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(54) Title: SUBSTITUTED FUSED BICYCLIC MACROCYCLIC COMPOUNDS AND RELATED METHODS OF TREATMENT

(57) Abstract: The present invention provides compounds useful as orexin-2 receptor agonists for the treatment of narcolepsy or cataplexy in a subject in need thereof. Related pharmaceutical compositions and methods are also provided herein.

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SUBSTITUTED FUSED BICYCLIC MACROCYCLIC COMPOUNDS AND RELATED METHODS OF TREATMENT

RELATED APPLICATION

5 This application claims the benefit of U.S. Provisional patent application serial No.: 63/193,243, filed on May 26, 2021. The entire contents of the above-identified application are herein incorporated by reference.

TECHNICAL FIELD

10 The present invention relates to substituted macrocyclic compounds, particularly, substituted macrocyclic compounds having agonist activity.

BACKGROUND OF THE INVENTION

15 Orexin is a neuropeptide synthesized and released by a subpopulation of neurons within the lateral hypothalamus and its surrounding regions. It consists of two subtypes: orexin A and orexin B. Orexin A and orexin B bind to orexin receptors. Orexin receptors are G protein-coupled receptors expressed preferentially in the brain. There are two subtypes (type 1 and type 2) of orexin receptors (Cell, Vol. 92, 573-585, 1998). Activation of orexin receptors is known to be important for a variety of central nervous system functions, such as maintenance of wakefulness, energy homeostasis, reward processing and motivation (Saper *et al.*, TRENDS in Neuroscience 2001; Yamanaka *et al.*, Neuron 2003; Sakurai, Nature Reviews Neuroscience 2014).

20 Narcolepsy is a neurological disease that results in excessive daytime sleepiness, sudden bouts of muscular paralysis (cataplexy), and disrupted sleep patterns (Mahoney *et al.*, Nature Reviews Neuroscience, 2019). It is known that narcolepsy is caused by the degeneration of orexin neurons. Narcoleptic symptoms can be modeled in transgenic mice engineered to degenerate orexin neurons, and their symptoms can be reversed by intraventricular administration of orexin peptides (Proc. Natl. Acad. Sci. USA, Vol. 101, 4649-4654, 2004). Studies of orexin-2 receptor knockout mice have suggested that the orexin-2 receptor plays a preferential role in maintaining wakefulness (Cell, Vol. 98, 437-451, 1999, Neuron, Vol. 38, 715-730, 2003). As such, orexin-2 receptor agonists can be therapeutic agents for narcolepsy or other disorders exhibiting excessive daytime sleepiness,

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such as Parkinson's disease (CNS Drugs, Vol. 27, 83-90, 2013; Brain, Vol. 130, 2007, 1586-1595).

5 A compound having agonist activity at the orexin-2 receptor is hypothesized to be useful as a novel therapeutic agent for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, disturbance of consciousness such as coma and the like, narcolepsy syndrome, hypersomnolence syndrome characterized by hypersomnia (e.g., in Parkinson's disease, Guillain-Barre syndrome or Kleine Levin syndrome), Alzheimer's disease, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, or sepsis and the like. (Cell Metabolism, Vol. 9, 64-76, 2009; Neuroscience, Vol. 121, 855-863, 2003; 10 Respiration, Vol. 71, 575-579, 2004; Peptides, Vol. 23, 1683-1688, 2002; WO 2015/073707; Journal of the American College of Cardiology, Vol. 66, 2015, pages 2522-2533; WO 2015/048091; WO 2015/147240).

Some compounds having orexin-2 receptor agonist activity have been reported (U.S. Pat. No. 8,258,163; WO 2015/088000; WO 2014/198880; Journal of Medicinal Chemistry, 15 Vol. 58, pages 7931-7937; US 20190040010; US 20190031611; US 20170226137).

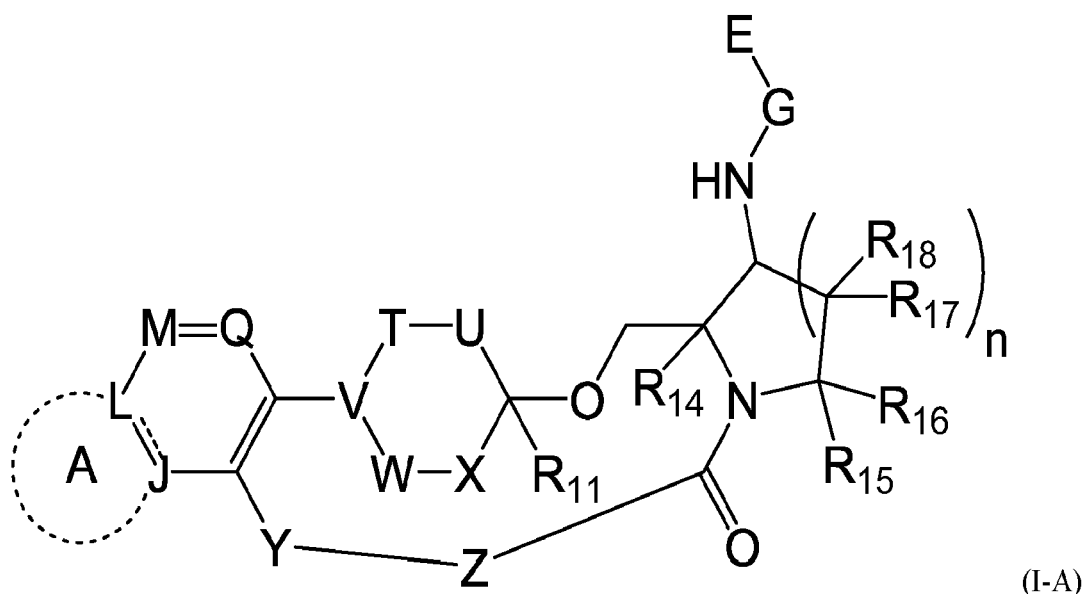
However, it is considered that these compounds are not satisfactory, for example, in terms of activity, pharmacokinetics, permeability into the brain/central nervous system or safety, and the development of an improved compound having orexin-2 receptor agonist activity is desired.

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SUMMARY OF THE INVENTION

The present invention aims to provide fused bicyclic macrocyclic compounds having orexin-2 receptor agonist activity.

Accordingly, in an initial aspect, the present invention provides a compound 25 represented by Formula I-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

10 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

5 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

10 and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

15 R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

20 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

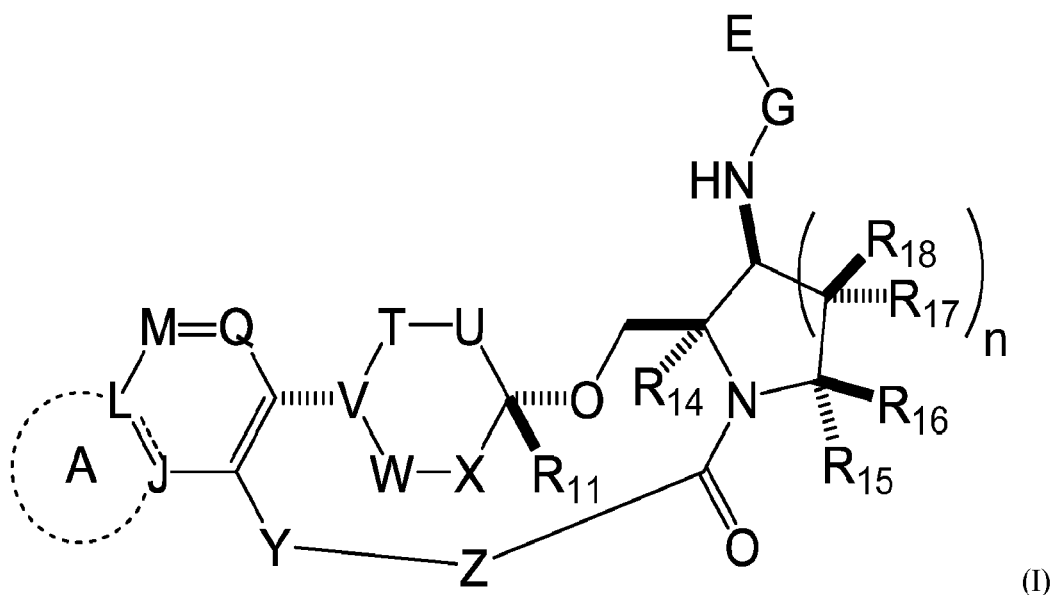
25 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

30 each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In one embodiment, provided herein are compounds of Formula I-A having the structure of Formula I or a pharmaceutically acceptable salt thereof:



wherein:

- 5 fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

- 10 ----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

- 15 n is 1, 2, or 3;

- E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and
 20 C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to

10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

5 U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

10 R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

15 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

20 or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

25 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

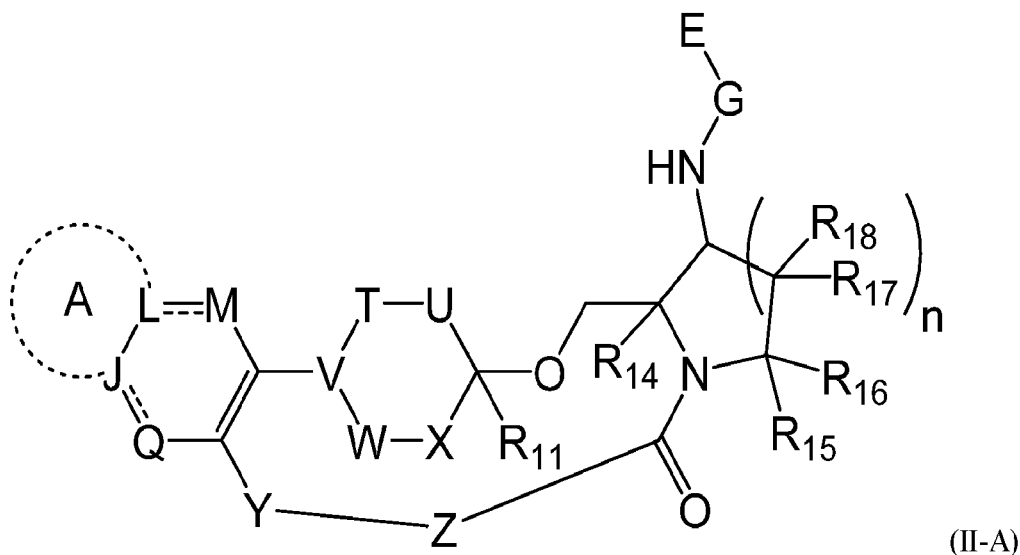
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

30 R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

Also provided herein are compounds having the structure of Formula II-A or a
5 pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium,
10 hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

15 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃
20 alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl),

4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

5 T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

10 Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

15 R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

20 R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

25 R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

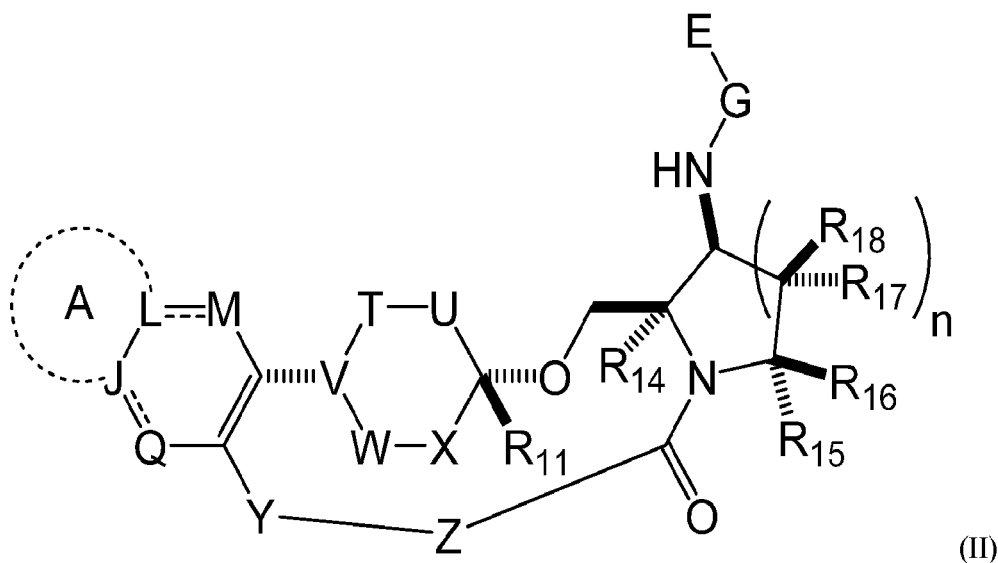
30 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula II-A having the structure of Formula II or a pharmaceutically acceptable salt thereof:



wherein:

10 fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

15 is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

20 n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered

heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

10 U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

15 R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

20 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

25 or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

30 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

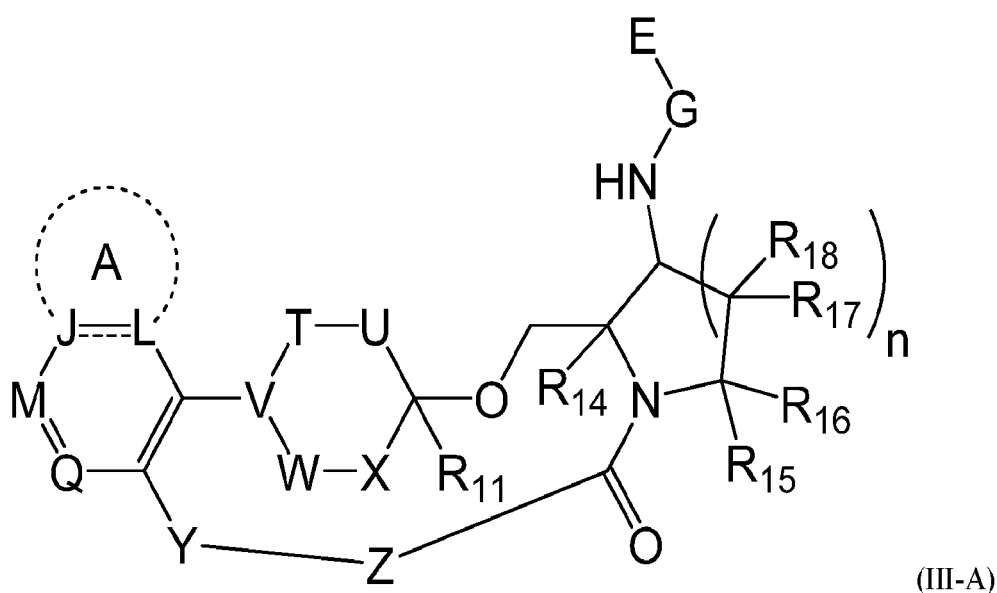
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

5 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

Also provided herein are compounds having the structure of Formula III-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

===== is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

20 Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b , $\text{C}(=\text{O})\text{NR}_a\text{R}_b$, $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, and
 5 $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl), wherein the $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, or $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,
 10 $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy;

T is CR_1R_2 or O;

W is CR_4R_5 or O;

U is CR_6R_7 ;

X is CR_8R_9 ;

15 V is CR_3 or N;

Y is NR_{10} , O or absent;

Z is $(\text{CR}_{12}\text{R}_{13})_m$;

R_a and R_b are each, independently, H or unsubstituted $\text{C}_1\text{-C}_3$ alkyl;

m is 1, 2, 3, or 4;

20 and further wherein:

R_1 , R_2 , R_4 , and R_5 are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R_2 and R_5 together with the carbon atoms to which they are attached, form a single bond;

25 R_3 is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R_3 and R_1 , together with the carbon atoms to which they are attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

or, alternatively, R_3 and R_4 , together with the carbon atoms to which they are
 30 attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

R_6 , R_7 , R_8 , R_9 , and R_{11} are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R_{10} is selected from the group consisting of H, unsubstituted $\text{C}_1\text{-C}_3$ alkyl, and $\text{C}_1\text{-C}_3$ alkyl substituted with one or more halogen;

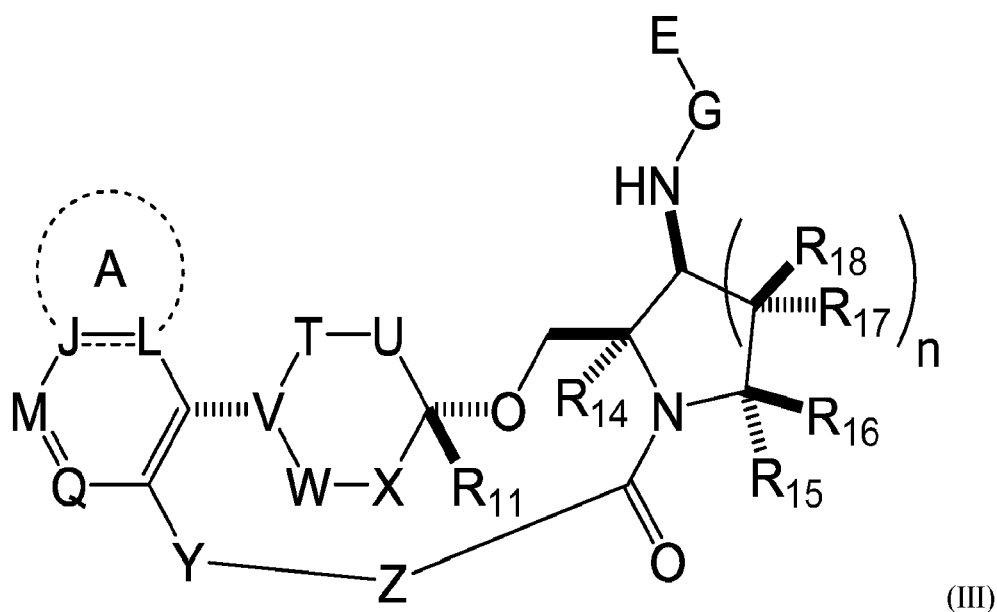
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula III-A having the structure of Formula III or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocycl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocycl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

===== is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

- 5 E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

- 15 T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

- 20 Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

- 25 R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;
or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;
- R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and
30 cyano;
or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;
or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

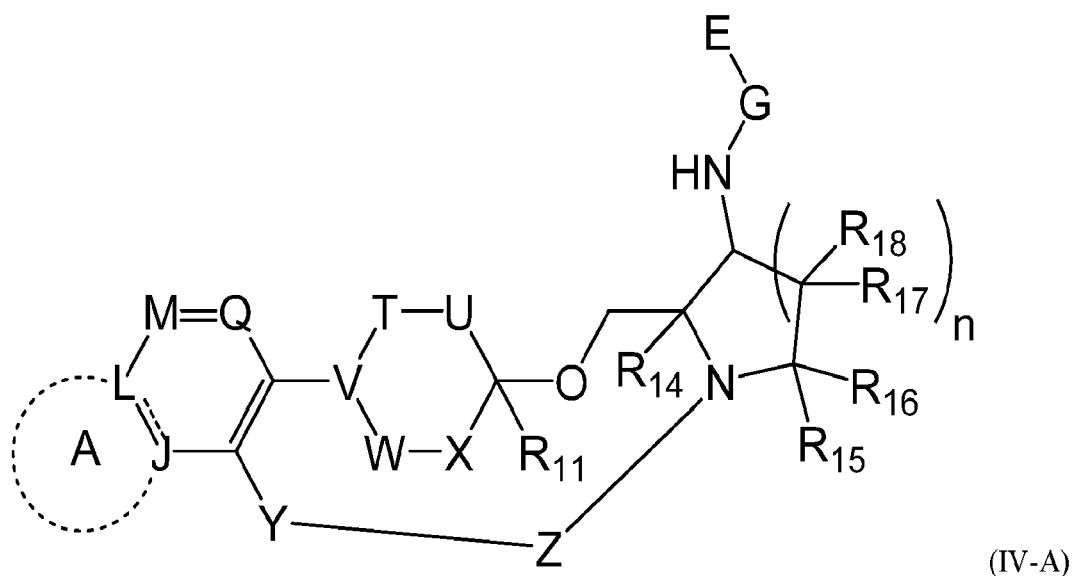
5 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

10 each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

15 Also provided herein are compounds having the structure of Formula IV-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-
 20 membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

5 G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

20 X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

25 m is 2, 3, 4, or 5 when Y is absent; or

m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

30 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

5 R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

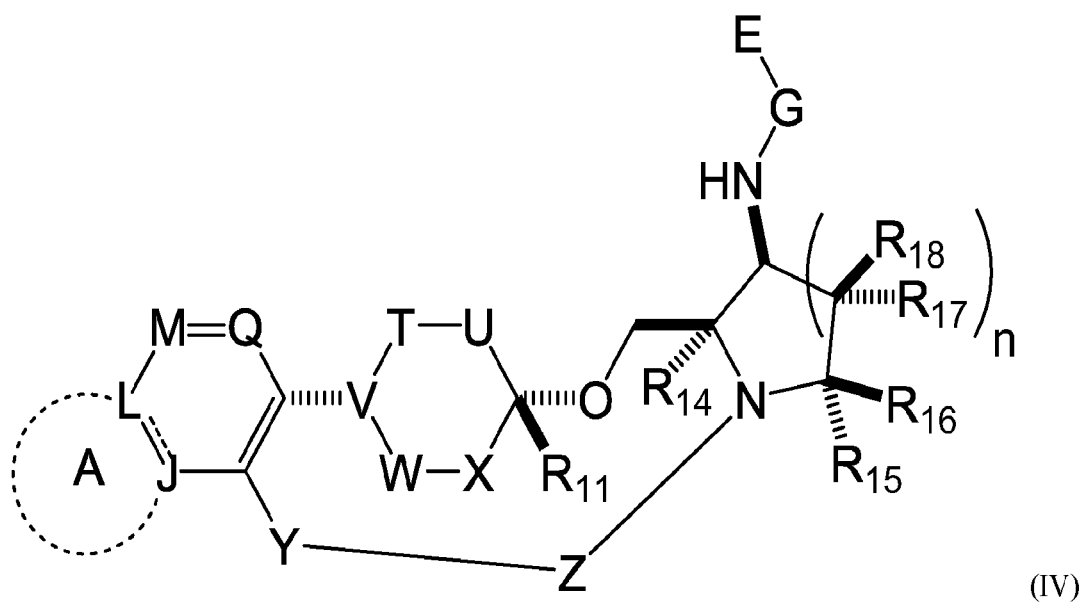
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen,
10 deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H,
15 unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula IV-A having the
20 structure of Formula IV or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

10 G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

25 X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

30 m is 2, 3, 4, or 5 when Y is absent; or

m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

5 or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

10 R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

15 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

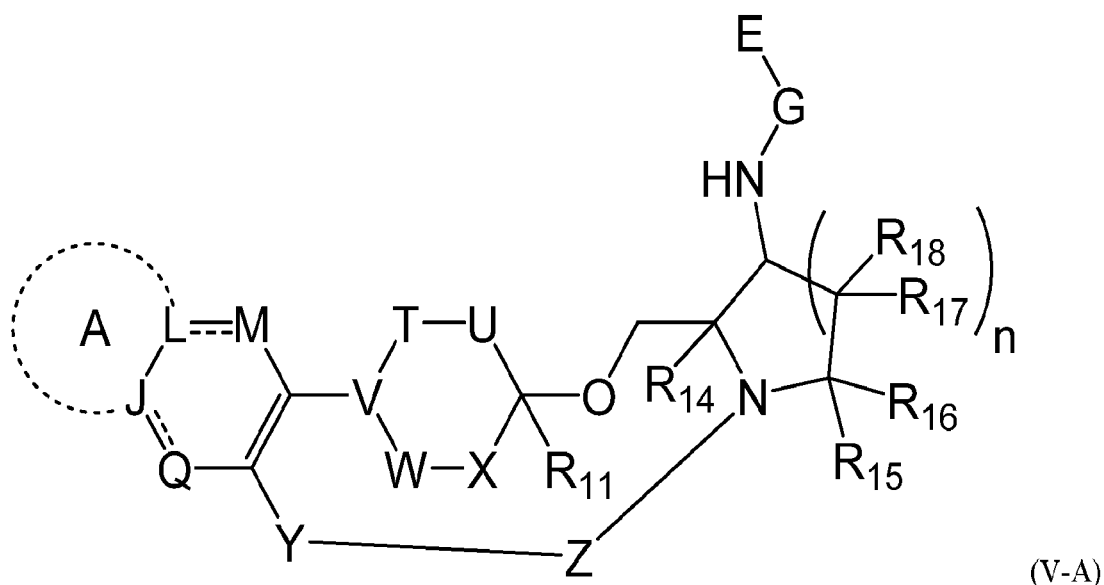
R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

20 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

Also provided herein are compounds having the structure of Formula V-A or a pharmaceutically acceptable salt thereof:

25



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

10 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

5 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

10 m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

15 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

20 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

25 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

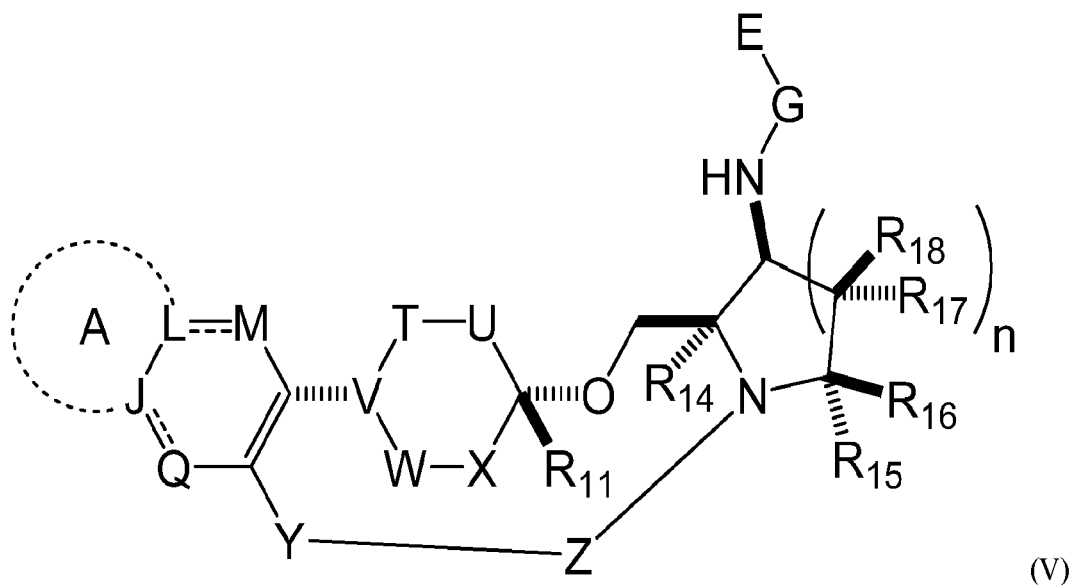
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

30 R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula V-A having the structure of Formula V or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-

