.25 eq) and ethanol (1.8 g, 39.9 mmol, 1.7 eq) at 15°C. The mixture was cooled to 0°C and 1M aq. potassium *tert*-butoxide (23.4 mL, 23.4 mmol, 1 eq) was added dropwise. The reaction was stirred at 40°C for 16 h. After cooling to rt, the reaction mixture was filtered through celite, washed with MTBE (30 mL), and concentrated under reduced pressure. The resulting residue was purified by FCC to afford *tert*-butyl 4-cyanoazepane-1-carboxylate (3.4 g, 15.2 mmol, 65% yield).

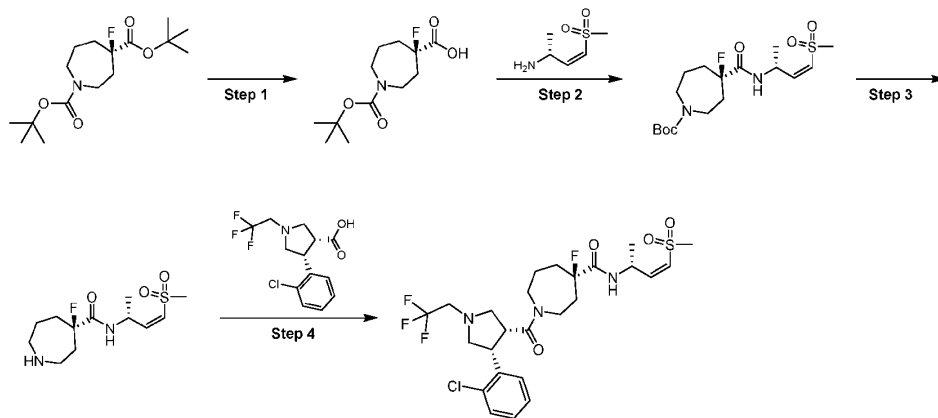
[00445] **Step 2.** A solution of *tert*-butyl 4-cyanoazepane-1-carboxylate (7.5 g, 33.4 mmol, 1.0 eq) in 10% aq. NaOH (112.5 mL) was stirred at 100°C for 16 h. After cooling to rt, the reaction mixture was concentrated in *vacuo* and the residue was dissolved in water (5 mL). The solution was adjusted to pH 2 and extracted with EtOAc (30 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 1-*tert*-butoxycarbonylazepane-4-carboxylic acid (6.5 g, 26.7 mmol, 80% yield).

[00446] **Step 3.** To a solution of 1-*tert*-butoxycarbonylazepane-4-carboxylic acid (2.0 g, 8.22 mmol, 1.0 eq) in *tert*-butanol (25 mL) was added di-*tert*-butyl dicarbonate (5.4 g, 24.7 mmol, 3.0 eq) and 4-(dimethylamino)pyridine (1.2 g, 9.86 mmol, 1.2 eq) slowly. The reaction was stirred at 15°C for 8 h before being poured into water (30 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC to give di-*tert*-butyl azepane-1,4-dicarboxylate (1.2 g, 4.01 mmol, 76% yield).

[00447] **Step 4.** To a solution of di-*tert*-butyl azepane-1,4-dicarboxylate (23 g, 76.8 mmol, 1.0 eq) in THF (260 mL, 0.19 M) was added LDA (76.8 mL, 154 mmol, 2.0 eq) dropwise at -60°C and the mixture was stirred at -45°C for 1.5 h. To the mixture was added *N*-fluorobenzenesulfonimide (421 mg, 1.34 mmol, 2.0 eq) in THF (100 mL, 0.21 M) dropwise and the resulting solution was stirred at -45°C for 1 h then allowed to warm to rt for 1 h. The reaction was quenched with sat. aq. ammonium chloride (200 mL) and extracted with EtOAc (150 mL × 2). The combined organic phases were washed with brine (50 mL × 2), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 95:5) to give di-*tert*-butyl 4-fluoroazepane-1,4-dicarboxylate (16 g, 50.4 mmol, 66% yield) as a colorless oil.

[00448] **Step 5.** Di-*tert*-butyl 4-fluoroazepane-1,4-dicarboxylate (30 g, 94.5 mmol, 1.0 eq) was separated by chiral SFC (Stationary phase: WHELK-O1 (25x5cm); Mobile phase: 11% *i*PrOH/CO₂) to give di-*tert*-butyl (*R*)-4-fluoroazepane-1,4-dicarboxylate (Rt = 5.9 min, 14 g, 44.1 mmol, 47% yield) as a colorless oil ¹H NMR (400 MHz, CDCl₃) δ ppm 3.81 (br d, *J* = 14.2 Hz, 0.5H), 3.64 (br d, *J* = 14.1 Hz, 1H), 3.54 (br d, *J* = 1.1 Hz, 0.5H), 3.30 (br s, 1H), 3.12 - 3.22 (m, 1H), 1.84 - 2.17 (m, 5H), 1.77 (br s, 1H), 1.48 (d, *J* = 4.2 Hz, 18H) and di-*tert*-butyl (*S*)-4-fluoroazepane-1,4-dicarboxylate (Rt = 6.9 min, 14 g, 44.1 mmol, 47% yield) as a colorless oil.

Scheme 52. Synthesis of (*R*)-1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (Compound 165)



[00449] **Step 1.** To a solution of di-*tert*-butyl (*R*)-4-fluoroazepane-1,4-dicarboxylate (5.0 g, 15.7 mmol, 1.0 eq) in methanol (15 mL, 0.88 M) and water (3 mL, 0.88 M) was added potassium hydroxide (1.3 g, 23.6 mmol, 1.5 eq) at 15°C. The reaction was placed under N₂ and stirred at 65°C for 10 h. After cooling to rt, the mixture was concentrated under reduced pressure. The resulting residue was dissolved in water (5 mL) and acidified with 1N HCl to pH = 2. The mixture was extracted with EtOAc (25 mL × 2). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated in *vacuo* to give

(*R*)-1-*tert*-butoxycarbonyl-4-fluoro-azepane-4-carboxylic acid (4.0 g, 15.3 mmol, 97% yield). MS (ESI): mass calculated for C₁₂H₂₀FNO₄, 261.1; *m/z* found, 206.1 [M+2H-tBu]⁺.

[00450] **Step 2.** To a solution of (*R*)-1-*tert*-butoxycarbonyl-4-fluoro-azepane-4-carboxylic acid (4.0 g, 15.3 mmol, 1.0 eq) in DCM (40 mL, 0.38 M) was added HATU (8.7 g, 23.0 mmol, 1.5 eq), DIPEA (5.0 g, 38.3 mmol, 2.5 eq) and (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine (TsOH salt, 3.0 g, 19.9 mmol, 1.3 eq) at 15°C. The reaction was stirred at 15°C for 4 h before being poured into water (15 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (15 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:1 - 1:2) to give *tert*-butyl (*R*)-4-fluoro-4-(((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)azepane-1-carboxylate (5.0 g, 12.7 mmol, 83% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.46 (br s, 1H), 6.30 (d, *J* = 11.1 Hz, 1H), 6.09 (t, *J* = 10.3 Hz, 1H), 5.29 - 5.44 (m, 1H), 3.56 - 3.81 (m, 2H), 3.26 - 3.47 (m, 3H), 3.20 (s, 3H), 2.14 - 2.33 (m, 2H), 1.99 (br d, *J* = 7.9 Hz, 3H), 1.46 (s, 9H), 1.41 (d, *J* = 6.8 Hz, 3H).

[00451] **Step 3.** To a solution of *tert*-butyl (*R*)-4-fluoro-4-(((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)azepane-1-carboxylate (1.2 g, 3.06 mmol, 1.0 eq) in ACN (12 mL, 0.25 M) was added *p*-toluene sulfonic acid monohydrate (697 mg, 3.67 mmol, 1.2 eq). The mixture was stirred at 60°C for 4 h. After cooling to rt, the reaction mixture was concentrated to dryness under reduced pressure. The resulting residue was washed with EtOAc (10 mL) to give the 4-methylbenzenesulfonate salt of (*R*)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (1.0 g, 2.26 mmol, 74% yield).

[00452] **Step 4.** To a solution of (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (800 mg, 2.60 mmol, 1 eq) in DCM (3 mL, 0.87 M) was added HATU (1.5 g, 3.9 mmol, 1.5 eq), DIPEA (840 mg, 6.5 mmol, 2.5 eq) and (*R*)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (988 mg, 3.39 mmol, 1.3 eq). The mixture was stirred at 15°C for 4 hours. The reaction mixture was poured into water (5 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give (*R*)-1-((3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (**Compound 165**) (648 mg, 1.11 mmol, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.25 (br dd, *J* = 7.6, 2.5 Hz, 1H), 7.30 - 7.44 (m, 2H), 7.18 - 7.29 (m, 2H), 6.40 - 6.52 (m, 1H), 6.21 - 6.33 (m, 1H), 5.24 - 5.37 (m, 1H), 4.00 - 4.16 (m, 1H), 3.70 - 3.90 (m, 1H), 3.48 - 3.61 (m, 1H), 3.34 - 3.48 (m, 3H), 3.18 - 3.28 (m, 3H), 3.08 - 3.15 (m, 3H), 2.82 - 3.05 (m, 2H), 2.68 (br dd, *J* = 12.9, 11.7 Hz, 1H), 1.45 - 2.02 (m, 6H), 1.16 - 1.24 (m, 3H). [M+H]⁺ calculated for C₂₅H₃₂ClF₄N₃O₄S, 581; found 582.

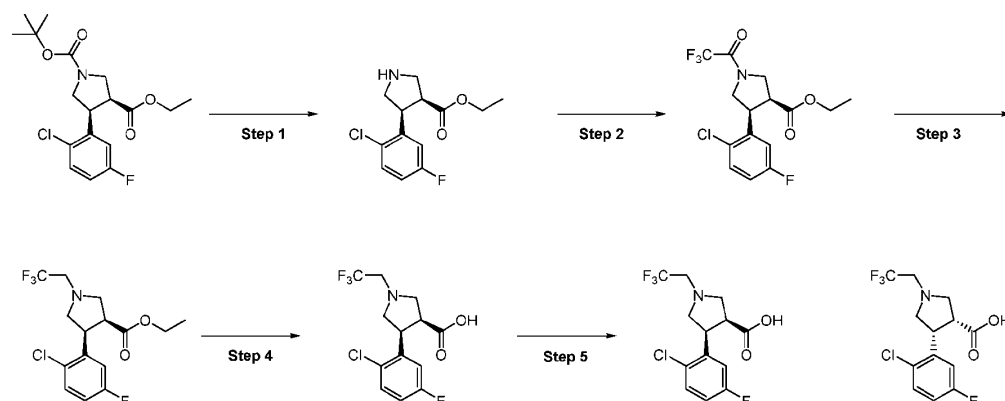
[00453] **Compound 198** was synthesized in a manner similar to **Compound 165** using (*R,Z*)-1-(methylsulfonyl)pent-1-en-3-amine in Step 2.

[00454] **Intermediate (*R*)-*N*-((*R,E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide** was synthesized in a manner analogous to (*R*)-4-fluoro-*N*-((*R,Z*)-4-

(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide using (*E*,4*R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one in Step 3.

[00455] **Compound 302** was synthesized in a manner analogous to **Compound 165**, Step 4, using (2*S*,4*S*)-4-fluoro-2-methyl-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide.

Scheme 53. Synthesis of Intermediate (3*R*,4*R*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid



[00456] **Step 1.** To a solution of *rac*-1-(*tert*-butyl) 3-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluorophenyl)pyrrolidine-1,3-dicarboxylate (2.0 g, 5.38 mmol, 1 eq) in DCM (20 mL) was added TFA (4 mL) under nitrogen. The reaction was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give crude *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluorophenyl)pyrrolidin-1-ium-3-carboxylate 2,2,2-trifluoroacetate (2.0 g, 5.18 mmol, 96% yield).

[00457] **Step 2.** To a solution of *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluorophenyl)pyrrolidin-1-ium-3-carboxylate 2,2,2-trifluoroacetate (2.0 g, 5.18 mmol, 1 eq) in DCM (20 mL) was added triethylamine (2.17 mL, 15.6 mmol, 3 eq) and trifluoroacetic anhydride (0.95 mL, 6.74 mmol, 1.3 eq) at 0°C under nitrogen. The reaction was stirred at 25°C for 2 h. The reaction mixture was poured into water (20 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by FCC to give *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate (1.8 g, 4.90 mmol, 94% yield).

[00458] **Step 3.** To a solution of *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxylate (1.8 g, 4.90 mmol, 1 eq) in THF (12 mL) was added 1 M borane tetrahydrofuran complex solution (7.34 mL, 7.34 mmol, 1.5 eq) at 0°C under nitrogen. The reaction was stirred at 65 °C for 3.5 h. The reaction mixture was quenched with MeOH (7 mL) at 0 °C and concentrated under reduced pressure. The residue was purified by FCC to give *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluoro-phenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (1.25 g, 3.53 mmol, 72% yield).

[00459] **Step 4.** To a solution of *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-5-fluoro-phenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (1.25 g, 3.53 mmol, 1 eq) in DCE (15 mL) was added trimethyltin hydroxide (3.19 g, 17.7 mmol, 5 eq). The reaction was stirred at 110°C for 16 h. After cooling to rt, the reaction was filtered, and the filtrate was concentrated. The residue was purified by prep-HPLC to give *rac*-(3*S*,4*S*)-4-(2-chloro-5-fluoro-phenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (850 mg, 2.61 mmol, 74% yield).

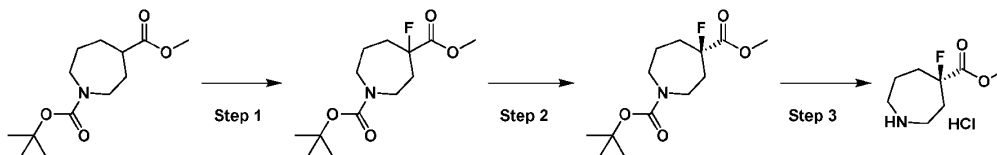
[00460] **Step 5.** *Rac*-(3*S*,4*S*)-4-(2-chloro-5-fluoro-phenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid was separated by chiral SFC to give (3**S*,4**S*)-4-(2-chloro-5-fluoro-phenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (170 mg) and (3**R*,4**R*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (170 mg).

[00461] **Intermediate (3**R*,4**R*)-4-(2-chloro-4-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner similar to (3**R*,4**R*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid.

[00462] **Intermediate (3*R*,4*R*)-1-(2-chloro-2,2-difluoroethyl)-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner similar to (3**R*,4**R*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid using 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate in Step 1 and 2-chloro-2,2-difluoroacetic anhydride in Step 2.

[00463] **Compound 195** was synthesized in a manner analogous to **Compound 165** using (3*R*,4*R*)-1-(2-chloro-2,2-difluoroethyl)-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid in Step 4.

Scheme 54. Synthesis of Intermediate methyl (R)-4-fluoroazepane-4-carboxylate



[00464] **Step 1.** To a solution of 1-(*tert*-butyl) 4-methyl azepane-1,4-dicarboxylate (9.0 g, 35.0 mmol, 1.0 eq) in THF (90 mL) was added LDA (26 mL, 52.5 mmol, 1.5 eq) dropwise at -45°C. The mixture was stirred at -45°C for 0.5 h before *N*-fluorobenzenesulfonimide (13.8 g, 43.7 mmol, 1.3 eq) in THF (90 mL) was added dropwise. The reaction was stirred at -45°C for 1 h then allowed to warm to rt over 1 h. The reaction was quenched with sat. aq. NH₄Cl (180 mL) and extracted with EtOAc (150 mL × 2). The combined organic phases were washed with brine (300 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 100:0 to 87:13) to give 1-(*tert*-butyl) 4-methyl 4-fluoroazepane-1,4-dicarboxylate (5.0 g, 18.1 mmol, 52%) as a light yellow oil. MS (ESI): mass calculated for C₁₃H₂₂FNO₄, 275.2; *m/z* found, 220.2 [M+2H-tBu]⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.79 (d, *J* = 3.0 Hz, 3H), 3.73 - 3.47 (m, 2H), 3.40 - 3.14 (m, 2H), 2.27 - 1.86 (m, 5H), 1.77 (br d, *J* = 10.9 Hz, 1H), 1.47 (s, 9H).

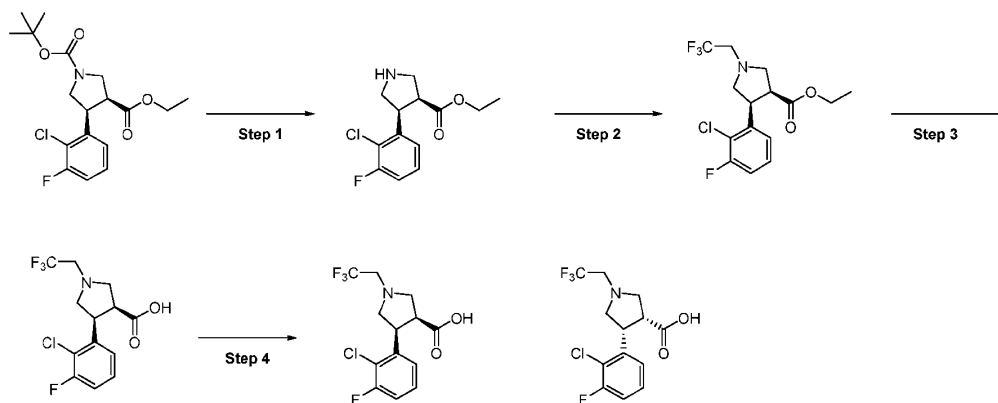
[00465] **Step 2.** 1-(*tert*-Butyl) 4-methyl 4-fluoroazepane-1,4-dicarboxylate (3.9 g, 14.2 mmol, 1.0 eq) was separated by chiral SFC to give 1-(*tert*-butyl) 4-methyl-(4*R*)-4-fluoroazepane-1,4-dicarboxylate (1.6

g, 5.81 mmol, 41% yield) as a colorless oil. MS (ESI): mass calculated for $C_{13}H_{22}FNO_4$, 275.2; m/z found, 220.1 $[M+2H-tBu]^+$.

[00466] Step 3. A solution of 1-(*tert*-butyl) 4-methyl-(4*R*)-4-fluoroazepane-1,4-dicarboxylate (500 mg, 1.82 mmol, 1.0 eq) in HCl (10 mL, 4M in EtOAc) was stirred at 25°C for 0.5 h. The reaction was concentrated under reduced pressure to give methyl (*R*)-4-fluoroazepane-4-carboxylate, hydrochloride (380 mg, 1.80 mmol, quant. yield) as a white solid, which was used in the next step directly.

[00467] Intermediate methyl (*S*)-4-fluoroazepane-4-carboxylate was synthesized in a manner analogous to methyl (*R*)-4-fluoroazepane-4-carboxylate using the isolated opposite enantiomer from Step 2 in Step 3.

Scheme 55. Synthesis of Intermediate (3R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid**



[00468] Step 1. Synthesized in a manner analogous to Step 1 of (3**R*,4**R*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid.

[00469] Step 2. To a solution of *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-3-fluorophenyl)pyrrolidine-3-carboxylate (1 g, 3.68 mmol, 1 eq) in toluene (30 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.7 g, 7.36 mmol, 2 eq) and triethylamine (1.54 mL, 11.0 mmol, 3 eq). The mixture was stirred at 80 °C for 16 hrs. After cooling to rt, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (1.1 g, 3.11 mmol, 84% yield).

[00470] Step 3. A solution of *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (1.1 g, 3.11 mmol, 1 eq) in HBr/ H_2O (10 mL) was stirred at 110°C for 16 hrs. After cooling to rt, the reaction mixture was filtered and concentrated under reduced pressure to give *rac*-(3*S*,4*S*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (900 mg, 2.76 mmol, 89% yield).

[00471] **Step 4.** *Rac*-(3*S*,4*S*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid was separated by chiral SFC to give (3**S*,4**S*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid and (3**R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid.

[00472] **Intermediates** (3**R*,4**R*)-4-(2-chloro-3-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid, (3**R*,4**R*)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid, (3**R*,4**R*)-4-(2-chloro-5-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid, (3**R*,4**R*)-4-(2-fluoro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid, (3**R*,4**R*)-4-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid, and (3**R*,4**R*)-4-(2-fluoro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid were synthesized in a manner similar to (3**R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid using either HBr or trimethyltin hydroxide for the hydrolysis of the ester in Step 3.

[00473] **Compounds 166-168, 170, and 172-173** were synthesized from the appropriate carboxylic acid in a manner similar to **Compound 165**.

[00474] **Compounds 174-176** were synthesized in a manner analogous to **Compound 164** using appropriate intermediates.

[00475] **Compound 177** was synthesized in a manner analogous to **Compound 165** using (*R,E*)-4-methylsulfonylbut-3-en-2-amine in Step 2.

[00476] **Intermediate (3*R*,4*R*)-4-(2-chlorophenyl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner analogous to (3**R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid using 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate in Step 1 and 3,3,3-trifluoropropyl 1,1,1-trifluoromethanesulfonate in Step 2.

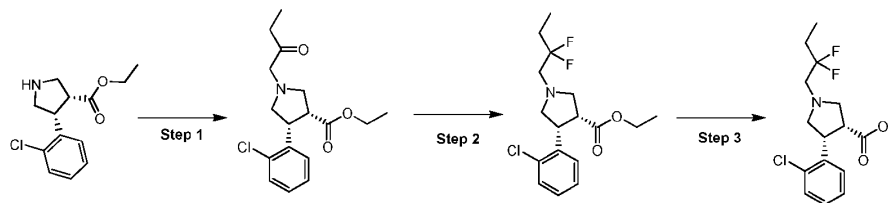
[00477] **Compound 196** was synthesized in a manner analogous to **Compound 165** using (3*R*,4*R*)-4-(2-chlorophenyl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carboxylic acid in Step 4.

[00478] **Intermediate (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner analogous to (3**R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid using 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate in Step 1, 2,2-difluoroethyl 1,1,1-trifluoromethanesulfonate in Step 2, and trimethyltin hydroxide for the hydrolysis of the ester in Step 3.

[00479] **Compound 197** was synthesized in a manner analogous to **Compound 165** using (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carboxylic acid in Step 4.

[00480] **Compound 206** was synthesized in a manner similar to **Compound 165** starting from 4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide, 4-methylbenzenesulfonic acid salt and (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carboxylic acid in Step 4.

Scheme 56. Synthesis of Intermediate (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carboxylic acid



[00481] **Step 1.** To a solution of ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (350 mg, 1.38 mmol, 1 eq) in DCM (5 mL, 0.28 M) was added TEA (419 mg, 4.14 mmol, 3 eq) and 1-bromo-2-butanone (250 mg, 1.66 mmol, 1.2 eq) at 0°C. The reaction was stirred at 25°C for 30 min. The solution was diluted with water (15 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na₂SO₄, filtered, and concentrated in *vacuo* to give a residue, which was purified by prep-TLC to give ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2-oxobutyl)pyrrolidine-3-carboxylate (300 mg, 0.93 mmol, 67%) as a yellow oil.

[00482] **Step 2.** To a solution of ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2-oxobutyl)pyrrolidine-3-carboxylate (200 mg, 0.62 mmol, 1 eq) in DCM (3 mL, 0.2 M) was added DAST (1.5 g, 9.26 mmol, 15 eq) at 0 °C and this was stirred at 25°C for 16 h. The solution was diluted with water (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na₂SO₄, filtered, and concentrated in *vacuo* to give a residue, which was purified by prep-TLC to give ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carboxylate (100 mg, 0.29 mmol, 47% yield) as a yellow oil.

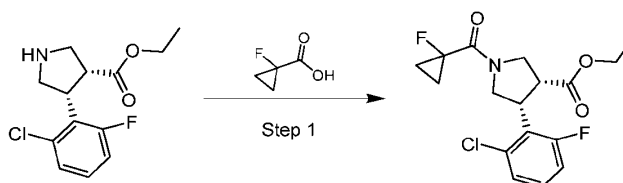
[00483] **Step 3.** To a solution of ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carboxylate (100 mg, 0.29 mmol, 1.0 eq) in DCE (5 mL, 0.06 M) was added Me₃SnOH (261 mg, 1.44 mmol, 5 eq) at 15°C. The reaction was stirred at 110 °C for 48 h. After cooling to rt, the solution was filtered and concentrated in *vacuo* to give a residue, which was diluted with water (10 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na₂SO₄, filtered, and concentrated in *vacuo* to give (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carboxylic acid (120 mg, 0.26 mmol, 91%) as a yellow oil. ¹HNMR (400 MHz, CDCl₃) δ ppm 7.44 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.33 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.21 - 7.10 (m, 2H), 4.16 (td, *J* = 7.3, 9.9 Hz, 1H), 3.67- 3.56 (m, 1H), 3.24 - 3.08 (m, 3H), 3.06 - 2.88 (m, 3H), 2.08 - 1.90 (m, 2H), 1.10 - 1.00 (m, 3H). [M+H] calculated for C₁₅H₁₈ClF₂NO₂, 317, found 318.

[00484] **Compound 178** was synthesized from (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carboxylic acid in a manner analogous to **Compound 158**, Step 2.

[00485] **Intermediates (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid, (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoro-2-phenyl-ethyl)pyrrolidine-3-carboxylic acid, and (3*R*,4*R*)-4-(2-chloro-6-fluoro-phenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid** were synthesized in a manner analogous to (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carboxylic acid.

- [00486] **Compound 179** was synthesized from (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid in a manner analogous to **Compound 158**, Step 2.
- [00487] **Compound 180** was synthesized in a manner analogous to **Compound 165** using (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid.
- [00488] **Compound 181** was synthesized from (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoro-2-phenylethyl)pyrrolidine-3-carboxylic acid in a manner analogous to **Compound 158**, Step 2.
- [00489] **Intermediate (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,3,3,3-pentafluoropropyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner similar to (3**R*,4**R*)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid starting with ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carboxylate and pentafluoropropionic anhydride.
- [00490] **Compound 182** was synthesized from (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,3,3,3-pentafluoropropyl)pyrrolidine-3-carboxylic acid in a manner analogous to **Compound 158**, Step 2.
- [00491] **Compound 183** was synthesized from (3**R*,4**R*)-4-(2-chloro-6-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid in a manner analogous to **Compound 165**.
- [00492] **Compound 221** was synthesized in a manner analogous to **Compound 164** using methyl (2**R*,4**S*)-4-fluoro-2-methylpiperidine-4-carboxylate and (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid in Step 1.
- [00493] **Intermediate (3**R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner analogous to (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carboxylic acid starting from *rac*-ethyl (3*S*,4*S*)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate and chloroacetone in Step 1.
- [00494] **Compound 222** was synthesized in a manner analogous to **Compound 165** using (3**R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid in Step 4.
- [00495] **Compound 225** was synthesized in a manner analogous to **Compound 164** using (3**R*,4**R*)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carboxylic acid and methyl (2**R*,4**S*)-4-fluoro-2-methylpiperidine-4-carboxylate in Step 1.

Scheme 57. Synthesis of Intermediate ethyl (3R*,4**R*)-4-(2-chloro-6-fluorophenyl)-1-(1-fluorocyclopropanecarbonyl) pyrrolidine-3-carboxylate**



- [00496] **Step 1.** To a solution of 1-fluorocyclopropane-1-carboxylic acid (129 mg, 1.24 mmol, 1.0 eq) in DCM (4 mL, 0.3 M) was added DIPEA (268 mg, 2.07 mmol, 2 eq) and HATU (591 mg, 1.56 mmol, 1.5 eq). The reaction solution was stirred at 20°C for 10 min. Then to the solution was added ethyl (3**R*,4**R*)-4-(2-chloro-6-fluoro-phenyl)pyrrolidine-3-carboxylate; 2,2,2-trifluoroacetic acid (400 mg,

1.04 mmol, 1.2 eq). The reaction solution was stirred at 20°C for 2 h. The reaction was quenched with water (10 mL) and extracted with DCM (5 mL $\times$ 3). The combined organic phases were washed with brine (10 mL $\times$ 2), dried over Na₂SO₄, and filtered. The filtrate was concentrated. The crude product was purified by column chromatography to give ethyl (3*,4*R)-4-(2-chloro-6-fluorophenyl)-1-(1-fluorocyclopropanecarbonyl)pyrrolidine-3-carboxylate (300 mg, 0.84 mmol, 81%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.15 - 7.26 (m, 2H), 6.86 - 7.06 (m, 1H), 4.25 - 4.42 (m, 3H), 4.05 - 4.18 (m, 2H), 3.88 - 4.00 (m, 2H), 3.44 - 3.68 (m, 1H), 1.39 - 1.47 (m, 2H), 1.21 - 1.27 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H).

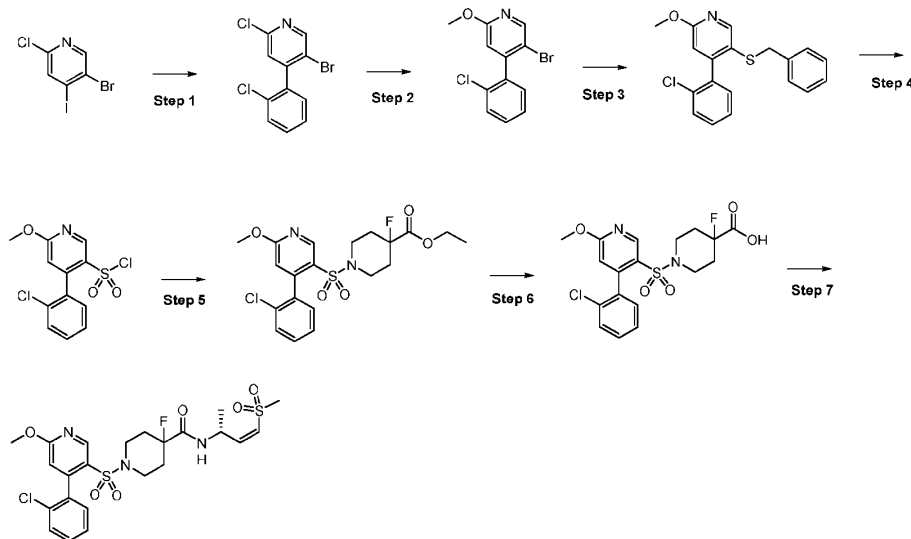
[00497] **Intermediate (3*,4*R)-4-(2-chloro-6-fluorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carboxylic acid** was synthesized from ethyl (3*,4*R)-4-(2-chloro-6-fluorophenyl)-1-(1-fluorocyclopropanecarbonyl)pyrrolidine-3-carboxylate in a manner similar to Steps 3-5 of the synthesis of (3*,4*R)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid.

[00498] **Compound 184** was synthesized from (3*,4*R)-4-(2-chloro-6-fluorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carboxylic acid in a manner similar to **Compound 165**.

[00499] **Intermediate (3R,4R)-4-(2-chlorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner similar to (3*,4*R)-4-(2-chloro-6-fluorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carboxylic acid.

[00500] **Compound 185** was synthesized from (3R,4R)-4-(2-chlorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carboxylic acid in a manner similar to **Compound 165**.

Scheme 58. Synthesis of (R,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 186)



[00501] **Step 1.** To a solution of 5-bromo-2-chloro-4-iodopyridine (5 g, 15.7 mmol, 1 eq), (2-chlorophenyl)boronic acid (2.7 g, 17.3 mmol, 1.1 eq), PPh₃ (412 mg, 1.57 mmol, 0.1 eq) and Pd(OAc)₂ (176 mg, 0.79 mmol, 0.05 eq) in DME (100 mL, 0.16 M) was added 2 M Na₂CO₃ aq. (25 mL) and the mixture was stirred at 90°C for 16 h. After cooling to rt, the mixture was diluted with water (300 mL) and extracted with EtOAc (200 mL × 2). The combined organic phases were washed with brine (400 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to give 5-bromo-2-chloro-4-(2-chlorophenyl)pyridine as a white solid (4 g, 13.2 mmol, 84% yield).

[00502] **Step 2.** To a solution of NaOMe (1.1 g, 19.8 mmol, 3.0 eq) in methanol (25 mL, 0.26 M) was added 5-bromo-2-chloro-4-(2-chlorophenyl)pyridine (2 g, 6.6 mmol, 1 eq) at 20°C and the mixture was stirred at 120°C for 24 h. After cooling to rt, the mixture was concentrated. The residue was dissolved with water (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (100 mL × 2), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography (PE:EtOAc = 98:2) to give 5-bromo-4-(2-chlorophenyl)-2-methoxy-pyridine as a white solid (1.9 g, 6.36 mmol, 96%).

[00503] **Step 3.** To a solution of 5-bromo-4-(2-chlorophenyl)-2-methoxy-pyridine (0.1 g, 0.33 mmol, 1 eq), DIPEA (130 mg, 1.01 mmol, 3 eq), Pd₂(dba)₃ (61 mg, 0.07 mmol, 0.2 eq) and XantPhos (77 mg, 0.13 mmol, 0.4 eq) in toluene (1 mL, 0.33 M) was added benzyl mercaptan (0.05 g, 0.37 mmol, 1.1 eq). The mixture was stirred at 140°C under microwave irradiation for 1 h. After cooling to rt, the reaction was filtered. The filtrate was diluted with water (100 mL) and extracted with MTBE (100 mL × 2). The combined organic phases were washed with brine (200 mL × 2), dried over Na₂SO₄, filtered, concentrated and purified by FCC to give 5-benzylsulfanyl-4-(2-chlorophenyl)-2-methoxy-pyridine as a yellow oil (62 mg, 0.11 mmol, 54%).

[00504] **Step 4.** To a solution of 5-benzylsulfanyl-4-(2-chlorophenyl)-2-methoxy-pyridine (0.62 g, 1.81 mmol, 1 eq) in acetic acid (9 mL, 0.15 M) and water (3 mL, 0.15 M) was added NCS (969 mg, 7.25 mmol, 4 eq) at 0°C and the mixture was stirred at 20°C for 2 h. The mixture was diluted with water (60 mL) and extracted with ethyl acetate (30 mL × 2). The extract was washed with brine (60 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to afford 4-(2-chlorophenyl)-6-methoxy-pyridine-3-sulfonyl chloride (540 mg, 1.7 mmol, 94%) as a colorless oil, which was used in the next step directly.

[00505] **Step 5.** To a solution of ethyl 4-fluoropiperidine-4-carboxylate hydrochloride (467 mg, 2.21 mmol, 1.3 eq) in DCM (10 mL, 0.17 M) was added Et₃N (515 mg, 5.09 mmol, 3 eq) and 4-(2-chlorophenyl)-6-methoxy-pyridine-3-sulfonyl chloride (540 mg, 1.7 mmol, 1 eq) in DCM (10 mL) at 0°C. The mixture was stirred at 20°C for 1 h. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (40 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford ethyl 1-[[4-(2-chlorophenyl)-6-methoxy-3-pyridyl]sulfonyl]-4-fluoropiperidine-4-carboxylate as a light yellow oil (700 mg, 1.53 mmol, 90%).

[00506] **Step 6.** To a solution of ethyl 1-[[4-(2-chlorophenyl)-6-methoxy-3-pyridyl]sulfonyl]-4-fluoro-piperidine-4-carboxylate (0.7 g, 1.53 mmol, 1 eq) in THF/water (v/v 3:1, 8 mL, 0.19 M) was added LiOH/H₂O (88 mg, 2.1 mmol, 1.2 eq) and the mixture was stirred at 20°C for 3 h. The mixture was concentrated *in vacuo* to give lithium 1-[[4-(2-chlorophenyl)-6-methoxy-3-pyridyl]sulfonyl]-4-fluoro-piperidine-4-carboxylate (660 mg, 1.52 mmol, 99%) as a light yellow solid, which was used in the next step directly.

[00507] **Step 7.** To a solution of lithium-1-[[4-(2-chlorophenyl)-6-methoxy-3-pyridyl]sulfonyl]-4-fluoro-piperidine-4-carboxylate (660 mg, 1.52 mmol, 1 eq) and (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine, TsOH salt (585 mg, 1.82 mmol, 1.2 eq) in DCM (8 mL, 0.19 M) was added DIPEA (588 mg, 4.55 mmol, 3 eq) and T₃P (2.4 g, 3.79 mmol, 2.5 eq) and the mixture was stirred at 25°C for 0.5 h. The mixture was quenched with water (20 mL) and extracted with DCM (10 mL × 2). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography (PE:EtOAc = 1:2) to give 1-[[4-(2-chlorophenyl)-6-methoxy-3-pyridyl]sulfonyl]-4-fluoro-*N*-[(*Z,1R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (**Compound 186**) (700 mg, 1.25 mmol, 82%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.78 (s, 1H), 8.38 (br d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.51 - 7.32 (m, 3H), 6.86 (s, 1H), 6.45 (d, *J* = 11.3 Hz, 1H), 6.36 - 6.20 (m, 1H), 5.46 - 5.26 (m, 1H), 3.99 (s, 3H), 3.26 - 2.97 (m, 5H), 2.79 - 2.66 (m, 1H), 2.59 (br t, *J* = 12.3 Hz, 1H), 2.02 - 1.63 (m, 4H), 1.21 (d, *J* = 6.9 Hz, 3H). [M+H]⁺ calculated for C₂₄H₂₈ClFN₂O₆S₂, 559; found 560.

[00508] **Compounds 187-194** were synthesized in a manner analogous to **Compound 186** using the appropriate boronic acid starting material and coupling with the appropriate amine in the final step.

[00509] **Intermediate 4-(2-chlorophenyl)-6-(trifluoromethyl)pyridine-3-sulfonyl chloride** was synthesized in a manner analogous to 4-(2-chlorophenyl)-6-methoxy-pyridine-3-sulfonyl chloride using 5-bromo-4-iodo-2-(trifluoromethyl)pyridine in Step 1 and excluding Step 2.

[00510] **Compound 207** was synthesized in a manner analogous to **Compound 186** using 5-bromo-4-iodo-2-(trifluoromethyl)pyridine in Step 1 and excluding Step 2.

[00511] **Compound 208** was synthesized in a manner analogous to **Compound 207** using (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine, 4-methylbenzenesulfonic acid salt in Step 7.

[00512] **Compound 209** was synthesized in a manner analogous to **Compound 207** using 2-chloro-3-fluorophenylboronic acid in Step 1.

[00513] **Compound 210** was synthesized in a manner analogous to **Compound 209** using (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine, 4-methylbenzenesulfonic acid salt in Step 7.

[00514] **Compound 211** was synthesized in a manner analogous to **Compound 207** using 2-chloro-4-fluorophenylboronic acid in Step 1.

[00515] **Compound 212** was synthesized in a manner analogous to **Compound 211** using (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine, 4-methylbenzenesulfonic acid salt in Step 7.

[00516] **Compound 213** was synthesized in a manner analogous to **Compound 207** using (*E,4R*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one in Step 7.

[00517] **Compound 214** was synthesized in a manner analogous to **Compound 141** from 4-(2-chlorophenyl)-6-(trifluoromethyl)pyridine-3-sulfonyl chloride.

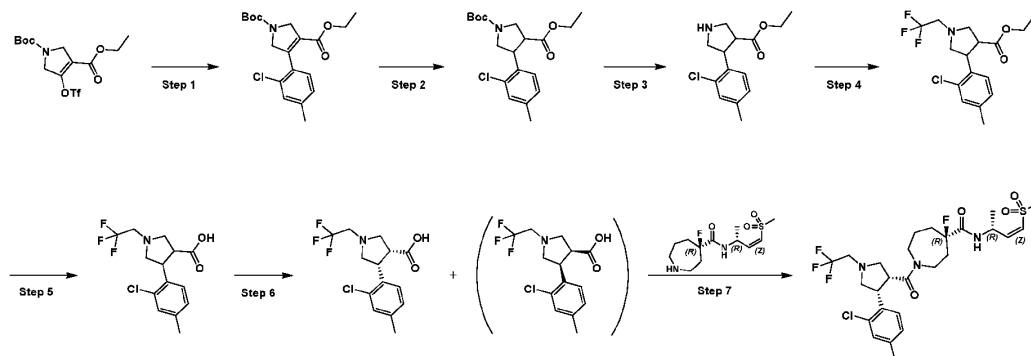
[00518] **Compound 215** was synthesized from 4-(2-chlorophenyl)-6-(trifluoromethyl)pyridine-3-sulfonyl chloride and (2*R*,4*S*)-*N*-((*R,E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide in a manner analogous to **Compound 141**.

[00519] **Compounds 217-218** were synthesized in a manner analogous to **Compound 186** using the appropriate starting material in Step 1 and excluding Step 2.

[00520] **Compound 231** was synthesized in a manner analogous to **Compound 186** excluding Step 2.

[00521] **Compound 232** was synthesized in a manner analogous to **Compound 231** using (*E*)-4-aminobut-2-enenitrile in Step 7.

Scheme 59. Synthesis of (*R*)-1-((3R*,4**R*)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (Compound 169)**



[00522] **Step 1.** To a solution of 1-*tert*-butyl 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylate (2.0 g, 5.30 mmol, 1.0 eq) in THF (20 mL, 0.26 M) was added (2-chloro-4-methyl-phenyl)boronic acid (993 mg, 5.83 mmol, 1.1 eq), K₃PO₄ (2.2 g, 10.6 mmol, 2.0 eq), and Pd(PPh₃)₄ (306 mg, 0.265 mmol, 0.05 eq). The reaction was placed under N₂ and stirred at 70°C for 12 h. After cooling to rt, the solution was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 5:1) to give 1-*tert*-butyl 3-ethyl 4-(2-chloro-4-methylphenyl)-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylate (1.6 g, 4.37 mmol, 83% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.26 - 7.22 (m, 1H), 7.14 - 6.97 (m, 2H), 4.61 - 4.40 (m, 4H), 4.11 - 4.01 (m, 2H), 2.38 - 2.32 (m, 3H), 1.50 (d, *J* = 12.4 Hz, 9H), 1.13 - 1.03 (m, 3H).

[00523] **Step 2.** To a solution of 1-*tert*-butyl 3-ethyl 4-(2-chloro-4-methylphenyl)-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylate (500 mg, 1.37 mmol, 1.0 eq) in EtOAc:ethanol (3:1 v/v, 20 mL, 0.068 M) was added PtO₂ (155 mg, 0.683 mmol, 0.5 eq). The reaction was placed under H₂ (15 psi) and stirred at 20°C for 16 h before being filtered. The filtrate was concentrated and the resulting residue was purified by

prep-TLC to give 1-*tert*-butyl 3-ethyl 4-(2-chloro-4-methylphenyl)pyrrolidine-1,3-dicarboxylate as a *cis* racemate (400 mg, 1.09 mmol, 80% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.24 - 7.18 (m, 1H), 7.15 - 7.08 (m, 1H), 7.05 - 6.97 (m, 1H), 4.13 - 4.02 (m, 1H), 3.91 - 3.73 (m, 5H), 3.72 - 3.62 (m, 1H), 3.60 - 3.49 (m, 1H), 2.35 - 2.26 (m, 3H), 1.50 (s, 9H), 0.92 (t, *J* = 7.1 Hz, 3H).

[00524] Step 3. To a solution of 1-*tert*-butyl 3-ethyl 4-(2-chloro-4-methylphenyl)pyrrolidine-1,3-dicarboxylate (*cis* racemate) (400 mg, 1.09 mmol, 1.0 eq) in DCM (4.5 mL, 0.24 M) was added TFA (1.5 mL) and the reaction was stirred at 25°C for 2 h. The reaction mixture was concentrated to obtain ethyl 4-(2-chloro-4-methylphenyl)pyrrolidine-3-carboxylate (*cis* racemate) (290 mg, 1.08 mmol, quant. yield) as a colorless oil, which was used directly in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.18 - 6.93 (m, 3H), 4.35 - 4.25 (m, 1H), 3.90 - 3.79 (m, 4H), 3.77 - 3.70 (m, 3H), 2.35 - 2.32 (m, 3H), 0.86 - 0.79 (m, 3H).

[00525] Step 4. To ethyl 4-(2-chloro-4-methylphenyl)pyrrolidine-3-carboxylate (*cis* racemate) (290 mg, 1.08 mmol, 1.0 eq) in toluene (5.0 mL, 0.22 M) was added TEA (329 mg, 3.25 mmol, 3.0 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (502 mg, 2.17 mmol, 2.0 eq). The mixture was stirred at 80°C for 16 h. After cooling to rt, the mixture was diluted with water (1.0 mL) and extracted with EtOAc (1.0 mL × 3). The combined organic layers were washed with brine (2.0 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give ethyl 4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (*cis* racemate) (300 mg, 0.858 mmol, 79% yield). This was used directly in the next step. MS (ESI): mass calculated for C₁₆H₁₉ClF₃NO₂, 349.1; *m/z* found, 350.1 [M+H]⁺.

[00526] Step 5. To ethyl 4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (*cis* racemate) (300 mg, 0.858 mmol, 1.0 eq) was added HBr (3.0 mL, 48% solution). The mixture was stirred at 110°C for 3 h. After cooling to rt, the mixture was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (15-45% ACN in 10 mM aq. NH₄HCO₃) to give 4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (*cis* racemate) (140 mg, 0.435 mmol, 51% yield) as a white solid. MS (ESI): mass calculated for C₁₄H₁₅ClF₃NO₂, 321.1; *m/z* found, 322.2 [M+H]⁺.

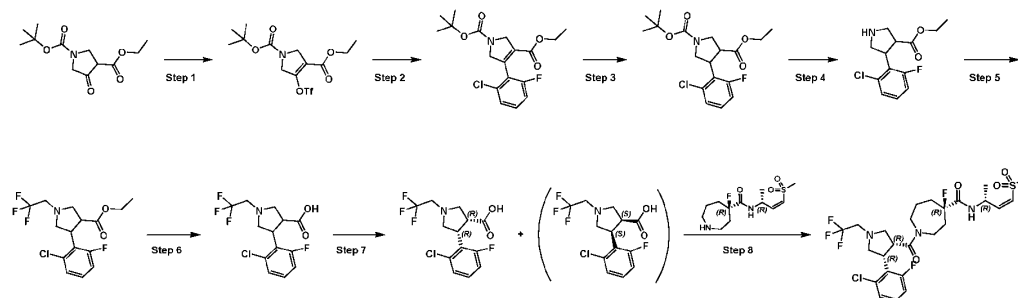
[00527] Step 6. 4-(2-Chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (*cis* racemate) (140 mg, 0.435 mmol, 1.0 eq) was separated by chiral SFC (Stationary phase: AD (250x30 mm), Mobile phase: 5-15% IPA/CO₂; Rt (P1) = 8.37 min, Rt (P2) = 9.37 min) to give two products. P1: (3**R*,4**R*)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (50 mg, 0.155 mmol, 36% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.23 - 7.16 (m, 2H), 7.06 - 6.98 (m, 1H), 4.29 - 4.17 (m, 1H), 3.62 - 3.47 (m, 1H), 3.33 - 3.12 (m, 6H), 2.30 (s, 3H).

[00528] Step 7. To a solution of (3**R*,4**R*)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (50 mg, 0.155 mmol, 1.0 eq) and (*R*)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (59 mg, 0.202 mmol, 1.3 eq) in DCM (1.0 mL, 0.16 M) was added DIPEA (60 mg, 0.466 mmol, 3.0 eq) and HATU (89 mg, 0.233 mmol, 1.5 eq). The reaction mixture was stirred under N₂ at 25°C for 12 h. The mixture was quenched with water (1.0 mL)

and extracted with DCM (1.0 mL $\times$ 3). The combined organic layers were washed with brine (3.0 mL), dried over with Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified via prep-HPLC (20-50% ACN in 0.075% aq. TFA) to give (*R*)-1-((3-*R*,4-*R*)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (as TFA salt, 80 mg, 0.135 mmol, 87% yield) as a white solid. MS (ESI): mass calculated for C₂₆H₃₄ClF₄N₃O₄S, 595.2; *m/z* found, 596.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.33 - 8.17 (m, 1H), 7.29 - 7.13 (m, 2H), 7.11 - 7.01 (m, 1H), 6.51 - 6.38 (m, 1H), 6.33 - 6.21 (m, 1H), 5.36 - 5.26 (m, 1H), 4.10 (br d, *J* = 9.1 Hz, 2H), 3.86 - 3.81 (m, 2H), 3.73 - 3.61 (m, 3H), 3.49 (br d, *J* = 10.6 Hz, 1H), 3.26 - 3.17 (m, 1H), 3.14 - 3.07 (m, 3H), 2.90 - 2.68 (m, 3H), 2.29 - 2.22 (m, 3H), 2.00 - 1.78 (m, 2H), 1.67 - 1.45 (m, 4H), 1.25 - 1.16 (m, 3H).

[00529] **Compound 224** was synthesized in a manner analogous to **Compound 169** using 2-methylphenylboronic acid in Step 1.

Scheme 60. Synthesis of (*R*)-1-((3*R*,4*R*)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (Compound 171)



[00530] **Step 1.** To a solution of 1-*tert*-butyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (5.0 g, 19.4 mmol, 1.0 eq) in toluene (100 mL, 0.19 M) was added DIPEA (3.8 g, 29.2 mmol, 1.5 eq) and trifluoromethanesulfonic anhydride (6.6 g, 23.3 mmol, 1.2 eq) at 0°C. The reaction was allowed to warm to 20°C and stirred for 16 h. The solution was evaporated to give 1-*tert*-butyl 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylate (7.5 g, 19.3 mmol, quant. yield) as a brown solid, which was used in the next step directly.

[00531] **Step 2.** To a solution of 1-*tert*-butyl 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylate (7.5 g, 19.3 mmol, 1.0 eq) in THF (80 mL, 0.24 M) was added (2-chloro-6-fluoro-phenyl)boronic acid (3.7 g, 21.2 mmol, 1.1 eq), K₃PO₄ (8.3 g, 38.5 mmol, 2.0 eq), and Pd(PPh₃)₄ (1.1 g, 0.960 mmol, 0.05 eq). The reaction was placed under N₂ and heated to 80°C for 12 h. After cooling to rt, the solution was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined organic phases were washed with brine (50 mL $\times$ 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 9:1) to provide 1-*tert*-butyl 3-ethyl 4-(2-chloro-6-fluorophenyl)-1*H*-pyrrole-1,3(2*H*,5*H*)-

dicarboxylate (6.0 g, 16.2 mmol, 84% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.33 - 7.27 (m, 1H), 7.26 - 7.21 (m, 1H), 7.07 - 7.01 (m, 1H), 4.60 - 4.42 (m, 4H), 4.11 - 4.03 (m, 2H), 1.51 (d, *J* = 11.8 Hz, 9H), 1.06 (dt, *J* = 10.5, 7.1 Hz, 3H).

[00532] Step 3. To a solution of 1-*tert*-butyl 3-ethyl 4-(2-chloro-6-fluorophenyl)-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylate (1.0 g, 2.70 mmol, 1.0 eq) in ethanol (10 mL, 0.27 M) was added wet Rh/C (0.40 g, 1.35 mmol, 0.5 eq). The reaction was placed under H₂ (50 psi) and stirred at 25°C for 16 h. The solution was filtered then evaporated under reduced pressure. The resulting residue was purified by prep-HPLC (40-75% ACN in 10 mM aq. NH₄HCO₃) to provide 1-*tert*-butyl 3-ethyl 4-(2-chloro-6-fluorophenyl)pyrrolidine-1,3-dicarboxylate as a *cis* racemate (900 mg, 2.42 mmol, 89% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.23 - 7.14 (m, 2H), 6.96 (ddd, *J* = 11.1, 7.9, 1.5 Hz, 1H), 4.27 (q, *J* = 8.1 Hz, 1H), 3.99 - 3.82 (m, 5H), 3.75 - 3.64 (m, 1H), 3.56 - 3.47 (m, 1H), 1.50 (s, 9H), 0.99 (t, *J* = 7.1 Hz, 3H).

[00533] Step 4. To a solution of 1-*tert*-butyl 3-ethyl 4-(2-chloro-6-fluorophenyl)pyrrolidine-1,3-dicarboxylate (*cis* racemate) (900 mg, 2.42 mmol, 1.0 eq) in DCM (10 mL, 0.24 M) was added TFA (3.0 mL, 39.2 mmol, 16 eq). The reaction was stirred at 25°C for 3 h before being slowly poured into sat. aq. NaHCO₃ (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to give ethyl 4-(2-chloro-6-fluorophenyl)pyrrolidine-3-carboxylate (*cis* racemate) (650 mg, 2.39 mmol, 98% yield) as a yellow oil. This was used in the next step directly without purification.

[00534] Step 5. To ethyl 4-(2-chloro-6-fluorophenyl)pyrrolidine-3-carboxylate (*cis* racemate) (650 mg, 2.39 mmol, 1.0 eq) in toluene (10 mL, 0.24 M) was added TEA (730 mg, 7.18 mmol, 3.0 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.1 g, 4.78 mmol, 2.0 eq) at 0°C. The reaction was stirred at 80°C for 16 h. After cooling to rt, the mixture was concentrated to remove solvent then diluted with water (30 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 10:1 - 1:1) to give ethyl 4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (*cis* racemate) (700 mg, 1.98 mmol, 83% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.22 - 7.19 (m, 1H), 7.18 - 7.12 (m, 1H), 6.94 (ddd, *J* = 10.9, 8.1, 1.3 Hz, 1H), 4.42 - 4.33 (m, 1H), 3.86 - 3.73 (m, 2H), 3.57 (dt, *J* = 11.0, 8.3 Hz, 1H), 3.49 - 3.41 (m, 2H), 3.31 - 3.19 (m, 2H), 3.18 - 3.12 (m, 1H), 3.06 (td, *J* = 9.5, 3.1 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H).

[00535] Step 6. To a solution of ethyl 4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate (*cis* racemate) (700 mg, 1.98 mmol, 1.0 eq) in DCE (10 mL, 0.19 M) was added Me₃SnOH (1.8 g, 9.89 mmol, 5.0 eq). The mixture was stirred at 110°C for 48 h. After cooling to rt, the solution was filtered and evaporated under reduced pressure. The resulting residue was purified by prep-HPLC (25-70% ACN in 10 mM aq. TFA) to provide 4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (*cis* racemate) (400 mg, 1.23 mmol, 62% yield) as a white

solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.25 - 7.15 (m, 2H), 7.00 - 6.93 (m, 1H), 4.46 - 4.37 (m, 1H), 3.65 - 3.57 (m, 1H), 3.45 - 3.27 (m, 6H).

[00536] **Step 7.** 4-(2-Chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (cis racemate) (400 mg, 1.23 mmol, 1.0 eq) was separated by chiral SFC (Stationary phase: AD (250x30 mm); Mobile phase: 15% MeOH/CO₂, Rt (P1) = 23.6 min, Rt (P2) = 27.5 min) to give two products. P1: (3*R*,4*R*)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (100 mg, 0.307 mmol, 25% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.26 - 7.19 (m, 2H), 7.03 - 6.94 (m, 1H), 4.62 (q, *J* = 9.0 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 3.86 (br s, 2H), 3.79 - 3.51 (m, 4H). P2: (3*S*,4*S*)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (100 mg, 0.307 mmol, 25% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.24 - 7.14 (m, 2H), 6.99 - 6.91 (m, 1H), 4.43 (q, *J* = 9.2 Hz, 1H), 3.69 - 3.55 (m, 1H), 3.46 (br s, 2H), 3.40 - 3.20 (m, 4H).

[00537] **Step 8.** To a mixture of (3*R*,4*R*)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid (100 mg, 0.307 mmol, 1.0 eq) in DCM (3.0 mL, 0.10 M) was added DIPEA (119 mg, 0.920 mmol, 3.0 eq), HATU (175 mg, 0.461 mmol, 1.5 eq), and (*R*)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide, TsOH salt (90 mg, 0.307 mmol, 1.0 eq). The reaction was stirred at 20°C for 2 h before being diluted with water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phases were washed with brine (5.0 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (10-55% ACN in 10 mM aq. TFA) to provide (*R*)-1-((3*R*,4*R*)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (as TFA salt, 78 mg, 0.125 mmol, 40% yield) as a white solid. MS (ESI): mass calculated for C₂₅H₃₁ClF₅N₃O₄S, 599.2; *m/z* found, 600.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.17 - 8.36 (m, 1H), 7.24 - 7.34 (m, 2H), 7.06 - 7.17 (m, 1H), 6.40 - 6.48 (m, 1H), 6.21 - 6.32 (m, 1H), 5.25 - 5.37 (m, 1H), 4.08 - 4.22 (m, 1H), 3.79 - 3.92 (m, 1H), 3.54 - 3.62 (m, 3H), 3.30 - 3.34 (m, 1H), 3.17 - 3.27 (m, 2H), 3.09 - 3.12 (m, 3H), 2.75 - 2.85 (m, 1H), 2.68 (br d, *J* = 12.8 Hz, 1H), 2.54 - 2.61 (m, 1H), 1.69 - 2.09 (m, 4H), 1.42 - 1.69 (m, 3H), 1.16 - 1.24 (m, 3H).

[00538] **Compound 223** was synthesized in a manner analogous to **Compound 171** using 2-fluorophenylboronic acid in Step 2.

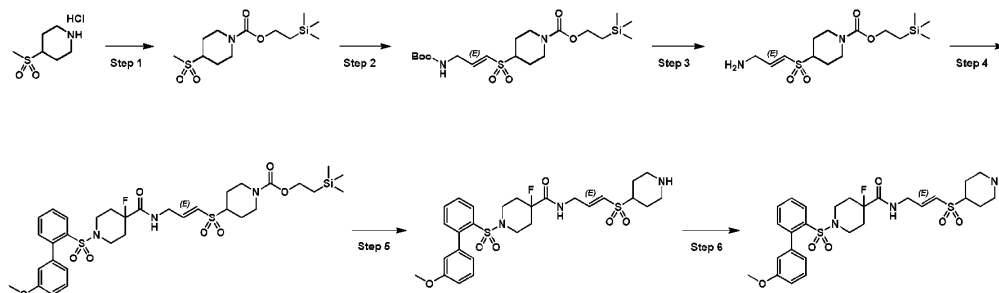
[00539] **Compound 226** was synthesized in a manner analogous to **Compound 171** using (2-chloro-3,6-difluorophenyl)boronic acid in Step 2.

[00540] **Compound 227** was synthesized in a manner analogous to **Compound 171** using 2-(2-chloro-4,6-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in Step 2.

[00541] **Compound 296** was synthesized in a manner analogous to **Compound 164** using methyl (*R*)-4-fluoroazepane-4-carboxylate and (3*R*,4*R*)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid in Step 1 and (*R*,*E*)-4-methylsulfonylbut-3-en-2-amine in Step 3.

[00542] **Compound 297** was synthesized in a manner analogous to **Compound 296** using (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine in Step 3.

Scheme 61. Synthesis of (*E*)-4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-*N*-(3-((1-methylpiperidin-4-yl)sulfonyl)allyl)piperidine-4-carboxamide (Compound 228)



[00543] **Step 1.** At 0°C, (2,5-dioxopyrrolidin-1-yl) 2-trimethylsilylethyl carbonate (2.7 g, 10.5 mmol, 1.05 eq) was added to the mixture of 4-methylsulfonylpiperidine hydrochloride (2.0 g, 10.0 mmol, 1 eq) and Et₃N (1.2 g, 12.0 mmol, 1.2 eq) in DCM/MeOH (1:1 v/v, 20 mL). The resulting mixture was stirred at 25°C for 16 h before being concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 1:1) to provide 2-(trimethylsilyl)ethyl 4-(methylsulfonyl)piperidine-1-carboxylate (3.2 g, 10.4 mmol, quant. yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.37 (br s, 2H), 4.24 - 4.16 (m, 2H), 2.99 (tt, *J* = 3.6, 12.1 Hz, 1H), 2.85 (s, 3H), 2.84 - 2.73 (m, 2H), 2.15 (br d, *J* = 13.6 Hz, 2H), 1.74 (dq, *J* = 4.5, 12.4 Hz, 2H), 1.05 - 0.97 (m, 2H), 0.05 (s, 9H).

[00544] **Step 2.** To a solution of 2-(trimethylsilyl)ethyl 4-methylsulfonylpiperidine-1-carboxylate (1.4 g, 4.55 mmol) in THF (19 mL) was added LiHMDS (11 mL, 1 M) dropwise at -78°C. The mixture was stirred at -78°C for 40 min before diphenyl phosphorochloridate (1.3 g, 5 mmol) was added dropwise at -78°C. The mixture was stirred at -78°C for 40 min before a solution of *N*-*tert*-butoxycarbonyl-2-aminoacetaldehyde (797 mg, 5 mmol) in THF (2 mL) was added dropwise at -78°C. The resulting mixture was stirred at -78°C for 1 h. The reaction mixture was quenched with NH₄Cl (100 mL) and extracted with EtOAc (80 mL × 3). The combined organic layers were washed with brine (80 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was stirred in DCM (20 mL) for 30 min and filtered. The residue was purified by FCC on silica (PE:EtOAc = 1:0 - 7:3) to provide (*E*)-2-(trimethylsilyl)ethyl 4-((3-((*tert*-butoxycarbonyl)amino)prop-1-en-1-yl)sulfonyl)piperidine-1-carboxylate (400 mg, 0.890 mmol, 20% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.84 (br d, *J* = 15.4 Hz, 1H), 6.30 (br d, *J* = 14.5 Hz, 1H), 4.76 (br s, 1H), 4.21 - 4.35 (m, 2H), 4.10 - 4.16 (m, 2H), 3.96 (br d, *J* = 9.2 Hz, 2H), 2.89 (br t, *J* = 12.0 Hz, 1H), 2.72 (br s, 2H), 1.99 - 2.10 (m, 2H), 1.55 - 1.79 (m, 2H), 1.41 (s, 9H), 0.96 (br t, *J* = 8.19 Hz, 2H), 0.00 (s, 9H).

[00545] **Step 3.** To a solution of 2-(trimethylsilyl)ethyl 4-[(*E*)-3-(*tert*-butoxycarbonylamino)prop-1-enyl]sulfonylpiperidine-1-carboxylate (200 mg, 0.440 mmol, 1 eq) in MeCN (5 mL) was added 4-methylbenzenesulfonic acid (84 mg, 0.490 mmol, 1.1 eq). The reaction mixture was stirred for 12 h at

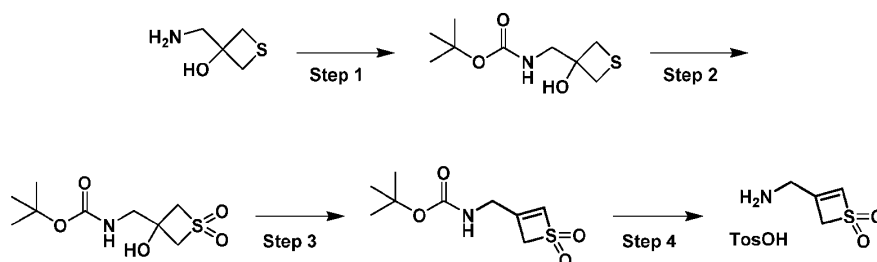
50°C. After cooling to rt, the reaction mixture was concentrated to give (*E*)-2-(trimethylsilyl)ethyl 4-((3-aminoprop-1-en-1-yl)sulfonyl)piperidine-1-carboxylate (TsOH salt, 200 mg) as a yellow solid, which was used in the next step without purification.

[00546] Step 4. To a solution of 4-methylbenzenesulfonate [(*E*)-3-[[1-(2-trimethylsilylethoxycarbonyl)-4-piperidyl]sulfonyl]allyl]ammonium (150 mg, 0.290 mmol, 1.0 eq) in DCM (5 mL) was added DIPEA (0.860 mmol, 3.0 eq) and 4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxylic acid (113 mg, 0.290 mmol, 1.0 eq). HATU (165 mg, 0.430 mmol, 1.5 eq) was added and the reaction mixture was stirred for 2 h at 25°C. The reaction mixture was quenched with water and extracted with DCM to give the crude product, which was purified by prep-TLC (PE:EtOAc = 1:1) to give 2-trimethylsilylethyl 4-[(*E*)-3-[[4-fluoro-1-[2-(3-methoxyphenyl)phenyl]sulfonyl]piperidine-4-carbonyl]amino]prop-1-enyl]sulfonylpiperidine-1-carboxylate (60 mg, 29% yield) as a yellow solid.