C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,

5 C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

10 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

15 m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

20 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

25 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

30 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

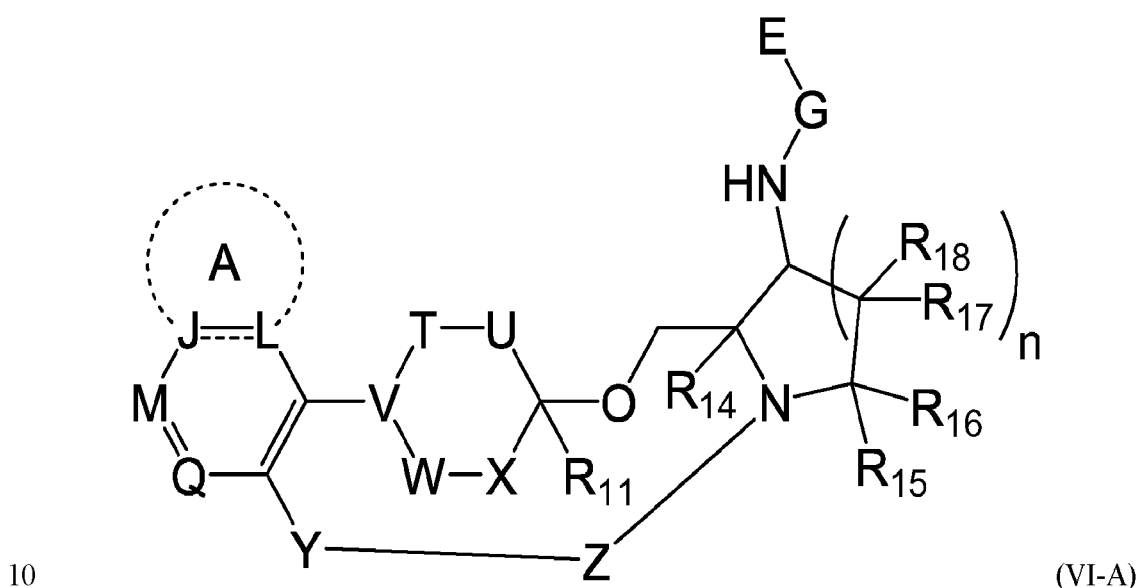
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

5 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

Also provided herein are compounds having the structure of Formula VI-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

===== is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉:

20 Q is N or CR₂₀.

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b , $\text{C}(=\text{O})\text{NR}_a\text{R}_b$, $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, and
 5 $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl), wherein the $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, or $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,
 10 $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy;

T is CR_1R_2 or O;

W is CR_4R_5 or O;

U is CR_6R_7 ;

X is CR_8R_9 ;

15 V is CR_3 or N;

Y is NR_{10} , O or absent;

Z is $(\text{CR}_{12}\text{R}_{13})_m$;

R_a and R_b are each, independently, H or unsubstituted $\text{C}_1\text{-C}_3$ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

20 m is 1, 2, 3, or 4 when Y is NR_{10} or O;

and further wherein:

R_1 , R_2 , R_4 , and R_5 are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R_2 and R_5 together with the carbon atoms to which they are attached,
 25 form a single bond;

R_3 is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R_3 and R_1 , together with the carbon atoms to which they are attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

30 or, alternatively, R_3 and R_4 , together with the carbon atoms to which they are attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

R_6 , R_7 , R_8 , R_9 , and R_{11} are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

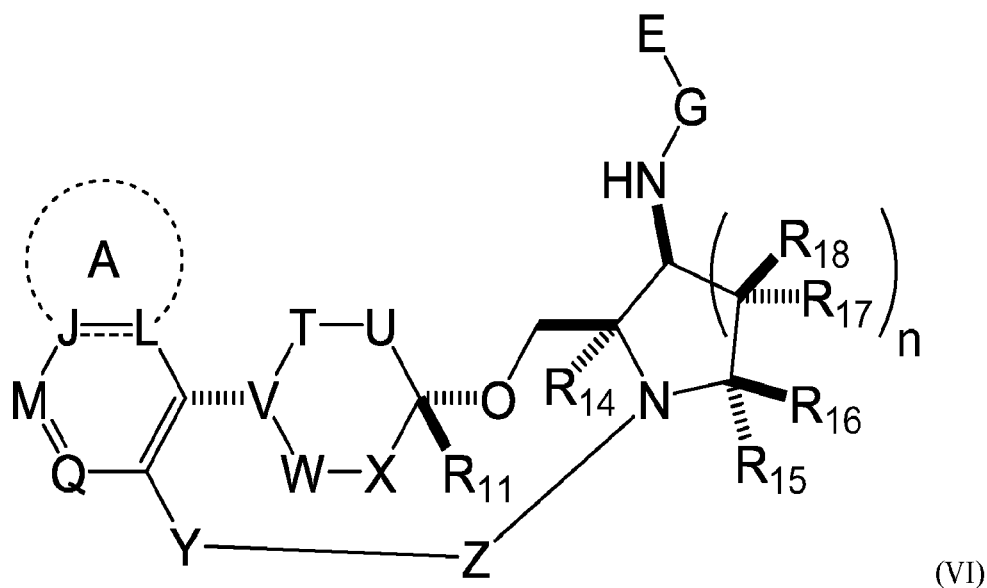
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula VI-A having the structure of Formula VI or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocycl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocycl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

5 E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

15 T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

20 Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

25 and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

30 R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

5 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

10 R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

15 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

Also provided herein is a pharmaceutical composition comprising a compound of any of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20 In another aspect, provided herein is a method of treating narcolepsy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of treating cataplexy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, 25 III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are compounds, e.g., the compounds of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or pharmaceutically acceptable salts thereof, that are 30 useful in the treatment of narcolepsy or cataplexy in a subject.

In a non-limiting aspect, these compounds may modulate the orexin-2 receptor. In a particular embodiment, the compounds provided herein are considered orexin-2 agonists. As such, in one aspect, the compounds provided herein are useful in treatment of narcolepsy in a subject by acting as an agonist of the orexin-2 receptor.

5

Definitions

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

10

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

15

As used herein, the articles “a” and “an” refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

As used herein, the term “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term “about” is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, including $\pm 5\%$, $\pm 1\%$, and $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

25

As used to herein, the term “EC₅₀” refers to the concentration of a compound required to achieve an effect that is 50% of the maximal observed effect of a compound.

The term “agonist,” as used herein, refers to a compound that, when contacted with a target of interest (e.g., the orexin-2 receptor), causes an increase in the magnitude of a certain activity or function of the target compared to the magnitude of the activity or function observed in the absence of the agonist.

The term “treat,” “treated,” “treating,” or “treatment” includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises bringing into contact with the orexin-2 receptor an effective amount of a compound of the invention for conditions related

to narcolepsy or cataplexy.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term “patient,” “individual” or “subject” refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such as ovine, bovine, porcine, canine, feline and murine mammals. Preferably, the patient, subject, or individual is human.

As used herein, the terms “effective amount,” “pharmaceutically effective amount,” and “therapeutically effective amount” refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term “pharmaceutically acceptable” refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, 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.

As used herein, the term “pharmaceutically acceptable salt” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. The phrase “pharmaceutically acceptable salt” is not limited to a mono, or 1:1, salt. For example, “pharmaceutically

acceptable salt” also includes bis-salts, such as a bis-hydrochloride salt. Lists of suitable salts are found in Remington’s Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

5 As used herein, the term “composition” or “pharmaceutical composition” refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic,
10 pulmonary, and topical administration.

 As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the
15 invention within or to the patient such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the invention, and not injurious to the patient. Some examples of materials that may
20 serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as
25 peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical
30 formulations.

 As used herein, “pharmaceutically acceptable carrier” also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the invention and are physiologically acceptable to the patient. Supplementary active compounds may also be

incorporated into the compositions. The “pharmaceutically acceptable carrier” may further include a pharmaceutically acceptable salt of the compound useful within the invention.

Other additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention are known in the art and described, for example in Remington’s
5 Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the term “alkyl,” by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (*i.e.*, C₁₋₆ alkyl means an alkyl having one to six carbon atoms) and includes
10 straight and branched chains. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, neopentyl, and hexyl. Other examples of C₁-C₆-alkyl include ethyl, methyl, isopropyl, isobutyl, n-pentyl, and n-hexyl.

As used herein, the term “halo” or “halogen” alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably,
15 fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

As used herein, the term “alkylene” refers to divalent aliphatic hydrocarbyl groups, for example, having from 1 to 4 carbon atoms that are either straight-chained or branched. This term includes, by way of example, methylene (-CH₂-), ethylene (-CH₂CH₂-), n-propylene (-CH₂CH₂CH₂-), iso-propylene (-CH₂CH(CH₃)-), and the like.

As used herein, the term “alkenyl” denotes a monovalent group derived from a hydrocarbon moiety containing at least two carbon atoms and at least one carbon-carbon double bond. The double bond may or may not be the point of attachment to another group. Alkenyl groups (*e.g.*, C₂-C₈-alkenyl) include, but are not limited to, for example, ethenyl, propenyl, prop-1-en-2-yl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.
20

As used herein, the term “alkynyl” denotes a monovalent group derived from a hydrocarbon moiety containing at least two carbon atoms and at least one carbon-carbon triple bond. The triple bond may or may not be the point of attachment to another group. Alkynyl groups (*e.g.*, C₂-C₈-alkynyl) include, but are not limited to, for example, ethynyl, propynyl, prop-1-yn-2-yl, butynyl, 1-methyl-2-butyne-1-yl, heptynyl, octynyl and the like.
25

As used herein, the term “alkoxy,” refers to the group -O-alkyl, wherein alkyl is as defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, t-butoxy and the like.
30

As used herein, the term “cycloalkyl” means a non-aromatic carbocyclic system that is partially or fully saturated having 1, 2 or 3 rings wherein such rings may be fused. The term “fused” means that a second ring is present (*i.e.*, attached or formed) by having two adjacent atoms in common (*i.e.*, shared) with the first ring. Cycloalkyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within the bicycle varying from 3-8 atoms. The term “cycloalkyl” includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[3.1.0]hexyl, spiro[3.3]heptanyl, and bicyclo[1.1.1]pentyl.

As used herein, the term “heterocyclyl” means a non-aromatic carbocyclic system containing 1, 2, 3 or 4 heteroatoms selected independently from N, O, and S and having 1, 2 or 3 rings wherein such rings may be fused, wherein fused is defined above. Heterocyclyl also includes bicyclic structures that may be bridged or spirocyclic in nature with each individual ring within the bicycle varying from 3-8 atoms, and containing 0, 1, or 2 N, O, or S atoms. The term “heterocyclyl” includes cyclic esters (*i.e.*, lactones) and cyclic amides (*i.e.*, lactams) and also specifically includes, but is not limited to, epoxidyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl (*i.e.*, oxanyl), pyranal, dioxanyl, aziridinyl, azetidiny, pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, oxazolidinyl, thiazolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, and the like. For example, the term “heterocyclyl” can include 4- to 10-membered heterocyclyl, 4- to 7-membered heterocyclyl, 5- to 10-membered heterocyclyl, 6- to 10-membered heterocyclyl, 4- to 6-membered heterocyclyl, 4-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 7-membered heterocyclyl, 8-membered heterocyclyl, 9-membered heterocyclyl, or 10-membered heterocyclyl.

As used herein, the term “aromatic” refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, *i.e.*, having $(4n + 2)$ delocalized π (pi) electrons, where n is an integer.

As used herein, the term “aryl” means an aromatic carbocyclic system containing 1, 2 or 3 rings, wherein such rings may be fused, wherein fused is defined above. If the rings are fused, one of the rings must be fully unsaturated and the fused ring(s) may be fully saturated, partially unsaturated or fully unsaturated. The term “aryl” includes, but is not limited to, phenyl, naphthyl, indanyl, and 1,2,3,4-tetrahydronaphthalenyl. For example, the term “aryl” can include C₆-C₁₀ aryl, C₆-C₈ aryl, or C₆ aryl (*i.e.*, phenyl).

As used herein, the term “heteroaryl” means an aromatic carbocyclic system containing 1, 2, 3, or 4 heteroatoms selected independently from N, O, and S and having 1, 2,

or 3 rings wherein such rings may be fused, wherein fused is defined above. The term “heteroaryl” includes, but is not limited to, furanyl, thiophenyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and the like. For example, the term

5 “heteroaryl” can include 5- to 10-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 6-membered heteroaryl, 6- to 10-membered heteroaryl, 6- to 8-membered heteroaryl, 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, or 10-membered heteroaryl.

It is to be understood that if an aryl, heteroaryl, cycloalkyl, or heterocyclyl moiety

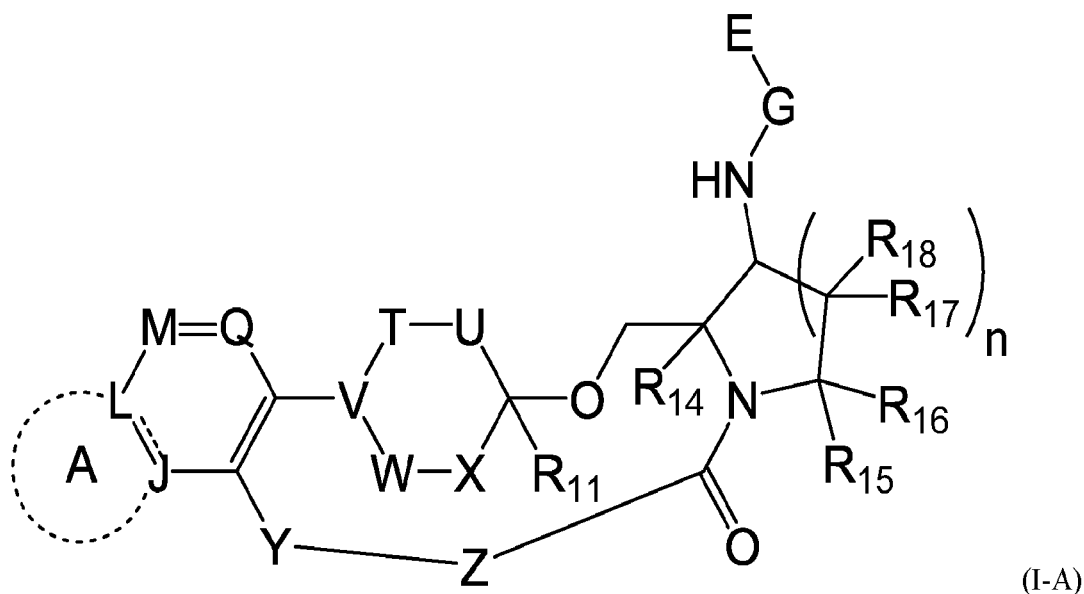
10 may be bonded or otherwise attached to a designated moiety through differing ring atoms (*i.e.*, shown or described without denotation of a specific point of attachment), then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term “pyridinyl” means 2-, 3- or 4-pyridinyl, the term “thiophenyl” means 2- or 3-thiophenyl, and so forth.

15 As used herein, the term “substituted” means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

Compounds of the Invention

Accordingly, in an initial aspect, the present invention provides a compound

20 represented by Formula I-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

5 or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

10 R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

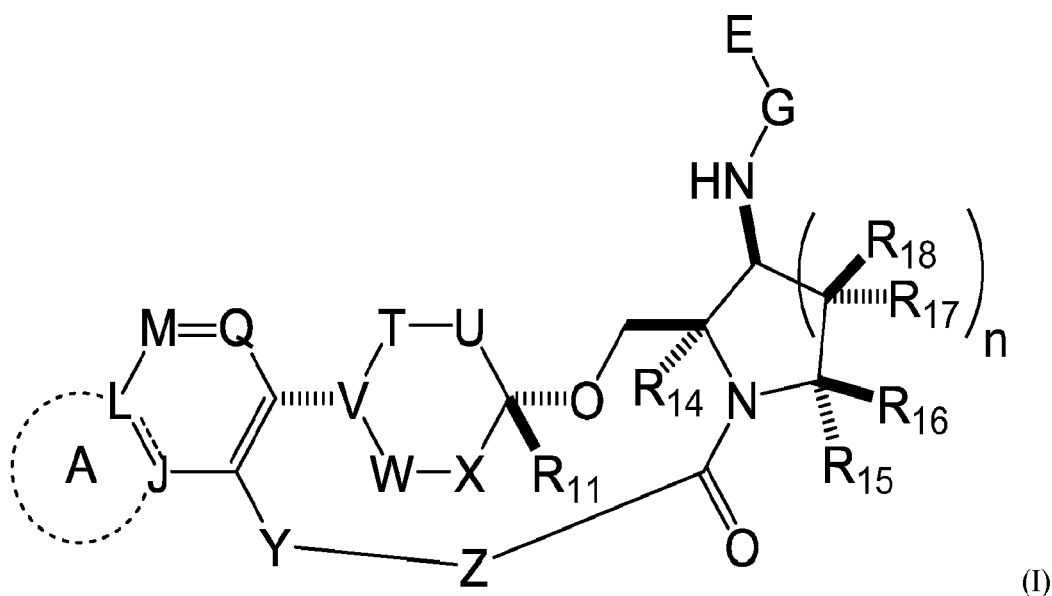
15 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

20 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In one embodiment, provided herein are compounds of Formula I-A having the structure of Formula I or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

10 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

5 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

10 and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

15 R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

20 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

25 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

30 each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In one embodiment of Formula (I), n is 1. In another embodiment of Formula (I), n is 2. In another embodiment of Formula (I), n is 3.

In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl. In another embodiment of Formula (I), fused ring A is C₄-C₆ cycloalkyl. In another embodiment of Formula (I), fused ring A is C₄-C₅ cycloalkyl. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl. In another embodiment of Formula (I), fused ring A is 5- to 6-membered heterocyclyl. In another embodiment of Formula (I), fused ring A is 5-membered heterocyclyl. In another embodiment of Formula (I), fused ring A is 6-membered heterocyclyl. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl. In another embodiment of Formula (I), fused ring A is 5- to 6-membered heteroaryl. In another embodiment of Formula (I), fused ring A is 5-membered heteroaryl. In another embodiment of Formula (I), fused ring A is 6-membered heteroaryl.

In another embodiment of Formula (I), fused ring A is cyclopentyl. In another embodiment of Formula (I), fused ring A is cyclopentenyl. In another embodiment of Formula (I), fused ring A is cyclohexyl. In another embodiment of Formula (I), fused ring A is cyclohexenyl. In another embodiment of Formula (I), fused ring A is pyrrolyl. In another embodiment of Formula (I), fused ring A is pyrazolyl. In another embodiment of Formula (I), fused ring A is 1-methylpyrazolyl. In another embodiment of Formula (I), fused ring A is imidazolyl. In another embodiment of Formula (I), fused ring A is isoxazolyl. In another embodiment of Formula (I), fused ring A is tetrahydropyranyl. In another embodiment of Formula (I), fused ring A is tetrahydrofuranyl. In another embodiment of Formula (I), fused ring A is dihydropyranyl. In another embodiment of Formula (I), fused ring A is dihydrofuranyl.

In another embodiment of Formula (I), Y is NR₁₀. In another embodiment of Formula (I), Y is O. In another embodiment of Formula (I), Y is absent. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl and Y is O. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl and Y is absent. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl and Y is O. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl and Y is absent. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl

and Y is O. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl and Y is absent.

In another embodiment of Formula (I), T is CR₁R₂. In another embodiment of Formula (I), T is O. In another embodiment of Formula (I), W is CR₄R₅. In another embodiment of Formula (I), W is O. In another embodiment of Formula (I), T is CR₁R₂ and W is CR₄R₅. In another embodiment of Formula (I), T is O and W is CR₄R₅. In another embodiment of Formula (I), T is CR₁R₂ and W is O.

In another embodiment of Formula (I), V is CR₃. In another embodiment of Formula (I), V is N.

In another embodiment of Formula (I), T is CR₁R₂ and V is CR₃. In another embodiment of Formula (I), T is O and V is CR₃. In another embodiment of Formula (I), T is CR₁R₂ and V is N. In another embodiment of Formula (I), T is O and V is N.

In another embodiment of Formula (I), W is CR₄R₅ and V is CR₃. In another embodiment of Formula (I), W is O and V is CR₃. In another embodiment of Formula (I), W is CR₄R₅ and V is N. In another embodiment of Formula (I), W is O and V is N.

In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, and V is CR₃. In another embodiment of Formula (I), T is CR₁R₂, W is O, and V is CR₃. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, and V is N. In another embodiment of Formula (I), T is CR₁R₂, W is O, and V is N. In another embodiment of Formula (I), T is O, W is CR₄R₅, and V is CR₃.

In another embodiment of Formula (I), E is H. In another embodiment of Formula (I), E is hydroxyl. In another embodiment of Formula (I), E is NR_aR_b. In another embodiment of Formula (I), E is C(=O)NR_aR_b. In another embodiment of Formula (I), E is C₁-C₃ alkylene-NR_aR_b. In another embodiment of Formula (I), E is unsubstituted C₁-C₃ alkyl, unsubstituted C₂-C₄ alkenyl or unsubstituted C₂-C₄ alkynyl. In another embodiment of Formula (I), E is C₁-C₃ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (I), E is C₁-C₃ alkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted C₃-C₈ cycloalkyl. In another embodiment of Formula (I), E is C₃-C₈ cycloalkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted C₁-C₃ alkylene-(C₃-C₈ cycloalkyl). In another embodiment of Formula (I), E is C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula

(I), E is unsubstituted 4- to 10-membered heterocyclyl. In another embodiment of Formula (I), E is 4- to 10-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted C₁-C₃ alkylene-(4- to 10-membered heterocyclyl). In another embodiment of Formula (I), E is C₁-C₃ alkylene-(4- to 10-membered heterocyclyl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted C₆-C₁₀ aryl. In another embodiment of Formula (I), E is C₆-C₁₀ aryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted C₁-C₃ alkylene-(C₆-C₁₀ aryl). In another embodiment of Formula (I), E is C₁-C₃ alkylene-(C₆-C₁₀ aryl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted 5- to 10-membered heteroaryl. In another embodiment of Formula (I), E is 5- to 10-membered heteroaryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), E is unsubstituted 4- to 7-membered heterocyclyl. In another embodiment of Formula (I), E is 4- to 7-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted 4- to 6-membered heterocyclyl. In another embodiment of Formula (I), E is 4- to 6-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted 4-membered heterocyclyl. In another embodiment of Formula (I), E is 4-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted 5-membered heterocyclyl. In another embodiment of Formula (I), E is 5-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is unsubstituted 6-membered heterocyclyl. In another embodiment of Formula (I), E is 6-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), E is NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered

heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), E is C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), E is methyl, wherein the methyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is methyl. In another embodiment of Formula (I), E is trifluoromethyl. In another embodiment of Formula (I), E is dioxanyl, wherein the dioxanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is tetrahydropyranyl, wherein the tetrahydropyranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is

tetrahydrofuranyl, wherein the tetrahydrofuranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is azetidiny, wherein the azetidiny is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is
5 oxetanyl, wherein the oxetanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (I), E is morpholinyl, wherein the morpholinyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (I), R₁₄ is H. In another embodiment of Formula
10 (I), R₁₄ is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (I), R₁₅ and R₁₆ are each H. In another embodiment of Formula (I), R₁₅ is unsubstituted C₁-C₃ alkyl and R₁₆ is H. In another embodiment of Formula (I), R₁₆ is unsubstituted C₁-C₃ alkyl and R₁₅ is H. In another embodiment of Formula (I), each R₁₇ and R₁₈ is H. In another embodiment of Formula (I), R₁₇ is unsubstituted C₁-C₃ alkyl and R₁₈ is H. In another embodiment of Formula
15 (I), R₁₈ is unsubstituted C₁-C₃ alkyl and R₁₇ is H. In another embodiment of Formula (I), one of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is unsubstituted C₁-C₃ alkyl and the others are each H. In another embodiment of Formula (I), each of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is H.

In another embodiment of Formula (I), m is 1. In another embodiment of Formula (I), m is 2. In another embodiment of Formula (I), m is 3. In another embodiment of Formula
20 (I), m is 4. In another embodiment of Formula (I), m is 1, 2 or 3. In another embodiment of Formula (I), m is 2, 3, or 4. In another embodiment of Formula (I), m is 1 or 2. In another embodiment of Formula (I), m is 3 or 4.

In another embodiment of Formula (I), Y is O and m is 1. In another embodiment of Formula (I), Y is O and m is 2. In another embodiment of Formula (I), Y is O and m is 3. In
25 another embodiment of Formula (I), Y is O and m is 4. In another embodiment of Formula (I), Y is O and m is 1, 2, or 3. In another embodiment of Formula (I), Y is O and m is 2, 3, or 4. In another embodiment of Formula (I), Y is O and m is 1 or 2. In another embodiment of Formula (I), Y is O and m is 3 or 4.

In another embodiment of Formula (I), Y is absent and m is 1. In another
30 embodiment of Formula (I), Y is absent and m is 2. In another embodiment of Formula (I), Y is absent and m is 3. In another embodiment of Formula (I), Y is absent and m is 4. In another embodiment of Formula (I), Y is absent and m is 1, 2, or 3. In another embodiment of Formula (I), Y is absent and m is 2, 3, or 4. In another embodiment of Formula (I), Y is absent and m is 1 or 2. In another embodiment of Formula (I), Y is absent and m is 3 or 4.

In another embodiment of Formula (I), Y is NR₁₀ and m is 1. In another embodiment of Formula (I), Y is NR₁₀ and m is 2. In another embodiment of Formula (I), Y is NR₁₀ and m is 3. In another embodiment of Formula (I), Y is NR₁₀ and m is 4. In another embodiment of Formula (I), Y is NR₁₀ and m is 1, 2, or 3. In another embodiment of Formula (I), Y is NR₁₀ and m is 2, 3, or 4. In another embodiment of Formula (I), Y is NR₁₀ and m is 1 or 2. In another embodiment of Formula (I), Y is NR₁₀ and m is 3 or 4.

In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl and n is 1. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl and n is 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl and n is 3. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl and n is 1. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl and n is 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl and n is 3. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl and n is 1. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl and n is 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl and n is 3.

In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is O. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is O. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is O. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is absent. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is absent. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is absent.

In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is O. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is O. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is O. In another embodiment of Formula (I), fused ring A is 4- to 7-membered

heterocyclyl, n is 1, and Y is absent. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is absent. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is absent.

5 In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is NR₁₀. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is O. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is O. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is O. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is absent. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is absent. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is absent.

15 In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 3 or 4. In

another embodiment of Formula (I), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (I),

fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (I), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 1 or 2. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 1 or 2. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 1 or 2. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 1 or 2. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 3 or 4. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 3 or 4. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 3 or 4. In another embodiment of Formula (I), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 3 or 4.

In another embodiment of Formula (I), R₁, R₂, R₄, and R₅ are each H. In another embodiment of Formula (I), R₁, R₂, R₄, and R₅ are each H; and R₃ is H. In another embodiment of Formula (I), R₁, R₂, R₄, and R₅ are each H; R₃ is H; and R₆, R₇, R₈, R₉, and R₁₁ are each H. In another embodiment of Formula (I), R₁, R₂, R₄, and R₅ are each H; R₃ is H; R₆, R₇, R₈, R₉, and R₁₁ are each H; and R₁₂ and R₁₃ are each H.