[00547] Step 5. To a solution of 2-trimethylsilylethyl 4-[(*E*)-3-[[4-fluoro-1-[2-(3-methoxyphenyl)phenyl]sulfonyl]piperidine-4-carbonyl]amino]prop-1-enyl] sulfonylpiperidine -1-carboxylate (60 mg, 0.086 mmol, 1.0 eq) in DCM (2 mL) was added TFA (1 mL). The reaction mixture was stirred for 12 h at 25°C before being concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to give 4-fluoro-1-[2-(3-methoxyphenyl)phenyl]sulfonyl-*N*-[(*E*)-3-(4-piperidylsulfonyl)allyl]piperidine-4-carboxamide (50 mg, 0.086 mmol, quant. yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.99 (br s, 1H), 8.59 (br s, 2H), 8.04 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.59 - 7.79 (m, 2H), 7.28 - 7.43 (m, 2H), 6.88 - 7.03 (m, 3H), 6.75 (dt, *J* = 15.3, 4.5 Hz, 1H), 6.50 (br d, *J* = 15.3 Hz, 1H), 3.97 (br s, 2H), 3.79 (s, 3H), 3.27 - 3.34 (m, 1H), 3.16 (br d, *J* = 13.0 Hz, 2H), 2.89 (q, *J* = 11.7 Hz, 2H), 2.57 - 2.58 (m, 1H), 2.40 - 2.45 (m, 2H), 2.34 (br d, *J* = 1.9 Hz, 4H), 2.06 (br d, *J* = 11.6 Hz, 2H), 1.65 - 1.83 (m, 6H).

[00548] Step 6. To a solution of 4-fluoro-1-[2-(3-methoxyphenyl)phenyl]sulfonyl-*N*-[(*E*)-3-(4-piperidylsulfonyl)allyl]piperidine-4-carboxamide (60 mg, 0.10 mmol, 1.0 eq) in methanol (5 mL) was added HCHO (37% in water, 0.5 mL) and NaBH₃CN (60 mg, 1.0 mmol, 10 eq). The reaction mixture was stirred for 16 h at 25°C before being concentrated. The crude product was purified by prep-HPLC to provide 4-fluoro-1-[2-(3-methoxyphenyl)phenyl]sulfonyl-*N*-[(*E*)-3-[(1-methyl-4piperidyl)sulfonyl]allyl]piperidine -4-carboxamide (27 mg, 0.045 mmol, 44% yield) as a white solid. MS (ESI): mass calculated for C₂₈H₃₆FN₃O₆S₂, 593; *m/z* found, 594 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.35 (br s, 1H), 8.61 (br s, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.57 - 7.80 (m, 2H), 7.27 - 7.46 (m, 2H), 6.84 - 7.03 (m, 3H), 6.66 - 6.81 (m, 1H), 6.53 (br d, *J* = 15.3 Hz, 1H), 3.98 (br s, 2H), 3.80 (s, 3H), 3.53 (br d, *J* = 11.9 Hz, 2H), 3.10 - 3.35 (m, 3H), 2.86 - 3.02 (m, 2H), 2.68 - 2.78 (m, 3H), 2.53 - 2.56 (m, 2H), 2.46 - 2.49 (m, 1H), 2.11 (br d, *J* = 12.8 Hz, 2H), 1.65 - 1.93 (m, 6H).

Scheme 62. Synthesis of Intermediate 3-(aminomethyl)-2*H*-thiete 1,1-dioxide



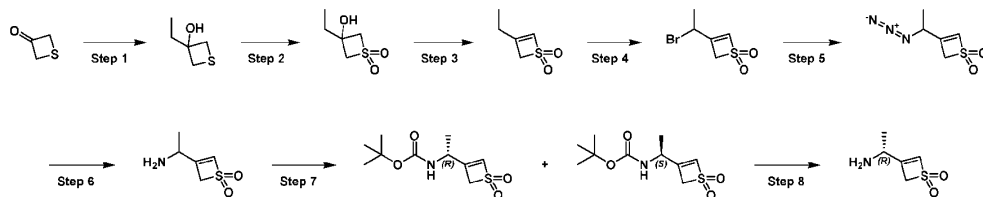
[00549] Step 1. To a solution of 3-(aminomethyl)thietan-3-ol (9.0 g, 75.5 mmol, 1.0 eq) and triethylamine (7.6 g, 75.5 mmol, 1.0 eq) in DCM (100 mL) was added di-*tert*-butyl dicarbonate (1.9 g, 86.8 mmol, 1.2 eq) at 0 °C. The reaction was stirred at 25°C for 12 h before being concentrated under vacuum. The residue was purified by FCC on silica (PE:EtOAc = 3:1 - 1:1) to give *tert*-butyl *N*-[(3-hydroxythietan-3-yl)methyl]carbamate (10 g, 45.6 mmol, 60% yield) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.21 (br s, 1H), 4.88 (s, 1H), 3.60 (d, *J* = 6.0 Hz, 2H), 3.42 (br d, *J* = 9.8 Hz, 2H), 2.98 (br d, *J* = 10.0 Hz, 2H), 1.39 - 1.49 (m, 9H).

[00550] Step 2. To a solution of *tert*-butyl *N*-[(3-hydroxythietan-3-yl)methyl]carbamate (10 g, 45.6 mmol, 1.0 eq) in EtOAc (150 mL, 0.3 M) was added 3-chloroperbenzoic acid (23 g, 114 mmol, 2.5 eq) in portions at 0°C. The reaction was stirred at 20°C for 2 h before being filtered. The filtrate was washed with a solution of disodium sulfite (8.6 g, 68.4 mmol, 1.5 eq) in H₂O (150 mL) at 0°C. The EtOAc layer was washed with sat. aq. NaHCO₃ (100 mL × 2) and brine (150 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give *tert*-butyl *N*-[(3-hydroxy-1,1-dioxo-thietan-3-yl)methyl]carbamate (8.0 g, 31.8 mmol, 70% yield).

[00551] Step 3. To a solution of *tert*-butyl *N*-[(3-hydroxy-1,1-dioxo-thietan-3-yl)methyl]carbamate (2.0 g, 7.96 mmol, 1.0 eq) in DCM (20 mL, 0.42 M) was added triethylamine (4.8 g, 47.7 mmol, 6.0 eq) at 0°C followed by dropwise addition of methanesulfonyl chloride (3.2 mg, 27.5 mmol, 3.5 eq) in DCM (10 mL). The reaction was stirred at 20°C for 4 h before being quenched with sat. aq. sodium bicarbonate (20 mL). The aq. phase was extracted with DCM (20 mL × 2) and the combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated to give *tert*-butyl *N*-[(1,1-dioxo-2H-thiet-3-yl)methyl]carbamate (1.9 g, 8.20 mmol). This was used directly in the next step.

[00552] Step 4. To a solution of *tert*-butyl *N*-[(1,1-dioxo-2H-thiet-3-yl)methyl]carbamate (4.5 g, 19.3 mmol, 1.0 eq) in MeCN (8.0 mL, 2.4 M) was added *p*-toluenesulfonic acid monohydrate (4.4 g, 23.1 mmol, 1.2 eq). The reaction was stirred at 60°C for 2 h before being cooled to 0°C and filtered. The filter cake was concentrated under reduced pressure to give 3-(aminomethyl)-2H-thiete 1,1-dioxide; 4-methylbenzenesulfonate (4.3 g, 14.1 mmol, 73% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.25 (br s, 3H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 1.8 Hz, 1H), 4.62 (s, 2H), 3.95 (br s, 2H), 2.29 (s, 3H).

[00553] Compound 233 was synthesized in a manner analogous to **Compound 47** using 3-(aminomethyl)-2H-thiete 1,1-dioxide in Step 5.

Scheme 63. Synthesis of Intermediate (*R*)-3-(1-aminoethyl)-2*H*-thiete 1,1-dioxide

[00554] **Step 1.** To a solution of thietan-3-one (20 g, 227 mmol, 1.0 eq) in THF (150 mL) was added EtMgBr (76 mL, 227 mmol, 1.0 eq) dropwise at 0°C under N₂. The reaction was stirred at 25°C for 2 h before being quenched by sat. aq. NH₄Cl (200 mL) and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 5:1) to give 3-ethylthietan-3-ol (7.0 g, 59.2 mmol, 26% yield) as a colorless oil.

[00555] **Step 2.** To a solution of 3-ethylthietan-3-ol (7.0 g, 59.2 mmol, 1.0 eq) in ethyl acetate (140 mL) at 0°C was added *m*-CPBA (28 g, 130 mmol, 2.2 eq) portionwise under N₂. The reaction was stirred at 25°C for 2 h before being filtered. The filtrate was washed with Na₂SO₃ (80 mL) and extracted with ethyl acetate (80 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by FCC on silica (PE:EtOAc = 9:1 - 7:3) to provide 3-ethyl-1,1-dioxo-thietan-3-ol (3.2 g, 21.3 mmol, 36% yield) as a yellow oil.

[00556] **Step 3.** To a solution of 3-ethyl-1,1-dioxo-thietan-3-ol (3.5 g, 23.3 mmol, 1.0 eq) in DCM (25 mL) at 0 °C was added Et₃N (14 g, 140 mmol, 6.0 eq) followed by a solution of methanesulfonyl chloride (4.9 g, 43.3 mmol) in DCM (5 mL) dropwise under N₂. The reaction was stirred for at 25°C for 2 h before being washed with NaHCO₃ (25 mL) and brine (25 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:1) to give 3-ethyl-2*H*-thiete 1,1-dioxide (2.7 g, 20.8 mmol, 89% yield) as a colorless oil.

[00557] **Step 4.** To a solution of 3-ethyl-2*H*-thiete 1,1-dioxide (2.7 g, 20.8 mmol, 1.0 eq) in MeCN (20 mL) was added a solution of *N*-bromosuccinimide (3.7 g, 20.8 mmol, 1.0 eq) and 2,2'-azobis(2-methylpropionitrile) (1.0 g, 6.24 mmol, 0.3 eq) in MeCN (20 mL). The reaction was stirred at 70°C for 2 h. After cooling to rt, the mixture was concentrated under reduced pressure. The residue was purified by FCC on silica (PE:EtOAc = 20:1 to 5:1) to give 3-(1-bromoethyl)-2*H*-thiete 1,1-dioxide (4.3 g, 20.4 mmol, 98% yield) as a colorless oil.

[00558] **Step 5.** A solution of 3-(1-bromoethyl)-2*H*-thiete 1,1-dioxide (4.3 g, 20.4 mmol, 1.0 eq) in THF (40 mL) was cooled to 0°C and a solution of sodium azide (1.7 g, 25.7 mmol, 1.3 eq) in water (40 mL) was added dropwise under N₂. The mixture was stirred at 0°C for 2 h before being poured into water (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to give 3-(1-azidoethyl)-2*H*-thiete 1,1-

dioxide (2.0 g, 11.5 mmol, 57% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 6.71 (d, J = 1.5 Hz, 1H), 4.44 - 4.53 (m, 2H), 4.41 (q, J = 6.9 Hz, 1H), 1.52 (d, J = 6.9 Hz, 3H)

[00559] Step 6. A mixture of 3-(1-azidoethyl)-2*H*-thiete 1,1-dioxide (1.0 g, 5.77 mmol, 1.0 eq) in ethanol (25 mL) were added zinc, granular (1.1 g, 17.3 mmol, 3.0 eq) and NH_4Cl (1.5 g, 28.9 mmol, 1.3 eq) under N_2 . The reaction was stirred at 20°C for 20 h before being filtered. The filtrate was concentrated under reduced pressure to give 1-(1,1-dioxo-2*H*-thiet-3-yl)ethanamine (1.0 g, 7.13 mmol) as a yellow oil, which was used in the next step directly.

[00560] Step 7. To a solution of 1-(1,1-dioxo-2*H*-thiet-3-yl)ethanamine (800 mg, 5.43 mmol, 1.0 eq) and DIPEA (1.4 g, 10.9 mmol, 2.0 eq) in DCM (2 mL) was added di-*tert*-butyl dicarbonate (1.4 g, 6.52 mmol, 1.2 eq). The reaction was stirred at 18°C for 6 h before being concentrated and purified by FCC on silica (PE: EtOAc = 5:1 to 1:2). The resulting racemic product was separated by chiral SFC to give *tert*-butyl *N*-[(1*R*)-1-(1,1-dioxo-2*H*-thiet-3-yl)ethyl]carbamate (50 mg, 0.20 mmol, 4% yield) as a white solid, and *tert*-butyl *N*-[(1*S*)-1-(1,1-dioxo-2*H*-thiet-3-yl)ethyl]carbamate (50 mg, 0.20 mmol, 4% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 6.58 (s, 1H), 4.60 - 4.61 (m, 1H), 4.46 (s, 2H), 1.46 (s, 9H), 1.39 - 1.42 (m, 3H).

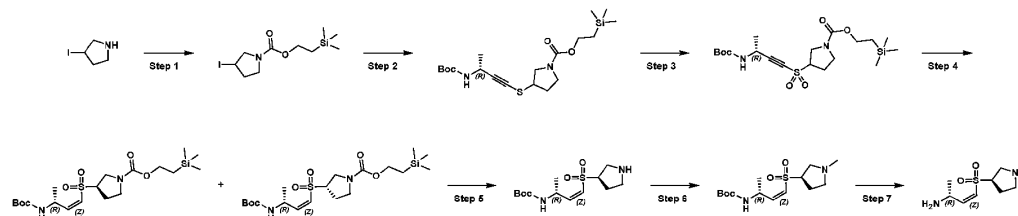
[00561] Step 8. A solution of *tert*-butyl *N*-[(1*R*)-1-(1,1-dioxo-2*H*-thiet-3-yl)ethyl]carbamate (50 mg, 0.200 mmol, 1.0 eq) and *p*-toluenesulfonic acid monohydrate (77 mg, 0.400 mmol, 2.0 eq) in ethyl acetate (2.0 mL) was stirred at 80°C for 24 h. The mixture was concentrated under reduced pressure to provide (*R*)-3-(1-aminoethyl)-2*H*-thiete 1,1-dioxide (90 mg, 0.280 mmol, TsOH salt) as a white solid, which was used in the next step directly.

[00562] Compound 234 was synthesized in a manner analogous to **Compound 47** using (*R*)-3-(aminoethyl)-2*H*-thiete 1,1-dioxide in Step 5.

[00563] Compound 235 was synthesized in a manner analogous to **Compound 1** using 1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid and (*R*)-3-(aminoethyl)-2*H*-thiete 1,1-dioxide in Step 5.

[00564] Compound 236 was synthesized in a manner analogous to **Compound 134** using (*R*)-3-(aminoethyl)-2*H*-thiete 1,1-dioxide in Step 5.

Scheme 64. Synthesis of Intermediate (*R,Z*)-4-(((*R*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-amine



[00565] Step 1. To a solution of 3-iodopyrrolidine (4.0 g, 20.3 mmol, 1.0 eq) and (2,5-dioxopyrrolidin-1-yl)2-trimethylsilyl ethyl carbonate (5.3 g, 20.3 mmol, 1.0 eq) in DCM (50 mL) was added triethylamine

(5.1 g, 50.8 mmol, 2.5 eq). The reaction was stirred at 25°C for 2 h before being quenched with H₂O (10 mL) and extracted with DCM (10 mL × 2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by FCC on silica (PE:EtOAc = 4:1 - 1:0) to afford 2-trimethylsilylethyl 3-iodopyrrolidine-1-carboxylate (5.3 g, 15.5 mmol, 76% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.38 (br s, 1 H), 4.20 (br d, *J* = 2.9 Hz, 2H), 3.83 - 3.91 (m, 1H), 3.40 - 3.81 (m, 3H), 2.21 - 2.29 (m, 2H), 0.96 - 1.07 (m, 2H), 0.04 (s, 9H).

[00566] **Step 2.** *n*-BuLi (10.4 mL, 26.0 mmol, 2.2 eq) was slowly added to a solution of *tert*-butyl (*R*)-but-3-yn-2-ylcarbamate (2.0 g, 11.8 mmol, 1.0 eq) in THF (20 mL, 0.59 M) under N₂ at -70°C. The reaction was stirred for 1 h before S₈ (380 mg, 1.48 mmol, 0.13 eq) was added in batches. The solution became red and the mixture was stirred for 0.5 h at -70 °C then 0.5 h at 0°C until complete consumption of sulfur (dark red solution). 2-Trimethylsilylethyl-3-iodopyrrolidine-1-carboxylate (4.0 g, 11.8 mmol, 1.0 eq) in THF (10 mL) was added and the reaction mixture was stirred at 0°C for 2 h. Sat. aq. NH₄Cl (30 mL) was added and the aq. phase was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EtOAc = 95:5 - 9:1) to give 2-(trimethylsilyl)ethyl-3-(((*R*)-3-((*tert*-butoxycarbonyl)amino)but-1-yn-1-yl)thio)pyrrolidine-1-carboxylate (2.3 g, 5.55 mmol, 47% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.44 - 4.83 (m, 2H), 4.15 - 4.22 (m, 2H), 3.37 - 3.77 (m, 5H), 2.06 - 2.32 (m, 2H), 1.45 (s, 9H), 1.39 (d, *J* = 6.9 Hz, 3H), 0.96 - 1.04 (m, 2H), 0.02 - 0.06 (m, 9H).

[00567] **Step 3.** To a solution of 2-(trimethylsilyl)ethyl-3-(((*R*)-3-((*tert*-butoxycarbonyl)amino)but-1-yn-1-yl)thio)pyrrolidine-1-carboxylate (2.0 g, 4.82 mmol, 1.0 eq) in DCM (20 mL, 0.24 M) was added 3-chloroperbenzoic acid (2.1 g, 12.1 mmol, 2.5 eq). The mixture was stirred at 25°C for 2 h before being poured into sat. aq. Na₂SO₃ (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with sat. aq. NaHCO₃ (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 2-(trimethylsilyl)ethyl 3-(((*R*)-3-((*tert*-butoxycarbonyl)amino)but-1-yn-1-yl)sulfonyl)pyrrolidine-1-carboxylate (2.0 g, 4.48 mmol, 93% yield) as a white solid. This was used in the next step directly.

[00568] **Step 4.** A mixture of 2-(trimethylsilyl)ethyl 3-(((*R*)-3-((*tert*-butoxycarbonyl)amino)but-1-yn-1-yl)sulfonyl)pyrrolidine-1-carboxylate (2.0 g, 4.48 mmol, 1.0 eq) and 5% Pd/C (2.0 g, with ~55% water) in THF (20 mL, 0.22 M) was stirred at 25°C for 2 h under H₂ (15 psi). After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 4:1 - 1:0) to give 2-(trimethylsilyl)ethyl (**R*)-3-(((*R,Z*)-3-((*tert*-butoxycarbonyl)amino)but-1-en-1-yl)sulfonyl)pyrrolidine-1-carboxylate (420 mg, 0.94 mmol, 21% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.10 - 6.38 (m, 2H), 5.07 (br s, 1H), 4.62 (br s, 1H), 4.15 - 4.21 (m, 2H), 3.43 - 4.02 (m, 4H), 2.32 (br d, *J* = 13.9 Hz, 2H), 1.39 - 1.46 (m, 9H), 1.32 (dd, *J* = 6.8, 2.6 Hz, 3H), 0.95 - 1.04 (m, 2H), 0.04 (d, *J* = 0.8 Hz, 9H).

[00569] **Step 5.** To a solution of 2-(trimethylsilyl)ethyl (**R*)-3-(((*R,Z*)-3-((*tert*-butoxycarbonyl)amino)but-1-en-1-yl)sulfonyl)pyrrolidine-1-carboxylate (200 mg, 0.450 mmol, 1.0 eq) in

THF (2.0 mL, 0.22 M) was added tetrabutylammonium fluoride (0.9 mL, 0.890 mmol, 2.0 eq). The mixture was stirred at 25°C for 1 h before being concentrated under reduced pressure to give *tert*-butyl ((*R,Z*)-4-(((*R*)-pyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)carbamate (140 mg, 0.460 mmol) as a white solid. This was used directly.

[00570] Step 6. A solution of *tert*-butyl ((*R,Z*)-4-(((*R*)-pyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)carbamate (140 mg, 0.460 mmol, 1.0 eq) in methanol (2.0 mL, 0.23 M) was added formaldehyde (373 mg, 4.60 mmol, 10 eq) and sodium cyanoborohydride (116 mg, 1.84 mmol, 4.0 eq). The mixture was stirred at 25°C for 1 h before being purified by prep-HPLC to afford *tert*-butyl ((*R,Z*)-4-(((*R*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)carbamate (100 mg, 0.314 mmol, 68% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.30 - 6.40 (m, 1H), 6.11 - 6.19 (m, 1H), 5.01 - 5.13 (m, 1H), 4.59 - 4.69 (m, 1H), 4.09 - 4.43 (m, 2H), 3.65 - 3.88 (m, 1H), 3.02 - 3.50 (m, 3H), 2.95 (s, 3H), 2.54 - 2.68 (m, 1H), 1.41 (s, 9H), 1.32 (d, *J* = 6.9 Hz, 3H).

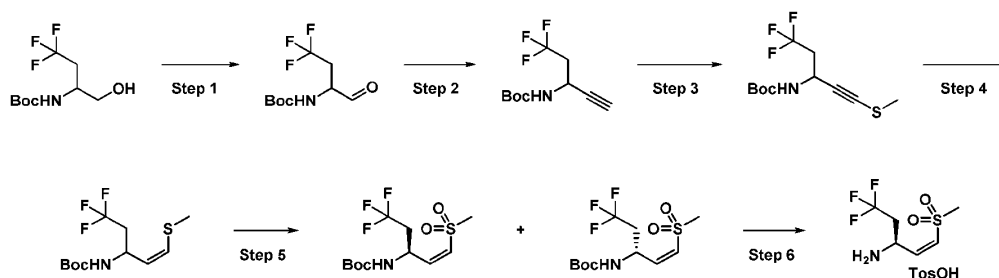
[00571] Step 7. To a solution of *tert*-butyl ((*R,Z*)-4-(((*R*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)carbamate (100 mg, 0.310 mmol, 1.0 eq) in DCM (0.8 mL, 0.26 M) was added trifluoroacetic acid (0.4 mL, 0.26 M). The mixture was stirred at 25°C for 1 h before being concentrated under reduced pressure to give (*R,Z*)-4-(((*R*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-amine (70 mg, 0.320 mmol) as a colorless oil. This was used directly in the next step.

[00572] Compound 237 was synthesized in a manner analogous to **Compound 47** using (*R,Z*)-4-(((*R*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-amine in Step 5.

[00573] Intermediate (*R,Z*)-4-(((*S*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-amine was synthesized in a manner analogous to (*R,Z*)-4-(((*R*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-amine, elaborating the other diastereomer obtained in Step 4.

[00574] Compound 238 was synthesized in a manner analogous to **Compound 47** using (*R,Z*)-4-(((*S*)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-amine in Step 5.

Scheme 65. Synthesis of Intermediate (*S,Z*)-5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-amine



[00575] Step 1. To a solution of *tert*-butyl *N*-[3,3,3-trifluoro-1-(hydroxymethyl)propyl]carbamate (3.0 g, 12.3 mmol, 1.0 eq) in MeCN (60 mL) was added 1-hydroxy-1-oxo-1λ⁵,2-benziodoxol-3-one (8.6 g, 30.8 mmol, 2.5 eq). The reaction was stirred at 65°C for 6 h. After cooling to rt, the mixture was filtered and concentrated under reduced pressure to give *tert*-butyl *N*-(3,3,3-trifluoro-1-formyl-propyl)carbamate

(2.4 g, 9.95 mmol, 81% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.60 (s, 1H), 5.30 (br s, 1H), 4.22 - 4.14 (m, 1H), 2.91 - 2.77 (m, 1H), 2.66 - 2.53 (m, 1H), 1.47 (s, 9H).

[00576] Step 2. To a solution of *tert*-butyl *N*-(3,3,3-trifluoro-1-formyl-propyl)carbamate (2.0 g, 8.29 mmol, 1.0 eq) in methanol (16 mL, 0.52 M) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (2.1 g, 10.8 mmol, 1.3 eq) and potassium carbonate (2.6 g, 19.1 mmol, 2.3 eq) at 0°C. The reaction was stirred at 0-25°C for 2 h before being diluted with MTBE (160 mL) and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 10:1 - 5:1) to give *tert*-butyl *N*-[1-(2,2,2-trifluoroethyl)prop-2-ynyl]carbamate (1.4 g, 5.9 mmol, 71% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.91 - 4.72 (m, 2H), 2.65 - 2.50 (m, 2H), 2.39 (d, *J* = 2.0 Hz, 1H), 1.46 (s, 9H).

[00577] Step 3. A solution of cuprous iodide (122 mg, 0.640 mmol, 0.2 eq) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (370 mg, 0.640 mmol, 0.2 eq) in DMSO (25 mL) was stirred for 0.5 h. *tert*-Butyl *N*-[1-(2,2,2-trifluoroethyl)prop-2-ynyl]carbamate (760 mg, 3.20 mmol, 1.0 eq), 1-methyl-4-methylsulfanylsulfonyl-benzene (972 mg, 4.81 mmol, 1.5 eq), and potassium carbonate (1.1 g, 8.00 mmol, 2.5 eq) were added at 25°C under O₂ (15 psi). The reaction was stirred for 48 h before being poured into water (100 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed brine (200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 10:1 - 5:1) to give *tert*-butyl *N*-[3-methylsulfanyl-1-(2,2,2-trifluoroethyl)prop-2-ynyl]carbamate (500 mg, 1.76 mmol, 55% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.85 (br s, 2H), 2.65 - 2.47 (m, 2H), 2.38 (s, 3H), 1.46 (s, 9H).

[00578] Step 4. *tert*-Butyl *N*-[3-methylsulfanyl-1-(2,2,2-trifluoroethyl)prop-2-ynyl]carbamate (300 mg, 1.06 mmol, 1.0 eq), quinoline (41 mg, 0.320 mmol, 0.3 eq), hexene (0.5 mL), and Lindlar catalyst (100 mg) were combined in methanol (20 mL). The mixture was stirred under H₂ (35 psi) at 25°C for 2 h. The reaction was filtered to provide *tert*-butyl *N*-[(*Z*)-3-methylsulfanyl-1-(2,2,2-trifluoroethyl)allyl]carbamate (300 mg, 1.05 mmol, quant. yield) as a yellow oil, which was used directly in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.12 (d, *J* = 9.5 Hz, 1H), 5.58 (br d, *J* = 6.5 Hz, 1H), 4.66 - 4.60 (m, 1H), 2.61 - 2.51 (m, 2H), 2.31 (s, 3H), 1.45 (s, 9H).

[00579] Step 5. To a solution of *tert*-butyl *N*-[(*Z*)-3-methylsulfanyl-1-(2,2,2-trifluoroethyl)allyl]carbamate (400 mg, 1.33 mmol, 1.0 eq) in DCM (5 mL) was added 3-chloroperbenzoic acid (676 mg, 3.33 mmol, 2.5 eq) at 0°C. The mixture was stirred at 25°C for 2 h before being quenched with 10% aq. Na₂S₂O₃ (5 mL) and sat. aq. NaHCO₃ (5 mL). The reaction was extracted with DCM (5 mL × 3) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EtOAc = 10:1 - 5:3) to give racemic product (400 mg). This was separated by chiral SFC to give *tert*-butyl *N*-[*rac*-(*Z*,1**S*)-3-methylsulfonyl-1-(2,2,2-trifluoroethyl)allyl]carbamate (150 mg, 0.470 mmol, 35% yield) and *tert*-butyl *N*-[*rac*-(*Z*,1**R*)-3-methylsulfonyl-1-(2,2,2-trifluoroethyl)allyl]carbamate (150 mg, 0.470 mmol, 35% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm

6.43 - 6.32 (m, 2H), 5.47 - 5.37 (m, 1H), 5.10 (br s, 1H), 3.13 (s, 3H), 2.73 - 2.56 (m, 2H), 1.44 (s, 9H).
¹H NMR (400 MHz, CDCl₃) δ ppm 6.43 - 6.32 (m, 2H), 5.46 - 5.36 (m, 1H), 5.10 (br s, 1H), 3.13 (s, 3H), 2.73 - 2.55 (m, 2H), 1.44 (s, 9H).

[00580] **Step 6.** To a solution of *tert*-butyl *N*-[*rac*-(*Z*,1**S*)-3-methylsulfonyl-1-(2,2,2-trifluoroethyl)allyl]carbamate (0.15 g, 0.470 mmol, 1.0 eq) in MeCN (3 mL) was added *p*-toluenesulfonic acid monohydrate (117 mg, 0.610 mmol, 1.3 eq). The mixture was stirred at 60°C for 6 h. After cooling to rt, the mixture was concentrated under reduced pressure to give (**S*,*Z*)-5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-amine, 4-methylbenzenesulfonate (180 mg, 0.460 mmol, 98% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.36 (br s, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 11.2 Hz, 1H), 6.34 (t, *J* = 10.8 Hz, 1H), 5.28 (br d, *J* = 2.6 Hz, 1H), 3.14 (s, 3H), 2.80 (dq, *J* = 7.3, 10.8 Hz, 3H), 2.29 (s, 3H).

[00581] **Compound 239** was synthesized in a manner analogous to **Compound 1** using 1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid and (**S*,*Z*)-5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-amine in Step 5.

[00582] **Compound 240** was synthesized in a manner analogous to **Compound 47** using (**S*,*Z*)-5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-amine in Step 5.

[00583] **Intermediate (*R*,*Z*)-1-methoxy-4-(methylsulfonyl)but-3-en-2-amine** was synthesized in a manner analogous to (**S*,*Z*)-5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-amine using 1,1-dimethylethyl *N*-[(1*S*)-2-hydroxy-1-(methoxymethyl)ethyl]carbamate in Step 1.

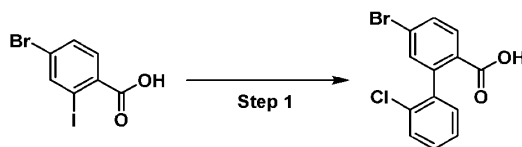
[00584] **Compound 246** was synthesized in a manner analogous to **Compound 47** using (*R*,*Z*)-1-methoxy-4-(methylsulfonyl)but-3-en-2-amine in Step 5.

[00585] **Compound 248** was synthesized in a manner analogous to **Compound 1** using (*R*,*Z*)-1-methoxy-4-(methylsulfonyl)but-3-en-2-amine and 1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid in Step 5.

[00586] **Intermediate (*S*,*Z*)-1-methoxy-4-(methylsulfonyl)but-3-en-2-amine** was synthesized in a manner analogous to (**S*,*Z*)-5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-amine using 1,1-dimethylethyl *N*-[(1*R*)-2-hydroxy-1-(methoxymethyl)ethyl]carbamate in Step 1.

[00587] **Compound 247** was synthesized in a manner analogous to **Compound 47** using (*S*,*Z*)-1-methoxy-4-(methylsulfonyl)but-3-en-2-amine in Step 5.

Scheme 66. Synthesis of Intermediate 5-bromo-2'-chloro-[1,1'-biphenyl]-2-carboxylic acid



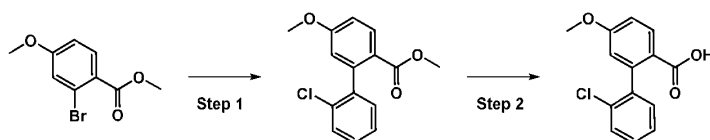
[00588] **Step 1.** To a solution of 4-bromo-2-iodobenzoic acid (5.0 g, 15.3 mmol, 1.0 eq) in NMP/water (1:1 v/v, 50 mL, 0.31 M) was added 2-chlorophenylboronic acid (2.6 g, 16.8 mmol), LiOH.H₂O (1.4 g, 33.6 mmol), and Pd₂(dba)₃ (140 mg, 0.150 mmol) under N₂. The mixture was stirred at 70°C for 16 h.

After cooling to rt, the reaction was poured into water (300 mL) and acidified with 2N HCl until pH = 2. The mixture was extracted with EtOAc (200 mL $\times$ 2) and the combined organic phases were dried over Na₂SO₄, filtered, concentrated under reduced pressure. Purification by column (PE:EtOAc = 5:1 - 4:1) provided 5-bromo-2'-chloro-[1,1'-biphenyl]-2-carboxylic acid (3.5 g, 9.55 mmol, 62% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.96 (d, J = 8.5 Hz, 1H), 7.63 (dd, J = 2.1, 8.4 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.41 (s, 1H), 7.35 - 7.29 (m, 2H), 7.24 (s, 1H). [M+H]⁺ calculated for C₁₃H₈BrClO₂, 310; found 311.

[00589] **Compound 241** was synthesized in a manner analogous to **Compound 165** using 5-bromo-2'-chloro-[1,1'-biphenyl]-2-carboxylic acid in Step 4.

[00590] **Compound 243** was synthesized in a manner analogous to **Compound 241** using (*R*)-*N*-((*R,E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide in Step 4.

Scheme 67. Synthesis of Intermediate 2-(2-chlorophenyl)-4-methoxy-benzoic acid



[00591] **Step 1.** To a solution of methyl 2-bromo-4-methoxybenzoate (20 g, 81.6 mmol, 1.0 eq) in water (15 mL, 0.38 M) and 1,4-dioxane (200 mL, 0.38 M) was added 2-chlorophenylboronic acid (15 g, 97.9 mmol, 1.2 eq), potassium carbonate (23 g, 163 mmol, 2.0 eq), and Pd(dppf)Cl₂ (5.9 g, 8.16 mmol, 0.1 eq). The reaction was stirred at 80°C for 16 h under N₂. After cooling to rt, the reaction was quenched with water (150 mL) and extracted with EtOAc (150 mL $\times$ 2). The combined organic phases were washed with brine (300 mL $\times$ 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 5:1) to give methyl 2-(2-chlorophenyl)-4-methoxybenzoate (18.5 g, 67.0 mmol, 82% yield) as a colorless oil. MS (ESI): mass calculated for C₁₅H₁₃ClO₃, 276.1; m/z found, 276.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.96 - 7.89 (m, 1H), 7.49 - 7.43 (m, 1H), 7.40 - 7.34 (m, 2H), 7.31 - 7.25 (m, 1H), 7.11 - 7.01 (m, 1H), 6.80 - 6.75 (m, 1H), 3.86 - 3.79 (m, 3H), 3.58 - 3.51 (m, 3H).

[00592] **Step 2.** To a solution of methyl 2-(2-chlorophenyl)-4-methoxybenzoate (20.6 g, 67.0 mmol, 1.0 eq) in THF/water/MeOH (v/v 2:1:1, 240 mL, 0.28 M) was added LiOH.H₂O (8.4 g, 201 mmol, 3.0 eq). The reaction was stirred at 50°C for 16 h. The reaction was concentrated under reduced pressure and the pH was adjusted to ~3-5 with 2M HCl. The mixture was filtered and purified by prep-HPLC to give 2-(2-chlorophenyl)-4-methoxybenzoic acid (17 g, 65.2 mmol, 97% yield) as a pale yellow solid. MS (ESI): mass calculated for C₁₄H₁₃ClO₃, 262.0; m/z found, 262.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.38 - 12.18 (m, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.38 - 7.32 (m, 2H), 7.30 - 7.25 (m, 1H), 7.06 (dd, J = 2.6, 8.7 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 3.83 (s, 3H).

[00593] **Compound 294** was synthesized in a manner analogous to **Compound 164** using methyl (*R*)-4-fluoroazepane-4-carboxylate and 2-(2-chlorophenyl)-4-methoxybenzoic acid in Step 1.

[00594] **Compound 295** was synthesized in a manner analogous to **Compound 164** using methyl (*S*)-4-fluoroazepane-4-carboxylate and 2-(2-chlorophenyl)-4-methoxy-benzoic acid in Step 1 and (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine in Step 3.

[00595] **Intermediate 2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid** was synthesized in a manner analogous to 2-(2-chlorophenyl)-4-methoxy-benzoic acid using methyl 2-bromo-4-(trifluoromethyl)benzoate.

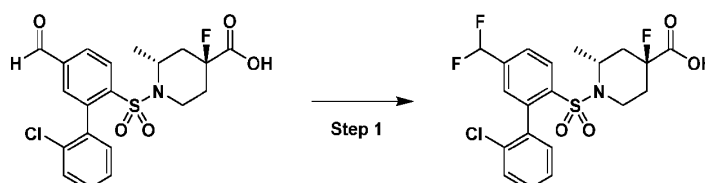
[00596] **Compound 242** was synthesized in a manner analogous to **Compound 165** using 2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid in Step 4.

[00597] **Compound 244** was synthesized in a manner analogous to **Compound 242** using (*R*)-*N*-((*R,E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide in Step 4.

[00598] **Intermediate 2'-chloro-6'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid** was synthesized in a manner analogous to 2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid using 2-chloro-6-fluorophenylboronic acid in Step 1.

[00599] **Compound 245** was synthesized in a manner analogous to **Compound 165** using 2'-chloro-6'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid and (*R*)-*N*-((*R,E*)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide in Step 4.

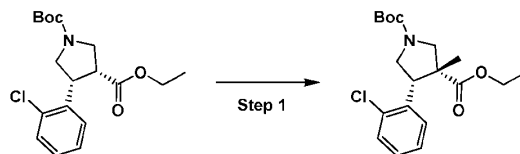
Scheme 68. Synthesis of Intermediate (2*R*,4*S*)-1-((2'-chloro-5-(difluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid



[00600] **Step 1.** To a solution of (2*R*,4*S*)-1-((2'-chloro-5-formyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid (150 mg, 0.340 mmol, 1.0 eq) in DCM (2.0 mL, 0.17 M) was added diethylaminosulfur trifluoride (549 mg, 3.40 mmol, 10 eq) and the solution was stirred at 25°C for 16 h. The reaction was quenched with sat. aq. NaHCO₃ (3 mL) and extracted with DCM (1 mL × 3). The combined organic layers were washed with brine (1 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (PE:EtOAc = 0:1) to give (2*R*,4*S*)-1-((2'-chloro-5-(difluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid (110 mg, 0.240 mmol, 70% yield) as a pale yellow oil.

[00601] **Compound 253** was synthesized in a manner analogous to **Compound 134**, Step 5, using (2*R*,4*S*)-1-((2'-chloro-5-(difluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methylpiperidine-4-carboxylic acid.

Scheme 69. Synthesis of Intermediate 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-3-methylpyrrolidine-1,3-dicarboxylate

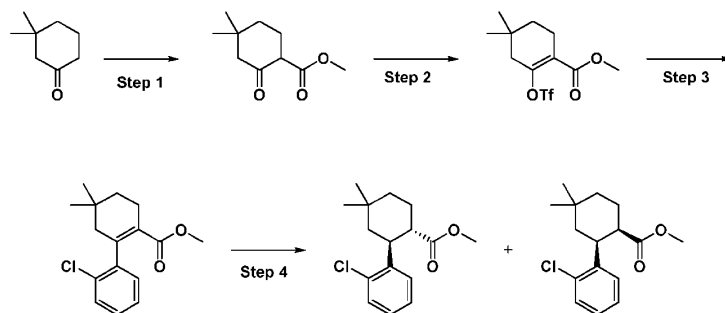


[00602] **Step 1.** To a solution of 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (300 mg, 0.880 mmol, 1.0 eq) and HMPA (506 mg, 2.83 mmol, 3.2 eq) in THF (10 mL, 0.09 M) was added LDA (2.2 mL, 4.41 mmol, 3.0 eq) at -78°C. The solution was stirred at -78°C for 1 h before MeI (250 mg, 1.77 mmol, 2.0 eq) was added. The reaction was stirred at 20°C for 2 h before being poured into water (10 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC to give 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-3-methylpyrrolidine-1,3-dicarboxylate (60 mg, 0.170 mmol, 19% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.38 (br d, *J* = 7.6 Hz, 1H), 7.16 - 7.22 (m, 3H), 4.01 - 4.09 (m, 2H), 3.85 - 3.97 (m, 3H), 3.70 (br d, *J* = 6.8 Hz, 1H), 3.38 (br s, 1H), 1.51 (br s, 9H), 1.45 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

[00603] **Intermediate (3*R*,4*R*)-4-(2-chlorophenyl)-3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid** was synthesized in a manner analogous to (3*R*,4*R*)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid starting from 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)-3-methylpyrrolidine-1,3-dicarboxylate.

[00604] **Compound 254** was synthesized in a manner analogous to **Compound 165** using (3*R*,4*R*)-4-(2-chlorophenyl)-3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylic acid in Step 4.

Scheme 70. Synthesis of Intermediate *rac*-methyl (1*S*,2*S*)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carboxylate



[00605] **Step 1.** To a solution of dimethyl carbonate (4.9 g, 547 mmol, 4.6 eq) in THF (112 mL, 1.0 M) was added NaH (9.6 g, 396 mmol, 2.0 eq, 60%) and 3,3-dimethylcyclohexanone (15 g, 119 mmol, 1.0 eq) at 0°C. The reaction was stirred at 80°C for 4 h. After cooling to rt, the solution was diluted with NH₄Cl (100 mL) and extracted with EtOAc (80 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 0:1 to 5:1) to provide methyl 4,4-dimethyl-

2-oxo-cyclohexanecarboxylate (14 g, 76.0 mmol, 64% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.73 - 3.80 (m, 3H), 2.16 - 2.32 (m, 2H), 2.05 (d, *J* = 2.8 Hz, 2H), 1.34 - 1.43 (m, 2H), 1.18 - 1.27 (m, 1H), 0.92 - 0.98 (m, 6H).

[00606] **Step 2.** To a solution of NaH (2.7 g, 68.4 mmol, 1.8 eq, 60%) in DCM (140 mL, 0.27 M) was added methyl 4,4-dimethyl-2-oxo-cyclohexanecarboxylate (7.0 g, 38.0 mmol, 1.0 eq) at 0°C under N₂. The mixture was stirred at 0°C for 1.5 h before being cooled to -65°C and adding Tf₂O (1.2 g, 42.2 mmol, 1.1 eq) dropwise. The reaction was stirred at -65°C for 30 min then 25°C for 16 h. The reaction was quenched with sat. aq. NH₄Cl (150 mL) and extracted with EtOAc (300 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohexene-1-carboxylate (12 g, 37.9 mmol, quant. yield) as a yellow oil.

[00607] **Step 3.** To a solution of methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohexene-1-carboxylate (12 g, 37.9 mmol, 1.0 eq), 2-chlorophenylboronic acid (7.1 g, 45.5 mmol, 1.2 eq), and K₂CO₃ (15.7 g, 114 mmol, 3.0 eq) in 1,4-dioxane (250 mL) and water (25 mL) was added Pd(dppf)Cl₂ (2.7 g, 3.79 mmol, 0.1 eq) under N₂. The reaction was stirred at 90°C for 16 h. After cooling to rt, the reaction was filtered and concentrated *in vacuo*. The resulting residue was purified by FCC on silica (PE:EtOAc = 100:1 to 10:1) to give methyl 2-(2-chlorophenyl)-4,4-dimethyl-cyclohexene-1-carboxylate (15 g, 53.8 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.20 (dq, *J* = 1.8, 7.3 Hz, 2H), 7.01 (dd, *J* = 2.1, 7.2 Hz, 1H), 3.46 (s, 3H), 2.56 - 2.48 (m, 2H), 2.28 - 2.19 (m, 1H), 2.04 - 1.96 (m, 1H), 1.55 - 1.44 (m, 2H), 1.03 (d, *J* = 11.6 Hz, 6H).

[00608] **Step 4.** To a solution of methyl 2-(2-chlorophenyl)-4,4-dimethyl-cyclohexene-1-carboxylate (6.0 g, 21.5 mmol, 1.0 eq) in methanol (120 mL, 0.18 M) was added Mg (5.2 g, 215 mmol, 10 eq) at 0°C under N₂. The mixture was stirred at 25°C for 3 h before being quenched with 2M HCl (500 mL) and extracted with EtOAc (300 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting residue was purified by prep-HPLC to give *rac*-methyl (1*S*,2*S*)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carboxylate (5.0 g, 17.8 mmol, 83% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.33 (dd, *J* = 0.9, 7.9 Hz, 1H), 7.25 - 7.16 (m, 2H), 7.13 - 7.07 (m, 1H), 3.74 - 3.60 (m, 1H), 3.48 (s, 3H), 2.67 (br s, 1H), 1.99 - 1.79 (m, 2H), 1.68 - 1.50 (m, 2H), 1.40 - 1.31 (m, 1H), 1.12 (s, 4H), 0.95 (s, 3H).

[00609] **Compound 255** was synthesized in a manner analogous to **Compound 158** starting from *rac*-methyl (1*S*,2*S*)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carboxylate.

[00610] **Intermediate *rac*-methyl (3*R*,4*S*)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2*H*-pyran-3-carboxylate** was synthesized in a manner analogous to *rac*-methyl (1*S*,2*S*)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carboxylate starting from 2,2-dimethyltetrahydropyran-4-one.

[00611] **Compound 256** was synthesized in a manner analogous to **Compound 158** starting from *rac*-methyl (3*R*,4*S*)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2*H*-pyran-3-carboxylate.

[00612] Intermediate *rac*-methyl (6*R*,7*R*)-6-(2-chlorophenyl)spiro[3.5]nonane-7-carboxylate was synthesized in a manner analogous to *rac*-methyl (1*S*,2*S*)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carboxylate starting from spiro[3.5]nonan-6-one.

[00613] Compound 257 was synthesized in a manner analogous to Compound 158 starting from *rac*-methyl (6*R*,7*R*)-6-(2-chlorophenyl)spiro[3.5]nonane-7-carboxylate.

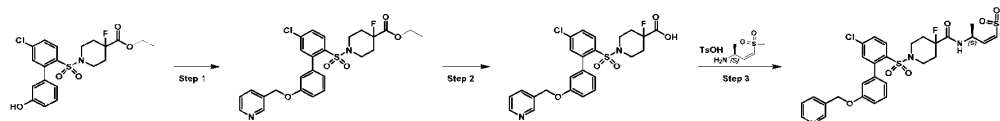
[00614] Intermediate 1-(*tert*-butyl) 4-ethyl 5-(2-chlorophenyl)-3,4-dihydropyridine-1,4(2*H*)-dicarboxylate was synthesized in a manner analogous to *rac*-methyl (1*S*,2*S*)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carboxylate, Steps 2-3, starting with 1-(1,1-dimethylethyl) 4-ethyl 3-oxo-1,4-piperidinedicarboxylate in Step 2.

[00615] Compound 258 was synthesized in a manner analogous to Compound 158 starting from 1-(*tert*-butyl) 4-ethyl 5-(2-chlorophenyl)-3,4-dihydropyridine-1,4(2*H*)-dicarboxylate.

[00616] Intermediate *rac*-1-(*tert*-butyl) 4-ethyl (3*R*,4*S*)-3-(2-chlorophenyl)piperidine-1,4-dicarboxylate was synthesized in a manner analogous to *rac*-methyl (1*S*,2*S*)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carboxylate, Steps 2-4, starting with 1-(1,1-dimethylethyl) 4-ethyl 3-oxo-1,4-piperidinedicarboxylate in Step 2.

[00617] Compound 259 was synthesized in a manner analogous to Compound 158 starting from *rac*-1-(*tert*-butyl) 4-ethyl (3*R*,4*S*)-3-(2-chlorophenyl)piperidine-1,4-dicarboxylate.

Scheme 71. Synthesis of (S,Z)-1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 260)



[00618] **Step 1.** To a solution of ethyl 1-((5-chloro-3'-hydroxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (100 mg, 0.219 mmol, 1.0 eq) in DMF (1.5 mL, 0.15 M) was added 3-(bromomethyl)pyridine (45 mg, 0.263 mmol, 1.2 eq) and potassium carbonate (64 mg, 0.461 mmol, 2.1 eq). The mixture was stirred at 25°C for 16 h before being diluted with H₂O (5.0 mL) and extracted with EtOAc (5.0 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC (PE:EtOAc = 3:1, R_f = 0.2) to give ethyl 1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (60 mg, 0.113 mmol, 51% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.70 (d, *J* = 1.6 Hz, 1H), 8.59 (dd, *J* = 1.4, 4.8 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.80 (td, *J* = 1.9, 7.9 Hz, 1H), 7.47 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.39 - 7.29 (m, 3H), 7.12 - 7.06 (m, 1H), 7.05 - 6.97 (m, 2H), 5.13 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.17 (br d, *J* = 13.2 Hz, 2H), 2.68 - 2.53 (m, 2H), 1.94 - 1.83 (m, 1H), 1.82 - 1.69 (m, 3H), 1.30 - 1.25 (m, 3H).

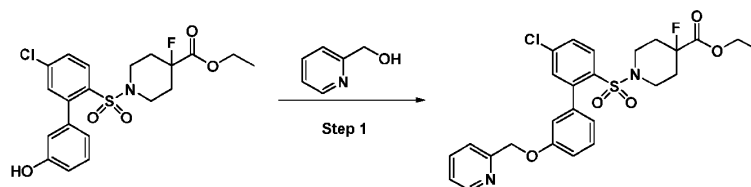
[00619] **Step 2.** To a solution of ethyl 1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (60 mg, 0.113 mmol, 1.0 eq) in THF (1.5 mL, 0.063 M) and water (0.30 mL, 0.063 M) was added LiOH·H₂O (14 mg, 0.338 mmol, 3.0 eq). The mixture was

stirred at 25°C for 2 h before being concentrated under reduced pressure. The resulting residue was acidified with 1N HCl until pH ~3-5. The resulting precipitate was collected by filtration and washed with water (5.0 mL) to afford 1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (40 mg, 0.079 mmol, 57% yield) as a white solid.

[00620] Step 3. To a solution of 1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (40 mg, 0.079 mmol, 1.0 eq) in DCM (2.0 mL, 0.04 M) was added (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine (TsOH salt, 31 mg, 0.095 mmol, 1.2 eq), T₃P (126 mg, 0.198 mmol, 2.5 eq), and DIPEA (31 mg, 0.238 mmol, 3.0 eq). The mixture was stirred at 25°C for 1 h before being diluted with water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting residue was purified by prep-TLC (PE:EtOAc = 1:2) to afford (*S,Z*)-1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (33 mg, 0.050 mmol, 63% yield) as a white solid. MS (ESI): mass calculated for C₂₉H₃₁ClFN₃O₆S₂, 635.1; *m/z* found, 636.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.68 (s, 1H), 8.56 (d, *J* = 3.6 Hz, 1H), 8.41 - 8.33 (m, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.71 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.50 - 7.41 (m, 2H), 7.39 - 7.31 (m, 1H), 7.13 - 7.05 (m, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 10.9 Hz, 1H), 6.27 (dd, *J* = 9.4, 11.1 Hz, 1H), 5.42 - 5.28 (m, 1H), 5.19 (s, 2H), 3.12 (br s, 2H), 3.09 (s, 3H), 2.58 - 2.52 (m, 1H), 2.48 - 2.45 (m, 1H), 1.82 - 1.69 (m, 1H), 1.68 - 1.55 (m, 3H), 1.19 (d, *J* = 6.8 Hz, 3H).

[00621] Compounds 261-266 were synthesized in a manner analogous to **Compound 260** using the appropriate bromide or benzyl chloride in Step 1.

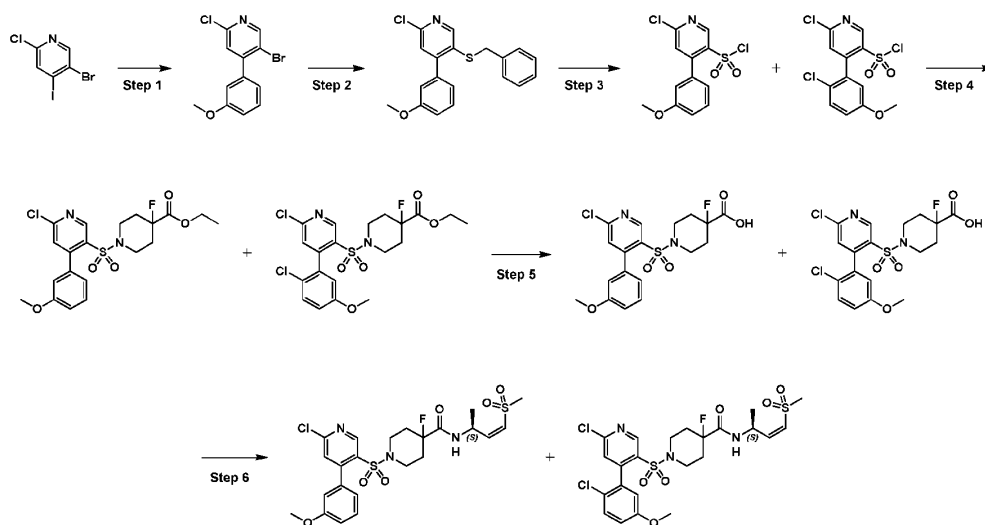
Scheme 72. Synthesis of Intermediate ethyl 1-((5-chloro-3'-(pyridin-2-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate



[00622] Step 1. To a solution of ethyl 1-((5-chloro-3'-hydroxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (4.5 g, 10.2 mmol, 1.0 eq) in THF (60 mL, 0.17 M) was added 2-pyridinemethanol (1.0 mL, 10.2 mmol, 1.0 eq), triphenylphosphine (3.2 g, 12.2 mmol, 1.2 eq), and diisopropyl azodicarboxylate (2.4 mL, 12.2 mmol, 1.2 eq) at 0°C. The mixture was stirred at 25°C for 3 h before being diluted with H₂O (50 mL) and extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting residue was purified by FCC on silica (PE:EtOAc = 40:60) to provide ethyl 1-((5-chloro-3'-(pyridin-2-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (4.1 g, 7.69 mmol, 75% yield) as a colorless oil. [M+H] calculated for C₂₆H₂₆ClFN₂O₅S, 532; found 533.

[00623] **Compound 269** was synthesized in a manner analogous to **Compound 260**, Steps 2-3, using ethyl 1-((5-chloro-3'-(pyridin-2-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate in Step 2.

Scheme 73. Synthesis of (S, Z)-1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 270) and (S, Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 271)



[00624] **Step 1.** To a solution of 5-bromo-2-chloro-4-iodo-pyridine (3.5 g, 11.0 mmol, 1.0 eq) and 3-methoxyphenylboronic acid (1.8 g, 12.1 mmol, 1.1 eq) in toluene/water (v/v 1:1, 42 mL, 0.26 M) was added K_2CO_3 (4.6 g, 33.0 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (1.3 g, 1.10 mmol, 0.1 eq) under N_2 . The reaction was stirred at 90°C for 16 h under N_2 . After cooling to rt, the reaction was quenched with water (30 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (PE:EtOAc = 10:1) to give 5-bromo-2-chloro-4-(3-methoxyphenyl)pyridine (2.0 g, 6.70 mmol, 61% yield) as a yellow oil. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.59 (s, 1H), 7.40 (t, J = 7.9 Hz, 1H), 7.33 (s, 1H), 7.04 - 6.97 (m, 2H), 6.96 - 6.92 (m, 1H), 3.87 (s, 3H).

[00625] **Step 2.** To a solution of 5-bromo-2-chloro-4-(3-methoxyphenyl)pyridine (1.0 g, 3.35 mmol, 1.0 eq) in 1,4-dioxane (15 mL, 0.22 M) was added benzyl mercaptan (624 mg, 5.02 mmol, 1.5 eq), DIPEA (866 mg, 6.70 mmol, 2.0 eq), and XantPhos (194 mg, 0.335 mmol, 0.1 eq). The reaction was purged with N_2 before addition of $Pd_2(dba)_3$ (307 mg, 0.335 mmol, 0.1 eq). The mixture was stirred at 80°C for 15 h. After cooling to rt, the mixture was poured into water (50 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO_2 , PE:EtOAc = 8:1) to give 5-(benzylthio)-2-chloro-4-(3-methoxyphenyl)pyridine (500 mg, 1.46 mmol, 44% yield) as

a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.31 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.26 - 7.20 (m, 4H), 7.18 - 7.11 (m, 2H), 7.02 - 6.90 (m, 3H), 3.91 (s, 2H), 3.85 (s, 3H).

[00626] **Step 3.** To a solution of 5-benzylsulfanyl-2-chloro-4-(3-methoxyphenyl)pyridine (500 mg, 1.46 mmol, 1.0 eq) dissolved in CCl₄ (12 mL) was added water (4.0 mL) at 0°C. Chlorine gas was passed through the stirred solution for 30 min at 0°C before the solution was purged with N₂ to remove excess chlorine gas. The aq. layer was extracted with DCM (30 mL × 2) and the combined organic layers were dried with anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to give a mixture of 6-chloro-4-(3-methoxyphenyl)pyridine-3-sulfonyl chloride and 6-chloro-4-(2-chloro-5-methoxyphenyl)pyridine-3-sulfonyl chloride in a 1:5 ratio (350 mg, 1.10 mmol, 75% yield).

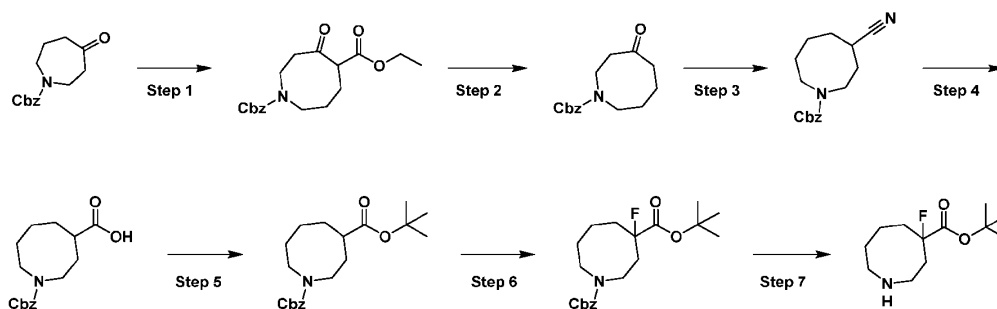
[00627] **Step 4.** At 0°C, a mixture of 6-chloro-4-(3-methoxyphenyl)pyridine-3-sulfonyl chloride and 6-chloro-4-(2-chloro-5-methoxyphenyl)pyridine-3-sulfonyl chloride (338 mg, 1.06 mmol, 1.5 eq) was added to ethyl 4-fluoropiperidine-4-carboxylate hydrochloride (150 mg, 0.709 mmol, 1.0 eq) and TEA (143 mg, 1.42 mmol, 2.0 eq) in DCM (5.0 mL, 0.14 M). The resulting mixture was stirred at 25°C for 2 h before being poured into water (15 mL) and extracted with DCM (15 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc= 3:1) to give a mixture of ethyl 1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate and ethyl 1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate in a 1:5 ratio (80 mg, 0.175 mmol, 25% yield).

[00628] **Step 5.** To a solution of ethyl 1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate and ethyl 1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (80 mg, 0.175 mmol, 1.0 eq) in THF (3.2 mL, 0.041 M) and water (1.1 mL, 0.041 M) was added LiOH.H₂O (59 mg, 1.40 mmol, 8.0 eq). The mixture was stirred at 50°C for 3 h. After cooling to rt, the mixture was acidified with 1N HCl to pH ~4 then poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to give a mixture of 1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid and 1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid in a 1:5 ratio (75 mg, 0.187 mmol, quant. yield).

[00629] **Step 6.** HATU (106 mg, 0.280 mmol, 1.5 eq) was added to a mixture of 1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid and 1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (80 mg, 0.187 mmol, 1.0 eq), (*S,Z*)-4-(methylsulfonyl)but-3-en-2-amine (as TsOH salt, 60 mg, 0.187 mmol, 1.0 eq), and DIPEA (60 mg, 0.466 mmol, 2.5 eq) in DCM (3.0 mL, 0.062 M). The reaction was stirred at 25°C for 2 h before being poured into H₂O (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (32-62% ACN in 10 mM aq. NH₄HCO₃) to give two products: (*S,Z*)-1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-*N*-(4-

(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (4.9 mg, 0.008 mmol, 4% yield) as a white solid. MS (ESI): mass calculated for $C_{23}H_{27}ClFN_3O_6S_2$, 559.1; m/z found, 560.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 9.06 - 8.83 (m, 1H), 8.35 (br s, 1H), 7.63 (br d, J = 11.9 Hz, 1H), 7.37 (br s, 1H), 7.03 (br s, 3H), 6.54 - 6.37 (m, 1H), 6.25 (br s, 1H), 5.33 (br s, 1H), 3.86 - 3.71 (m, 3H), 3.30 (br s, 3H), 3.20 - 3.07 (m, 4H), 1.64 (br s, 4H), 1.18 (br d, J = 6.8 Hz, 3H) and (S, Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (25 mg, 0.041 mmol, 22% yield) as a white solid. MS (ESI): mass calculated for $C_{23}H_{26}Cl_2FN_3O_6S_2$, 593.1; m/z found, 594.1 $[M+H]^+$. 1H NMR (400 MHz, Methanol- d_4) δ ppm 9.01 (s, 1H), 7.50 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.07 - 7.02 (m, 1H), 7.02 - 6.99 (m, 1H), 6.39 (d, J = 11.0 Hz, 1H), 6.28 - 6.18 (m, 1H), 5.49 - 5.38 (m, 1H), 3.82 (s, 3H), 3.37 (br s, 1H), 3.24 - 3.15 (m, 2H), 3.13 (s, 3H), 2.92 (br t, J = 13.0 Hz, 1H), 2.70 (br t, J = 12.9 Hz, 1H), 2.15 - 1.89 (m, 2H), 1.83 - 1.65 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H).

Scheme 74. Synthesis of Intermediate *tert*-butyl 4-fluoroazocane-4-carboxylate



[00630] Step 1. A solution of benzyl 4-oxoazepane-1-carboxylate (6.0 g, 24.3 mmol, 1.0 eq) in THF (120 mL, 0.2 M) was placed under N_2 and cooled to $-60^\circ C$. To this was added ethyl diazoacetate (4.1 g, 34.0 mmol, 1.4 eq) and trifluoroborane (4.0 g, 27.9 mmol, 1.2 eq). The reaction was stirred at $-60^\circ C$ for 1 hour then $25^\circ C$ for 16 hours. The mixture was diluted with H_2O (150 mL) and extracted with EtOAc (200 mL $\times$ 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 7:3) to give 1-benzyl 5-ethyl 4-oxoazocane-1,5-dicarboxylate (1.1 g, 3.30 mmol, 14% yield) as a yellow oil.

[00631] Step 2. To a solution of 1-benzyl 5-ethyl 4-oxoazocane-1,5-dicarboxylate (2.5 g, 7.50 mmol, 1.0 eq) in ethanol (25 mL, 0.3 M) was added potassium hydroxide (24 mL, 24 mmol, 3.2 eq). The reaction was stirred at $80^\circ C$ for 3 h. After cooling to rt, the mixture was evaporated, diluted with H_2O (20 mL), and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give benzyl 4-oxoazocane-1-carboxylate (1.8 g, 6.89 mmol, 91% yield) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.43 (m, 5H), 5.17 (s, 2H), 3.63 - 3.74 (m, 2H), 3.22 (dt, J = 16.2, 6.2 Hz, 2H), 2.56 - 2.68 (m, 2H), 2.38 - 2.44 (m, 2H), 1.59 - 1.96 (m, 4H).

[00632] **Step 3.** To a solution of benzyl 4-oxoazocane-1-carboxylate (1.8 g, 6.89 mmol, 1.0 eq) in DME (18 mL) was added 1-(isocyanomethane)sulfonyl-4-methylbenzene (1.7 g, 8.61 mmol, 1.3 eq) and ethanol (0.5 g, 11.7 mmol, 1.7 eq) at 15°C. The mixture was then cooled to 0°C and potassium *tert*-butoxide (7.6 mL, 7.58 mmol, 1.1 eq) was added slowly. After stirring at 40°C for 16 hours, the reaction was filtered through celite and washed with EtOAc (40 mL). The organic phase was concentrated under reduced pressure and the resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 7:3) to afford benzyl 4-cyanoazocane-1-carboxylate (1.5 g, 5.51 mmol, 80% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.22 - 7.35 (m, 5H), 5.01 - 5.16 (m, 2H), 3.27 - 3.63 (m, 3H), 3.07 - 3.25 (m, 1H), 2.61 - 2.82 (m, 1H), 1.61 - 2.12 (m, 8H).

[00633] **Step 4.** To a solution of benzyl 4-cyanoazocane-1-carboxylate (0.5 g, 1.84 mmol, 1.0 eq) in glycol/water (v/v 1:1, 10 mL, 0.22 M) was added potassium hydroxide (515 mg, 9.18 mmol, 5.0 eq) and the mixture was stirred at 120°C for 16 hours under N₂. After cooling to rt, the reaction was diluted with water (10 mL) and acidified with 1N HCl until pH ~2. The mixture was extracted with EtOAc (30 mL × 3) and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated to give 1-((benzyloxy)carbonyl)azocane-4-carboxylic acid (0.2 g, 0.690 mmol, 37% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.21 - 7.33 (m, 5H), 4.99 - 5.27 (m, 2H), 3.48 - 3.59 (m, 1H), 3.28 - 3.38 (m, 3H), 2.37 - 2.53 (m, 1H), 1.52 - 2.05 (m, 8H).

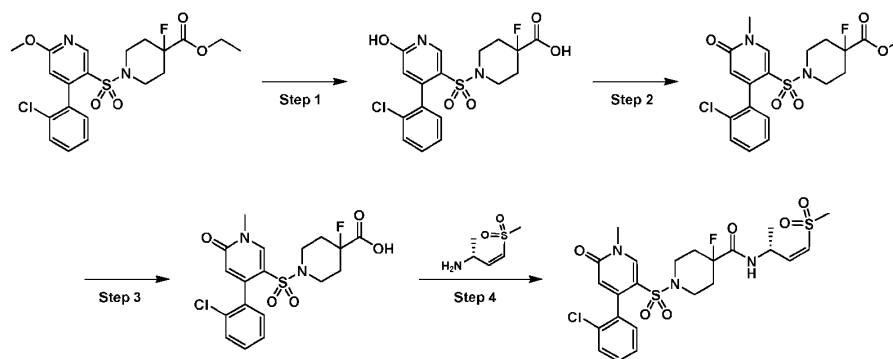
[00634] **Step 5.** To a solution of 1-((benzyloxy)carbonyl)azocane-4-carboxylic acid (1.2 g, 4.12 mmol, 1.0 eq) and 4-(dimethylamino)pyridine (302 mg, 2.47 mmol, 0.6 eq) in *tert*-butanol (20 mL, 0.21 M) was added di-*tert*-butyl dicarbonate (0.9 g, 4.12 mmol, 1.0 eq) in *t*-BuOH (200 mL) at 10-15°C. The solution was stirred at 15°C for 12 hours before being poured into water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 100:1 - 5:1) to give 1-benzyl 4-(*tert*-butyl) azocane-1,4-dicarboxylate (500 mg, 1.44 mmol, 35% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.30 - 7.49 (m, 5H), 5.10 - 5.24 (m, 2H), 3.52 - 3.70 (m, 1H), 3.32 - 3.51 (m, 3H), 2.34 - 2.47 (m, 1H), 1.60 - 2.05 (m, 8H), 1.43 (br d, *J* = 5.8 Hz, 9H).

[00635] **Step 6.** To a solution of 1-benzyl 4-(*tert*-butyl) azocane-1,4-dicarboxylate (500 mg, 1.44 mmol, 1.0 eq) in THF (5 mL, 0.02 M) was added lithium diisopropylazide (1.4 mL, 2.88 mmol, 2.0 eq) dropwise at -60°C and the mixture was stirred at -45°C for 1 hour. To the mixture was added *N*-fluorobenzenesulfonimide (681 mg, 2.16 mmol, 1.5 eq) in THF (3 mL, 0.21 M) dropwise and the resulting solution was stirred at -45°C for 1 hour then 15°C for 1 hour. The reaction was quenched with sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phases were washed with brine (50 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 100:0 - 19:1) to give 1-benzyl 4-(*tert*-butyl) 4-fluoroazocane-1,4-dicarboxylate (150 mg, 0.410 mmol, 28% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.19 - 7.47 (m, 5H), 5.04 - 5.28 (m, 2H), 3.51 - 3.80 (m, 4H), 2.13 - 2.44 (m, 1H), 1.90 - 2.09 (m, 3H), 1.52 - 1.73 (m, 4H), 1.33 - 1.47 (m, 9H).

[00636] **Step 7.** To a solution of 1-benzyl 4-(*tert*-butyl) 4-fluoroazocane-1,4-dicarboxylate (150 mg, 0.410 mmol, 1.0 eq) in methanol (20 mL, 0.02 M) was added 5% Pd/C (80 mg, with ca. 55% water). The reaction was stirred at 25°C under H₂ (15 psi) for 16 hours. The mixture was filtered and the filtrate evaporated to give *tert*-butyl 4-fluoroazocane-4-carboxylate (80 mg, 0.350 mmol, 84% yield) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.67 (dt, *J* = 13.6, 6.8 Hz, 2H), 2.83 - 3.13 (m, 2H), 2.06 - 2.32 (m, 3H), 1.53 - 2.01 (m, 5H), 1.20 (d, *J* = 6.8 Hz, 9H).

[00637] **Compound 272** was synthesized in a manner analogous to **Compound 164** using *tert*-butyl 4-fluoroazocane-4-carboxylate in Step 1 and (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine in Step 3.

Scheme 75. Synthesis of (*R,Z*)-1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 274)



[00638] **Step 1.** To a solution of ethyl 1-[[4-(2-chlorophenyl)-6-methoxy-3-pyridyl]sulfonyl]-4-fluoropiperidine-4-carboxylate (350 mg, 0.766 mmol, 1.0 eq) in acetic acid (4.0 mL, 0.19 M) was added HCl (4.0 mL, 0.19 M). The mixture was stirred at 80°C for 3 h. After cooling to rt, the mixture was concentrated under reduced pressure to give 1-((4-(2-chlorophenyl)-6-hydroxypyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (300 mg, 0.723 mmol, 94% yield) as a yellow solid. MS (ESI): mass calculated for C₁₈H₁₈ClFN₂O₅S, 428.1; *m/z* found, 429.1.

[00639] **Step 2.** A solution of 1-((4-(2-chlorophenyl)-6-hydroxypyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (100 mg, 0.241 mmol, 1.0 eq) in DMF (2.0 mL, 0.12 M) was degassed and purged with N₂ for 3 times. NaH (29 mg, 0.723 mmol, 3.0 eq) was added to the mixture at 0°C and this was stirred at 0°C for 0.5 h. Iodomethane (171 mg, 1.20 mmol, 5.0 eq) was added dropwise and the mixture was stirred at 0°C for 16 h. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (20 mL). The extract was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (PE:EtOAc = 1:1) to afford methyl 1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (80 mg, 0.180 mmol, 75% yield) as a colorless oil. MS (ESI): mass calculated for C₁₉H₂₀ClFN₂O₅S, 442.1; *m/z* found, 443.1. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.25 (s,

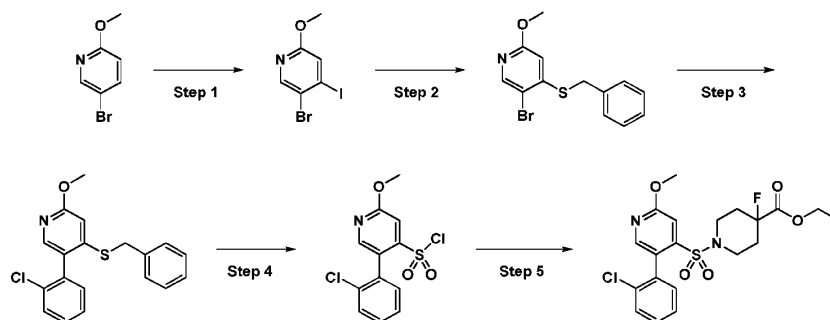
1H), 7.51 - 7.44 (m, 1H), 7.41 - 7.29 (m, 3H), 6.42 (s, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.27 - 3.12 (m, 1H), 3.03 - 2.96 (m, 2H), 2.72 - 2.53 (m, 1H), 2.04 - 1.72 (m, 4H).

[00640] Step 3. To a solution of methyl 1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (80 mg, 0.181 mmol, 1.0 eq) in THF (2.0 mL, 0.067 M) and water (0.70 mL, 0.067 M) was added LiOH.H₂O (23 mg, 0.542 mmol, 3.0 eq). The reaction mixture was stirred at 25°C for 2 h before being concentrated to remove THF. The resulting residue was acidified with 1N HCl until pH ~3-5. The resulting precipitate was collected by filtration to afford 1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (60 mg, 0.140 mmol, 77% yield) as a white solid.

[00641] Step 4. To a solution of 1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (60 mg, 0.140 mmol, 1.0 eq) in DCM (3.0 mL, 0.046 M) was added (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine (54 mg, 0.168 mmol, 1.2 eq), T₃P (223 mg, 0.349 mmol, 2.5 eq), and DIPEA (541 mg, 0.419 mmol, 3.0 eq). The reaction was stirred at 25°C for 1 h before being diluted with H₂O (10 mL) and extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC (PE:EtOAc = 0:1) to afford (*R,Z*)-1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (44 mg, 0.078 mmol, 56% yield) as a white solid. MS (ESI): mass calculated for C₂₃H₂₇ClFN₃O₆S₂, 559.1; m/z found, 560.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 8.36 (br d, *J* = 6.0 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.46 (d, *J* = 11.3 Hz, 1H), 6.35 - 6.22 (m, 2H), 5.49 - 5.23 (m, 1H), 3.58 (s, 3H), 3.18 - 2.96 (m, 5H), 2.73 - 2.55 (m, 2H), 1.98 - 1.66 (m, 4H), 1.21 (d, *J* = 6.9 Hz, 3H).

[00642] Compound 276 was synthesized in a manner analogous to **Compound 274**, Step 5 using 1-((4-(2-chlorophenyl)-6-hydroxypyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid.

Scheme 76. Synthesis of Intermediate ethyl 1-((5-(2-chlorophenyl)-2-methoxypyridin-4-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate



[00643] Step 1. A solution of 5-bromo-2-methoxypyridine (5.0 g, 26.6 mmol, 1.0 eq) in anhydrous THF (100 mL, 0.27 M) was degassed and purged with N₂. LDA (10.5 mL, 29.3 mmol, 1.1 eq, 2 M in THF) was added dropwise at -78°C. The mixture was stirred for 1 h at -78°C before a solution of iodine

(6.7 g, 26.6 mmol, 1.0 eq) in anhydrous THF (30 mL) was added dropwise at over 30 min. The reaction was allowed to warm to rt and was stirred for 16 h. The reaction was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (60 mL) and extracted with MTBE (50 mL $\times$ 3). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 , filtered, and concentration under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 0:1) to give 5-bromo-4-iodo-2-methoxypyridine (7.7 g, 12.3 mmol, 46% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.28 - 8.22 (m, 1 H), 7.36 - 7.29 (m, 1 H), 3.90 - 3.89 (m, 3 H).

[00644] Step 2. To a stirred solution of 5-bromo-4-iodo-2-methoxypyridine (4.7 g, 9.73 mmol, 1.0 eq) in DMSO (47 mL, 0.20 M) was added phenylthioalcohol (1.2 g, 9.73 mmol, 1.0 eq) and K_2CO_3 (2.0 g, 14.6 mmol, 1.5 eq) at 0°C. The reaction was stirred at 55°C for 3 h. After cooling to rt, the mixture was poured into water (300 mL) and extracted with EtOAc (200 mL $\times$ 3). The combined organic layers were washed with brine (600 mL $\times$ 3), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by FCC on silica (PE:EtOAc = 1:0 to 20:1) to give 4-(benzylthio)-5-bromo-2-methoxypyridine (2.2 g, 7.22 mmol, 74% yield) as a yellow solid. MS (ESI): mass calculated for $\text{C}_{13}\text{H}_{12}\text{BrNOS}$, 309.0; m/z found, 310.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.10 (s, 1 H), 7.50 - 7.40 (m, 2 H), 7.40 - 7.28 (m, 3 H), 6.55 (s, 1 H), 4.16 (s, 2 H), 3.89 (s, 3 H).

[00645] Step 3. A mixture of 4-(benzylthio)-5-bromo-2-methoxypyridine (400 mg, 1.29 mmol, 1.0 eq), (2-chlorophenyl)boronic acid (242 mg, 1.55 mmol, 1.2 eq), $\text{Pd}(\text{OAc})_2$ (29 mg, 0.129 mmol, 0.10 eq), PPh_3 (68 mg, 0.258 mmol, 0.20 eq), and K_2CO_3 (356 mg, 2.58 mmol, 2.0 eq) in toluene/water (v/v 10:1, 2.2 mL, 0.59 M) was placed under N_2 . The reaction was stirred at 100°C for 16 h. After cooling to rt, the mixture was filtered and the filtrate concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 to 49:1) to give 4-(benzylthio)-5-(2-chlorophenyl)-2-methoxypyridine (250 mg, 0.731 mmol, 57% yield) as a colorless oil. MS (ESI): mass calculated for $\text{C}_{19}\text{H}_{16}\text{ClNOS}$, 341.1; m/z found, 342.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.84 (s, 1H), 7.48 (d, J = 7.3 Hz, 1 H), 7.40 - 7.27 (m, 7 H), 7.26 (d, J = 3.8 Hz, 1 H), 6.66 (s, 1 H), 4.13 - 4.10 (m, 2 H), 3.96 (s, 3 H).

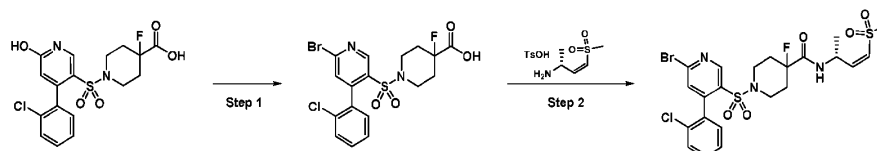
[00646] Step 4. To a solution of 4-(benzylthio)-5-(2-chlorophenyl)-2-methoxypyridine (250 mg, 0.731 mmol, 1.0 eq) in acetic acid/water (v/v 3:1, 4.0 mL, 0.18 M) was added NCS (391 mg, 2.93 mmol, 4.0 eq) at 0°C. The reaction was stirred at 25°C for 2 h before being diluted with H_2O (60 mL) and extracted with ethyl acetate (30 mL $\times$ 2). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 to 49:1) to give 5-(2-chlorophenyl)-2-methoxypyridine-4-sulfonyl chloride (218 mg, 0.685 mmol, 94% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.14 (s, 1 H), 7.44 - 7.41 (m, 1 H), 7.36 - 7.28 (m, 3 H), 7.17 (s, 1 H), 3.99 (s, 3 H).

[00647] Step 5. To a solution of ethyl 4-fluoropiperidine-4-carboxylate HCl (160 mg, 0.754 mmol, 1.1 eq) in DCM (5.0 mL, 0.14 M) was added TEA (208 mg, 2.06 mmol, 3.0 eq) and 5-(2-chlorophenyl)-2-methoxypyridine-4-sulfonyl chloride (218 mg, 0.685 mmol, 1.0 eq) in DCM (5.0 mL, 0.14 M) at 0°C. The reaction was stirred at 25°C for 1 h before being poured into water (30 mL) and extracted with

EtOAc (20 mL $\times$ 2). The combined organic layers were washed with brine (40 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 to 5:1) to give ethyl 1-((5-(2-chlorophenyl)-2-methoxypyridin-4-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate (230 mg, 0.503 mmol, 73% yield) as a colorless oil. MS (ESI): mass calculated for $\text{C}_{20}\text{H}_{22}\text{ClFN}_2\text{O}_5\text{S}$, 456.1; m/z found, 457.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.11 (s, 1 H), 7.50 (dd, $J = 1.7, 7.6$ Hz, 1 H), 7.47 - 7.42 (m, 2 H), 7.39 - 7.32 (m, 2 H), 4.23 (q, $J = 7.1$ Hz, 2 H), 4.05 (s, 3 H), 3.30 (td, $J = 2.3, 13.3$ Hz, 1 H), 3.09 (td, $J = 2.4, 13.4$ Hz, 1 H), 2.95 (dt, $J = 2.9, 12.7$ Hz, 1 H), 2.66 (dt, $J = 2.8, 12.9$ Hz, 1 H), 2.05 - 1.77 (m, 4 H), 1.32 - 1.28 (m, 3 H).

[00648] **Compound 275** was synthesized in a manner analogous to **Compound 274** starting with ethyl 1-((5-(2-chlorophenyl)-2-methoxypyridin-4-yl)sulfonyl)-4-fluoropiperidine-4-carboxylate in Step 1.

Scheme 77. Synthesis of (*R,Z*)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (Compound 277)



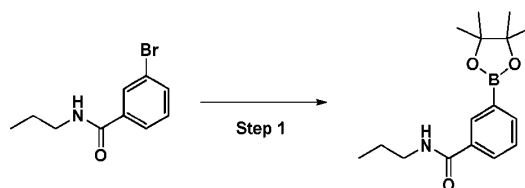
[00649] **Step 1.** To a solution of 1-((4-(2-chlorophenyl)-6-hydroxypyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (100 mg, 0.241 mmol, 1.0 eq) in MeCN (1.0 mL, 0.24 M) was added POBr_3 (138 mg, 0.482 mmol, 2.0 eq). The reaction was stirred at 85°C for 3 h under N_2 . After cooling to rt, the mixture was quenched with H_2O (5.0 mL) and extracted with EtOAc (5.0 mL $\times$ 2). The combined organic layers were washed with brine (5.0 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (SiO_2 , PE:EtOAc = 3:1) to give 1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (60 mg, 0.126 mmol, 52% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 9.07 (s, 1H), 7.56 - 7.47 (m, 2H), 7.47 - 7.37 (m, 3H), 3.33 (br d, $J = 12.0$ Hz, 1H), 3.12 (br d, $J = 14.3$ Hz, 1H), 3.03 - 2.90 (m, 1H), 2.68 (br t, $J = 12.9$ Hz, 1H), 2.02 - 1.80 (m, 4H).

[00650] **Step 2.** To a solution of 1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoropiperidine-4-carboxylic acid (60 mg, 0.126 mmol, 1.0 eq) in DCM (1.0 mL, 0.13 M) was added (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine (TsOH salt, 48 mg, 0.151 mmol, 1.2 eq), DIPEA (65 mg, 0.502 mmol, 4.0 eq), and T_3P (80 mg, 0.251 mmol, 2.0 eq). The reaction was stirred at 25°C for 1 h before being quenched with H_2O (5.0 mL) and extracted with DCM (5.0 mL $\times$ 2). The combined organic layers were washed with brine (5.0 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (100% EtOAc) to give (*R,Z*)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-*N*-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (85 mg, 0.136 mmol, 97% yield) as a white solid. MS (ESI): mass calculated for $\text{C}_{22}\text{H}_{24}\text{BrClFN}_3\text{O}_5\text{S}_2$, 607.0; m/z found, 608.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.95 (s, 1H), 8.44 - 8.35 (m, 1H), 7.86 (s, 1H), 7.61 - 7.57 (m, 1H), 7.53 - 7.47 (m, 1H), 7.44 (d, $J = 4.1$ Hz, 2H),

6.45 (d, $J = 11.1$ Hz, 1H), 6.28 (dd, $J = 9.4, 11.2$ Hz, 1H), 5.38 - 5.29 (m, 1H), 3.20 (br d, $J = 13.0$ Hz, 2H), 3.11 (s, 3H), 2.84 - 2.73 (m, 1H), 2.65 (br t, $J = 11.2$ Hz, 1H), 1.95 - 1.67 (m, 4H), 1.20 (d, $J = 6.8$ Hz, 3H).

[00651] **Compound 278** was synthesized in a manner analogous to **Compound 277** using (*E*)-4-aminobut-2-enenitrile in Step 2.

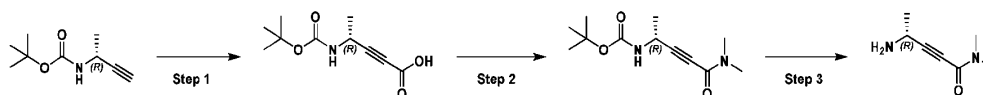
Scheme 78. Synthesis of Intermediate *N*-propyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



[00652] **Step 1.** To a solution of 3-bromo-*N*-propylbenzamide (400 mg, 1.65 mmol, 1.0 eq) in 1,4-dioxane (10 mL, 0.17 M) was added bis(pinacolato)diboron (503 mg, 1.98 mmol, 1.2 eq), potassium acetate (515 mg, 4.95 mmol, 3.0 eq), and Pd(dppf)Cl₂ (100 mg, 0.165 mmol, 0.1 eq). The reaction was stirred at 100°C under N₂ for 12 h. After cooling to rt, the mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 9:1 - 7:3) to give *N*-propyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (430 mg, 1.48 mmol, 90% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.07 (s, 1H), 8.01 - 7.89 (m, 2H), 7.46 (t, $J = 7.6$ Hz, 1H), 6.25 (br s, 1H), 3.46 - 3.39 (m, 2H), 1.65 (dq, $J = 14.6, 7.4$ Hz, 2H), 1.36 (s, 12H), 0.99 (t, $J = 7.4$ Hz, 3H).

[00653] **Compound 279** was synthesized in a manner analogous to **Compound 1** using *N*-propyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide in Step 3.

Scheme 79. Synthesis of Intermediate (*R*)-4-amino-*N,N*-dimethylpent-2-ynamide



[00654] **Step 1.** A solution of *tert*-butyl *N*-[(1*R*)-1-methylprop-2-ynyl]carbamate (500 mg, 2.95 mmol, 1.0 eq) in anhydrous THF (8.0 mL, 0.37 M) was purged with N₂ and cooled to -60°C. To the solution was added *n*-BuLi (2.6 mL, 5.9 mmol, 2.0 eq) and the mixture was stirred at -60°C for 0.5 h. CO₂ (dry ice, ~5 g) was added and the mixture was stirred at 20°C for 2 h. The reaction mixture was quenched with 1N HCl to adjust pH to 2-3 then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give (4*R*)-4-(*tert*-butoxycarbonylamino)pent-2-ynoic acid (400 mg, 1.88 mmol, 63% yield) as a yellow oil. ¹H

NMR (400 MHz, CDCl_3) δ ppm 9.88 (br s, 1H), 4.97 - 4.54 (m, 1H), 1.65 - 1.49 (m, 3H), 1.48 - 1.44 (m, 9H).

[00655] Step 2. To a solution of (4*R*)-4-(*tert*-butoxycarbonylamino)pent-2-ynoic acid (200 mg, 0.938 mmol, 1.0 eq) in DMF (2.5 mL, 0.38 M) was added HATU (535 mg, 1.41 mmol, 1.5 eq), DIPEA (0.39 mL, 2.34 mmol, 2.5 eq), and dimethylamine (42 mg, 0.938 mmol, 1.0 eq). The reaction was stirred at 20°C for 1h before being diluted with H_2O (40 mL) and extracted with EtOAc (80 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (DCM:MeOH = 10:1) to afford *tert*-butyl *N*-[(1*R*)-4-(dimethylamino)-1-methyl-4-oxo-but-2-ynyl]carbamate (130 mg, 0.541 mmol, 58% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.82 - 4.61 (m, 1H), 2.81 (s, 6H), 1.72 (d, J = 7.0 Hz, 3H), 1.48 - 1.46 (m, 9 H).

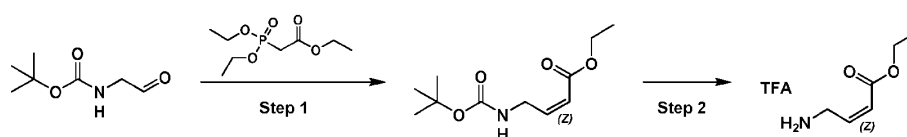
[00656] Step 3. To a solution of *tert*-butyl *N*-[(1*R*)-4-(dimethylamino)-1-methyl-4-oxo-but-2-ynyl]carbamate (130 mg, 0.541 mmol, 1.0 eq) in DCM (3.0 mL, 0.21 M) was added trifluoroacetic acid (1.0 mL, 0.21 M). The reaction was stirred at 20°C for 1 h before being concentrated *in vacuo* to afford (*R*)-4-amino-*N,N*-dimethylpent-2-ynamide (65 mg, 0.460 mmol, 86% yield) as a yellow oil. This was used in the next step directly. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.50 - 4.42 (m, 1H), 2.92 (s, 3H), 2.81 (s, 3H), 1.82 (d, J = 7.0 Hz, 3H).

[00657] Intermediate (*S*)-4-amino-*N,N*-dimethylpent-2-ynamide was synthesized in a manner analogous to (*R*)-4-amino-*N,N*-dimethylpent-2-ynamide starting with *tert*-butyl *N*-[(1*S*)-1-methylprop-2-ynyl]carbamate.

[00658] Compound 280 was synthesized in a manner analogous to **Compound 47** using (*R*)-4-amino-*N,N*-dimethylpent-2-ynamide in Step 5.

[00659] Compound 281 was synthesized in a manner analogous to **Compound 47** using (*S*)-4-amino-*N,N*-dimethylpent-2-ynamide in Step 5.

Scheme 80. Synthesis of Intermediate ethyl (*Z*)-4-aminobut-2-enoate



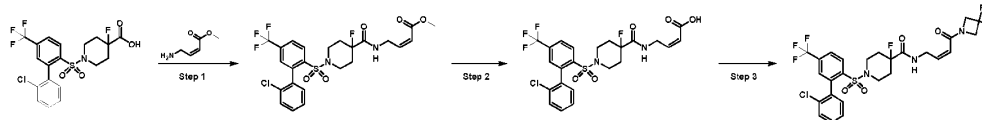
[00660] Step 1. To a solution of ethyl 2-(diethoxyphosphoryl)acetate (6.0 g, 26.8 mmol, 1.2 eq) in THF (40 mL, 0.56 M) was added LiHMDS (19 mL, 1.4 eq) at -70°C. This was stirred 1 h before addition of *tert*-butyl (2-oxoethyl)carbamate (3.5 g, 22.0 mmol, 1.0 eq). The reaction was stirred at -70°C for 1 h before being quenched with NH_4Cl (40 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 to 5:1) to give (*Z*)-ethyl 4-((*tert*-butoxycarbonyl)amino)but-2-enoate (3.0 g, 13.1 mmol, 59% yield) as a colorless oil. ^1H NMR (400

MHz, DMSO- d_6) δ ppm 6.28 (dt, $J = 11.3, 5.8$ Hz, 1H), 5.83 (dt, $J = 11.5, 1.8$ Hz, 1H), 4.99 (br s, 1H), 4.25 (br t, $J = 4.9$ Hz, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 1.45 (s, 9H), 1.29 (t, $J = 7.1$ Hz, 3H).

[00661] **Step 2.** A solution of (Z)-ethyl 4-((*tert*-butoxycarbonyl)amino)but-2-enoate (0.30 g, 1.31 mmol, 1.0 eq) in DCM (7.5 mL, 0.13 M) and trifluoroacetic acid (2.5 mL, 0.13 M) was stirred at 15°C for 2 h. The solution was concentrated under reduced pressure to give (Z)-ethyl 4-aminobut-2-enoate (as TFA salt, 150 mg, 1.16 mmol, 89% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.24 (br s, 2H), 6.41 - 6.28 (m, 1H), 6.07 (br d, $J = 11.4$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.12 - 4.04 (m, 2H), 1.29 (t, $J = 7.1$ Hz, 3H).

[00662] **Intermediate methyl (Z)-4-aminobut-2-enoate** was synthesized in a manner analogous to ethyl (Z)-4-aminobut-2-enoate.

Scheme 81. Synthesis of (Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide (Compound 284)



[00663] **Step 1.** To a solution of 1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoropiperidine-4-carboxylic acid (350 mg, 0.750 mmol, 1.0 eq) in DCM (5.0 mL, 0.15 M) was added methyl (Z)-4-aminobut-2-enoate (103 mg, 0.900 mmol, 1.2 eq), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (358 mg, 1.13 mmol, 1.5 eq), and DIPEA (243 mg, 1.88 mmol, 2.5 eq). The reaction was stirred at 25°C for 1 h before being poured into water (5 mL) and extracted with DCM (15 mL $\times$ 3). The combined organic layers were washed with brine (15 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (PE:EtOAc = 1:1) to afford methyl (Z)-4-[[1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoropiperidine-4-carboxyl]amino]but-2-enoate (240 mg, 0.430 mmol, 57% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.30 (d, $J = 8.4$ Hz, 1H), 7.80 (dd, $J = 8.4, 1.3$ Hz, 1H), 7.59 (d, $J = 1.1$ Hz, 1H), 7.54 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.43 - 7.47 (m, 1H), 7.33 - 7.42 (m, 2H), 6.85 - 6.95 (t, 1H), 6.23 (dt, $J = 11.4, 6.5$ Hz, 1H), 5.91 (d, $J = 11.5$ Hz, 1H), 4.37 (td, $J = 6.3, 1.1$ Hz, 2H), 3.74 (s, 3H), 3.28 (dt, $J = 13.2, 2.1$ Hz, 1H), 3.12 (dt, $J = 13.2, 2.1$ Hz, 1H), 2.92 (td, $J = 12.7, 2.9$ Hz, 1H), 2.69 (td, $J = 12.8, 2.9$ Hz, 1H), 1.93 - 2.30 (m, 2H), 1.70 (br s, 2H).

[00664] **Step 2.** To a solution of methyl (Z)-4-[[1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoropiperidine-4-carboxyl]amino]but-2-enoate (240 mg, 0.430 mmol, 1.0 eq) in DCE (10 mL, 0.04 M) was added hydroxy(trimethyl)stannane (385 mg, 2.13 mmol, 5.0 eq). The reaction was stirred at 110°C under N_2 for 24 h. After cooling to rt, the mixture was poured into water (5 mL) and extracted with DCM (15 mL $\times$ 3). The combined organic layers were washed with brine (15 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give crude (Z)-4-[[1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoropiperidine-4-carboxyl]amino]but-2-enoic acid (220 mg, 0.401 mmol, 94% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.30 (d, $J = 8.4$ Hz, 1H), 7.81 (s, 1H), 7.59 (s, 1H), 7.53 - 7.56 (m, 1H), 7.44 - 7.46

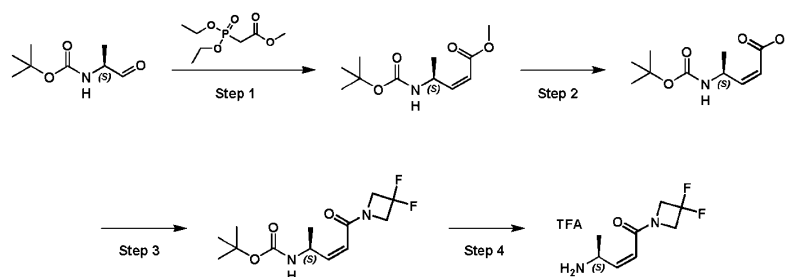
(m, 1H), 7.37 - 7.40 (m, 2H), 6.97 - 7.07 (m, 1H), 6.09 - 6.18 (m, 1H), 5.93 (d, $J = 11.4$ Hz, 1H), 4.31 (t, $J = 6.13$ Hz, 2H), 3.04 (dd, $J = 18.0, 7.3$ Hz, 1H), 2.93 (br d, $J = 12.5$ Hz, 1H), 2.66 - 2.74 (m, 2H), 2.10 - 2.31 (m, 2H), 1.89 - 2.03 (m, 1H), 1.68 - 1.73 (m, 2H).

[00665] Step 3. To a solution of (Z)-4-[[1-[2-(2-chlorophenyl)-4-(trifluoromethyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carbonyl]amino]but-2-enoic acid (220 mg, 0.400 mmol, 1.0 eq) in DCM (5.0 mL, 0.08 M) was added 3,3-difluoroazetidine hydrochloride (62 mg, 0.480 mmol, 1.2 eq), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (191 mg, 0.600 mmol, 1.5 eq), and DIPEA (129 mg, 1.00 mmol, 2.5 eq). The reaction was stirred at 25°C for 1 h before being poured into water (5 mL) and extracted with DCM (15 mL $\times$ 3). The combined organic layers were washed with brine (15 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (PE:EtOAc = 2:1) to afford (Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide (63 mg, 0.100 mmol, 25% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.47 - 8.52 (m, 1H), 8.26 (d, $J = 8.5$ Hz, 1H), 8.06 (dd, $J = 8.5, 1.6$ Hz, 1H), 7.74 (d, $J = 1.3$ Hz, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.45 - 7.51 (m, 1H), 7.40 - 7.44 (m, 2H), 5.96 - 6.05 (m, 1H), 5.86 - 5.93 (m, 1H), 4.61 (br t, $J = 12.5$ Hz, 2H), 4.31 (br t, $J = 12.8$ Hz, 2H), 4.19 - 4.25 (m, 2H), 3.13 - 3.22 (m, 2H), 2.64 - 2.84 (m, 2H), 1.68 - 2.00 (m, 4H). [M+H]⁺ calculated for $\text{C}_{26}\text{H}_{24}\text{ClF}_6\text{N}_3\text{O}_4\text{S}$, 623; found 624.

[00666] Compound 285 was synthesized in a manner analogous to **Compound 284** starting with 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-piperidine-4-carboxylic acid and ethyl (Z)-aminobut-2-enoate.

[00667] Compound 286 was synthesized in a manner analogous to **Compound 285** using azetidine in Step 3.

Scheme 82. Synthesis of Intermediate (S,Z)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one



[00668] Step 1. A solution of trimethyl phosphonoacetate (6.2 g, 33.9 mmol, 1.2 eq) in THF (40 mL, 0.71 M) was placed under N_2 and cooled to -70°C. LiHMDS (40 mL, 39.6 mmol, 1.4 eq, 1.0 M) was added and the solution was stirred at -70°C for 1 h. *tert*-Butyl (S)-1-oxopropan-2-ylcarbamate (4.9 g, 28.3 mmol, 1.0 eq) in THF (20 mL) was added and the reaction was stirred at -70°C for 1 h. The reaction mixture was quenched with NH_4Cl (40 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 to 5:1) to give

methyl (*S,Z*)-4-((*tert*-butoxycarbonyl)amino)pent-2-enoate (2.0 g, 8.72 mmol, 31% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.19 - 6.06 (m, 1H), 5.76 (dd, *J* = 11.6, 1.1 Hz, 1H), 5.22 - 5.11 (m, 1H), 4.77 (br s, 1H), 3.72 (s, 3H), 1.43 (s, 9H), 1.27 (br d, *J* = 6.8 Hz, 3H).

[00669] **Step 2.** To a solution of methyl (*S,Z*)-4-((*tert*-butoxycarbonyl)amino)pent-2-enoate (1.5 g, 6.54 mmol, 1.0 eq) in DCE (20 mL, 0.33 M) under N₂ was added Me₃SnOH (4.7 g, 26.2 mmol, 4.0 eq). The reaction was stirred at 85°C for 96 h. After cooling to rt, the mixture was poured into water (50 mL) and extracted with DCM (35 mL × 3). The combined organic layers were washed with brine (15 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give crude (*S,Z*)-4-((*tert*-butoxycarbonyl)amino)pent-2-enoic acid (1.2 g, 5.57 mmol, 85% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.02 (br s, 1H), 5.78 (d, *J* = 11.7 Hz, 1H), 5.18 - 4.83 (m, 2H), 1.43 (s, 9H), 1.26 (br d, *J* = 6.7 Hz, 3H).

[00670] **Step 3.** To a solution of (*S,Z*)-4-((*tert*-butoxycarbonyl)amino)pent-2-enoic acid (1.2 g, 5.57 mmol, 1.0 eq) in DCM (20 mL, 0.28 M) was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (2.7 g, 8.36 mmol, 1.5 eq), DIPEA (1.8 g, 13.9 mmol, 2.5 eq), and 3,3-difluoroazetidine (HCl salt, 867 mg, 6.69 mmol, 1.2 eq). The reaction was stirred at 25°C for 1 h before being poured into water (50 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (15 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1: 1) to afford *tert*-butyl (*S,Z*)-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)carbamate (650 mg, 2.24 mmol, 40% yield) as a white solid. MS (ESI): mass calculated for C₁₃H₂₀F₂N₂O₃, 290.1; *m/z* found, 235.1 [M+2H-tBu]⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.06 (br dd, *J* = 11.1, 8.3 Hz, 1H), 5.72 (d, *J* = 11.6 Hz, 1H), 5.04 (br s, 1H), 4.53 - 4.30 (m, 4H), 1.43 (s, 9H), 1.31 - 1.26 (m, 3H).

[00671] **Step 4.** To a solution of *tert*-butyl (*S,Z*)-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)carbamate (450 mg, 1.55 mmol, 1.0 eq) in DCM (3.0 mL, 0.52 M) was added 2,2,2-trifluoroacetic acid (353 mg, 3.10 mmol, 2.0 eq) at 0°C. The reaction was stirred at 25°C for 1 h under N₂ before being concentrated to give (*S,Z*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one (TFA salt, 285 mg, 1.50 mmol, 97% yield) as a yellow oil. MS (ESI): mass calculated for C₈H₁₂F₂N₂O, 190.1; *m/z* found, 191.1 [M+H]⁺.

[00672] **Compound 287** was synthesized in a manner analogous to **Compound 47** using (*S,Z*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one in Step 5.

[00673] **Intermediate (Z)-4-amino-1-(3,3-difluoroazetidin-1-yl)but-2-en-1-one** was synthesized in a manner analogous to (*S,Z*)-4-amino-1-(3,3-difluoroazetidin-1-yl)pent-2-en-1-one starting with (2-oxoethyl)carbamic acid *tert*-butyl ester.

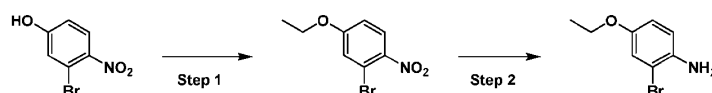
[00674] **Intermediate (2*R*,4*S*)-*N*-((*Z*)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide** was synthesized in a manner analogous to (2*R*,4*S*)-4-fluoro-2-methyl-*N*-((*R*,*Z*)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide using (*Z*)-4-amino-1-(3,3-difluoroazetidin-1-yl)but-2-en-1-one and omitting the chiral separation.

[00675] **Compound 288** was synthesized in a manner analogous to **Compound 141** using (2*R*,4*S*)-*N*-((*Z*)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide.

[00676] **Compounds 289-292** were synthesized in manner analogous to **Compound 288** using the appropriate sulfonyl chloride.

[00677] **Compound 293** was synthesized in a manner analogous to **Compound 158** using methyl (3*R*,4*S*)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2*H*-pyran-3-carboxylate in Step 1 and (2*R*,4*S*)-*N*-((*Z*)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide in Step 2.

Scheme 83. Synthesis of Intermediate 2-bromo-4-ethoxyaniline



[00678] **Step 1.** To a solution of 3-bromo-4-nitrophenol (5.0 g, 22.9 mmol, 1.0 eq) in DMF (50 mL, 0.46 M) was added iodoethane (5.3 mL, 68.8 mmol, 3.0 eq) and K_2CO_3 (9.5 g, 68.8 mmol, 3.0 eq). The reaction was stirred at 20°C for 16 h before being poured into water (200 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 to 4:1) to give 2-bromo-4-ethoxy-1-nitrobenzene (5.7 g, 23.2 mmol, quant. yield) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 - 7.93 (m, 1H), 7.19 (d, J = 2.5 Hz, 1H), 6.89 (dd, J = 9.1, 2.6 Hz, 1H), 4.10 (q, J = 6.9 Hz, 2H), 1.49 - 1.41 (m, 3H).

[00679] **Step 2.** To a solution of 2-bromo-4-ethoxy-1-nitrobenzene (5.7 g, 23.2 mmol, 1.0 eq) in ethanol/water (v/v 1:1, 50 mL, 0.46 M) was added NH_4Cl (6.2 g, 116 mmol, 5.0 eq) and iron powder (6.5 g, 116 mmol, 5.0 eq). The reaction was stirred at 80°C for 1 h. After cooling to rt, the suspension was filtered through silica gel and washed with EtOH (50 mL). The filtrate was concentrated to dryness to give 2-bromo-4-ethoxyaniline (2.4 g, 11.1 mmol, 48% yield) as a yellow solid.

[00680] **Compound 298** was synthesized in a manner analogous to **Compound 134** using 2-bromo-4-ethoxyaniline in Step 1 and methyl (2*R*,4*S*)-4-fluoro-2-methylpiperidine-4-carboxylate in Step 2.

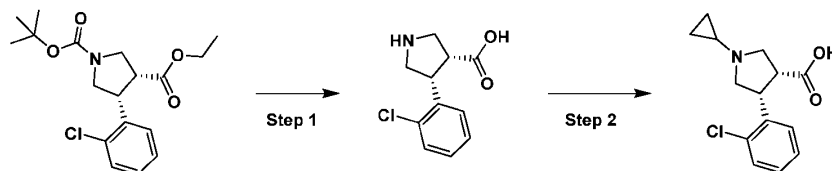
[00681] **Compound 299** was synthesized in a manner analogous to **Compound 298** using (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine in Step 5.

[00682] **Intermediate 2-bromo-4-(methoxy- d_3)aniline** was synthesized in a manner analogous to 2-bromo-4-ethoxyaniline using deuterated iodomethane in Step 1.

[00683] **Compound 300** was synthesized in a manner analogous to **Compound 134** using 2-bromo-4-(methoxy- d_3)aniline in Step 1 and methyl (2*R*,4*S*)-4-fluoro-2-methylpiperidine-4-carboxylate in Step 2.

[00684] **Compound 301** was synthesized in a manner analogous to **Compound 300** using (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine in Step 5.

Scheme 84. Synthesis of Intermediate (3*R*,4*R*)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carboxylic acid



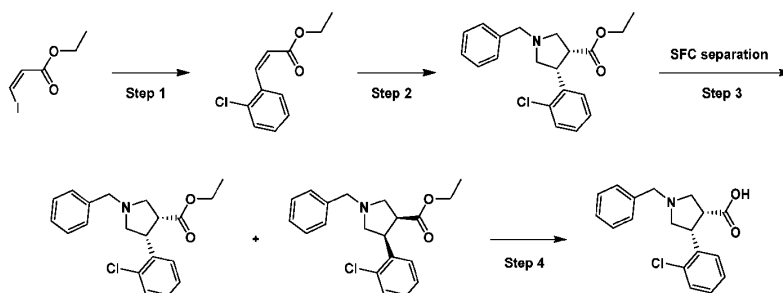
[00685] **Step 1.** A solution of 1-(*tert*-butyl) 3-ethyl (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-1,3-dicarboxylate (400 mg, 1.13 mmol, 1.0 eq) in HBr (3.0 mL, aq. in water) was stirred at 110°C for 6 h. After cooling to rt, the mixture was concentrated *in vacuo* to give (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid (250 mg, 1.11 mmol, 98% yield) as a pink solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 7.52 - 7.46 (m, 1H), 7.37 - 7.28 (m, 3H), 4.28 (dt, *J* = 12.2, 7.5 Hz, 1H), 3.91 - 3.63 (m, 5H).

[00686] **Step 2.** To a solution of (3*R*,4*R*)-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid (250 mg, 1.11 mmol, 1.0 eq) and (1-ethoxycyclopropoxy)trimethylsilane (772 mg, 4.43 mmol, 4.0 eq) in methanol (5.0 mL, 0.22 M) was added acetic acid (1.3 mL, 22.2 mmol, 20 eq) and NaBH₃CN (209 mg, 3.32 mmol, 3.0 eq) under N₂. The reaction was stirred at 60°C for 4 h. After cooling to rt, the mixture was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (1-40% ACN in 0.1% aq. TFA) to give (3*R*,4*R*)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carboxylic acid (200 mg, 0.753 mmol, 68% yield) as a white solid. MS (ESI): mass calculated for C₁₄H₁₆ClNO₂, 265.1; *m/z* found, 266.2 [M+H]⁺. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 7.51 - 7.45 (m, 1H), 7.35 - 7.29 (m, 3H), 4.41 - 4.26 (m, 1H), 4.14 - 3.89 (m, 4H), 3.85 - 3.76 (m, 1 H), 3.20 (tt, *J* = 7.3, 3.8 Hz, 1H), 1.13 - 0.98 (m, 4H).

[00687] **Compound 303** was synthesized in a manner analogous to **Compound 165** using (3*R*,4*R*)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carboxylic acid in Step 4.

[00688] **Compound 304** was synthesized in a manner similar to **Compound 165** starting from 4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide, 4-methylbenzenesulfonic acid salt and (3*R*,4*R*)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carboxylic acid in Step 4.

Scheme 85. Synthesis of Intermediate (3R*,4**R*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid**



[00689] **Step 1.** A solution of ethyl (*Z*)-3-iodoprop-2-enoate (2.0 kg, 8.85 mol, 1.0 eq), 2-chlorophenylboronic acid (1.5 kg, 9.73 mol, 1.1 eq), and K₃PO₄ (5.6 kg, 26.5 mol, 3.0 eq) in toluene (3.5

L, 1.8 M) and water (1.5 L, 1.8 M) was purged with N₂. Pd(dppf)Cl₂·DCM (7.2 g, 8.85 mmol, 0.001 eq) was added and the reaction was heated to 60°C for 16 h under N₂. After cooling to rt, the mixture was extracted with EtOAc (1.0 L × 2). The combined organic layers were washed with brine (1.5 L), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to afford ethyl (Z)-3-(2-chlorophenyl)prop-2-enoate (1.7 kg, 7.91 mol, 89% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45 (dd, *J* = 2.0, 7.3 Hz, 1H), 7.33 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.25 - 7.14 (m, 2H), 7.08 (d, *J* = 12.3 Hz, 1H), 6.03 (d, *J* = 12.3 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H).

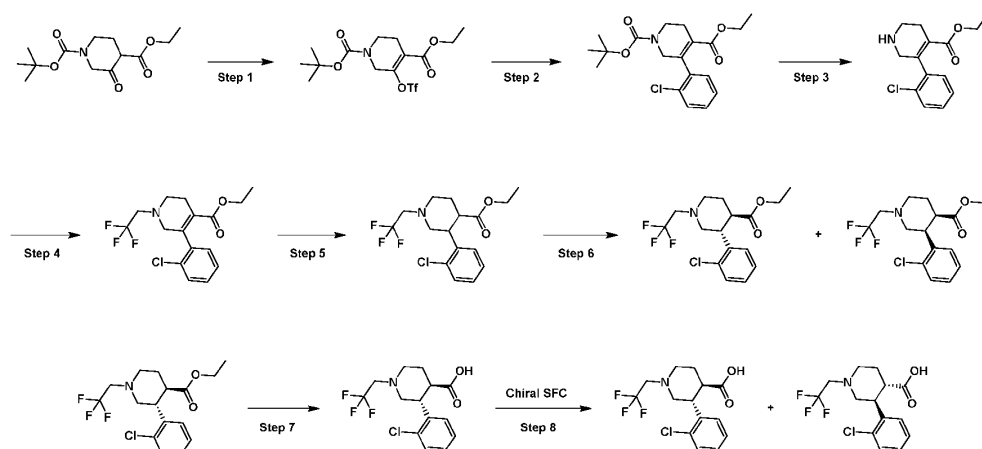
[00690] **Step 2.** To a solution of ethyl (Z)-3-(2-chlorophenyl)prop-2-enoate (23 g, 109 mmol, 1.0 eq) and 2,2,2-trifluoroacetic acid (1.25 g, 10.9 mmol, 0.1 eq) in toluene (300 mL, 0.36 M) was added *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (34.6 g, 131 mmol, 1.2 eq) dropwise at 50°C. The reaction was stirred at 70°C for 2 h. After cooling to rt, the mixture was quenched with water (200 mL) and extracted with toluene (200 mL × 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 3:1) to give ethyl *rac*-(3*R*,4*R*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (30 g, 87.2 mmol, 80% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.47 - 7.41 (m, 3H), 7.34 - 7.27 (m, 6H), 4.26 (dt, *J* = 6.6, 9.7 Hz, 1H), 3.82 (s, 2H), 3.75 - 3.51 (m, 3H), 3.22 - 3.13 (m, 1H), 3.12 - 3.05 (m, 2H), 2.91 (t, *J* = 9.0 Hz, 1H), 0.82 (t, *J* = 7.2 Hz, 3H).

[00691] **Step 3.** Ethyl *rac*-(3*R*,4*R*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (400 mg, 1.16 mmol, 1.0 eq) was separated by SFC (Stationary phase: OJ (250x30mm); Mobile phase: 15% EtOH/CO₂) to give two enantiomers: P1, Rt = 4.5 min: ethyl (3**R*,4**R*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (150 mg, 0.436 mmol, 38% yield) was obtained as colorless oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 7.42 - 7.07 (m, 9H), 4.22 - 4.04 (m, 1H), 3.79 - 3.66 (m, 2H), 3.62 - 3.37 (m, 3H), 3.10 - 2.72 (m, 4H), 0.79 - 0.63 (m, 3H). P2, Rt = 5.9 min: ethyl (3**S*,4**S*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (120 mg, 0.349 mmol, 30% yield) was obtained as colorless oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 7.53 - 7.16 (m, 9H), 4.27 - 4.14 (m, 1H), 3.89 - 3.75 (m, 2H), 3.71 - 3.42 (m, 3H), 3.18 - 2.81 (m, 4H), 0.92 - 0.63 (m, 3H).

[00692] **Step 4.** To a solution of ethyl (3**R*,4**R*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylate (100 mg, 0.291 mmol, 1.0 eq) in DCE (5.0 mL, 0.058 M) was added trimethyltin hydroxide (263 mg, 1.45 mmol, 5.0 eq). The reaction was stirred at 110°C for 48 h. After cooling to rt, the mixture was concentrated to give (3**R*,4**R*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid (90 mg, 0.285 mmol, 98% yield) as a white solid. This was used in the next step without purification.

[00693] **Compound 305** was synthesized in a manner analogous to **Compound 165** using (3**R*,4**R*)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carboxylic acid in Step 4.

Scheme 86. Synthesis of Intermediate (3R*,4**R*)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylic acid**



[00694] Step 1. To a solution of 1-(*tert*-butyl) 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (10 g, 36.9 mmol, 1.0 eq) in toluene (120 mL, 0.31 M) was added DIPEA (7.1 g, 55.3 mmol, 1.5 eq) and Tf_2O (12.5 g, 44.2 mmol, 1.2 eq) at 0°C. The reaction was stirred at 20°C for 16 h before being evaporated to give 1-(*tert*-butyl) 4-ethyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (14.8 g, 36.7 mmol, 98% yield) as a brown oil.

[00695] Step 2. To a solution of 1-(*tert*-butyl) 4-ethyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (30 g, 37.2 mmol, 1.0 eq) in THF (360 mL, 0.16 M) was added (2-chlorophenyl)boronic acid (6.4 g, 40.9 mmol, 1.1 eq), K_3PO_4 (15.8 g, 74.4 mmol, 2.0 eq), and $\text{Pd}(\text{PPh}_3)_4$ (1.3 g, 1.12 mmol, 0.03 eq). The reaction was placed under N_2 and stirred at 70°C for 12 h. After cooling to rt, the solution was diluted with H_2O (300 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by FCC on silica (PE:EtOAc = 1:0 - 5:1) to give 1-(*tert*-butyl) 4-ethyl 5-(2-chlorophenyl)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (9.0 g, 24.6 mmol, 66% yield) as a yellow solid. MS (ESI): mass calculated for $\text{C}_{19}\text{H}_{24}\text{ClNO}_4$, 365.1; m/z found, 310.0 $[\text{M}+2\text{H}-\text{tBu}]^+$.

[00696] Step 3. To a solution of 1-(*tert*-butyl) 4-ethyl 5-(2-chlorophenyl)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (6.0 g, 16.3 mmol, 1.0 eq) in DCM (30 mL, 0.54 M) was added TFA (10 mL). The reaction was stirred at 20°C for 1 h. The mixture was filtered and concentrated under reduced pressure to give ethyl 5-(2-chlorophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (as TFA salt, 5.6 g, 14.7 mmol, 98% yield) as a white solid. The product was used directly without further purification.

[00697] Step 4. To a solution of ethyl 5-(2-chlorophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (5.6 g, 14.7 mmol, 1.0 eq) in MeCN (30 mL, 0.49 M) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (6.8 g, 29.5 mmol, 2.0 eq) and TEA (7.5 g, 73.7 mmol, 5.0 eq). The reaction was stirred at 80°C for 12 h. After cooling to rt, the mixture was poured into water (100 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 20:1) to give ethyl 5-(2-chlorophenyl)-1-(2,2,2-

trifluoroethyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (5.6 g, 16.1 mmol, 87% yield) as a yellow oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.54 - 7.41 (m, 1H), 7.35 - 7.30 (m, 2H), 7.20 - 7.16 (m, 1H), 3.83 - 3.78 (m, 2H), 3.32 - 3.25 (m, 2H), 2.89 (t, *J* = 5.8 Hz, 2H), 2.58 - 2.51 (m, 2H), 2.49 - 2.38 (m, 2H), 0.77 (t, *J* = 7.1 Hz, 3H).

[00698] Step 5. To a solution of ethyl 5-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (5.6 g, 16.1 mmol, 1.0 eq) in methanol (50 mL, 0.32 M) was added magnesium (3.9 g, 161 mmol, 10 eq) in portions and the reaction was stirred at 20°C for 12 h. The mixture was filtered and concentrated under vacuum. The resulting residue was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 50:1) to give ethyl 3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (2.0 g, 5.72 mmol, 35% yield) as a colorless oil. MS (ESI): mass calculated for C₁₆H₁₉ClF₃NO₂, 349.1; *m/z* found, 350.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.53 - 7.40 (m, 2H), 7.31 - 7.18 (m, 2H), 3.91 - 3.69 (m, 2H), 3.60 - 3.44 (m, 1H), 3.29 - 3.15 (m, 3H), 3.03 - 2.63 (m, 4H), 2.02 - 1.61 (m, 2H), 0.93 - 0.85 (m, 3H).

[00699] Step 6. Ethyl 3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (2.0 g, 5.72 mmol) was separated by prep-HPLC (40-70% ACN in 10 mM aq. NH₄HCO₃) to give two products:

[00700] P1: ethyl (3**R*,4**R*)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (trans racemate, 330 mg, 0.943 mmol, 17% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.44 - 7.39 (m, 1H), 7.36 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.22 - 7.13 (m, 2H), 3.96 - 3.78 (m, 2H), 3.74 - 3.65 (m, 1H), 3.37 (t, *J* = 10.4 Hz, 1H), 3.15 - 2.96 (m, 4H), 2.89 (dd, *J* = 10.9, 3.6 Hz, 1H), 2.86 - 2.76 (m, 1H), 2.09 - 2.00 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).

[00701] P2: ethyl (3**S*,4**R*)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (cis racemate, 1.50 g, 4.29 mmol, 75% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.36 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.29 (d, *J* = 1.7 Hz, 1H), 7.27 - 7.12 (m, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.73 (td, *J* = 10.9, 3.2 Hz, 1H), 3.16 - 3.01 (m, 4H), 2.75 (br d, *J* = 3.3 Hz, 1H), 2.59 (td, *J* = 11.3, 3.7 Hz, 1H), 2.39 (br t, *J* = 9.8 Hz, 1H), 2.07 - 1.92 (m, 2H), 1.04 - 0.98 (m, 3H).

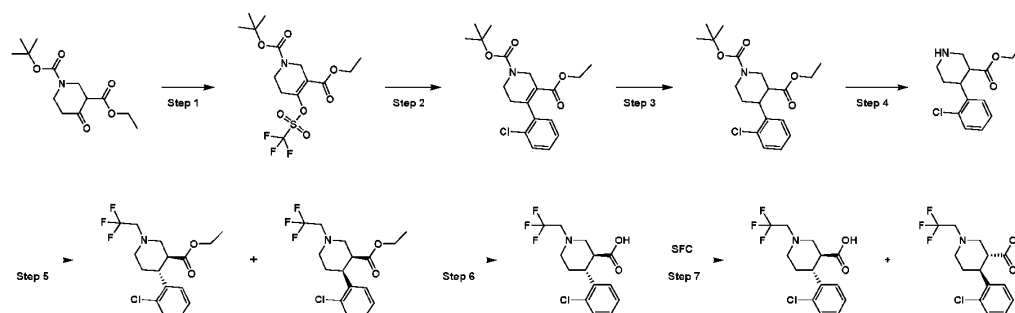
[00702] Step 7. To a solution of ethyl (3**R*,4**R*)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (trans racemate, 330 mg, 0.945 mmol, 1.0 eq) in THF/water (v/v 3:1, 4.0 mL, 0.24 M) was added LiOH·H₂O (59 mg, 1.42 mmol, 1.5 eq). The reaction was stirred at 20°C for 16 h before being acidified with 2N HCl to pH ~2. The white precipitate was collected via filtration to give (3**R*,4**R*)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylic acid (200 mg, 0.622 mmol, 66% yield) as a white solid.

[00703] Step 8. (3**R*,4**R*)-3-(2-Chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylic acid (200 mg, 0.622 mmol, 1.0 eq) was separated by chiral SFC (Stationary phase: OZ (250x25mm); Mobile phase: 10% EtOH/CO₂; Rt(P1) = 4.26 min, Rt(P2) = 6.75 min) to give P1: (3**R*,4**R*)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylic acid (65 mg, 0.202 mmol, 33% yield) as a white solid. MS (ESI): mass calculated for C₁₄H₁₅ClF₃NO₂, 321.1; *m/z* found, 322.1 [M+H]⁺.

[00704] **Compound 306** was synthesized in a manner analogous to **Compound 165** using (3*R,4*R)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylic acid in Step 4.

[00705] **Compound 307** was synthesized in a manner similar to **Compound 165** starting from 4-fluoro-*N*-[(Z,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide, 4-methylbenzenesulfonic acid salt and (3*R,4*R)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylic acid in Step 4.

Scheme 87. Synthesis of Intermediate (3*R,4*S)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylic acid



[00706] **Step 1.** A solution of 1-*tert*-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (5.0 g, 18.4 mmol, 1.0 eq) and DIPEA (5.9 g, 46.1 mmol, 2.5 eq) in DCM (50 mL, 0.37 M) was placed under N₂. To this was added trifluoromethanesulfonyl anhydride (6.8 g, 23.9 mmol, 1.3 eq) at -78°C under N₂. The reaction was stirred at -78°C for 0.5 h before being extracted with water (50 mL) and DCM (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over with Na₂SO₄, filtered, and concentrated under reduced pressure. 1-*tert*-Butyl 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (7.4 g, 18.3 mmol, quant.) was obtained as a yellow solid.

[00707] **Step 2.** A mixture of 1-*tert*-butyl 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (7.4 g, 18.3 mmol, 1.0 eq) and (2-chlorophenyl)boronic acid (3.2 g, 20.2 mmol, 1.1 eq) in THF (75 mL, 0.24 M) was placed under N₂. To the mixture was added K₃PO₄ (7.8 g, 36.7 mmol, 2.0 eq) and Pd(PPh₃)₄ (1.1 g, 0.917 mmol, 0.05 eq) and the reaction was heated to 65°C for 12 h. After cooling to rt, the mixture was extracted with water (50 mL) and EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over with Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica (PE:EtOAc = 1:0 - 5:1) to obtain 1-*tert*-butyl 3-ethyl 4-(2-chlorophenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (6.5 g, 17.8 mmol, 97% yield) as a yellow solid. MS (ESI): mass calculated for C₁₉H₂₄ClNO₄, 365.1; m/z found, 309.9 [M+2H-tBu]⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.34 - 7.27 (m, 1H), 7.16 (br dd, *J* = 3.6, 5.5 Hz, 2H), 7.01 - 6.94 (m, 1H), 4.43 - 4.30 (m, 1H), 4.07 - 4.01 (m, 1H), 3.90 - 3.82 (m, 2H), 3.80 - 3.72 (m, 1H), 3.34 (td, *J* = 4.4, 8.5 Hz, 1H), 2.43 (br s, 1H), 2.32 (br d, *J* = 2.1 Hz, 1H), 1.44 (s, 9H), 0.83 (br s, 3H).

[00708] **Step 3.** To a solution of 1-*tert*-butyl 3-ethyl 4-(2-chlorophenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (4.5 g, 12.3 mmol, 1.0 eq) in methanol (45 mL, 0.27 M) was added magnesium (3.0 g, 123

mmol, 10 eq) at 0°C. The reaction was stirred under N₂ at 25°C for 3 h. The mixture was quenched with 1M HCl (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (70 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. 1-*tert*-Butyl 3-ethyl 4-(2-chlorophenyl)piperidine-1,3-dicarboxylate (4.3 g, 11.7 mmol, 95% yield) was obtained as a yellow solid. MS (ESI): mass calculated for C₁₉H₂₆ClNO₄, 367.1; m/z found, 312.2 [M+2H-tBu]⁺.

[00709] **Step 4.** To a solution of 1-*tert*-butyl 3-ethyl 4-(2-chlorophenyl)piperidine-1,3-dicarboxylate (2.5 g, 6.83 mmol, 1.0 eq) in DCM (25 mL, 0.27 M) was added TFA (2.3 g, 20.5 mmol, 3.0 eq) under N₂. The reaction was stirred at 25°C for 2 h before being concentrated under reduced pressure. The mixture was extracted with H₂O (20 mL) and DCM (20 mL × 3). The combined organic layers were washed with brine (50 mL), dried over with Na₂SO₄, filtered, and concentrated under reduced. Ethyl 4-(2-chlorophenyl)piperidine-3-carboxylate (2.5 g, 6.71 mmol, 98% yield) was obtained as a white solid.

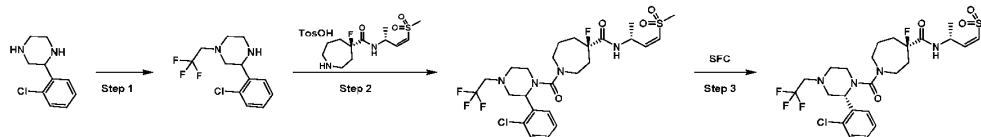
[00710] **Step 5.** To ethyl 4-(2-chlorophenyl)piperidine-3-carboxylate (2.5 g, 6.58 mmol, 1.0 eq) in toluene (25 mL, 0.26 M) was added DIPEA (2.0 g, 19.7 mmol, 3.0 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (3.1 g, 13.2 mmol, 2.0 eq). The reaction was stirred at 80°C for 16 h. After cooling to rt, the mixture was poured into H₂O (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (90 mL), dried over with Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 1:0 - 3:1) to obtain ethyl 4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylate (trans racemate, 300 mg, 0.863 mmol, 13% yield) as a white solid and ethyl 4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylate (cis racemate, 1.5 g, 4.31 mmol, 65% yield) as a colorless oil. MS (ESI): mass calculated for C₁₆H₁₉ClF₃NO₂, 349.1; m/z found, 350.1 [M+H]⁺.

[00711] **Step 6.** A solution of ethyl 4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylate (trans racemate, 300 mg, 0.858 mmol, 1.0 eq) in HBr (7.0 mL, 48% in water) was stirred at 110°C for 2 h. After cooling to rt, the mixture was extracted with H₂O (5.0 mL) and EtOAc (5.0 mL × 3). The combined organic layers were washed with brine (15 mL), dried over with Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified via prep-HPLC (15-55% ACN in 10 mM aq. NH₄HCO₃) to obtain 4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylic acid (trans racemate, 150 mg, 0.466 mmol, 54% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.38 - 7.30 (m, 1H), 7.26 (br s, 2H), 7.17 - 7.11 (m, 1H), 3.42 - 3.33 (m, 1H), 3.33 - 3.27 (m, 1H), 3.14 - 3.01 (m, 4H), 2.72 - 2.65 (m, 1H), 2.64 - 2.56 (m, 1H), 1.94 - 1.86 (m, 1H), 1.68 - 1.55 (m, 1H).