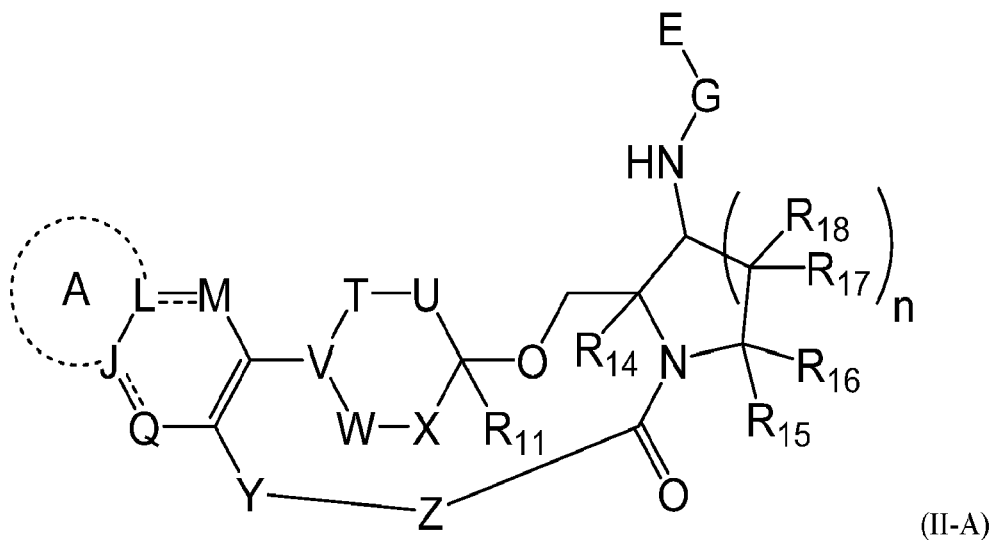
In another embodiment of Formula (I), one or more of R₁, R₂, R₄, and R₅ is fluorine. In another embodiment of Formula (I), one or more of R₁, R₂, R₄, and R₅ is deuterium. In

another embodiment of Formula (I), one or more of R₆, R₇, R₈, R₉, and R₁₁ is fluorine. In another embodiment of Formula (I), one or more of R₆, R₇, R₈, R₉, and R₁₁ is deuterium. In another embodiment of Formula (I), one or more of each R₁₂ and R₁₃ is fluorine. In another embodiment of Formula (I), one or more of each R₁₂ and R₁₃ is deuterium.

5 In another embodiment of Formula (I), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and R₁₁ is H. In another embodiment of Formula (I), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, R₁₁ is H, and m is 1. In another embodiment of Formula (I), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (I), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 1. In another embodiment of Formula (I), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (I), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 1.

Each of the embodiments described herein with respect to compounds of Formula I
15 also applies to compounds of Formula I-A.

Also provided herein is a compound having the structure of Formula II-A or a pharmaceutically acceptable salt thereof:



wherein:

20 fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxyl, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

5 G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

20 X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

25 m is 1, 2, 3, or 4;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, 30 form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

5 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

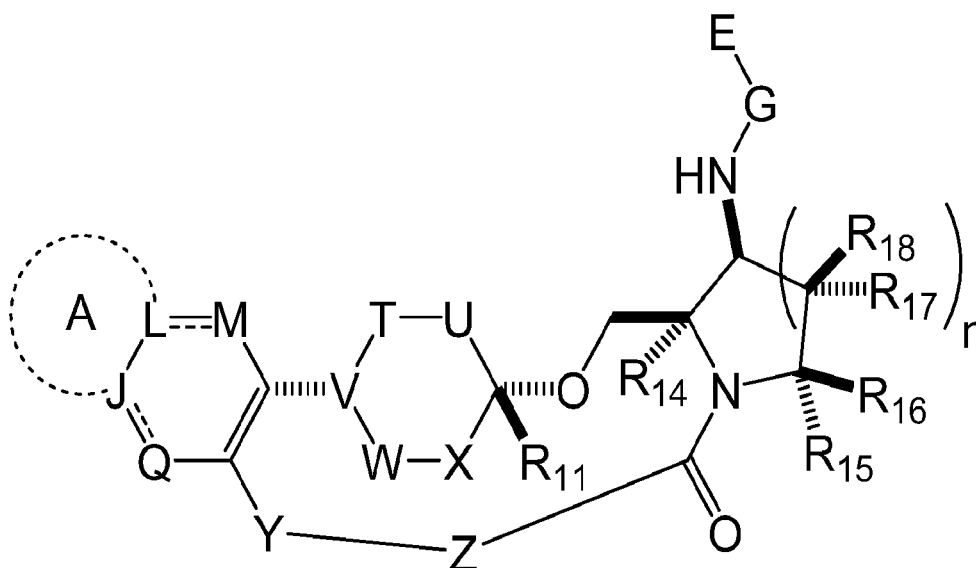
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

10 R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, 15 deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula II-A having the structure of Formula II or a pharmaceutically acceptable salt thereof:



20 (II)

wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to

8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

5 J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

10 E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

20 T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

25 Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

30 R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

5 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

10 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

15 each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

20 In one embodiment of Formula (II), n is 1. In another embodiment of Formula (II), n is 2. In another embodiment of Formula (II), n is 3.

In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl. In another embodiment of Formula (II), fused ring A is C₄-C₆ cycloalkyl. In another embodiment of Formula (II), fused ring A is C₄-C₅ cycloalkyl. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl. In another embodiment of Formula (II), fused ring A is 5- to 6-membered heterocyclyl. In another embodiment of Formula (II), fused ring A is 5-membered heterocyclyl. In another embodiment of Formula (II), fused ring A is 6-membered heterocyclyl. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl. In another embodiment of Formula (II), fused ring A is 5- to 6-membered heteroaryl. In another embodiment of Formula (II), fused ring A is 5-membered heteroaryl. In another embodiment of Formula (II), fused ring A is 6-membered heteroaryl.

In another embodiment of Formula (II), fused ring A is cyclopentyl. In another embodiment of Formula (II), fused ring A is cyclopentenyl. In another embodiment of

Formula (II), fused ring A is cyclohexyl. In another embodiment of Formula (II), fused ring A is cyclohexenyl. In another embodiment of Formula (II), fused ring A is pyrrolyl. In another embodiment of Formula (II), fused ring A is pyrazolyl. In another embodiment of Formula (II), fused ring A is 1-methylpyrazolyl. In another embodiment of Formula (II), fused ring A is imidazolyl. In another embodiment of Formula (II), fused ring A is isoxazolyl. In another embodiment of Formula (II), fused ring A is tetrahydropyranyl. In another embodiment of Formula (II), fused ring A is tetrahydrofuranyl. In another embodiment of Formula (II), fused ring A is dihydropyranyl. In another embodiment of Formula (II), fused ring A is dihydrofuranyl.

10 In another embodiment of Formula (II), Y is NR₁₀. In another embodiment of Formula (II), Y is O. In another embodiment of Formula (II), Y is absent. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl and Y is O. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl and Y is absent. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl and Y is O. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl and Y is absent. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl and Y is O. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl and Y is absent.

In another embodiment of Formula (II), T is CR₁R₂. In another embodiment of Formula (II), T is O. In another embodiment of Formula (II), W is CR₄R₅. In another embodiment of Formula (II), W is O. In another embodiment of Formula (II), T is CR₁R₂ and W is CR₄R₅. In another embodiment of Formula (II), T is O and W is CR₄R₅. In another embodiment of Formula (II), T is CR₁R₂ and W is O.

In another embodiment of Formula (II), V is CR₃. In another embodiment of Formula (II), V is N.

30 In another embodiment of Formula (II), T is CR₁R₂ and V is CR₃. In another embodiment of Formula (II), T is O and V is CR₃. In another embodiment of Formula (II), T is CR₁R₂ and V is N. In another embodiment of Formula (II), T is O and V is N.

In another embodiment of Formula (II), W is CR₄R₅ and V is CR₃. In another embodiment of Formula (II), W is O and V is CR₃. In another embodiment of Formula (II), W is CR₄R₅ and V is N. In another embodiment of Formula (II), W is O and V is N.

In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, and V is CR₃. In another embodiment of Formula (II), T is CR₁R₂, W is O, and V is CR₃. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, and V is N. In another embodiment of Formula (II), T is CR₁R₂, W is O, and V is N. In another embodiment of Formula (II), T is O, W is CR₄R₅, and V is CR₃.

In another embodiment of Formula (II), E is H. In another embodiment of Formula (II), E is hydroxyl. In another embodiment of Formula (II), E is NR_aR_b. In another embodiment of Formula (II), E is C(=O)NR_aR_b. In another embodiment of Formula (II), E is C₁-C₃ alkylene-NR_aR_b. In another embodiment of Formula (II), E is unsubstituted C₁-C₃ alkyl, unsubstituted C₂-C₄ alkenyl or unsubstituted C₂-C₄ alkynyl. In another embodiment of Formula (II), E is C₁-C₃ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (II), E is C₁-C₃ alkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted C₃-C₈ cycloalkyl. In another embodiment of Formula (II), E is C₃-C₈ cycloalkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted C₁-C₃ alkylene-(C₃-C₈ cycloalkyl). In another embodiment of Formula (II), E is C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted 4- to 10-membered heterocycl. In another embodiment of Formula (II), E is 4- to 10-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted C₁-C₃ alkylene-(4- to 10-membered heterocycl). In another embodiment of Formula (II), E is C₁-C₃ alkylene-(4- to 10-membered heterocycl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted C₆-C₁₀ aryl. In another embodiment of Formula (II), E is C₆-C₁₀ aryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted C₁-C₃ alkylene-(C₆-C₁₀ aryl). In another embodiment of Formula (II), E is C₁-C₃ alkylene-(C₆-C₁₀ aryl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted 5- to 10-membered heteroaryl. In another embodiment of Formula (II), E is 5- to 10-membered heteroaryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (II), E is unsubstituted 4- to 7-membered heterocyclyl. In another embodiment of Formula (II), E is 4- to 7-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted 4- to 6-membered heterocyclyl. In another embodiment of Formula (II), E is 4- to 6-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted 4-membered heterocyclyl. In another embodiment of Formula (II), E is 4-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted 5-membered heterocyclyl. In another embodiment of Formula (II), E is 5-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is unsubstituted 6-membered heterocyclyl. In another embodiment of Formula (II), E is 6-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (II), E is NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (II), E is C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (II), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered

heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

5 In another embodiment of Formula (II), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

10 In another embodiment of Formula (II), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (II), E is methyl, wherein the methyl is
15 unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is methyl. In another embodiment of Formula (II), E is trifluoromethyl. In another embodiment of Formula (II), E is dioxanyl, wherein the dioxanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is tetrahydropyranyl,
20 wherein the tetrahydropyranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is tetrahydrofuranyl, wherein the tetrahydrofuranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is azetidiny, wherein the azetidiny is unsubstituted or substituted with one or more
25 halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is oxetanyl, wherein the oxetanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (II), E is morpholinyl, wherein the morpholinyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

30 In another embodiment of Formula (II), R₁₄ is H. In another embodiment of Formula (II), R₁₄ is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (II), R₁₅ and R₁₆ are each H. In another embodiment of Formula (II), R₁₅ is unsubstituted C₁-C₃ alkyl and R₁₆ is H. In another embodiment of Formula (II), R₁₆ is unsubstituted C₁-C₃ alkyl and R₁₅ is H. In another embodiment of Formula (II), each R₁₇ and R₁₈ is H. In another embodiment of

Formula (II), R₁₇ is unsubstituted C₁-C₃ alkyl and R₁₈ is H. In another embodiment of Formula (II), R₁₈ is unsubstituted C₁-C₃ alkyl and R₁₇ is H. In another embodiment of Formula (II), one of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is unsubstituted C₁-C₃ alkyl and the others are each H. In another embodiment of Formula (II), each of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is H.

5 In another embodiment of Formula (II), m is 1. In another embodiment of Formula (II), m is 2. In another embodiment of Formula (II), m is 3. In another embodiment of Formula (II), m is 4. In another embodiment of Formula (II), m is 1, 2 or 3. In another embodiment of Formula (II), m is 2, 3, or 4. In another embodiment of Formula (II), m is 1 or 2. In another embodiment of Formula (II), m is 3 or 4.

10 In another embodiment of Formula (II), Y is O and m is 1. In another embodiment of Formula (II), Y is O and m is 2. In another embodiment of Formula (II), Y is O and m is 3. In another embodiment of Formula (II), Y is O and m is 4. In another embodiment of Formula (II), Y is O and m is 1, 2, or 3. In another embodiment of Formula (II), Y is O and m is 2, 3, or 4. In another embodiment of Formula (II), Y is O and m is 1 or 2. In another
15 embodiment of Formula (II), Y is O and m is 3 or 4.

In another embodiment of Formula (II), Y is absent and m is 1. In another embodiment of Formula (II), Y is absent and m is 2. In another embodiment of Formula (II), Y is absent and m is 3. In another embodiment of Formula (II), Y is absent and m is 4. In another embodiment of Formula (II), Y is absent and m is 1, 2, or 3. In another embodiment
20 of Formula (II), Y is absent and m is 2, 3, or 4. In another embodiment of Formula (II), Y is absent and m is 1 or 2. In another embodiment of Formula (II), Y is absent and m is 3 or 4.

In another embodiment of Formula (II), Y is NR₁₀ and m is 1. In another embodiment of Formula (II), Y is NR₁₀ and m is 2. In another embodiment of Formula (II), Y is NR₁₀ and m is 3. In another embodiment of Formula (II), Y is NR₁₀ and m is 4. In another
25 embodiment of Formula (II), Y is NR₁₀ and m is 1, 2, or 3. In another embodiment of Formula (II), Y is NR₁₀ and m is 2, 3, or 4. In another embodiment of Formula (II), Y is NR₁₀ and m is 1 or 2. In another embodiment of Formula (II), Y is NR₁₀ and m is 3 or 4.

In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl and n is 1. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl and n is 2. In
30 another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl and n is 3. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl and n is 1. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl and n is 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl and n is 3. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heterocyclyl

and n is 1. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl and n is 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl and n is 3.

In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, and
5 Y is NR₁₀. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is O. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is O. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n
10 is 3, and Y is O. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is absent. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is absent. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is absent.

In another embodiment of Formula (II), fused ring A is 4- to 7-membered
15 heterocyclyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is O. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n
20 is 2, and Y is O. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is O. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is absent. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is absent. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is
25 absent.

In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is NR₁₀. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is NR₁₀. In another embodiment of
30 Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is O. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is O. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is O. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is absent. In another embodiment of Formula (II), fused ring A is 5-

to 8-membered heteroaryl, n is 2, and Y is absent. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is absent.

In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (II),

fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of
5 Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 3 or 4. In another
10 embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is
15 absent, and m is 3 or 4.

In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 1 or 2.
20 In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered
25 heteroaryl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 5- to 8-membered
30 heteroaryl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring

A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (II), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 1 or 2. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 1 or 2. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 1 or 2. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 1 or 2. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 3 or 4. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 3 or 4. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 3 or 4. In another embodiment of Formula (II), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 3 or 4.

In another embodiment of Formula (II), R₁, R₂, R₄, and R₅ are each H. In another embodiment of Formula (II), R₁, R₂, R₄, and R₅ are each H; and R₃ is H. In another embodiment of Formula (II), R₁, R₂, R₄, and R₅ are each H; R₃ is H; and R₆, R₇, R₈, R₉, and R₁₁ are each H. In another embodiment of Formula (II), R₁, R₂, R₄, and R₅ are each H; R₃ is H; R₆, R₇, R₈, R₉, and R₁₁ are each H; and R₁₂ and R₁₃ are each H.

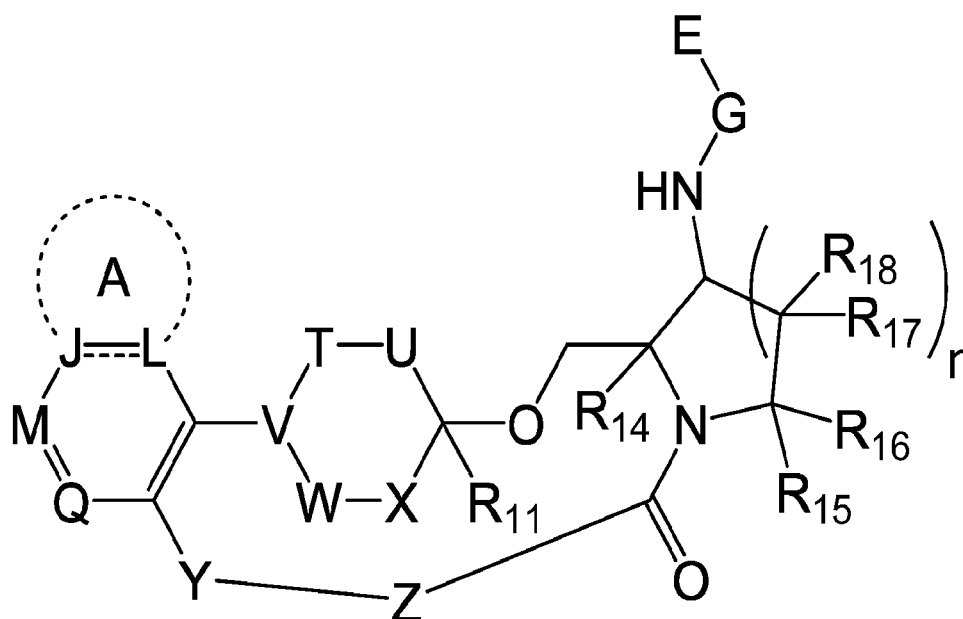
In another embodiment of Formula (II), one or more of R₁, R₂, R₄, and R₅ is fluorine. In another embodiment of Formula (II), one or more of R₁, R₂, R₄, and R₅ is deuterium. In another embodiment of Formula (II), one or more of R₆, R₇, R₈, R₉, and R₁₁ is fluorine. In another embodiment of Formula (II), one or more of R₆, R₇, R₈, R₉, and R₁₁ is deuterium. In another embodiment of Formula (II), one or more of each R₁₂ and R₁₃ is fluorine. In another embodiment of Formula (II), one or more of each R₁₂ and R₁₃ is deuterium.

In another embodiment of Formula (II), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and R₁₁ is H. In another embodiment of Formula (II), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, R₁₁ is H, and m is 1. In another embodiment of Formula (II), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (II), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 1. In another embodiment of Formula (II), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another

embodiment of Formula (II), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 1.

Each of the embodiments described herein with respect to compounds of Formula II also applies to compounds of Formula II-A.

5 Also provided herein is a compound having the structure of Formula III-A or a pharmaceutically acceptable salt thereof:



(III-A)

wherein:

10 fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

15 ----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

20 n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-

(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl),
 5 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxyl;

T is CR₁R₂ or O;

10 W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

15 Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

20 R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

25 or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

30 R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

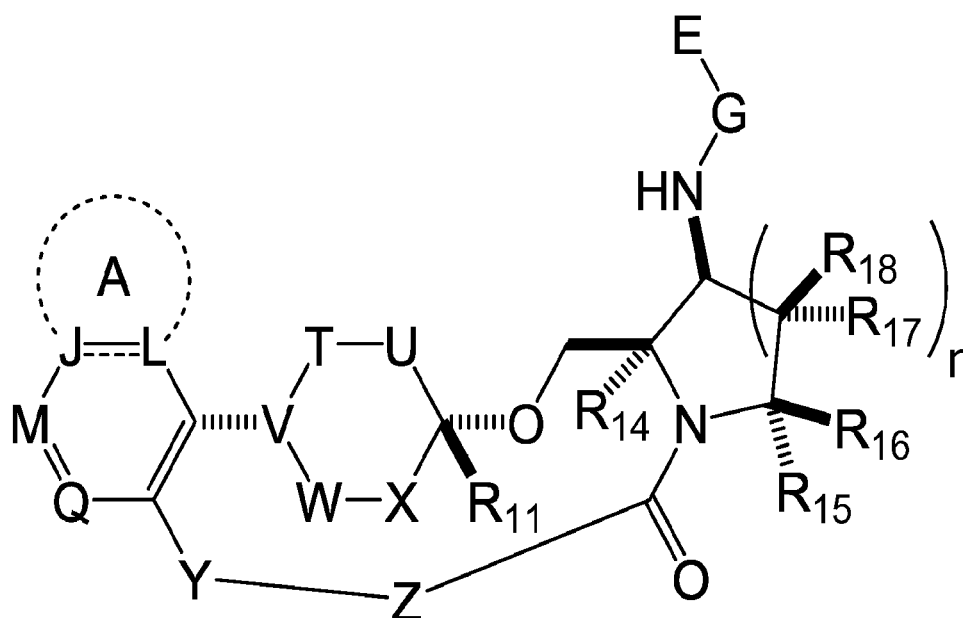
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula III-A having the structure of Formula III or a pharmaceutically acceptable salt thereof:



(III)

wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocycl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocycl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

- 5 E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

- 15 T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

- 20 Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

- 25 R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;
or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;
- R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and
30 cyano;
or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;
or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

5 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

10 each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

15 In one embodiment of Formula (III), n is 1. In another embodiment of Formula (III), n is 2. In another embodiment of Formula (III), n is 3.

In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl. In another embodiment of Formula (III), fused ring A is C₄-C₆ cycloalkyl. In another embodiment of Formula (III), fused ring A is C₄-C₅ cycloalkyl. In another embodiment of Formula (III),
20 fused ring A is 4- to 7-membered heterocyclyl. In another embodiment of Formula (III), fused ring A is 5- to 6-membered heterocyclyl. In another embodiment of Formula (III), fused ring A is 5-membered heterocyclyl. In another embodiment of Formula (III), fused ring A is 6-membered heterocyclyl. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl. In another embodiment of Formula (III), fused ring A is 5- to
25 6-membered heteroaryl. In another embodiment of Formula (III), fused ring A is 5-membered heteroaryl. In another embodiment of Formula (III), fused ring A is 6-membered heteroaryl.

In another embodiment of Formula (III), fused ring A is cyclopentyl. In another embodiment of Formula (III), fused ring A is cyclopentenyl. In another embodiment of
30 Formula (III), fused ring A is cyclohexyl. In another embodiment of Formula (III), fused ring A is cyclohexenyl. In another embodiment of Formula (III), fused ring A is pyrrolyl. In another embodiment of Formula (III), fused ring A is pyrazolyl. In another embodiment of Formula (III), fused ring A is 1-methylpyrazolyl. In another embodiment of Formula (III), fused ring A is imidazolyl. In another embodiment of Formula (III), fused ring A is

isoxazolyl. In another embodiment of Formula (III), fused ring A is tetrahydropyranyl. In another embodiment of Formula (III), fused ring A is tetrahydrofuranyl. In another embodiment of Formula (III), fused ring A is dihydropyranyl. In another embodiment of Formula (III), fused ring A is dihydrofuranyl.

5 In another embodiment of Formula (III), Y is NR₁₀. In another embodiment of Formula (III), Y is O. In another embodiment of Formula (III), Y is absent. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl and Y is O. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl and Y is absent. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl and Y is O. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl and Y is absent. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl and Y is O. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl and Y is absent.

In another embodiment of Formula (III), T is CR₁R₂. In another embodiment of Formula (III), T is O. In another embodiment of Formula (III), W is CR₄R₅. In another embodiment of Formula (III), W is O. In another embodiment of Formula (III), T is CR₁R₂ and W is CR₄R₅. In another embodiment of Formula (III), T is O and W is CR₄R₅. In another embodiment of Formula (III), T is CR₁R₂ and W is O.

In another embodiment of Formula (III), V is CR₃. In another embodiment of Formula (III), V is N.

25 In another embodiment of Formula (III), T is CR₁R₂ and V is CR₃. In another embodiment of Formula (III), T is O and V is CR₃. In another embodiment of Formula (III), T is CR₁R₂ and V is N. In another embodiment of Formula (III), T is O and V is N.

In another embodiment of Formula (III), W is CR₄R₅ and V is CR₃. In another embodiment of Formula (III), W is O and V is CR₃. In another embodiment of Formula (III), W is CR₄R₅ and V is N. In another embodiment of Formula (III), W is O and V is N.

30 In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, and V is CR₃. In another embodiment of Formula (III), T is CR₁R₂, W is O, and V is CR₃. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, and V is N. In another embodiment of Formula (III), T is CR₁R₂, W is O, and V is N. In another embodiment of Formula (III), T is O, W is CR₄R₅, and V is CR₃.

In another embodiment of Formula (III), E is H. In another embodiment of Formula (III), E is hydroxyl. In another embodiment of Formula (III), E is NR_aR_b . In another embodiment of Formula (III), E is $\text{C}(=\text{O})\text{NR}_a\text{R}_b$. In another embodiment of Formula (III), E is $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b . In another embodiment of Formula (III), E is unsubstituted $\text{C}_1\text{-C}_3$ alkyl, unsubstituted $\text{C}_2\text{-C}_4$ alkenyl or unsubstituted $\text{C}_2\text{-C}_4$ alkynyl. In another embodiment of Formula (III), E is $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl or $\text{C}_2\text{-C}_4$ alkynyl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted $\text{C}_1\text{-C}_3$ alkyl. In another embodiment of Formula (III), E is $\text{C}_1\text{-C}_3$ alkyl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted $\text{C}_3\text{-C}_8$ cycloalkyl. In another embodiment of Formula (III), E is $\text{C}_3\text{-C}_8$ cycloalkyl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl). In another embodiment of Formula (III), E is $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl) substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted 4- to 10-membered heterocycl. In another embodiment of Formula (III), E is 4- to 10-membered heterocycl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocycl). In another embodiment of Formula (III), E is $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocycl) substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted $\text{C}_6\text{-C}_{10}$ aryl. In another embodiment of Formula (III), E is $\text{C}_6\text{-C}_{10}$ aryl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl). In another embodiment of Formula (III), E is $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl) substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted 5- to 10-membered heteroaryl. In another embodiment of Formula (III), E is 5- to 10-membered heteroaryl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy.

In another embodiment of Formula (III), E is unsubstituted 4- to 7-membered heterocycl. In another embodiment of Formula (III), E is 4- to 7-membered heterocycl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula (III), E is unsubstituted 4- to 6-membered heterocycl. In another embodiment of Formula (III), E is 4- to 6-membered heterocycl substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy. In another embodiment of Formula

(III), E is unsubstituted 4-membered heterocyclyl. In another embodiment of Formula (III), E is 4-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is unsubstituted 5-membered heterocyclyl. In another embodiment of Formula (III), E is 5-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is unsubstituted 6-membered heterocyclyl. In another embodiment of Formula (III), E is 6-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (III), E is NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (III), E is C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (III), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (III), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), wherein the C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈

cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (III), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), wherein the C₁-C₃ alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (III), E is methyl, wherein the methyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is methyl. In another embodiment of Formula (III), E is trifluoromethyl. In another embodiment of Formula (III), E is dioxanyl, wherein the dioxanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is tetrahydropyranyl, wherein the tetrahydropyranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is tetrahydrofuranyl, wherein the tetrahydrofuranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is azetidiny, wherein the azetidiny is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is oxetanyl, wherein the oxetanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (III), E is morpholinyl, wherein the morpholinyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (III), R₁₄ is H. In another embodiment of Formula (III), R₁₄ is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (III), R₁₅ and R₁₆ are each H. In another embodiment of Formula (III), R₁₅ is unsubstituted C₁-C₃ alkyl and R₁₆ is H. In another embodiment of Formula (III), R₁₆ is unsubstituted C₁-C₃ alkyl and R₁₅ is H. In another embodiment of Formula (III), each R₁₇ and R₁₈ is H. In another embodiment of Formula (III), R₁₇ is unsubstituted C₁-C₃ alkyl and R₁₈ is H. In another embodiment of Formula (III), R₁₈ is unsubstituted C₁-C₃ alkyl and R₁₇ is H. In another embodiment of Formula (III), one of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is unsubstituted C₁-C₃ alkyl and the others are each H. In another embodiment of Formula (III), each of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is H.