[00712] **Step 7.** 4-(2-Chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylic acid (trans racemate, 150 mg, 0.466 mmol) was purified by SFC (Stationary phase: AD (250x30mm); Mobile phase: 11% MeOH/CO₂, 7 min) to give two products. P2: (3*R,4*S)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylic acid (40 mg, 0.124 mmol, 26% yield) as a pale yellow oil. MS (ESI): mass calculated for C₁₄H₁₃ClF₃NO₂, 321.1; m/z found, 322.1 [M+H]⁺.

[00713] **Compound 308** was synthesized in a manner analogous to **Compound 165** using (3*R,4*S)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylic acid in Step 4.

Scheme 88. Synthesis of (*R*)-1-((*R*)-2-(2-chlorophenyl)-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (Compound 309)

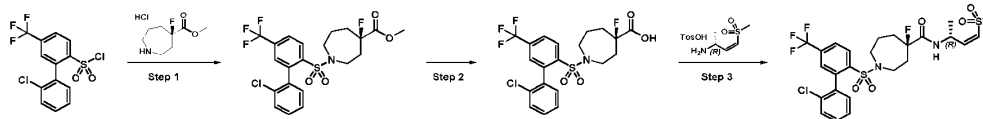


[00714] Step 1. To a solution of 2-(2-chlorophenyl)piperazine (1.4 g, 7.12 mmol, 1.0 eq) in toluene (15 mL, 0.47 M) was added TEA (3.0 mL, 21.4 mmol, 3.0 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.6 g, 7.12 mmol, 1.0 eq) at 15 °C. The reaction was stirred at 80 °C for 16 h. After cooling to rt, the mixture was poured into water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed brine (30 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford 3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperazine (500 mg, 1.79 mmol, 25% yield) as a yellow oil.

[00715] Step 2. To a solution of 3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperazine (200 mg, 0.718 mmol, 1.0 eq) in DCM (2.0 mL, 0.36 M) was added triphosgene (74.5 mg, 0.251 mmol, 0.4 eq) and DIPEA (0.4 mL, 2.15 mmol, 3.0 eq). The reaction was stirred at 25 °C for 0.5 h before (4*R*)-4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]azepane-4-carboxamide (TsOH salt, 333 mg, 0.718 mmol, 1.0 eq) was added. The reaction was stirred at 25 °C for 16 h before being poured into water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (35-65% ACN in 0.1% aq. TFA) to afford (4*R*)-1-[2-(2-chlorophenyl)-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl]-4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]azepane-4-carboxamide (200 mg, 0.335 mmol, 47% yield) as a colorless oil. MS (ESI): mass calculated for C₂₅H₃₃ClF₄N₄O₄S, 596.2; *m/z* found, 597.1 [M+H]⁺.

[00716] Step 3. (4*R*)-1-[2-(2-chlorophenyl)-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl]-4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]azepane-4-carboxamide (200 mg, 0.335 mmol) was separated by SFC (Stationary phase: WHELK-O1 (250x30mm); Mobile phase: 50% IPA/CO₂; Rt (P1) = 7.6 min, Rt (P2) = 10.7 min) to give two products. P2: (*R*)-1-((*R*)-2-(2-chlorophenyl)-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (105 mg, 0.175 mmol, 52% yield) as a white solid. MS (ESI): mass calculated for C₂₅H₃₃ClF₄N₄O₄S, 596.2; *m/z* found, 597.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.32 (dd, *J* = 7.7, 2.1 Hz, 1H), 7.52 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.43 - 7.34 (m, 1H), 7.30 - 7.18 (m, 2H), 6.47 (d, *J* = 11.2 Hz, 1H), 6.36 - 6.24 (m, 1H), 5.44 - 5.30 (m, 1H), 4.60 (dd, *J* = 8.7, 3.2 Hz, 1H), 3.68 - 3.50 (m, 2H), 3.39 - 3.34 (m, 1H), 3.33 - 3.30 (m, 1H), 3.30 - 3.19 (m, 3H), 3.13 (s, 3H), 2.96 - 2.80 (m, 3H), 2.74 - 2.65 (m, 1H), 2.46 (br d, *J* = 10.9 Hz, 1H), 2.13 - 1.83 (m, 4H), 1.75 (br s, 2H), 1.22 (d, *J* = 6.8 Hz, 3H).

Scheme 89. Synthesis of (*R*)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (Compound 310)



[00717] Step 1. To a solution of methyl (*R*)-4-fluoroazepane-4-carboxylate (HCl salt, 149 mg, 0.704 mmol, 1.0 eq) in DCM (5.0 mL, 0.14 M) was added DIPEA (273 mg, 2.11 mmol, 3.0 eq). 2-(2-Chlorophenyl)-4-(trifluoromethyl)benzenesulfonyl chloride (250 mg, 0.704 mmol, 1.0 eq) in DCM (2.0 mL) was added to the solution at 0°C. The reaction was stirred at 20°C for 2 h before being poured into water (10 mL) and extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by FCC on silica (PE:EtOAc = 10:1) to give methyl (*R*)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoroazepane-4-carboxylate (320 mg, 0.648 mmol, 92% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.33 - 8.25 (m, 1H), 7.79 (br d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.54 - 7.36 (m, 4H), 3.77 (d, *J* = 5.2 Hz, 3H), 3.30 - 2.56 (m, 4H), 2.30 - 2.11 (m, 2H), 2.03 - 1.52 (m, 4H).

[00718] Step 2. To a solution of methyl (*R*)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoroazepane-4-carboxylate (320 mg, 0.648 mmol, 1.0 eq) in THF/water (v/v 3:1, 4.0 mL, 0.16 M) was added LiOH.H₂O (33 mg, 0.778 mmol, 1.2 eq). The reaction was stirred at 20°C for 3 h before being diluted with water (5 mL) and acidified with 1M aq. HCl until pH 3-4. The mixture was extracted with EtOAc (10 mL $\times$ 3) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to give (*R*)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoroazepane-4-carboxylic acid (300 mg, 0.625 mmol, 96% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.34 - 8.24 (m, 1H), 7.80 (br d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.55 - 7.35 (m, 4H), 3.28 - 2.65 (m, 4H), 2.32 - 2.09 (m, 3H), 2.05 - 1.65 (m, 3H).

[00719] Step 3. To a solution of (*R*)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (200 mg, 0.417 mmol, 1.0 eq) in DMF (3.0 mL, 0.14 M) was added K₂CO₃ (288 mg, 2.08 mmol, 5.0 eq) and HATU (476 mg, 1.25 mmol, 3.0 eq). The mixture was stirred at 20°C for 10 mins before addition of (*R,Z*)-4-(methylsulfonyl)but-3-en-2-amine (TsOH salt, 174 mg, 0.542 mmol, 1.3 eq). The reaction was stirred at 20°C for 1 h before being poured into water (20 mL) and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with brine (20 mL $\times$ 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by prep-HPLC (40-70% ACN in 10 mM aq. NH₄HCO₃) to give (*R*)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((*R,Z*)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide (154 mg, 0.252 mmol, 62% yield) as a white solid. MS (ESI): mass calculated for C₂₅H₂₇ClF₄N₂O₅S₂, 610.1; *m/z* found, 611.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.35 - 8.20 (m, 2H), 8.03 (br d, *J* = 8.3 Hz, 1H), 7.73 (s,

1H), 7.63 - 7.56 (m, 1H), 7.52 - 7.39 (m, 3H), 6.44 (d, $J = 11.1$ Hz, 1H), 6.33 - 6.23 (m, 1H), 5.39 - 5.26 (m, 1H), 3.11 (s, 3H), 3.09 - 2.83 (m, 4H), 2.12 - 1.82 (m, 4H), 1.79 - 1.60 (m, 2H), 1.20 (d, $J = 6.8$ Hz, 3H).

[00720] **Compound 311** was synthesized in a manner analogous to **Compound 310** using methyl (*S*)-4-fluoroazepane-4-carboxylate in Step 1.

[00721] **Compound 312** was synthesized in a manner analogous to **Compound 310** using 2'-chloro-5-methoxy-[1,1'-biphenyl]-2-sulfonyl chloride in Step 1.

[00722] **Compound 313** was synthesized in a manner analogous to **Compound 312** using methyl (*S*)-4-fluoroazepane-4-carboxylate in Step 1.

Example 2. General Analytical Methods

[00723] The compounds were analyzed by LCMS using the following methods:

[00724] **Method 1:** Shimadzu LC-30AD MSD:LCMS-2020 with a Kinetex EVO C18 5 μ m 2.1*30mm column set to 40°C with a mobile phase A of 0.04 % TFA in water and mobile phase B of 0.02 % TFA in ACN with a flow rate of 0.8mL/min used the following gradient:

Time (min)	%B
0.01	5
1.6	95
2.5	100
2.52	5
3	5

[00725] **Method 2:** Agilent 1200 HPLC MSD:6120 single quadrupole with a Luna C18, 2.0*50mm 5 μ m column set to 40°C with a mobile phase A of 0.037 % TFA in water and mobile phase B of 0.018 % TFA in ACN with a flow rate of 1 mL/min used the following gradient:

Time (min)	%B
0.01	5
0.4	5
3	95
4	95
4.01	5
4.5	5

[00726] **Method 3:** Agilent 1200 HPLC MSD:1956A single quadrupole MSD with a Luna C18, 2.0*50mm 5 μ m column set to 40°C with a mobile phase A of 0.04 % TFA in water and mobile phase B of 0.02 % TFA in ACN with a flow rate of 1 mL/min used the following gradient:

Time (min)	%B
0.01	5
0.4	5
3	95
4	95

Time (min)	%B
4.01	5
4.5	5

[00727] **Method 4:** Agilent 1260 HPLC MSD:6125B single quadrupole MSD with a Xbridge C18, 2.1*50mm 5µm column set to 40°C with a mobile phase A of 10nM NH₄HCO₃ in water and mobile phase B of ACN with a flow rate of 0.8 mL/min used the following gradient:

Time (min)	%B
0.01	5
0.4	5
3.4	95
3.85	95
3.86	5
4.5	5

[00728] **Method 5:** Agilent 1260 HPLC MSD:6125B single quadrupole MSD with a Luna C18, 2.0*50mm 5µm column set to 40°C with a mobile phase A of 0.04 % TFA in water and mobile phase B of 0.02 % TFA in ACN with a flow rate of 1 mL/min used the following gradient:

Time (min)	%B
0.01	5
0.4	5
3	95
4	95
4.01	5
4.5	5

[00729] **Method 6:** Agilent 1260 HPLC MSD:6120 single quadrupole MSD with a Xbridge C18, 2.1*50mm 5µm column set to 40°C with a mobile phase A of 10 nM NH₄HCO₃ in water and mobile phase B of ACN with a flow rate of 0.8 mL/min used the following gradient:

Time (min)	%B
0.01	5
3.4	95
3.85	95
3.86	5
4.5	5

[00730] **Method 8:** 1260 HPLC MSD:6135B single quadrupole MSD with a Luna C18, 2.0*50mm 5µm column set to 40°C with a **mobile** phase A of 0.04 % TFA in water and mobile phase B of 0.02 % TFA in ACN with a flow rate of 0.8 mL/min used the following gradient:

Time (min)	%B
0.01	5
0.4	5
3	95

4	95
4.01	5
4.5	5

[00731] **Method 9:** Agilent 1200 HPLC MSD:6130 single quadrupole MSD with a Xbridge C18, 2.1*50mm 5µm column set to 40°C with a mobile phase A of 10 mM NH₄HCO₃ in water and mobile phase B of ACN with a flow rate of 0.8 mL/min used the following gradient:

Time (min)	%B
0.01	5
0.4	5
3.4	95
3.85	95
3.86	5
4.5	5

[00732] **Method 11:** Shimadzu LC-20AD MSD:LCMS-2020 with a Xbridge C18, 2.1*50mm 5µm column set to 40°C with a mobile phase A of 10 mM NH₄HCO₃ in water and mobile phase B of ACN with a flow rate of 1 mL/min used the following gradient:

Time (min)	%B
0.01	5
3.0	95
3.50	95
3.51	5
4.3	5

[00733] **Method 12:** Shimadzu LC-20ADXR MSD:LCMS-2020 set to 40°C with a mobile phase A of 0.04 % TFA in water and mobile phase B of 0.02 % TFA in ACN with a flow rate of 1 mL/min used the following gradient:

Time (min)	%B
0.00	5
3.5	95
4.5	95

[00734] **Method 13:** Agilent 1200 & 6125B with a Ascentis Express C18 100*4.6mm 2.7µm column set to 40°C with a mobile phase A of 0.037 % TFA in water and mobile phase B of 0.018 % TFA in ACN with a flow rate of 1 mL/min used the following gradient:

Time (min)	%B
0.00	60
0.4	60
6.0	70
8.0	100
8.01	60
10	60

[00735] **Method 14:** Agilent 1260 HPLC (w 1290 Quad Pump) and 6120B Single Quad MSD.

Equipped with a Infinity Lab Poroshell 120 EC-C18, 4.6X150mm 4 μ m column using water with 0.1% formic acid as the mobile phase A, and acetonitrile with 0.1% formic acid as the mobile phase B. The gradient was 5-100% with mobile phase B over 10.5 min then held at 100% for 3.35 mins. The flow rate was 1 mL/min.

[00736] **Method 15:** Shimadzu LC-20AD set to 40°C with a mobile phase A of 0.04 % TFA in water and mobile phase B of 0.02 % TFA in ACN used the following gradient:

Time (min)	%B	Flow (mL/min)
0.00	30	0.5
3.0	90	0.5
3.9	90	0.5
3.91	30	1
4.5	30	1

[00737] **Method 16:** Agilent 1200+6110MS with HALO 90A C18 5 μ m 3*30mm column set to 40°C with a mobile phase A of 0.04 % TFA in water and mobile phase B of 0.02 % TFA in ACN used the following gradient:

Time (min)	%B	Flow (mL/min)
0.00	5	1.5
0.70	95	1.5
1.16	95	1.5
1.50	5	1.5

Table 3. Representative Analytical Data for Compounds of the Disclosure.

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
1	Method 1	1.735	559.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 7.9 Hz, 1H), 8.04 (d, <i>J</i> = 8.5 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.47 (d, <i>J</i> = 2.3 Hz, 1H), 7.34 (t, <i>J</i> = 8.0 Hz, 1H), 6.93 - 7.03 (m, 3H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.25 - 5.41 (m, 1H), 3.78 (s, 3H), 3.12 (s, 5H), 2.52 - 2.56 (m, 2H), 1.58 - 1.84 (m, 4H), 1.20 (d, <i>J</i> = 6.78 Hz, 3H)
2	Method 1	1.728	529.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 7.8 Hz, 1H), 8.04 (d, <i>J</i> = 8.7 Hz, 1H), 7.71 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.36 - 7.47 (m, 6H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.21 - 6.31 (m, 1H), 5.23 - 5.44 (m, 1H), 3.30 (br s, 2H), 3.11 (s, 5H), 1.59 - 1.78 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
3	Method 14	11.36	563	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.30 (dd, <i>J</i> = 7.8, 2.4 Hz, 1H), 7.97 (d, <i>J</i> = 8.6 Hz, 1H), 7.67 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 7.50 - 7.36 (m, 4H), 7.28 (dt, <i>J</i> = 7.3, 1.6 Hz, 1H), 6.38 (dd, <i>J</i> =

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				11.2, 1.0 Hz, 1H), 6.20 (dd, <i>J</i> = 11.2, 9.5 Hz, 1H), 5.27 (q, <i>J</i> = 7.7 Hz, 1H), 3.08 (d, <i>J</i> = 14.5 Hz, 2H), 3.04 (s, 3H), 2.53 (m, 2H), 1.78 – 1.56 (m, 4H), 1.13 (d, <i>J</i> = 6.8 Hz, 3H)
4	Method 1	1.621	525.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 (dd, <i>J</i> = 2.2, 7.5 Hz, 1H), 7.97 (d, <i>J</i> = 9.2 Hz, 1H), 7.46 - 7.32 (m, 5H), 7.14 (dd, <i>J</i> = 2.6, 8.8 Hz, 1H), 6.84 (d, <i>J</i> = 3.1 Hz, 1H), 6.44 (d, <i>J</i> = 11.4 Hz, 1H), 6.26 (dd, <i>J</i> = 9.4, 11.2 Hz, 1H), 5.39 - 5.27 (m, 1H), 3.86 (s, 3H), 3.11 (s, 3H), 3.05 (br d, <i>J</i> = 12.7 Hz, 2H), 2.47 - 2.36 (m, 2H), 1.81 - 1.56 (m, 4H), 1.19 (d, <i>J</i> = 7.0 Hz, 3H)
5	Method 1	1.625	555.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 (br d, <i>J</i> = 7.9 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.30 (t, <i>J</i> = 7.9 Hz, 1H), 7.13 (dd, <i>J</i> = 2.7, 9.0 Hz, 1H), 6.98 - 6.91 (m, 3H), 6.86 (d, <i>J</i> = 2.6 Hz, 1H), 6.44 (d, <i>J</i> = 11.2 Hz, 1H), 6.29 - 6.21 (m, 1H), 5.38 - 5.26 (m, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.11 (s, 3H), 3.07 (br d, <i>J</i> = 12.7 Hz, 2H), 2.46 - 2.40 (m, 2H), 1.77 - 1.54 (m, 4H), 1.18 (d, <i>J</i> = 6.9 Hz, 3H)
6	Method 15	2.844		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 6.0 Hz, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.75 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.55 (d, <i>J</i> = 7.9 Hz, 1H), 7.47 - 7.50 (m, 1H), 7.42 - 7.46 (m, 1H), 7.39 (d, <i>J</i> = 4.3 Hz, 2H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.27 (dd, <i>J</i> = 11.0, 9.5 Hz, 1H), 5.29 - 5.40 (m, 1H), 3.12 - 3.19 (m, 2H), 3.10 (s, 3H), 2.58 - 2.76 (m, 2H), 1.64 - 1.99 (m, 4H), 1.20 (d, <i>J</i> = 6.7 Hz, 3H)
7	Method 1	1.692	559	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 5.9 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.39 - 7.52 (m, 3H), 7.32 (d, <i>J</i> = 7.1 Hz, 1H), 7.17 (dd, <i>J</i> = 8.9, 2.6 Hz, 1H), 6.90 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.21 - 6.31 (m, 1H), 5.25 - 5.41 (m, 1H), 3.87 (s, 3H), 3.11 (s, 5H), 2.52 - 2.58 (m, 2H), 1.61 - 1.88 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
8	Method 13	2.28	554	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 6.3 Hz, 1H), 8.04 (d, <i>J</i> = 8.5 Hz, 1H), 7.86 - 7.93 (m, 2H), 7.71 - 7.79 (m, 2H), 7.60 - 7.68 (m, 1H), 7.57 (d, <i>J</i> = 2.1 Hz, 1H), 6.44 (d, <i>J</i> = 10.7 Hz, 1H), 6.22 - 6.31 (m, 1H), 5.33 (br d, <i>J</i> = 9.0 Hz, 1H), 3.11 (s, 5H), 2.58 (br s, 2H), 1.64 - 1.84 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
9	Method 2	2.535	543.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 (br d, <i>J</i> = 5.9 Hz, 1H), 8.10 (dd, <i>J</i> = 5.7, 8.9 Hz, 1H), 7.47 (dt, <i>J</i> = 2.8, 8.5 Hz, 1H), 7.37 - 7.24 (m, 2H), 7.02 - 6.92 (m, 3H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 9.5, 11.1 Hz, 1H), 5.39 - 5.27 (m, 1H), 3.78 (s, 3H), 3.11 (s, 5H), 2.59 - 2.51 (m, 2H), 1.82 - 1.57 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
10	Method 2	2.739	573.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 8.03 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.46 (d, <i>J</i> = 2.2 Hz, 1H), 7.32 (t, <i>J</i> = 7.9 Hz, 1H), 6.90 - 7.00 (m, 3H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 10.9, 9.6 Hz, 1H), 5.25 - 5.41 (m, 1H), 4.05 (q, <i>J</i> = 7.0 Hz, 2H), 3.34 - 3.40 (m, 1H), 3.25 - 3.32 (m, 1H), 3.11 (s, 5H), 1.56 - 1.87 (m, 4H), 1.33 (t, <i>J</i> = 6.9 Hz, 3H), 1.19 (d, <i>J</i> = 6.7 Hz, 3H)
11	Method 3	2.519	559.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 (br d, <i>J</i> = 6.3 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.52 (d, <i>J</i> = 8.0 Hz, 1H), 7.45 - 7.34 (m, 3H), 7.19 (dd, <i>J</i> = 2.6, 8.9 Hz, 1H), 6.85 (d, <i>J</i> = 2.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.32 - 6.24 (m, 1H), 5.40 - 5.30 (m, 1H), 3.86 (s, 3H), 3.11 (s, 5H), 2.66 (br d, <i>J</i> = 12.0 Hz, 2H), 1.95 - 1.67 (m, 4H), 1.20 (d, <i>J</i> = 6.8 Hz, 3H)
12	Method 3	2.539	539.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (dd, <i>J</i> = 2.1, 7.8 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.31 - 7.10 (m, 5H), 6.77 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.32 - 6.23 (m, 1H), 5.41 - 5.29 (m, 1H), 3.85 (s, 3H), 3.11 (s, 3H), 3.10 - 2.98 (m, 2H), 2.56 (br d, <i>J</i> = 2.6 Hz, 2H), 2.01 (s, 3H), 1.91 - 1.62 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
13	Method 2	2.958	601.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (dd, <i>J</i> = 7.8, 2.0 Hz, 1H), 8.03 (d, <i>J</i> = 8.6 Hz, 1H), 7.69 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 7.46 (d, <i>J</i> = 2.2 Hz, 1H), 7.31 (t, <i>J</i> = 7.9 Hz, 1H), 6.90 - 7.00 (m, 3H), 6.45 (dd, <i>J</i> = 11.1, 0.7 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.4 Hz, 1H), 5.23 - 5.42 (m, 1H), 3.99 (t, <i>J</i> = 6.5 Hz, 2H), 3.11 (s, 5H), 2.55 (br s, 2H), 1.57 - 1.86 (m, 6H), 1.43 (dq, <i>J</i> = 14.9, 7.4 Hz, 2H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H), 0.93 (t, <i>J</i> = 7.4 Hz, 3H)
14	Method 2	2.854	587.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (dd, <i>J</i> = 7.9, 2.0 Hz, 1H), 8.03 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.46 (d, <i>J</i> = 2.4 Hz, 1H), 7.32 (t, <i>J</i> = 7.8 Hz, 1H), 6.89 - 7.00 (m, 3H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.26 (dd, <i>J</i> = 11.0, 9.5 Hz, 1H), 5.25 - 5.40 (m, 1H), 3.95 (t, <i>J</i> = 6.5 Hz, 2H), 3.05 - 3.31 (m, 6H), 1.54 - 1.88 (m, 7H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H), 0.97 (t, <i>J</i> = 7.5 Hz, 3H)
15	Method 1	1.81	585.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (dd, <i>J</i> = 7.6, 1.9 Hz, 1H), 8.05 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.47 (d, <i>J</i> = 2.1 Hz, 1H), 7.35 (t, <i>J</i> = 7.9 Hz, 1H), 7.05 - 7.15 (m, 2H), 6.98 (d, <i>J</i> = 7.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 11.0, 9.5 Hz, 1H), 5.33 (sxt, <i>J</i> = 7.6 Hz, 1H), 3.86 (tt, <i>J</i> = 5.9, 2.9 Hz, 1H), 3.06 - 3.17 (m, 5H), 2.45 (br s, 2H), 1.55 -

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				1.84 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H), 0.61 - 0.84 (m, 4H)
16	Method 1	1.744	593.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 7.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.5 Hz, 1H), 7.75 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.38 - 7.51 (m, 2H), 6.95 - 7.08 (m, 2H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.22 - 6.33 (m, 1H), 5.26 - 5.43 (m, 1H), 3.76 (s, 3H), 3.20 (br d, <i>J</i> = 11.8 Hz, 2H), 3.11 (s, 3H), 2.57 - 2.80 (m, 2H), 1.65 - 2.05 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
17	Method 1	1.773	587.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 7.7, 1.7 Hz, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.71 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.24 - 7.48 (m, 5H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.21 - 6.31 (m, 1H), 5.23 - 5.45 (m, 1H), 4.51 (s, 2H), 3.50 (q, <i>J</i> = 6.9 Hz, 2H), 3.34 (s, 3H), 3.12 (s, 4H), 1.56 - 1.79 (m, 4H), 1.11 - 1.25 (m, 6H)
18	Method 1	1.715	597	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (dd, <i>J</i> = 7.8, 1.9 Hz, 1H), 8.27 (d, <i>J</i> = 8.2 Hz, 1H), 8.06 (dd, <i>J</i> = 8.4, 1.5 Hz, 1H), 7.74 (d, <i>J</i> = 1.4 Hz, 1H), 7.58 (d, <i>J</i> = 7.7 Hz, 1H), 7.48 (td, <i>J</i> = 5.4, 3.0 Hz, 1H), 7.39 - 7.45 (m, 2H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.28 - 5.41 (m, 1H), 3.15 - 3.24 (m, 2H), 3.11 (s, 3H), 2.78 (td, <i>J</i> = 12.6, 2.9 Hz, 1H), 2.62 - 2.68 (m, 1H), 1.81 - 2.02 (m, 2H), 1.67 - 1.80 (m, 2H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
19	Method 14	9.798	525	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (dd, <i>J</i> = 7.9, 2.5 Hz, 1H), 8.04 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 7.73 (td, <i>J</i> = 7.5, 1.4 Hz, 1H), 7.63 (td, <i>J</i> = 7.7, 1.4 Hz, 1H), 7.40 (dd, <i>J</i> = 7.6, 1.4 Hz, 1H), 7.33 (t, <i>J</i> = 8.1 Hz, 1H), 7.04 - 6.86 (m, 3H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.27 (dd, <i>J</i> = 11.2, 9.4 Hz, 1H), 5.42 - 5.24 (m, 1H), 3.78 (s, 3H), 3.12 (s, 5H), 1.83 - 1.56 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
20	Method 1	1.727	529.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 6.4 Hz, 1H), 8.04 (d, <i>J</i> = 8.5 Hz, 1H), 7.71 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.35 - 7.49 (m, 6H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.21 - 6.33 (m, 1H), 5.23 - 5.44 (m, 1H), 3.27 - 3.32 (m, 2H), 3.11 (s, 5H), 1.59 - 1.80 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
21	Method 1	1.62	525.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 (dd, <i>J</i> = 1.7, 7.6 Hz, 1H), 7.97 (d, <i>J</i> = 8.9 Hz, 1H), 7.44 - 7.34 (m, 5H), 7.14 (dd, <i>J</i> = 2.7, 9.0 Hz, 1H), 6.84 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.26 (dd, <i>J</i> = 9.6, 11.1 Hz, 1H), 5.40 - 5.28 (m, 1H), 3.86 (s, 3H), 3.11 (s, 3H), 3.05 (br d, <i>J</i> = 12.5 Hz, 2H), 2.46 - 2.38 (m, 2H), 1.79 - 1.56 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
22	Method 1	1.697	559	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 7.8 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.39

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				- 7.50 (m, 3H), 7.32 (d, <i>J</i> = 7.3 Hz, 1H), 7.17 (dd, <i>J</i> = 8.9, 2.6 Hz, 1H), 6.90 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.22 - 6.33 (m, 1H), 5.27 - 5.41 (m, 1H), 3.87 (s, 3H), 3.06 - 3.17 (m, 5H), 2.55 (br s, 2H), 1.60 - 1.87 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
23	Method 1	1.736	563	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 6.8 Hz, 1H), 8.04 (d, <i>J</i> = 8.7 Hz, 1H), 7.75 (dd, <i>J</i> = 2.0, 8.5 Hz, 1H), 7.55 (d, <i>J</i> = 7.8 Hz, 1H), 7.51 - 7.42 (m, 2H), 7.40 (d, <i>J</i> = 4.1 Hz, 2H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.31 - 6.23 (m, 1H), 5.35 (br d, <i>J</i> = 6.9 Hz, 1H), 3.11 (s, 5H), 2.76 - 2.58 (m, 2H), 1.72 (br d, <i>J</i> = 13.6 Hz, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
24	Method 1	1.645	539.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 5.9 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.32 - 7.08 (m, 5H), 6.77 (d, <i>J</i> = 2.8 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.33 - 6.22 (m, 1H), 5.44 - 5.26 (m, 1H), 3.85 (s, 3H), 3.11 (s, 3H), 3.03 (br d, <i>J</i> = 12.4 Hz, 2H), 2.61 - 2.53 (m, 2H), 2.02 (s, 3H), 1.94 - 1.73 (m, 2H), 1.68 (br d, <i>J</i> = 11.0 Hz, 2H), 1.20 (d, <i>J</i> = 6.8 Hz, 3H)
25	Method 1	1.635	559.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 7.9 Hz, 1H), 7.97 (d, <i>J</i> = 8.9 Hz, 1H), 7.58 - 7.48 (m, 1H), 7.46 - 7.31 (m, 3H), 7.19 (dd, <i>J</i> = 2.7, 8.9 Hz, 1H), 6.85 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.28 (dd, <i>J</i> = 9.5, 11.0 Hz, 1H), 5.43 - 5.27 (m, 1H), 3.86 (s, 3H), 3.11 (s, 5H), 2.60 - 2.52 (m, 2H), 2.01 - 1.79 (m, 2H), 1.78 - 1.68 (m, 2H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
26	Method 1	1.655	577.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.28 - 8.43 (m, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.32 - 7.51 (m, 2H), 7.17 - 7.28 (m, 2H), 6.91 (d, <i>J</i> = 2.8 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.18 - 6.34 (m, 1H), 5.35 (sxt, <i>J</i> = 7.5 Hz, 1H), 3.86 (s, 3H), 3.12 - 3.25 (m, 2H), 3.11 (s, 3H), 2.53 - 2.73 (m, 2H), 1.64 - 2.03 (m, 4H), 1.18 - 1.25 (m, 3H)
27	Method 1	1.677	577.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 6.5 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.53 (dd, <i>J</i> = 8.9, 2.5 Hz, 1H), 7.41 (dd, <i>J</i> = 8.5, 6.3 Hz, 1H), 7.15 - 7.30 (m, 2H), 6.88 (d, <i>J</i> = 2.6 Hz, 1H), 6.46 (d, <i>J</i> = 11.3 Hz, 1H), 6.29 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.26 - 5.42 (m, 1H), 3.87 (s, 3H), 3.12 - 3.22 (m, 2H), 3.12 (s, 3H), 2.54 - 2.73 (m, 2H), 1.59 - 2.03 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
28	Method 1	1.661	576.9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (dd, <i>J</i> = 7.8, 2.1 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.56 (dd, <i>J</i> = 8.8, 5.1 Hz, 1H), 7.19 - 7.35 (m, 3H), 6.90 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.30 - 5.40 (m, 1H), 3.86 (s, 3H), 3.14 - 3.22 (m, 2H),

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				3.11 (s, 3H), 2.57 - 2.74 (m, 2H), 1.70 - 2.00 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
29	Method 1	1.709	593.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.15 (s, 1H), 7.50 (br d, <i>J</i> = 7.3 Hz, 1H), 7.46 - 7.41 (m, 1H), 7.40 - 7.30 (m, 2H), 6.81 (s, 1H), 6.41 (br s, 1H), 6.29 (d, <i>J</i> = 11.0 Hz, 1H), 6.07 (ddd, <i>J</i> = 3.4, 9.5, 11.0 Hz, 1H), 5.41 - 5.27 (m, 1H), 3.95 (s, 3H), 3.29 (br s, 1H), 3.19 (s, 3H), 3.16 - 3.09 (m, 1H), 2.92 - 2.54 (m, 2H), 2.23 - 1.94 (m, 2H), 1.76 - 1.59 (m, 2H), 1.38 (d, <i>J</i> = 6.9 Hz, 3H)
30	Method 1	1.633	577.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 7.4 Hz, 1H), 7.98 (d, <i>J</i> = 8.9 Hz, 1H), 7.44 - 7.51 (m, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 1H), 7.20 - 7.31 (m, 2H), 6.96 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.24 - 6.32 (m, 1H), 5.35 (br d, <i>J</i> = 7.7 Hz, 1H), 3.87 (s, 3H), 3.11 (s, 3H), 2.63 - 2.71 (m, 1H), 1.79 - 2.05 (m, 4H), 1.73 (s, 1H), 1.23 (s, 3H)
31	Method 1	1.672	547.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 5.9 Hz, 1H), 8.11 (dd, <i>J</i> = 8.9, 5.7 Hz, 1H), 7.28 - 7.60 (m, 6H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.26 - 5.44 (m, 1H), 3.04 - 3.19 (m, 5H), 2.67 - 2.77 (m, 1H), 2.55 - 2.64 (m, 1H), 1.68 - 2.05 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
32	Method 1	1.712	593	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 5.9 Hz, 1H), 7.99 (s, 1H), 7.50 - 7.60 (m, 1H), 7.34 - 7.47 (m, 3H), 7.10 (s, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.24 - 5.45 (m, 1H), 3.93 (s, 3H), 3.10 (s, 5H), 2.64 - 2.74 (m, 2H), 1.66 - 1.97 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
33	Method 1	1.655	597	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 - 8.41 (m, 1H), 8.26 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (dd, <i>J</i> = 8.4, 1.4 Hz, 1H), 7.75 (d, <i>J</i> = 1.2 Hz, 1H), 7.58 (d, <i>J</i> = 7.7 Hz, 1H), 7.45 - 7.51 (m, 1H), 7.40 - 7.45 (m, 2H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.4 Hz, 1H), 5.28 - 5.41 (m, 1H), 3.13 - 3.24 (m, 2H), 3.11 (s, 3H), 2.78 (td, <i>J</i> = 12.6, 2.5 Hz, 1H), 2.58 - 2.65 (m, 1H), 1.79 - 2.02 (m, 2H), 1.65 - 1.78 (m, 2H), 1.20 (d, <i>J</i> = 6.7 Hz, 3H)
34	Method 1	1.674	613	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 6.1 Hz, 1H), 8.18 (d, <i>J</i> = 8.7 Hz, 1H), 7.68 (br d, <i>J</i> = 7.6 Hz, 1H), 7.57 (d, <i>J</i> = 7.7 Hz, 1H), 7.44 - 7.49 (m, 1H), 7.35 - 7.43 (m, 3H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.23 - 6.32 (m, 1H), 5.29 - 5.41 (m, 1H), 3.04 - 3.23 (m, 5H), 2.69 - 2.84 (m, 1H), 2.55 - 2.64 (m, 1H), 1.64 - 2.05 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
35	Method 1	1.545	554.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 - 8.41 (m, 1H), 8.12 - 8.22 (m, 2H), 7.94 - 7.97

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 1H), 7.55 - 7.59 (m, 1H), 7.37 - 7.50 (m, 3H), 6.42 - 6.47 (m, 1H), 6.23 - 6.31 (m, 1H), 5.29 - 5.38 (m, 1H), 3.13 - 3.19 (m, 2H), 3.10 (s, 3H), 2.72 - 2.83 (m, 2H), 2.62 - 2.68 (m, 2H), 1.68 - 1.78 (m, 2H), 1.20 (d, <i>J</i> = 6.7 Hz, 3H)
36	Method 1	1.678	545	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.56 (br s, 1H), 8.04 (d, <i>J</i> = 8.5 Hz, 1H), 7.70 (dd, <i>J</i> = 8.5, 2.3 Hz, 1H), 7.46 (d, <i>J</i> = 2.1 Hz, 1H), 7.30 - 7.38 (m, 1H), 6.94 - 7.02 (m, 3H), 6.64 - 6.73 (m, 1H), 6.55 - 6.62 (m, 1H), 3.91 (br s, 2H), 3.78 (s, 3H), 3.13 (br d, <i>J</i> = 13.2 Hz, 2H), 2.99 (s, 3H), 2.54 (br s, 2H), 1.65 - 1.86 (m, 4H)
37	Method 1	1.67	515.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.55 (br s, 1H), 7.99 - 8.11 (m, 1H), 7.71 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.33 - 7.52 (m, 6H), 6.65 - 6.73 (m, 1H), 6.54 - 6.63 (m, 1H), 3.92 (br s, 2H), 3.30 (br s, 2H), 3.10 (br d, <i>J</i> = 13.2 Hz, 2H), 2.99 (s, 3H), 1.62 - 1.85 (m, 4H)
38	Method 1	1.554	511.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.54 (br t, <i>J</i> = 5.3 Hz, 1H), 7.98 (d, <i>J</i> = 8.8 Hz, 1H), 7.43 - 7.36 (m, 5H), 7.15 (dd, <i>J</i> = 2.6, 8.8 Hz, 1H), 6.85 (d, <i>J</i> = 2.6 Hz, 1H), 6.74 - 6.65 (m, 1H), 6.62 - 6.54 (m, 1H), 3.91 (br t, <i>J</i> = 4.4 Hz, 2H), 3.86 (s, 3H), 3.07 (br d, <i>J</i> = 12.7 Hz, 2H), 2.99 (s, 3H), 2.47 - 2.41 (m, 2H), 1.79 - 1.62 (m, 4H)
39	Method 1	1.568	541.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.54 (br s, 1H), 7.97 (d, <i>J</i> = 8.9 Hz, 1H), 7.35 - 7.28 (m, 1H), 7.14 (dd, <i>J</i> = 2.6, 8.9 Hz, 1H), 6.98 - 6.92 (m, 3H), 6.87 (d, <i>J</i> = 2.6 Hz, 1H), 6.73 - 6.65 (m, 1H), 6.62 - 6.55 (m, 1H), 3.92 (br s, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.10 (br d, <i>J</i> = 12.9 Hz, 2H), 2.99 (s, 3H), 2.45 (br s, 2H), 1.71 (br d, <i>J</i> = 17.6 Hz, 4H)
40	Method 14	10.593	549	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.59 (d, <i>J</i> = 2.8 Hz, 1H), 8.05 (d, <i>J</i> = 8.6 Hz, 1H), 7.76 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.53 - 7.38 (m, 4H), 6.71 (dt, <i>J</i> = 15.3, 4.2 Hz, 1H), 6.60 (dt, <i>J</i> = 15.2, 1.7 Hz, 1H), 3.98 - 3.91 (m, 2H), 3.18 (d, <i>J</i> = 12.8 Hz, 2H), 3.00 (s, 3H), 2.78 - 2.59 (m, 2H), 2.00 - 1.78 (m, 4H)
41	Method 1	1.628	545	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.57 (br s, 1H), 7.97 (d, <i>J</i> = 8.9 Hz, 1H), 7.39 - 7.52 (m, 3H), 7.33 (d, <i>J</i> = 6.9 Hz, 1H), 7.17 (dd, <i>J</i> = 8.9, 2.6 Hz, 1H), 6.91 (d, <i>J</i> = 2.6 Hz, 1H), 6.65 - 6.76 (m, 1H), 6.55 - 6.64 (m, 1H), 3.92 (br s, 2H), 3.87 (s, 3H), 3.13 (br d, <i>J</i> = 12.9 Hz, 2H), 2.99 (s, 3H), 2.52 - 2.58 (m, 2H), 1.68 - 1.89 (m, 4H)
42	Method 1	1.608	525.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.56 (br s, 1H), 7.92 (d, <i>J</i> = 8.2 Hz, 1H), 7.42 (d, <i>J</i> = 8.2 Hz, 1H), 7.32 (t, <i>J</i> = 8.0 Hz, 1H), 7.21 (s, 1H), 6.88 - 7.02 (m, 3H), 6.64 - 6.76 (m, 1H), 6.54 - 6.62 (m, 1H), 3.91 (br s, 2H), 3.77 (s, 3H), 3.31

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(br s, 2H), 3.12 (br d, <i>J</i> = 12.7 Hz, 2H), 2.99 (s, 3H), 2.41 (s, 3H), 1.59 - 1.86 (m, 4H)
43	Method 3	2.42	545.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.62 - 8.57 (m, 1H), 7.97 (d, <i>J</i> = 8.9 Hz, 1H), 7.52 (d, <i>J</i> = 7.4 Hz, 1H), 7.45 - 7.35 (m, 3H), 7.19 (dd, <i>J</i> = 2.6, 8.9 Hz, 1H), 6.85 (d, <i>J</i> = 2.6 Hz, 1H), 6.74 - 6.66 (m, 1H), 6.63 - 6.56 (m, 1H), 3.93 (br t, <i>J</i> = 4.1 Hz, 2H), 3.86 (s, 3H), 3.13 (br d, <i>J</i> = 12.3 Hz, 2H), 3.00 (s, 3H), 2.70 - 2.60 (m, 2H), 1.98 - 1.77 (m, 4H)
44	Method 1	1.596	525.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.62 - 8.55 (m, 1H), 7.97 (d, <i>J</i> = 8.8 Hz, 1H), 7.29 - 7.23 (m, 2H), 7.20 (dt, <i>J</i> = 1.9, 7.1 Hz, 1H), 7.17 - 7.11 (m, 2H), 6.77 (d, <i>J</i> = 2.9 Hz, 1H), 6.74 - 6.66 (m, 1H), 6.62 - 6.55 (m, 1H), 3.93 (br t, <i>J</i> = 4.1 Hz, 2H), 3.85 (s, 3H), 3.15 - 3.01 (m, 2H), 2.99 (s, 3H), 2.61 - 2.53 (m, 2H), 2.02 (s, 3H), 1.96 - 1.73 (m, 4H)
45	Method 1	1.721	549	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.59 (br s, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.73 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.43 - 7.54 (m, 4H), 7.35 (d, <i>J</i> = 7.3 Hz, 1H), 6.66 - 6.74 (m, 1H), 6.56 - 6.62 (m, 1H), 3.92 (br s, 2H), 3.16 (br d, <i>J</i> = 12.8 Hz, 2H), 2.99 (s, 3H), 2.57 (br d, <i>J</i> = 12.6 Hz, 2H), 1.72 - 1.90 (m, 4H)
46	Method 1	1.741	553.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.57 (br s, 1H), 8.03 (d, <i>J</i> = 8.5 Hz, 1H), 7.93 - 7.98 (m, 1H), 7.72 (dd, <i>J</i> = 8.5, 2.2 Hz, 1H), 7.27 - 7.52 (m, 5H), 6.65 - 6.75 (m, 1H), 6.54 - 6.63 (m, 1H), 3.92 (br s, 2H), 3.14 (br d, <i>J</i> = 12.8 Hz, 2H), 2.99 (s, 3H), 2.53 - 2.62 (m, 1H), 2.04 (s, 3H), 1.69 - 1.93 (m, 4H)
47	Method 1	1.592	607	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 6.0 Hz, 1H), 7.99 - 7.92 (m, 1H), 7.92 - 7.86 (m, 1H), 7.60 (d, <i>J</i> = 2.0 Hz, 1H), 7.58 - 7.51 (m, 1H), 7.49 - 7.41 (m, 1H), 7.39 (d, <i>J</i> = 4.1 Hz, 2H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 9.5, 11.1 Hz, 1H), 5.44 - 5.27 (m, 1H), 3.21 - 3.05 (m, 5H), 2.79 - 2.69 (m, 1H), 2.65 - 2.56 (m, 1H), 2.02 - 1.61 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
48	Method 2	2.791	624.9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 (br d, <i>J</i> = 6.4 Hz, 1H), 7.89 - 7.96 (m, 2H), 7.67 (d, <i>J</i> = 1.7 Hz, 1H), 7.55 - 7.63 (m, 1H), 7.30 - 7.38 (m, 2H), 6.45 (d, <i>J</i> = 11.4 Hz, 1H), 6.23 - 6.32 (m, 1H), 5.28 - 5.40 (m, 1H), 3.21 (br s, 2H), 3.11 (s, 3H), 2.72 - 2.81 (m, 1H), 2.70 (br s, 1H), 1.70 - 1.96 (m, 4H), 1.20 - 1.26 (m, 3H)
49	Method 2	2.799	587	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 6.6 Hz, 1H), 7.96 (d, <i>J</i> = 8.5 Hz, 1H), 7.84 (dd, <i>J</i> = 8.5, 1.9 Hz, 1H), 7.52 (d, <i>J</i> = 1.9 Hz, 1H), 7.09 - 7.34 (m, 4H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.21 - 6.33 (m, 1H), 5.27 - 5.40 (m, 1H),

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				3.43 (br s, 3H), 3.14 (br s, 1H), 3.06 (br d, <i>J</i> = 12.8 Hz, 1H), 2.61 - 2.67 (m, 2H), 2.01 (s, 3H), 1.66 - 1.95 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
50	Method 1	1.678	625	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 (br d, <i>J</i> = 6.5 Hz, 1H), 7.87 - 8.00 (m, 2H), 7.64 (d, <i>J</i> = 1.8 Hz, 1H), 7.56 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 7.46 (dd, <i>J</i> = 8.7, 6.3 Hz, 1H), 7.25 - 7.34 (m, 1H), 6.46 (d, <i>J</i> = 11.4 Hz, 1H), 6.23 - 6.34 (m, 1H), 5.36 (br d, <i>J</i> = 8.4 Hz, 1H), 3.19 (br d, <i>J</i> = 5.1 Hz, 2H), 3.11 (s, 3H), 2.65 - 2.82 (m, 2H), 1.74 - 1.95 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
51	Method 1	1.723	601	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 7.5 Hz, 1H), 7.96 (d, <i>J</i> = 8.7 Hz, 1H), 7.83 - 7.89 (m, 1H), 7.53 (d, <i>J</i> = 2.0 Hz, 1H), 7.29 - 7.42 (m, 2H), 7.23 (t, <i>J</i> = 8.0 Hz, 1H), 7.14 (d, <i>J</i> = 8.3 Hz, 1H), 6.46 (d, <i>J</i> = 11.4 Hz, 1H), 6.23 - 6.34 (m, 1H), 5.28 - 5.43 (m, 1H), 3.05 - 3.18 (m, 4H), 2.58 (br s, 3H), 2.22 (dq, <i>J</i> = 14.9, 7.5 Hz, 2H), 1.65 - 1.89 (m, 4H), 1.21 (d, <i>J</i> = 6.8 Hz, 3H), 1.06 (t, <i>J</i> = 7.5 Hz, 3H)
52	Method 1	1.669	625	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (dd, <i>J</i> = 7.9, 1.9 Hz, 1H), 7.88 - 8.00 (m, 2H), 7.69 (d, <i>J</i> = 1.9 Hz, 1H), 7.39 - 7.51 (m, 2H), 7.25 (d, <i>J</i> = 7.1 Hz, 1H), 6.45 (d, <i>J</i> = 11.4 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.29 - 5.40 (m, 1H), 3.14 - 3.27 (m, 2H), 3.11 (s, 3H), 2.69 - 2.80 (m, 1H), 2.57 - 2.66 (m, 1H), 1.70 - 2.02 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
53	Method 1	1.732	621	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.40 (br d, <i>J</i> = 7.3 Hz, 1H), 7.79 - 8.02 (m, 2H), 7.58 (d, <i>J</i> = 1.9 Hz, 1H), 7.40 (s, 1H), 7.19 - 7.31 (m, 2H), 6.47 (d, <i>J</i> = 11.4 Hz, 1H), 6.25 - 6.35 (m, 1H), 5.26 - 5.50 (m, 1H), 3.13 (s, 4H), 2.56 - 2.81 (m, 2H), 2.34 - 2.41 (m, 3H), 1.70 - 1.99 (m, 4H), 1.22 (d, <i>J</i> = 6.9 Hz, 3H)
54	Method 1	1.681	641	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 (dd, <i>J</i> = 1.8, 7.8 Hz, 1H), 7.95 - 7.84 (m, 2H), 7.81 (d, <i>J</i> = 7.4 Hz, 1H), 7.74 - 7.61 (m, 2H), 7.59 (s, 1H), 7.44 (d, <i>J</i> = 7.3 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 9.6, 11.1 Hz, 1H), 5.43 - 5.26 (m, 1H), 3.27 (br s, 1H), 3.16 (br d, <i>J</i> = 12.5 Hz, 1H), 3.12 - 3.06 (m, 3H), 2.80 - 2.61 (m, 2H), 2.02 - 1.67 (m, 4H), 1.21 (d, <i>J</i> = 6.8 Hz, 3H)
55	Method 1	1.725	607	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (dd, <i>J</i> = 7.8, 2.1 Hz, 1H), 7.93 - 7.96 (m, 1H), 7.85 - 7.89 (m, 1H), 7.64 (d, <i>J</i> = 2.0 Hz, 1H), 7.48 - 7.52 (m, 1H), 7.43 - 7.48 (m, 2H), 7.33 - 7.36 (m, 1H), 6.45 (dd, <i>J</i> = 11.1, 0.8 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.29 - 5.39 (m, 1H), 3.15 (br d, <i>J</i> = 13.0 Hz, 2H), 3.11 (s, 3H), 2.53 - 2.63 (m, 2H), 1.65 - 1.87 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
56	Method 1	1.716	605.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 6.2 Hz, 1H), 7.83 - 8.00 (m, 2H), 7.57 (s, 1H), 7.16 - 7.32 (m, 2H), 7.02 (br d, <i>J</i> = 6.7 Hz, 1H), 6.45 (br d, <i>J</i> = 11.6 Hz, 1H), 6.28 (br t, <i>J</i> = 10.5 Hz, 1H), 5.34 (br d, <i>J</i> = 8.2 Hz, 1H), 3.20 (br d, <i>J</i> = 12.5 Hz, 4H), 3.11 (s, 3H), 1.90 (br s, 3H), 1.67 - 1.84 (m, 4H), 1.20 (br d, <i>J</i> = 6.7 Hz, 3H)
57	Method 1	1.658	573.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 7.6 Hz, 1H), 7.97 (d, <i>J</i> = 8.6 Hz, 1H), 7.85 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 7.58 (d, <i>J</i> = 2.0 Hz, 1H), 7.42 - 7.47 (m, 3H), 7.38 - 7.41 (m, 2H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.27 (dd, <i>J</i> = 10.9, 9.6 Hz, 1H), 5.29 - 5.41 (m, 1H), 3.30 (br s, 2H), 3.12 (s, 3H), 3.08 (br s, 2H), 1.59 - 1.81 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
58	Method 1	1.865	650.9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (dd, <i>J</i> = 7.7, 1.9 Hz, 1H), 7.91 - 7.99 (m, 1H), 7.83 - 7.89 (m, 1H), 7.57 - 7.70 (m, 3H), 7.34 - 7.45 (m, 2H), 6.45 (d, <i>J</i> = 11.5 Hz, 1H), 6.27 (dd, <i>J</i> = 11.7, 9.6 Hz, 1H), 5.25 - 5.42 (m, 1H), 3.09 - 3.19 (m, 5H), 2.58 (br t, <i>J</i> = 12.3 Hz, 2H), 1.58 - 1.92 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
59	Method 1	1.179	621.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 7.7 Hz, 1H), 7.93 - 8.02 (m, 1H), 7.85 - 7.90 (m, 1H), 7.59 (d, <i>J</i> = 2.0 Hz, 1H), 7.41 (br d, <i>J</i> = 7.5 Hz, 1H), 7.29 (t, <i>J</i> = 7.6 Hz, 1H), 7.19 - 7.24 (m, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.22 - 6.33 (m, 1H), 5.27 - 5.40 (m, 1H), 3.11 (s, 3H), 2.65 - 2.75 (m, 4H), 2.39 (s, 3H), 1.65 - 1.93 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
60	Method 1	1.769	621	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 7.7 Hz, 1H), 7.82 - 8.02 (m, 2H), 7.56 (d, <i>J</i> = 1.9 Hz, 1H), 7.38 (s, 1H), 7.15 - 7.29 (m, 2H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.23 - 6.32 (m, 1H), 5.27 - 5.41 (m, 1H), 3.15 (br d, <i>J</i> = 11.5 Hz, 2H), 3.11 (s, 3H), 2.65 - 2.78 (m, 2H), 2.36 (s, 3H), 1.69 - 1.94 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
61	Method 1	1.746	603	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 - 8.33 (m, 1H), 7.95 (d, <i>J</i> = 8.6 Hz, 1H), 7.84 (dd, <i>J</i> = 2.1, 8.6 Hz, 1H), 7.59 (d, <i>J</i> = 2.0 Hz, 1H), 7.33 (t, <i>J</i> = 7.8 Hz, 1H), 7.01 - 6.93 (m, 3H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 9.6, 11.1 Hz, 1H), 5.38 - 5.28 (m, 1H), 3.78 (s, 3H), 3.14 - 3.12 (m, 1H), 3.11 (s, 3H), 3.11 - 3.08 (m, 1H), 2.53 - 2.52 (m, 2H), 1.80 - 1.59 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
62	Method 1	1.568	607	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (dd, <i>J</i> = 7.9, 1.7 Hz, 1H), 7.93 - 7.99 (m, 1H), 7.86 - 7.92 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.52 - 7.57 (m, 1H), 7.41 - 7.48 (m, 1H), 7.39 (d, <i>J</i> = 4.1 Hz, 2H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.28 - 5.40 (m, 1H), 3.06 -

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				3.21 (m, 5H), 2.72 (td, $J = 12.6, 2.9$ Hz, 1H), 2.59 (br t, $J = 12.3$ Hz, 1H), 1.80 - 2.01 (m, 2H), 1.66 - 1.78 (m, 2H), 1.20 (d, $J = 6.9$ Hz, 3H)
63	Method 1	1.68	589	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.57 (br s, 1H), 7.76 - 8.04 (m, 2H), 7.59 (d, $J = 1.7$ Hz, 1H), 7.34 (t, $J = 8.1$ Hz, 1H), 6.89 - 7.08 (m, 3H), 6.65 - 6.77 (m, 1H), 6.54 - 6.63 (m, 1H), 3.84 - 3.98 (m, 2H), 3.78 (s, 3H), 3.13 (br d, $J = 12.9$ Hz, 2H), 2.99 (s, 3H), 2.54 (br d, $J = 3.6$ Hz, 2H), 1.63 - 1.84 (m, 4H)
64	Method 3	2.736	592.9	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.63 - 8.55 (m, 1H), 7.98 - 7.95 (m, 1H), 7.92 - 7.87 (m, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.56 (d, $J = 7.7$ Hz, 1H), 7.48 - 7.42 (m, 1H), 7.42 - 7.39 (m, 2H), 6.74 - 6.67 (m, 1H), 6.63 - 6.56 (m, 1H), 3.93 (br t, $J = 4.2$ Hz, 2H), 3.20 - 3.12 (m, 2H), 2.79 - 2.69 (m, 1H), 2.65 - 2.56 (m, 1H), 2.04 - 1.76 (m, 4H)
65	Method 2	2.713	590.9	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.86 (br d, $J = 6.6$ Hz, 1H), 7.84 - 8.00 (m, 2H), 7.51 - 7.64 (m, 2H), 7.37 - 7.48 (m, 3H), 7.18 (dd, $J = 6.6, 2.2$ Hz, 1H), 6.78 (dd, $J = 6.7, 2.3$ Hz, 1H), 5.07 - 5.19 (m, 1H), 3.67 - 3.76 (m, 2H), 3.16 (br dd, $J = 13.5, 5.6$ Hz, 2H), 2.60 - 2.77 (m, 2H), 1.82 - 2.02 (m, 2H), 1.78 (br d, $J = 12.1$ Hz, 2H)
66	Method 1	1.657	591	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.81 - 8.88 (m, 1H), 7.87 - 7.98 (m, 2H), 7.51 - 7.63 (m, 2H), 7.37 - 7.49 (m, 3H), 7.18 (dd, $J = 6.7, 2.3$ Hz, 1H), 6.78 (dd, $J = 6.6, 2.4$ Hz, 1H), 5.07 - 5.22 (m, 1H), 3.69 (dd, $J = 13.6, 8.0$ Hz, 1H), 3.16 (br dd, $J = 13.5, 5.4$ Hz, 3H), 2.69 - 2.78 (m, 1H), 2.55 - 2.65 (m, 1H), 1.71 - 2.02 (m, 4H)
67	Method 1	1.653	591	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.85 (br d, $J = 7.1$ Hz, 1H), 7.85 - 8.00 (m, 2H), 7.52 - 7.63 (m, 2H), 7.37 - 7.48 (m, 3H), 7.18 (dd, $J = 6.6, 2.2$ Hz, 1H), 6.78 (dd, $J = 6.7, 2.3$ Hz, 1H), 5.14 (br d, $J = 6.1$ Hz, 1H), 3.69 (dd, $J = 13.6, 8.0$ Hz, 1H), 3.16 (br dd, $J = 13.4, 5.6$ Hz, 3H), 2.69 - 2.79 (m, 1H), 2.60 - 2.65 (m, 1H), 1.85 - 2.01 (m, 2H), 1.73 (br d, $J = 1.0$ Hz, 2H)
68	Method 1	1.588	542	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.53 (br d, $J = 2.1$ Hz, 1H), 7.94 - 7.98 (m, 1H), 7.87 - 7.91 (m, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.53 - 7.57 (m, 1H), 7.42 - 7.48 (m, 1H), 7.37 - 7.42 (m, 2H), 6.83 (dt, $J = 16.4, 4.6$ Hz, 1H), 5.60 (dt, $J = 16.5, 1.9$ Hz, 1H), 3.82 - 3.91 (m, 2H), 3.10 - 3.21 (m, 2H), 2.61 - 2.80 (m, 2H), 1.75 - 2.01 (m, 4H)
69	Method 1	1.645	496	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.54 (br d, $J = 2.0$ Hz, 1H), 8.04 (d, $J = 8.5$ Hz, 1H), 7.76 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.54 - 7.57 (m, 1H), 7.49 (d, $J = 2.3$ Hz, 1H), 7.42 - 7.48 (m, 1H), 7.40 (d, $J = 4.1$ Hz, 2H), 6.83 (dt, $J = 16.4, 4.5$

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				Hz, 1H), 5.60 (dt, $J = 16.4, 1.9$ Hz, 1H), 3.86 (br t, $J = 4.0$ Hz, 2H), 3.08 - 3.23 (m, 2H), 2.69 - 2.81 (m, 1H), 2.55 - 2.65 (m, 1H), 1.75 - 1.98 (m, 4H)
70	Method 1	1.584	542	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.60 - 8.66 (m, 1H), 7.93 - 7.99 (m, 1H), 7.85 - 7.92 (m, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.53 - 7.57 (m, 1H), 7.42 - 7.48 (m, 1H), 7.40 (d, $J = 4.2$ Hz, 2H), 6.46 - 6.54 (m, 1H), 5.75 (dt, $J = 11.2, 1.6$ Hz, 1H), 3.93 - 4.00 (m, 2H), 3.11 - 3.20 (m, 2H), 2.73 (td, $J = 12.6, 2.7$ Hz, 1H), 2.60 (td, $J = 12.8, 2.9$ Hz, 1H), 1.81 - 2.03 (m, 2H), 1.71 - 1.80 (m, 2H)
71	Method 1	1.507	492	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.63 (br d, $J = 2.1$ Hz, 1H), 7.97 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 7.4$ Hz, 1H), 7.35 - 7.45 (m, 3H), 7.20 (dd, $J = 8.9, 2.7$ Hz, 1H), 6.85 (d, $J = 2.6$ Hz, 1H), 6.47 - 6.54 (m, 1H), 5.75 (dt, $J = 11.2, 1.7$ Hz, 1H), 3.95 - 4.00 (m, 2H), 3.86 (s, 3H), 3.13 (br d, $J = 11.6$ Hz, 2H), 2.54 - 2.71 (m, 2H), 1.72 - 2.01 (m, 4H)
72	Method 1	1.682	540	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.70 - 8.79 (m, 1H), 7.93 - 7.99 (m, 1H), 7.86 - 7.92 (m, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.52 - 7.57 (m, 1H), 7.43 - 7.47 (m, 1H), 7.38 - 7.42 (m, 2H), 6.11 (s, 1H), 5.96 (t, $J = 1.5$ Hz, 1H), 3.88 (br d, $J = 6.0$ Hz, 2H), 3.15 (br d, $J = 11.4$ Hz, 2H), 2.74 (br dd, $J = 12.4, 10.0$ Hz, 2H), 1.70 - 1.97 (m, 4H)
73	Method 1	1.482	606	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.56 (br t, $J = 6.7$ Hz, 1H), 8.01 - 7.92 (m, 1H), 7.92 - 7.86 (m, 1H), 7.61 (d, $J = 1.9$ Hz, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.49 - 7.42 (m, 1H), 7.39 (d, $J = 4.4$ Hz, 2H), 6.85 - 6.62 (m, 2H), 5.39 - 5.20 (m, 1H), 3.79 - 3.61 (m, 3H), 3.15 (br s, 2H), 2.76 - 2.56 (m, 3H), 2.01 - 1.63 (m, 4H), 1.25 (d, $J = 6.8$ Hz, 3H)
74	Method 1	1.486	606	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.47 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.94 - 8.02 (m, 1H), 7.91 (d, $J = 2.0$ Hz, 1H), 7.62 (d, $J = 2.0$ Hz, 1H), 7.53 - 7.58 (m, 1H), 7.42 - 7.49 (m, 1H), 7.40 (d, $J = 4.1$ Hz, 2H), 6.54 - 6.59 (m, 1H), 6.51 (s, 1H), 5.28 - 5.45 (m, 1H), 3.44 (s, 3H), 3.13 - 3.21 (m, 2H), 2.53 - 2.81 (m, 2H), 1.70 - 1.96 (m, 5H), 1.23 (d, $J = 6.9$ Hz, 3H)
75	Method 2	2.331	648	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.18 - 8.98 (m, 2H), 8.52 - 8.42 (m, 1H), 7.97 - 7.85 (m, 2H), 7.59 (d, $J = 2.0$ Hz, 1H), 7.53 (d, $J = 7.9$ Hz, 1H), 7.48 - 7.35 (m, 3H), 6.85 (dd, $J = 5.0, 15.2$ Hz, 1H), 6.65 (dd, $J = 1.2, 15.3$ Hz, 1H), 4.65 - 4.54 (m, 1H), 4.49 - 4.37 (m, 1H), 4.29 - 4.18 (m, 2H), 4.12 - 4.00 (m, 2H), 3.19 - 3.09 (m, 2H), 2.78 - 2.67 (m, 1H), 2.63 - 2.52 (m,

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				1H), 1.97 - 1.67 (m, 4H), 1.22 (d, <i>J</i> = 7.0 Hz, 3H)
76	Method 2	2.327	648	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.19 - 9.01 (m, 1H), 8.47 (dd, <i>J</i> = 1.8, 7.9 Hz, 1H), 7.98 - 7.87 (m, 2H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 7.8 Hz, 1H), 7.48 - 7.37 (m, 3H), 6.87 (dd, <i>J</i> = 5.0, 15.3 Hz, 1H), 6.67 (dd, <i>J</i> = 1.3, 15.3 Hz, 1H), 4.66 - 4.57 (m, 1H), 4.50 - 4.39 (m, 1H), 4.30 - 4.21 (m, 2H), 4.13 - 4.01 (m, 2H), 3.22 - 3.09 (m, 2H), 2.73 (dt, <i>J</i> = 2.7, 12.4 Hz, 1H), 2.64 - 2.56 (m, 1H), 2.00 - 1.72 (m, 4H), 1.24 (d, <i>J</i> = 7.0 Hz, 3H)
77	Method 3	2.388	662	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.23 - 8.94 (m, 2H), 8.41 - 8.33 (m, 1H), 7.99 - 7.94 (m, 1H), 7.93 - 7.88 (m, 1H), 7.62 (d, <i>J</i> = 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 7.8 Hz, 1H), 7.45 (qd, <i>J</i> = 4.1, 8.1 Hz, 1H), 7.42 - 7.37 (m, 2H), 6.89 - 6.82 (m, 1H), 6.74 - 6.66 (m, 1H), 4.49 - 4.40 (m, 2H), 4.30 - 4.21 (m, 2H), 4.13 - 4.01 (m, 2H), 3.22 - 3.11 (m, 2H), 2.81 - 2.70 (m, 1H), 2.64 - 2.57 (m, 1H), 2.02 - 1.72 (m, 4H), 1.70 - 1.51 (m, 2H), 0.81 (t, <i>J</i> = 7.3 Hz, 3H)
78	Method 3	2.382	662	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.25 - 8.94 (m, 2H), 8.37 (dd, <i>J</i> = 2.1, 8.4 Hz, 1H), 7.98 - 7.93 (m, 1H), 7.91 - 7.87 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.54 (d, <i>J</i> = 7.8 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.40 - 7.37 (m, 2H), 6.88 - 6.81 (m, 1H), 6.73 - 6.66 (m, 1H), 4.49 - 4.39 (m, 2H), 4.29 - 4.21 (m, 2H), 4.06 (td, <i>J</i> = 6.1, 11.6 Hz, 2H), 3.22 - 3.10 (m, 2H), 2.79 - 2.68 (m, 1H), 2.64 - 2.55 (m, 1H), 2.00 - 1.71 (m, 4H), 1.69 - 1.51 (m, 2H), 0.80 (t, <i>J</i> = 7.3 Hz, 3H)
79	Method 2	2.746	606.9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.46 (dd, <i>J</i> = 1.9, 8.3 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.92 - 7.87 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 7.7 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.42 - 7.38 (m, 2H), 6.76 - 6.58 (m, 2H), 4.68 - 4.56 (m, 1H), 3.24 - 3.08 (m, 2H), 3.04 - 2.94 (m, 3H), 2.79 - 2.68 (m, 1H), 2.65 - 2.54 (m, 1H), 2.05 - 1.68 (m, 4H), 1.22 (d, <i>J</i> = 7.1 Hz, 3H)
80	Method 3	2.397	559.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.42 (br d, <i>J</i> = 6.1 Hz, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.47 (d, <i>J</i> = 2.2 Hz, 1H), 7.31 - 7.37 (m, 1H), 6.94 - 7.01 (m, 3H), 6.66 - 6.74 (m, 1H), 6.58 - 6.65 (m, 1H), 4.51 - 4.68 (m, 1H), 3.78 (s, 3H), 3.13 (br d, <i>J</i> = 12.8 Hz, 2H), 2.99 (s, 3H), 2.54 (br s, 2H), 1.62 - 1.84 (m, 4H), 1.21 (d, <i>J</i> = 7.0 Hz, 3H)
81	Method 2	2.744	607	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.46 (br d, <i>J</i> = 8.4 Hz, 1H), 7.98 - 7.88 (m, 2H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 7.7 Hz, 1H), 7.48 - 7.37 (m, 3H), 6.74 - 6.61 (m, 2H), 4.66 - 4.57 (m, 1H), 3.21 - 3.11 (m, 2H), 3.00 (s, 3H), 2.77 -

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				2.67 (m, 1H), 2.64 - 2.54 (m, 1H), 1.98 - 1.71 (m, 4H), 1.22 (d, <i>J</i> = 7.1 Hz, 3H)
82	Method 2	2.809	620.9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.26 - 8.33 (m, 1H), 7.93 - 7.97 (m, 1H), 7.87 - 7.91 (m, 1H), 7.61 (d, <i>J</i> = 2.2 Hz, 1H), 7.52 - 7.56 (m, 1H), 7.41 - 7.47 (m, 1H), 7.39 (d, <i>J</i> = 3.9 Hz, 2H), 6.49 (d, <i>J</i> = 11.2 Hz, 1H), 6.23 (dd, <i>J</i> = 11.2, 9.9 Hz, 1H), 5.21 (br dd, <i>J</i> = 8.9, 6.5 Hz, 1H), 3.11 - 3.19 (m, 2H), 3.09 (s, 3H), 2.53 - 2.78 (m, 2H), 1.80 - 2.02 (m, 2H), 1.65 - 1.78 (m, 2H), 1.45 - 1.63 (m, 2H), 0.79 (t, <i>J</i> = 7.4 Hz, 3H)
83	Method 1	1.761	573.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.27 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.46 (d, <i>J</i> = 2.1 Hz, 1H), 7.25 - 7.39 (m, 1H), 6.86 - 7.07 (m, 3H), 6.49 (d, <i>J</i> = 11.1 Hz, 1H), 6.11 - 6.32 (m, 1H), 5.08 - 5.31 (m, 1H), 3.77 (s, 3H), 3.03 - 3.17 (m, 5H), 2.53 (br s, 2H), 1.43 - 1.81 (m, 6H), 0.78 (t, <i>J</i> = 7.3 Hz, 3H)
84	Method 1	1.755	543.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.27 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 8.05 (d, <i>J</i> = 8.6 Hz, 1H), 7.71 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.32 - 7.50 (m, 6H), 6.49 (d, <i>J</i> = 11.1 Hz, 1H), 6.12 - 6.31 (m, 1H), 5.12 - 5.30 (m, 1H), 2.99 - 3.16 (m, 5H), 2.45 (br s, 2H), 1.45 - 1.80 (m, 6H), 0.78 (t, <i>J</i> = 7.3 Hz, 3H)
85	Method 1	1.701	586.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.26 (dd, <i>J</i> = 8.3, 1.7 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.46 - 7.50 (m, 1H), 7.35 - 7.41 (m, 1H), 7.31 - 7.35 (m, 2H), 6.82 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.49 (d, <i>J</i> = 11.1 Hz, 1H), 6.43 (d, <i>J</i> = 2.6 Hz, 1H), 6.24 (dd, <i>J</i> = 11.0, 10.0 Hz, 1H), 5.17 - 5.27 (m, 1H), 3.09 (s, 5H), 3.00 (s, 6H), 2.52 - 2.67 (m, 2H), 1.67 - 2.04 (m, 4H), 1.46 - 1.65 (m, 2H), 0.79 (t, <i>J</i> = 7.4 Hz, 3H)
86	Method 2	2.506	568.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 (br d, <i>J</i> = 7.7 Hz, 1H), 7.78 (d, <i>J</i> = 9.0 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.96 - 6.89 (m, 3H), 6.78 (dd, <i>J</i> = 2.8, 9.2 Hz, 1H), 6.50 - 6.41 (m, 2H), 6.26 (dd, <i>J</i> = 9.6, 11.1 Hz, 1H), 5.40 - 5.26 (m, 1H), 3.77 (s, 3H), 3.12 (s, 3H), 3.06 (br d, <i>J</i> = 12.7 Hz, 2H), 3.01 (s, 6H), 2.43 (br d, <i>J</i> = 12.7 Hz, 2H), 1.75 - 1.56 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
87	Method 1	1.67	602.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 6.1 Hz, 1H), 7.75 (d, <i>J</i> = 9.1 Hz, 1H), 7.36 (d, <i>J</i> = 8.9 Hz, 1H), 6.95 (dd, <i>J</i> = 8.8, 2.9 Hz, 1H), 6.89 (d, <i>J</i> = 3.0 Hz, 1H), 6.82 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.41 - 6.49 (m, 2H), 6.23 - 6.33 (m, 1H), 5.26 - 5.42 (m, 1H), 3.75 (s, 3H), 3.09 - 3.21 (m, 5H), 3.00 (s, 6H), 2.55 - 2.70 (m, 2H), 1.62 - 2.02 (m, 4H), 1.15 - 1.26 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
88	Method 1	1.625	538.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.31 (br d, <i>J</i> = 7.7 Hz, 1H), 7.78 (d, <i>J</i> = 9.01 Hz, 1H), 7.36 (s, 5H), 6.79 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.40 - 6.52 (m, 2H), 6.21 - 6.30 (m, 1H), 5.26 - 5.41 (m, 1H), 3.11 (s, 3H), 3.01 (s, 8H), 2.39 (br t, <i>J</i> = 12.1 Hz, 2H), 1.54 - 1.75 (m, 4H), 1.16 - 1.24 (m, 3H)
89	Method 1	1.657	572.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 6.4 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.48 (d, <i>J</i> = 7.5 Hz, 1H), 7.27 - 7.42 (m, 3H), 6.82 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.40 - 6.50 (m, 2H), 6.22 - 6.35 (m, 1H), 5.25 - 5.45 (m, 1H), 3.05 - 3.18 (m, 5H), 3.00 (s, 6H), 2.54 - 2.69 (m, 2H), 1.61 - 1.99 (m, 4H), 1.18 - 1.23 (m, 3H)
90	Method 1	1.637	602.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 5.9 Hz, 1H), 7.74 (d, <i>J</i> = 9.0 Hz, 1H), 7.25 - 7.31 (m, 1H), 7.12 (d, <i>J</i> = 7.9 Hz, 1H), 6.89 (d, <i>J</i> = 6.6 Hz, 1H), 6.81 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.38 - 6.48 (m, 2H), 6.23 - 6.32 (m, 1H), 5.29 - 5.38 (m, 1H), 3.87 (s, 3H), 3.12 - 3.19 (m, 2H), 3.11 (d, <i>J</i> = 1.3 Hz, 3H), 2.99 (s, 6H), 2.52 - 2.71 (m, 2H), 1.63 - 1.98 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
91	Method 1	1.63	538.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 (br d, <i>J</i> = 6.0 Hz, 1H), 7.78 (d, <i>J</i> = 9.0 Hz, 1H), 7.36 (s, 5H), 6.79 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.37 - 6.51 (m, 2H), 6.20 - 6.33 (m, 1H), 5.25 - 5.42 (m, 1H), 3.11 (s, 3H), 3.01 (s, 8H), 2.32 - 2.43 (m, 2H), 1.54 - 1.78 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
92	Method 1	1.655	572.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 6.2 Hz, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.48 (d, <i>J</i> = 7.6 Hz, 1H), 7.29 - 7.42 (m, 3H), 6.82 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.41 - 6.49 (m, 2H), 6.23 - 6.32 (m, 1H), 5.24 - 5.46 (m, 1H), 3.05 - 3.19 (m, 5H), 3.00 (s, 6H), 2.53 - 2.69 (m, 2H), 1.63 - 1.99 (m, 4H), 1.17 - 1.23 (m, 3H)
93	Method 1	1.688	552	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 (br d, <i>J</i> = 5.9 Hz, 1H), 7.77 (d, <i>J</i> = 9.0 Hz, 1H), 7.13 - 7.27 (m, 3H), 7.07 - 7.11 (m, 1H), 6.78 (dd, <i>J</i> = 9.1, 2.8 Hz, 1H), 6.44 (d, <i>J</i> = 11.3 Hz, 1H), 6.36 (d, <i>J</i> = 2.6 Hz, 1H), 6.23 - 6.30 (m, 1H), 5.29 - 5.40 (m, 1H), 3.10 (s, 5H), 2.99 (s, 6H), 2.43 - 2.48 (m, 2H), 2.03 (s, 3H), 1.62 - 1.88 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
94	Method 1	1.563	524.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.53 (br s, 1H), 7.79 (d, <i>J</i> = 9.0 Hz, 1H), 7.37 (s, 5H), 6.79 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 6.64 - 6.74 (m, 1H), 6.54 - 6.62 (m, 1H), 6.45 (d, <i>J</i> = 2.6 Hz, 1H), 3.91 (br s, 2H), 3.06 (br s, 2H), 3.01 (s, 6H), 2.99 (s, 3H), 2.38 (br s, 2H), 1.69 (br d, <i>J</i> = 18.4 Hz, 4H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
95	Method 1	1.592	558.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.57 (br s, 1H), 7.76 (d, <i>J</i> = 9.1 Hz, 1H), 7.45 - 7.53 (m, 1H), 7.31 - 7.42 (m, 3H), 6.82 (dd, <i>J</i> = 9.1, 2.4 Hz, 1H), 6.65 - 6.75 (m, 1H), 6.55 - 6.63 (m, 1H), 6.44 (d, <i>J</i> = 2.6 Hz, 1H), 3.93 (br s, 2H), 3.07 - 3.16 (m, 2H), 2.96 - 3.03 (m, 9H), 2.60 (br s, 2H), 1.69 - 2.02 (m, 4H)
96	Method 1	1.567	554.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.54 (br s, 1H), 7.79 (d, <i>J</i> = 9.2 Hz, 1H), 7.25 - 7.33 (m, 1H), 6.91 - 6.96 (m, 3H), 6.79 (dd, <i>J</i> = 9.1, 2.7 Hz, 1H), 6.66 - 6.74 (m, 1H), 6.54 - 6.62 (m, 1H), 6.48 (d, <i>J</i> = 2.6 Hz, 1H), 3.92 (br s, 2H), 3.77 (s, 3H), 3.08 (br d, <i>J</i> = 12.4 Hz, 2H), 3.02 (s, 6H), 3.00 (s, 3H), 2.37 - 2.44 (m, 2H), 1.64 - 1.77 (m, 4H)
97	Method 2	2.67	505	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.51 (br s, 1H), 7.76 (d, <i>J</i> = 9.0 Hz, 1H), 7.41 - 7.52 (m, 1H), 7.29 - 7.40 (m, 3H), 6.77 - 6.85 (m, 2H), 6.44 (d, <i>J</i> = 2.6 Hz, 1H), 5.59 (d, <i>J</i> = 16.5 Hz, 1H), 3.86 (br s, 2H), 3.05 - 3.16 (m, 2H), 3.00 (s, 6H), 2.65 - 2.71 (m, 2H), 1.82 - 2.00 (m, 2H), 1.76 - 1.81 (m, 2H)
98	Method 1	1.848	583.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 5.7 Hz, 1H), 7.94 (d, <i>J</i> = 8.3 Hz, 1H), 7.45 - 7.55 (m, 2H), 7.30 - 7.44 (m, 3H), 7.14 (s, 1H), 6.44 (d, <i>J</i> = 11.8 Hz, 1H), 6.16 - 6.30 (m, 1H), 5.34 (s, 1H), 3.56 - 3.71 (m, 1H), 3.03 - 3.18 (m, 5H), 2.61 - 2.74 (m, 1H), 2.23 - 2.38 (m, 3H), 2.11 (br s, 2H), 1.62 - 2.02 (m, 6H), 1.19 (d, <i>J</i> = 6.6 Hz, 3H)
99	Method 1	1.757	584.2 (M-Boc)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 7.9 Hz, 1H), 8.02 (d, <i>J</i> = 8.3 Hz, 1H), 7.68 - 7.62 (m, 1H), 7.54 (d, <i>J</i> = 8.1 Hz, 1H), 7.48 - 7.36 (m, 3H), 7.30 (d, <i>J</i> = 1.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.4 Hz, 1H), 6.33 - 6.23 (m, 1H), 5.43 - 5.25 (m, 1H), 4.27 (br t, <i>J</i> = 8.0 Hz, 2H), 4.02 - 3.79 (m, 3H), 3.11 (s, 5H), 2.76 - 2.54 (m, 2H), 1.80 - 1.65 (m, 2H), 2.02 - 1.64 (m, 2H), 1.39 (s, 9H), 1.21 (d, <i>J</i> = 6.8 Hz, 3H)
100	Method 1	1.8	567.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 7.7, 1.9 Hz, 1H), 8.03 (d, <i>J</i> = 8.6 Hz, 1H), 7.71 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.45 - 7.49 (m, 1H), 7.36 - 7.45 (m, 3H), 7.30 - 7.35 (m, 1H), 6.44 (d, <i>J</i> = 11.3 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.4 Hz, 1H), 5.27 - 5.39 (m, 1H), 3.11 (s, 5H), 2.51 - 2.58 (m, 2H), 2.04 (s, 3H), 1.60 - 1.90 (m, 4H), 1.18 - 1.23 (m, 3H)
101	Method 1	1.729	585.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 5.9 Hz, 1H), 7.98 (d, <i>J</i> = 8.9 Hz, 1H), 7.47 - 7.57 (m, 1H), 7.27 - 7.46 (m, 4H), 6.93 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.25 - 5.43 (m, 1H), 3.91 - 4.05 (m, 1H), 3.11 (s, 5H), 2.55 - 2.72 (m, 2H),

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				1.67 - 2.01 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H), 0.78 - 0.86 (m, 2H), 0.63 - 0.77 (m, 2H)
102	Method 1	1.718	553	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 7.8, 2.0 Hz, 1H), 7.94 (d, <i>J</i> = 8.9 Hz, 1H), 7.16 - 7.30 (m, 3H), 7.09 - 7.14 (m, 2H), 6.73 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.24 - 6.31 (m, 1H), 5.29 - 5.40 (m, 1H), 4.13 (q, <i>J</i> = 7.0 Hz, 2H), 3.11 (s, 3H), 3.03 (br d, <i>J</i> = 13.1 Hz, 2H), 2.52 - 2.59 (m, 2H), 2.01 (s, 3H), 1.62 - 1.89 (m, 4H), 1.33 (t, <i>J</i> = 6.9 Hz, 3H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
103	Method 1	1.765	567	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 7.7, 1.9 Hz, 1H), 7.93 (d, <i>J</i> = 9.0 Hz, 1H), 7.22 - 7.30 (m, 2H), 7.16 - 7.21 (m, 1H), 7.08 - 7.14 (m, 2H), 6.71 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.24 - 6.31 (m, 1H), 5.29 - 5.40 (m, 1H), 4.76 (sept, <i>J</i> = 6.0 Hz, 1H), 3.11 (s, 3H), 2.98 - 3.10 (m, 2H), 2.52 - 2.59 (m, 2H), 2.02 (s, 3H), 1.62 - 1.94 (m, 4H), 1.28 (t, <i>J</i> = 5.4 Hz, 6H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
104	Method 1	1.347	545	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.67 (br s, 1H), 8.35 (br d, <i>J</i> = 5.7 Hz, 1H), 7.85 (d, <i>J</i> = 8.9 Hz, 1H), 7.50 (d, <i>J</i> = 7.4 Hz, 1H), 7.30 - 7.45 (m, 3H), 6.97 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 6.62 (d, <i>J</i> = 2.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.26 - 5.45 (m, 1H), 3.11 (s, 5H), 2.55 - 2.70 (m, 2H), 1.68 - 2.02 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
105	Method 1	1.759	587	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 5.6 Hz, 1H), 7.93 (d, <i>J</i> = 8.9 Hz, 1H), 7.51 (d, <i>J</i> = 7.6 Hz, 1H), 7.32 - 7.43 (m, 3H), 7.15 (dd, <i>J</i> = 9.0, 2.6 Hz, 1H), 6.79 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.20 - 6.33 (m, 1H), 5.29 - 5.41 (m, 1H), 4.76 (dt, <i>J</i> = 12.0, 6.0 Hz, 1H), 3.11 (s, 5H), 2.61 - 2.72 (m, 2H), 1.64 - 2.03 (m, 4H), 1.29 (t, <i>J</i> = 6.1 Hz, 6H), 1.20 (d, <i>J</i> = 6.7 Hz, 3H)
106	Method 1	1.619	565	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 9.8 Hz, 1H), 7.98 (d, <i>J</i> = 8.9 Hz, 1H), 7.24 - 7.29 (m, 3H), 7.18 - 7.23 (m, 1H), 7.12 - 7.16 (m, 1H), 6.88 (d, <i>J</i> = 2.5 Hz, 1H), 6.46 (d, <i>J</i> = 11.2 Hz, 1H), 6.23 - 6.33 (m, 1H), 5.35 (br d, <i>J</i> = 7.9 Hz, 1H), 3.99 (dt, <i>J</i> = 6.0, 3.0 Hz, 1H), 3.12 (s, 3H), 3.01 - 3.11 (m, 2H), 2.53 - 2.61 (m, 2H), 2.03 (s, 3H), 1.63 - 1.96 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H), 0.65 - 0.86 (m, 4H)
107	Method 2	2.66	555	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (dd, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.98 (d, <i>J</i> = 8.2 Hz, 1H), 7.76 (dd, <i>J</i> = 8.3, 1.7 Hz, 1H), 7.49 - 7.57 (m, 1H), 7.33 - 7.48 (m, 4H), 6.84 (dd, <i>J</i> = 17.8, 11.0 Hz, 1H), 6.44 (d, <i>J</i> = 11.3 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 6.07 (d, <i>J</i> = 17.6 Hz, 1H), 5.48 (d, <i>J</i> = 11.1 Hz, 1H), 5.28 - 5.41 (m, 1H), 3.07 -

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				3.21 (m, 5H), 2.65 - 2.75 (m, 1H), 2.58 (br t, <i>J</i> = 12.6 Hz, 1H), 1.66 - 1.99 (m, 4H), 1.20 (d, <i>J</i> = 6.7 Hz, 3H)
108	Method 1	1.74	535	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 5.6 Hz, 1H), 7.96 - 8.02 (m, 1H), 7.67 - 7.76 (m, 1H), 7.35 - 7.38 (m, 1H), 7.25 - 7.30 (m, 2H), 7.18 - 7.24 (m, 1H), 7.11 - 7.17 (m, 1H), 6.83 (dd, <i>J</i> = 17.6, 11.1 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.23 - 6.33 (m, 1H), 6.06 (d, <i>J</i> = 17.8 Hz, 1H), 5.47 (d, <i>J</i> = 11.3 Hz, 1H), 5.27 - 5.39 (m, 1H), 3.15 (br s, 1H), 3.11 (s, 3H), 3.05 (br s, 1H), 2.55 - 2.62 (m, 2H), 2.00 (s, 3H), 1.76 - 1.96 (m, 2H), 1.70 (br s, 2H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
109	Method 1	1.775	569	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 6.5 Hz, 1H), 8.00 (br d, <i>J</i> = 8.3 Hz, 1H), 7.77 (br d, <i>J</i> = 8.2 Hz, 1H), 7.54 (br d, <i>J</i> = 7.2 Hz, 1H), 7.41 (br d, <i>J</i> = 10.9 Hz, 3H), 6.45 (br d, <i>J</i> = 10.9 Hz, 1H), 6.28 (br t, <i>J</i> = 10.3 Hz, 1H), 5.63 (br s, 1H), 5.24 - 5.42 (m, 2H), 3.97 - 4.07 (m, 1H), 3.05 - 3.19 (m, 4H), 2.65 - 2.77 (m, 2H), 2.60 (br s, 1H), 2.14 (br s, 3H), 1.65 - 2.01 (m, 4H), 1.15 - 1.22 (m, 3H)
110	Method 1	1.796	549	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 6.0 Hz, 1H), 8.00 (d, <i>J</i> = 8.5 Hz, 1H), 7.73 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 7.34 (d, <i>J</i> = 1.9 Hz, 1H), 7.24 - 7.31 (m, 2H), 7.21 (td, <i>J</i> = 6.9, 2.2 Hz, 1H), 7.13 - 7.17 (m, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.23 - 6.32 (m, 1H), 5.62 (s, 1H), 5.31 - 5.40 (m, 1H), 5.28 (s, 1H), 3.02 - 3.19 (m, 5H), 2.58 (br t, <i>J</i> = 12.7 Hz, 2H), 2.13 (s, 3H), 2.00 (s, 3H), 1.62 - 1.96 (m, 4H), 1.20 (d, <i>J</i> = 6.7 Hz, 3H)
111	Method 1	1.755	557.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 5.9 Hz, 1H), 7.94 (d, <i>J</i> = 8.1 Hz, 1H), 7.48 - 7.55 (m, 2H), 7.31 - 7.45 (m, 3H), 7.18 (d, <i>J</i> = 1.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.29 - 5.40 (m, 1H), 3.10 (s, 5H), 2.70 - 2.76 (m, 2H), 2.64 - 2.69 (m, 1H), 2.55 - 2.60 (m, 1H), 1.79 - 2.01 (m, 2H), 1.71 (br d, <i>J</i> = 10.4 Hz, 2H), 1.17 - 1.24 (m, 6H)
112	Method 1	1.713	523.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (dd, <i>J</i> = 7.7, 1.9 Hz, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 1H), 7.46 (dd, <i>J</i> = 8.2, 1.7 Hz, 1H), 7.38 - 7.43 (m, 3H), 7.34 - 7.38 (m, 2H), 7.20 (d, <i>J</i> = 1.6 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.27 - 5.39 (m, 1H), 3.11 (s, 3H), 3.08 (br d, <i>J</i> = 12.8 Hz, 2H), 2.66 - 2.77 (m, 2H), 2.37 - 2.46 (m, 2H), 1.57 - 1.80 (m, 4H), 1.17 - 1.24 (m, 6H)
113	Method 2	2.743	537	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 5.6 Hz, 1H), 7.93 (d, <i>J</i> = 8.2 Hz, 1H), 7.44 (dd, <i>J</i> = 8.3, 1.6 Hz, 1H), 7.23 - 7.29 (m, 2H),

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				7.16 - 7.22 (m, 1H), 7.08 - 7.14 (m, 2H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.23 - 6.30 (m, 1H), 5.28 - 5.38 (m, 1H), 3.03 - 3.15 (m, 5H), 2.65 - 2.74 (m, 2H), 2.54 - 2.60 (m, 2H), 1.98 (s, 3H), 1.76 - 1.95 (m, 2H), 1.67 (br d, <i>J</i> = 11.1 Hz, 2H), 1.17 - 1.23 (m, 6H)
114	Method 1	1.808	571	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 6.0 Hz, 1H), 7.95 (d, <i>J</i> = 8.2 Hz, 1H), 7.49 - 7.56 (m, 2H), 7.34 - 7.45 (m, 3H), 7.20 (d, <i>J</i> = 1.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.28 - 5.40 (m, 1H), 3.09 - 3.21 (m, 5H), 3.02 (dt, <i>J</i> = 13.7, 6.8 Hz, 1H), 2.64 - 2.75 (m, 1H), 2.54 - 2.61 (m, 1H), 1.64 - 2.00 (m, 4H), 1.17 - 1.25 (m, 9H)
115	Method 1	1.823	551	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.30 - 8.39 (m, 1H), 7.95 (br d, <i>J</i> = 8.2 Hz, 1H), 7.48 (br d, <i>J</i> = 8.1 Hz, 1H), 7.10 - 7.29 (m, 5H), 6.45 (br d, <i>J</i> = 11.1 Hz, 1H), 6.20 - 6.35 (m, 1H), 5.26 - 5.41 (m, 1H), 3.11 (s, 5H), 2.95 - 3.03 (m, 1H), 2.54 - 2.63 (m, 2H), 1.99 (s, 3H), 1.64 - 1.88 (m, 4H), 1.16 - 1.27 (m, 9H)
116	Method 1	1.726	564.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 5.7 Hz, 1H), 7.76 (d, <i>J</i> = 8.8 Hz, 1H), 7.04 - 7.27 (m, 4H), 6.41 - 6.53 (m, 2H), 6.22 - 6.34 (m, 1H), 6.07 (d, <i>J</i> = 2.4 Hz, 1H), 5.27 - 5.41 (m, 1H), 3.93 (t, <i>J</i> = 7.3 Hz, 4H), 2.93 - 3.13 (m, 5H), 2.47 (br s, 2H), 2.34 (quin, <i>J</i> = 7.3 Hz, 2H), 1.96 - 2.06 (m, 3H), 1.59 - 1.95 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
117	Method 1	1.728	564.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 7.8 Hz, 1H), 7.78 (d, <i>J</i> = 8.9 Hz, 1H), 7.39 - 7.31 (m, 5H), 6.64 (dd, <i>J</i> = 2.5, 9.0 Hz, 1H), 6.46 (d, <i>J</i> = 11.1 Hz, 1H), 6.36 - 6.20 (m, 2H), 5.43 - 5.25 (m, 1H), 3.31 (br s, 4H), 3.12 (s, 3H), 3.03 (br d, <i>J</i> = 12.5 Hz, 1H), 3.08 - 2.96 (m, 1H), 2.41 (br d, <i>J</i> = 13.0 Hz, 2H), 1.99 - 1.91 (m, 4H), 1.81 - 1.57 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
118	Method 1	1.645	713	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 7.9 Hz, 1H), 7.80 (d, <i>J</i> = 9.0 Hz, 1H), 7.49 (d, <i>J</i> = 7.4 Hz, 1H), 7.29 - 7.41 (m, 3H), 7.06 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.73 (d, <i>J</i> = 2.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.0 Hz, 1H), 6.28 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.28 - 5.42 (m, 1H), 3.43 (br d, <i>J</i> = 5.2 Hz, 4H), 3.34 - 3.38 (m, 4H), 3.11 (s, 5H), 2.54 - 2.68 (m, 2H), 1.63 - 1.87 (m, 4H), 1.41 (s, 9H), 1.20 (br d, <i>J</i> = 6.9 Hz, 3H)
119	Method 1	1.759	598.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 7.7 Hz, 1H), 7.74 (d, <i>J</i> = 8.9 Hz, 1H), 7.44 - 7.53 (m, 1H), 7.29 - 7.40 (m, 3H), 6.66 (dd, <i>J</i> = 9.0, 2.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.20 - 6.34 (m, 2H), 5.25 - 5.44 (m, 1H), 3.29 (br d, <i>J</i> = 4.5 Hz, 4H), 3.11 (s, 5H), 2.52 - 2.64 (m, 2H),

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				1.96 (br t, <i>J</i> = 6.4 Hz, 4H), 1.63 - 1.92 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
120	Method 1	1.779	578	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 7.8, 2.1 Hz, 1H), 7.76 (d, <i>J</i> = 8.9 Hz, 1H), 7.13 - 7.28 (m, 3H), 7.06 - 7.12 (m, 1H), 6.63 (dd, <i>J</i> = 9.0, 2.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.24 - 6.34 (m, 1H), 6.22 (d, <i>J</i> = 2.5 Hz, 1H), 5.29 - 5.41 (m, 1H), 3.29 (br t, <i>J</i> = 6.3 Hz, 4H), 3.11 (d, <i>J</i> = 1.1 Hz, 3H), 2.99 (br d, <i>J</i> = 12.6 Hz, 1H), 2.46 (br s, 2H), 2.04 (s, 3H), 1.95 (br t, <i>J</i> = 6.4 Hz, 4H), 1.92 - 1.99 (m, 1H), 1.60 - 1.91 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
121	Method 1	1.6	614	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 6.3 Hz, 1H), 7.80 (d, <i>J</i> = 9.0 Hz, 1H), 7.54 - 7.45 (m, 1H), 7.42 - 7.28 (m, 3H), 7.08 (dd, <i>J</i> = 2.5, 9.1 Hz, 1H), 6.75 (d, <i>J</i> = 2.4 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.33 - 6.22 (m, 1H), 5.44 - 5.26 (m, 1H), 3.70 (br t, <i>J</i> = 4.6 Hz, 4H), 3.29 (br d, <i>J</i> = 2.3 Hz, 5H), 3.11 (s, 4H), 2.69 - 2.52 (m, 2H), 2.01 - 1.68 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
122	Method 1	1.608	594	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.82 (d, <i>J</i> = 9.0 Hz, 1H), 7.20 - 7.27 (m, 2H), 7.14 - 7.20 (m, 1H), 7.09 - 7.12 (m, 1H), 7.05 (dd, <i>J</i> = 9.1, 2.6 Hz, 1H), 6.67 (d, <i>J</i> = 2.5 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.24 - 6.31 (m, 1H), 5.29 - 5.40 (m, 1H), 3.70 (t, <i>J</i> = 4.7 Hz, 4H), 3.25 - 3.31 (m, 4H), 3.11 (s, 3H), 2.97 - 3.10 (m, 2H), 2.54 (br d, <i>J</i> = 3.0 Hz, 2H), 2.03 (s, 3H), 1.76 - 1.97 (m, 2H), 1.62 - 1.72 (m, 2H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
123	Method 1	1.655	616	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 5.9 Hz, 1H), 7.73 (d, <i>J</i> = 8.9 Hz, 1H), 7.45 (dd, <i>J</i> = 8.9, 2.6 Hz, 1H), 7.35 (dd, <i>J</i> = 8.5, 6.3 Hz, 1H), 7.21 (td, <i>J</i> = 8.5, 2.6 Hz, 1H), 6.67 (dd, <i>J</i> = 8.9, 2.4 Hz, 1H), 6.45 (d, <i>J</i> = 11.4 Hz, 1H), 6.22 - 6.32 (m, 2H), 5.28 - 5.40 (m, 1H), 3.29 (br d, <i>J</i> = 4.5 Hz, 4H), 3.16 (br d, <i>J</i> = 12.1 Hz, 2H), 3.10 (s, 3H), 2.53 - 2.63 (m, 2H), 1.64 - 1.99 (m, 8H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
124	Method 1	1.707	584.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 (dd, <i>J</i> = 7.8, 2.3 Hz, 1H), 7.72 (d, <i>J</i> = 8.8 Hz, 1H), 7.44 (dd, <i>J</i> = 7.9, 1.1 Hz, 1H), 7.26 - 7.37 (m, 3H), 6.39 - 6.49 (m, 2H), 6.24 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 6.10 (d, <i>J</i> = 2.4 Hz, 1H), 5.26 - 5.37 (m, 1H), 3.85 - 3.95 (m, 4H), 3.08 (s, 5H), 2.48 - 2.61 (m, 2H), 2.27 - 2.36 (m, 2H), 1.59 - 1.96 (m, 4H), 1.17 (d, <i>J</i> = 6.8 Hz, 3H)
125	Method 3	2.451	587.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 (br d, <i>J</i> = 5.9 Hz, 1H), 8.05 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (dd, <i>J</i> = 8.5, 2.2 Hz, 1H), 7.44 (d, <i>J</i> = 2.2 Hz, 1H), 7.18 - 7.36 (m, 4H), 6.44 (d, <i>J</i> = 11.3 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.27 - 5.39

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 1H), 3.57 (t, <i>J</i> = 6.7 Hz, 2H), 3.24 (s, 3H), 3.02 - 3.13 (m, 5H), 2.85 (t, <i>J</i> = 6.7 Hz, 2H), 2.38 - 2.46 (m, 2H), 1.53 - 1.78 (m, 4H), 1.19 (d, <i>J</i> = 6.7 Hz, 3H)
126	Method 1	1.709	573.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 8.2 Hz, 1H), 8.05 (d, <i>J</i> = 8.5 Hz, 1H), 7.71 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 7.30 - 7.47 (m, 5H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.19 - 6.32 (m, 1H), 5.25 - 5.41 (m, 1H), 4.47 (s, 2H), 3.30 (s, 3H), 3.05 - 3.13 (m, 5H), 2.36 - 2.46 (m, 2H), 1.58 - 1.75 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
127	Method 2	2.722	586.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (dd, <i>J</i> = 7.8, 2.1 Hz, 1H), 8.26 (s, 1H), 8.05 (d, <i>J</i> = 8.5 Hz, 1H), 7.73 (dd, <i>J</i> = 8.5, 2.3 Hz, 1H), 7.64 - 7.68 (m, 1H), 7.60 (s, 1H), 7.40 - 7.51 (m, 3H), 6.44 (dd, <i>J</i> = 11.1, 0.8 Hz, 1H), 6.26 (dd, <i>J</i> = 11.2, 9.5 Hz, 1H), 5.26 - 5.38 (m, 1H), 3.89 (s, 3H), 3.11 (s, 5H), 2.52 - 2.60 (m, 2H), 1.60 - 1.86 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
128	Method 1	1.423	573.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 - 8.49 (m, 1H), 7.99 (d, <i>J</i> = 8.1 Hz, 1H), 7.54 - 7.63 (m, 2H), 7.38 - 7.52 (m, 3H), 7.26 (d, <i>J</i> = 1.4 Hz, 1H), 6.52 (d, <i>J</i> = 11.1 Hz, 1H), 6.34 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.33 - 5.50 (m, 1H), 4.78 (t, <i>J</i> = 5.1 Hz, 1H), 3.67 - 3.78 (m, 2H), 3.15 - 3.27 (m, 5H), 2.90 (t, <i>J</i> = 6.6 Hz, 2H), 2.61 - 2.75 (m, 2H), 1.67 - 2.10 (m, 4H), 1.27 (d, <i>J</i> = 6.9 Hz, 3H)
129	Method 1	1.444	573.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 - 8.44 (m, 1H), 7.98 (d, <i>J</i> = 8.2 Hz, 1H), 7.62 (dd, <i>J</i> = 8.2, 1.6 Hz, 1H), 7.54 (d, <i>J</i> = 7.7 Hz, 1H), 7.33 - 7.48 (m, 3H), 7.29 (d, <i>J</i> = 1.2 Hz, 1H), 6.46 (d, <i>J</i> = 11.1 Hz, 1H), 6.28 (dd, <i>J</i> = 11.0, 9.6 Hz, 1H), 5.45 (dd, <i>J</i> = 4.4, 2.9 Hz, 1H), 5.28 - 5.41 (m, 1H), 4.79 (s, 1H), 3.07 - 3.19 (m, 5H), 2.58 - 2.70 (m, 2H), 1.63 - 2.04 (m, 4H), 1.35 (dd, <i>J</i> = 6.4, 2.1 Hz, 3H), 1.21 (d, <i>J</i> = 6.7 Hz, 3H)
130	Method 1	1.405	559.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 - 8.39 (m, 1H), 7.96 - 8.01 (m, 1H), 7.57 - 7.61 (m, 1H), 7.53 (dd, <i>J</i> = 7.8, 1.2 Hz, 1H), 7.32 - 7.45 (m, 3H), 7.24 - 7.27 (m, 1H), 6.41 - 6.49 (m, 1H), 6.23 - 6.32 (m, 1H), 5.44 - 5.51 (m, 1H), 5.27 - 5.38 (m, 1H), 4.58 - 4.66 (m, 2H), 3.12 - 3.19 (m, 2H), 3.09 - 3.12 (m, 3H), 2.63 - 2.73 (m, 1H), 2.54 - 2.61 (m, 1H), 1.68 - 2.00 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
131	Method 1	1.619	567	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 7.0 Hz, 1H), 7.93 - 8.01 (m, 1H), 7.62 - 7.92 (m, 1H), 7.38 - 7.62 (m, 4H), 7.28 - 7.37 (m, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.20 - 6.34 (m, 1H), 5.27 - 5.42 (m, 1H), 3.11 (s, 5H), 2.69

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(br d, $J = 16.6$ Hz, 1H), 2.58 - 2.64 (m, 1H), 1.54 - 2.19 (m, 7H), 1.20 (d, $J = 6.9$ Hz, 3H)
132	Method 1	1.408	585	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.42 - 8.29 (m, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 7.79 - 7.67 (m, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.46 - 7.29 (m, 4H), 6.45 (d, $J = 11.4$ Hz, 1H), 6.32 - 6.23 (m, 1H), 5.39 - 5.29 (m, 1H), 4.96 (ddd, $J = 1.6, 6.2, 8.1$ Hz, 2H), 4.63 (td, $J = 6.3, 14.4$ Hz, 2H), 4.43 - 4.33 (m, 1H), 3.28 - 3.25 (m, 1H), 3.20 - 3.02 (m, 4H), 2.74 - 2.65 (m, 1H), 2.61 - 2.57 (m, 1H), 1.98 - 1.68 (m, 4H), 1.23 (s, 3H)
133	Method 1	1.649	619	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.11 (d, $J = 8.3$ Hz, 1H), 7.81 - 7.94 (m, 2H), 7.56 (d, $J = 1.7$ Hz, 1H), 7.48 - 7.53 (m, 1H), 7.37 - 7.44 (m, 1H), 7.32 - 7.36 (m, 2H), 6.40 (d, $J = 11.0$ Hz, 1H), 6.24 (d, $J = 9.4$ Hz, 1H), 5.25 - 5.35 (m, 1H), 3.08 (s, 3H), 2.99 (s, 3H), 2.92 - 2.98 (m, 2H), 2.50 - 2.54 (m, 2H), 1.61 - 1.71 (m, 4H), 1.15 (d, $J = 6.8$ Hz, 3H)
134	Method 1	1.71	638.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.34 (dd, $J = 1.7, 8.2$ Hz, 1H), 8.26 (d, $J = 8.4$ Hz, 1H), 8.06 (dd, $J = 1.4, 8.4$ Hz, 1H), 7.74 (s, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.52 - 7.39 (m, 3H), 6.66 (dd, $J = 5.9, 15.5$ Hz, 1H), 5.93 (dd, $J = 1.2, 15.4$ Hz, 1H), 4.62 (br t, $J = 10.9$ Hz, 2H), 4.56 - 4.48 (m, 1H), 4.31 (br t, $J = 11.4$ Hz, 2H), 3.24 - 3.18 (m, 2H), 2.78 (dt, $J = 2.6, 12.6$ Hz, 1H), 2.69 - 2.58 (m, 1H), 2.06 - 1.75 (m, 4H), 1.19 (d, $J = 7.0$ Hz, 3H)
135	Method 1	1.698	648	¹ H NMR (400 MHz, CD ₃ SOCD ₃) δ ppm 8.35 (br d, $J = 7.2$ Hz, 1H), 7.98 - 7.94 (m, 1H), 7.91 - 7.87 (m, 1H), 7.61 (d, $J = 1.8$ Hz, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.48 - 7.42 (m, 1H), 7.40 (d, $J = 4.6$ Hz, 2H), 6.66 (dd, $J = 6.0, 15.2$ Hz, 1H), 5.94 (d, $J = 15.3$ Hz, 1H), 4.66 - 4.59 (m, 2H), 4.56 - 4.49 (m, 1H), 4.36 - 4.28 (m, 2H), 3.19 - 3.13 (m, 2H), 2.77 - 2.69 (m, 1H), 2.64 - 2.56 (m, 1H), 2.02 - 1.81 (m, 2H), 1.80 - 1.72 (m, 2H), 1.19 (d, $J = 7.0$ Hz, 3H)
136	Method 1	1.549	595.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.33 - 8.40 (m, 1H), 8.19 - 8.24 (m, 1H), 8.13 - 8.17 (m, 1H), 7.97 (d, $J = 1.5$ Hz, 1H), 7.55 - 7.61 (m, 1H), 7.41 - 7.50 (m, 3H), 6.66 (dd, $J = 15.4, 5.8$ Hz, 1H), 5.93 (dd, $J = 15.4, 0.9$ Hz, 1H), 4.57 - 4.68 (m, 2H), 4.49 - 4.56 (m, 1H), 4.25 - 4.37 (m, 2H), 3.14 - 3.22 (m, 2H), 2.73 - 2.84 (m, 1H), 2.57 - 2.68 (m, 1H), 1.71 - 1.95 (m, 4H), 1.19 (d, $J = 7.0$ Hz, 3H)
137	Method 1	1.571	600.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.30 - 8.38 (m, 1H), 7.92 - 8.01 (m, 1H), 7.52 (d, $J = 7.5$ Hz, 1H), 7.39 - 7.45 (m, 1H), 7.34 - 7.38 (m, 2H), 7.19 (dd, $J = 8.9, 2.6$ Hz, 1H), 6.85 (d, $J = 2.6$ Hz, 1H), 6.66 (dd, $J = 15.4, 5.9$ Hz, 1H), 5.93

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(d, $J = 15.4$ Hz, 1H), 4.56 - 4.70 (m, 2H), 4.47 - 4.56 (m, 1H), 4.31 (br t, $J = 12.0$ Hz, 2H), 3.86 (s, 3H), 3.13 (br d, $J = 12.0$ Hz, 2H), 2.53 - 2.73 (m, 2H), 1.81 - 2.03 (m, 2H), 1.68 - 1.78 (m, 2H), 1.19 (d, $J = 6.9$ Hz, 3H)
138	Method 4	2.949	612.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.34 (br d, $J = 6.6$ Hz, 1H), 8.14 - 8.23 (m, 2H), 7.82 (s, 1H), 7.57 (d, $J = 7.5$ Hz, 1H), 7.37 - 7.51 (m, 3H), 6.66 (dd, $J = 15.4, 5.9$ Hz, 1H), 5.94 (dd, $J = 15.4, 1.1$ Hz, 1H), 4.45 - 4.74 (m, 3H), 4.31 (br t, $J = 11.8$ Hz, 2H), 3.20 (br d, $J = 11.5$ Hz, 2H), 2.75 (br t, $J = 11.5$ Hz, 1H), 2.55 - 2.67 (m, 4H), 1.69 - 2.06 (m, 4H), 1.19 (d, $J = 7.0$ Hz, 3H)
139	Method 3	2.884	609	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.23 (d, $J = 8.5$ Hz, 1H), 8.14 (d, $J = 8.3$ Hz, 1H), 8.02 - 8.07 (m, 1H), 7.73 (s, 1H), 7.56 (d, $J = 7.9$ Hz, 1H), 7.43 - 7.50 (m, 1H), 7.40 - 7.42 (m, 2H), 6.40 - 6.45 (m, 1H), 6.21 - 6.29 (m, 1H), 5.28 - 5.38 (m, 1H), 3.10 (s, 3H), 2.97 - 3.06 (m, 5H), 2.68 - 2.79 (m, 1H), 2.57 - 2.62 (m, 1H), 1.60 - 1.76 (m, 4H), 1.18 (d, $J = 7.0$ Hz, 3H)
140	Method 4	2.789	614.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.28 - 8.36 (m, 1H), 7.98 (d, $J = 8.3$ Hz, 1H), 7.62 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.53 (d, $J = 7.9$ Hz, 1H), 7.34 - 7.45 (m, 3H), 7.29 (d, $J = 1.4$ Hz, 1H), 6.66 (dd, $J = 15.4, 5.9$ Hz, 1H), 5.93 (dd, $J = 15.5, 1.3$ Hz, 1H), 5.43 (dd, $J = 4.4, 2.9$ Hz, 1H), 4.78 - 4.90 (m, 1H), 4.46 - 4.68 (m, 3H), 4.24 - 4.40 (m, 2H), 3.16 (br s, 2H), 2.69 (br t, $J = 11.4$ Hz, 1H), 2.56 (br t, $J = 12.5$ Hz, 1H), 1.68 - 2.03 (m, 4H), 1.35 (dd, $J = 6.5, 2.1$ Hz, 3H), 1.19 (d, $J = 7.0$ Hz, 3H)
141	Method 3	2.734, 2.781	573	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.35 (br dd, $J = 2.6, 7.6$ Hz, 1H), 8.05 - 7.92 (m, 1H), 7.62 - 7.49 (m, 1H), 7.46 - 7.31 (m, 3H), 7.19 - 7.11 (m, 1H), 6.89 - 6.75 (m, 1H), 6.44 (d, $J = 11.1$ Hz, 1H), 6.26 (dd, $J = 9.6, 11.1$ Hz, 1H), 5.41 - 5.25 (m, 1H), 3.85 (s, 3H), 3.15 - 3.07 (m, 3H), 2.95 - 2.72 (m, 1H), 2.31 - 2.23 (m, 1H), 2.13 - 1.74 (m, 2H), 1.74 - 1.44 (m, 3H), 1.24 - 1.15 (m, 3H), 1.08 - 0.97 (m, 3H)
142	Method 1	1.714	611.1	¹ H NMR (400 MHz, CD ₃ SOCD ₃ , 298 K) δ ppm 8.43 (br d, $J = 5.5$ Hz, 1H), 8.35 (d, $J = 8.4$ Hz, 1H), 8.10 (dd, $J = 1.3, 8.4$ Hz, 1H), 7.80 (s, 1H), 7.72 - 7.61 (m, 1H), 7.59 - 7.44 (m, 3H), 6.51 (d, $J = 11.1$ Hz, 1H), 6.32 (dd, $J = 9.6, 11.0$ Hz, 1H), 5.40 (td, $J = 7.5, 15.5$ Hz, 1H), 3.57 - 3.45 (m, 1H), 3.18 (d, $J = 1.5$ Hz, 3H), 3.08 - 2.82 (m, 1H), 2.47 - 2.35 (m, 1H), 2.21 - 2.02 (m, 1H), 2.01 - 1.83 (m, 1H), 1.82 - 1.74 (m, 1H), 1.72 - 1.62 (m, 1H), 1.27 (d, $J = 6.9$ Hz, 3H), 1.15 - 1.06 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
143	Method 1	1.704	621	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 5.4 Hz, 1H), 7.98 (d, <i>J</i> = 8.5 Hz, 1H), 7.86 (br d, <i>J</i> = 8.7 Hz, 1H), 7.51 - 7.64 (m, 2H), 7.32 - 7.50 (m, 3H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.26 (t, <i>J</i> = 10.3 Hz, 1H), 5.26 - 5.42 (m, 1H), 3.40 (br dd, <i>J</i> = 10.4, 7.3 Hz, 1H), 3.11 (d, <i>J</i> = 2.0 Hz, 3H), 2.60 - 2.99 (m, 1H), 2.33 (br s, 1H), 1.76 - 2.16 (m, 2H), 1.50 - 1.72 (m, 2H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H), 1.00 - 1.09 (m, 3H)
144	Method 1	1.566	568.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 - 8.41 (m, 1H), 8.23 (d, <i>J</i> = 8.3 Hz, 1H), 8.13 (dd, <i>J</i> = 8.3, 1.8 Hz, 1H), 7.95 (d, <i>J</i> = 1.2 Hz, 1H), 7.56 - 7.67 (m, 1H), 7.35 - 7.52 (m, 3H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.28 - 5.39 (m, 1H), 3.38 - 3.52 (m, 1H), 3.10 - 3.13 (m, 3H), 2.65 - 2.99 (m, 1H), 2.31 - 2.41 (m, 1H), 1.57 - 2.11 (m, 4H), 1.20 (d, <i>J</i> = 6.8 Hz, 3H), 1.00 - 1.06 (m, 3H)
145	Method 1	1.903	621.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 7.6 Hz, 1H), 7.96 (d, <i>J</i> = 8.4 Hz, 1H), 7.85 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 7.62 (d, <i>J</i> = 2.0 Hz, 1H), 7.41 - 7.55 (m, 3H), 7.35 (d, <i>J</i> = 7.2 Hz, 1H), 6.44 (d, <i>J</i> = 11.2 Hz, 1H), 6.20 - 6.29 (m, 1H), 5.26 - 5.41 (m, 1H), 3.32 - 3.40 (m, 1H), 3.11 (s, 3H), 3.05 - 3.11 (m, 1H), 2.55 (br d, <i>J</i> = 2.8 Hz, 1H), 1.52 - 1.98 (m, 4H), 1.12 - 1.26 (m, 3H), 0.93 (d, <i>J</i> = 6.8 Hz, 3H)
146	Method 1	1.567	571	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.11 (d, <i>J</i> = 8.0 Hz, 1H), 7.93 (d, <i>J</i> = 8.9 Hz, 1H), 7.50 (d, <i>J</i> = 7.7 Hz, 1H), 7.44 - 7.31 (m, 3H), 7.18 (dd, <i>J</i> = 2.7, 9.0 Hz, 1H), 6.83 (d, <i>J</i> = 2.6 Hz, 1H), 6.43 (d, <i>J</i> = 11.2 Hz, 1H), 6.30 - 6.23 (m, 1H), 5.40 - 5.28 (m, 1H), 3.85 (s, 3H), 3.11 (s, 3H), 3.02 (s, 3H), 3.00 - 2.92 (m, 2H), 2.65 - 2.52 (m, 2H), 1.74 - 1.56 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
147	Method 12	2.592	573	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (ddd, <i>J</i> = 2.4, 7.7, 15.0 Hz, 1H), 7.99 (d, <i>J</i> = 8.9 Hz, 1H), 7.54 - 7.46 (m, 1H), 7.45 - 7.23 (m, 3H), 7.21 - 7.14 (m, 1H), 6.83 (dd, <i>J</i> = 2.7, 9.8 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.28 (ddd, <i>J</i> = 4.0, 9.5, 11.1 Hz, 1H), 5.42 - 5.27 (m, 1H), 3.85 (s, 3H), 3.77 - 3.59 (m, 1H), 3.16 - 3.10 (m, 3H), 3.06 - 2.91 (m, 2H), 2.09 - 1.57 (m, 4H), 1.23 - 1.16 (m, 3H), 1.14 - 1.00 (m, 3H)
148	Method 2	2.652	573	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (ddd, <i>J</i> = 2.3, 8.0, 16.0 Hz, 1H), 7.99 (d, <i>J</i> = 8.9 Hz, 1H), 7.51 (d, <i>J</i> = 7.8 Hz, 1H), 7.45 - 7.23 (m, 3H), 7.17 (td, <i>J</i> = 2.1, 9.0 Hz, 1H), 6.83 (dd, <i>J</i> = 2.6, 9.3 Hz, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.28 (ddd, <i>J</i> = 2.4, 9.3, 11.3 Hz, 1H), 5.44 - 5.27 (m, 1H), 3.85 (s, 3H), 3.75 - 3.61 (m, 1H), 3.15 - 3.07 (m, 3H), 3.06 - 2.94 (m, 2H), 2.13 - 1.58 (m, 4H), 1.24 - 1.16 (m, 3H), 1.15 - 0.99 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
149	Method 1	1.72	587.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br dd, <i>J</i> = 7.5, 2.5 Hz, 1H), 8.03 (d, <i>J</i> = 8.2 Hz, 1H), 7.52 - 7.63 (m, 2H), 7.33 - 7.47 (m, 3H), 7.22 - 7.27 (m, 1H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.34 (dt, <i>J</i> = 15.6, 7.6 Hz, 1H), 4.53 (s, 2H), 3.33 (s, 2H), 3.11 (d, <i>J</i> = 2.1 Hz, 3H), 2.65 - 3.00 (m, 2H), 2.25 - 2.37 (m, 1H), 1.94 - 2.13 (m, 1H), 1.49 - 1.90 (m, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H), 1.04 (br d, <i>J</i> = 7.1 Hz, 3H)
150	Method 1	1.741	587.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.45 - 8.26 (m, 1H), 8.08 - 7.95 (m, 1H), 7.58 - 7.33 (m, 4H), 7.25 - 7.11 (m, 1H), 6.85 - 6.78 (m, 1H), 6.46 (d, <i>J</i> = 11.2 Hz, 1H), 6.32 - 6.18 (m, 1H), 5.44 - 5.30 (m, 1H), 3.85 (s, 3H), 3.19 - 3.11 (m, 3H), 3.11 - 2.84 (m, 2H), 2.10 - 1.50 (m, 3H), 1.48 - 1.39 (m, 1H), 1.36 - 1.28 (m, 3H), 1.23 - 1.18 (m, 3H), 1.14 - 1.03 (m, 3H)
151	Method 1	1.624	614.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 (br d, <i>J</i> = 7.7 Hz, 1H), 7.98 (dd, <i>J</i> = 8.8, 1.8 Hz, 1H), 7.31 - 7.64 (m, 4H), 7.16 (dt, <i>J</i> = 8.8, 3.3 Hz, 1H), 6.83 (t, <i>J</i> = 3.1 Hz, 1H), 6.56 - 6.72 (m, 1H), 5.82 - 6.03 (m, 1H), 4.62 (br t, <i>J</i> = 11.6 Hz, 2H), 4.44 - 4.55 (m, 1H), 4.31 (br t, <i>J</i> = 11.6 Hz, 2H), 3.85 (s, 3H), 3.34 - 3.39 (m, 1H), 2.73 - 2.94 (m, 1H), 2.22 - 2.35 (m, 1H), 1.66 - 2.16 (m, 3H), 1.51 - 1.61 (m, 1H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H), 0.96 - 1.09 (m, 3H)
152	Method 5	2.948, 2.83	652.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.26 - 8.37 (m, 2H), 8.04 (br d, <i>J</i> = 8.1 Hz, 1H), 7.74 (s, 1H), 7.55 - 7.67 (m, 1H), 7.38 - 7.52 (m, 3H), 6.66 (dd, <i>J</i> = 15.4, 6.1 Hz, 1H), 5.96 (d, <i>J</i> = 15.4 Hz, 1H), 4.47 - 4.71 (m, 3H), 4.24 - 4.39 (m, 2H), 3.37 - 3.51 (m, 1H), 2.67 - 3.01 (m, 1H), 2.29 - 2.40 (m, 1H), 1.56 - 1.67 (m, 1H), 1.55 - 2.17 (m, 3H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H), 1.01 - 1.09 (m, 3H)
153	Method 1	1.733	662.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.29 - 8.36 (m, 1H), 7.99 (d, <i>J</i> = 8.6 Hz, 1H), 7.84 - 7.90 (m, 1H), 7.52 - 7.64 (m, 2H), 7.32 - 7.51 (m, 3H), 6.65 (ddd, <i>J</i> = 15.4, 6.1, 1.2 Hz, 1H), 5.96 (dd, <i>J</i> = 15.4, 1.0 Hz, 1H), 4.44 - 4.71 (m, 3H), 4.31 (br t, <i>J</i> = 11.5 Hz, 2H), 3.41 (td, <i>J</i> = 7.3, 3.7 Hz, 1H), 2.94 (dt, <i>J</i> = 13.4, 4.2 Hz, 1H), 2.78 (dt, <i>J</i> = 13.8, 3.8 Hz, 1H), 2.33 (br t, <i>J</i> = 11.8 Hz, 1H), 1.83 - 2.18 (m, 1H), 1.69 - 1.79 (m, 1H), 1.49 - 1.66 (m, 1H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H), 0.99 - 1.10 (m, 3H)
154	Method 1	1.596	609.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.29 - 8.39 (m, 1H), 8.24 (d, <i>J</i> = 8.2 Hz, 1H), 8.13 (dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 7.95 (s, 1H), 7.55 - 7.66 (m, 1H), 7.35 - 7.52 (m, 3H), 6.65 (dd, <i>J</i> = 15.5, 6.1 Hz, 1H), 5.96 (d, <i>J</i> = 15.4 Hz, 1H), 4.58 - 4.68

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 2H), 4.48 - 4.54 (m, 1H), 4.33 (br d, <i>J</i> = 11.1 Hz, 2H), 3.38 - 3.53 (m, 1H), 2.64 - 3.03 (m, 2H), 2.36 (br t, <i>J</i> = 11.6 Hz, 1H), 1.85 - 2.12 (m, 1H), 1.70 - 1.82 (m, 1H), 1.54 - 1.66 (m, 1H), 1.19 (d, <i>J</i> = 6.7 Hz, 3H), 0.97 - 1.09 (m, 3H)
155	Method 4	3.428	661.9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 7.8 Hz, 1H), 7.97 (d, <i>J</i> = 8.5 Hz, 1H), 7.85 (br d, <i>J</i> = 8.4 Hz, 1H), 7.61 (s, 1H), 7.43 - 7.57 (m, 3H), 7.35 (br d, <i>J</i> = 7.0 Hz, 1H), 6.65 (dd, <i>J</i> = 15.4, 6.1 Hz, 1H), 5.95 (br d, <i>J</i> = 15.3 Hz, 1H), 4.44 - 4.72 (m, 3H), 4.22 - 4.42 (m, 2H), 3.35 (br dd, <i>J</i> = 6.8, 3.6 Hz, 1H), 3.05 - 3.15 (m, 1H), 2.54 (br s, 1H), 1.79 - 2.00 (m, 1H), 1.50 - 1.77 (m, 3H), 1.14 - 1.24 (m, 3H), 0.95 (br d, <i>J</i> = 6.7 Hz, 3H)
156	Method 1	1.74	628.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.24 - 8.38 (m, 1H), 8.04 (br d, <i>J</i> = 8.0 Hz, 1H), 7.50 - 7.64 (m, 2H), 7.31 - 7.48 (m, 3H), 7.24 (br d, <i>J</i> = 5.2 Hz, 1H), 6.65 (br dd, <i>J</i> = 15.3, 5.9 Hz, 1H), 5.95 (br d, <i>J</i> = 15.3 Hz, 1H), 4.57 - 4.73 (m, 2H), 4.45 - 4.56 (m, 3H), 4.21 - 4.41 (m, 2H), 3.38 - 3.46 (m, 2H), 2.66 - 3.05 (m, 2H), 2.27 - 2.44 (m, 1H), 1.82 - 2.17 (m, 2H), 1.47 - 1.79 (m, 3H), 1.19 (br d, <i>J</i> = 6.6 Hz, 3H) 0.97 - 1.08 (m, 3H)
157	Method 1	1.637	585.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.80 (s, 1H), 8.37 (dd, <i>J</i> = 7.9, 2.3 Hz, 1H), 8.15 (d, <i>J</i> = 5.4 Hz, 1H), 7.84 (s, 1H), 7.52 - 7.64 (m, 2H), 7.35 - 7.48 (m, 3H), 6.45 (dd, <i>J</i> = 11.2, 0.7 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.25 - 5.41 (m, 1H), 3.06 - 3.20 (m, 5H), 2.68 - 2.79 (m, 1H), 2.56 - 2.65 (m, 1H), 1.78 - 2.07 (m, 2H), 1.64 - 1.77 (m, 2H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
158	Method 1	1.536	586.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 - 8.17 (m, 1H), 7.50 - 7.40 (m, 1H), 7.20 - 7.14 (m, 1H), 7.36 - 7.13 (m, 2H), 6.50 - 6.40 (m, 1H), 6.31 - 6.20 (m, 1H), 5.32 (br d, <i>J</i> = 8.5 Hz, 1H), 4.14 - 3.95 (m, 2H), 3.90 (br s, 1H), 3.74 - 3.45 (m, 5H), 3.29 (br s, 1H), 3.18 - 3.03 (m, 3H), 2.69 - 2.56 (m, 1H), 2.42 - 2.30 (m, 1H), 2.03 - 1.72 (m, 2H), 1.70 - 1.49 (m, 2H), 1.47 - 1.38 (m, 9H), 1.26 - 1.14 (m, 3H)
159	Method 1	1.478	572	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 - 8.20 (m, 1H), 7.45 (br d, <i>J</i> = 7.2 Hz, 1H), 7.34 - 7.13 (m, 3H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.31 - 6.21 (m, 1H), 5.33 (br s, 1H), 4.85 - 4.74 (m, 1H), 4.15 - 3.99 (m, 3H), 3.78 - 3.59 (m, 4H), 3.58 - 3.53 (m, 1H), 3.12 (d, <i>J</i> = 17.9 Hz, 3H), 2.69 - 2.54 (m, 1H), 2.40 - 2.31 (m, 1H), 2.01 - 1.72 (m, 1H), 1.69 - 1.44 (m, 2H), 1.28 - 1.23 (m, 1H), 1.20 (t, <i>J</i> = 7.3 Hz, 9H)
160	Method 1	1.429	558	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 - 8.21 (m, 1H), 7.47 - 7.42 (m, 1H), 7.33 - 7.15