In another embodiment of Formula (III), m is 1. In another embodiment of Formula (III), m is 2. In another embodiment of Formula (III), m is 3. In another embodiment of

Formula (III), m is 4. In another embodiment of Formula (III), m is 1, 2 or 3. In another embodiment of Formula (III), m is 2, 3, or 4. In another embodiment of Formula (III), m is 1 or 2. In another embodiment of Formula (III), m is 3 or 4.

In another embodiment of Formula (III), Y is O and m is 1. In another embodiment of Formula (III), Y is O and m is 2. In another embodiment of Formula (III), Y is O and m is 3. In another embodiment of Formula (III), Y is O and m is 4. In another embodiment of Formula (III), Y is O and m is 1, 2, or 3. In another embodiment of Formula (III), Y is O and m is 2, 3, or 4. In another embodiment of Formula (III), Y is O and m is 1 or 2. In another embodiment of Formula (III), Y is O and m is 3 or 4.

In another embodiment of Formula (III), Y is absent and m is 1. In another embodiment of Formula (III), Y is absent and m is 2. In another embodiment of Formula (III), Y is absent and m is 3. In another embodiment of Formula (III), Y is absent and m is 4. In another embodiment of Formula (III), Y is absent and m is 1, 2, or 3. In another embodiment of Formula (III), Y is absent and m is 2, 3, or 4. In another embodiment of Formula (III), Y is absent and m is 1 or 2. In another embodiment of Formula (III), Y is absent and m is 3 or 4.

In another embodiment of Formula (III), Y is NR₁₀ and m is 1. In another embodiment of Formula (III), Y is NR₁₀ and m is 2. In another embodiment of Formula (III), Y is NR₁₀ and m is 3. In another embodiment of Formula (III), Y is NR₁₀ and m is 4. In another embodiment of Formula (III), Y is NR₁₀ and m is 1, 2, or 3. In another embodiment of Formula (III), Y is NR₁₀ and m is 2, 3, or 4. In another embodiment of Formula (III), Y is NR₁₀ and m is 1 or 2. In another embodiment of Formula (III), Y is NR₁₀ and m is 3 or 4.

In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl and n is 1. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl and n is 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl and n is 3. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl and n is 1. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl and n is 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl and n is 3. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl and n is 1. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl and n is 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl and n is 3.

In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2,

and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is O. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is O. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is O. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is absent. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is absent. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is absent.

In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is O. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is O. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is O. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is absent. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is absent. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is absent.

In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is NR₁₀. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is O. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is O. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is O. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is absent. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is absent. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is absent.

In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused

ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 3 or

4. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 3 or 4. In
5 another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 4- to 7-membered heterocyclyl,
10 n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 1 or 2.
15 In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is
20 absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 1 or 2. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 5- to 8-
25 membered heteroaryl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula
30 (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (III), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 1 or 2. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 1 or 2. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 1 or 2. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 1 or 2. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 3 or 4. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 3 or 4. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 3 or 4. In another embodiment of Formula (III), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 3 or 4.

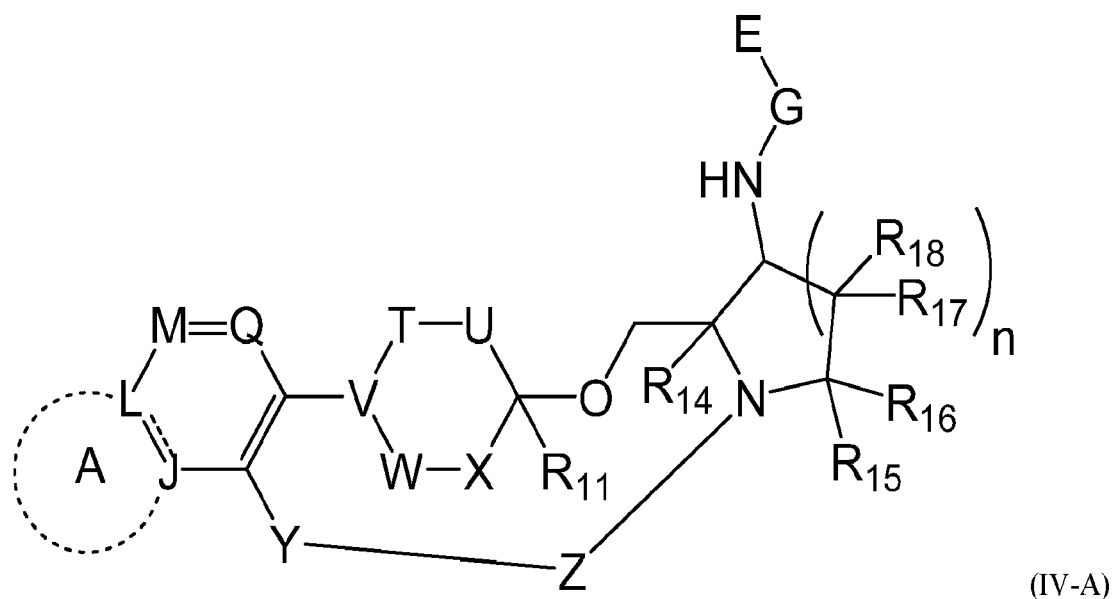
In another embodiment of Formula (III), R₁, R₂, R₄, and R₅ are each H. In another embodiment of Formula (III), R₁, R₂, R₄, and R₅ are each H; and R₃ is H. In another embodiment of Formula (III), R₁, R₂, R₄, and R₅ are each H; R₃ is H; and R₆, R₇, R₈, R₉, and R₁₁ are each H. In another embodiment of Formula (III), R₁, R₂, R₄, and R₅ are each H; R₃ is H; R₆, R₇, R₈, R₉, and R₁₁ are each H; and R₁₂ and R₁₃ are each H.

In another embodiment of Formula (III), one or more of R₁, R₂, R₄, and R₅ is fluorine. In another embodiment of Formula (III), one or more of R₁, R₂, R₄, and R₅ is deuterium. In another embodiment of Formula (III), one or more of R₆, R₇, R₈, R₉, and R₁₁ is fluorine. In another embodiment of Formula (III), one or more of R₆, R₇, R₈, R₉, and R₁₁ is deuterium. In another embodiment of Formula (III), one or more of each R₁₂ and R₁₃ is fluorine. In another embodiment of Formula (III), one or more of each R₁₂ and R₁₃ is deuterium.

In another embodiment of Formula (III), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and R₁₁ is H. In another embodiment of Formula (III), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, R₁₁ is H, and m is 1. In another embodiment of Formula (III), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (III), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 1. In another embodiment of Formula (III), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (III), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 1.

Each of the embodiments described herein with respect to compounds of Formula III also applies to compounds of Formula III-A.

Also provided herein is a compound having the structure of Formula IV-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

===== is a single bond or double bond:

J and L are each, independently, C or N;

10 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b , $\text{C}(=\text{O})\text{NR}_a\text{R}_b$, $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene- $(\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene- $(\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, and $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl), wherein the $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene- $(\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene- $(\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, or $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

5 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

10 m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

15 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

20 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

25 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

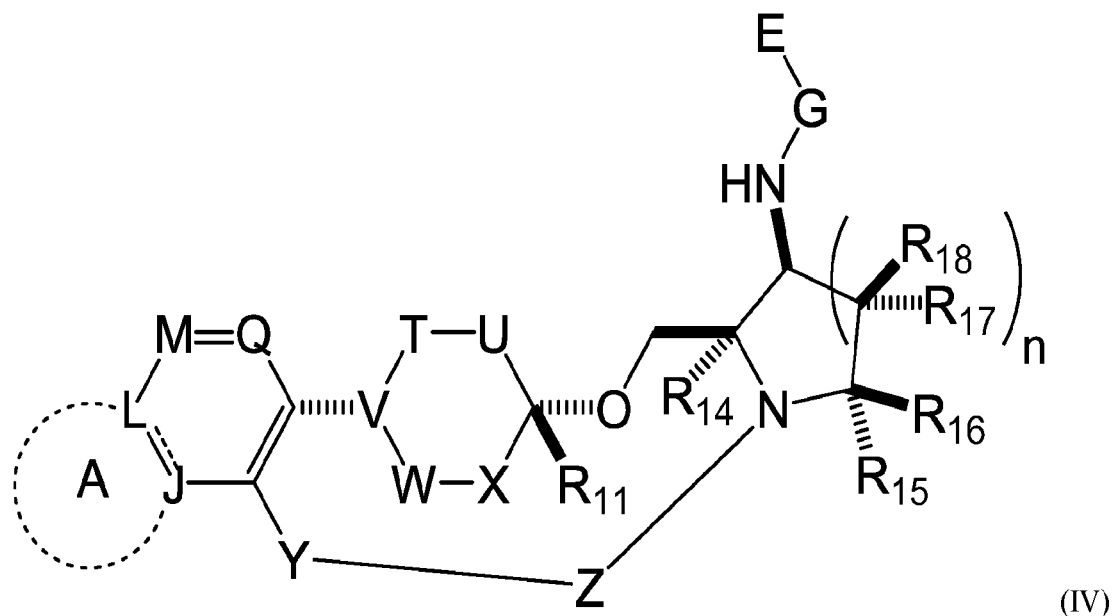
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

30 R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula IV-A having the structure of Formula IV or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocycl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocycl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocycl, C₁-C₃ alkylene-(4- to 10-membered heterocycl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and

C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

10 X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

15 m is 2, 3, 4, or 5 when Y is absent; or

m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

20 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

25 or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

30 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

5 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In one embodiment of Formula (IV), n is 1. In another embodiment of Formula (IV), n is 2. In another embodiment of Formula (IV), n is 3.

10 In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl. In another embodiment of Formula (IV), fused ring A is C₄-C₆ cycloalkyl. In another embodiment of Formula (IV), fused ring A is C₄-C₅ cycloalkyl. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl. In another embodiment of Formula (IV), fused ring A is 5- to 6-membered heterocyclyl. In another embodiment of Formula (IV),
15 fused ring A is 5-membered heterocyclyl. In another embodiment of Formula (IV), fused ring A is 6-membered heterocyclyl. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl. In another embodiment of Formula (IV), fused ring A is 5- to 6-membered heteroaryl. In another embodiment of Formula (IV), fused ring A is 6-membered heteroaryl.
20 heteroaryl.

In another embodiment of Formula (IV), fused ring A is cyclopentyl. In another embodiment of Formula (IV), fused ring A is cyclopentenyl. In another embodiment of Formula (IV), fused ring A is cyclohexyl. In another embodiment of Formula (IV), fused ring A is cyclohexenyl. In another embodiment of Formula (IV), fused ring A is pyrrolyl. In
25 another embodiment of Formula (IV), fused ring A is pyrazolyl. In another embodiment of Formula (IV), fused ring A is 1-methylpyrazolyl. In another embodiment of Formula (IV), fused ring A is imidazolyl. In another embodiment of Formula (IV), fused ring A is isoxazolyl. In another embodiment of Formula (IV), fused ring A is tetrahydropyranyl. In another embodiment of Formula (IV), fused ring A is tetrahydrofuranyl. In another
30 embodiment of Formula (IV), fused ring A is dihydropyranyl. In another embodiment of Formula (IV), fused ring A is dihydrofuranyl.

In another embodiment of Formula (IV), Y is NR₁₀. In another embodiment of Formula (IV), Y is O. In another embodiment of Formula (IV), Y is absent. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl and Y is NR₁₀. In

another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl and Y is O. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl and Y is absent. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl and Y is O. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl and Y is absent. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl and Y is O. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl and Y is absent.

10 In another embodiment of Formula (IV), T is CR₁R₂. In another embodiment of Formula (IV), T is O. In another embodiment of Formula (IV), W is CR₄R₅. In another embodiment of Formula (IV), W is O. In another embodiment of Formula (IV), T is CR₁R₂ and W is CR₄R₅. In another embodiment of Formula (IV), T is O and W is CR₄R₅. In another embodiment of Formula (IV), T is CR₁R₂ and W is O.

15 In another embodiment of Formula (IV), V is CR₃. In another embodiment of Formula (IV), V is N.

In another embodiment of Formula (IV), T is CR₁R₂ and V is CR₃. In another embodiment of Formula (IV), T is O and V is CR₃. In another embodiment of Formula (IV), T is CR₁R₂ and V is N. In another embodiment of Formula (IV), T is O and V is N.

20 In another embodiment of Formula (IV), W is CR₄R₅ and V is CR₃. In another embodiment of Formula (IV), W is O and V is CR₃. In another embodiment of Formula (IV), W is CR₄R₅ and V is N. In another embodiment of Formula (IV), W is O and V is N.

In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, and V is CR₃. In another embodiment of Formula (IV), T is CR₁R₂, W is O, and V is CR₃. In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, and V is N. In another embodiment of Formula (IV), T is CR₁R₂, W is O, and V is N. In another embodiment of Formula (IV), T is O, W is CR₄R₅, and V is CR₃.

25 In another embodiment of Formula (IV), E is H. In another embodiment of Formula (IV), E is hydroxyl. In another embodiment of Formula (IV), E is NR_aR_b. In another embodiment of Formula (IV), E is C(=O)NR_aR_b. In another embodiment of Formula (IV), E is C₁-C₃ alkylene-NR_aR_b. In another embodiment of Formula (IV), E is unsubstituted C₁-C₃ alkyl, unsubstituted C₂-C₄ alkenyl or unsubstituted C₂-C₄ alkynyl. In another embodiment of Formula (IV), E is C₁-C₃ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E

is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (IV), E is C₁-C₃ alkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted C₃-C₈ cycloalkyl. In another embodiment of Formula (IV), E is C₃-C₈ cycloalkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted C₁-C₃ alkylene-(C₃-C₈ cycloalkyl). In another embodiment of Formula (IV), E is C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted 4- to 10-membered heterocycl. In another embodiment of Formula (IV), E is 4- to 10-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted C₁-C₃ alkylene-(4- to 10-membered heterocycl). In another embodiment of Formula (IV), E is C₁-C₃ alkylene-(4- to 10-membered heterocycl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted C₆-C₁₀ aryl. In another embodiment of Formula (IV), E is C₆-C₁₀ aryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted C₁-C₃ alkylene-(C₆-C₁₀ aryl). In another embodiment of Formula (IV), E is C₁-C₃ alkylene-(C₆-C₁₀ aryl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted 5- to 10-membered heteroaryl. In another embodiment of Formula (IV), E is 5- to 10-membered heteroaryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), E is unsubstituted 4- to 7-membered heterocycl. In another embodiment of Formula (IV), E is 4- to 7-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted 4- to 6-membered heterocycl. In another embodiment of Formula (IV), E is 4- to 6-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted 4-membered heterocycl. In another embodiment of Formula (IV), E is 4-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted 5-membered heterocycl. In another embodiment of Formula (IV), E is 5-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is unsubstituted 6-membered heterocycl. In another

embodiment of Formula (IV), E is 6-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), E is NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), E is C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-

(C₃-C₈ cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), E is methyl, wherein the methyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is methyl. In another embodiment of Formula (IV), E is trifluoromethyl. In another embodiment of Formula (IV), E is dioxanyl, wherein the dioxanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is tetrahydropyranyl, wherein the tetrahydropyranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is tetrahydrofuranyl, wherein the tetrahydrofuranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is azetidiny, wherein the azetidiny is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is oxetanyl, wherein the oxetanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (IV), E is morpholinyl, wherein the morpholinyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (IV), R₁₄ is H. In another embodiment of Formula (IV), R₁₄ is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (IV), R₁₅ and R₁₆ are each H. In another embodiment of Formula (IV), R₁₅ is unsubstituted C₁-C₃ alkyl and R₁₆ is H. In another embodiment of Formula (IV), R₁₆ is unsubstituted C₁-C₃ alkyl and R₁₅ is H. In another embodiment of Formula (IV), each R₁₇ and R₁₈ is H. In another embodiment of Formula (IV), R₁₇ is unsubstituted C₁-C₃ alkyl and R₁₈ is H. In another embodiment of Formula (IV), R₁₈ is unsubstituted C₁-C₃ alkyl and R₁₇ is H. In another embodiment of Formula (IV), one of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is unsubstituted C₁-C₃ alkyl and the others are each H. In another embodiment of Formula (IV), each of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is H.

In another embodiment of Formula (IV), m is 1. In another embodiment of Formula (IV), m is 2. In another embodiment of Formula (IV), m is 3. In another embodiment of Formula (IV), m is 4. In another embodiment of Formula (IV), m is 1, 2 or 3. In another embodiment of Formula (IV), m is 2, 3, or 4. In another embodiment of Formula (IV), m is 1 or 2. In another embodiment of Formula (IV), m is 3 or 4.

In another embodiment of Formula (IV), Y is O and m is 1. In another embodiment of Formula (IV), Y is O and m is 2. In another embodiment of Formula (IV), Y is O and m is

3. In another embodiment of Formula (IV), Y is O and m is 4. In another embodiment of Formula (IV), Y is O and m is 1, 2, or 3. In another embodiment of Formula (IV), Y is O and m is 2, 3, or 4. In another embodiment of Formula (IV), Y is O and m is 1 or 2. In another embodiment of Formula (IV), Y is O and m is 3 or 4.

5 In another embodiment of Formula (IV), Y is absent and m is 2. In another embodiment of Formula (IV), Y is absent and m is 3. In another embodiment of Formula (IV), Y is absent and m is 4. In another embodiment of Formula (IV), Y is absent and m is 2, 3, or 4. In another embodiment of Formula (IV), Y is absent and m is 2 or 3. In another embodiment of Formula (IV), Y is absent and m is 3 or 4.

10 In another embodiment of Formula (IV), Y is NR₁₀ and m is 1. In another embodiment of Formula (IV), Y is NR₁₀ and m is 2. In another embodiment of Formula (IV), Y is NR₁₀ and m is 3. In another embodiment of Formula (IV), Y is NR₁₀ and m is 4. In another embodiment of Formula (IV), Y is NR₁₀ and m is 1, 2, or 3. In another embodiment of Formula (IV), Y is NR₁₀ and m is 2, 3, or 4. In another embodiment of Formula (IV), Y is NR₁₀ and m is 1 or 2. In another embodiment of Formula (IV), Y is NR₁₀ and m is 3 or 4.

15 In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl and n is 1. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl and n is 2. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl and n is 3. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl and n is 1. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl and n is 2. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl and n is 3. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl and n is 1. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl and n is 2. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl and n is 3.

25 In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is O. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is O. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is O. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is absent. In another embodiment of Formula (IV), fused ring A is

C₄-C₈ cycloalkyl, n is 2, and Y is absent. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is absent.

In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is O. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is O. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is O. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is absent. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is absent. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is absent.

In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is NR₁₀. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is O. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is O. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is O. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is absent. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is absent. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is absent.

In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is C₄-C₈

cycloalkyl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula

(IV), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 3 or 4.

5 In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (IV), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 3 or 4.

20 In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 1 or 2. In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 1 or 2. In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 1 or 2. In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 1 or 2. In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 3 or 4. In another

embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 3 or 4. In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 3 or 4. In another embodiment of Formula (IV), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 3 or 4.

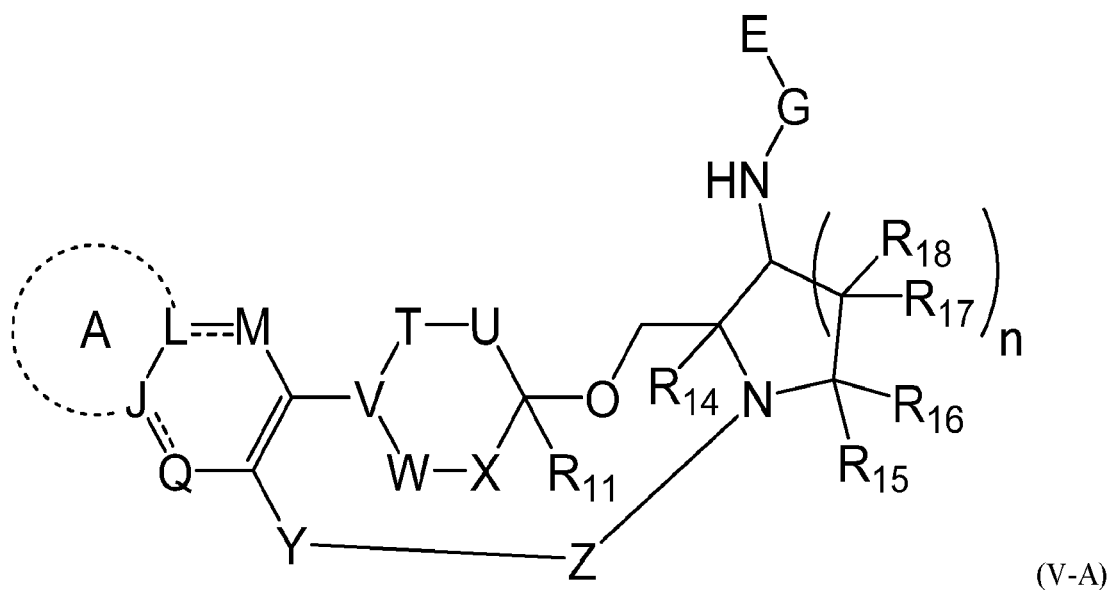
5 In another embodiment of Formula (IV), R₁, R₂, R₄, and R₅ are each H. In another embodiment of Formula (IV), R₁, R₂, R₄, and R₅ are each H; and R₃ is H. In another embodiment of Formula (IV), R₁, R₂, R₄, and R₅ are each H; R₃ is H; and R₆, R₇, R₈, R₉, and R₁₁ are each H. In another embodiment of Formula (IV), R₁, R₂, R₄, and R₅ are each H; R₃ is H; R₆, R₇, R₈, R₉, and R₁₁ are each H; and R₁₂ and R₁₃ are each H.

10 In another embodiment of Formula (IV), one or more of R₁, R₂, R₄, and R₅ is fluorine. In another embodiment of Formula (IV), one or more of R₁, R₂, R₄, and R₅ is deuterium. In another embodiment of Formula (IV), one or more of R₆, R₇, R₈, R₉, and R₁₁ is fluorine. In another embodiment of Formula (IV), one or more of R₆, R₇, R₈, R₉, and R₁₁ is deuterium. In another embodiment of Formula (IV), one or more of each R₁₂ and R₁₃ is fluorine. In another
15 embodiment of Formula (IV), one or more of each R₁₂ and R₁₃ is deuterium.

 In another embodiment of Formula (IV), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and R₁₁ is H. In another embodiment of Formula (IV), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, R₁₁ is H, and m is 2. In another embodiment of Formula (IV), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment
20 of Formula (IV), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 2. In another embodiment of Formula (IV), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (IV), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 2.

25 Each of the embodiments described herein with respect to compounds of Formula IV also applies to compounds of Formula IV-A.

 Also provided herein is a compound having the structure of Formula V-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

10 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

5 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

10 m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

15 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

20 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

25 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

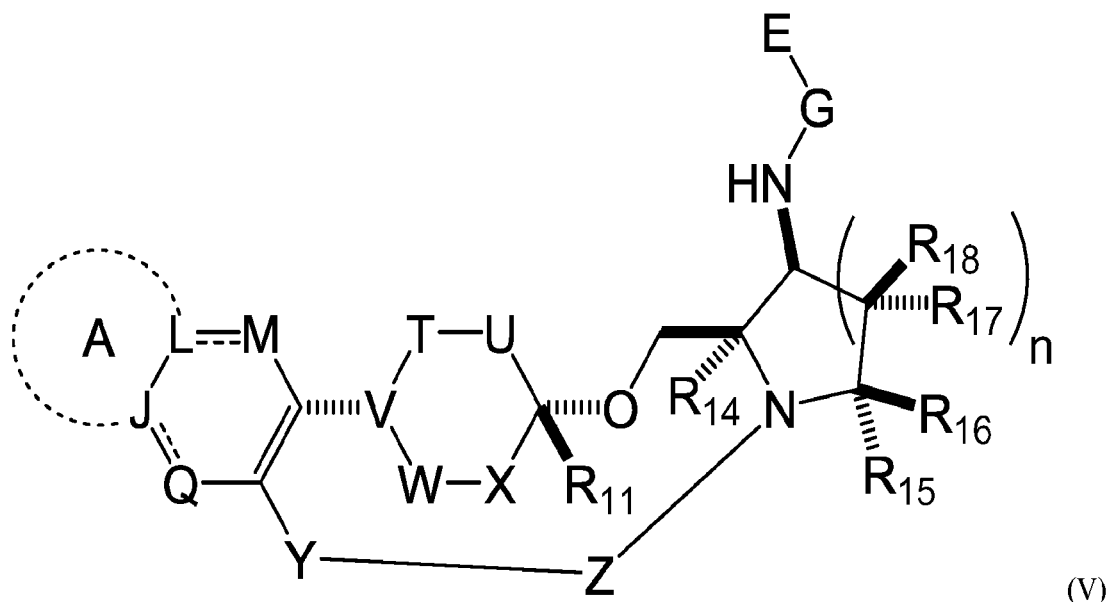
each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

30 R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula V-A having the structure of Formula V or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-

C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,

5 C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

10 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

15 m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

20 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

25 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

30 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

5 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In one embodiment of Formula (V), n is 1. In another embodiment of Formula (V), n is 2. In another embodiment of Formula (V), n is 3.

10 In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl. In another embodiment of Formula (V), fused ring A is C₄-C₆ cycloalkyl. In another embodiment of Formula (V), fused ring A is C₄-C₅ cycloalkyl. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl. In another embodiment of Formula (V), fused ring A is 5- to 6-membered heterocyclyl. In another embodiment of Formula (V), fused ring A is 5-membered heterocyclyl. In another embodiment of Formula (V), fused ring A is 6-membered heterocyclyl. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl. In another embodiment of Formula (V), fused ring A is 5- to 6-membered heteroaryl. In another embodiment of Formula (V), fused ring A is 5-membered heteroaryl. In another embodiment of Formula (V), fused ring A is 6-membered heteroaryl.

20 In another embodiment of Formula (V), fused ring A is cyclopentyl. In another embodiment of Formula (V), fused ring A is cyclopentenyl. In another embodiment of Formula (V), fused ring A is cyclohexyl. In another embodiment of Formula (V), fused ring A is cyclohexenyl. In another embodiment of Formula (V), fused ring A is pyrrolyl. In another embodiment of Formula (V), fused ring A is pyrazolyl. In another embodiment of Formula (V), fused ring A is 1-methylpyrazolyl. In another embodiment of Formula (V), fused ring A is imidazolyl. In another embodiment of Formula (V), fused ring A is isoxazolyl. In another embodiment of Formula (V), fused ring A is tetrahydropyranyl. In another embodiment of Formula (V), fused ring A is tetrahydrofuranyl. In another embodiment of Formula (V), fused ring A is dihydropyranyl. In another embodiment of Formula (V), fused ring A is dihydrofuranyl.

In another embodiment of Formula (V), Y is NR₁₀. In another embodiment of Formula (V), Y is O. In another embodiment of Formula (V), Y is absent. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl and Y is O.

In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl and Y is absent. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl and Y is O. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl and Y is absent. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl and Y is O. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl and Y is absent.

In another embodiment of Formula (V), T is CR₁R₂. In another embodiment of Formula (V), T is O. In another embodiment of Formula (V), W is CR₄R₅. In another embodiment of Formula (V), W is O. In another embodiment of Formula (V), T is CR₁R₂ and W is CR₄R₅. In another embodiment of Formula (V), T is O and W is CR₄R₅. In another embodiment of Formula (V), T is CR₁R₂ and W is O.