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 3H), 6.45 (d, $J = 11.2$ Hz, 1H), 6.32 - 6.21 (m, 1H), 5.33 (br d, $J = 6.3$ Hz, 1H), 4.15 - 4.01 (m, 4H), 3.91 (br s, 1H), 3.80 - 3.50 (m, 5H), 3.12 (d, $J = 18.1$ Hz, 3H), 2.69 - 2.52 (m, 1H), 2.40 - 2.30 (m, 1H), 2.01 - 1.73 (m, 1H), 1.70 - 1.56 (m, 1H), 1.53 (br d, $J = 12.2$ Hz, 1H), 1.32 - 1.22 (m, 0.5H), 1.22 - 1.14 (m, 6H), 0.94 - 0.70 (m, 0.5H)
161	Method 1	1.439	570	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.38 - 8.23 (m, 1H), 7.44 (br t, $J = 7.3$ Hz, 1H), 7.35 - 7.14 (m, 3H), 6.45 (d, $J = 11.0$ Hz, 1H), 6.27 (dt, $J = 5.5, 10.3$ Hz, 1H), 5.33 (br s, 1H), 4.18 - 3.98 (m, 3H), 3.96 - 3.53 (m, 5H), 3.12 (d, $J = 16.9$ Hz, 3H), 2.62 (br s, 1H), 2.43 - 2.34 (m, 1H), 2.04 - 1.76 (m, 1H), 1.69 - 1.47 (m, 2H), 1.35 (br s, 1H), 1.24 - 1.07 (m, 12H)
162	Method 1	1.439	590	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.36 - 8.21 (m, 1H), 7.61 - 7.52 (m, 2H), 7.50 - 7.40 (m, 4H), 7.38 - 7.14 (m, 3H), 6.48 - 6.41 (m, 1H), 6.32 - 6.22 (m, 1H), 5.32 (br d, $J = 6.7$ Hz, 1H), 4.26 - 3.98 (m, 3H), 3.95 - 3.66 (m, 4H), 3.64 - 3.43 (m, 1H), 3.17 - 3.06 (m, 3H), 2.48 - 2.45 (m, 1H), 2.38 (br d, $J = 12.4$ Hz, 1H), 1.98 - 1.84 (m, 1H), 1.76 - 1.58 (m, 1H), 1.49 (br s, 2H), 1.19 (td, $J = 3.5, 6.8$ Hz, 3H)
163	Method 3	2.151	568	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.39 - 8.16 (m, 1H), 7.52 - 7.39 (m, 1H), 7.34 - 7.20 (m, 3H), 6.45 (d, $J = 11.2$ Hz, 1H), 6.26 (ddd, $J = 4.1, 9.5, 11.1$ Hz, 1H), 5.36 - 5.31 (m, 1H), 4.25 - 4.11 (m, 1H), 4.05 (br d, $J = 13.0$ Hz, 1H), 3.99 - 3.60 (m, 4H), 3.58 - 3.41 (m, 4H), 3.34 - 3.15 (m, 1H), 3.12 (d, $J = 17.5$ Hz, 3H), 2.65 - 2.56 (m, 1H), 2.39 - 2.32 (m, 1H), 2.19 (dt, $J = 2.8, 12.7$ Hz, 1H), 2.00 - 1.66 (m, 1H), 1.63 - 1.45 (m, 2H), 1.25 - 1.13 (m, 3H), 1.10 - 0.84 (m, 1H)
164	Method 1	1.249	552.1	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.68 - 8.88 (m, 1H), 7.38 - 7.44 (m, 1H), 7.29 - 7.34 (m, 1H), 7.22 - 7.28 (m, 2H), 7.18 (dt, $J = 6.7, 2.3$ Hz, 1H), 6.76 (td, $J = 6.4, 2.5$ Hz, 1H), 5.05 - 5.22 (m, 1H), 3.96 - 4.24 (m, 2H), 3.53 - 3.93 (m, 3H), 3.41 (q, $J = 10.0$ Hz, 2H), 3.06 - 3.25 (m, 4H), 2.80 - 2.98 (m, 1H), 2.56 - 2.66 (m, 1H), 2.12 - 2.25 (m, 1H), 1.67 - 2.07 (m, 1H), 1.49 - 1.64 (m, 2H), 0.98 - 1.17 (m, 1H)
165	Method 1	1.326	582.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.24 (br d, $J = 4.8$ Hz, 1H), 7.44 - 7.29 (m, 2H), 7.26 - 7.18 (m, 2H), 6.48 - 6.38 (m, 1H), 6.34 - 6.18 (m, 1H), 5.36 - 5.24 (m, 1H), 4.14 - 3.97 (m, 1H), 3.87 - 3.69 (m, 1H), 3.59 - 3.45 (m, 1H), 3.39 (br d, $J = 10.2$ Hz, 2H), 3.31 - 3.16 (m, 4H), 3.15 - 2.98 (m, 3H), 2.86 (q, $J = 9.0$ Hz, 2H), 2.74 - 2.62 (m, 1H), 2.01 - 1.45 (m, 6H), 1.26 - 1.13 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
166	Method 4	3.04	600.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.22 - 8.33 (m, 1H), 7.37 - 7.47 (m, 1H), 7.16 - 7.27 (m, 1H), 7.05 - 7.14 (m, 1H), 6.39 - 6.48 (m, 1H), 6.22 - 6.31 (m, 1H), 5.31 (dt, <i>J</i> = 15.6, 7.7 Hz, 1H), 3.77 - 4.09 (m, 2H), 3.51 - 3.63 (m, 1H), 3.35 - 3.46 (m, 3H), 3.26 - 3.30 (m, 1H), 3.14 - 3.22 (m, 2H), 3.08 - 3.13 (m, 3H), 2.97 - 3.06 (m, 1H), 2.62 - 2.88 (m, 2H), 1.55 - 2.04 (m, 6H), 1.17 - 1.23 (m, 3H)
167	Method 1	1.434	600.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 - 8.21 (m, 1H), 7.45 - 7.29 (m, 2H), 7.20 - 7.08 (m, 1H), 6.50 - 6.37 (m, 1H), 6.32 - 6.20 (m, 1H), 5.38 - 5.23 (m, 1H), 4.10 - 3.93 (m, 1H), 3.88 - 3.71 (m, 1H), 3.57 - 3.50 (m, 1H), 3.43 - 3.36 (m, 3H), 3.26 (br dd, <i>J</i> = 6.7, 9.4 Hz, 1H), 3.22 - 3.16 (m, 2H), 3.14 - 3.08 (m, 3H), 3.02 - 2.91 (m, 1H), 2.88 - 2.64 (m, 2H), 2.01 - 1.53 (m, 6H), 1.24 - 1.15 (m, 3H)
168	Method 2	2.344	600.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.18 - 8.30 (m, 1H), 7.14 - 7.36 (m, 3H), 6.38 - 6.50 (m, 1H), 6.21 - 6.33 (m, 1H), 5.24 - 5.39 (m, 1H), 3.97 - 4.17 (m, 1H), 3.74 - 3.91 (m, 1H), 3.48 - 3.57 (m, 1H), 3.34 - 3.47 (m, 3H), 3.17 - 3.29 (m, 3H), 3.12 (s, 1H), 3.09 (s, 2H), 2.83 - 3.06 (m, 2H), 2.64 - 2.80 (m, 1H), 1.46 - 2.02 (m, 6H), 1.14 - 1.25 (m, 3H)
169	Method 1	1.438	596.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.17 - 8.33 (m, 1H), 7.13 - 7.29 (m, 2H), 7.01 - 7.11 (m, 1H), 6.38 - 6.51 (m, 1H), 6.21 - 6.33 (m, 1H), 5.26 - 5.36 (m, 1H), 4.10 (br d, <i>J</i> = 9.1 Hz, 2H), 3.81 - 3.86 (m, 2H), 3.61 - 3.73 (m, 3H), 3.49 (br d, <i>J</i> = 10.6 Hz, 1H), 3.17 - 3.26 (m, 1H), 3.07 - 3.14 (m, 3H), 2.68 - 2.90 (m, 3H), 2.22 - 2.29 (m, 3H), 1.78 - 2.00 (m, 2H), 1.45 - 1.67 (m, 4H), 1.16 - 1.25 (m, 3H)
170	Method 4	3.117	596.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.20 - 8.28 (m, 1H), 7.22 - 7.30 (m, 1H), 7.12 - 7.17 (m, 1H), 6.99 - 7.08 (m, 1H), 6.39 - 6.49 (m, 1H), 6.19 - 6.32 (m, 1H), 5.24 - 5.40 (m, 1H), 3.94 - 4.09 (m, 1H), 3.69 - 3.83 (m, 1H), 3.40 - 3.54 (m, 4H), 3.17 - 3.25 (m, 3H), 3.09 - 3.14 (m, 3H), 2.70 - 2.90 (m, 2H), 2.22 (s, 3H), 1.66 - 2.11 (m, 3H), 1.31 - 1.64 (m, 4H), 1.14 - 1.22 (m, 3H)
171	Method 5	2.224	600.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.17 - 8.36 (m, 1H), 7.24 - 7.34 (m, 2H), 7.06 - 7.17 (m, 1H), 6.40 - 6.48 (m, 1H), 6.21 - 6.32 (m, 1H), 5.25 - 5.37 (m, 1H), 4.08 - 4.22 (m, 1H), 3.79 - 3.92 (m, 1H), 3.54 - 3.62 (m, 3H), 3.30 - 3.34 (m, 1H), 3.17 - 3.27 (m, 2H), 3.09 - 3.12 (m, 3H), 2.75 - 2.85 (m, 1H), 2.68 (br d, <i>J</i> = 12.8 Hz, 1H), 2.54 - 2.61 (m, 1H), 1.69 - 2.09 (m, 4H), 1.42 - 1.69 (m, 3H), 1.16 - 1.24 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
172	Method 5	2.283	596.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.25 (br d, <i>J</i> = 7.1 Hz, 1H), 7.10 - 7.29 (m, 3H), 6.40 - 6.49 (m, 1H), 6.20 - 6.30 (m, 1H), 5.27 - 5.36 (m, 1H), 4.17 (br dd, <i>J</i> = 9.1, 7.5 Hz, 1H), 3.83 - 3.91 (m, 1H), 3.64 - 3.79 (m, 2H), 3.33 - 3.50 (m, 4H), 3.22 - 3.31 (m, 1H), 3.13 (s, 1H), 3.09 (s, 2H), 2.71 - 2.86 (m, 2H), 2.28 - 2.40 (m, 3H), 1.69 - 2.07 (m, 3H), 1.35 - 1.67 (m, 4H), 1.14 - 1.26 (m, 3H)
173	Method 1	1.415	584.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.13 - 8.40 (m, 1H), 7.04 - 7.29 (m, 3H), 6.40 - 6.48 (m, 1H), 6.23 - 6.32 (m, 1H), 5.22 - 5.40 (m, 1H), 3.90 - 4.03 (m, 1H), 3.70 - 3.85 (m, 1H), 3.49 - 3.65 (m, 1H), 3.34 - 3.46 (m, 3H), 3.21 - 3.30 (m, 2H), 3.08 - 3.20 (m, 4H), 2.96 - 3.08 (m, 1H), 2.81 - 2.92 (m, 1H), 2.58 - 2.78 (m, 1H), 1.82 - 2.04 (m, 2H), 1.43 - 1.81 (m, 4H), 1.11 - 1.28 (m, 3H)
174	Method 8	2.061	566.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.69 - 8.84 (m, 1H), 7.27 - 7.45 (m, 2H), 7.20 - 7.26 (m, 2H), 7.14 - 7.19 (m, 1H), 6.70 - 6.82 (m, 1H), 5.10 (br d, <i>J</i> = 5.1 Hz, 1H), 4.53 (br t, <i>J</i> = 6.9 Hz, 0.5H), 3.95 - 4.23 (m, 2H), 3.78 - 3.93 (m, 1.5H), 3.65 - 3.72 (m, 1H), 3.39 - 3.49 (m, 2H), 3.20 - 3.27 (m, 2H), 3.09 - 3.18 (m, 2H), 2.64 - 2.90 (m, 2H), 1.50 - 2.06 (m, 4H), 1.14 - 1.24 (m, 1H), 0.40 (dd, <i>J</i> = 7.1, 1.5 Hz, 2H)
175	Method 8	2.167	584.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.72 - 8.86 (m, 1H), 7.20 - 7.34 (m, 3H), 7.11 - 7.18 (m, 1H), 6.67 - 6.83 (m, 1H), 5.11 (br d, <i>J</i> = 5.6 Hz, 1H), 4.54 (br t, <i>J</i> = 7.0 Hz, 0.5H), 4.06 - 4.27 (m, 2H), 3.86 - 4.02 (m, 2H), 3.77 - 3.85 (m, 1.5H), 3.38 - 3.44 (m, 2H), 3.34 (br s, 1H), 3.11 - 3.20 (m, 2H), 2.92 (br d, <i>J</i> = 7.7 Hz, 1H), 2.65 - 2.74 (m, 1H), 1.61 - 2.00 (m, 4H), 1.17 (br d, <i>J</i> = 6.5 Hz, 1H), 0.45 (br d, <i>J</i> = 7.1 Hz, 2H)
176	Method 1	1.34	566.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.71 (br d, <i>J</i> = 6.4 Hz, 1H), 7.36 - 7.44 (m, 1H), 7.20 - 7.33 (m, 3H), 7.10 - 7.18 (m, 1H), 6.69 - 6.79 (m, 1H), 5.06 (br dd, <i>J</i> = 5.3, 2.0 Hz, 1H), 4.00 - 4.15 (m, 1H), 3.75 - 3.92 (m, 1H), 3.46 - 3.72 (m, 4H), 2.75 - 3.45 (m, 7H), 2.57 - 2.69 (m, 1H), 1.49 - 1.96 (m, 6H)
177	Method 1	1.373	582.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.31 (br dd, <i>J</i> = 7.9, 2.6 Hz, 1H), 7.29 - 7.44 (m, 2H), 7.16 - 7.27 (m, 2H), 6.66 - 6.74 (m, 1H), 6.57 - 6.65 (m, 1H), 4.48 - 4.64 (m, 1H), 3.97 - 4.14 (m, 1H), 3.72 - 3.88 (m, 1H), 3.47 - 3.62 (m, 1H), 3.40 (q, <i>J</i> = 10.3 Hz, 3H), 3.11 - 3.29 (m, 4H), 2.97 - 3.02 (m, 3H), 2.84 - 2.91 (m, 1H), 2.61 - 2.71 (m, 1H), 1.73 - 2.03 (m, 3H), 1.44 - 1.71 (m, 3H), 1.17 - 1.26 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
178	Method 6	3.078	578.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 - 8.20 (m, 1H), 7.43 - 7.29 (m, 2H), 7.27 - 7.18 (m, 2H), 6.45 (br d, <i>J</i> = 11.4 Hz, 1H), 6.33 - 6.19 (m, 1H), 5.39 - 5.24 (m, 1H), 4.16 - 3.96 (m, 2H), 3.90 - 3.54 (m, 2H), 3.24 - 3.04 (m, 8H), 2.96 (br t, <i>J</i> = 14.5 Hz, 3H), 2.80 - 2.65 (m, 1H), 2.23 - 1.86 (m, 3H), 1.55 (br s, 2H), 1.19 (br d, <i>J</i> = 6.8 Hz, 3H), 1.03 - 0.90 (m, 3H)
179	Method 6	2.902	564.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 - 8.20 (m, 1H), 7.42 - 7.17 (m, 3H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dt, <i>J</i> = 6.1, 10.3 Hz, 1H), 5.40 - 5.26 (m, 1H), 4.20 - 3.97 (m, 2H), 3.88 - 3.55 (m, 2H), 3.26 - 3.03 (m, 7H), 2.96 (br t, <i>J</i> = 14.2 Hz, 2H), 2.84 - 2.63 (m, 3H), 2.21 - 1.78 (m, 2H), 1.75 - 1.58 (m, 4H), 1.47 (br s, 1H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
180	Method 1	1.224	578.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.19 - 8.28 (m, 1H), 7.30 - 7.43 (m, 2H), 7.16 - 7.27 (m, 2H), 6.40 - 6.47 (m, 1H), 6.22 - 6.31 (m, 1H), 5.24 - 5.36 (m, 1H), 3.97 - 4.15 (m, 1H), 3.68 - 3.89 (m, 1H), 3.48 - 3.62 (m, 1H), 3.35 - 3.42 (m, 1H), 3.05 - 3.26 (m, 6H), 2.86 - 3.02 (m, 3H), 2.53 - 2.78 (m, 2H), 1.45 - 2.00 (m, 9H), 1.14 - 1.26 (m, 3H)
181	Method 6	3.204	626.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 - 8.19 (m, 1H), 7.57 (br s, 2H), 7.50 (br s, 3H), 7.36 (br d, <i>J</i> = 6.6 Hz, 1H), 7.28 - 7.10 (m, 3H), 6.44 (br d, <i>J</i> = 10.8 Hz, 1H), 6.34 - 6.17 (m, 1H), 5.40 - 5.22 (m, 1H), 4.07 - 3.90 (m, 2H), 3.85 - 3.52 (m, 2H), 3.29 - 3.17 (m, 2H), 3.16 - 3.02 (m, 6H), 2.82 - 2.58 (m, 1H), 2.14 (br t, <i>J</i> = 12.3 Hz, 1H), 1.95 - 1.62 (m, 2H), 1.61 - 1.44 (m, 2H), 1.18 (br d, <i>J</i> = 6.4 Hz, 3H), 1.12 - 0.87 (m, 1H)
182	Method 9	3.047	618.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.40 - 8.17 (m, 1H), 7.48 - 7.36 (m, 1H), 7.34 - 7.16 (m, 3H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.27 (br dd, <i>J</i> = 5.4, 9.5 Hz, 1H), 5.42 - 5.26 (m, 1H), 4.17 - 3.96 (m, 2H), 3.91 - 3.57 (m, 2H), 3.46 (br t, <i>J</i> = 16.4 Hz, 2H), 3.30 - 3.16 (m, 3H), 3.11 (d, <i>J</i> = 14.8 Hz, 3H), 2.99 - 2.81 (m, 1H), 2.59 (br d, <i>J</i> = 10.8 Hz, 1H), 2.44 - 2.11 (m, 1H), 1.98 - 1.45 (m, 3H), 1.19 (d, <i>J</i> = 6.9 Hz, 2H), 1.23 (br s, 1H), 1.15 - 0.95 (m, 1H)
183	Method 1	1.212	596	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.28 (d, <i>J</i> = 6.3 Hz, 1H), 7.32 - 7.47 (m, 2H), 7.13 - 7.26 (m, 1H), 6.40 - 6.50 (m, 1H), 6.21 - 6.34 (m, 1H), 5.26 - 5.37 (m, 1H), 4.23 (dd, <i>J</i> = 16.5, 12.9 Hz, 2H), 3.78 - 4.11 (m, 5H), 3.52 - 3.71 (m, 2H), 3.33 - 3.44 (m, 1H), 3.04 - 3.16 (m, 3H), 2.76 (t, <i>J</i> = 12.7 Hz, 1H), 2.54 (s, 1H), 1.45 - 2.15 (m, 9H), 1.12 - 1.25 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
184	Method 1	1.208	590	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.07 - 10.48 (m, 1H), 8.29 (br d, <i>J</i> = 7.6 Hz, 1H), 7.36 - 7.47 (m, 2H), 7.19 - 7.29 (m, 1H), 6.37 - 6.52 (m, 1H), 6.20 - 6.32 (m, 1H), 5.22 - 5.42 (m, 1H), 4.21 - 4.67 (m, 1H), 3.86 - 4.15 (m, 5H), 3.53 - 3.82 (m, 4H), 3.35 - 3.49 (m, 1H), 3.05 - 3.20 (m, 3H), 2.67 - 2.84 (m, 1H), 2.53 - 2.62 (m, 1H), 1.59 - 2.12 (m, 5H), 1.18 - 1.27 (m, 4H), 0.95 - 1.08 (m, 2H)
185	Method 1	1.225	572.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.17 - 8.31 (m, 1H), 7.14 - 7.42 (m, 4H), 6.19 - 6.52 (m, 2H), 5.24 - 5.36 (m, 1H), 3.99 - 4.15 (m, 1H), 3.69 - 3.87 (m, 1H), 3.42 - 3.62 (m, 2H), 3.05 - 3.27 (m, 7H), 2.81 - 2.97 (m, 3H), 1.48 - 1.96 (m, 7H), 1.15 - 1.21 (m, 3H), 0.91 - 1.02 (m, 2H), 0.62 - 0.73 (m, 2H)
186	Method 1	1.636	560.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.78 (s, 1H), 8.37 (dd, <i>J</i> = 1.9, 7.8 Hz, 1H), 7.60 - 7.52 (m, 1H), 7.50 - 7.35 (m, 3H), 6.86 (s, 1H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.28 (dd, <i>J</i> = 9.4, 11.2 Hz, 1H), 5.43 - 5.27 (m, 1H), 4.00 (s, 3H), 3.20 - 3.05 (m, 5H), 2.78 - 2.66 (m, 1H), 2.64 - 2.54 (m, 1H), 2.01 - 1.65 (m, 4H), 1.20 (d, <i>J</i> = 6.8 Hz, 3H)
187	Method 3	2.497	560.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.78 (s, 1H), 8.36 (br d, <i>J</i> = 6.4 Hz, 1H), 7.53 - 7.59 (m, 1H), 7.44 - 7.49 (m, 1H), 7.36 - 7.43 (m, 2H), 6.86 (s, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.21 - 6.35 (m, 1H), 5.28 - 5.42 (m, 1H), 4.00 (s, 3H), 3.14 (br s, 2H), 3.11 (s, 3H), 2.65 - 2.77 (m, 2H), 1.70 - 1.94 (m, 4H), 1.21 (d, <i>J</i> = 6.8 Hz, 3H)
188	Method 3	2.390	546.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.78 (s, 1H), 8.57 (br d, <i>J</i> = 2.2 Hz, 1H), 7.53 - 7.60 (m, 1H), 7.46 (td, <i>J</i> = 7.4, 2.3 Hz, 1H), 7.35 - 7.43 (m, 2H), 6.86 (s, 1H), 6.66 - 6.76 (m, 1H), 6.53 - 6.64 (m, 1H), 4.00 (s, 3H), 3.89 - 3.95 (m, 2H), 3.14 (br d, <i>J</i> = 5.1 Hz, 2H), 2.99 (s, 3H), 2.59 - 2.77 (m, 2H), 1.74 - 1.97 (m, 4H)
189	Method 1	1.571	526.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.77 (s, 1H), 8.59 (br d, <i>J</i> = 1.9 Hz, 1H), 7.11 - 7.36 (m, 4H), 6.77 (s, 1H), 6.66 - 6.74 (m, 1H), 6.54 - 6.63 (m, 1H), 3.98 (s, 3H), 3.88 - 3.96 (m, 2H), 3.02 - 3.18 (m, 2H), 2.99 (s, 3H), 2.55 - 2.64 (m, 2H), 2.04 (s, 3H), 1.71 - 1.99 (m, 4H)
190	Method 2	2.512	540.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.77 (s, 1H), 8.32 - 8.43 (m, 1H), 7.31 (dd, <i>J</i> = 7.5, 6.2 Hz, 2H), 7.24 (s, 1H), 7.11 - 7.19 (m, 1H), 6.78 (s, 1H), 6.46 (d, <i>J</i> = 11.2 Hz, 1H), 6.24 - 6.34 (m, 1H), 5.28 - 5.43 (m, 1H), 3.99 (s, 3H), 3.01 - 3.19 (m, 5H), 2.59 (br t, <i>J</i> = 12.5 Hz, 2H), 2.05 (s, 3H), 1.76 - 2.00 (m, 2H), 1.53 - 1.73 (m, 2H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
191	Method 2	2.310	512.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.76 (s, 1H), 8.53 (br d, <i>J</i> = 2.4 Hz, 1H), 7.47 - 7.41 (m, 5H), 6.81 (s, 1H), 6.69 (td, <i>J</i> = 4.3, 15.3 Hz, 1H), 6.63 - 6.55 (m, 1H), 3.99 (s, 3H), 3.92 (br t, <i>J</i> = 4.2 Hz, 2H), 3.30 (s, 2H), 3.12 (br d, <i>J</i> = 12.8 Hz, 2H), 2.99 (s, 3H), 1.76 - 1.65 (m, 4H)
192	Method 2	2.419	526.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.75 (s, 1H), 8.31 (dd, <i>J</i> = 2.0, 7.8 Hz, 1H), 7.48 - 7.40 (m, 5H), 6.80 (s, 1H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 9.5, 11.2 Hz, 1H), 5.39 - 5.28 (m, 1H), 3.99 (s, 3H), 3.11 m, 7H), 1.74 - 1.57 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
193	Method 1	1.634	540.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.76 (s, 1H), 8.36 (br d, <i>J</i> = 5.8 Hz, 1H), 7.36 - 7.18 (m, 3H), 7.17 - 7.10 (m, 1H), 6.76 (s, 1H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.34 - 6.22 (m, 1H), 5.42 - 5.27 (m, 1H), 3.98 (s, 3H), 3.17 - 2.99 (m, 5H), 2.63 - 2.55 (m, 2H), 2.03 (s, 3H), 1.93 - 1.73 (m, 2H), 1.69 (br s, 2H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
194	Method 1	1.476	493	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.78 (s, 1H), 8.64 (br s, 1H), 7.56 (d, <i>J</i> = 7.9 Hz, 1H), 7.50 - 7.32 (m, 3H), 6.87 (s, 1H), 6.56 - 6.45 (m, 1H), 5.75 (d, <i>J</i> = 11.3 Hz, 1H), 4.11 - 3.89 (m, 5H), 3.14 (br d, <i>J</i> = 11.1 Hz, 2H), 2.67 (br s, 2H), 2.03 - 1.84 (m, 2H), 1.81 - 1.68 (m, 2H)
195	Method 6	3.134	598	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.25 (br dd, <i>J</i> = 7.8, 2.1 Hz, 1H), 7.16 - 7.42 (m, 4H), 6.39 - 6.49 (m, 1H), 6.20 - 6.32 (m, 1H), 5.23 - 5.38 (m, 1H), 3.98 - 4.12 (m, 1H), 3.66 - 3.89 (m, 1H), 3.46 - 3.62 (m, 4H), 3.19 - 3.30 (m, 3H), 2.84 - 3.15 (m, 5H), 2.61 - 2.72 (m, 1H), 1.45 - 2.03 (m, 6H), 1.10 - 1.29 (m, 3H)
196	Method 1	1.227	596	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.16 - 8.30 (m, 1H), 7.29 - 7.43 (m, 2H), 7.14 - 7.26 (m, 2H), 6.37 - 6.49 (m, 1H), 6.20 - 6.31 (m, 1H), 5.21 - 5.39 (m, 1H), 3.98 - 4.14 (m, 1H), 3.68 - 3.84 (m, 1H), 3.46 - 3.61 (m, 1H), 3.34 - 3.42 (m, 1H), 3.19 - 3.29 (m, 1H), 3.00 - 3.16 (m, 5H), 2.85 - 2.96 (m, 1H), 2.60 - 2.79 (m, 3H), 2.52 - 2.55 (m, 1H), 2.42 - 2.49 (m, 2H), 1.47 - 2.05 (m, 6H), 1.14 - 1.23 (m, 3H)
197	Method 5	1.982	564	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.19 - 8.34 (m, 1H), 7.44 - 7.55 (m, 1H), 7.24 - 7.38 (m, 3H), 6.41 - 6.47 (m, 1H), 6.38 (br s, 1H), 6.22 - 6.30 (m, 1H), 5.22 - 5.42 (m, 1H), 4.20 - 4.36 (m, 2H), 4.02 - 4.10 (m, 1H), 3.87 (br d, <i>J</i> = 8.2 Hz, 1H), 3.77 (br s, 3H), 3.30 - 3.51 (m, 2H), 3.13 (s, 1H), 3.09 (s, 2H), 2.57 - 2.72 (m, 2H), 1.78 - 2.06 (m, 2H), 1.36 - 1.77 (m, 5H), 1.15 - 1.23 (m, 3H)
198	Method 1	1.424	596	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.16 (dd, <i>J</i> = 8.5, 2.5 Hz, 1H), 7.35 - 7.45 (m, 1H), 7.29 - 7.34 (m, 1H), 7.20 - 7.29 (m, 2H), 6.48 (d, <i>J</i> =

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				11.1 Hz, 1H), 6.22 (br dd, $J = 11.1, 9.9$ Hz, 1H), 5.14 - 5.23 (m, 1H), 4.05 - 4.16 (m, 1H), 3.79 - 3.95 (m, 1H), 3.55 - 3.71 (m, 2H), 3.41 (br d, $J = 2.5$ Hz, 2H), 3.37 (br d, $J = 5.2$ Hz, 2H), 3.13 - 3.30 (m, 1H), 3.09 - 3.13 (m, 1H), 3.07 (s, 3H), 2.74 - 2.88 (m, 1H), 2.67 (br t, $J = 12.3$ Hz, 1H), 1.76 - 2.08 (m, 2H), 1.42 - 1.71 (m, 6H), 0.74 - 0.85 (m, 3H)
199	Method 2	2.464	572	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.23 - 8.46 (m, 1H), 7.44 - 7.53 (m, 1H), 7.19 - 7.40 (m, 3H), 6.46 - 6.55 (m, 1H), 6.31 (t, $J = 10.3$ Hz, 1H), 5.34 - 5.44 (m, 1H), 4.82 - 4.89 (m, 1H), 3.88 - 4.24 (m, 3H), 3.47 - 3.87 (m, 5H), 3.12 - 3.24 (m, 3H), 2.58 - 2.75 (m, 1H), 2.41 (br dd, $J = 12.9, 10.6$ Hz, 1H), 1.75 - 2.10 (m, 1H), 1.46 - 1.73 (m, 2H), 1.19 - 1.34 (m, 9H), 0.63 - 1.15 (m, 1H)
200	Method 2	2.555	560	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.79 (d, $J = 2.3$ Hz, 1H), 8.42 (br d, $J = 7.8$ Hz, 1H), 8.15 (d, $J = 2.2$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.04 - 7.11 (m, 2H), 7.02 (br d, $J = 8.1$ Hz, 1H), 6.47 (d, $J = 10.9$ Hz, 1H), 6.23 - 6.37 (m, 1H), 5.31 - 5.49 (m, 1H), 3.79 (s, 3H), 3.69 (br d, $J = 12.7$ Hz, 2H), 3.19 - 3.27 (m, 2H), 3.12 (s, 3H), 1.78 - 2.05 (m, 4H), 1.23 (d, $J = 6.8$ Hz, 3H)
201	Method 1	1.721	555	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 7.99 (d, $J = 8.7$ Hz, 1H), 7.59 - 7.72 (m, 2H), 7.44 (d, $J = 2.1$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 6.87 - 7.03 (m, 3H), 6.87 - 7.03 (m, 1H), 6.42 (d, $J = 11.0$ Hz, 1H), 6.36 - 6.46 (m, 1H), 6.16 (t, $J = 10.4$ Hz, 1H), 5.18 - 5.35 (m, 1H), 3.78 (s, 3H), 3.12 (s, 3H), 2.87 (br d, $J = 12.9$ Hz, 2H), 2.29 - 2.44 (m, 2H), 1.82 (br d, $J = 13.9$ Hz, 2H), 1.17 (d, $J = 6.8$ Hz, 3H), 0.99 - 1.10 (m, 2H), 0.99 - 1.10 (m, 1H), 0.96 (s, 3H)
202	Method 1	1.591	589	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.37 (dd, $J = 1.8, 7.8$ Hz, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.46 - 7.31 (m, 4H), 6.86 (s, 1H), 6.45 (d, $J = 11.1$ Hz, 1H), 6.33 - 6.22 (m, 1H), 5.42 - 5.28 (m, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.17 (br d, $J = 12.1$ Hz, 2H), 3.11 (s, 3H), 2.71 - 2.61 (m, 1H), 2.60 - 2.53 (m, 1H), 2.03 - 1.62 (m, 4H), 1.20 (d, $J = 6.8$ Hz, 3H)
203	Method 1	1.717	555	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 7.99 (d, $J = 8.7$ Hz, 1H), 7.72 - 7.60 (m, 2H), 7.44 (d, $J = 2.1$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.02 - 6.90 (m, 3H), 6.42 (d, $J = 11.2$ Hz, 1H), 6.20 - 6.11 (m, 1H), 5.20 - 5.34 (m, 1H), 3.78 (s, 3H), 3.12 (s, 3H), 2.91 - 2.81 (m, 2H), 2.31 - 2.46 (m, 2H), 1.82 (br d, $J = 13.8$ Hz, 2H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.10 - 0.99 (m, 2H), 0.96 (s, 3H)
204	Method 1	1.418	610	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.54 (dd, $J = 4.7, 1.2$ Hz, 1H), 8.36 - 8.41 (m, 1H), 8.02

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(dd, $J = 8.2, 1.3$ Hz, 1H), 7.93 - 7.98 (m, 1H), 7.89 - 7.93 (m, 1H), 7.72 (d, $J = 1.9$ Hz, 1H), 7.50 (dd, $J = 8.1, 4.7$ Hz, 1H), 6.45 (d, $J = 11.8$ Hz, 1H), 6.24 - 6.33 (m, 1H), 5.28 - 5.40 (m, 1H), 3.47 - 3.58 (m, 1H), 3.10 (s, 4H), 2.68 - 2.78 (m, 2H), 1.87 - 2.05 (m, 2H), 1.77 - 1.85 (m, 2H), 1.21 (d, $J = 6.9$ Hz, 3H)
205	Method 1	1.481	612	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.36 (dd, $J = 7.7, 1.9$ Hz, 1H), 8.01 (d, $J = 8.9$ Hz, 1H), 7.84 (dd, $J = 8.9, 2.4$ Hz, 1H), 7.78 (d, $J = 2.2$ Hz, 1H), 7.51 - 7.56 (m, 1H), 7.33 - 7.46 (m, 3H), 6.45 (d, $J = 11.1$ Hz, 1H), 6.27 (dd, $J = 11.1, 9.5$ Hz, 1H), 5.24 - 5.41 (m, 1H), 3.81 - 3.97 (m, 2H), 3.07 - 3.20 (m, 5H), 2.59 - 2.72 (m, 2H), 2.56 (s, 2H), 2.07 (quin, $J = 7.5$ Hz, 2H), 1.63 - 1.95 (m, 4H), 1.20 (d, $J = 6.7$ Hz, 3H)
206	Method 9	2.532	550	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.16 - 8.38 (m, 1H), 7.36 - 7.45 (m, 1H), 7.27 - 7.35 (m, 1H), 7.16 - 7.27 (m, 2H), 6.44 (d, $J = 11.2$ Hz, 1H), 6.24 - 6.30 (m, 1H), 5.95 - 6.23 (m, 1H), 5.24 - 5.39 (m, 1H), 3.93 - 4.18 (m, 2H), 3.55 - 3.89 (m, 2H), 3.07 - 3.20 (m, 6H), 2.97 (m, 2H), 2.58 - 2.81 (m, 2H), 2.07 - 2.38 (m, 1H), 1.64 - 1.97 (m, 1H), 1.42 - 1.62 (m, 2H), 1.19 (d, $J = 6.9$ Hz, 3H), 0.90 - 1.14 (m, 1H)
207	Method 1	1.646	598	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.34 (s, 1H), 8.39 (br d, $J = 6.0$ Hz, 1H), 8.08 (s, 1H), 7.62 (d, $J = 7.9$ Hz, 1H), 7.57 - 7.41 (m, 3H), 6.45 (d, $J = 11.3$ Hz, 1H), 6.28 (dd, $J = 9.5, 11.1$ Hz, 1H), 5.50 - 5.18 (m, 1H), 3.27 (br d, $J = 13.7$ Hz, 2H), 3.11 (s, 3H), 2.84 (br t, $J = 11.4$ Hz, 1H), 2.73 - 2.63 (m, 1H), 2.03 - 1.71 (m, 4H), 1.30 - 1.19 (m, 3H)
208	Method 1	1.616	598	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.34 (s, 1H), 8.39 (br d, $J = 7.0$ Hz, 1H), 8.09 (s, 1H), 7.62 (d, $J = 7.9$ Hz, 1H), 7.57 - 7.46 (m, 3H), 6.45 (d, $J = 11.0$ Hz, 1H), 6.34 - 6.22 (m, 1H), 5.47 - 5.24 (m, 1H), 3.27 (br d, $J = 11.7$ Hz, 2H), 3.11 (s, 3H), 2.89 - 2.79 (m, 1H), 2.68 (br d, $J = 12.0$ Hz, 1H), 1.96 - 1.70 (m, 4H), 1.21 (d, $J = 6.8$ Hz, 3H)
209	Method 1	1.641	616	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.31 - 9.39 (m, 1H), 8.33 - 8.47 (m, 1H), 8.14 - 8.21 (m, 1H), 7.48 - 7.61 (m, 2H), 7.30 - 7.39 (m, 1H), 6.41 - 6.51 (m, 1H), 6.24 - 6.32 (m, 1H), 5.30 - 5.43 (m, 1H), 3.24 - 3.29 (m, 2H), 3.09 - 3.13 (m, 3H), 2.72 - 2.91 (m, 2H), 1.74 - 1.99 (m, 4H), 1.20 - 1.24 (m, 3H)
210	Method 1	1.645	616	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.30 - 9.39 (m, 1H), 8.32 - 8.46 (m, 1H), 8.17 (s, 1H), 7.48 - 7.64 (m, 2H), 7.34 (br d, $J = 7.2$ Hz, 1H), 6.45 (d, $J = 11.0$ Hz, 1H), 6.28 (dd, $J = 11.0, 9.5$

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				Hz, 1H), 5.30 - 5.44 (m, 1H), 3.20 - 3.24 (m, 2H), 3.10 (s, 3H), 2.90 (br s, 2H), 1.75 - 1.96 (m, 4H), 1.21 (d, <i>J</i> = 6.7 Hz, 3H)
211	Method 1	1.650	616	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.33 (s, 1H), 8.40 (br d, <i>J</i> = 7.7 Hz, 1H), 8.12 (s, 1H), 7.65 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 7.55 (dd, <i>J</i> = 8.6, 6.1 Hz, 1H), 7.38 (td, <i>J</i> = 8.5, 2.4 Hz, 1H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (dd, <i>J</i> = 11.0, 9.6 Hz, 1H), 5.30 - 5.41 (m, 1H), 3.11 (s, 3H), 2.70 - 2.92 (m, 4H), 1.85 - 2.02 (m, 2H), 1.75 - 1.84 (m, 2H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
212	Method 1	1.649	616	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.33 (s, 1H), 8.34 - 8.44 (m, 1H), 8.12 (s, 1H), 7.65 (dd, <i>J</i> = 8.7, 2.4 Hz, 1H), 7.55 (dd, <i>J</i> = 8.6, 6.1 Hz, 1H), 7.38 (td, <i>J</i> = 8.5, 2.4 Hz, 1H), 6.46 (d, <i>J</i> = 11.1 Hz, 1H), 6.24 - 6.34 (m, 1H), 5.27 - 5.42 (m, 1H), 3.11 (s, 3H), 2.82 - 2.91 (m, 2H), 2.77 (br d, <i>J</i> = 12.3 Hz, 2H), 1.86 - 2.03 (m, 2H), 1.76 - 1.85 (m, 2H), 1.18 - 1.25 (m, 3H)
213	Method 1	1.773	639	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.34 (s, 1H), 8.31 - 8.40 (m, 1H), 8.09 (s, 1H), 7.63 (d, <i>J</i> = 7.9 Hz, 1H), 7.43 - 7.58 (m, 3H), 6.67 (dd, <i>J</i> = 15.4, 5.9 Hz, 1H), 5.94 (dd, <i>J</i> = 15.4, 1.2 Hz, 1H), 4.55 - 4.72 (m, 2H), 4.48 - 4.55 (m, 1H), 4.32 (br t, <i>J</i> = 11.1 Hz, 2H), 3.28 (br d, <i>J</i> = 12.1 Hz, 2H), 2.80 - 2.90 (m, 1H), 2.65 - 2.76 (m, 1H), 1.72 - 2.04 (m, 4H), 1.20 (d, <i>J</i> = 7.0 Hz, 3H)
214	Method 1	1.638	612	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.36 (d, <i>J</i> = 2.7 Hz, 1H), 8.34 - 8.48 (m, 1H), 8.09 (d, <i>J</i> = 3.0 Hz, 1H), 7.60 - 7.71 (m, 1H), 7.42 - 7.58 (m, 3H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.21 - 6.32 (m, 1H), 5.35 (dt, <i>J</i> = 14.6, 7.5 Hz, 1H), 3.40 - 3.64 (m, 1H), 3.32 (s, 1H), 2.73 - 3.07 (m, 2H), 2.40 - 2.48 (m, 1H), 1.55 - 2.17 (m, 5H), 1.21 (br d, <i>J</i> = 6.9 Hz, 3H), 1.07 (br dd, <i>J</i> = 6.6, 3.2 Hz, 3H)
215	Method 1	1.672	653	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.36 (d, <i>J</i> = 2.6 Hz, 1H), 8.29 - 8.43 (m, 1H), 8.10 (d, <i>J</i> = 3.5 Hz, 1H), 7.60 - 7.71 (m, 1H), 7.42 - 7.58 (m, 3H), 6.66 (ddd, <i>J</i> = 15.4, 6.2, 1.8 Hz, 1H), 5.96 (dd, <i>J</i> = 15.4, 1.2 Hz, 1H), 4.46 - 4.72 (m, 3H), 4.32 (br t, <i>J</i> = 11.8 Hz, 2H), 3.41 - 3.63 (m, 1H), 2.72 - 3.10 (m, 1H), 2.39 - 2.47 (m, 1H), 1.59 - 2.17 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H), 1.08 (dd, <i>J</i> = 6.6, 3.4 Hz, 3H)
216	Method 1	1.770	620	¹ H NMR (400 MHz, CD ₃ SOCD ₃ , 298 K) δ ppm 8.34 (br d, <i>J</i> = 7.6 Hz, 1H), 8.27 (d, <i>J</i> = 8.4 Hz, 1H), 8.07 (br d, <i>J</i> = 7.6 Hz, 1H), 7.76 (s, 1H), 7.59 (d, <i>J</i> = 8.0 Hz, 1H), 7.52 - 7.41 (m, 3H), 6.62 (dd, <i>J</i> = 6.0, 15.5 Hz, 1H), 5.92 (br d, <i>J</i> = 15.2 Hz, 1H), 5.52 - 5.29 (m, 1H), 4.57 - 4.39 (m, 2H), 4.31 - 4.15 (m, 2H), 3.99 - 3.84 (m,

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				1H), 3.25 - 3.14 (m, 2H), 2.86 - 2.59 (m, 2H), 2.03 - 1.73 (m, 4H), 1.19 (d, <i>J</i> = 7.2 Hz, 3H)
217	Method 1	1.683	594	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.98 (s, 1H), 8.38 (br d, <i>J</i> = 7.6 Hz, 1H), 7.72 (s, 1H), 7.52 - 7.37 (m, 1H), 7.15 - 6.94 (m, 2H), 6.45 (d, <i>J</i> = 11.3 Hz, 1H), 6.28 (t, <i>J</i> = 10.3 Hz, 1H), 5.45 - 5.24 (m, 1H), 3.76 (s, 3H), 3.26 (br d, <i>J</i> = 13.0 Hz, 2H), 3.11 (s, 3H), 2.80 (br t, <i>J</i> = 11.6 Hz, 1H), 2.73 - 2.61 (m, 1H), 2.04 - 1.63 (m, 4H), 1.23 - 1.16 (m, 3H)
218	Method 1	1.519	610	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.96 (d, <i>J</i> = 2.0 Hz, 1H), 8.41 (br d, <i>J</i> = 8.3 Hz, 1H), 8.30 (d, <i>J</i> = 2.1 Hz, 1H), 7.61 - 7.51 (m, 1H), 7.49 - 7.31 (m, 3H), 6.46 (d, <i>J</i> = 11.3 Hz, 1H), 6.30 (t, <i>J</i> = 10.2 Hz, 1H), 5.46 - 5.27 (m, 1H), 3.66 (br s, 2H), 3.26 - 3.07 (m, 5H), 2.07 - 1.92 (m, 2H), 1.90 - 1.81 (m, 2H), 1.22 (d, <i>J</i> = 6.9 Hz, 4H)
219	Method 3	2.442	555	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (br d, <i>J</i> = 6.3 Hz, 1H), 7.94 (d, <i>J</i> = 8.9 Hz, 1H), 7.36 (br t, <i>J</i> = 7.9 Hz, 1H), 7.15 (dd, <i>J</i> = 7.5, 1.6 Hz, 1H), 7.11 (dd, <i>J</i> = 8.9, 2.7 Hz, 1H), 7.05 (dd, <i>J</i> = 8.3, 1.7 Hz, 1H), 6.95 (t, <i>J</i> = 7.4 Hz, 1H), 6.77 (d, <i>J</i> = 2.6 Hz, 1H), 6.45 (dd, <i>J</i> = 11.3, 1.9 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.29 - 5.40 (m, 1H), 3.83 (s, 3H), 3.70 (d, <i>J</i> = 2.2 Hz, 3H), 3.12 (d, <i>J</i> = 3.8 Hz, 3H), 3.03 (br s, 2H), 2.43 - 2.36 (m, 2H), 1.59 - 1.77 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H)
220	Method 1	1.585	573	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 (br d, <i>J</i> = 6.0 Hz, 1H), 8.04 (d, <i>J</i> = 8.5 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 7.44 (d, <i>J</i> = 2.1 Hz, 1H), 7.36 - 7.19 (m, 4H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.38 - 5.27 (m, 1H), 4.62 (t, <i>J</i> = 5.2 Hz, 1H), 3.69 - 3.58 (m, 2H), 3.29 (s, 2H), 3.11 (s, 5H), 2.77 (t, <i>J</i> = 7.1 Hz, 2H), 1.52 - 1.82 (m, 4H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
221	Method 1	1.185	562	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.87 - 8.72 (m, 1H), 7.54 - 7.46 (m, 1H), 7.38 - 7.24 (m, 3H), 7.18 (dd, <i>J</i> = 6.7, 2.3 Hz, 1H), 6.74 (dt, <i>J</i> = 6.7, 2.6 Hz, 1H), 5.16 - 5.05 (m, 1H), 4.59 (dt, <i>J</i> = 14.0, 7.0 Hz, 1H), 4.32 - 4.07 (m, 4H), 3.83 - 3.54 (m, 6H), 3.18 - 3.10 (m, 1H), 2.72 - 2.52 (m, 1H), 2.13 - 1.87 (m, 1H), 1.86 - 1.59 (m, 5H), 1.18 (br d, <i>J</i> = 6.0 Hz, 1H), 1.14 - 0.73 (m, 1H), 0.51 (br d, <i>J</i> = 6.8 Hz, 2H)
222	Method 1	1.237	596	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 - 8.20 (m, 1H), 7.44 - 7.26 (m, 2H), 7.13 (br s, 1H), 6.48 - 6.40 (m, 1H), 6.26 (t, <i>J</i> = 10.4 Hz, 1H), 5.37 - 5.25 (m, 1H), 4.34 - 4.19 (m, 1H), 4.11 - 3.94 (m, 2H), 3.93 - 3.59 (m, 4H), 3.55 - 3.22 (m, 3H), 3.17 - 3.06 (m, 3H), 2.83 - 2.63 (m, 2H), 2.10 - 1.39 (m, 9H), 1.25 - 1.14 (m, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
223	Method 1	1.339	566	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.27 (br dd, <i>J</i> = 7.5, 2.1 Hz, 1H), 7.41 - 7.21 (m, 2H), 7.15 - 7.03 (m, 2H), 6.51 - 6.37 (m, 1H), 6.36 - 6.18 (m, 1H), 5.39 - 5.24 (m, 1H), 4.07 - 3.94 (m, 1H), 3.88 - 3.75 (m, 1H), 3.68 (br d, <i>J</i> = 4.3 Hz, 2H), 3.60 - 3.51 (m, 1H), 3.42 (br d, <i>J</i> = 8.3 Hz, 3H), 3.36 - 3.18 (m, 2H), 3.14 - 3.08 (m, 3H), 2.93 - 2.83 (m, 1H), 2.70 - 2.60 (m, 1H), 2.07 - 1.79 (m, 2H), 1.79 - 1.70 (m, 1H), 1.69 - 1.45 (m, 3H), 1.25 - 1.15 (m, 3H)
224	Method 1	1.283	562	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.31 - 8.17 (m, 1H), 7.18 - 6.99 (m, 4H), 6.48 - 6.39 (m, 1H), 6.30 - 6.17 (m, 1H), 5.42 - 5.21 (m, 1H), 4.00 - 3.87 (m, 2H), 3.85 - 3.63 (m, 3H), 3.51 - 3.24 (m, 5H), 3.14 - 3.08 (m, 3H), 3.05 - 2.88 (m, 1H), 2.71 - 2.60 (m, 1H), 2.48 - 2.41 (m, 1H), 2.37 (s, 3H), 2.05 - 1.83 (m, 1H), 1.81 - 1.67 (m, 1H), 1.67 - 1.46 (m, 3H), 1.40 - 1.29 (m, 1H), 1.26 - 1.14 (m, 3H)
225	Method 1	1.203	580	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.91 - 8.75 (m, 1H), 7.37 (br d, <i>J</i> = 6.0 Hz, 2H), 7.26 - 7.10 (m, 2H), 6.80 - 6.71 (m, 1H), 5.11 (br d, <i>J</i> = 5.6 Hz, 1H), 4.68 - 4.54 (m, 1H), 4.39 - 4.07 (m, 3H), 3.62 - 4.00 (m, 7H), 3.09 - 3.21 (m, 1H), 2.77 - 2.56 (m, 1H), 2.00 - 1.55 (m, 6H), 1.30 - 1.14 (m, 1H), 1.10 - 0.75 (m, 1H), 0.52 (br d, <i>J</i> = 6.5 Hz, 2H)
226	Method 1	1.447	618	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 - 8.22 (m, 1H), 7.46 - 7.22 (m, 1H), 7.25 - 7.12 (m, 1H), 6.49 - 6.38 (m, 1H), 6.32 - 6.22 (m, 1H), 5.42 - 5.21 (m, 1H), 4.19 - 4.02 (m, 1H), 3.93 - 3.75 (m, 1H), 3.67 - 3.50 (m, 1H), 3.48 - 3.36 (m, 3H), 3.35 - 3.23 (m, 3H), 3.19 - 3.11 (m, 2H), 3.07 (br d, <i>J</i> = 2.3 Hz, 1H), 3.04 - 2.86 (m, 2H), 2.81 - 2.62 (m, 1H), 2.09 - 1.81 (m, 2H), 1.80 - 1.44 (m, 4H), 1.25 - 1.15 (m, 3H)
227	Method 1	1.446	618	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.40 - 8.10 (m, 1H), 7.38 - 7.14 (m, 2H), 6.51 - 6.36 (m, 1H), 6.32 - 6.21 (m, 1H), 5.31 (dt, <i>J</i> = 15.9, 7.9 Hz, 1H), 4.18 - 3.96 (m, 1H), 3.80 (dt, <i>J</i> = 18.1, 9.0 Hz, 1H), 3.64 - 3.43 (m, 2H), 3.42 - 3.33 (m, 2H), 3.30 - 3.22 (m, 2H), 3.16 - 3.05 (m, 4H), 3.02 - 2.85 (m, 2H), 2.82 - 2.62 (m, 1H), 2.12 - 1.81 (m, 2H), 1.80 - 1.62 (m, 3H), 1.62 - 1.45 (m, 1H), 1.26 - 1.15 (m, 3H)
228	Method 1	1.411	594	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.35 (br s, 1H), 8.61 (br s, 1H), 8.05 (d, <i>J</i> = 7.9 Hz, 1H), 7.57 - 7.80 (m, 2H), 7.27 - 7.46 (m, 2H), 6.84 - 7.03 (m, 3H), 6.66 - 6.81 (m, 1H), 6.53 (br d, <i>J</i> = 15.3 Hz, 1H), 3.98 (br s, 2H), 3.80 (s, 3H), 3.53 (br d, <i>J</i> = 11.9 Hz, 2H), 3.10 - 3.35 (m, 3H), 2.86 - 3.02 (m, 2H), 2.68 - 2.78 (m, 3H), 2.53 - 2.56

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 2H), 2.46 - 2.49 (m, 1H), 2.11 (br d, <i>J</i> = 12.8 Hz, 2H), 1.65 - 1.93 (m, 6H)
229	Method 1	1.702	506	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 (br d, <i>J</i> = 6.5 Hz, 1H), 7.97 (d, <i>J</i> = 8.9 Hz, 1H), 7.47 - 7.57 (m, 1H), 7.40 - 7.46 (m, 1H), 7.29 - 7.40 (m, 2H), 7.20 (dd, <i>J</i> = 9.0, 2.7 Hz, 1H), 6.77 - 6.89 (m, 2H), 5.63 (d, <i>J</i> = 16.6 Hz, 1H), 4.45 - 4.57 (m, 1H), 3.86 (s, 3H), 3.13 (br d, <i>J</i> = 12.0 Hz, 2H), 2.52 - 2.72 (m, 2H), 1.65 - 1.98 (m, 4H), 1.19 (d, <i>J</i> = 7.2 Hz, 3H)
230	Method 1	1.452	571	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 7.95 (d, <i>J</i> = 8.9 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.45 - 7.33 (m, 3H), 7.18 (dd, <i>J</i> = 2.7, 8.9 Hz, 1H), 6.84 (d, <i>J</i> = 2.6 Hz, 1H), 6.77 (dd, <i>J</i> = 8.8, 11.0 Hz, 1H), 6.57 (d, <i>J</i> = 11.5 Hz, 1H), 4.60 - 4.47 (m, 1H), 4.29 - 4.07 (m, 3H), 3.85 (s, 3H), 3.76 (dd, <i>J</i> = 5.5, 9.5 Hz, 1H), 3.18 - 2.99 (m, 5H), 2.65 - 2.54 (m, 2H), 1.95 - 1.69 (m, 4H)
231	Method 1	1.650	564	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.99 (s, 1H), 8.46 - 8.36 (m, 1H), 7.75 (s, 1H), 7.60 (d, <i>J</i> = 7.9 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.47 (br d, <i>J</i> = 1.3 Hz, 2H), 6.49 - 6.41 (m, 1H), 6.28 (dd, <i>J</i> = 9.5, 11.1 Hz, 1H), 5.41 - 5.28 (m, 1H), 3.25 - 3.16 (m, 2H), 3.11 (s, 3H), 2.84 - 2.73 (m, 1H), 2.70 - 2.59 (m, 1H), 1.97 - 1.72 (m, 4H), 1.23 - 1.19 (m, 3H)
232	Method 1	1.568	497	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.00 (s, 1H), 8.55 (br d, <i>J</i> = 2.1 Hz, 1H), 7.74 (s, 1H), 7.57 - 7.63 (m, 1H), 7.49 - 7.55 (m, 1H), 7.45 (d, <i>J</i> = 4.1 Hz, 2H), 6.84 (dt, <i>J</i> = 16.5, 4.5 Hz, 1H), 5.60 (dt, <i>J</i> = 16.5, 2.0 Hz, 1H), 3.87 (br t, <i>J</i> = 4.0 Hz, 2H), 3.21 (br d, <i>J</i> = 12.8 Hz, 2H), 2.74 - 2.85 (m, 1H), 2.64 - 2.72 (m, 1H), 2.04 - 1.77 (m, 4H)
233	Method 3	2.763	593	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.79 - 8.70 (m, 1H), 7.99 - 7.94 (m, 1H), 7.93 - 7.88 (m, 1H), 7.62 (d, <i>J</i> = 2.0 Hz, 1H), 7.56 (d, <i>J</i> = 7.7 Hz, 1H), 7.49 - 7.43 (m, 1H), 7.40 (d, <i>J</i> = 4.2 Hz, 2H), 6.89 (s, 1H), 4.51 (s, 2H), 4.07 (br d, <i>J</i> = 5.3 Hz, 2H), 3.22 - 3.11 (m, 2H), 2.79 - 2.70 (m, 1H), 2.65 - 2.56 (m, 1H), 2.03 - 1.77 (m, 4H)
234	Method 1	1.681	605	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.63 (br d, <i>J</i> = 8.6 Hz, 1H), 7.94 - 7.99 (m, 1H), 7.88 - 7.93 (m, 1H), 7.61 (d, <i>J</i> = 1.9 Hz, 1H), 7.56 (d, <i>J</i> = 7.9 Hz, 1H), 7.42 - 7.49 (m, 1H), 7.40 (d, <i>J</i> = 4.3 Hz, 2H), 6.93 (s, 1H), 4.76 (br t, <i>J</i> = 6.9 Hz, 1H), 4.50 (s, 2H), 3.12 - 3.20 (m, 2H), 2.72 - 2.77 (m, 2H), 1.71 - 1.94 (m, 4H), 1.28 (d, <i>J</i> = 7.0 Hz, 3H)
235	Method 1	1.534	557	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.62 (br dd, <i>J</i> = 8.1, 1.7 Hz, 1H), 7.97 (d, <i>J</i> = 8.9 Hz, 1H), 7.52 (d, <i>J</i> = 7.4 Hz, 1H), 7.32 - 7.46 (m, 3H), 7.19 (dd, <i>J</i> = 8.9, 2.7 Hz, 1H), 6.93 (s, 1H), 6.85 (d, <i>J</i> = 2.6 Hz, 1H), 4.76 (br t, <i>J</i> = 7.1 Hz, 1H),

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				4.49 (s, 2H), 3.86 (s, 3H), 3.02 - 3.21 (m, 2H), 2.55 - 2.65 (m, 2H), 1.68 - 2.00 (m, 4H), 1.28 (d, $J = 7.0$ Hz, 3H)
236	Method 1	1.652	595	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.61 - 8.68 (m, 1H), 8.27 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.6$ Hz, 1H), 7.75 (s, 1H), 7.58 (d, $J = 7.6$ Hz, 1H), 7.38 - 7.53 (m, 3H), 6.90 - 6.96 (m, 1H), 4.76 (br t, $J = 7.2$ Hz, 1H), 4.50 (s, 2H), 3.11 - 3.25 (m, 2H), 2.73 - 2.84 (m, 1H), 2.59 - 2.68 (m, 1H), 1.72 - 2.00 (m, 4H), 1.28 (d, $J = 7.1$ Hz, 3H)
237	Method 1	1.428	676	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.70 - 10.14 (m, 1H), 8.40 - 8.51 (m, 1H), 7.92 - 7.97 (m, 1H), 7.86 - 7.91 (m, 1H), 7.61 (d, $J = 1.9$ Hz, 1H), 7.51 - 7.57 (m, 1H), 7.41 - 7.49 (m, 1H), 7.34 - 7.41 (m, 2H), 6.40 - 6.64 (m, 2H), 5.22 - 5.37 (m, 1H), 4.18 - 4.40 (m, 1H), 3.84 - 4.04 (m, 1H), 3.55 - 3.69 (m, 1H), 3.08 - 3.26 (m, 4H), 2.81 - 2.93 (m, 3H), 2.58 - 2.80 (m, 4H), 1.80 - 2.07 (m, 2H), 1.67 - 1.79 (m, 2H), 1.20 - 1.25 (m, 3H)
238	Method 1	1.438	676	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.81 - 10.30 (m, 1H), 8.43 - 8.53 (m, 1H), 7.94 - 7.98 (m, 1H), 7.87 - 7.91 (m, 1H), 7.59 - 7.63 (m, 1H), 7.52 - 7.57 (m, 1H), 7.44 - 7.49 (m, 1H), 7.36 - 7.42 (m, 2H), 6.45 - 6.57 (m, 2H), 5.26 - 5.42 (m, 1H), 4.25 - 4.36 (m, 1H), 3.10 - 3.22 (m, 4H), 2.87 (s, 3H), 2.61 - 2.78 (m, 6H), 1.81 (br s, 2H), 1.72 - 1.80 (m, 2H), 1.23 (d, $J = 6.9$ Hz, 3H)
239	Method 6	3.159	627	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.59 (dd, $J = 2.3, 8.5$ Hz, 1H), 7.96 (d, $J = 9.0$ Hz, 1H), 7.55 - 7.49 (m, 1H), 7.44 - 7.33 (m, 3H), 7.19 (dd, $J = 2.7, 8.9$ Hz, 1H), 6.84 (d, $J = 2.6$ Hz, 1H), 6.59 (d, $J = 11.1$ Hz, 1H), 6.32 - 6.22 (m, 1H), 5.76 (dq, $J = 3.4, 9.2$ Hz, 1H), 3.86 (s, 3H), 3.16 - 3.08 (m, 5H), 2.84 - 2.61 (m, 2H), 2.60 - 2.53 (m, 1H), 2.47 - 2.38 (m, 1H), 1.99 - 1.75 (m, 2H), 1.75 - 1.61 (m, 2H)
240	Method 6	3.411	675	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.61 (dd, $J = 2.0, 8.5$ Hz, 1H), 7.99 - 7.93 (m, 1H), 7.92 - 7.86 (m, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.57 - 7.52 (m, 1H), 7.48 - 7.41 (m, 1H), 7.39 (d, $J = 4.6$ Hz, 2H), 6.60 (d, $J = 10.9$ Hz, 1H), 6.32 - 6.22 (m, 1H), 5.81 - 5.69 (m, 1H), 3.19 - 3.13 (m, 2H), 3.12 (s, 3H), 2.84 - 2.67 (m, 2H), 2.66 - 2.52 (m, 2H), 2.01 - 1.78 (m, 2H), 1.76 - 1.63 (m, 2H)
241	Method 1	1.597	587	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.28 (br s, 1H), 7.78 - 7.66 (m, 1H), 7.64 - 7.48 (m, 2H), 7.47 - 7.22 (m, 4H), 6.54 - 6.41 (m, 1H), 6.27 (t, $J = 10.3$ Hz, 1H), 5.45 - 5.21 (m, 1H), 3.68 (br s,

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				2H), 3.24 - 3.02 (m, 5H), 2.03 - 1.35 (m, 6H), 1.20 (br d, <i>J</i> = 6.9 Hz, 3H)
242	Method 1	1.614	575	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.27 (br s, 1H), 7.87 (br d, <i>J</i> = 7.0 Hz, 1H), 7.78 - 7.54 (m, 3H), 7.47 - 7.30 (m, 3H), 6.51 - 6.41 (m, 1H), 6.34 - 6.19 (m, 1H), 5.42 - 5.24 (m, 1H), 3.32 - 3.07 (m, 7H), 1.97 - 1.42 (m, 6H), 1.23 - 1.18 (m, 3H)
243	Method 1	1.725	626	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.15 - 8.28 (m, 1H), 7.67 - 7.75 (m, 2H), 7.48 - 7.62 (m, 2H), 7.33 - 7.41 (m, 3H), 6.67 (br dd, <i>J</i> = 15.3, 5.9 Hz, 1H), 5.95 (br d, <i>J</i> = 15.3 Hz, 1H), 4.56 - 4.72 (m, 2H), 4.51 (br d, <i>J</i> = 4.2 Hz, 1H), 4.25 - 4.39 (m, 2H), 3.38 (br s, 3H), 3.11 - 3.26 (m, 2H), 1.56 - 1.92 (m, 5H), 1.20 (br d, <i>J</i> = 6.6 Hz, 3H)
244	Method 1	1.742	616	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.23 (br s, 1H), 7.88 (br d, <i>J</i> = 7.5 Hz, 1H), 7.73 - 7.79 (m, 1H), 7.53 - 7.69 (m, 2H), 7.38 - 7.50 (m, 2H), 7.30 - 7.37 (m, 1H), 6.67 (dd, <i>J</i> = 15.4, 5.9 Hz, 1H), 5.96 (br d, <i>J</i> = 15.2 Hz, 1H), 4.63 (br s, 2H), 4.52 (br d, <i>J</i> = 5.9 Hz, 1H), 4.24 - 4.38 (m, 2H), 3.52 - 3.87 (m, 1H), 2.93 - 3.41 (m, 3H), 1.41 - 2.13 (m, 6H), 1.16 - 1.25 (m, 3H)
245	Method 2	2.725	634	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.19 - 8.32 (m, 1H), 7.88 - 7.96 (m, 1H), 7.79 (br d, <i>J</i> = 7.9 Hz, 1H), 7.68 - 7.76 (m, 1H), 7.35 - 7.52 (m, 2H), 7.21 - 7.34 (m, 1H), 6.69 (ddd, <i>J</i> = 15.4, 5.9, 3.9 Hz, 1H), 5.91 - 6.01 (m, 1H), 4.49 - 4.74 (m, 3H), 4.33 (br d, <i>J</i> = 9.5 Hz, 2H), 3.65 - 3.83 (m, 1H), 3.14 - 3.31 (m, 3H), 1.66 - 2.07 (m, 6H), 1.21 (dd, <i>J</i> = 6.9, 2.9 Hz, 3H)
246	Method 2	2.801	637	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.29 (dd, <i>J</i> = 2.3, 8.1 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.92 - 7.87 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.57 - 7.53 (m, 1H), 7.48 - 7.42 (m, 1H), 7.39 (d, <i>J</i> = 4.2 Hz, 2H), 6.59 (dd, <i>J</i> = 0.7, 11.3 Hz, 1H), 6.26 (dd, <i>J</i> = 9.5, 11.2 Hz, 1H), 5.62 - 5.52 (m, 1H), 3.47 (dd, <i>J</i> = 7.5, 10.0 Hz, 1H), 3.36 (dd, <i>J</i> = 5.1, 10.0 Hz, 1H), 3.23 (s, 3H), 3.20 - 3.12 (m, 2H), 3.09 (s, 3H), 2.78 - 2.56 (m, 2H), 2.02 - 1.78 (m, 2H), 1.78 - 1.68 (m, 2H)
247	Method 2	2.801	637	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.30 (dd, <i>J</i> = 2.1, 8.1 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.92 - 7.87 (m, 1H), 7.61 (d, <i>J</i> = 2.1 Hz, 1H), 7.58 - 7.53 (m, 1H), 7.49 - 7.42 (m, 1H), 7.39 (d, <i>J</i> = 4.2 Hz, 2H), 6.59 (d, <i>J</i> = 11.2 Hz, 1H), 6.26 (dd, <i>J</i> = 9.6, 11.2 Hz, 1H), 5.64 - 5.52 (m, 1H), 3.47 (dd, <i>J</i> = 7.5, 10.0 Hz, 1H), 3.36 (dd, <i>J</i> = 5.2, 10.0 Hz, 1H), 3.23 (s, 3H), 3.20 - 3.12 (m, 2H), 3.09 (s, 3H), 2.78 - 2.56 (m, 2H), 2.03 - 1.79 (m, 2H), 1.78 - 1.67 (m, 2H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
248	Method 6	3.007	589	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.29 (dd, <i>J</i> = 8.1, 2.0 Hz, 1H), 7.96 (d, <i>J</i> = 8.9 Hz, 1H), 7.48 - 7.54 (m, 1H), 7.32 - 7.45 (m, 3H), 7.19 (dd, <i>J</i> = 8.9, 2.7 Hz, 1H), 6.84 (d, <i>J</i> = 2.6 Hz, 1H), 6.58 (d, <i>J</i> = 11.3 Hz, 1H), 6.26 (dd, <i>J</i> = 11.2, 9.6 Hz, 1H), 5.50 - 5.62 (m, 1H), 3.85 (s, 3H), 3.34 - 3.50 (m, 2H), 3.22 (s, 3H), 3.13 (br s, 2H), 3.09 (s, 3H), 2.52 - 2.71 (m, 2H), 1.72 (br d, <i>J</i> = 13.5 Hz, 4H)
249	Method 1	1.890	652	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.27 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (dd, <i>J</i> = 8.4, 1.4 Hz, 1H), 7.74 (d, <i>J</i> = 1.9 Hz, 2H), 7.58 (d, <i>J</i> = 7.9 Hz, 1H), 7.39 - 7.51 (m, 3H), 6.78 (d, <i>J</i> = 15.6 Hz, 1H), 5.82 (d, <i>J</i> = 15.6 Hz, 1H), 4.61 (br t, <i>J</i> = 11.6 Hz, 2H), 4.31 (br t, <i>J</i> = 11.9 Hz, 2H), 3.19 (br t, <i>J</i> = 12.6 Hz, 2H), 2.72 - 2.82 (m, 1H), 2.62 (td, <i>J</i> = 12.5, 2.6 Hz, 1H), 1.74 - 2.00 (m, 4H), 1.36 (s, 6H)
250	Method 1	1.900	627	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.31 - 8.41 (m, 1H), 8.14 - 8.23 (m, 1H), 7.62 - 7.67 (m, 1H), 7.53 - 7.62 (m, 1H), 7.46 - 7.50 (m, 1H), 7.44 (dt, <i>J</i> = 9.0, 1.6 Hz, 1H), 7.40 (dd, <i>J</i> = 10.1, 2.3 Hz, 1H), 7.37 (d, <i>J</i> = 2.0 Hz, 1H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.25 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.26 - 5.39 (m, 1H), 3.06 - 3.14 (m, 3H), 2.89 - 3.04 (m, 1H), 2.72 - 2.82 (m, 1H), 2.26 - 2.34 (m, 1H), 1.94 - 2.11 (m, 1H), 1.75 - 1.93 (m, 1H), 1.65 - 1.74 (m, 1H), 1.56 - 1.64 (m, 1H), 1.16 - 1.23 (m, 3H), 0.98 - 1.07 (m, 3H)
251	Method 1	1.767	650	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.26 - 8.37 (m, 1H), 8.12 (dd, <i>J</i> = 8.9, 1.4 Hz, 1H), 7.53 - 7.66 (m, 1H), 7.25 - 7.51 (m, 5H), 7.15 (t, <i>J</i> = 2.2 Hz, 1H), 6.65 (ddd, <i>J</i> = 15.5, 6.2, 1.4 Hz, 1H), 5.96 (dd, <i>J</i> = 15.4, 1.3 Hz, 1H), 4.55 - 4.69 (m, 2H), 4.48 - 4.54 (m, 1H), 4.19 - 4.40 (m, 2H), 3.37 - 3.44 (m, 1H), 2.72 - 3.00 (m, 1H), 2.61 - 2.70 (m, 0.5H), 2.23 - 2.41 (m, 1H), 1.82 - 2.16 (m, 1.5H), 1.68 - 1.77 (m, 1H), 1.55 - 1.63 (m, 1H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H), 0.96 - 1.10 (m, 3H)
252	Method 4	2.833	628	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.26 - 8.35 (m, 1H), 8.00 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 7.49 - 7.63 (m, 2H), 7.30 - 7.47 (m, 3H), 7.23 - 7.28 (m, 1H), 6.65 (ddd, <i>J</i> = 15.4, 6.1, 1.9 Hz, 1H), 5.91 - 6.00 (m, 1H), 5.42 (t, <i>J</i> = 4.4 Hz, 1H), 4.83 (br dd, <i>J</i> = 10.2, 3.9 Hz, 1H), 4.47 - 4.69 (m, 3H), 4.24 - 4.40 (m, 2H), 3.34 - 3.44 (m, 1H), 2.59 - 3.02 (m, 2H), 1.66 - 2.38 (m, 3H), 1.46 - 1.61 (m, 1H), 1.34 (dd, <i>J</i> = 6.4, 3.1 Hz, 3H), 1.19 (d, <i>J</i> = 7.0 Hz, 3H), 1.00 - 1.08 (m, 3H)
253	Method 1	1.761	634	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.29 - 8.39 (m, 1H), 8.17 - 8.27 (m, 1H), 7.81 - 7.90

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 1H), 7.34 - 7.67 (m, 5H), 7.17 (t, <i>J</i> = 55.3 Hz, 1H), 6.66 (dd, <i>J</i> = 15.5, 6.1 Hz, 1H), 5.96 (dd, <i>J</i> = 15.5, 1.1 Hz, 1H), 4.47 - 4.71 (m, 3H), 4.25 - 4.40 (m, 2H), 2.65 - 3.04 (m, 2H), 2.26 - 2.40 (m, 1H), 2.08 (s, 4H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H), 1.00 - 1.09 (m, 3H)
254	Method 1	1.725	596	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.23 (dd, <i>J</i> = 7.8, 2.2 Hz, 1H), 7.41 (br d, <i>J</i> = 7.8 Hz, 1H), 7.18 - 7.29 (m, 3H), 6.43 (d, <i>J</i> = 11.1 Hz, 1H), 6.25 (t, <i>J</i> = 10.3 Hz, 1H), 5.24 - 5.36 (m, 1H), 3.71 (br d, <i>J</i> = 10.3 Hz, 2H), 3.56 - 3.60 (m, 1H), 3.33 - 3.48 (m, 3H), 3.19 - 3.30 (m, 1H), 3.09 (s, 3H), 2.77 - 2.89 (m, 2H), 2.59 (br d, <i>J</i> = 13.1 Hz, 1H), 2.41 (br dd, <i>J</i> = 9.2, 5.6 Hz, 1H), 1.94 - 2.12 (m, 1H), 1.69 - 1.84 (m, 1H), 1.51 - 1.65 (m, 6H), 1.16 - 1.24 (m, 4H)
255	Method 1	1.663	527	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 - 8.46 (m, 1H), 7.12 - 7.38 (m, 4H), 6.41 - 6.52 (m, 1H), 6.23 - 6.36 (m, 1H), 5.30 - 5.45 (m, 1H), 4.13 (br d, <i>J</i> = 10.3 Hz, 2H), 3.59 (br s, 1H), 3.25 (br d, <i>J</i> = 12.9 Hz, 2H), 3.12 (s, 3H), 2.56 - 2.71 (m, 1H), 1.58 - 1.97 (m, 5H), 1.29 - 1.49 (m, 4H), 1.11 - 1.26 (m, 4H), 1.04 (s, 3H), 0.91 (s, 3H)
256	Method 1	1.473	529	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 (br s, 1H), 7.33 - 7.49 (m, 2H), 7.08 - 7.32 (m, 2H), 6.46 (br dd, <i>J</i> = 10.9, 6.6 Hz, 1H), 6.24 - 6.35 (m, 1H), 5.36 (br d, <i>J</i> = 6.7 Hz, 1H), 4.03 - 4.22 (m, 2H), 3.73 - 3.94 (m, 2H), 3.50 - 3.67 (m, 2H), 3.27 (br s, 1H), 3.12 (s, 3H), 2.58 - 2.76 (m, 1H), 1.59 - 1.82 (m, 4H), 1.41 (br d, <i>J</i> = 13.1 Hz, 2H), 1.30 (s, 3H), 1.22 (br d, <i>J</i> = 6.0 Hz, 3H), 1.17 (s, 3H)
257	Method 1	1.676	539	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 - 8.43 (m, 1H), 7.19 - 7.37 (m, 3H), 7.12 - 7.17 (m, 1H), 6.43 - 6.49 (m, 1H), 6.25 - 6.34 (m, 1H), 5.32 - 5.42 (m, 1H), 4.04 - 4.19 (m, 2H), 3.37 (br d, <i>J</i> = 10.5 Hz, 1H), 3.18 - 3.30 (m, 2H), 3.12 (s, 3H), 2.56 - 2.69 (m, 1H), 1.79 - 1.98 (m, 8H), 1.64 - 1.77 (m, 4H), 1.35 - 1.61 (m, 3H), 1.22 (br dd, <i>J</i> = 6.4, 3.8 Hz, 4H)
258	Method 2	2.680	498	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.41 - 8.28 (m, 1H), 7.45 - 7.38 (m, 1H), 7.30 - 7.18 (m, 3H), 6.93 - 6.80 (m, 1H), 6.45 (br d, <i>J</i> = 10.9 Hz, 1H), 6.27 (br t, <i>J</i> = 9.8 Hz, 1H), 5.43 - 5.25 (m, 1H), 4.26 - 4.12 (m, 1H), 4.11 - 3.98 (m, 1H), 3.85 - 3.50 (m, 3H), 3.29 - 3.16 (m, 1H), 3.16 - 3.09 (m, 3H), 3.08 - 2.77 (m, 1H), 2.66 - 2.54 (m, 1H), 2.03 - 1.88 (m, 3H), 1.88 - 1.51 (m, 3H), 1.45 (br d, <i>J</i> = 7.9 Hz, 9H), 1.20 (br s, 3H)

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
259	Method 2	2.695	[M+H-56] = 544	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.20 - 8.45 (m, 1H), 7.41 - 7.46 (m, 1H), 7.19 - 7.32 (m, 3H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.22 - 6.30 (m, 1H), 5.24 - 5.40 (m, 1H), 3.78 - 4.25 (m, 2H), 3.43 - 3.76 (m, 5H), 3.06 - 3.19 (m, 3H), 2.37 - 2.43 (m, 2H), 1.54 - 1.92 (m, 6H), 1.29 - 1.45 (m, 9H), 1.15 - 1.22 (m, 3H), 0.67 - 1.09 (m, 1H)
260	Method 1	1.467	636.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.68 (s, 1H), 8.56 (d, <i>J</i> = 3.6 Hz, 1H), 8.41 - 8.33 (m, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.91 (d, <i>J</i> = 7.9 Hz, 1H), 7.71 (dd, <i>J</i> = 2.2, 8.6 Hz, 1H), 7.50 - 7.41 (m, 2H), 7.39 - 7.31 (m, 1H), 7.13 - 7.05 (m, 2H), 7.00 (d, <i>J</i> = 7.6 Hz, 1H), 6.45 (d, <i>J</i> = 10.9 Hz, 1H), 6.27 (dd, <i>J</i> = 9.4, 11.1 Hz, 1H), 5.42 - 5.28 (m, 1H), 5.19 (s, 2H), 3.12 (br s, 2H), 3.09 (s, 3H), 2.58 - 2.52 (m, 1H), 2.48 - 2.45 (m, 1H), 1.82 - 1.69 (m, 1H), 1.68 - 1.55 (m, 3H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
261	Method 1	1.872	665	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (dd, <i>J</i> = 2.2, 7.8 Hz, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.70 (dd, <i>J</i> = 2.3, 8.5 Hz, 1H), 7.46 (d, <i>J</i> = 2.3 Hz, 1H), 7.37 - 7.27 (m, 2H), 7.08 - 7.00 (m, 4H), 6.97 (d, <i>J</i> = 7.6 Hz, 1H), 6.89 (dd, <i>J</i> = 1.9, 8.1 Hz, 1H), 6.45 (d, <i>J</i> = 11.8 Hz, 1H), 6.27 (dd, <i>J</i> = 9.4, 11.2 Hz, 1H), 5.41 - 5.27 (m, 1H), 5.11 (s, 2H), 3.75 (s, 3H), 3.12 (br s, 2H), 3.09 (s, 3H), 2.52 (br s, 1H), 2.47 (br s, 1H), 1.83 - 1.69 (m, 1H), 1.68 - 1.55 (m, 3H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
262	Method 2	3.053	615	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 (br d, <i>J</i> = 6.4 Hz, 1H), 8.03 (d, <i>J</i> = 8.7 Hz, 1H), 7.69 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 7.46 (d, <i>J</i> = 2.2 Hz, 1H), 7.31 (t, <i>J</i> = 7.8 Hz, 1H), 6.89-7.01 (m, 3H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1H), 5.24-5.40 (m, 1H), 3.99 (t, <i>J</i> = 6.5 Hz, 2H), 3.10 (s, 5H), 2.55 (br s, 2H), 1.61-1.80 (m, 6H), 1.30-1.42 (m, 4H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H), 0.83-0.93 (m, 3H)
263	Method 1	1.872	599	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.36 (br d, <i>J</i> = 8.2 Hz, 1 H), 8.04 (d, <i>J</i> = 8.7 Hz, 1 H), 7.70 (dd, <i>J</i> = 8.6, 2.3 Hz, 1 H), 7.45 (d, <i>J</i> = 2.2 Hz, 1 H), 7.32 (t, <i>J</i> = 8.0 Hz, 1 H), 6.83 - 6.97 (m, 3 H), 6.45 (d, <i>J</i> = 11.3 Hz, 1 H), 6.27 (dd, <i>J</i> = 11.1, 9.5 Hz, 1 H), 5.28 - 5.40 (m, 1 H), 4.72 (t, <i>J</i> = 7.0 Hz, 1 H), 3.30 (s, 2 H), 3.12 (s, 5 H), 2.41 - 2.46 (m, 2 H), 2.05 (quin, <i>J</i> = 9.8 Hz, 2 H), 1.71 - 1.86 (m, 2 H), 1.56 - 1.70 (m, 4 H), 1.20 (d, <i>J</i> = 6.9 Hz, 3 H)
264	Method 1	1.800	597	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.35 (br d, <i>J</i> = 5.8 Hz, 1H), 8.04 (d, <i>J</i> = 8.5 Hz, 1H), 7.70 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.46 (d, <i>J</i> = 2.3 Hz, 1H), 7.28 - 7.40 (m, 1H), 6.95 - 7.06 (m, 3H),

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				6.45 (d, $J = 11.2$ Hz, 1H), 6.26 (dd, $J = 11.1$, 9.5 Hz, 1H), 5.25 - 5.40 (m, 1H), 4.75 (d, $J = 2.4$ Hz, 2H), 3.29 - 3.32 (m, 2H), 3.11 (s, 5H), 1.58 - 1.86 (m, 7H), 1.19 (d, $J = 6.9$ Hz, 3H)
265	Method 1	1.944	669	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.31 - 8.39 (m, 1H), 8.04 (d, $J = 8.6$ Hz, 1H), 7.71 (dd, $J = 8.6$, 2.3 Hz, 1H), 7.59 - 7.66 (m, 1H), 7.46 - 7.56 (m, 2H), 7.32 - 7.44 (m, 3H), 7.05 - 7.13 (m, 2H), 7.00 (d, $J = 7.5$ Hz, 1H), 6.45 (d, $J = 11.2$ Hz, 1H), 6.27 (dd, $J = 11.1$, 9.5 Hz, 1H), 5.29 - 5.41 (m, 1H), 5.19 (s, 2H), 3.07 - 3.17 (m, 5H), 2.52 - 2.58 (m, 2H), 1.57 - 1.84 (m, 4H), 1.19 (d, $J = 6.8$ Hz, 3H)
266	Method 1	1.948	669	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.34 (br d, $J = 5.8$ Hz, 1H), 8.04 (d, $J = 8.6$ Hz, 1H), 7.70 (dd, $J = 2.1$, 8.6 Hz, 1H), 7.52 (s, 1H), 7.48 - 7.27 (m, 5H), 7.12 - 7.04 (m, 2H), 6.99 (d, $J = 7.5$ Hz, 1H), 6.45 (d, $J = 11.3$ Hz, 1H), 6.33 - 6.21 (m, 1H), 5.41 - 5.27 (m, 1H), 5.16 (s, 2H), 3.08 (s, 5H), 2.54 (br s, 2H), 1.84 - 1.70 (m, 1H), 1.70 - 1.51 (m, 3H), 1.19 (d, $J = 6.9$ Hz, 3H)
267	Method 14	12.064	621.0	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.39 (dd, $J = 7.9$, 2.4 Hz, 1H), 8.01 (d, $J = 8.6$ Hz, 1H), 7.70 (dd, $J = 8.6$, 2.3 Hz, 1H), 7.49 (d, $J = 2.2$ Hz, 1H), 7.47 - 7.37 (m, 3H), 7.20 - 7.11 (m, 2H), 7.11 - 7.03 (m, 3H), 6.99 (t, $J = 2.1$ Hz, 1H), 6.46 (d, $J = 11.2$ Hz, 1H), 6.28 (dd, $J = 11.2$, 9.4 Hz, 1H), 5.35 (h, $J = 7.1$ Hz, 1H), 3.17 (d, $J = 13.2$ Hz, 2H), 3.11 (s, 3H), 2.60 - 2.51 (m, 2H), 1.90 - 1.76 (m, 1H), 1.77 - 1.61 (m, 3H), 1.20 (d, $J = 6.8$ Hz, 3H)
268	Method 14	12.076	635.0	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.37 (dd, $J = 7.9$, 2.5 Hz, 1H), 8.04 (d, $J = 8.6$ Hz, 1H), 7.70 (dd, $J = 8.6$, 2.3 Hz, 1H), 7.50 - 7.44 (m, 3H), 7.44 - 7.37 (m, 2H), 7.37 - 7.29 (m, 2H), 7.10 - 7.02 (m, 2H), 6.98 (dt, $J = 7.5$, 1.2 Hz, 1H), 6.45 (dd, $J = 11.1$, 1.0 Hz, 1H), 6.27 (dd, $J = 11.1$, 9.4 Hz, 1H), 5.35 (h, $J = 7.1$ Hz, 1H), 5.13 (s, 2H), 3.15 - 3.06 (m, 5H), 2.56 - 2.45 (m, 2H), 1.81 - 1.69 (m, 1H), 1.69 - 1.56 (m, 3H), 1.19 (d, $J = 6.8$ Hz, 3H)
269	Method 1	1.515	636	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.58 (d, $J = 4.4$ Hz, 1H), 8.35 (br d, $J = 8.0$ Hz, 1H), 8.04 (d, $J = 8.6$ Hz, 1H), 7.84 (dt, $J = 1.8$, 7.7 Hz, 1H), 7.71 (dd, $J = 2.3$, 8.6 Hz, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.46 (d, $J = 2.1$ Hz, 1H), 7.40 - 7.30 (m, 2H), 7.13 - 7.05 (m, 2H), 7.00 (d, $J = 7.6$ Hz, 1H), 6.45 (d, $J = 11.0$ Hz, 1H), 6.32 - 6.23 (m, 1H), 5.38 - 5.30 (m, 1H), 5.22 (s, 2H), 3.09 (s, 5H), 2.60 - 2.53 (m, 2H), 1.87 - 1.71 (m, 1H), 1.69 - 1.53 (m, 3H), 1.20 (d, $J = 6.9$ Hz, 3H)
270	Method 1	1.639	560.1	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 9.06 - 8.83 (m, 1H), 8.35 (br s, 1H), 7.63 (br d, $J = 11.9$

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				Hz, 1H), 7.37 (br s, 1H), 7.03 (br s, 3H), 6.54 - 6.37 (m, 1H), 6.25 (br s, 1H), 5.33 (br s, 1H), 3.86 - 3.71 (m, 3H), 3.30 - 3.27 (m, 1H), 3.30 (br s, 3H), 3.20 - 3.07 (m, 3H), 1.64 (br s, 4H), 1.18 (br d, <i>J</i> = 6.8 Hz, 3H)
271	Method 2	2.577	594.1	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ ppm 9.01 (s, 1H), 7.50 (s, 1H), 7.45 (d, <i>J</i> = 8.8 Hz, 1H), 7.07 - 7.02 (m, 1H), 7.02 - 6.99 (m, 1H), 6.39 (d, <i>J</i> = 11.0 Hz, 1H), 6.28 - 6.18 (m, 1H), 5.49 - 5.38 (m, 1H), 3.82 (s, 3H), 3.37 (br s, 1H), 3.24 - 3.15 (m, 2H), 3.13 (s, 3H), 2.92 (br t, <i>J</i> = 13.0 Hz, 1H), 2.70 (br t, <i>J</i> = 12.9 Hz, 1H), 2.15 - 1.89 (m, 2H), 1.83 - 1.65 (m, 2H), 1.31 (d, <i>J</i> = 6.9 Hz, 3H)
272	Method 4	3.112	596	¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.30 - 7.45 (m, 2H), 7.10 - 7.21 (m, 2H), 6.21 - 6.44 (m, 2H), 6.07 (td, <i>J</i> = 10.2, 5.4 Hz, 1H), 5.21 - 5.39 (m, 1H), 4.19 - 4.35 (m, 1H), 3.44 - 3.81 (m, 3H), 3.24 - 3.40 (m, 3H), 3.17 (br d, <i>J</i> = 4.1 Hz, 3H), 2.90 - 3.07 (m, 1H), 2.63 - 2.81 (m, 1H), 2.16 - 2.50 (m, 2H), 1.60 - 2.05 (m, 8H), 1.39 (br dd, <i>J</i> = 10.9, 6.9 Hz, 3H), 1.26 (s, 1H)
273	Method 14	11.103	604.8	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.01 (d, <i>J</i> = 8.6 Hz, 1H), 7.67 (dd, <i>J</i> = 8.5, 2.1 Hz, 1H), 7.54 - 7.45 (m, 2H), 7.42 (dd, <i>J</i> = 7.0, 2.4 Hz, 1H), 7.39 - 7.29 (m, 2H), 6.32 (d, <i>J</i> = 10.3 Hz, 1H), 5.29 (s, 1H), 5.01 (d, <i>J</i> = 11.6 Hz, 1H), 4.73 (s, 1H), 3.25 (d, <i>J</i> = 14.0 Hz, 1H), 3.09 (d, <i>J</i> = 13.5 Hz, 1H), 2.97 (s, 1H), 2.88 (t, <i>J</i> = 11.5 Hz, 1H), 2.72 - 2.57 (m, 1H), 2.25 - 1.91 (m, 3H), 1.81 - 1.64 (m, 2H)
274	Method 2	2.137	560.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.53 (s, 1H), 8.36 (br d, <i>J</i> = 6.0 Hz, 1H), 7.53 (d, <i>J</i> = 7.9 Hz, 1H), 7.48 - 7.31 (m, 3H), 6.46 (d, <i>J</i> = 11.3 Hz, 1H), 6.35 - 6.22 (m, 2H), 5.49 - 5.23 (m, 1H), 3.58 (s, 3H), 3.18 - 2.96 (m, 5H), 2.73 - 2.55 (m, 2H), 1.98 - 1.66 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
275	Method 1	1.263	560.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.38 (dd, <i>J</i> = 1.9, 7.8 Hz, 1H), 7.91 (s, 1H), 7.58 - 7.51 (m, 1H), 7.47 - 7.33 (m, 3H), 6.93 (s, 1H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.28 (dd, <i>J</i> = 9.4, 11.2 Hz, 1H), 5.35 (br d, <i>J</i> = 8.2 Hz, 1H), 3.50 (s, 3H), 3.22 - 3.05 (m, 5H), 2.87 - 2.75 (m, 1H), 2.71 - 2.60 (m, 1H), 2.02 - 1.65 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
276	Method 1	1.375	546	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 12.44 (br s, 1H), 8.37 (br d, <i>J</i> = 6.1 Hz, 1H), 8.06 (s, 1H), 7.53 (d, <i>J</i> = 7.9 Hz, 1H), 7.47 - 7.29 (m, 3H), 6.45 (d, <i>J</i> = 11.4 Hz, 1H), 6.28 (dd, <i>J</i> = 9.6, 11.1 Hz, 1H), 6.21 (s, 1H), 5.45 - 5.25 (m, 1H), 3.13 - 2.99 (m, 5H), 2.78 - 2.68 (m, 1H), 2.62 - 2.56

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 1H), 2.01 - 1.65 (m, 4H), 1.21 (d, <i>J</i> = 6.9 Hz, 3H)
277	Method 1	1.488	610	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.95 (s, 1H), 8.44 - 8.35 (m, 1H), 7.86 (s, 1H), 7.61 - 7.57 (m, 1H), 7.53 - 7.47 (m, 1H), 7.44 (d, <i>J</i> = 4.1 Hz, 2H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.28 (dd, <i>J</i> = 9.4, 11.2 Hz, 1H), 5.38 - 5.29 (m, 1H), 3.20 (br d, <i>J</i> = 13.0 Hz, 2H), 3.11 (s, 3H), 2.84 - 2.73 (m, 1H), 2.65 (br t, <i>J</i> = 11.2 Hz, 1H), 1.95 - 1.67 (m, 4H), 1.20 (d, <i>J</i> = 6.8 Hz, 3H)
278	Method 1	1.583	430	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.73 - 9.94 (m, 1H), 7.45 - 7.53 (m, 1H), 7.29 - 7.40 (m, 2H), 7.14 - 7.24 (m, 1H), 6.17 - 6.30 (m, 1H), 6.01 - 6.11 (m, 1H), 5.64 (br d, <i>J</i> = 10.3 Hz, 1H), 4.76 (br s, 1H), 3.78 - 3.92 (m, 3H), 3.00 - 3.47 (m, 10H), 2.82 (br dd, <i>J</i> = 9.9, 3.1 Hz, 1H), 1.66 - 1.94 (m, 5H), 1.14 - 1.57 (m, 4H), 0.53 - 0.73 (m, 1H)
279	Method 1	1.607	614	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.46 (t, <i>J</i> = 5.7 Hz, 1H), 8.35 (br d, <i>J</i> = 7.7 Hz, 1H), 8.05 (d, <i>J</i> = 8.7 Hz, 1H), 7.92 - 7.84 (m, 2H), 7.74 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 7.55 - 7.48 (m, 3H), 6.45 (d, <i>J</i> = 11.1 Hz, 1H), 6.30 - 6.23 (m, 1H), 5.39 - 5.27 (m, 1H), 3.22 (q, <i>J</i> = 6.5 Hz, 2H), 3.10 (s, 5H), 2.61 - 2.52 (m, 2H), 1.89 - 1.59 (m, 4H), 1.53 (sxt, <i>J</i> = 7.3 Hz, 2H), 1.19 (d, <i>J</i> = 6.9 Hz, 3H), 0.88 (t, <i>J</i> = 7.4 Hz, 3H)
280	Method 1	1.706	598	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.80 (br d, <i>J</i> = 7.8 Hz, 1H), 7.99 - 7.94 (m, 1H), 7.92 - 7.88 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.56 (d, <i>J</i> = 7.8 Hz, 1H), 7.48 - 7.43 (m, 1H), 7.40 (d, <i>J</i> = 4.1 Hz, 2H), 4.85 - 4.73 (m, 1H), 3.16 (br d, <i>J</i> = 11.8 Hz, 2H), 3.10 (s, 3H), 2.83 (s, 3H), 2.77 - 2.64 (m, 2H), 1.92 - 1.73 (m, 4H), 1.37 (d, <i>J</i> = 7.1 Hz, 3H)
281	Method 1	1.687	598	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.81 (d, <i>J</i> = 7.7 Hz, 1H), 7.97 - 7.94 (m, 1H), 7.91 - 7.88 (m, 1H), 7.61 (d, <i>J</i> = 2.2 Hz, 1H), 7.57 - 7.54 (m, 1H), 7.48 - 7.43 (m, 1H), 7.41 - 7.39 (m, 2H), 4.81 - 4.75 (m, 1H), 3.15 (br d, <i>J</i> = 14.5 Hz, 2H), 3.10 (s, 3H), 2.83 (s, 3H), 2.52 - 2.76 (m, 3H), 1.68 - 2.08 (m, 3H), 1.36 (d, <i>J</i> = 7.0 Hz, 3H)
282	Method 1	1.663	634	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.52 (br d, <i>J</i> = 5.3 Hz, 1H), 7.87 - 8.01 (m, 2H), 7.54 - 7.63 (m, 2H), 7.36 - 7.45 (m, 3H), 6.57 - 6.67 (m, 1H), 5.92 (br d, <i>J</i> = 15.4 Hz, 1H), 4.56 - 4.67 (m, 2H), 4.27 - 4.37 (m, 2H), 3.85 (br s, 2H), 2.62 - 2.74 (m, 4H), 1.79 - 1.99 (m, 4H)
283	Method 1	1.668	624	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.53 (td, <i>J</i> = 5.6, 2.4 Hz, 1H), 8.28 (d, <i>J</i> = 8.4 Hz, 1H), 8.07 (dd, <i>J</i> = 8.4, 1.5 Hz, 1H), 7.75 (d, <i>J</i> = 1.5 Hz, 1H), 7.59 (d, <i>J</i> = 7.8 Hz, 1H), 7.41 - 7.53 (m, 3H), 6.63 (dt, <i>J</i> = 15.4, 5.0 Hz, 1H), 5.93 (dt, <i>J</i> =

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				15.4, 1.7 Hz, 1H), 4.51 - 4.72 (m, 2H), 4.25 - 4.42 (m, 2H), 3.87 (br t, <i>J</i> = 4.6 Hz, 2H), 3.14 - 3.26 (m, 2H), 2.75 - 2.86 (m, 1H), 2.61 - 2.70 (m, 1H), 1.74 - 2.04 (m, 4H)
284	Method 1	1.720	624	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.47 - 8.52 (m, 1H), 8.26 (d, <i>J</i> = 8.5 Hz, 1H), 8.06 (dd, <i>J</i> = 8.5, 1.6 Hz, 1H), 7.74 (d, <i>J</i> = 1.3 Hz, 1H), 7.58 (d, <i>J</i> = 7.9 Hz, 1H), 7.45 - 7.51 (m, 1H), 7.40 - 7.44 (m, 2H), 5.96 - 6.05 (m, 1H), 5.86 - 5.93 (m, 1H), 4.61 (br t, <i>J</i> = 12.5 Hz, 2H), 4.31 (br t, <i>J</i> = 12.8 Hz, 2H), 4.19 - 4.25 (m, 2H), 3.13 - 3.22 (m, 2H), 2.64 - 2.84 (m, 2H), 1.68 - 2.00 (m, 4H).
285	Method 1	1.720	634	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.50 (br d, <i>J</i> = 1.9 Hz, 1H), 7.98 - 7.93 (m, 1H), 7.92 - 7.86 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.55 (d, <i>J</i> = 7.7 Hz, 1H), 7.49 - 7.37 (m, 3H), 6.05 - 5.95 (m, 1H), 5.94 - 5.86 (m, 1H), 4.61 (br t, <i>J</i> = 12.5 Hz, 2H), 4.31 (br t, <i>J</i> = 12.4 Hz, 2H), 4.22 (br t, <i>J</i> = 4.6 Hz, 2H), 3.15 (br d, <i>J</i> = 12.2 Hz, 2H), 2.78 - 2.68 (m, 1H), 2.62 (br s, 1H), 2.02 - 1.83 (m, 2H), 1.77 - 1.67 (m, 2H)
286	Method 1	1.657	598	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.49 (br d, <i>J</i> = 2.4 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.92 - 7.86 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.58 - 7.53 (m, 1H), 7.48 - 7.36 (m, 3H), 5.95 - 5.77 (m, 2H), 4.21 (br t, <i>J</i> = 4.7 Hz, 2H), 4.12 (t, <i>J</i> = 7.6 Hz, 2H), 3.87 (t, <i>J</i> = 7.7 Hz, 2H), 3.14 (br d, <i>J</i> = 11.2 Hz, 2H), 2.78 - 2.69 (m, 1H), 2.63 - 2.55 (m, 1H), 2.18 (quin, <i>J</i> = 7.7 Hz, 2H), 2.04 - 1.69 (m, 4H)
287	Method 1	1.743	648	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.27 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 7.91 - 7.97 (m, 1H), 7.85 - 7.90 (m, 1H), 7.59 (d, <i>J</i> = 2.0 Hz, 1H), 7.51 - 7.55 (m, 1H), 7.39 - 7.46 (m, 1H), 7.37 (d, <i>J</i> = 4.3 Hz, 2H), 6.09 (dd, <i>J</i> = 11.5, 8.5 Hz, 1H), 5.81 (dd, <i>J</i> = 11.6, 0.7 Hz, 1H), 5.25 - 5.44 (m, 1H), 4.43 - 4.71 (m, 2H), 4.30 (br t, <i>J</i> = 12.8 Hz, 2H), 3.12 (br dd, <i>J</i> = 9.6, 3.5 Hz, 2H), 2.55 - 2.75 (m, 2H), 1.64 - 1.97 (m, 4H), 1.13 (d, <i>J</i> = 6.8 Hz, 3H)
288	Method 1	1.624	600	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.42 - 8.51 (m, 1H), 7.93 - 8.01 (m, 1H), 7.48 - 7.61 (m, 1H), 7.30 - 7.45 (m, 3H), 7.11 - 7.19 (m, 1H), 6.78 - 6.85 (m, 1H), 5.95 - 6.03 (m, 1H), 5.85 - 5.93 (m, 1H), 4.61 (br t, <i>J</i> = 12.5 Hz, 2H), 4.31 (br t, <i>J</i> = 12.3 Hz, 2H), 4.21 (br t, <i>J</i> = 4.9 Hz, 2H), 3.85 (s, 3H), 3.28 - 3.42 (m, 1H), 2.72 - 2.96 (m, 1H), 2.26 - 2.35 (m, 1H), 1.97 - 2.17 (m, 1H), 1.95 (s, 1H), 1.58 - 1.72 (m, 1H), 1.43 - 1.57 (m, 1H), 0.97 - 1.10 (m, 3H)
289	Method 1	1.670	639	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 9.36 (d, <i>J</i> = 2.5 Hz, 1H), 8.47 - 8.57 (m, 1H), 8.10 (d, <i>J</i> =

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				3.5 Hz, 1H), 7.60 - 7.73 (m, 1H), 7.42 - 7.58 (m, 3H), 5.95 - 6.04 (m, 1H), 5.85 - 5.94 (m, 1H), 4.62 (br t, J = 12.4 Hz, 2H), 4.31 (br t, J = 12.6 Hz, 2H), 4.22 (br t, J = 5.1 Hz, 2H), 3.40 - 3.62 (m, 1H), 2.72 - 3.06 (m, 1H), 2.37 - 2.48 (m, 1H), 1.58 - 2.16 (m, 4H), 1.08 (br d, J = 6.9 Hz, 3H)
290	Method 1	1.743	638	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.49 (br s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.04 (br d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.55 - 7.68 (m, 1H), 7.37 - 7.54 (m, 3H), 5.95 - 6.03 (m, 1H), 5.86 - 5.93 (m, 1H), 4.61 (br t, J = 12.4 Hz, 2H), 4.31 (br t, J = 12.6 Hz, 2H), 4.17 - 4.25 (m, 2H), 3.44 (br d, J = 8.4 Hz, 1H), 2.76 - 3.04 (m, 1H), 2.33 (br t, J = 12.1 Hz, 1H), 2.01 - 2.20 (m, 1H), 1.50 - 1.79 (m, 3H), 0.98 - 1.13 (m, 3H)
291	Method 1	1.736	650	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.49 (br s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.81 - 7.90 (m, 1H), 7.52 - 7.64 (m, 2H), 7.28 - 7.50 (m, 3H), 5.93 - 6.04 (m, 1H), 5.86 - 5.92 (m, 1H), 4.61 (br t, J = 12.4 Hz, 2H), 4.31 (br t, J = 12.4 Hz, 2H), 4.21 (br t, J = 4.4 Hz, 2H), 3.35 - 3.46 (m, 1H), 2.56 - 3.00 (m, 1H), 1.48 - 2.37 (m, 5H), 0.98 - 1.10 (m, 3H)
292	Method 1	1.595	595	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.46 - 8.52 (m, 1H), 8.23 (d, J = 8.3 Hz, 1H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 7.55 - 7.67 (m, 1H), 7.42 - 7.52 (m, 2H), 7.34 - 7.42 (m, 1H), 5.95 - 6.02 (m, 1H), 5.91 (br d, J = 1.5 Hz, 1H), 4.61 (br t, J = 12.3 Hz, 2H), 4.30 (br d, J = 13.0 Hz, 2H), 4.22 (br s, 2H), 3.37 - 3.50 (m, 1H), 2.93 - 3.00 (m, 0.5H), 2.66 - 2.80 (m, 1H), 2.31 - 2.37 (m, 0.5H), 1.89 - 2.12 (m, 1H), 1.55 - 1.77 (m, 3H), 1.02 - 1.06 (m, 3H)
293	Method 1	1.515	570	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.50 (br s, 1H), 7.31 - 7.42 (m, 2H), 7.26 (t, J = 7.1 Hz, 1H), 7.14 - 7.21 (m, 1H), 6.97 - 6.05 (m, 1H), 5.87 - 5.94 (m, 1H), 4.62 (br t, J = 12.5 Hz, 2H), 4.32 (br t, J = 12.6 Hz, 2H), 4.24 (br t, J = 4.8 Hz, 2H), 4.14 - 4.02 (m, 1H), 3.89 - 3.81 (m, 2H), 3.70 - 3.60 (m, 2H), 3.41 (td, J = 10.6, 4.2 Hz, 1H), 3.27 - 2.96 (m, 1H), 2.30 - 2.11 (m, 1H), 2.02 - 1.59 (m, 4H), 1.52 - 1.39 (m, 1H), 1.32 (s, 3H), 1.18 (s, 3H), 0.51 - 0.75 (m, 2H)
294	Method 1	1.445	521.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.69 - 8.78 (m, 1H), 7.52 (br d, J = 7.4 Hz, 1H), 7.24 - 7.41 (m, 4H), 7.17 (dd, J = 6.6, 2.2 Hz, 1H), 7.04 (dd, J = 8.5, 2.2 Hz, 1H), 6.88 - 6.92 (m, 1H), 6.78 (dd, J = 6.6, 2.2 Hz, 1H), 5.02 - 5.15 (m, 1H), 3.80 (s, 3H), 3.61 - 3.73 (m, 2H), 3.07 - 3.30 (m, 4H), 1.55 - 2.07 (m, 6H)
295	Method 2	2.446	537	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 - 8.20 (m, 1H), 7.56 - 7.47 (m, 1H), 7.41 - 7.24

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 4H), 7.04 (br dd, $J = 2.3, 8.4$ Hz, 1H), 6.90 (br s, 1H), 6.46 (br d, $J = 11.2$ Hz, 1H), 6.33 - 6.23 (m, 1H), 5.38 - 5.29 (m, 1H), 3.80 (s, 3H), 3.72 - 3.58 (m, 1H), 3.14 (br d, $J = 16.1$ Hz, 6H), 2.11 - 1.42 (m, 6H), 1.20 (br d, $J = 6.7$ Hz, 3H)
296	Method 16	0.798	600.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.39 - 8.28 (m, 1H), 7.34 - 7.22 (m, 2H), 7.17 - 7.05 (m, 1H), 6.75 - 6.66 (m, 1H), 6.66 - 6.57 (m, 1H), 4.66 - 4.52 (m, 1H), 4.20 - 4.06 (m, 1H), 3.89 - 3.73 (m, 1H), 3.66 - 3.53 (m, 1H), 3.52 - 3.44 (m, 1H), 3.43 - 3.33 (m, 2H), 3.31 - 3.20 (m, 2H), 3.19 - 3.09 (m, 1H), 3.06 - 2.92 (m, 3H), 2.87 - 2.81 (m, 1H), 2.75 - 2.57 (m, 1H), 2.10 - 2.00 (m, 1H), 1.96 - 1.75 (m, 3H), 1.73 - 1.45 (m, 3H), 1.26 - 1.19 (m, 3H)
297	Method 16	0.795	600.2	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.33 - 8.19 (m, 1H), 7.34 - 7.20 (m, 2H), 7.16 - 7.04 (m, 1H), 6.51 - 6.38 (m, 1H), 6.35 - 6.21 (m, 1H), 5.43 - 5.23 (m, 1H), 4.20 - 3.99 (m, 1H), 3.91 - 3.68 (m, 1H), 3.64 - 3.53 (m, 1H), 3.51 - 3.43 (m, 1H), 3.43 - 3.33 (m, 2H), 3.31 - 3.20 (m, 2H), 3.18 - 3.07 (m, 4H), 3.06 - 2.90 (m, 1H), 2.87 - 2.76 (m, 1H), 2.74 - 2.57 (m, 1H), 2.07 - 1.44 (m, 6H), 1.24 - 1.16 (m, 3H)
298	Method 1	1.820	628.1	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.36 - 8.27 (m, 1H), 7.96 (dd, $J = 8.9, 1.8$ Hz, 1H), 7.62 - 7.49 (m, 1H), 7.46 - 7.31 (m, 3H), 7.14 (dt, $J = 8.9, 3.2$ Hz, 1H), 6.80 (dd, $J = 4.1, 2.7$ Hz, 1H), 6.65 (ddd, $J = 15.4, 6.1, 1.6$ Hz, 1H), 5.95 (dd, $J = 15.4, 1.4$ Hz, 1H), 4.74 - 4.45 (m, 3H), 4.40 - 4.23 (m, 2H), 4.20 - 4.07 (m, 2H), 3.44 - 3.33 (m, 1H), 2.98 - 2.74 (m, 1H), 2.34 - 2.25 (m, 1H), 2.14 - 1.48 (m, 4H), 1.33 (t, $J = 6.9$ Hz, 3H), 1.19 (d, $J = 6.9$ Hz, 3H), 1.08 - 1.00 (m, 3H)
299	Method 1	1.810	587	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.29 - 8.40 (m, 1H), 7.91 - 8.00 (m, 1H), 7.49 - 7.63 (m, 1H), 7.30 - 7.46 (m, 3H), 7.13 (dt, $J = 8.9, 3.0$ Hz, 1H), 6.76 - 6.82 (m, 1H), 6.44 (d, $J = 11.1$ Hz, 1H), 6.26 (dd, $J = 11.1, 9.7$ Hz, 1H), 5.34 (dt, $J = 15.8, 8.0$ Hz, 1H), 4.07 - 4.19 (m, 2H), 3.33 - 3.41 (m, 1H), 3.09 - 3.13 (m, 3H), 2.72 - 2.96 (m, 1H), 2.56 - 2.67 (m, 0.5H), 2.24 - 2.36 (m, 0.5H), 1.48 - 2.13 (m, 4H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.20 (d, $J = 6.9$ Hz, 3H), 0.98 - 1.08 (m, 3H)
300	Method 1	1.743	617	¹ H NMR (400 MHz, DMSO- d_6) δ ppm 8.23 - 8.38 (m, 1H), 7.88 - 8.07 (m, 1H), 7.48 - 7.63 (m, 1H), 7.32 - 7.45 (m, 3H), 7.15 (ddd, $J = 8.9, 3.8, 2.8$ Hz, 1H), 6.78 - 6.86 (m, 1H), 6.65 (ddd, $J = 15.4, 6.1, 1.6$ Hz, 1H), 5.95 (dd, $J = 15.4, 1.4$ Hz, 1H), 4.62 (br t, $J = 10.2$ Hz, 2H), 4.52 (dq, $J = 13.8, 6.8$ Hz, 1H), 4.38 - 4.26 (m, 2H), 3.27 - 3.44 (m, 1H), 2.95 - 2.72 (m, 1H), 2.38 - 2.24

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				(m, 1H), 2.15 - 1.81 (m, 2H), 1.78 - 1.65 (m, 1H), 1.61 - 1.50 (m, 1H), 1.19 (d, <i>J</i> = 7.0 Hz, 3H), 0.98 - 1.08 (m, 3H)
301	Method 1	1.715	576	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.33 - 8.41 (m, 1H), 7.98 (dd, <i>J</i> = 9.0, 2.1 Hz, 1H), 7.48 - 7.63 (m, 1H), 7.31 - 7.47 (m, 3H), 7.08 - 7.19 (m, 1H), 6.78 - 6.86 (m, 1H), 6.45 (d, <i>J</i> = 11.2 Hz, 1H), 6.26 (dd, <i>J</i> = 11.1, 9.6 Hz, 1H), 5.34 (dquin, <i>J</i> = 15.6, 7.6 Hz, 1H), 3.31 - 3.41 (m, 1H), 3.09 - 3.16 (m, 3H), 2.97 - 2.73 (m, 1H), 2.66 - 2.55 (m, 0.5H), 2.35 - 2.31 (m, 0.5H), 2.12 - 1.73 (m, 2H), 1.71 - 1.53 (m, 2H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H), 1.00 - 1.07 (m, 3H)
302	Method 1	1.571	582	¹ H NMR (400 MHz, CD ₃ SOCD ₃ , 298 K) δ ppm 8.35 - 8.21 (m, 1H), 7.64 - 7.15 (m, 4H), 6.50 - 6.41 (m, 1H), 6.34 - 6.20 (m, 1H), 5.41 - 5.25 (m, 1H), 4.83 - 4.26 (m, 1H), 4.21 - 3.50 (m, 3H), 3.45 - 3.34 (m, 3H), 3.27 - 3.07 (m, 5H), 2.91 - 2.59 (m, 2H), 1.97 - 1.49 (m, 3H), 1.26 - 0.37 (m, 7H)
303	Method 4	2.767	540	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.18 - 8.28 (m, 1H), 7.31 - 7.40 (m, 2H), 7.21 (m, 2H), 6.40 - 6.46 (m, 1H), 6.21 - 6.31 (m, 1H), 5.24 - 5.39 (m, 1H), 3.89 - 4.08 (m, 1H), 3.67 - 3.81 (m, 1H), 3.38 - 3.59 (m, 2H), 3.11 - 3.24 (m, 3H), 3.09 (s, 3H), 2.85 - 2.98 (m, 1H), 2.53 - 2.77 (m, 2H), 1.77 - 2.01 (m, 3H), 1.48 - 1.76 (m, 4H), 1.15 - 1.25 (m, 3H), 0.29 - 0.46 (m, 4H)
304	Method 6	2.717	526	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.37 - 8.21 (m, 1H), 7.42 - 7.27 (m, 2H), 7.26 - 7.17 (m, 2H), 6.44 (br d, <i>J</i> = 11.1 Hz, 1H), 6.25 (dt, <i>J</i> = 5.4, 10.3 Hz, 1H), 5.37 - 5.25 (m, 1H), 4.10 - 3.96 (m, 2H), 3.86 - 3.55 (m, 2H), 3.29 - 3.01 (m, 7H), 2.83 - 2.60 (m, 2H), 2.29 - 2.01 (m, 1H), 1.95 - 1.46 (m, 4H), 1.19 (br d, <i>J</i> = 6.8 Hz, 3H), 0.48 - 0.28 (m, 4H)
305	Method 1	1.299	590	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.17 - 8.33 (m, 1H), 7.12 - 7.45 (m, 9H), 6.36 - 6.54 (m, 1H), 6.15 - 6.33 (m, 1H), 5.19 - 5.41 (m, 1H), 4.00 - 4.18 (m, 1H), 3.43 - 3.88 (m, 5H), 2.83 - 3.17 (m, 7H), 2.56 - 2.76 (m, 2H), 1.42 - 2.03 (m, 6H), 1.09 - 1.26 (m, 3H)
306	Method 14	2.408	596.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.39 - 8.21 (m, 1H), 7.42 - 7.31 (m, 2H), 7.29 - 7.11 (m, 2H), 6.53 - 6.40 (m, 1H), 6.36 - 6.24 (m, 1H), 5.45 - 5.24 (m, 1H), 3.77 - 3.35 (m, 4H), 3.30 - 3.07 (m, 7H), 3.01 - 2.88 (m, 2H), 2.60 (br d, <i>J</i> = 12.5 Hz, 1H), 2.39 - 2.27 (m, 1H), 2.22 - 1.95 (m, 1H), 1.94 - 1.45 (m, 7H), 1.29 - 1.12 (m, 3H)
307	Method 1	1.370	582	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 - 8.43 (m, 1H), 7.16 - 7.44 (m, 4H), 6.24 - 6.56 (m, 2H), 5.25 - 5.40 (m, 1H), 4.13 (br d, <i>J</i> = 12.0

Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				Hz, 2H), 3.54 - 3.67 (m, 1H), 3.35 - 3.44 (m, 1H), 3.10 - 3.29 (m, 6H), 2.86 - 3.03 (m, 2H), 2.56 - 2.65 (m, 2H), 1.29 - 2.02 (m, 7H), 1.23 (br d, <i>J</i> = 6.7 Hz, 3H)
308	Method 7	2.074	596.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.34 - 8.22 (m, 1H), 7.45 - 7.38 (m, 1H), 7.37 - 7.33 (m, 1H), 7.28 - 7.21 (m, 1H), 7.19 - 7.13 (m, 1H), 6.49 - 6.42 (m, 1H), 6.34 - 6.25 (m, 1H), 5.45 - 5.25 (m, 1H), 3.73 - 3.53 (m, 2H), 3.52 - 3.46 (m, 1H), 3.37 (br s, 2H), 3.36 - 3.33 (m, 1H), 3.27 (br s, 2H), 3.23 (br d, <i>J</i> = 4.9 Hz, 1H), 3.17 - 3.09 (m, 4H), 3.06 - 2.92 (m, 2H), 2.15 - 1.92 (m, 1H), 1.92 - 1.78 (m, 3H), 1.71 (br d, <i>J</i> = 13.1 Hz, 2H), 1.67 - 1.59 (m, 1H), 1.58 - 1.47 (m, 1H), 1.26 - 1.18 (m, 3H)
309	Method 1	1.648	597.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.32 (dd, <i>J</i> = 7.7, 2.1 Hz, 1H), 7.52 (dd, <i>J</i> = 7.2, 2.0 Hz, 1H), 7.43 - 7.34 (m, 1H), 7.30 - 7.18 (m, 2H), 6.47 (d, <i>J</i> = 11.2 Hz, 1H), 6.36 - 6.24 (m, 1H), 5.44 - 5.30 (m, 1H), 4.60 (dd, <i>J</i> = 8.7, 3.2 Hz, 1H), 3.68 - 3.50 (m, 2H), 3.39 - 3.34 (m, 1H), 3.33 - 3.30 (m, 1H), 3.30 - 3.19 (m, 3H), 3.13 (s, 3H), 2.96 - 2.80 (m, 3H), 2.74 - 2.65 (m, 1H), 2.46 (br d, <i>J</i> = 10.9 Hz, 1H), 2.13 - 1.83 (m, 4H), 1.75 (br s, 2H), 1.22 (d, <i>J</i> = 6.8 Hz, 3H)
310	Method 3	2.929	611	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.20 - 8.35 (m, 2H), 8.03 (br d, <i>J</i> = 8.3 Hz, 1H), 7.73 (s, 1H), 7.56 - 7.63 (m, 1H), 7.39 - 7.52 (m, 3H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.23 - 6.33 (m, 1H), 5.26 - 5.39 (m, 1H), 3.11 (s, 3H), 2.83 - 3.09 (m, 4H), 1.82 - 2.12 (m, 4H), 1.60 - 1.79 (m, 2H), 1.20 (d, <i>J</i> = 6.7 Hz, 3H)
311	Method 3	2.929	611	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.19 - 8.35 (m, 2H), 8.03 (dd, <i>J</i> = 8.5, 1.3 Hz, 1H), 7.73 (s, 1H), 7.55 - 7.62 (m, 1H), 7.38 - 7.52 (m, 3H), 6.44 (d, <i>J</i> = 11.1 Hz, 1H), 6.22 - 6.33 (m, 1H), 5.33 (sxt, <i>J</i> = 7.3 Hz, 1H), 3.11 (s, 3H), 2.81 - 3.09 (m, 4H), 1.80 - 2.08 (m, 4H), 1.65 - 1.79 (m, 2H), 1.20 (d, <i>J</i> = 6.8 Hz, 3H)
312	Method 3	2.698	573	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.27 (br d, <i>J</i> = 7.8 Hz, 1H), 7.95 (dd, <i>J</i> = 9.0, 3.1 Hz, 1H), 7.51 - 7.60 (m, 1H), 7.31 - 7.46 (m, 3H), 7.15 (dd, <i>J</i> = 8.9, 2.6 Hz, 1H), 6.81 (t, <i>J</i> = 2.5 Hz, 1H), 6.44 (d, <i>J</i> = 11.3 Hz, 1H), 6.23 - 6.31 (m, 1H), 5.21 - 5.39 (m, 1H), 3.84 (s, 3H), 3.10 (s, 3H), 2.71 - 3.03 (m, 4H), 1.63 - 2.10 (m, 6H), 1.19 (d, <i>J</i> = 6.8 Hz, 3H)
313	Method 3	2.702	573	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 8.28 (br d, <i>J</i> = 8.2 Hz, 1H), 7.95 (dd, <i>J</i> = 8.9, 3.4 Hz, 1H), 7.54 (ddd, <i>J</i> = 7.5, 4.3, 1.6 Hz, 1H), 7.31 - 7.49 (m, 3H), 7.16 (dd, <i>J</i> = 8.9, 2.5 Hz, 1H), 6.82 (t, <i>J</i> = 2.5 Hz, 1H), 6.44 (d, <i>J</i> = 11.3 Hz, 1H), 6.21 - 6.33 (m, 1H), 5.33 (br d, <i>J</i> = 7.6 Hz, 1H), 3.85 (s,

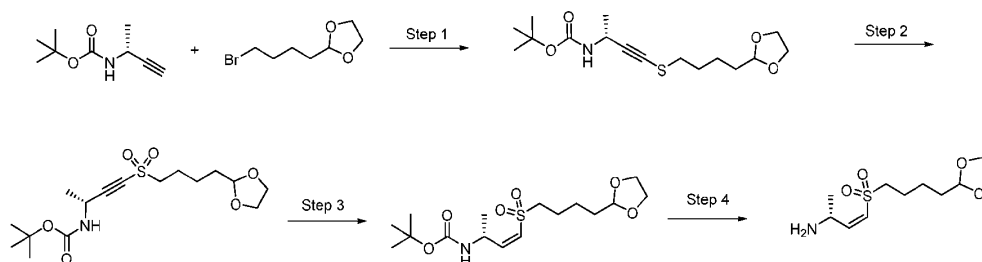
Cmpd. No.	LCMS Method	LCMS retention time (min)	LCMS M+H	¹ H NMR
				3H), 3.11 (s, 3H), 2.94 - 3.05 (m, 1H), 2.70 - 2.92 (m, 3H), 1.86 - 2.11 (m, 3H), 1.61 - 1.84 (m, 3H), 1.20 (d, <i>J</i> = 6.9 Hz, 3H)
314	Method 14	2.123	554.2	¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.39 – 7.27 (m, 2H), 7.22 – 7.13 (m, 2H), 6.63 – 6.43 (m, 1H), 6.34 – 6.24 (m, 1H), 6.15 – 6.02 (m, 1H), 5.43 – 5.27 (m, 1H), 4.35 – 4.18 (m, 1H), 3.79 – 3.27 (m, 8H), 3.27 – 3.04 (m, 6H), 2.48 – 2.12 (m, 1H), 2.06 – 1.85 (m, 1H), 1.38 (dd, <i>J</i> = 12.5, 6.9 Hz, 3H)

Example 3. *In vitro* ELISA Target Engagement Assay for PIK3CA

[00738] Engagement of compounds on PIK3CA were assessed in Jurkat cellular lysate via a sandwich ELISA.

Synthesis of PIK3CA Biotin Probe

Scheme 90. Synthesis of (*R,Z*)-4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-en-2-amine



[00739] **Step 1.** To a solution of *tert*-butyl (*R*)-but-3-yn-2-ylcarbamate (0.90 g, 5.32 mmol, 1.0 eq) in THF (50 mL, 0.09 M) under nitrogen at -70°C was slowly added 2.5M *n*-butyllithium (4.7 mL, 11.7 mmol, 2.2 eq). The mixture was stirred for 1 h before sulfur (171 mg, 0.660 mmol, 0.12 eq) was added, causing the solution to become red. The reaction mixture was stirred 30 min at -70°C then 30 min at 0°C until consumption of sulfur was complete (dark red solution). 2-(4-Bromobutyl)-1,3-dioxolane (1.1 g, 5.32 mmol, 1.0 eq) in THF (10 mL) was added and the reaction mixture was stirred at 0°C for 2 h. Sat. aq. ammonium chloride was added and the aq. phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give *tert*-butyl (*R*)-4-((4-(1,3-dioxolan-2-yl)butyl)thio)but-3-yn-2-ylcarbamate (1.0 g, 57% yield).

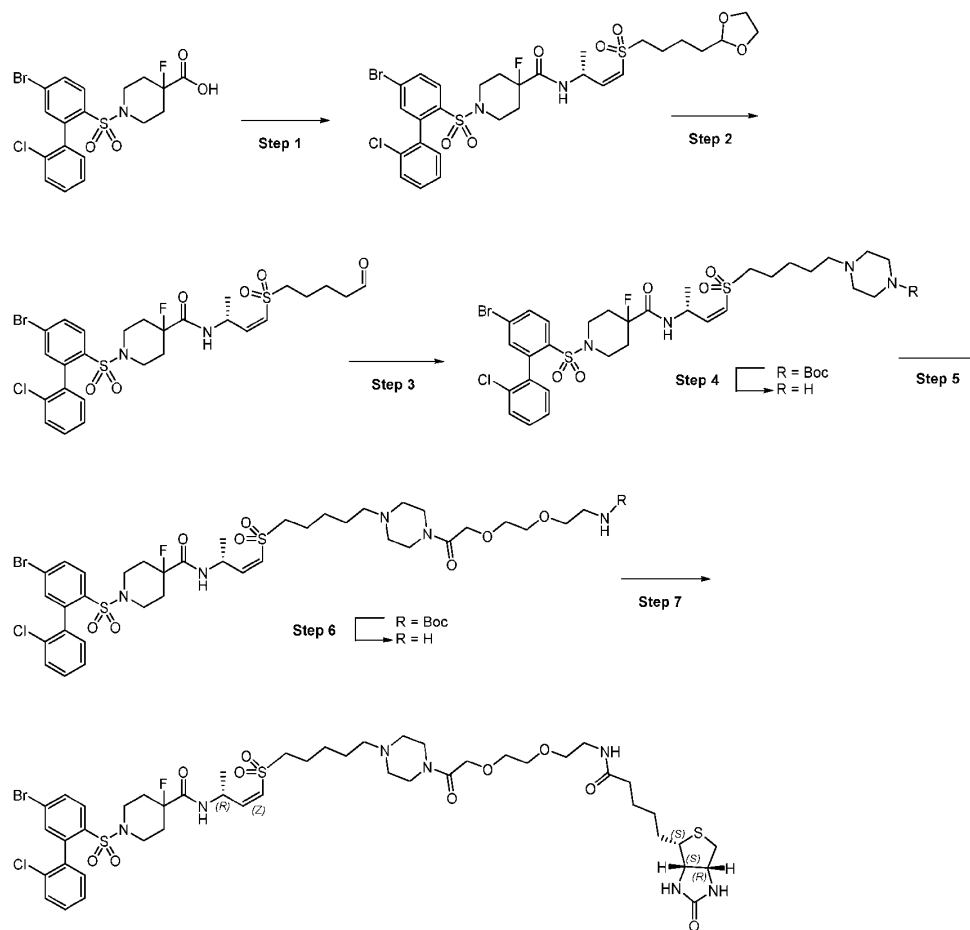
[00740] **Step 2.** To a solution of *tert*-butyl (*R*)-4-((4-(1,3-dioxolan-2-yl)butyl)thio)but-3-yn-2-ylcarbamate (200 mg, 0.610 mmol, 1.0 eq) in ethyl acetate (2.0 mL, 0.3 M) was added 3-chloroperbenzoic acid (262 mg, 1.52 mmol, 2.5 eq) at 0°C. The mixture was allowed to warm to rt and

stirred 16 hours. The mixture was poured into sat. aq. Na₂SO₃ and extracted with ethyl acetate. The combined organic layers were washed with sat. aq. sodium bicarbonate, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product *tert*-butyl (*R*)-4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-yn-2-yl)carbamate (250 mg, quant. yield) was used the next step directly without further purification.

[00741] **Step 3.** To a solution of *tert*-butyl (*R*)-4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-yn-2-yl)carbamate (250 mg, 0.690 mmol, 1.0 eq) in THF (3.0 mL, 0.23 M) was added Pd/C (250 mg) and the reaction was stirred at rt for 30 min under H₂ (50 psi). The solution was filtered to get the crude product which was purified by FCC (0-25% EtOAc in PE) to provide *tert*-butyl (*R,Z*)-4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-en-2-yl)carbamate (130 mg, 52% yield) as a white solid.

[00742] **Step 4.** To a solution of *tert*-butyl (*R,Z*)-4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-en-2-yl)carbamate (130 mg, 0.358 mmol, 1.0 eq) in acetonitrile (2.0 mL, 0.18 M) was added *p*-toluenesulfonic acid monohydrate (82 mg, 0.430 mmol, 1.2 eq) and the reaction was stirred at 50°C for 2 h. The crude solution was evaporated to get the 4-methylbenzenesulfonic acid salt of (*R,Z*)-4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-en-2-amine (160 mg, quant. yield).

Scheme 91. Synthesis of 1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((*R,Z*)-4-((5-(4-(2-(2-(5-((3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)ethoxy)ethoxy)acetyl)piperazin-1-yl)pentyl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (PIK3CA Biotin Probe)



[00743] Step 1. To a solution of (*R,Z*)-4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-en-2-amine, 4-methylbenzenesulfonic acid (153 mg, 0.352 mmol, 1.2 eq) in DCM (5.0 mL, 0.06 M) was added HATU (167 mg, 0.440 mmol, 1.5 eq) and DIPEA (0.13 mL, 0.734 mmol, 2.5 eq). After 5 mins, 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoropiperidine-4-carboxylic acid (140 mg, 0.294 mmol, 1.0 eq) was added and the reaction was stirred at rt for 2 h. The reaction was quenched with sat. aq. ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC (SiO₂, PE:EtOAc = 1:1) to give (*R,Z*)-*N*-(4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide (210 mg, quant. yield).

[00744] Step 2. To a solution of (*R,Z*)-*N*-(4-((4-(1,3-dioxolan-2-yl)butyl)sulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide (210 mg, 0.290 mmol, 1.0 eq) in trifluoroacetic acid (3.0 mL, 0.02 M) was added concentrated HCl (0.6 mL) under nitrogen. The reaction was stirred at rt for 2 h before being filtered and the filtrate concentrated to provide (*R,Z*)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-(4-((5-oxopentyl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (200 mg, 96% yield).