In another embodiment of Formula (V), V is CR₃. In another embodiment of Formula (V), V is N.

In another embodiment of Formula (V), T is CR₁R₂ and V is CR₃. In another embodiment of Formula (V), T is O and V is CR₃. In another embodiment of Formula (V), T is CR₁R₂ and V is N. In another embodiment of Formula (V), T is O and V is N.

In another embodiment of Formula (V), W is CR₄R₅ and V is CR₃. In another embodiment of Formula (V), W is O and V is CR₃. In another embodiment of Formula (V), W is CR₄R₅ and V is N. In another embodiment of Formula (V), W is O and V is N.

In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, and V is CR₃. In another embodiment of Formula (V), T is CR₁R₂, W is O, and V is CR₃. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, and V is N. In another embodiment of Formula (V), T is CR₁R₂, W is O, and V is N. In another embodiment of Formula (V), T is O, W is CR₄R₅, and V is CR₃.

In another embodiment of Formula (V), E is H. In another embodiment of Formula (V), E is hydroxyl. In another embodiment of Formula (V), E is NR_aR_b. In another embodiment of Formula (V), E is C(=O)NR_aR_b. In another embodiment of Formula (V), E is C₁-C₃ alkylene-NR_aR_b. In another embodiment of Formula (V), E is unsubstituted C₁-C₃ alkyl, unsubstituted C₂-C₄ alkenyl or unsubstituted C₂-C₄ alkynyl. In another embodiment of Formula (V), E is C₁-C₃ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (V), E is C₁-C₃ alkyl

substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted C₃-C₈ cycloalkyl. In another embodiment of Formula (V), E is C₃-C₈ cycloalkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted C₁-C₃ alkylene-(C₃-C₈ cycloalkyl). In another embodiment of Formula (V), E is C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted 4- to 10-membered heterocycl. In another embodiment of Formula (V), E is 4- to 10-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted C₁-C₃ alkylene-(4- to 10-membered heterocycl). In another embodiment of Formula (V), E is C₁-C₃ alkylene-(4- to 10-membered heterocycl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted C₆-C₁₀ aryl. In another embodiment of Formula (V), E is C₆-C₁₀ aryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted C₁-C₃ alkylene-(C₆-C₁₀ aryl). In another embodiment of Formula (V), E is C₁-C₃ alkylene-(C₆-C₁₀ aryl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted 5- to 10-membered heteroaryl. In another embodiment of Formula (V), E is 5- to 10-membered heteroaryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (V), E is unsubstituted 4- to 7-membered heterocycl. In another embodiment of Formula (V), E is 4- to 7-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted 4- to 6-membered heterocycl. In another embodiment of Formula (V), E is 4- to 6-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted 4-membered heterocycl. In another embodiment of Formula (V), E is 4-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted 5-membered heterocycl. In another embodiment of Formula (V), E is 5-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is unsubstituted 6-membered heterocycl. In another embodiment of Formula (V), E is 6-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (V), E is NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (V), E is C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (V), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (V), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

30 In another embodiment of Formula (V), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (V), E is methyl, wherein the methyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is methyl. In another embodiment of Formula (V), E is trifluoromethyl. In another embodiment of Formula (V), E is dioxanyl, wherein the dioxanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is tetrahydropyranyl, wherein the tetrahydropyranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is tetrahydrofuranyl, wherein the tetrahydrofuranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is azetidiny, wherein the azetidiny is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is oxetanyl, wherein the oxetanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (V), E is morpholinyl, wherein the morpholinyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (V), R₁₄ is H. In another embodiment of Formula (V), R₁₄ is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (V), R₁₅ and R₁₆ are each H. In another embodiment of Formula (V), R₁₅ is unsubstituted C₁-C₃ alkyl and R₁₆ is H. In another embodiment of Formula (V), R₁₆ is unsubstituted C₁-C₃ alkyl and R₁₅ is H. In another embodiment of Formula (V), each R₁₇ and R₁₈ is H. In another embodiment of Formula (V), R₁₇ is unsubstituted C₁-C₃ alkyl and R₁₈ is H. In another embodiment of Formula (V), R₁₈ is unsubstituted C₁-C₃ alkyl and R₁₇ is H. In another embodiment of Formula (V), one of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is unsubstituted C₁-C₃ alkyl and the others are each H. In another embodiment of Formula (V), each of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is H.

In another embodiment of Formula (V), m is 1. In another embodiment of Formula (V), m is 2. In another embodiment of Formula (V), m is 3. In another embodiment of Formula (V), m is 4. In another embodiment of Formula (V), m is 1, 2 or 3. In another embodiment of Formula (V), m is 2, 3, or 4. In another embodiment of Formula (V), m is 1 or 2. In another embodiment of Formula (V), m is 3 or 4.

In another embodiment of Formula (V), Y is O and m is 1. In another embodiment of Formula (V), Y is O and m is 2. In another embodiment of Formula (V), Y is O and m is 3. In another embodiment of Formula (V), Y is O and m is 4. In another embodiment of Formula (V), Y is O and m is 1, 2, or 3. In another embodiment of Formula (V), Y is O and

m is 2, 3, or 4. In another embodiment of Formula (V), Y is O and m is 1 or 2. In another embodiment of Formula (V), Y is O and m is 3 or 4.

In another embodiment of Formula (V), Y is absent and m is 2. In another embodiment of Formula (V), Y is absent and m is 3. In another embodiment of Formula (V), Y is absent and m is 4. In another embodiment of Formula (V), Y is absent and m is 5. In another embodiment of Formula (V), Y is absent and m is 2, 3, or 4. In another embodiment of Formula (V), Y is absent and m is 2 or 3. In another embodiment of Formula (V), Y is absent and m is 4 or 5.

In another embodiment of Formula (V), Y is NR₁₀ and m is 1. In another embodiment of Formula (V), Y is NR₁₀ and m is 2. In another embodiment of Formula (V), Y is NR₁₀ and m is 3. In another embodiment of Formula (V), Y is NR₁₀ and m is 4. In another embodiment of Formula (V), Y is NR₁₀ and m is 1, 2, or 3. In another embodiment of Formula (V), Y is NR₁₀ and m is 2, 3, or 4. In another embodiment of Formula (V), Y is NR₁₀ and m is 1 or 2. In another embodiment of Formula (V), Y is NR₁₀ and m is 3 or 4.

In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl and n is 1. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl and n is 2. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl and n is 3. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl and n is 1. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl and n is 2. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl and n is 3. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl and n is 1. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl and n is 2. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl and n is 3.

In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is O. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is O. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is O. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is absent. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is absent. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is absent.

In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is NR₁₀. In another
5 embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is O. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is O. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is O. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is absent. In another
10 embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is absent. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is absent.

In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is 5- to 8-
15 membered heteroaryl, n is 2, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is NR₁₀. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is O. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is O. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3,
20 and Y is O. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is absent. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is absent. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is absent.

In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is
25 NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 1 or 2. In another
embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 1 or 2.
30 In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of

Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 3 or 4. In another

embodiment of Formula (V), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (V), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 1 or 2. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 1 or 2. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 1 or 2. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 1 or 2. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 3 or 4. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 3 or 4. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2,

and m is 3 or 4. In another embodiment of Formula (V), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 3 or 4.

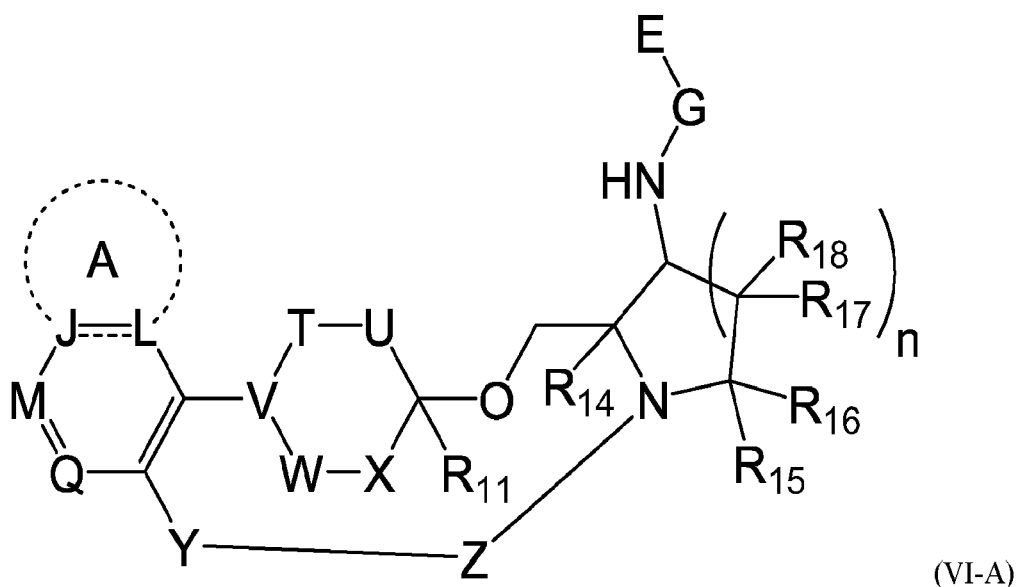
In another embodiment of Formula (V), R₁, R₂, R₄, and R₅ are each H. In another embodiment of Formula (V), R₁, R₂, R₄, and R₅ are each H; and R₃ is H. In another
5 embodiment of Formula (V), R₁, R₂, R₄, and R₅ are each H; R₃ is H; and R₆, R₇, R₈, R₉, and R₁₁ are each H. In another embodiment of Formula (V), R₁, R₂, R₄, and R₅ are each H; R₃ is H; R₆, R₇, R₈, R₉, and R₁₁ are each H; and R₁₂ and R₁₃ are each H.

In another embodiment of Formula (V), one or more of R₁, R₂, R₄, and R₅ is fluorine. In another embodiment of Formula (V), one or more of R₁, R₂, R₄, and R₅ is deuterium. In
10 another embodiment of Formula (V), one or more of R₆, R₇, R₈, R₉, and R₁₁ is fluorine. In another embodiment of Formula (V), one or more of R₆, R₇, R₈, R₉, and R₁₁ is deuterium. In another embodiment of Formula (V), one or more of each R₁₂ and R₁₃ is fluorine. In another embodiment of Formula (V), one or more of each R₁₂ and R₁₃ is deuterium.

In another embodiment of Formula (V), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅,
15 and R₁₁ is H. In another embodiment of Formula (V), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, R₁₁ is H, and m is 2. In another embodiment of Formula (V), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (V), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 2. In another embodiment of Formula (V), Y is O, T is CR₁R₂, V is
20 CR₃, W is CR₄R₅, and each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (V), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 2.

Each of the embodiments described herein with respect to compounds of Formula V also applies to compounds of Formula V-A.

25 Also provided herein is a compound having the structure of Formula VI-A or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

10 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR_1R_2 or O;

W is CR_4R_5 or O;

U is CR_6R_7 ;

X is CR_8R_9 ;

5 V is CR_3 or N;

Y is NR_{10} , O or absent;

Z is $(\text{CR}_{12}\text{R}_{13})_m$;

R_a and R_b are each, independently, H or unsubstituted $\text{C}_1\text{-C}_3$ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

10 m is 1, 2, 3, or 4 when Y is NR_{10} or O;

and further wherein:

R_1 , R_2 , R_4 , and R_5 are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

15 or, alternatively, R_2 and R_5 together with the carbon atoms to which they are attached, form a single bond;

R_3 is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R_3 and R_1 , together with the carbon atoms to which they are attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

20 or, alternatively, R_3 and R_4 , together with the carbon atoms to which they are attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

R_6 , R_7 , R_8 , R_9 , and R_{11} are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

25 R_{10} is selected from the group consisting of H, unsubstituted $\text{C}_1\text{-C}_3$ alkyl, and $\text{C}_1\text{-C}_3$ alkyl substituted with one or more halogen;

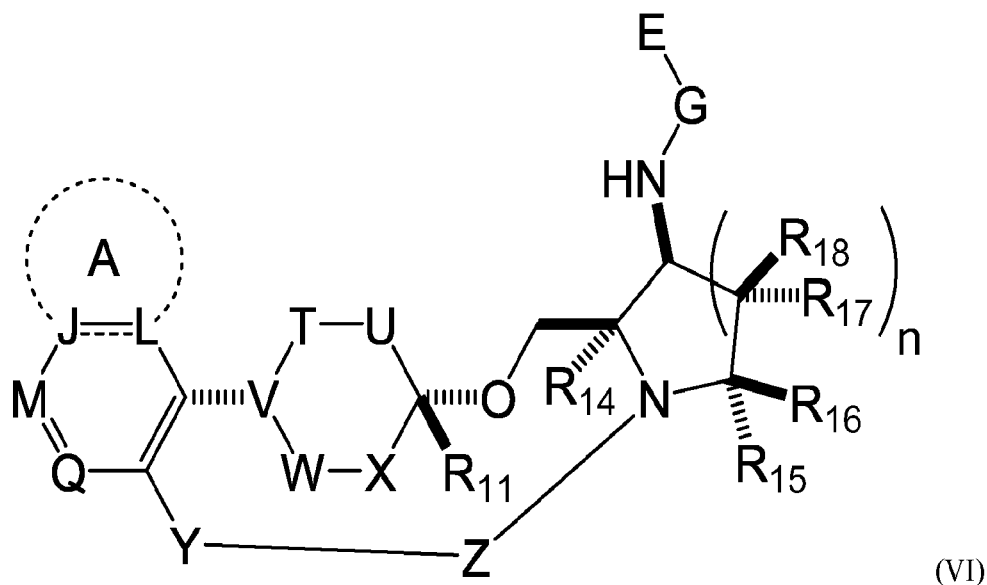
each R_{12} and R_{13} is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted $\text{C}_1\text{-C}_3$ alkyl, and $\text{C}_1\text{-C}_3$ alkyl substituted with hydroxyl or one or more halogen; and

30 R_{14} , R_{15} , and R_{16} are each, independently, selected from the group consisting of H, unsubstituted $\text{C}_1\text{-C}_3$ alkyl or $\text{C}_1\text{-C}_3$ alkyl substituted with one or more halogen;

each R_{17} and R_{18} is, independently, selected from the group consisting of H, unsubstituted $\text{C}_1\text{-C}_3$ alkyl or $\text{C}_1\text{-C}_3$ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In another embodiment, provided herein are compounds of Formula VI-A having the
5 structure of Formula VI or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium,
10 hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

===== is a single bond or double bond;

J and L are each, independently, C or N;

15 M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃
20 alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-

C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,

5 C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

10 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

15 m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

20 or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

25 or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

30 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

5 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

In one embodiment of Formula (VI), n is 1. In another embodiment of Formula (VI), n is 2. In another embodiment of Formula (VI), n is 3.

10 In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl. In another embodiment of Formula (VI), fused ring A is C₄-C₆ cycloalkyl. In another embodiment of Formula (VI), fused ring A is C₄-C₅ cycloalkyl. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl. In another embodiment of Formula (VI), fused ring A is 5- to 6-membered heterocyclyl. In another embodiment of Formula (VI),
15 fused ring A is 5-membered heterocyclyl. In another embodiment of Formula (VI), fused ring A is 6-membered heterocyclyl. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl. In another embodiment of Formula (VI), fused ring A is 5- to 6-membered heteroaryl. In another embodiment of Formula (VI), fused ring A is 6-membered heteroaryl.
20 heteroaryl.

In another embodiment of Formula (VI), fused ring A is cyclopentyl. In another embodiment of Formula (VI), fused ring A is cyclopentenyl. In another embodiment of Formula (VI), fused ring A is cyclohexyl. In another embodiment of Formula (VI), fused ring A is cyclohexenyl. In another embodiment of Formula (VI), fused ring A is pyrrolyl. In
25 another embodiment of Formula (VI), fused ring A is pyrazolyl. In another embodiment of Formula (VI), fused ring A is 1-methylpyrazolyl. In another embodiment of Formula (VI), fused ring A is imidazolyl. In another embodiment of Formula (VI), fused ring A is isoxazolyl. In another embodiment of Formula (VI), fused ring A is tetrahydropyranyl. In another embodiment of Formula (VI), fused ring A is tetrahydrofuranyl. In another
30 embodiment of Formula (VI), fused ring A is dihydropyranyl. In another embodiment of Formula (VI), fused ring A is dihydrofuranyl.

In another embodiment of Formula (VI), Y is NR₁₀. In another embodiment of Formula (VI), Y is O. In another embodiment of Formula (VI), Y is absent. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl and Y is NR₁₀. In

another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl and Y is O. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl and Y is absent. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl and Y is O. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl and Y is absent. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl and Y is O. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl and Y is absent.

In another embodiment of Formula (VI), T is CR₁R₂. In another embodiment of Formula (VI), T is O. In another embodiment of Formula (VI), W is CR₄R₅. In another embodiment of Formula (VI), W is O. In another embodiment of Formula (VI), T is CR₁R₂ and W is CR₄R₅. In another embodiment of Formula (VI), T is O and W is CR₄R₅. In another embodiment of Formula (VI), T is CR₁R₂ and W is O.

In another embodiment of Formula (VI), V is CR₃. In another embodiment of Formula (VI), V is N.

In another embodiment of Formula (VI), T is CR₁R₂ and V is CR₃. In another embodiment of Formula (VI), T is O and V is CR₃. In another embodiment of Formula (VI), T is CR₁R₂ and V is N. In another embodiment of Formula (VI), T is O and V is N.

In another embodiment of Formula (VI), W is CR₄R₅ and V is CR₃. In another embodiment of Formula (VI), W is O and V is CR₃. In another embodiment of Formula (VI), W is CR₄R₅ and V is N. In another embodiment of Formula (VI), W is O and V is N.

In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, and V is CR₃. In another embodiment of Formula (VI), T is CR₁R₂, W is O, and V is CR₃. In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, and V is N. In another embodiment of Formula (VI), T is CR₁R₂, W is O, and V is N. In another embodiment of Formula (VI), T is O, W is CR₄R₅, and V is CR₃.

In another embodiment of Formula (VI), E is H. In another embodiment of Formula (VI), E is hydroxyl. In another embodiment of Formula (VI), E is NR_aR_b. In another embodiment of Formula (VI), E is C(=O)NR_aR_b. In another embodiment of Formula (VI), E is C₁-C₃ alkylene-NR_aR_b. In another embodiment of Formula (VI), E is unsubstituted C₁-C₃ alkyl, unsubstituted C₂-C₄ alkenyl or unsubstituted C₂-C₄ alkynyl. In another embodiment of Formula (VI), E is C₁-C₃ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E

is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (VI), E is C₁-C₃ alkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted C₃-C₈ cycloalkyl. In another embodiment of Formula (VI), E is C₃-C₈ cycloalkyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted C₁-C₃ alkylene-(C₃-C₈ cycloalkyl). In another embodiment of Formula (VI), E is C₁-C₃ alkylene-(C₃-C₈ cycloalkyl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted 4- to 10-membered heterocycl. In another embodiment of Formula (VI), E is 4- to 10-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted C₁-C₃ alkylene-(4- to 10-membered heterocycl). In another embodiment of Formula (VI), E is C₁-C₃ alkylene-(4- to 10-membered heterocycl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted C₆-C₁₀ aryl. In another embodiment of Formula (VI), E is C₆-C₁₀ aryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted C₁-C₃ alkylene-(C₆-C₁₀ aryl). In another embodiment of Formula (VI), E is C₁-C₃ alkylene-(C₆-C₁₀ aryl) substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted 5- to 10-membered heteroaryl. In another embodiment of Formula (VI), E is 5- to 10-membered heteroaryl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), E is unsubstituted 4- to 7-membered heterocycl. In another embodiment of Formula (VI), E is 4- to 7-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted 4- to 6-membered heterocycl. In another embodiment of Formula (VI), E is 4- to 6-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted 4-membered heterocycl. In another embodiment of Formula (VI), E is 4-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted 5-membered heterocycl. In another embodiment of Formula (VI), E is 5-membered heterocycl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is unsubstituted 6-membered heterocycl. In another

embodiment of Formula (VI), E is 6-membered heterocyclyl substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), E is NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), E is C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, or C₁-C₃ alkylene-(C₆-C₁₀ aryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, or C₁-C₃ alkylene-(4- to 10-membered heterocyclyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), E is C₁-C₃ alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or C₁-C₃ alkylene-

(C₃-C₈ cycloalkyl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), E is methyl, wherein the methyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is methyl. In another embodiment of Formula (VI), E is trifluoromethyl. In another embodiment of Formula (VI), E is dioxanyl, wherein the dioxanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is tetrahydropyranyl, wherein the tetrahydropyranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is tetrahydrofuranyl, wherein the tetrahydrofuranyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is azetidiny, wherein the azetidiny is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is oxetanyl, wherein the oxetanyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy. In another embodiment of Formula (VI), E is morpholinyl, wherein the morpholinyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

In another embodiment of Formula (VI), R₁₄ is H. In another embodiment of Formula (VI), R₁₄ is unsubstituted C₁-C₃ alkyl. In another embodiment of Formula (VI), R₁₅ and R₁₆ are each H. In another embodiment of Formula (VI), R₁₅ is unsubstituted C₁-C₃ alkyl and R₁₆ is H. In another embodiment of Formula (VI), R₁₆ is unsubstituted C₁-C₃ alkyl and R₁₅ is H. In another embodiment of Formula (VI), each R₁₇ and R₁₈ is H. In another embodiment of Formula (VI), R₁₇ is unsubstituted C₁-C₃ alkyl and R₁₈ is H. In another embodiment of Formula (VI), R₁₈ is unsubstituted C₁-C₃ alkyl and R₁₇ is H. In another embodiment of Formula (VI), one of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is unsubstituted C₁-C₃ alkyl and the others are each H. In another embodiment of Formula (VI), each of R₁₄, R₁₅, R₁₆, R₁₇ and R₁₈ is H.

In another embodiment of Formula (VI), m is 1. In another embodiment of Formula (VI), m is 2. In another embodiment of Formula (VI), m is 3. In another embodiment of Formula (VI), m is 4. In another embodiment of Formula (VI), m is 1, 2 or 3. In another embodiment of Formula (VI), m is 2, 3, or 4. In another embodiment of Formula (VI), m is 1 or 2. In another embodiment of Formula (VI), m is 3 or 4.

In another embodiment of Formula (VI), Y is O and m is 1. In another embodiment of Formula (VI), Y is O and m is 2. In another embodiment of Formula (VI), Y is O and m is

3. In another embodiment of Formula (VI), Y is O and m is 4. In another embodiment of Formula (VI), Y is O and m is 1, 2, or 3. In another embodiment of Formula (VI), Y is O and m is 2, 3, or 4. In another embodiment of Formula (VI), Y is O and m is 1 or 2. In another embodiment of Formula (VI), Y is O and m is 3 or 4.

5 In another embodiment of Formula (VI), Y is absent and m is 2. In another embodiment of Formula (VI), Y is absent and m is 3. In another embodiment of Formula (VI), Y is absent and m is 4. In another embodiment of Formula (VI), Y is absent and m is 2, 3, or 4. In another embodiment of Formula (VI), Y is absent and m is 2 or 3. In another embodiment of Formula (VI), Y is absent and m is 4 or 5.

10 In another embodiment of Formula (VI), Y is NR₁₀ and m is 1. In another embodiment of Formula (VI), Y is NR₁₀ and m is 2. In another embodiment of Formula (VI), Y is NR₁₀ and m is 3. In another embodiment of Formula (VI), Y is NR₁₀ and m is 4. In another embodiment of Formula (VI), Y is NR₁₀ and m is 1, 2, or 3. In another embodiment of Formula (VI), Y is NR₁₀ and m is 2, 3, or 4. In another embodiment of Formula (VI), Y is NR₁₀ and m is 1 or 2. In another embodiment of Formula (VI), Y is NR₁₀ and m is 3 or 4.

15 In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl and n is 1. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl and n is 2. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl and n is 3. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl and n is 1. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl and n is 2. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl and n is 3. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl and n is 1. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl and n is 2. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl and n is 3.

25 In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is O. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 2, and Y is O. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is O. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, and Y is absent. In another embodiment of Formula (VI), fused ring A is

C₄-C₈ cycloalkyl, n is 2, and Y is absent. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, and Y is absent.

In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is O. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is O. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is O. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, and Y is absent. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, and Y is absent. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, and Y is absent.

In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is NR₁₀. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is O. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is O. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is O. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, and Y is absent. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, and Y is absent. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, and Y is absent.

In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is C₄-C₈

cycloalkyl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is C₄-C₈ cycloalkyl, n is 3, Y is absent, and m is 3 or 4.

In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula

(VI), fused ring A is 4- to 7-membered heterocyclyl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 4- to 7-membered heterocyclyl, n is 3, Y is absent, and m is 3 or 4.

5 In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 2 or 3. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is NR₁₀, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is O, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 1, Y is absent, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 2, Y is absent, and m is 3 or 4. In another embodiment of Formula (VI), fused ring A is 5- to 8-membered heteroaryl, n is 3, Y is absent, and m is 3 or 4.

20 In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 1 or 2. In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 1 or 2. In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 1 or 2. In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 1 or 2. In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, and m is 3 or 4. In another

embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 1, and m is 3 or 4. In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 2, and m is 3 or 4. In another embodiment of Formula (VI), T is CR₁R₂, W is CR₄R₅, V is CR₃, Y is O, n is 3, and m is 3 or 4.

5 In another embodiment of Formula (VI), R₁, R₂, R₄, and R₅ are each H. In another embodiment of Formula (VI), R₁, R₂, R₄, and R₅ are each H; and R₃ is H. In another embodiment of Formula (VI), R₁, R₂, R₄, and R₅ are each H; R₃ is H; and R₆, R₇, R₈, R₉, and R₁₁ are each H. In another embodiment of Formula (VI), R₁, R₂, R₄, and R₅ are each H; R₃ is H; R₆, R₇, R₈, R₉, and R₁₁ are each H; and R₁₂ and R₁₃ are each H.