[00745] **Step 3.** To a solution of (*R,Z*)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-(4-((5-oxopentyl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (200 mg, 0.300 mmol, 1.0 eq) in THF/DCE (1:1, 4.0 mL, 0.07 M) was added *tert*-butyl piperazine-1-carboxylate (66 mg, 0.354 mmol, 1.2 eq). DIPEA was added until pH ~5 and the mixture was stirred for 5 min at rt. NaBH(OAc)₃ (248 mg, 4.0 eq) was added and the mixture was stirred at rt for 1 hour. The reaction was quenched with the water and extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting residue was purified by prep-HPLC to give *tert*-butyl (*R,Z*)-4-(5-((3-(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamido)but-1-en-1-yl)sulfonyl)pentyl)piperazine-1-carboxylate (160 mg, 64% yield).

[00746] **Step 4.** To a solution of *tert*-butyl (*R,Z*)-4-(5-((3-(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamido)but-1-en-1-yl)sulfonyl)pentyl)piperazine-1-carboxylate (160 mg, 0.190 mmol, 1.0 eq) in acetonitrile (2.0 mL, 0.09 M) was added 4-methylbenzenesulfonic acid (39 mg, 0.230 mmol, 1.2 eq). The reaction was stirred at 50°C for 30 min before the solution was evaporated to provide (*R,Z*)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-(4-((5-(piperazin-1-yl)pentyl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (150 mg, quant. yield), which was used in the next step without further purification.

[00747] **Step 5.** To a solution of (*R,Z*)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-(4-((5-(piperazin-1-yl)pentyl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (142 mg, 0.190 mmol, 1 eq) in DCM (5.0 mL, 0.04 M) was added HATU (108 mg, 0.280 mmol, 1.5 eq) and DIPEA (83 µL, 0.470 mmol, 2.5 eq). After 5 min, 2-[2-(2-(*tert*-butoxycarbonylamino)ethoxy)ethoxy]acetic acid (50 mg, 0.190 mmol, 1 eq) was added and the reaction mixture was stirred at rt for 2 h. The reaction was quenched with sat. aq. NH₄Cl extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC to give *tert*-butyl (*R,Z*)-(2-(2-(2-(4-(5-((3-(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamido)but-1-en-1-yl)sulfonyl)pentyl)piperazin-1-yl)-2-oxoethoxy)ethoxy)ethyl)carbamate (110 mg, 58% yield).

[00748] **Step 6.** To a solution of *tert*-butyl (*R,Z*)-(2-(2-(2-(4-(5-((3-(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamido)but-1-en-1-yl)sulfonyl)pentyl)piperazin-1-yl)-2-oxoethoxy)ethoxy)ethyl)carbamate (110 mg, 0.110 mmol, 1.0 eq) in MeCN (20 mL, 0.006 M) was added 4-methylbenzenesulfonic acid (23 mg, 0.130 mmol, 1.2 eq). The reaction was stirred at 50 °C for 2 h before the solvent was evaporated to provide (*R,Z*)-*N*-(4-(5-(4-(2-(2-(2-aminoethoxy)ethoxy)acetyl)piperazin-1-yl)pentyl)sulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide (90 mg, 91% yield), which was used in the next step without further purification.

[00749] **Step 7.** To a solution of (*R,Z*)-*N*-(4-(5-(4-(2-(2-(2-aminoethoxy)ethoxy)acetyl)piperazin-1-yl)pentyl)sulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide (88 mg, 0.098 mmol, 1.2 eq) in DCM (5.0 mL, 0.02 M) was added HATU (47 mg, 0.120 mmol, 1.5 eq) and DIPEA (36 µL, 0.200 mmol, 2.5 eq). After 5 min, D-Biotin (20

mg, 0.082 mmol, 1.0 eq) was added and the reaction was stirred at RT for 2 h. The reaction was quenched with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The resulting residue was purified by prep-TLC to give 1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-*N*-((*R,Z*)-4-((5-(4-(2-(2-(5-((3*aS*,4*S*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)ethoxy)ethoxy)acetyl)piperazin-1-yl)pentyl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide (**PIK3CA Biotin Probe**) (10.9 mg, 12% yield). MS (ESI): mass calculated for C₄₇H₆₆BrClFN₇O₁₀S₃, 1119; m/z found, 1120 [M+H]⁺.

Biochemical Assay

[00750] A solution of **PIK3CA Biotin Probe** was generated at 10 mM and used in the biological testing.

Table 4. Materials and Methods.

Reagents	Reagent Working Solutions	Supplier and Catalog Number	Stock Conc.
Plating Buffer	1) 10 mL 0.2M solution of anhydrous sodium carbonate (2.2g/100mL) 2) 115 mL 0.2M solution of sodium bicarbonate 3) 375 mL DI water		
PIK3CA Capture Antibody	Diluted in Plating Buffer 1:83	Cell Signaling #4249S	
500 mL-Pierce 20X PBS Tween 20 Buffer (PBST)		Thermo Fisher #29352	
Intercept (PBS) Blocking Buffer		Fisher Scientific #NC1660556	
Dilution Buffer	1:1 mixture of 1X PBST and Intercept Blocking Buffer		
Pierce NeutrAvidin High Sensitivity Protein HRP Conjugates (Neutravidin HRP)	Diluted in Dilution Buffer	Thermo Scientific #PI31030	1:500
SuperSignal West Pico PLUS Chemiluminescent Substrate (HRP Substrate)		Thermo Fisher #34580	1:1 A/B

[00751] **Treatment Protocol:** Jurkat cellular lysate was generated from frozen cell pellets. Cells were thawed on ice and resuspended in cold Dulbecco's phosphate buffered saline (DPBS) (12 mL/300e⁶ cells) then lysed by probe sonication (12 × 3 second pulses). Jurkat lysate was plated (50 µl/well) in Armadillo 96 well PCR plates (Thermo Fisher catalog number AB2396). The lysate was treated with serial dilutions of test compounds up to 200 µM and incubated for 1 hour at rt. Following compound incubation, PIK3CA Biotin Probe was added to a final concentration of 500 nM, and lysate was mixed by pipetting gently and incubated for an additional 1 hour at rt. The mixture was then diluted in 75 µL

Dilution buffer. The mixture was centrifuged for 5 minutes at 4122 g and stored at -80°C until ELISA TE detection.

[00752] **ELISA TE Detection:** Quantification of PIK3CA TE was initiated by coating of the ELISA plate (Thermo Scientific White 384-Well Immuno plates; Thermo Fisher catalog number 460372). The capture antibody was diluted in plating buffer (1:83) and added to the ELISA plate, 20 µl/well, overnight at 4°C. The plate was then washed twice with PBST, 100 µl/well, and blocked with addition of blocking buffer (100 µl/well, 1 hour at rt). During block, treated and probe labeled lysate was thawed. After Block, the block buffer was removed and the thawed lysate was added to the ELISA plate, 30 µl/well, for 1.5 hours at rt. Following lysate incubation, the assay plate was washed 3 times with PBST, 100 µl/well. The Neutravidin-HRP was then diluted (1:500 in dilution buffer) and added for 1 hour at rt, 20 µl/well. Following incubation, the assay plate was washed 4 times with PBST, 100 µl/well, HRP substrate was added to plate, 20 µl/well and luminescence signal was read (Clariostar Plate Reader). For each compound the potency of target engagement (TE₅₀) was determined using Graphpad Prism.

Example 4. Proteomic TE₅₀

[00753] *In vitro* TE₅₀ values for PIK3CA_C242 were obtained by treating 500 µg of cell lysate generated from Jurkat cells with DMSO or compound for 1 hour at rt followed by the addition of 200 µM desthiobiotin polyethyleneoxide iodoacetamide (IA-DTB) in DMSO for one hour at rt. Compounds were serially diluted 1:5 for a total of 7 points in order to generate dose response curves. Samples were then precipitated by the addition of 8x ice cold acetone and incubated at -80°C for two hours. Protein was then pelleted by centrifugation (4,200 RPM, 45 min, 4°C). The pelleted material was resuspended in 9M urea, 50 mM ammonium bicarbonate and proteins were reduced and alkylated by the addition of DTT and iodoacetamide (10 and 30 mM, respectively). Following reduction and alkylation, samples were exchanged into 2M urea (Zeba spin desalting plates, Thermo Fisher) and digested with Trypsin. IA-DTB labeled peptides were isolated with streptavidin agarose resin. Enriched peptides were eluted by the addition of 50% acetonitrile (ACN) 0.1% formic acid (FA) and dried in a SpeedVac vacuum concentrator.

[00754] Dried peptides were resuspended in 0.2 M EPPS pH 8.5 and each sample was labelled with 6.5 µL of 16-plex tandem mass tag (TMT, Thermo Fisher; 8.3 µg/µL in anhydrous ACN) for 1-2 hours at rt. Reactions were quenched by the addition of 6.5 µL of 5% hydroxylamine. Samples were then combined and desalted on a Evolute express ABN plate (Biotage, 600-0010-PX01).

[00755] Targeted TMT measurements were collected using an Orbitrap Lumos Tribrid Mass Spectrometer (Thermo Scientific) coupled to an UltiMate 3000 Series Rapid Separation LC system and autosampler (Thermo Scientific Dionex). Peptides were eluted onto a custom C18 capillary analytical column (75-µm inner diameter fused silica, packed with Acclaim PepMap C18 resin; Thermo Scientific) using an Acclaim PepMap 100 (Thermo 164535) loading column, and separated at a flow rate of 1.0 µl/min. Data were acquired using a specific MS3-based TMT method targeting the peptide containing PIK3CA_C242 (LC[+324.2]VLEYQGK, +2 charge state) where MS2 peptide fragmentation is triggered

upon detection of the peptide precursor ion. Subsequent MS3 analysis was then performed using pre-selected peptide fragment ions that were isolated for fragmentation using synchronous precursor selection. RAW files were converted to MZXML format and searched with the SEQUEST algorithm using the MassPike software package. TMT quantitation was performed with a filter requiring at least ten summed signal-to-noise (S/N) for control channels. TE₅₀ values were calculated from 7-point dose response curves created using the reporter ion S/N for each channel.

[00756] Representative proteomic data and Elisa target engagement is presented in Table 5.

Table 5. Representative Proteomic Biochemical Data.

Compound No.	Elisa Target Engagement Assay (μM)	Proteomic TE ₅₀ (μM)
1	0.11	0.2455
2		0.08852
3	0.09	0.11
4	0.14	0.2063
5	0.2	0.1866
6	0.05	0.026
7	0.09	0.1069
8	0.69	1.354
9	0.57	0.5074
10	0.32	0.275
11		0.07014
12		0.066
13	0.48	0.34
14	0.47	0.33
15	0.41	0.4
16	0.2	0.21
17	0.76	
18	0.038	
19	0.7436	
20	0.68	0.4618
21	1	1.23
22	0.77	0.7848
23	0.091	
24	0.17	0.232
25	0.29	0.2379
26	0.3842	0.3709
27	0.45	0.4299
28		0.63
29	0.57	0.39
30	0.56	0.34
31	0.76	0.62
32	0.93	0.82
33	0.158	0.1327
34	0.55	0.7
35	0.1645	0.14
36		0.7504
37		0.2973
38		0.6437
39		0.7155
40		0.21

Compound No.	Elisa Target Engagement Assay (μM)	Proteomic TE ₅₀ (μM)
41		0.2904
42		0.6239
43		0.2642
44		0.313
45		0.42
46		0.46
47	0.09897	0.09829
48	0.4815	
49	0.1249	
50	0.3194	
51	0.55	
52	0.14	
53	0.96	
54	0.86	
55	0.71	
56	0.15	
57	0.58	
58	0.85	
59	0.71	
60	0.81	
61		0.06672
62	0.03453	0.028
63		0.36
64	0.075	
65	0.054	
66	0.03795	
67	0.09555	
68	0.465	0.33
69		0.52
70	0.095	0.07
71		0.16
72	0.67	
73	0.3041	
74	0.41	
75	0.14	
76	0.032	
77	0.1285	
78	0.4613	
79	0.13	
80		0.51
81	0.34	
82	0.1977	
83	0.52	0.54
84	0.51	0.45
85		0.93
86	0.06	0.1066
87	0.39	0.4
88	0.079	0.086
89		0.047
90	0.25	0.33
91	0.28	0.43
92	0.13	0.139
93	0.1497	0.0755

Compound No.	Elisa Target Engagement Assay (μM)	Proteomic TE ₅₀ (μM)
94		0.19
95		0.1
96		0.41
97		0.37
98		0.52
99		0.83
100	0.099	0.096
101		0.86
102	0.73	0.61
103		0.83
104		0.62
105		0.78
106	0.8205	0.31
107	0.2	0.32
108		0.12
109	0.36	0.28
110	0.83	0.3633
111	0.32	0.21
112	0.78	0.66
113		0.17
114	0.61	0.68
115	0.52	0.41
116	0.34	0.2615
117	0.83	0.81
118		0.43
119	0.67	0.46
120		0.25
121	1	0.88
122	0.61	0.49
123	0.82	0.063
124	0.32	0.15
125	0.61	
126	0.43	0.8165
127	1.1	0.96
128	0.28	
129	0.44	
130	0.47	
131		0.2092
132	0.5244	0.4682
133	0.22	
134	0.1767	0.15
135	0.08718	0.12
136	0.19	
137	0.38	
138	0.34	
139	0.33	
140	0.35	
141	0.07498	0.05
142	0.12	
143	0.06648	
144	0.055	
145	0.27	
146	0.61	

Compound No.	Elisa Target Engagement Assay (μM)	Proteomic TE ₅₀ (μM)
147	0.39	
148	0.6	
149	0.1612	
150	0.31	
151	0.2261	0.2
152	0.45	
153	0.1833	
154	0.19	
155	0.3	
156	0.52	
157	0.2	
158		0.8947
159	0.98	
160	0.67	
161	0.8	
162	0.77	
163	0.5	
164	0.37	
165	0.164	
166	0.3	
167	0.58	
168	0.2149	
169	0.21	
170	0.76	
171	0.09274	
172	0.58	
173	0.54	
174	0.2764	
175	0.62	
176	0.75	
177	0.79	
178	0.54	
179	0.39	
180	0.1272	
181	0.7	
182	0.91	
183	0.078	
184	0.085	
185	0.29	
186	0.4934	0.2256
187		0.06809
188		0.1889
189		0.2632
190	0.11	0.061
191		0.95
192	0.28	0.24
193	0.29	0.2843
194		0.27
195	0.19	
196	0.53	
197	0.1342	
198	0.54	
199	0.9	

Compound No.	Elisa Target Engagement Assay (μM)	Proteomic TE ₅₀ (μM)
200		0.7884
201	0.35	0.31
202	0.18	0.18
203	0.98	1.11
204	0.34	0.7297
205	0.65	
206	0.8	
207	0.1844	0.15
208	0.05367	
209	0.24	
210	0.11	
211	1	
212	0.38	
213	0.23	
214	0.22	
215	0.49	
216	0.55	
217	1.449	0.98
218	0.56	0.44
219	0.97	1.09
220	0.92	1.528
221	0.21	
222	0.21	
223	0.51	
224	0.52	
225	0.64	
226	0.17	
227	0.34	
228		0.69
229	1.1	0.97
230		0.14
231	0.13	0.1137
232	0.52	
233	0.29	
234	0.14	
235	0.37	
236	0.39	
237	0.055	
238	0.025	
239	0.28	
240	0.12	
241	0.062	
242	0.072	
243	0.67	
244	0.78	
245	0.62	
246	0.042	
247	0.41	
248	0.17	
249	0.62	
250	0.35	
251	0.26	
252	0.28	

Compound No.	Elisa Target Engagement Assay (μM)	Proteomic TE ₅₀ (μM)
253	0.16	
254	0.88	
255	0.43	
256	0.78	
257	0.42	
258	0.8832	
259	0.66	
260	0.15	0.21
261	0.48	0.73
262	0.78	0.43
263	1	0.93
264	0.48	0.51
265	0.33	0.39
266	0.75	0.6
267		0.7029
268		0.3561
269	0.09001	0.063
270		0.55
271	0.17	0.2089
272	0.88	
273	0.83	
274	1.1	0.57
275	1.3	0.91
276		0.57
277	0.097	0.082
278		0.24
279	1	1.53
280	0.15	
281	0.16	
282	0.14	
283	0.2	
284	0.061	
285	0.05411	
286	0.64	
287	0.83	
288	0.49	
289	0.46	
290	1	
291	0.32	
292	0.16	
293	0.82	
294	0.12	
295	0.35	
296	0.4	
297	0.91	
298	0.72	
299	0.21	
300	0.31	
301	0.077	
302	0.44	
303	0.5572	
304	0.74	
305	0.65	

Compound No.	Elisa Target Engagement Assay (μM)	Proteomic TE ₅₀ (μM)
306	0.31	
307	0.8449	
308	0.85	
309	0.39	
310	0.085	
311	0.82	
312	0.08	
313	0.53	
314	1.1	

Example 5. *In vitro* Phospho-AKT(S473) Analysis

[00757] Functional activity of the compounds to inhibit pAKT were assessed in FaDu or H358 cell lines as indicated below.

[00758] Materials

- Complete Media
- FBS, Corning catalog #35-010-CV
- Anti-Anti, Gibco catalog # 15240-062
- 96 well plate, Corning catalog# 3610
- TrypLE, Gibco catalog # 12604013
- Phospho-AKT(S473) HTRF kit, Cisbio catalog # 64AKSPET

[00759] Cells were detached from the tissue culture flask with TrypLE. The cells were pelleted at 500 xg for 5 min, TrypLE was removed and then resuspended in the necessary volume of media + 1% FBS to give the appropriate cell density (17,500 cells/mL for FaDu; 20,000 cells/mL for H358). 100 μL of cell suspension/well was dispensed into the 96-well plate while keeping the outer wells of the plate free of cells and filled with PBS to prevent evaporation of interior wells. The plate was incubated at 37°C and allowed to adhere overnight. The cells were treated with a dose response of compound and incubated at 37°C for 30 minutes. The cells were then processed and pAKT(S473) levels were assessed following the specifications of the Cisbio HTRF kit.

[00760] 1-[4-Bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide (**Compound 47**) was used as an internal standard for the assay to normalize I_{max} and the absolute inhibition of pAKT for 1-[4-bromo-2-(2-chlorophenyl)phenyl]sulfonyl-4-fluoro-*N*-[(*Z*,1*R*)-1-methyl-3-methylsulfonyl-allyl]piperidine-4-carboxamide varied from 40-89% for the H358 cell line and 43-98% for the FaDu cell line.

[00761] Representative biochemical data for inhibition of pAKT is presented in **Table 6**.

Table 6. Representative pAKT Inhibition Data.

Compound Number	H358 pAKT IC ₅₀ (μM)	H358 pAKT I _{max} %control	FaDu pAKT IC ₅₀ (μM)	FaDu pAKT I _{max} %control
33			0.4091	86.2
35			0.3301	103.1
47			0.09648	100

Compound Number	H358 pAKT IC ₅₀ (μM)	H358 pAKT I _{max} %control	FaDu pAKT IC ₅₀ (μM)	FaDu pAKT I _{max} %control
58			0.7433	97.55
62			0.02754	85.2
134			0.3479	96.27
138			0.2921	93.55
140			0.4271	87.65
141			0.08243	102.5
143			0.1172	111.2
145			0.1307	102.3
149			0.2478	108.8
151			0.2843	100.5
153			0.2045	103.6
155			0.3046	105.5
156			0.3475	99.2
164			0.8341	103.1
165	0.115	95.68	0.2137	96.65
166			0.1872	78.9
167			0.5181	93.6
168			0.1359	90.6
169	0.2023	106	0.1545	107.5
170			0.4838	83.2
171	0.0826	100.6	0.07892	97.8
172			0.5052	97.9
173	0.4642	85.55		
174			0.168	91.75
175	0.1508	75.6		
176			0.6789	83.3
177			0.672	69.45
179	0.1651	106.2		
180			0.1357	96.9
183	0.0566	93.2		
184	0.0646	102		
185	0.1233	95.63		
187			0.1521	70.1
195	0.123	85.05	0.1129	96.9
196	0.3288	96.3	0.4498	86.4
197	0.1026	91.4	0.1291	89
198			0.472	95.25
205			1.122	
206			0.7178	105.6
207			0.8028	75.2
208	0.08157	95.9	0.08823	
210			0.214	
213			0.2907	90.8
216			0.6883	107.6
217	0.9533	74.6		
221	0.123	85		
222	0.1465	91		
223	0.3457	87.5		
224	0.3264	81.2		
225	0.4647	78.8		
227	0.2504	101.6		
234			0.1001	

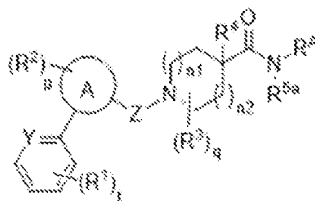
Compound Number	H358 pAKT IC ₅₀ (μM)	H358 pAKT I _{max} %control	FaDu pAKT IC ₅₀ (μM)	FaDu pAKT I _{max} %control
237			0.07363	
238			0.02921	
240			0.4374	
241			0.2812	95.3
242			0.1376	
243			0.7608	68.7
244			1.199	76.3
245			0.9215	86.15
246			0.1632	
248			0.5574	
249			1.2	82.75
250			1.645	96.8
251			0.2488	102.5
252			0.2485	85.85
253			0.2669	77.25
254			0.9109	92.5
255	0.06705	86.65		
272	0.6944	89.85		
282			0.3673	
284			0.0674	
285			0.1238	
294			2.119	
296	0.6416	69.4		
297	1.501	87.6		
298			0.3215	101.5
299			0.1465	99.6
300			0.4177	94.25
301			0.117	99.75
302	0.4639	87.15	0.6955	100.8
303			0.243	101.8
305	0.3955	90.7	0.4281	94.35
306	0.2631	88.03	0.3336	93
308	0.4077	91.05	0.5804	93.4
309	0.2759	91.75		
310			0.07707	
312			0.1405	
314	0.622	100.4		

[00762] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (I),

wherein,

Z is C(=O) or S(=O)₂;

Ring A is phenyl, 5 to 10-membered heteroaryl, C₃-C₈ cycloalkyl, C₈-C₉ spirocyclyl, or 5 to 8-membered heterocycloalkyl;

Y is N, CH, or CR¹:

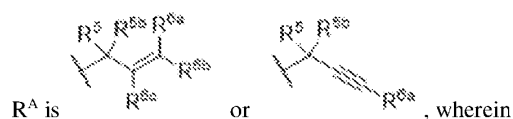
each R¹ is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deutoalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, oxo (=O), optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkylamino, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R³ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R⁴ is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;



R^5 is H, optionally substituted C_1 - C_3 alkyl, optionally substituted C_1 - C_3 haloalkyl, or optionally substituted C_1 - C_3 hydroxyalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_6 cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^{5a} is H; or R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring; or R^{5a} is absent and R^{6c} is bound directly to the nitrogen to which R^A is attached to form a 4-membered heterocyclic ring;

or R^{5a} and R^5 together with the nitrogen and carbon atoms to which they are attached form a 4-membered heterocyclic ring;

R^{5b} is H or C_1 - C_3 alkyl;

each R^a is independently H, C_1 - C_6 alkyl, C_1 - C_6 deuterioalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, C_5 - C_8 aryl, C_5 - C_8 heteroaryl, - C_1 - C_6 alkyl(aryl), - C_1 - C_6 alkyl(heteroaryl), - C_1 - C_6 alkyl(cycloalkyl), or - C_1 - C_6 alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkoxy;

each R^b is independently H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

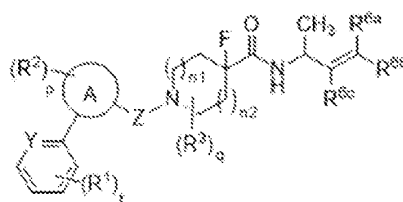
n_1 and n_2 are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is halogen.
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{5a} and R^{5b} are each H.
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_1 - C_3 alkyl.
5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein R^5 is CH_3 or CH_2CH_3 .
6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^{5a} and R^{6c} together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring.
7. The compound of claim 1, wherein the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (Ia),

wherein,

Z is $C(=O)$ or $S(=O)_2$;

Ring A is phenyl, 5 to 10-membered heteroaryl, C_3 - C_8 cycloalkyl, C_8 - C_9 spirocyclyl, or 5 to 8-membered heterocycloalkyl;

Y is CH or CR^1 ;

each R^1 is independently halogen, $-CN$, $-OH$, $-OR^a$, $-SH$, $-SR^a$, $-NO_2$, $-N(R^b)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^b$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 hydroxyalkyl or optionally substituted C_3 - C_6 cycloalkyl;

each R^2 is independently halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NO₂, -N(R^b)₂, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, oxo (=O), optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkylamino, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R^2 together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R^3 is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R^7 is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R^7 together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

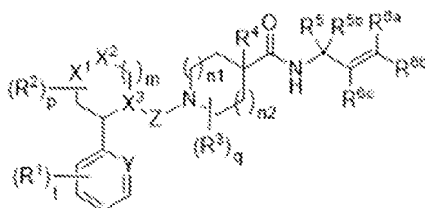
n_1 and n_2 are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein ring A is a C₅-C₇ cycloalkyl or 5 to 7-membered heterocycloalkyl.
9. The compound of claim 1, wherein the compound has the structure of Formula (II), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (II),

wherein,

X¹ and X² are each independently CH₂, CHR², CR²R², O, or NR^{2a}; wherein at least one of X¹ or X² is CH₂, CHR², or CR²R²;

X³ is CR⁸ or N, provided that when X³ is N, R⁸ is absent;

Y is N, CH, or CR¹;

Z is C(=O) or S(=O)₂;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, or optionally substituted C₁-C₆ hydroxyalkyl or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl;

R^{2a} is H, -S(=O)₂R^a, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or phenyl;

each R³ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R^4 is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;

R^5 is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

R^8 is absent, H, halogen, -OCH₃, or -CH₃;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl,

C₂C₆ alkenyl, C₂C₆ alkynyl, C₃C₆ cycloalkyl, C₃C₆ heterocycloalkyl, C₅C₈ aryl, C₅C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl,

heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

m is 0 or 1;

n₁ and n₂ are each independently 0, 1, 2, or 3;

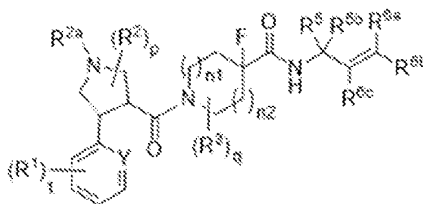
p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein X³ is CR⁸; and R⁸ is H.

11. The compound of claim 9 or 10, or a pharmaceutically acceptable salt thereof, wherein X^1 is NR^{2a} ; and X^2 is CH_2 .
12. The compound of any one of claims 9-11, or a pharmaceutically acceptable salt thereof, wherein R^4 is halogen.
13. The compound of any one of claims 9-12, or a pharmaceutically acceptable salt thereof, wherein Z is $-C(=O)-$.
14. The compound of any one of claims 9-13, or a pharmaceutically acceptable salt thereof, wherein m is 0.
15. The compound of claim 9, wherein the compound has the structure of Formula (IIb), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIb),

wherein,

Y is CH or CR^1 ;

each R^1 is independently halogen, $-CN$, $-OH$, $-OR^a$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 deuterioalkyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 haloalkyl, or C_1 - C_6 hydroxyalkyl;

each R^2 is independently optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 deuterioalkyl, optionally substituted C_1 - C_6 haloalkyl, or optionally substituted C_3 - C_6 cycloalkyl;

R^{2a} is H , $-C(=O)OR^a$, $-C(=O)NR^bR^b$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted arylalkyl, or optionally substituted C_3 - C_6 cycloalkyl;

each R^3 is independently C_1 - C_3 alkyl or C_1 - C_3 deuterioalkyl;

R^5 is H , C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, or C_1 - C_3 hydroxyalkyl;

R^{5b} is H or C_1 - C_3 alkyl;

R^{6a} and R^{6b} are each independently H , $-CN$, $-C(=O)OR^7$, $-C(=O)N(R^7)_2$, $-S(=O)R^7$, $-S(=O)_2R^7$, or $-S(=O)(=NH)R^7$; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;
 or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;
 or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂C₆ alkenyl, C₂C₆ alkynyl, C₃C₆ cycloalkyl, C₃C₆ heterocycloalkyl, C₅C₈ aryl, C₅C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;
 or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

n₁ and n₂ are each independently 0, 1, 2, or 3;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 1, 2, or 3.

16. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein

Y is CH or R¹;

R¹ is halogen;

R^{2a} is C₁-C₆ haloalkyl;

R⁵ is C₁-C₃ alkyl;

R^{5b} is H;

R^{6a} and R^{6b} are each independently H or -S(=O)(=NH)R⁷ wherein each R⁷ is independently C₁-C₆ alkyl, or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H;

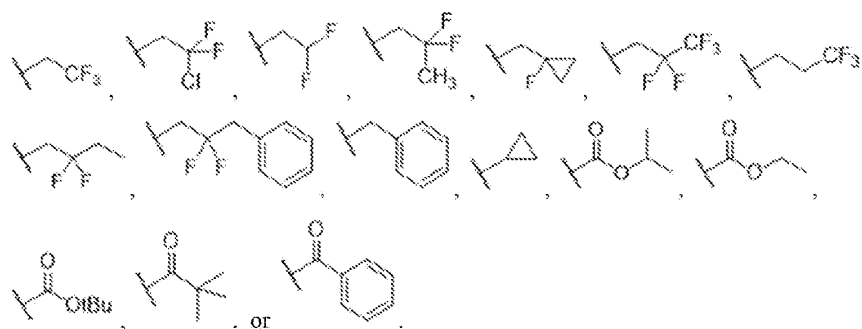
n_1 and n_2 are each independently 1 or 2;

p is 0 or 1;

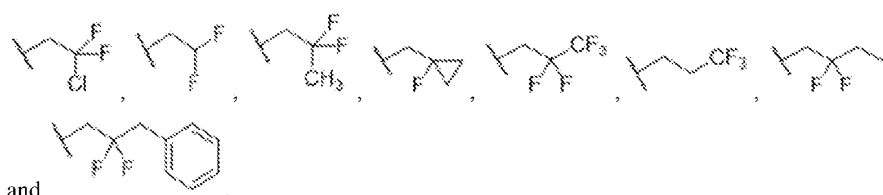
q is 0 or 1; and

t is 1 or 2.

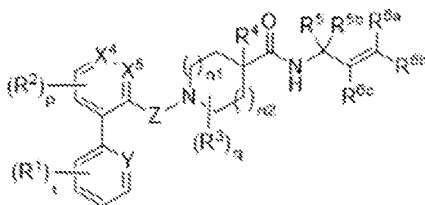
17. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is -
C(=O) R^a , -C(=O)OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ haloalkyl,
or optionally substituted C₃-C₆ cycloalkyl; wherein each R^a is independently C₁-C₆ alkyl or aryl.
18. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is



19. The compound of claim 18, wherein R^{Za} is selected from the group consisting of:



20. The compound of any one of claims 15-19, or a pharmaceutically acceptable salt thereof, wherein p is 0.
21. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl or a 5 to 10-membered heteroaryl.
22. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl or pyridinyl.
23. The compound of claim 1, wherein the compound has the structure of Formula (III), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (III),

wherein,

Y is N, CH, or CR¹;

Z is C(=O) or S(=O)₂;

X⁴ is CH, CR², or N;

X⁵ is CH, CR², or N;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl or optionally substituted 4 to 6-membered heterocycloalkyl;

or two R² together with the atom(s) to which they are attached combine to form a C₃-C₅ cycloalkyl, 4 to 5-membered heterocycloalkyl, or a 5-membered heteroaryl ring;

each R³ is independently halogen, -CN, -OH, -OR^a, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, or C₁-C₆ haloalkyl;

R⁴ is H, halogen, -OH, -OR^a, or C₁-C₆ alkyl;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)₂, -S(=O)R⁷, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷; wherein

each R⁷ is independently optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl ring;

or two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered heterocycloalkyl ring;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R^7 together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deutoalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂C₆ alkenyl, C₂C₆ alkynyl, C₃C₆ cycloalkyl, C₃C₆ heterocycloalkyl, C₅C₈ aryl, C₅C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deutoalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

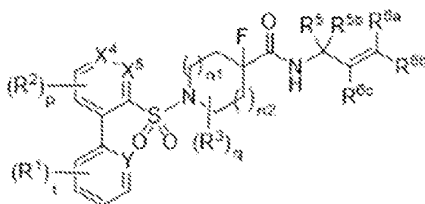
n_1 and n_2 are each independently 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein Z is -S(=O)₂-.
25. The compound of claim 23 or 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is halogen.
26. The compound of claim 23, wherein the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof:



Formula (IIIa),

wherein,

Y is CH or CR¹;

X⁴ is CH, CR² or N;

X⁵ is CH, CR² or N;

each R¹ is independently halogen, -CN, -OH, -OR^a, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl or optionally substituted C₃-C₆ cycloalkyl;

each R² is independently halogen, -CN, -OH, -OR^a, -N(R^b)₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ deuterioalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted arylalkyl or optionally substituted 4 to 6-membered heterocycloalkyl;

each R³ is independently C₁-C₃ alkyl or C₁-C₃ deuterioalkyl;

R⁵ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ hydroxyalkyl;

R^{5b} is H or C₁-C₃ alkyl;

R^{6a} and R^{6b} are each independently H, -CN, -C(=O)N(R⁷)₂, -S(=O)₂R⁷, or -S(=O)(=NH)R⁷;

wherein

each R⁷ is independently C₁-C₃ alkyl, or a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;

or two R⁷ together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;

or R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

or R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring;

each R^a is independently H, C₁-C₆ alkyl, C₁-C₆ deuterioalkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, C₅-C₈ aryl, C₅-C₈ heteroaryl, -C₁-C₆ alkyl(aryl), -C₁-C₆ alkyl(heteroaryl), -C₁-C₆ alkyl(cycloalkyl), or -C₁-C₆ alkyl(heterocycloalkyl); wherein each alkyl, deuterioalkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyl(aryl), alkyl(heteroaryl), alkyl(cycloalkyl) and alkyl(heterocycloalkyl) is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₁-C₆ alkoxy;

each R^b is independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

or two R^b groups on a nitrogen atom are taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl which is optionally substituted with one, two, or three

C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

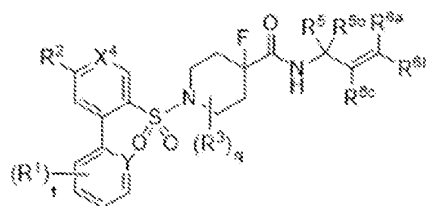
n_1 and n_2 are each independently 0, 1, or 2;

p is 0, 1, 2, or 3;

q is 0, 1, or 2; and

t is 0, 1, 2, or 3.

27. The compound of any one of claims 23-26, or a pharmaceutically acceptable salt thereof, wherein X^4 is CH or CR^2 ; and X^5 is CH or CR^2 .
28. The compound of any one of claims 23-26, or a pharmaceutically acceptable salt thereof, wherein X^4 is N; and X^5 is CH or CR^2 .
29. The compound of any one of claims 23-26, or a pharmaceutically acceptable salt thereof, wherein X^4 is CH or CR^2 ; and X^5 is N.
30. The compound of any one of claims 23-29, or a pharmaceutically acceptable salt thereof, wherein p is 1.
31. The compound of claim 26, wherein the compound has the structure of Formula (IIIb), or a pharmaceutically acceptable salt thereof:



Formula (IIIb),

wherein,

X^4 is CH or N;

Y is CR^1 or CH;

each R^1 is independently halogen, -CN, -OR^a, optionally substituted C_1 - C_4 alkyl, C_1 - C_4 deutoalkyl, C_2 - C_4 alkynyl, or C_1 - C_3 fluoroalkyl;

R^2 is halogen, -CN, -OH, -OR^a, -N(R^b)₂, -C(=O)R^a, optionally substituted C_1 - C_4 alkyl, C_1 - C_4 deutoalkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_1 - C_3 fluoroalkyl, optionally substituted C_1 - C_3 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl;

each R^3 is independently -CH₃ or -CD₃;

R^5 is H, -CH₃, or -CH₂CH₃;

R^{5b} is H or C_1 - C_3 alkyl;

R^{6a} and R^{6b} are each independently H, -CN, $-C(=O)N(R^7)_2$, $-S(=O)_2R^7$, or $-S(=O)(=NH)R^7$;

wherein

each R^7 is independently C_1 - C_3 alkyl, or a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;

or two R^7 together with the nitrogen atom to which they are attached combine to form a 4-membered heterocycloalkyl ring optionally substituted with up to two fluorine atoms;

or R^5 and R^7 together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring;

R^{6c} is H or -CN;

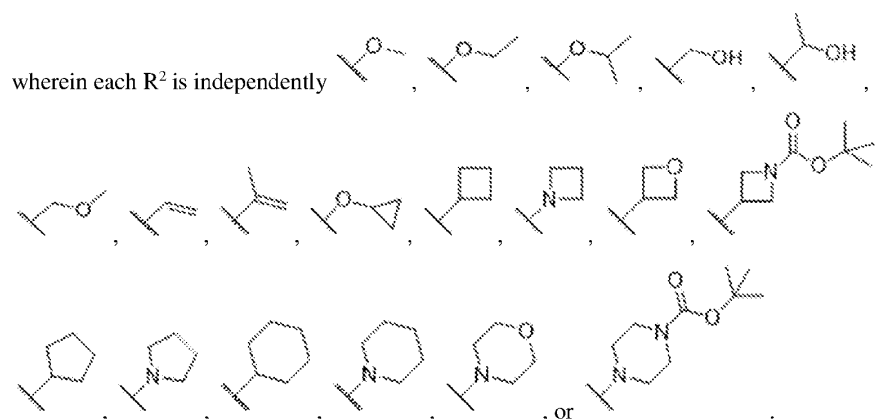
each R^a is independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or C_1 - C_3 fluoroalkyl;

each R^b is independently H or C_1 - C_3 alkyl;

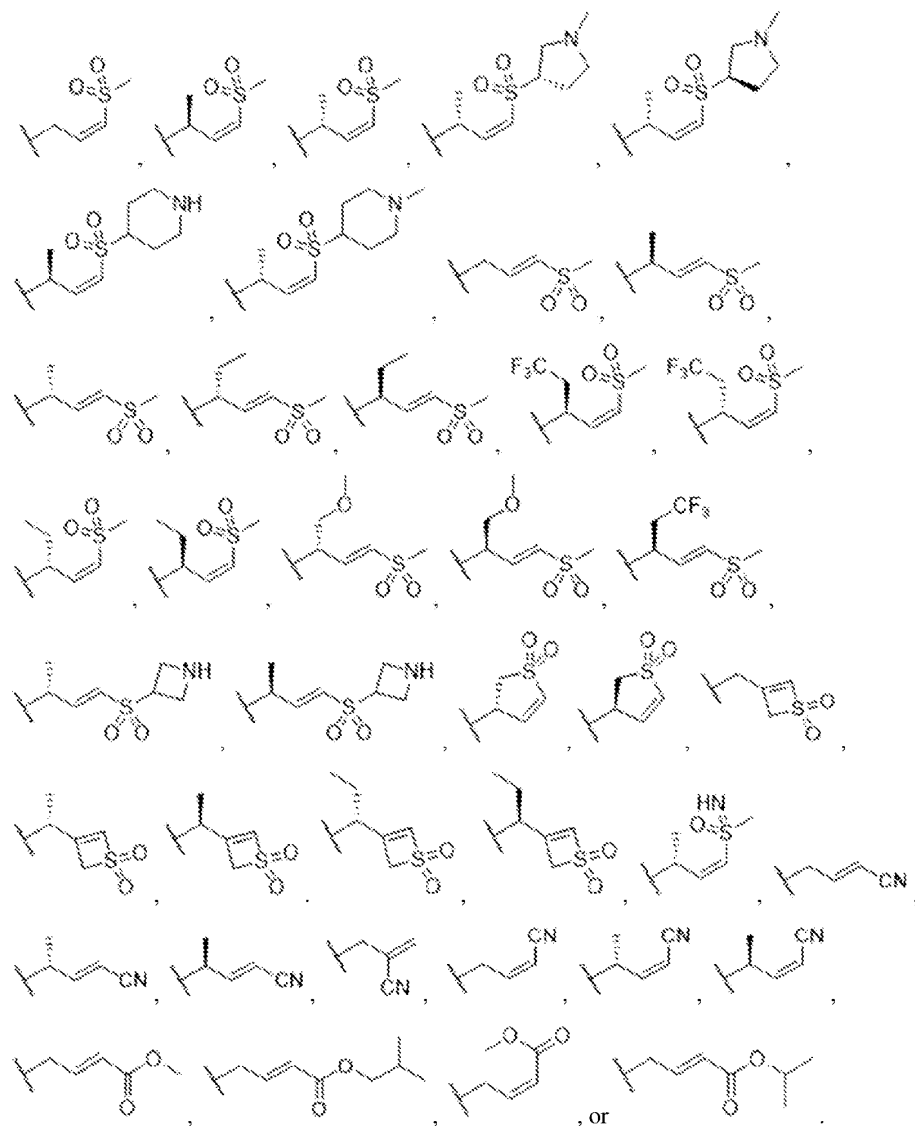
q is 0, 1, or 2; and

t is 0, 1, or 2.

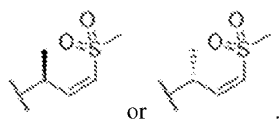
32. The compound of any one of claims 23-31, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently halogen, -CN, -OH, $-OR^a$, $-N(R^b)_2$, $-C(=O)R^a$, optionally substituted C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_1 - C_3 fluoroalkyl, optionally substituted C_1 - C_3 hydroxyalkyl, optionally substituted C_3 - C_6 cycloalkyl, or optionally substituted 4 to 6-membered heterocycloalkyl.
33. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently halogen, -CN, -OH, $-OR^a$, $-N(R^b)_2$, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 hydroxyalkyl, or 4 to 6-membered heterocycloalkyl.
34. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently Cl, Br, F, -CN, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CF_3$, $-CH_2CF_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-N(CH_3)_2$, azetidine, oxetane, pyrrolidine, piperazine, or morpholine.
35. The compound of any one of claims 23-31, or a pharmaceutically acceptable salt thereof,



36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently halogen, -CN, -OH, -OR^a, -C(=O)OR^a, -C(=O)NR^aR^b, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, or optionally substituted C₁-C₆ haloalkyl.
37. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently halogen, -OR^a, or optionally substituted C₁-C₆ alkyl.
38. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently Cl, Br, F, -OCH₃, or CH₃.
39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof, wherein t is 1 or 2.
40. The compound of claim 39, or a pharmaceutically acceptable salt thereof, wherein t is 1.
41. The compound of claim 39, or a pharmaceutically acceptable salt thereof, wherein t is 2.
42. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently C₁-C₃ alkyl.
43. The compound of claim 42, or a pharmaceutically acceptable salt thereof, wherein each R^3 is -CH₃.
44. The compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, wherein q is 1.
45. The compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, wherein q is 0.
46. The compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, wherein n₁ is 1; and n₂ is 1.
47. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^{6a} is S(=O₂)R⁷; and R^{6b} and R^{6c} are each H.
48. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, wherein R^{6b} is S(=O₂)R⁷; and R^{6a} and R^{6c} are each H.
49. The compound of claim 47 or 48, or a pharmaceutically acceptable salt thereof, wherein R⁷ is independently optionally substituted C₁-C₃ alkyl.
50. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁷ together with the atoms to which they are attached combine to form a 5-membered heterocycloalkyl ring.
51. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^{6c} and R⁷ together with the atoms to which they are attached combine to form a 4-membered heterocycloalkyl ring.
52. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^A is:



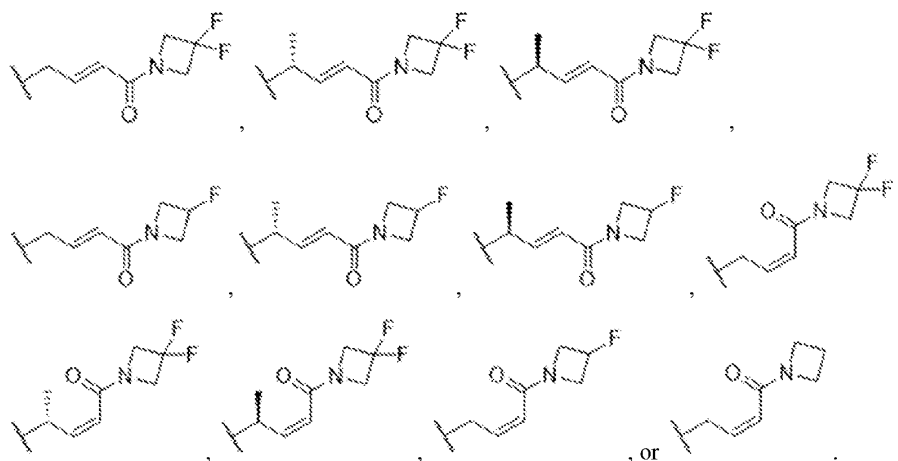
53. The compound of claim 52, or a pharmaceutically acceptable salt thereof wherein R^A is:



54. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein:
 R^{6a} is $-C(=O)N(R^7)_2$, and R^{6b} and R^{6c} are each H;

or R^{6b} is -C(=O)N(R⁷)₂, and R^{6a} and R^{6c} are each H, wherein two R⁷ together with the nitrogen atom to which they are attached combine to form an optionally substituted 4 to 5-membered ring.

55. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^A is:



56. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:
- (S,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-1-((3',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-4-fluoro-1-((5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-1-((3',5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-1-((3'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-1-((5-chloro-3'-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
- (S,Z)-4-fluoro-1-((5-fluoro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((5-chloro-3'-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-4-fluoro-1-((5-methoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((5-chloro-3'-propoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((5-chloro-3'-cyclopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((2',5-dichloro-5'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((5-chloro-3'-(ethoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-4-fluoro-1-((5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((3'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-4-fluoro-1-((5-methoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2'-chloro-3'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2'-chloro-4'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2'-chloro-5'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2',4-dichloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
1-((2'-chloro-6'-fluoro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
1-((2',6-dichloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(E)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-4-fluoro-1-((5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((3',5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((3'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-4-fluoro-1-((3'-methoxy-5-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-4-fluoro-1-((5-methoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((3',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((5-chloro-3'-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-chloro-5'-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-chloro-4'-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-ethyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-chloro-3'-fluoro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-chloro-4'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-3'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-3'-fluoro-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((3',5-dibromo-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((5-bromo-2'-chloro-3'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

1-((5-bromo-2'-chloro-6'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((5-bromo-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(E)-1-((5-bromo-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,

(E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,

1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide,
(R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide,
(S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide,
(E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide,
(E)-N-(3-cyanoallyl)-1-((2',5-dichloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide,
(Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide,
(Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide,
1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(2-cyanoallyl)-4-fluoropiperidine-4-carboxamide,
1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((2R,Z)-4-(S-methylsulfonimidoyl)but-3-en-2-yl)piperidine-4-carboxamide,
1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-((R)-S-methylsulfonimidoyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,E)-N-(4-(azetidin-3-ylsulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide,
(R,E)-N-(4-(azetidin-3-ylsulfonyl)but-3-en-2-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide,
(R,E)-N-(1-(azetidin-3-ylsulfonyl)pent-1-en-3-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide,
(S,E)-N-(1-(azetidin-3-ylsulfonyl)pent-1-en-3-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide,
(R,E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,E)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide,

(S,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide,
(S,Z)-1-((5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide,
(S,Z)-1-((5-(dimethylamino)-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,Z)-1-((2'-chloro-5-(dimethylamino)-5'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,Z)-1-((5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,Z)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,Z)-1-((2'-chloro-5-(dimethylamino)-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-(dimethylamino)-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(E)-1-((5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((5-(dimethylamino)-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
(E)-1-((2'-chloro-5-(dimethylamino)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-cyclobutyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
tert-butyl (R,Z)-3-(2'-chloro-6-((4-fluoro-4-((4-(methylsulfonyl)but-3-en-2-yl)carbonyl)piperidin-1-yl)sulfonyl)-[1,1'-biphenyl]-3-yl)azetidine-1-carboxylate,
(S,Z)-1-((5-chloro-3'-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2'-chloro-5-cyclopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-ethoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-4-fluoro-1-((5-isopropoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-isopropoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-cyclopropoxy-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-vinyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-4-fluoro-1-((2'-methyl-5-vinyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(prop-1-en-2-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-4-fluoro-1-((2'-methyl-5-(prop-1-en-2-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-ethyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-ethyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-ethyl-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-isopropyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-4-fluoro-1-((5-isopropyl-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-(azetidin-1-yl)-2'-methyl-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)-1-((5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)piperidine-4-carboxamide,
tert-butyl (R,Z)-4-(2'-chloro-6-((4-fluoro-4-((4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidin-1-yl)sulfonyl)-[1,1'-biphenyl]-3-yl)piperazine-1-carboxylate,

(R,Z)-1-((2'-chloro-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-4-fluoro-1-((2'-methyl-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-morpholino-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-4-fluoro-1-((2'-methyl-5-morpholino-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-4'-fluoro-5-(pyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-(azetidin-1-yl)-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,Z)-1-((5-chloro-3'-(2-methoxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(S,Z)-1-((5-chloro-3'-(methoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
1-((5-chloro-3'-(E)-(methoxyimino)methyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((S,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(2-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
1-((2'-chloro-5-(1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(hydroxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(prop-1-yn-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((2'-chloro-5-(oxetan-3-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methoxy-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R,E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide,
(R,E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide,
(R,E)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide,

(R,E)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide,

(R,E)-1-((5-acetyl-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide,

(R,Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methoxy-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

1-((2'-chloro-5-(1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2R,4S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2R,4S)-1-((5-bromo-3'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methoxy-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2R,4R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2S,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-(methoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2,2-dimethyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,

(2R,4S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,

(2R,4S)-1-((5-bromo-3'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,

(2R,4S)-1-((2'-chloro-5-(methoxymethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,

(R,Z)-1-((5-(2-chlorophenyl)benzo[b]thiophen-6-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

tert-butyl cis-(3RS,4RS)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate;

isopropyl (3R,4R)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate;

ethyl (3R,4R)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate;

1-((3R,4R)-4-(2-chlorophenyl)-1-pivaloylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-1-benzoyl-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2-chloro-4-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2-chloro-5-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2-chloro-3-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2*S,4*S)-1-((3*R,4*R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoroazepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoro-2-phenylethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,3,3,3-pentafluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2-chloro-6-fluorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(E)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide;

(E)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide;

(S,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(E)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide;

(S,Z)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide;

(R)-1-((3R,4R)-1-(2-chloro-2,2-difluoroethyl)-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-1-(methylsulfonyl)pent-1-en-3-yl)azepane-4-carboxamide;

isopropyl (3S,4S)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate;

(S,Z)-1-((5-chloro-3-(3-methoxyphenyl)pyridin-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((2'-chloro-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-bromo-2-(3-chloropyridin-2-yl)phenyl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((2'-chloro-5-(2-oxopyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chloro-3-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((4-(2-chloro-3-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chloro-4-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((4-(2-chloro-4-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,E)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;

(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R,E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5-(3-fluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((5-bromo-3-(2-chlorophenyl)pyridin-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((2,5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(2-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-4-fluoro-1-((3*R,4*R)-4-(2-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)-1-((3*R,4*R)-4-(o-tolyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)azepane-4-carboxamide;

(2*S,4*S)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-3,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-4,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(E)-4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-((1-methylpiperidin-4-yl)sulfonyl)allyl)piperidine-4-carboxamide;
(R,E)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-cyanobut-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;
(Z)-(1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidin-4-yl)(3-(2-(methylsulfonyl)vinyl)azetidin-1-yl)methanone;
(R,Z)-1-((6-chloro-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
(E)-1-((6-chloro-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide;
1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((1,1-dioxido-2H-thiet-3-yl)methyl)-4-fluoropiperidine-4-carboxamide;
(*R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide;
(R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide;
(R)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide;
1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(((R)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(((S)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
(*S,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide;
(*S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide;
(R)-1-(5-bromo-2'-chloro-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-(2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-(5-bromo-2'-chloro-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide;
(R)-1-(2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide;

(4R)-1-(2'-chloro-6'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide;

(R,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-2-methyl-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(difluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-((RS)-1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(difluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((1*S,2*S)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3*R,4*S)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2H-pyran-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((6*R,7*R)-6-(2-chlorophenyl)spiro[3.5]nonane-7-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

tert-butyl 5-(2-chlorophenyl)-4-(4-fluoro-4-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)-3,4-dihydropyridine-1(2H)-carboxylate;

tert-butyl (3*R,4*S)-3-(2-chlorophenyl)-4-(4-fluoro-4-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)piperidine-1-carboxylate;

(S,Z)-1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-((3-methoxybenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(pentyloxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-cyclobutoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((3'-(but-2-yn-1-yloxy)-5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-((2-chlorobenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-((3-chlorobenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-phenoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((3'-(benzyloxy)-5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(pyridin-2-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(*R,Z)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azocane-4-carboxamide;

1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidin-4-yl(3-(methylsulfonyl)methylene)azetidin-1-yl)methanone;

(R,Z)-1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((5-(2-chlorophenyl)-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chlorophenyl)-6-hydroxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(E)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(propylcarbonyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(dimethylamino)-5-oxopent-3-yn-2-yl)-4-fluoropiperidine-4-carboxamide;

- (S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(dimethylamino)-5-oxopent-3-yn-2-yl)-4-fluoropiperidine-4-carboxamide;
- (E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;
- (E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;
- (Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;
- (Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;
- (Z)-N-(4-(azetidin-1-yl)-4-oxobut-2-en-1-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide;
- (S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;
- (2R,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;
- (2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;
- (2R,4S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;
- (2R,4S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;
- (2R,4S)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;
- (2*R,4*S)-1-((3*R,4*S)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2H-pyran-3-carbonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;
- (R)-1-(2'-chloro-5-methoxy-[1,1'-biphenyl]-2-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoroazepane-4-carboxamide;
- (R)-1-(2'-chloro-5-methoxy-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
- (R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
- (R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((S,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
- (2R,4S)-1-((2'-chloro-5-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(methoxy-d3)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(methoxy-d3)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3*R,4*R)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3*S,4*S)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3*R,4*S)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((R)-2-(2-chlorophenyl)-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-3-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)pyrrolidine-3-carboxamide;

or

a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof.

57. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:
- (R,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
 - (S,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
 - (E)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
 - (E)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
 - (S,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
 - (E)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide,
 - (S,Z)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
 - (R,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
 - (Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide, or
- a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof .
58. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:
- tert*-butyl (3R,4R)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate,
 - isopropyl (3R,4R)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate,
 - ethyl (3R,4R)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate,
 - 1-((3R,4R)-4-(2-chlorophenyl)-1-pivaloylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
 - 1-((3R,4R)-1-benzoyl-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
 - 1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-4-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-5-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-3-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(2S,4S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,
(2S,4S)-1-((3R,4R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoroazepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoro-2-phenylethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,3,3,3-pentafluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-((1-fluorocyclopropyl)methyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide,
(R,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
(S,Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
(E)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-4-fluoro-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide;
(E)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide;
(S,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
(E)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(3-(methylsulfonyl)allyl)piperidine-4-carboxamide;
(S,Z)-4-fluoro-1-((6-methoxy-4-phenylpyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
(R,Z)-4-fluoro-1-((6-methoxy-4-(o-tolyl)pyridin-3-yl)sulfonyl)-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
(Z)-1-((4-(2-chlorophenyl)-6-methoxypyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide;
(R)-1-((3R,4R)-1-(2-chloro-2,2-difluoroethyl)-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-1-(methylsulfonyl)pent-1-en-3-yl)azepane-4-carboxamide;
isopropyl (3S,4S)-3-(2-chlorophenyl)-4-(4-fluoro-4-(((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)pyrrolidine-1-carboxylate;

(S,Z)-1-((5-chloro-3-(3-methoxyphenyl)pyridin-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((2'-chloro-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((5-chloro-3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-methyl-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-bromo-2-(3-chloropyridin-2-yl)phenyl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((2'-chloro-5-(2-oxopyrrolidin-1-yl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chloro-3-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((4-(2-chloro-3-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chloro-4-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((4-(2-chloro-4-fluorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,E)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;

(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R,E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5-(3-fluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((5-bromo-3-(2-chlorophenyl)pyridin-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((2',5-dimethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(2-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-4-fluoro-1-((3*R,4*R)-4-(2-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)-1-((3*R,4*R)-4-(o-tolyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)azepane-4-carboxamide;

(2*S,4*S)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-3,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-4,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(E)-4-fluoro-1-((3'-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(3-((1-methylpiperidin-4-yl)sulfonyl)allyl)piperidine-4-carboxamide;

(R,E)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-cyanobut-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;

(Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidin-4-yl)(3-(2-(methylsulfonyl)vinyl)azetidin-1-yl)methanone;

(R,Z)-1-((6-chloro-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(E)-1-((6-chloro-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide;

1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((1,1-dioxido-2H-thiet-3-yl)methyl)-4-fluoropiperidine-4-carboxamide;

(*R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide;

(R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide;

(R)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(1-(1,1-dioxido-2H-thiet-3-yl)ethyl)-4-fluoropiperidine-4-carboxamide;

1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(((R)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(((S)-1-methylpyrrolidin-3-yl)sulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(*S,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide;

(*S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(5,5,5-trifluoro-1-(methylsulfonyl)pent-1-en-3-yl)piperidine-4-carboxamide;

(R)-1-(5-bromo-2'-chloro-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-(2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-(5-bromo-2'-chloro-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide;

(R)-1-(2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide;

(4R)-1-(2'-chloro-6'-fluoro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoroazepane-4-carboxamide;

(R,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(1-methoxy-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-2-methyl-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;(2R,4S)-1-((2'-chloro-5-(difluoromethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-((RS)-1-hydroxyethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(difluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((1*S,2*S)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((1*S,2*S)-2-(2-chlorophenyl)-4,4-dimethylcyclohexane-1-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((6*R,7*R)-6-(2-chlorophenyl)spiro[3.5]nonane-7-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

tert-butyl 5-(2-chlorophenyl)-4-(4-fluoro-4-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)-3,4-dihydropyridine-1(2H)-carboxylate;

tert-butyl (3*R,4*S)-3-(2-chlorophenyl)-4-(4-fluoro-4-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)carbamoyl)piperidine-1-carbonyl)piperidine-1-carboxylate;

(S,Z)-1-((5-chloro-3'-(pyridin-3-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-((3-methoxybenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(pentyloxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-cyclobutoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((3'-(but-2-yn-1-yloxy)-5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-((2-chlorobenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-((3-chlorobenzyl)oxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-phenoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((3'-(benzyloxy)-5-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(pyridin-2-ylmethoxy)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((6-chloro-4-(3-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(S,Z)-1-((6-chloro-4-(2-chloro-5-methoxyphenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(*R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azocane-4-carboxamide;

(1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidin-4-yl)(3-(methylsulfonyl)methylene)azetidin-1-yl)methanone;

(R,Z)-1-((4-(2-chlorophenyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((5-(2-chlorophenyl)-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((4-(2-chlorophenyl)-6-hydroxypyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R,Z)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(E)-1-((6-bromo-4-(2-chlorophenyl)pyridin-3-yl)sulfonyl)-N-(3-cyanoallyl)-4-fluoropiperidine-4-carboxamide;

(S,Z)-1-((5-chloro-3'-(propylcarbamoyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-(4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(dimethylamino)-5-oxopent-3-yn-2-yl)-4-fluoropiperidine-4-carboxamide;

(S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(dimethylamino)-5-oxopent-3-yn-2-yl)-4-fluoropiperidine-4-carboxamide;

(E)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;

(E)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;

(Z)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;

(Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoropiperidine-4-carboxamide;

(Z)-N-(4-(azetidin-1-yl)-4-oxobut-2-en-1-yl)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoropiperidine-4-carboxamide;

(S,Z)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-(5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoropiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((4-(2-chlorophenyl)-6-(trifluoromethyl)pyridin-3-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((5-bromo-2'-chloro-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-cyano-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2*R,4*S)-1-((3*R,4*S)-4-(2-chlorophenyl)-6,6-dimethyltetrahydro-2H-pyran-3-carbonyl)-N-((Z)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-(2'-chloro-5-methoxy-[1,1'-biphenyl]-2-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoroazepane-4-carboxamide;

(R)-1-(2'-chloro-5-methoxy-[1,1'-biphenyl]-2-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((S,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-ethoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(methoxy-d3)-[1,1'-biphenyl]-2-yl)sulfonyl)-N-((R,E)-5-(3,3-difluoroazetidin-1-yl)-5-oxopent-3-en-2-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2R,4S)-1-((2'-chloro-5-(methoxy-d3)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-cyclopropylpyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3*R,4*R)-1-benzyl-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3*S,4*S)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3*R,4*S)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((R)-2-(2-chlorophenyl)-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(S)-1-((2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(S)-1-((2'-chloro-5-methoxy-[1,1'-biphenyl]-2-yl)sulfonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide; or
a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof.

59. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;
1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoropiperidine-4-carboxamide;
(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3*R,4*R)-4-(2-chloro-5-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3*R,4*R)-4-(2-chloro-4-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3*R,4*R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3*R,4*R)-4-(2-chloro-4-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3*R,4*R)-4-(2-chloro-5-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;
(R)-1-((3*R,4*R)-4-(2-chloro-3-methylphenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*R,4*R)-4-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(2*S,4*S)-1-((3*R,4*R)-4-(2-chloro-3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoroazepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluorobutyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,3,3,3-pentafluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-1-(2-chloro-2,2-difluoroethyl)-4-(2-chlorophenyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-1-(methylsulfonyl)pent-1-en-3-yl)azepane-4-carboxamide;

1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-4-fluoro-1-((3*R,4*R)-4-(2-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)-1-((3*R,4*R)-4-(o-tolyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)azepane-4-carboxamide;

(2*S,4*S)-1-((3*S,4*S)-4-(2-chloro-3-fluorophenyl)-1-(2,2-difluoropropyl)pyrrolidine-3-carbonyl)-N-((R)-1,1-dioxido-2,3-dihydrothiophen-3-yl)-4-fluoro-2-methylpiperidine-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-3,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3*S,4*S)-4-(2-chloro-4,6-difluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chlorophenyl)-3-methyl-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(*R)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azocane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((R,E)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(R)-1-((3R,4R)-4-(2-chloro-6-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-N-((S,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

(2*S,4*S)-1-((3R,4R)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidine-3-carbonyl)-4-fluoro-2-methyl-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3*R,4*R)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide;

1-((3*S,4*S)-3-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)piperidine-4-carboxamide;

(R)-1-((3*R,4*S)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)piperidine-3-carbonyl)-4-fluoro-N-((R,Z)-4-(methylsulfonyl)but-3-en-2-yl)azepane-4-carboxamide; or

a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof.

60. A pharmaceutical composition comprising a compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof; and a pharmaceutically acceptable excipient or carrier.
61. A method of modulating RAS-PI3K, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically

acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof.

62. The method of claim 61, wherein the method comprises inhibition of RAS-PI3K.
63. The method of claim 61, wherein the method comprises activation of RAS-PI3K.
64. A method of treating a disease or condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound any one of claims 1-59, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of an atropisomer thereof.
65. The method of claim 64, wherein the disease or condition is mediated by the modulation of RAS-PI3K.
66. The method of claim 64 or 65, wherein the disease is a cancer.
67. The method of claim 66, wherein the cancer is selected from the group consisting of bladder cancer, uterine cancer, head and neck cancer, esophageal cancer, ovarian cancer, liver cancer, lung cancer, colorectal cancer, cervical cancer, cholangiocarcinoma, gastric cancer, kidney cancer, and pancreatic cancer.
68. The method of claim 64 or 65, wherein the disease or condition is an immunological disorder.
69. The method of claim 68, wherein the immunological disease or condition is promotion of wound healing.