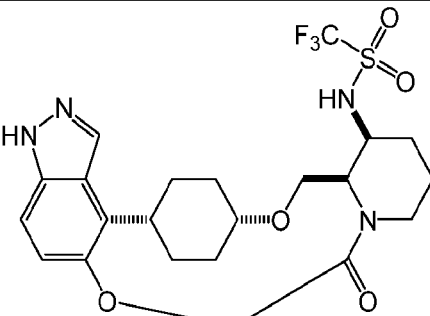
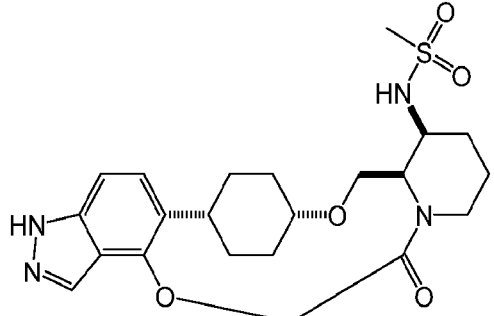
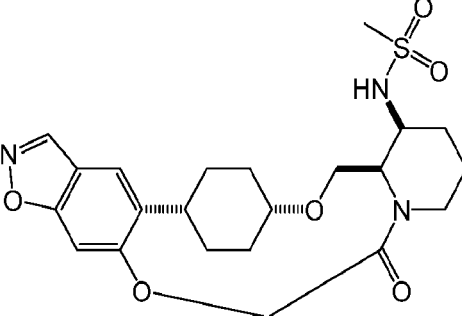
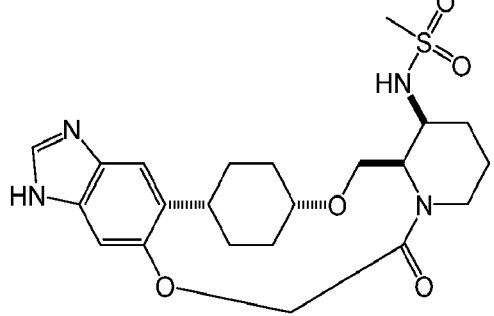
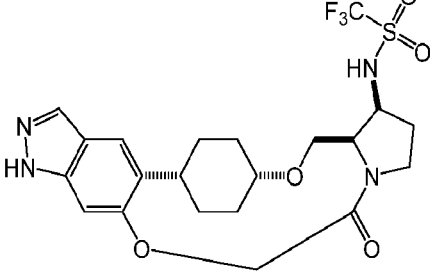
10 In another embodiment of Formula (VI), one or more of R₁, R₂, R₄, and R₅ is fluorine. In another embodiment of Formula (VI), one or more of R₁, R₂, R₄, and R₅ is deuterium. In another embodiment of Formula (VI), one or more of R₆, R₇, R₈, R₉, and R₁₁ is fluorine. In another embodiment of Formula (VI), one or more of R₆, R₇, R₈, R₉, and R₁₁ is deuterium. In another embodiment of Formula (VI), one or more of each R₁₂ and R₁₃ is fluorine. In another embodiment of Formula (VI), one or more of each R₁₂ and R₁₃ is deuterium.

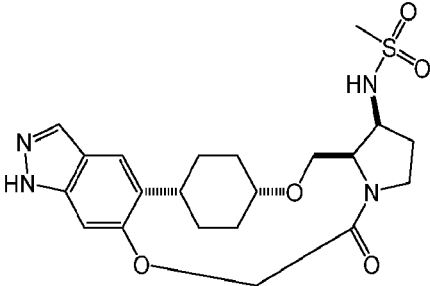
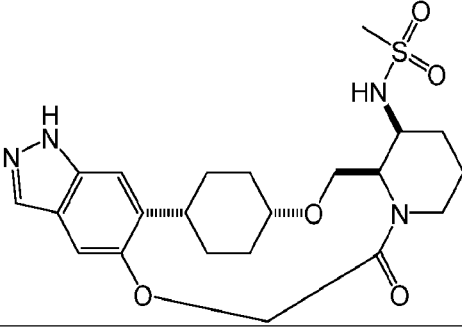
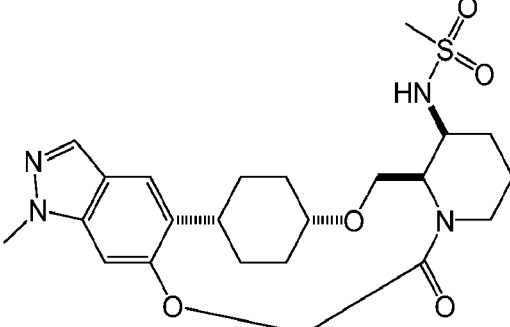
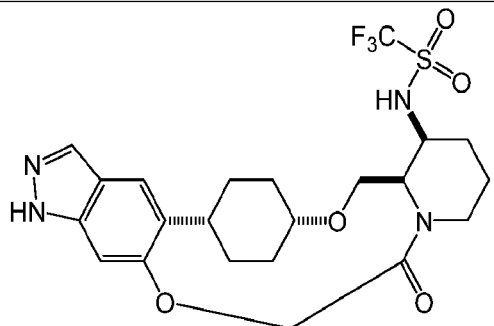
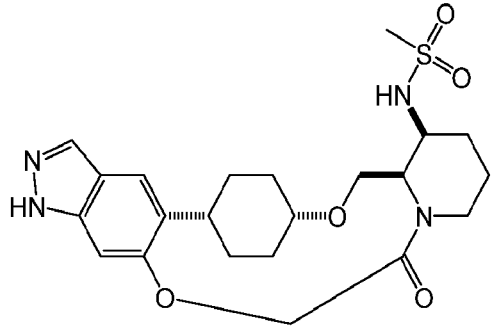
In another embodiment of Formula (VI), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and R₁₁ is H. In another embodiment of Formula (VI), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, R₁₁ is H, and m is 2. In another embodiment of Formula (VI), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (VI), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 2. In another embodiment of Formula (VI), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, and each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H. In another embodiment of Formula (VI), Y is O, T is CR₁R₂, V is CR₃, W is CR₄R₅, each of R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, and R₁₈ is H, and m is 2.

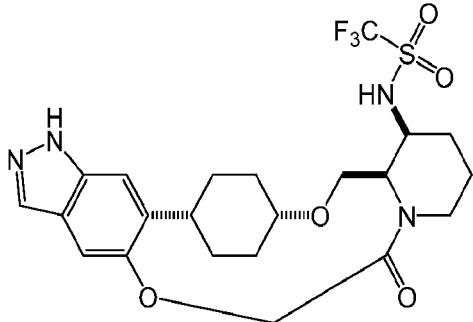
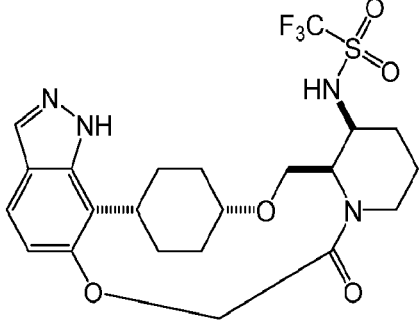
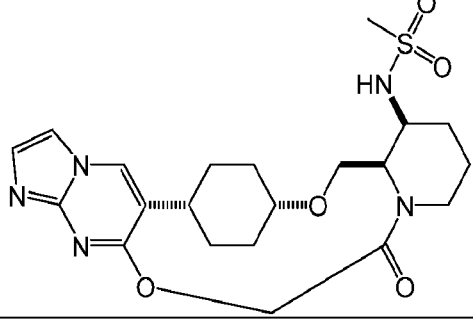
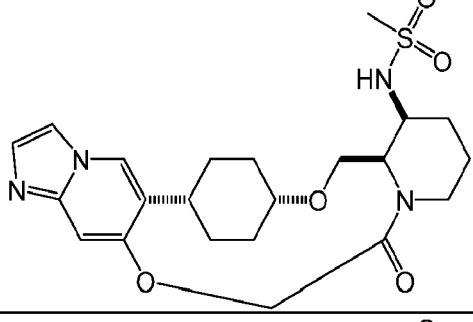
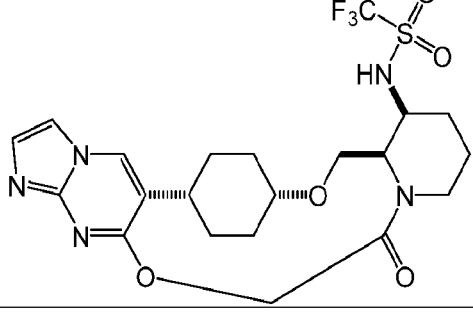
25 Each of the embodiments described herein with respect to compounds of Formula VI also applies to compounds of Formula VI-A.

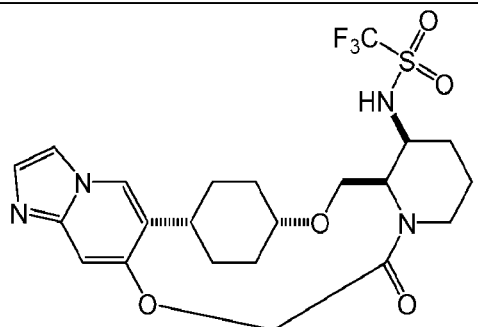
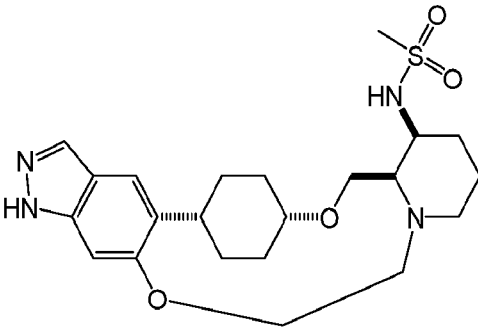
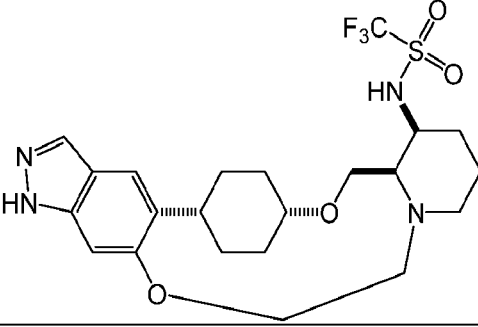
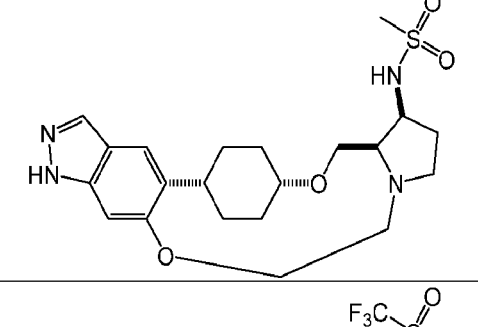
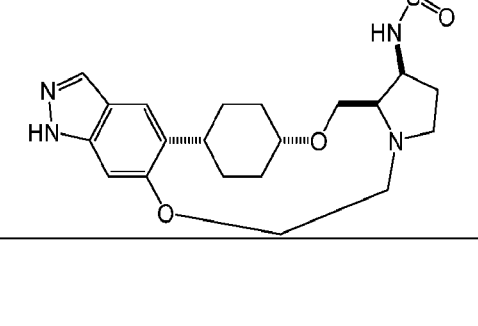
Certain embodiments of compounds of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or pharmaceutically acceptable salts thereof, are shown below in Table 1. Compounds of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or pharmaceutically acceptable salts thereof, and compounds of Table 1, or pharmaceutically acceptable salts thereof, collectively or individually are sometimes referred to herein as “compounds of the invention” or “compounds provided herein”.

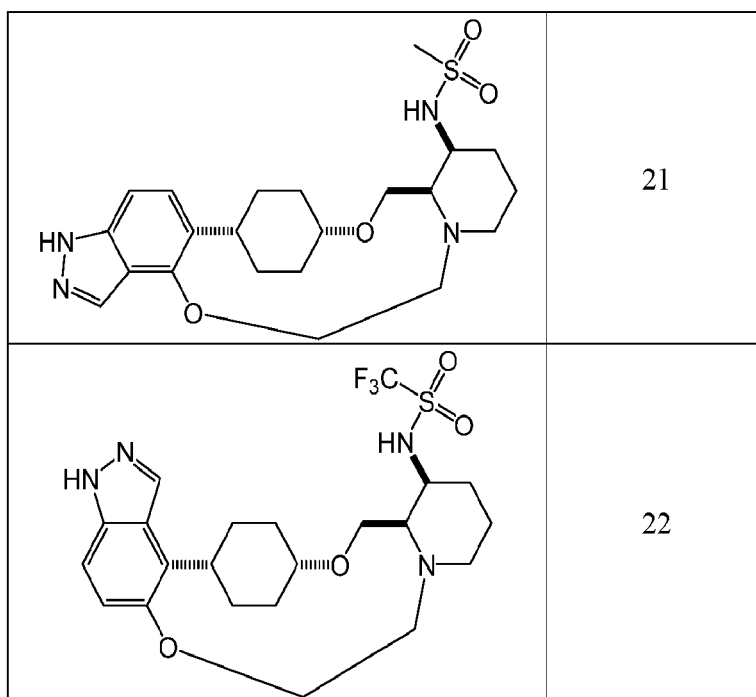
Table 1

Structure	Compound No.
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The disclosed compounds possess one or more stereocenters, and each stereocenter may exist independently in either the R or S configuration. In one embodiment, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds described herein encompass racemic, optically-active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein.

Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. In one embodiment, a mixture of two or more isomers is utilized as the disclosed compound described herein. In another embodiment, a pure isomer is utilized as the disclosed compound described herein. In another embodiment, compounds described herein contain one or more chiral centers. These compounds are prepared by any means, including stereoselective synthesis, enantioselective synthesis or separation of a mixture of enantiomers or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, and chromatography.

In one embodiment, the disclosed compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

Compounds described herein also include isotopically-labeled compounds wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{36}Cl , ^{18}F , ^{123}I , ^{125}I , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , and ^{35}S . In one embodiment, isotopically-labeled compounds are useful in drug or substrate tissue distribution studies. In another embodiment, substitution with heavier isotopes such as deuterium affords greater metabolic stability (for example, increased in vivo half-life or reduced dosage requirements). In another embodiment, the compounds described herein include a ^2H (*i.e.*, deuterium) isotope.

In yet another embodiment, substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , is useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The specific compounds described herein, and other compounds encompassed by one or more of the Formulas described herein having different substituents are synthesized using techniques and materials described herein and as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, Advanced Organic Chemistry 4th Ed., (Wiley 1992); Carey and Sundberg, Advanced Organic Chemistry 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, Protective Groups in Organic Synthesis 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compounds as described herein are modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the Formulas as provided herein.

Compounds described herein are synthesized using any suitable procedures starting from compounds that are available from commercial sources or are prepared using procedures described herein.

Methods of Treatment

The compounds of the invention can be used in a method of treating a disease or condition in a subject, said method comprising administering to the subject a compound of the invention, or a pharmaceutical composition comprising a compound of the invention. In one embodiment of the methods described herein, the subject is human. In one aspect, the compounds provided herein are useful in treatment of a disease or condition by acting as an agonist of the orexin-2 receptor.

The compounds of the invention can be used to treat a disease or condition selected from the group consisting of narcolepsy, cataplexy, or hypersomnia in a subject in need thereof.

In one embodiment, the compounds of the invention can be used to treat narcolepsy in a subject. In one embodiment, the compounds of the invention can be used to treat cataplexy in a subject. In one embodiment, the compounds of the invention can be used to treat hypersomnia in a subject.

Orexin-2 receptors are important in a wide range of biological functions. This suggests that orexin-2 receptors play a role in diverse disease processes in humans or other species. The compound of the present invention is useful for treating, preventing, or ameliorating the risk of one or more of the following symptoms or diseases of various neurological and psychiatric diseases associated with alterations in sleep/wake function. That is, narcolepsy, narcolepsy with cataplexy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome, hypersomnolence syndrome characterized by hypersomnia (e.g., in subjects with Kleine Levin syndrome, major depression with hypersomnia, Lewy body dementia, Parkinson's disease, progressive supranuclear paralysis, Prader-Willi syndrome, Mobius syndrome, hypoventilation syndrome, Niemann-Pick disease type C, brain contusion, cerebral infarction, brain tumor, muscular dystrophy, multiple sclerosis, multiple systems atrophy, acute disseminated encephalomyelitis, Guillain-Barre syndrome, Rasmussen's encephalitis, Wernicke's encephalitis, limbic encephalitis, or Hashimoto's encephalopathy), coma, loss of consciousness, obesity (e.g., malignant mastocytosis, exogenous obesity, hyperinsular obesity, hyperplasmic obesity, hypop hyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, or central obesity), insulin resistance syndrome, Alzheimer's disease, disturbance of consciousness such as coma and the like, side effects and

complications due to anesthesia, sleep disturbance, excessive daytime sleepiness, sleep
 problem, insomnia, intermittent sleep, nocturnal myoclonus, REM sleep interruption, jet lag,
 jet lag syndrome, sleep disorder of alternating worker, sleep disorder, night terror, depression,
 major depression, sleepwalking disease, enuresis, sleep disorder, Alzheimer's dusk,
 5 sundowning, diseases associated with circadian rhythm, fibromyalgia, condition arising from
 decline in the quality of sleep, overeating, obsessive compulsive eating disorder, obesity-
 related disease, hypertension, diabetes, elevated plasma insulin concentration and insulin
 resistance, hyperlipidemia, hyperlipemia, endometrial cancer, breast cancer, prostate cancer,
 colorectal cancer, cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones,
 10 cardiac disease, abnormal heartbeat, arrhythmia, myocardial infarction, congestive cardiac
 failure, cardiac failure, coronary heart disease, cardiovascular disorder, polycystic ovarian
 disease, craniopharyngioma, Prader-Willi syndrome, Froelich's syndrome, growth hormone
 deficient, normal mutant short stature, Turner's syndrome, children suffering from acute
 lymphoblastic leukemia, syndrome X, reproductive hormone abnormality, declining fertility,
 15 infertility, male gonadal function decline, sexual and reproductive dysfunction such as female
 male hirsutism, fetal defects associated with pregnant women obesity, gastrointestinal
 motility disorders such as obesity-related gastroesophageal reflux, obesity hypoventilation
 syndrome (Pickwick syndrome), respiratory diseases such as dyspnea, inflammation such as
 systemic inflammation of the vascular system, arteriosclerosis, hypercholesterolemia,
 20 hyperuricemia, lower back pain, gall bladder disease, gout, kidney cancer, risk of secondary
 outcomes of obesity, such as lowering the risk of left ventricular hypertrophy, migraine pain,
 headache, neuropathic pain, Parkinson's disease, psychosis, autoimmune encephalitis, cancer
 related fatigue (such as excessive daytime sleepiness or fatigue associated with cancer and/or
 chemotherapy), cancer related nausea and vomiting, corticobasal degeneration, Huntington's
 25 disease, neuromyelitis optica, nociception, progressive supranuclear palsy, schizophrenia,
 systemic lupus erythematosus, traumatic brain injury, facial flushing, night sweats, diseases
 of the genital/urinary system, diseases related to sexual function or fertility, dysthymic
 disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, acute
 stress disorder, agoraphobia, generalized anxiety disorder, obsessive disorder, panic attack,
 30 panic disorder, post-traumatic stress disorder (PTSD), separation anxiety disorder, social
 phobia, anxiety disorder, acute neurological and psychiatric disorders such as cardiac bypass
 surgery and post-transplant cerebral deficit, stroke, ischemic stroke, cerebral ischemia, spinal
 cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic nerve injury,
 Huntington's chorea, amyotrophic lateral sclerosis, eye damage, retinopathy, cognitive

impairment, muscle spasm, tremor, epilepsy, disorders associated with muscle spasticity, delirium, amnesic disorder, age-related cognitive decline, schizoaffective disorder, delusional disorder, drug addiction, dyskinesia, chronic fatigue syndrome, fatigue, medication-induced Parkinsonism syndrome, Jil-do La Tourette's syndrome, chorea, myoclonus, tic, restless legs syndrome, dystonia, dyskinesia, attention deficit hyperactivity disorder (ADHD), behavior disorder, urinary incontinence, withdrawal symptoms, trigeminal neuralgia, hearing loss, tinnitus, nerve damage, retinopathy, macular degeneration, vomiting, cerebral edema, pain, bone pain, arthralgia, toothache, cataplexy, and traumatic brain injury (TBI).

10 Particularly, the compound of the present invention is useful as a therapeutic or prophylactic drug for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome, hypersomnolence syndrome characterized by hypersomnia (e.g., in Parkinson's disease, Guillain-Barre syndrome or Kleine Levin syndrome), Alzheimer's disease, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma and the like, side effects and complications due to anesthesia, and the like, or anesthetic antagonist.

 In one embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for narcolepsy.

 In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy type-1. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy type-2. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy and excessive daytime sleepiness. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy, cataplexy, and excessive daytime sleepiness. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for narcolepsy and cataplexy. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for excessive daytime sleepiness. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for idiopathic hypersomnia. In another embodiment, the compound of the present invention is useful as a prophylactic or therapeutic agent for obstructive sleep apnea.

 In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for hypersomnia in Parkinson's disease.

In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for hypersomnia. In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity and is useful as a prophylactic or therapeutic agent for excessive daytime sleepiness associated with Parkinson's disease.

In another embodiment, the compound of the present invention has orexin-2 receptor agonist activity, and is useful as a prophylactic or therapeutic agent for excessive daytime sleepiness or fatigue associated with cancer and/or chemotherapy.

In another embodiment, the present invention provides a method of treating narcolepsy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy type-1 in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy type-2 in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy and excessive daytime sleepiness in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy, cataplexy, and excessive daytime sleepiness in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating narcolepsy and cataplexy in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating excessive daytime sleepiness in a subject in need thereof comprising administering to the subject a

compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating idiopathic hypersomnia in a subject in need thereof comprising administering to the subject a compound
5 of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating excessive daytime sleepiness and idiopathic hypersomnia in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A,
10 V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating obstructive sleep apnea in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

15 In another embodiment, the present invention provides a method of treating excessive daytime sleepiness and obstructive sleep apnea in a subject in need thereof comprising administering to the subject a compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof.

In any of the methods as described herein, the subject is administered a compound of
20 Formula I. In any of the methods as described herein, the subject is administered a compound of Formula II. In any of the methods as described herein, the subject is administered a compound of Formula III. In any of the methods as described herein, the subject is administered a compound of Formula IV. In any of the methods as described herein, the subject is administered a compound of Formula V. In any of the methods as
25 described herein, the subject is administered a compound of Formula VI.

Each of the embodiments described herein with respect to the use of compounds of Formula I also applies to compounds of Formula I-A. Each of the embodiments described herein with respect to the use of compounds of Formula II also applies to compounds of Formula II-A. Each of the embodiments described herein with respect to the use of
30 compounds of Formula III also applies to compounds of Formula III-A. Each of the embodiments described herein with respect to the use of compounds of Formula IV also applies to compounds of Formula IV-A. Each of the embodiments described herein with respect to the use of compounds of Formula V also applies to compounds of Formula V-A.

Each of the embodiments described herein with respect to the use of compounds of Formula VI also applies to compounds of Formula VI-A.

In any of the compositions or methods as described herein, the compound of Formula I-A, I, II-A, II, III-A, III, IV-A, IV, V-A, V, VI-A, or VI, or a pharmaceutically acceptable salt thereof, is present and/or administered in a therapeutically effective amount.

Administration / Dosage / Formulations

In another aspect, provided herein is a pharmaceutical composition comprising at least one compound of the invention, together with a pharmaceutically acceptable carrier.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

In particular, the selected dosage level will depend upon a variety of factors including the activity of the particular compound employed, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination with the compound, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A medical doctor, *e.g.*, physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could begin administration of the pharmaceutical composition to dose the disclosed compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it is especially advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of the disclosed compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the disclosed compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a disclosed compound for the treatment of narcolepsy or cataplexy in a patient.

In one embodiment, the compounds of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

5 In some embodiments, the dose of a disclosed compound is from about 1 mg to about 1,000 mg. In some embodiments, a dose of a disclosed compound used in compositions described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 20 mg, or less than about 10 mg. For example, a dose is about 10 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70
10 mg, 80 mg, 90 mg, 100 mg, 120 mg, 140 mg, 160 mg, 180 mg, 200 mg, 220 mg, 240, 260 mg, 280 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, or about 600 mg.

Routes of administration of any of the compositions of the invention include oral, nasal, rectal, intravaginal, parenteral, buccal, sublingual or topical. The compounds for use in
15 the invention may be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical
20 administration. In one embodiment, the preferred route of administration is oral.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or
25 aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

For oral application, particularly suitable are tablets, dragees, liquids, drops,
30 suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as

cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

5 For parenteral administration, the disclosed compounds may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose or continuous infusion. Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing or dispersing agents may be used.

10 Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents are considered to be within the scope of this invention and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction
15 times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, *e.g.*, nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values
20 and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present invention. However, they
25 are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

Examples

The invention is further illustrated by the following examples, which should not be construed as further limiting. The practice of the present invention will employ, unless
30 otherwise indicated, conventional techniques of organic synthesis, cell biology, cell culture, molecular biology, transgenic biology, microbiology and immunology, which are within the skill of the art.

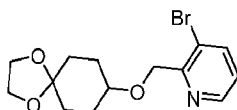
General ProceduresExample 1: Synthesis Procedures

Synthesis procedures for preparation of the compounds of the invention are readily available to the ordinary skilled artisan. Unless otherwise indicated, starting materials were generally obtained from commercial sources. Synthetic procedures for other macrocyclic compounds can be found, for example, in U.S. Application No.: 17/104,993 and in PCT Application No.: PCT/US20/62320, both filed November 25, 2020, in U.S. Provisional Application No. 63/128,404, filed December 21, 2020, and in U.S. Provisional Application No. 63/179,616, filed April 26, 2021; all of which are expressly incorporated by reference herein.

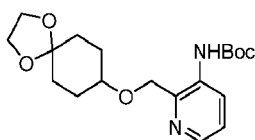
The following abbreviations may be used in the synthetic examples below:

AcOH = acetic acid
 DCM = dichloromethane
 MsCl = methanesulfonyl chloride
 MeOH = methanol
 THF = tetrahydrofuran
 EtOH = ethanol
 PtO₂ = platinum dioxide
 HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
 DIPEA or DIEA = *N,N*-diisopropylethylamine
^tBu = *tert*-butyl
 ACN or MeCN = acetonitrile
 EtOAc = ethyl acetate
 DMF = dimethyl formamide
 TFA = trifluoroacetic acid
 LiOH = lithium hydroxide
 min = minutes
 hr = hours
 Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium(0)
 DMSO = dimethyl sulfoxide
i-PrOH = isopropanol
 Pd/C = palladium on carbon
 XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
 Boc = *tert*-butoxycarbonyl
 Ms = methanesulfonyl
 Bn = benzyl
 Et = ethyl
 Cbz = carboxybenzyl
 Pd(dppf)Cl₂ = [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
 TfO = trifluoromethanesulfonate
 KHMDS = Potassium bis(trimethylsilyl)amide solution
 Et₃N or TEA = triethylamine.

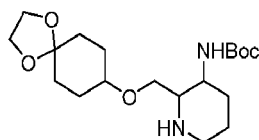
Example 1.1



To a stirred solution of 1,4-dioxaspiro[4.5]decan-8-ol (753.0 g, 1.0 equiv., 4.8 mol) in THF (10 L) was added potassium *t*-butoxide (534.3 g, 1.3 equiv., 4.8 mol) in portions at 0
 5 degrees C under nitrogen atmosphere. The resulting solution was stirred for 30 min at 0 degrees C. To this was added a solution of 3-bromo-2-(bromomethyl)pyridine (919.0 g, 1.0 equiv., 4.8 mol) in THF (1.0 L) dropwise with stirring at 0 degrees C. The resulting solution was allowed to stir overnight at room temperature. The reaction was then quenched by the addition of 10 L of sat. NH₄Cl (aq.). The resulting solution was extracted with 3x1 L of ethyl
 10 acetate, the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography, to afford 3-bromo-2-([1,4-dioxaspiro[4.5]decan-8-yloxy]methyl)pyridine (962.0 g, 80.0%) as an oil.

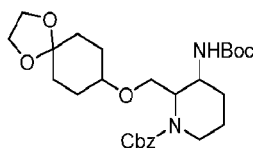


To a stirred solution of 3-bromo-2-([1,4-dioxaspiro[4.5]decan-8-
 15 yloxy]methyl)pyridine (962.0 g, 1.0 equiv., 2.9 mol) and *tert*-butyl carbamate (686.7 g, 2.0 equiv., 5.9 mol) in dioxane (10.0 L) was added Pd₂(dba)₃ (134.2 g, 0.05 equiv., 0.15 mol), XantPhos (169.6 g, 0.10 equiv., 0.29 mol) and Cs₂CO₃ (2395 g, 2.5 equiv., 7.3 mol) under nitrogen atmosphere. The resulting solution was stirred for 20 hr at 100 degrees C. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was
 20 purified by a silica gel column to afford *tert*-butyl N-[2-([1,4-dioxaspiro[4.5]decan-8-yloxy]methyl)pyridin-3-yl]carbamate (620.0 g, 58.0%) as a solid.

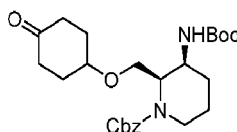


To a stirred solution of *tert*-butyl N-[2-([1,4-dioxaspiro[4.5]decan-8-
 25 yloxy]methyl)pyridin-3-yl]carbamate (620.0 g, 1.0 equiv., 1.7 mmol) in methanol (6.0 L) and acetic acid (600 mL) was added Pt₂O (77.26 g, 0.20 equiv., 340.2 mmol). The mixture was hydrogenated under 20 atm of hydrogen at room temperature. The resulting solution was stirred overnight at room temperature. The solids were filtered out. The resulting mixture was

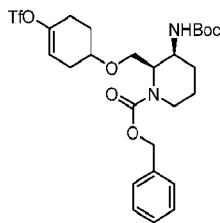
concentrated under vacuum to afford *tert*-butyl N-[2-([1,4-dioxaspiro[4.5]decan-8-yloxy)methyl]piperidin-3-yl]carbamate (620.0 g, 99.9%) as an oil.



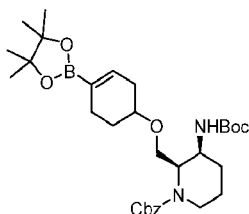
To a stirred mixture of *tert*-butyl N-[2-([1,4-dioxaspiro[4.5]decan-8-yloxy)methyl]piperidin-3-yl]carbamate (620.0 g, 1.0 equiv., 1.7 mmol) in DCM (6.0 L) was added N-(benzyloxycarbonyloxy)succinimide (845.9 g, 1.2 equiv., 2.0 mol) and DIEA (648.9 g, 3.0 equiv., 5.0 mol) at room temperature. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 5 L of water/ice. The resulting mixture was extracted with 2x2 L of DCM. The mixture was dried over anhydrous sodium sulfate and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford benzyl 3-[(*tert*-butoxycarbonyl)amino]-2-([1,4-dioxaspiro[4.5]decan-8-yloxy)methyl]piperidine-1-carboxylate (422.0 g, 50.0%) as an oil.



To a stirred solution of benzyl 3-[(*tert*-butoxycarbonyl)amino]-2-([1,4-dioxaspiro[4.5]decan-8-yloxy)methyl]piperidine-1-carboxylate (422.0 g, 1.0 equiv., 0.84 mol) in acetic acid (280 mL) was added water (140 mL) at room temperature. The resulting solution was stirred for 12 hr at 30 degrees C. The mixture was allowed to cool down to 10 degrees C. The reaction was then quenched by the addition of 6 L of ice water. The resulting solution was stirred for 1 hr at 10 degrees C. The precipitated solids were collected by filtration. The crude product was purified by re-crystallization from diethylether:ethyl acetate=5:1(10 mL/g) three times to afford benzyl (2R,3S)-3-[(*tert*-butoxycarbonyl)amino]-2-[[4-(4-oxocyclohexyl)oxy]methyl]piperidine-1-carboxylate (108.7 g, 28.2%) as a solid. LCMS (ESI): m/z $[M+H]^+ = 461$; ^1H -NMR (300 MHz, DMSO- d_6) δ 7.38 - 7.26 (m, 5H), 6.97 - 6.95 (m, 1H), 5.06 (brs, 2H), 4.60 (brs, 1H), 3.92 - 3.81 (m, 1H), 3.76 - 3.42 (m, 4H), 2.95 - 2.72 (m, 1H), 2.39 - 2.23 (s, 2H), 2.18 - 2.05 (m, 2H), 1.93 - 1.80 (m, 4H), 1.73 - 1.48 (m, 3H), 1.39 - 1.36 (m, 10H).

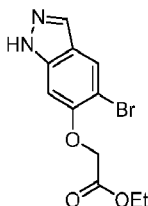


To a stirred solution of benzyl (2R,3S)-3-[(*tert*-butoxycarbonyl)amino]-2-[[4-oxocyclohexyl]oxy]methyl]piperidine-1-carboxylate (30.0 g, 1.0 equiv., 65.1 mmol) in THF (300 mL) was added KHMDS (78.2 mL, 1.2 equiv., 78.2 mmol) at -78 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 3 hr at -78 degrees C and followed by addition of 1,1,1-trifluoro-N-phenyl-N-trifluoromethanesulfonylmethanesulfonamide (27.9 g, 1.2 equiv., 78.2 mmol) in THF (100 mL) dropwise at -78 degrees C. The resulting mixture was stirred for 2 hr at -78 degrees C. The mixture was added dropwise to 200 mL of sat. NH₄Cl (aq.) at 0 degrees C. The resulting mixture was extracted with ethyl acetate (2x50 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford benzyl (2R,3S)-3-[(*tert*-butoxycarbonyl)amino]-2-[[4-(trifluoromethanesulfonyloxy)cyclohex-3-en-1-yl]oxy]methyl]piperidine-1-carboxylate (41.0 g, crude) as an oil.

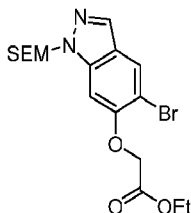


To a solution of benzyl (2R,3S)-3-[(*tert*-butoxycarbonyl)amino]-2-[[4-(trifluoromethanesulfonyloxy)cyclohex-3-en-1-yl]oxy]methyl]piperidine-1-carboxylate (350 g, 1.0 equiv., 0.59 mol) and bis(pinacolato)diboron (180 g, 1.2 equiv., 0.71 mol) in 1,4-dioxane (3.5 L) were added Pd(dppf)Cl₂.CH₂Cl₂ (24.1 g, 0.05 equiv., 29.5 mmol) and potassium acetate (116 g, 2.0 equiv., 1.18 mol) under nitrogen atmosphere. The resulting mixture was stirred for 16 hr at 100 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product. The crude product was purified by reverse flash chromatography to afford benzyl (2R,3S)-3-[(*tert*-butoxycarbonyl)amino]-2-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]oxy]methyl]piperidine-1-carboxylate (90.8 g, 26.2%) as a solid. LCMS (ESI): m/z [M+H]⁺ = 571; ¹H-NMR (300 MHz, DMSO-*d*₆): δ 7.41-7.24 (m, 5H), 6.91 (brs, 1H), 6.30 (brs, 1H), 5.08 (brs, 2H), 4.54

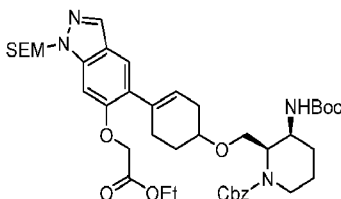
(brs, 1H), 3.85 (d, $J = 13.3$ Hz, 1H), 3.75 - 3.40 (m, 4H), 2.91 - 2.70 (s, 1H), 2.40 - 2.24 (m, 1H), 2.21 - 2.05 (m, 1H), 2.02 - 1.85 (m, 2H), 1.80 - 1.70 (m, 1H), 1.70 - 1.61 (m, 1H), 1.60 - 1.50 (m, 2H), 1.39 (s, 11H), 1.18 (s, 12H).



5 To a solution of 5-bromo-1H-indazol-6-ol (8.00 g, 1.0 equiv., 37.6 mmol) in MeCN (200 mL) were added ethyl 2-bromoacetate (7.53 g, 1.2 equiv., 45.1 mmol) and K_2CO_3 (10.4 g, 2.0 equiv., 75.1 mmol) at room temperature. The mixture solution was stirred for 4 hr at 20 degrees C. The mixture was filtered through Celite pad, the filter cake was washed with ethyl acetate (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was
10 purified by Prep-TLC to afford ethyl 2-((5-bromo-1H-indazol-6-yl)oxy)acetate (8.00 g, 71.2 %) as a solid. ^1H NMR (400 MHz, $DMSO-d_6$) δ 12.99 (s, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 7.02 (d, $J = 1.0$ Hz, 1H), 4.98 (s, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 1.23 (t, $J = 7.1$ Hz, 3H).

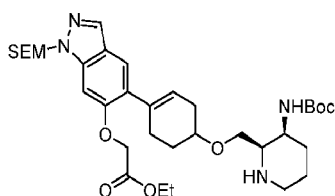


To the solution of ethyl 2-((5-bromo-1H-indazol-6-yl)oxy)acetate (8.00 g, 1.0 equiv.,
15 26.7 mmol) in DCM (200 mL) was added chloromethyl 2-trimethylsilylethyl ether (6.69 g, 1.5 equiv., 40.1 mmol) and K_3PO_4 (17.0 g, 3.0 equiv., 80.2 mmol) at room temperature. The mixture solution was stirred for 4 hr at 25 degrees C. The resulting solution was filtered and concentrated under reduced pressure. The residue was purified by reverse flash chromatography to provide ethyl 2-((5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-
20 indazol-6-yl)oxy)acetate (8.9 g, 77 %) as a solid. LCMS (ESI): m/z $[M+H]^+ = 431$.

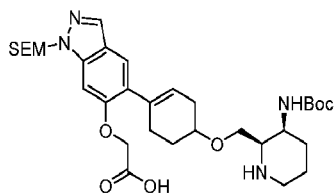


To the solution of ethyl 2-((5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetate (2.00 g, 1.0 equiv., 4.66 mmol) in 1,4-dioxane (30 mL) were added

benzyl (2R,3S)-3-((*tert*-butoxycarbonyl)amino)-2-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)oxy)methyl)piperidine-1-carboxylate (2.66 g, 1.0 equiv., 4.66 mmol), H₂O (7.5 mL), Na₂CO₃ (1.48 g, 3.0 equiv., 14.0 mmol) and Pd(dppf)Cl₂ (511 mg, 0.15 equiv., 699 μmol) at room temperature. The mixture solution was stirred for 2
 5 hr at 80 degrees C under N₂ atmosphere. The resulting mixture was diluted with water and extracted with ethyl acetate. The organic phase was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford benzyl (2R,3S)-3-((*tert*-butoxycarbonyl)amino)-2-(((4-(6-(2-ethoxy-2-oxoethoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)cyclohex-3-en-1-yl)oxy)methyl)piperidine-1-
 10 carboxylate (2.16 g, 58.5 %) as a solid. LCMS (ESI): *m/z* [M+H]⁺ = 794.

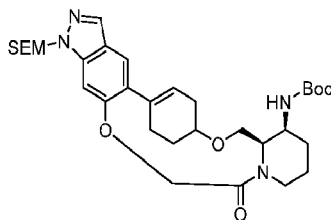


To a solution of benzyl (2R,3S)-3-((*tert*-butoxycarbonyl)amino)-2-(((4-(6-(2-ethoxy-2-oxoethoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)cyclohex-3-en-1-yl)oxy)methyl)piperidine-1-carboxylate (2.06 g, 1.0 equiv., 2.60 mmol) in *i*-PrOH (20
 15 mL) was added Pd/C (387 mg, 1.4 equiv., 3.64 mmol) at nitrogen atmosphere. The resulting mixture was hydrogenated at room temperature for 2 hr under hydrogen atmosphere using a hydrogen balloon. The reaction solution was filtered through a Celite pad and concentrated under reduced pressure to afford ethyl 2-((5-(4-(((2R,3S)-3-((*tert*-
 butoxycarbonyl)amino)piperidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetate (1.65 g, 96.4 %) as an oil.
 20

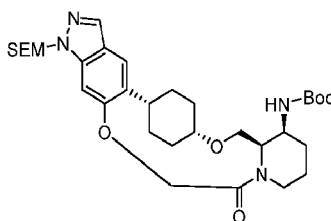


To a solution of ethyl 2-((5-(4-(((2R,3S)-3-((*tert*-butoxycarbonyl)amino)piperidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetate (1.55 g, 1.0 equiv., 2.35 mmol) in MeOH (28 mL) was added LiOH (169 mg,
 25 3.0 equiv., 7.06 mmol) in H₂O (14 mL). The resulting mixture was stirred for 1 hr at 25 degrees C. The mixture was basified to pH= 7 with aq. 1 M HCl solution. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash

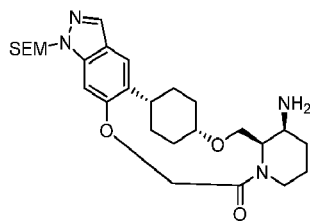
chromatography to provide 2-((5-(4-(((2R,3S)-3-((*tert*-butoxycarbonyl)amino)piperidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetic acid (1.4 g, 94.0 %) as a solid. LCMS (ESI): m/z $[M+H]^+ = 631$.



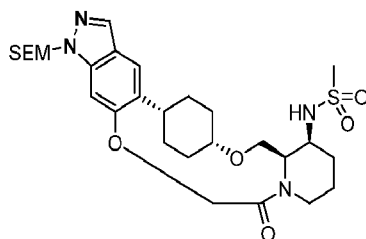
5 To a stirred mixture of HATU (1.2 g, 1.5 equiv., 3.1 mmol) and DIEA (0.80 g, 3.0 equiv., 6.2 mmol) in MeCN (390 mL) was added a solution of 2-((5-(4-(((2R,3S)-3-((*tert*-butoxycarbonyl)amino)piperidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetic acid (1.3 g, 1.0 equiv., 2.1 mmol) in MeCN (390 mL) dropwise. The resulting mixture was stirred for 1 hr at 25 degrees
10 C under nitrogen atmosphere. Then the mixture was concentrated under reduced pressure. The crude was purified by reverse flash chromatography to afford *tert*-butyl ((5²R, 5³S, *E*)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphan-2¹-en-5³-yl)carbamate (860 mg, 68.0 %) as a solid. LCMS (ESI): m/z $[M+H]^+ = 613$.



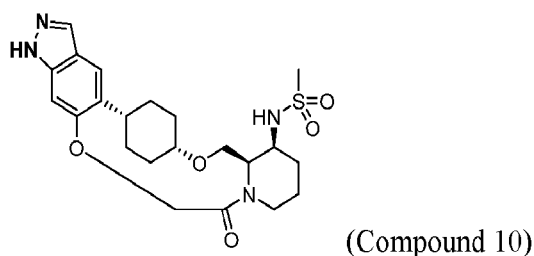
15 To a solution of *tert*-butyl ((5²R, 5³S, *E*)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphan-2¹-en-5³-yl)carbamate (860 mg, 1.0 equiv., 1.40 mmol) in MeOH (60 mL) was added Pd/C (2.99 g, 10 % Wt, 2 Eq, 2.81 mmol) at nitrogen atmosphere. The resulting mixture was hydrogenated at
20 room temperature for 12 hr under hydrogen atmosphere using a hydrogen balloon. The reaction solution was filtered through a Celite pad and concentrated under reduced pressure to afford *tert*-butyl ((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)carbamate (700 mg, 81.1
25 %) as an oil. LCMS (ESI): m/z $[M+H]^+ = 616$.



To a stirred solution of *tert*-butyl *tert*-butyl ((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)carbamate (690 mg, 1.0 equiv., 1.12 mmol) in DCM (8 mL) was added trifluoroacetic acid (2 mL) at room temperature. The mixture solution was stirred for 1 hr at room temperature. The reaction was quenched with water and extracted with EtOAc (3*20 mL). The combined organic layers were washed with brine (3*20 mL). After filtration, the filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography to afford (2¹S, 2⁴S, 5²R, 5³S)-5³-amino-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphan-6-one (300 mg, 51.9 %) as a solid. LCMS (ESI): *m/z* [M+H]⁺ = 515.

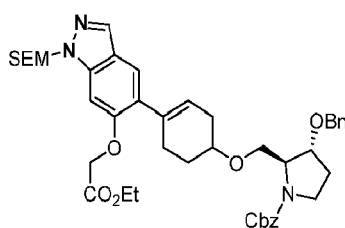


To a solution of (2¹S, 2⁴S, 5²R, 5³S)-5³-amino-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphan-6-one (300 mg, equiv., 583 μmol) in DCM (12 mL) was added TEA (177 mg, 244 μL, 3.0 equiv., 1.75 mmol). The resulting mixture was stirred for 10 min at 0 degrees C. Then to the mixture was added Ms₂O (122 mg, 1.2 equiv., 699 μmol). The resulting mixture was stirred for 30 min at 25 degrees C. The mixture was quenched with saturated NaHCO₃ solution. The resulting mixture was diluted with H₂O (10 mL) and extracted with DCM (3*10 mL), ethyl acetate (10 mL). The combined organic layers were concentrated under reduced pressure. The crude was purified by reverse flash chromatography to afford N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (300 mg, 86.8 %) as a solid. LCMS (ESI): *m/z* [M+H]⁺ = 593.



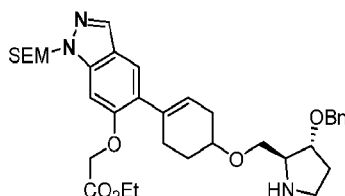
To a solution of N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (300 mg, 1.0 equiv., 506 μ mol) in DCM (20 mL) was added TFA (4 mL). The resulting mixture was stirred for 30 min at 25 degrees C. The resulting mixture was diluted with H₂O (20 mL), quenched with saturated Na₂CO₃ solution and extracted with DCM (3*30 mL). The combined organic layers were concentrated under reduced pressure to afford N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-piperidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (180 mg, 76.9 %) as a solid. LCMS (ESI): m/z [M+H]⁺ = 463. ¹H NMR (400 MHz, MeOD-d₄) δ 7.88 (s, 1H), 7.47 (s, 1H), 7.11 - 6.77 (m, 1H), 5.37 (d, J = 10.1 Hz, 1H), 5.26 (dt, J = 10.3, 4.7 Hz, 1H), 4.22 (d, J = 10.3 Hz, 1H), 3.97 (dd, J = 11.1, 9.1 Hz, 1H), 3.91 - 3.77 (m, 1H), 3.74 (s, 1H), 3.66 (dt, J = 11.1, 5.0 Hz, 1H), 3.56 (dd, J = 9.0, 4.0 Hz, 1H), 3.49 - 3.47 (m, 1H), 3.01 - 2.99 (m, 3H), 2.75 - 2.72 (m, 2H), 2.46 - 2.42 (m, 1H), 2.20 - 2.17 (m, 1H), 2.08 - 1.80 (m, 3H), 1.73 (t, J = 10.0 Hz, 2H), 1.58 - 1.35 (m, 3H), 1.31 (s, 1H).

Example 1.2

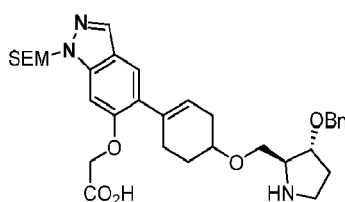


To a solution of benzyl (2S,3R)-3-(benzyloxy)-2-(((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)oxy)methyl)pyrrolidine-1-carboxylate (10.4 g, 1.0 equiv., 19.0 mmol) and ethyl 2-((5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetate (8.97 g, 1.1 equiv., 20.9 mmol) in 1,4-dioxane (120 mL) and H₂O (30.0 mL) were added Na₂CO₃ (6.04 g, 3.0 equiv., 57.0 mmol) and Pd(dppf)Cl₂ (2.78 g, 0.2 equiv., 3.80 mmol) under nitrogen atmosphere, the resulting mixture was stirred for 2 hr at 80 degrees C. The reaction solution was diluted with water (50 mL). The resulting mixture was extracted

with ethyl acetate (3 x 100 mL). The organic phase was washed with saturated aqueous NaCl (1 x 100 mL). The resulting organic phase was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford benzyl (2S,3R)-3-(benzyloxy)-2-(((4-(6-(2-ethoxy-2-oxoethoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)cyclohex-3-en-1-yl)oxy)methyl)cyclopentane-1-carboxylate (12.0 g, 82.2 %) as an oil. LCMS (ESI): m/z $[M+H]^+ = 771$.



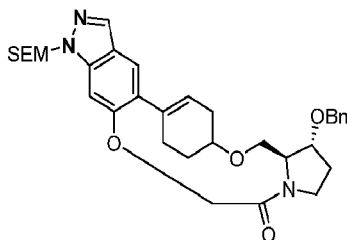
To a solution of benzyl (2S,3R)-3-(benzyloxy)-2-(((4-(6-(2-ethoxy-2-oxoethoxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)cyclohex-3-en-1-yl)oxy)methyl)pyrrolidine-1-carboxylate (12.0 g, 1.0 equiv., 15.6 mmol) in *i*-PrOH (300 mL) was added Pd/C (3.32 g, 10% Wt, 0.2 equiv., 3.11 mmol) at nitrogen atmosphere. The resulting mixture was hydrogenated at room temperature for 2 hr under hydrogen atmosphere using a hydrogen balloon. The resulting solution was filtered through Celite pad; the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford ethyl 2-((5-(4-(((2S,3R)-3-(benzyloxy)pyrrolidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetate (8.00 g, 80.7 %) as an oil. LCMS (ESI): m/z $[M+H]^+ = 637$.



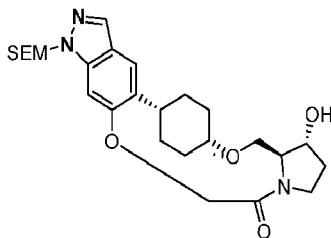
To the solution of ethyl 2-((5-(4-(((2S,3R)-3-(benzyloxy)pyrrolidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetate (8.00 g, 1.0 equiv., 12.6 mmol) in MeOH (150 mL) was added the solution of lithium hydroxide (904 mg, 3.0 equiv., 37.7 mmol) in H₂O (75.0 mL) at room temperature. The mixture solution was stirred for 1 hr at 25 degrees C. The mixture was basified to pH= 7 with aq. 1M HCl. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to provide 2-((5-(4-(((2S,3R)-3-(benzyloxy)pyrrolidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-

(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetic acid (5.30 g, 69.3 %) as a solid.

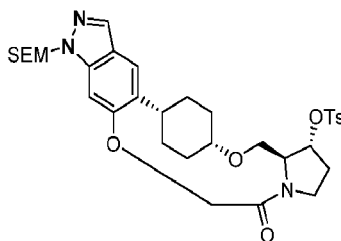
LCMS (ESI): m/z $[M+H]^+ = 608$.



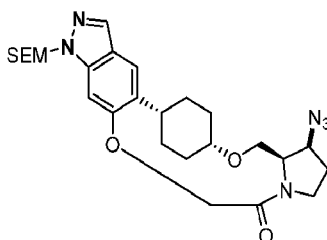
To a stirred mixture of HATU (4.97 g, 1.5 equiv., 13.1 mmol) and DIEA (3.38 g, 3.0 equiv., 26.2 mmol) in ACN (1.2 L) was added a solution of 2-((5-(4-(((2S,3R)-3-(benzyloxy)pyrrolidin-2-yl)methoxy)cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)oxy)acetic acid (5.30 g, 1.0 equiv., 8.72 mmol). The resulting mixture was stirred for 2 hr at 25 degrees C. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to provide (5²S, 5³R, *E*)-5³-(benzyloxy)-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-2¹-en-6-one (2.60 g, 4.41 mmol, 50.6 %) as an oil. LCMS (ESI): m/z $[M+H]^+ = 590$.



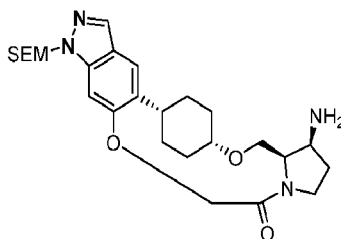
To a solution of (5²S, 5³R, *E*)-5³-(benzyloxy)-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-2¹-en-6-one (2.60 g, 1.0 equiv., 5.20 mmol) in MeOH (300 mL) was added Pd/C (1.11 g, 10% Wt, 0.2 equiv., 1.04 mmol) at nitrogen atmosphere. The resulting mixture was hydrogenated at room temperature for 3 hr under hydrogen atmosphere using a hydrogen balloon. The resulting solution was filtered through a Celite pad; the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford (2¹R, 2⁴R, 5²S, 5³R)-5³-hydroxy-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-6-one (1.98 g, 3.95 mmol, 75.8 %) as an oil. LCMS (ESI): m/z $[M+H]^+ = 502$.



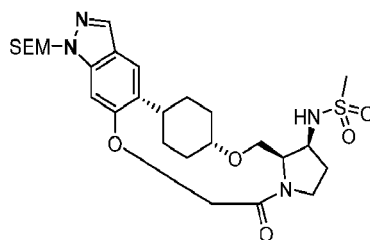
To a stirred mixture of (2¹R, 2⁴R, 5²S, 5³R)-5³-hydroxy-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-6-one (1.98 g, 1.0 equiv., 3.95 mmol) in DCM (40 mL) was added 4-methylbenzenesulfonyl chloride (1.13 g, 1.5 equiv., 5.92 mmol), triethylamine (1.20 g, 3.0 equiv., 11.8 mmol) and N,N-dimethylpyridin-4-amine (96.4 mg, 0.2 equiv., 789 μmol). The resulting mixture was stirred for 16 hr at 40 degrees C. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to provide (2¹R, 2⁴R, 5²S, 5³R)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl 4-methylbenzenesulfonate (1.80 g, 69.5 %) as a solid. LCMS (ESI): m/z [M+H]⁺ = 656.



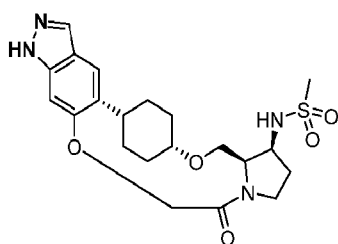
To a stirred solution of (2¹R, 2⁴R, 5²S, 5³R)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl 4-methylbenzenesulfonate (1.80 g, 1.0 equiv., 2.74 mmol) in DMF (20 mL) was added tetrabutylammonium azide (2.34 g, 3.0 equiv., 8.23 mmol). The resulting mixture was stirred for 16 hr at 100 degrees C. The reaction solution was diluted with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic phase was washed with saturated aqueous NaCl (1 x 20 mL). The resulting organic phase was concentrated under reduced pressure to afford (2¹S, 2⁴S, 5²R, 5³S)-5³-azido-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazole-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-6-one (1.30 g, 89.9 %) as an oil. LCMS (ESI): m/z [M+H]⁺ = 527.



To a solution of (2¹S, 2⁴S, 5²R, 5³S)-5³-azido-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-6-one (1.30 g, 1.0 equiv., 2.47 mmol) in MeOH (400 mL) was added Pd/C (525 mg, 10% Wt, 0.2 equiv., 494 μ mol) at nitrogen atmosphere. The resulting mixture was hydrogenated at room temperature for 1 hr under hydrogen atmosphere using a hydrogen balloon. The resulting solution was filtered through a Celite pad, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The crude was purified by reverse flash chromatography to afford (2¹S, 2⁴S, 5²R, 5³S)-5³-amino-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-6-one (1.00 g, 80.9 %) as an oil. LCMS (ESI): m/z [M+H]⁺ = 501.



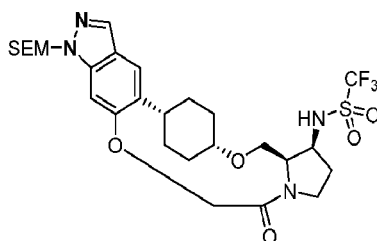
To the solution of (2¹S, 2⁴S, 5²R, 5³S)-5³-amino-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-6-one (100.0 mg, 1.0 equiv., 199.7 μ mol) in DCM (2 mL) were added triethylamine (30.3 mg, 1.5 equiv., 299.6 μ mol) and methanesulfonic anhydride (104.4 mg, 3.0 equiv., 599.1 μ mol) dropwise at room temperature. The solution was stirred for 2 hr at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 5 mL). The organic phase was washed with saturated aqueous NaCl (1 x 5 mL). The resulting organic phase was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (50.0 mg, 43.3 %) as an oil. LCMS (ESI): m/z [M+H]⁺ = 579.



(Compound 6)

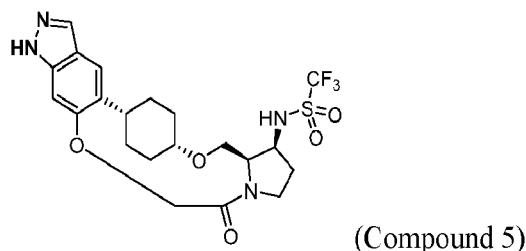
To the solution of N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-11-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (50.0 mg, 1.0 equiv., 86.4 μmol) in DCM (2 mL) was added TFA (0.5 mL) at room temperature. The mixture was stirred for 2 hr at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (12.3 mg, 31.7 %) as a solid. LCMS (ESI): m/z [M+H]⁺ = 449. ¹H NMR (400 MHz, Methanol-d₄) δ 7.89 (s, 1H), 7.49 (s, 1H), 6.93 (s, 1H), 5.22 (d, J = 10.0 Hz, 1H), 4.39 (s, 1H), 4.31 - 4.05 (m, 3H), 3.82 (s, 1H), 3.74 (d, J = 9.2 Hz, 1H), 3.53 (d, J = 9.4 Hz, 1H), 3.05 (s, 2H), 2.68 - 2.65 (m, 1H), 2.44 (t, J = 10.8 Hz, 1H), 2.31 (d, J = 11.1 Hz, 1H), 2.17 - 2.13 (m, 1H), 1.91 (s, 1H), 1.69 - 1.36 (m, 2H), 1.31 (s, 1H).

Example 1.3



To the solution of (2¹S, 2⁴S, 5²R, 5³S)-5³-amino-1¹-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphan-6-one (70.0 mg, 1.0 equiv., 139.8 μmol) in DCM (0.5 mL) were added trifluoromethanesulfonic anhydride (47.3 mg, 1.2 equiv., 167.8 μmol) and triethylamine (42.4 mg, 3.0 equiv., 419.4 μmol). The resulting mixture was stirred for 6 min at 25 degrees C. The resulting solution was diluted with water (10 ml) and extracted with DCM (3 x 10 mL). The organic phase was washed with saturated aqueous NaCl (5 mL). The resulting organic phase was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford 1,1,1-trifluoro-N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-11-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-

cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (60.0 mg, 67.8 %) as an oil. LCMS (ESI): m/z [M+H]⁺ = 634.



To the solution of 1,1,1-trifluoro-N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-11-((2-(trimethylsilyl)ethoxy)methyl)-1¹H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (60.0 mg, 1.0 equiv., 94.8 μmol) in DCM (2 mL) was added TFA (0.5 mL) at room temperature. The mixture was stirred for 2 hr at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to provide 1,1,1-trifluoro-N-((2¹S, 2⁴S, 5²R, 5³S)-6-oxo-11H-3,8-dioxo-1(5,6)-indazola-5(2,1)-pyrrolidina-2(1,4)-cyclohexanacyclooctaphane-5³-yl)methanesulfonamide (13.9 mg, 29.2 %) as a solid. LCMS (ESI): m/z [M+H]⁺ = 503. ¹H NMR (400 MHz, Methanol-d₄) δ 7.88 (s, 1H), 7.48 (s, 1H), 6.93 (s, 1H), 5.20 (dd, J = 10.1, 2.5 Hz, 1H), 4.36 (dd, J = 7.9, 3.1 Hz, 1H), 4.32 – 4.23 (m, 2H), 4.15 (dd, J = 9.3, 3.4 Hz, 1H), 3.82 (s, 1H), 3.73 - 3.70 (m, 1H), 3.45 (d, J = 9.4 Hz, 1H), 2.76 - 2.43 (m, 3H), 2.27 (t, J = 10.3 Hz, 2H), 2.16 - 2.13 (m, 1H), 1.99 - 1.88 (m, 1H), 1.58 - 1.28 (m, 5H).

Example 2: Human OX₂R IP1 assay

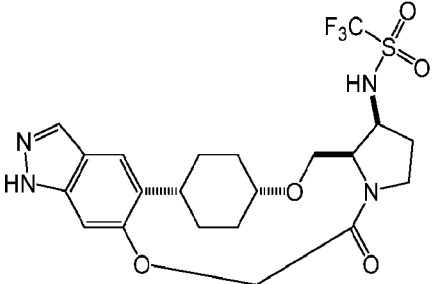
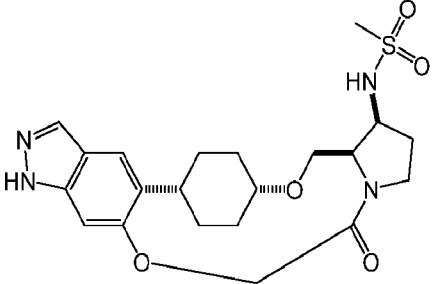
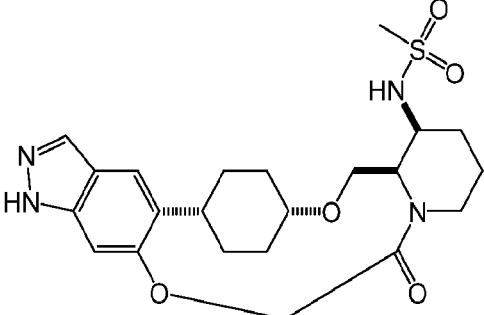
T-Rex CHO cells stably overexpressing the human orexin-2 receptor (OX₂R) were induced overnight with 1 μg/mL of doxycycline in a T225 flask. 24 hours post induction, cells were lifted with accutase and plated into a 384-well proxy plate at 30,000 cells/well. Cells were then treated with different test compounds in 1X stimulation buffer containing 10 mM Hepes, 1 mM CaCl₂, 0.5 mM MgCl₂, 4.2 mM KCl, 146 mM NaCl, 5.5 mM glucose, and 50 mM LiCl, pH 7.4, for 1 hr at 37 degrees C. Following incubation, the reaction was terminated by the addition of detection mix, which is composed of IP1-d2 and anti-IP1-cryptate diluted in lysis buffer as well as 1X stimulation buffer. The plates were allowed to incubate for 1 hour at room temperature and were then read in the EnVision® multimode plate reader, measuring inositol phosphate levels.

Cisbio IP1 is a cell-based functional assay quantifying the accumulation of inositol monophosphate (IP), a metabolite released as a result of orexin 2 receptor activation through the phospholipase C-Gq signaling pathway. This is a competitive immunoassay in which the IP1 produced by the cells upon receptor activation competes with the IP1 analog coupled to the d2 fluorophore (acceptor) for binding to an anti-IP1 monoclonal antibody labeled with Eu cryptate (donor). The measured HTRF-FRET based signal is inversely proportional to the IP1 concentration produced.

The EC₅₀ values reported in Table 2 were obtained according to the human OX₂R IP1 assay described above. Data are the mean EC₅₀ values ± S.E.M.

10

Table 2

Compound	Compound No.	EC ₅₀ (nM)
	5	**
	6	**
	10	***

***EC₅₀ < 100 nM

**EC₅₀ 100-1,000 nM

*EC₅₀ > 1,000 nM

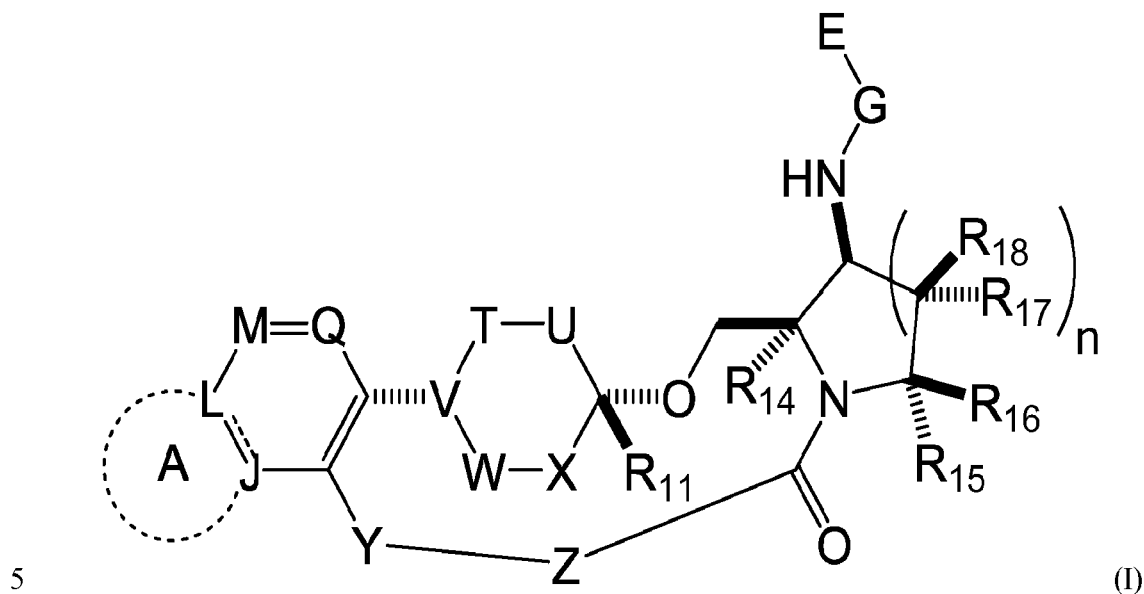
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While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound of Formula I or a pharmaceutically acceptable salt thereof:



wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

===== is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

15 Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b , $\text{C}(=\text{O})\text{NR}_a\text{R}_b$, $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-
20 ($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, and $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl), wherein the $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, and $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl) are defined as follows:

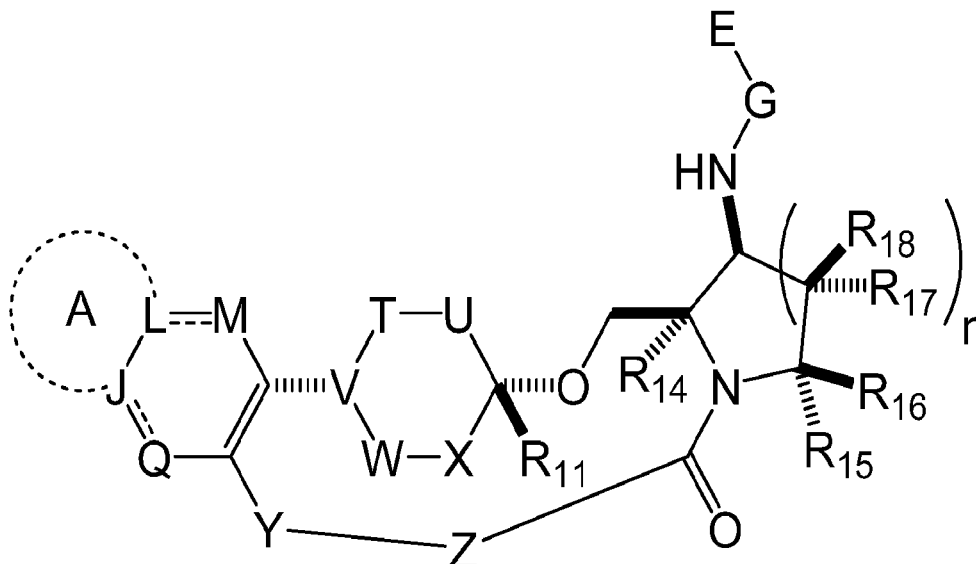
- C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,
- 5 C₁-C₃ alkyl, or C₁-C₃ alkoxy;
- T is CR₁R₂ or O;
- W is CR₄R₅ or O;
- U is CR₆R₇;
- X is CR₈R₉;
- 10 V is CR₃ or N;
- Y is NR₁₀, O or absent;
- Z is (CR₁₂R₁₃)_m;
- R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;
- m is 1, 2, 3, or 4;
- 15 and further wherein:
- R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;
- or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;
- 20 R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;
- or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;
- or, alternatively, R₃ and R₄, together with the carbon atoms to which they are
- 25 attached, form a C₃-C₅ cycloalkyl;
- R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;
- R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;
- 30 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and
- R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

2. The compound of claim 1, wherein n is 1.
3. The compound of claim 1, wherein n is 2.
4. The compound of any one of claims 1-3, wherein Y is O.
5. The compound of any one of claims 1-3, wherein Y is absent.
- 10 6. The compound of any one of claims 1-3, wherein Y is NR₁₀.
7. The compound of any one of the preceding claims, wherein T is CR₁R₂.
8. The compound of any one of claims 1-6, wherein T is O.
9. The compound of any one of the preceding claims, wherein W is CR₄R₅.
10. The compound of any one of the claims 1-8, wherein W is O.
- 15 11. The compound of any one of the preceding claims, wherein V is CR₃.
12. The compound of any one of the preceding claims, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.
- 20 13. The compound of any one of claims 1-11, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₃-C₈ cycloalkyl, and 4- to 10-membered heterocyclyl, wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or 4- to 10-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.
- 25 14. The compound of any one of claims 1-7, 9, and 11-13, wherein T is CR₁R₂, W is CR₄R₅, and V is CR₃.
- 30

15. The compound of any one of the preceding claims, wherein m is 1 or 2.
16. The compound of any one of claims 1-14, wherein m is 1.
17. A compound of Formula II or a pharmaceutically acceptable salt thereof:



5 (II)

wherein:

fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

15 Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl),

4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

5 T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

10 Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

15 R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

20 R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

25 R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

30 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

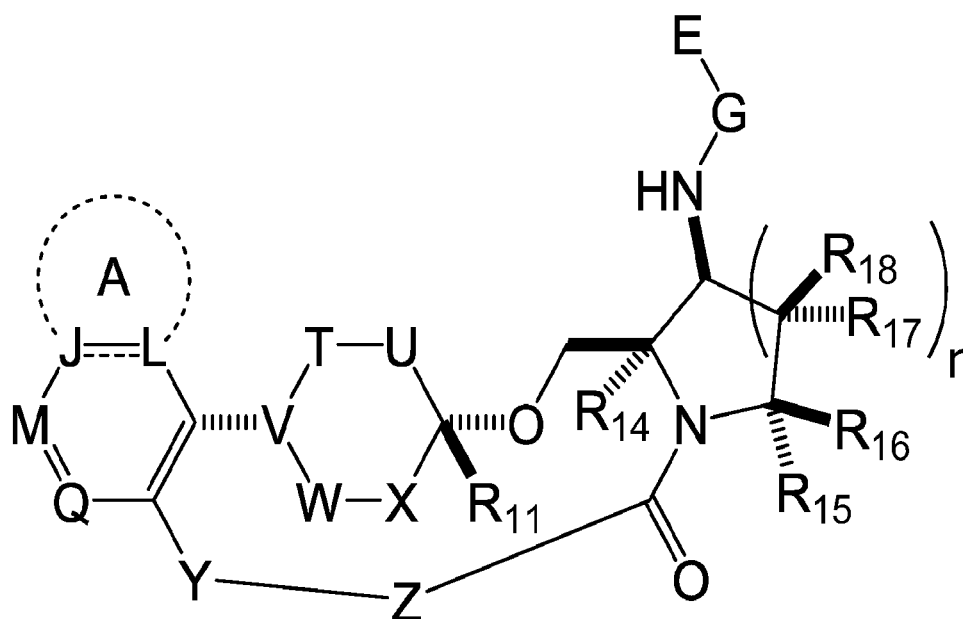
R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

18. The compound of claim 17, wherein n is 1.
19. The compound of claim 17, wherein n is 2.
20. The compound of any one of claims 17-19, wherein Y is O.
21. The compound of any one of claims 17-19, wherein Y is absent.
22. The compound of any one of claims 17-19, wherein Y is NR₁₀.
23. The compound of any one of claims 17-22, wherein T is CR₁R₂.
24. The compound of any one of claims 17-22, wherein T is O.
25. The compound of any one of claims 17-24, wherein W is CR₄R₅.
26. The compound of any one of claims 17-24, wherein W is O.
27. The compound of any one of claims 17-26, wherein V is CR₃.
28. The compound of any one of claims 17-27, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxyl.
29. The compound of any one of claims 17-27, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₃-C₈ cycloalkyl, and 4- to 10-membered heterocyclyl, wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or 4- to 10-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxyl.

30. The compound of any one of claims 17-23, 25, and 27-29, wherein T is CR₁R₂, W is CR₄R₅, and V is CR₃.
31. The compound of any one of claims 17-30, wherein m is 1 or 2.
32. The compound of any one of claims 17-30, wherein m is 1.
- 5 33. A compound of Formula III or a pharmaceutically acceptable salt thereof:



(III)

wherein:

- fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-
 10 membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to
 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium,
 hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one
 or more halogen or deuterium;

----- is a single bond or double bond;

- 15 J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

- 20 E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃
 alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-

(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl),
 5 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

10 W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

15 Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 1, 2, 3, or 4;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H,
 20 hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached, form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

25 or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of
 30 H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H,
5 unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H,
unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen,
10 deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one
or more halogen or deuterium.

34. The compound of claim 33, wherein n is 1.

35. The compound of claim 33, wherein n is 2.

36. The compound of any one of claims 33-35, wherein Y is O.

37. The compound of any one of claims 33-35, wherein Y is absent.

15 38. The compound of any one of claims 33-35, wherein Y is NR₁₀.

39. The compound of any one of claims 33-38, wherein T is CR₁R₂.

40. The compound of any one of claims 33-38, wherein T is O.

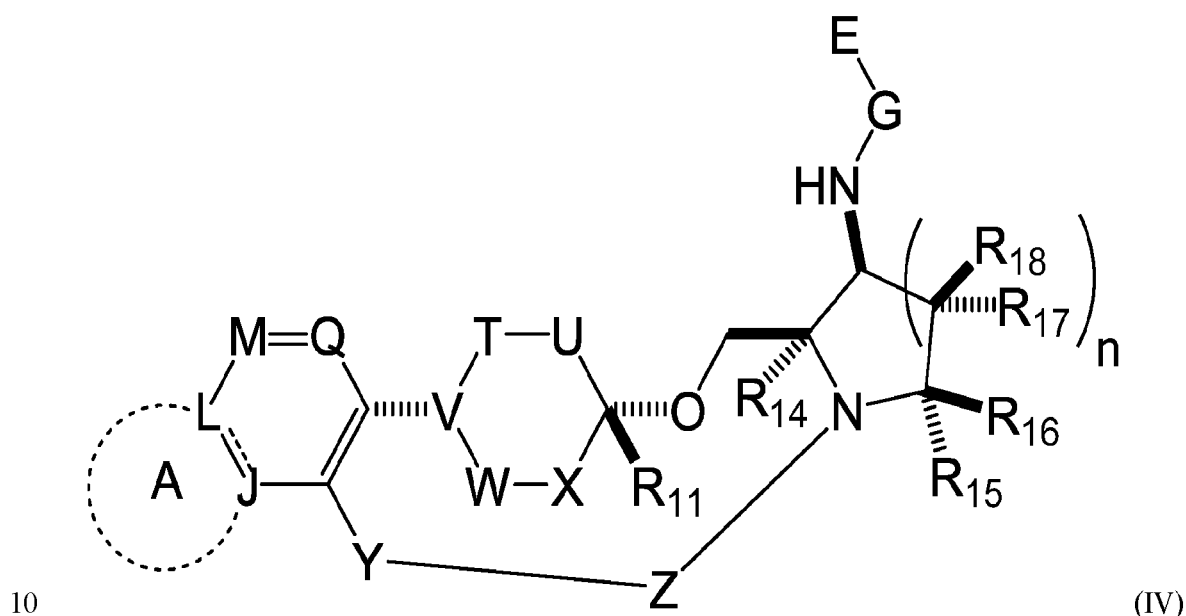
41. The compound of any one of claims 33-40, wherein W is CR₄R₅.

42. The compound of any one of claims 33-40, wherein W is O.

20 43. The compound of any one of claims 33-42, wherein V is CR₃.

44. The compound of any one of claims 33-43, wherein E is selected from the group
consisting of C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-
C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered
heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-
25 C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄
alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl,
C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl),
5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is
unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

45. The compound of any one of claims 33-43, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₃-C₈ cycloalkyl, and 4- to 10-membered heterocyclyl, wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or 4- to 10-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.
46. The compound of any one of claims 33-39, 41, and 43-45, wherein T is CR₁R₂, W is CR₄R₅, and V is CR₃.
47. The compound of any one of claims 33-46, wherein m is 1 or 2.
48. The compound of any one of claims 33-46, wherein m is 1.
49. A compound of Formula IV or a pharmaceutically acceptable salt thereof:



wherein:

- fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

----- is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

20 Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b , $\text{C}(=\text{O})\text{NR}_a\text{R}_b$, $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, and $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl), wherein the $\text{C}_1\text{-C}_3$ alkylene- NR_aR_b , $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_3\text{-C}_8$ cycloalkyl), 4- to 10-membered heterocyclyl, $\text{C}_1\text{-C}_3$ alkylene-(4- to 10-membered heterocyclyl), $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_1\text{-C}_3$ alkylene-($\text{C}_6\text{-C}_{10}$ aryl), 5- to 10-membered heteroaryl, or $\text{C}_1\text{-C}_3$ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, $\text{C}_1\text{-C}_3$ alkyl, or $\text{C}_1\text{-C}_3$ alkoxy;

T is CR_1R_2 or O;

W is CR_4R_5 or O;

U is CR_6R_7 ;

15 X is CR_8R_9 ;

V is CR_3 or N;

Y is NR_{10} , O or absent;

Z is $(\text{CR}_{12}\text{R}_{13})_m$;

R_a and R_b are each, independently, H or unsubstituted $\text{C}_1\text{-C}_3$ alkyl;

20 m is 2, 3, 4, or 5 when Y is absent; or

m is 1, 2, 3, or 4 when Y is NR_{10} or O;

and further wherein:

R_1 , R_2 , R_4 , and R_5 are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

25 or, alternatively, R_2 and R_5 together with the carbon atoms to which they are attached, form a single bond;

R_3 is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

30 or, alternatively, R_3 and R_1 , together with the carbon atoms to which they are attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

or, alternatively, R_3 and R_4 , together with the carbon atoms to which they are attached, form a $\text{C}_3\text{-C}_5$ cycloalkyl;

R_6 , R_7 , R_8 , R_9 , and R_{11} are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

50. The compound of claim 49, wherein n is 1.

51. The compound of claim 49, wherein n is 2.

52. The compound of any one of claims 49-51, wherein Y is O.

53. The compound of any one of claims 49-51, wherein Y is absent.

54. The compound of any one of claims 49-51, wherein Y is NR₁₀.

55. The compound of any one of claims 49-54, wherein T is CR₁R₂.

56. The compound of any one of claims 49-54, wherein T is O.

57. The compound of any one of claims 49-56, wherein W is CR₄R₅.

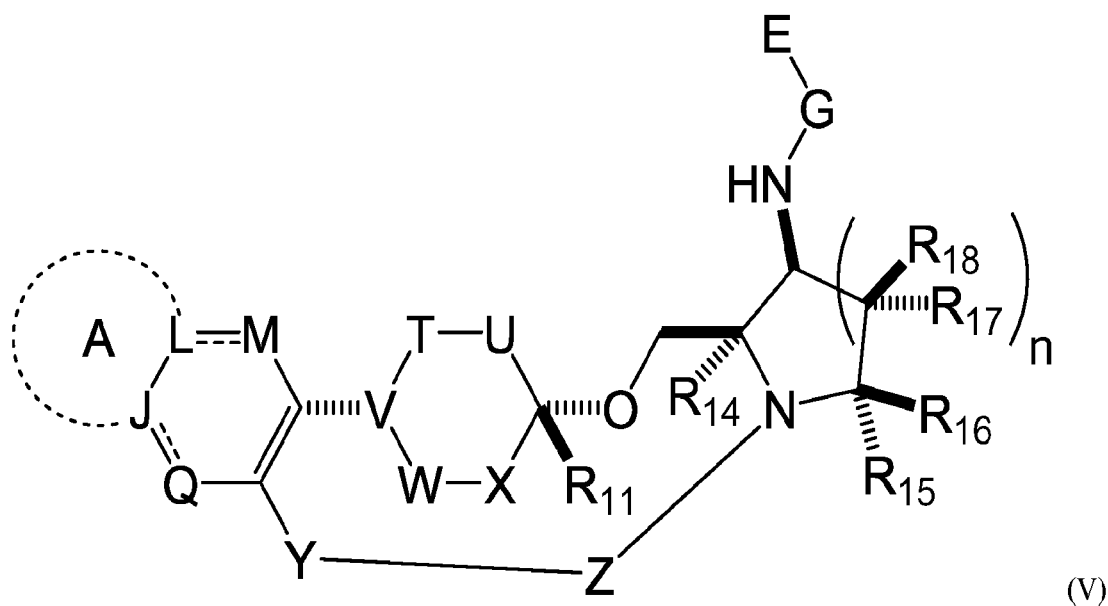
58. The compound of any one of claims 49-56, wherein W is O.

59. The compound of any one of claims 49-58, wherein V is CR₃.

60. The compound of any one of claims 49-59, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered

heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

61. The compound of any one of claims 49-59, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₃-C₈ cycloalkyl, and 4- to 10-membered heterocyclyl, wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or 4- to 10-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.
62. The compound of any one of claims 49-55, 57, and 59-61, wherein T is CR₁R₂, W is CR₄R₅, and V is CR₃.
63. The compound of any one of claims 49-62, wherein m is 2 or 3.
64. The compound of any one of claims 49-62, wherein m is 2.
65. A compound of Formula V or a pharmaceutically acceptable salt thereof:



wherein:

- fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

==== is a single bond or double bond;

- J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃
 5 alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-
 (C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered
 heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and
 C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-
 C₃alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl),
 10 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀
 aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to
 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,
 C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

15 W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

V is CR₃ or N;

Y is NR₁₀, O or absent;

20 Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

25 R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H,
 hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached,
 form a single bond;

30 R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and
 cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are
 attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are
 attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

5 each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

10 each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

15 66. The compound of claim 65, wherein n is 1.

67. The compound of claim 65, wherein n is 2.

68. The compound of any one of claims 65-67, wherein Y is O.

69. The compound of any one of claims 65-67, wherein Y is absent.

70. The compound of any one of claims 65-67, wherein Y is NR₁₀.

20 71. The compound of any one of claims 65-70, wherein T is CR₁R₂.

72. The compound of any one of claims 65-70, wherein T is O.

73. The compound of any one of claims 65-72, wherein W is CR₄R₅.

74. The compound of any one of claims 65-72, wherein W is O.

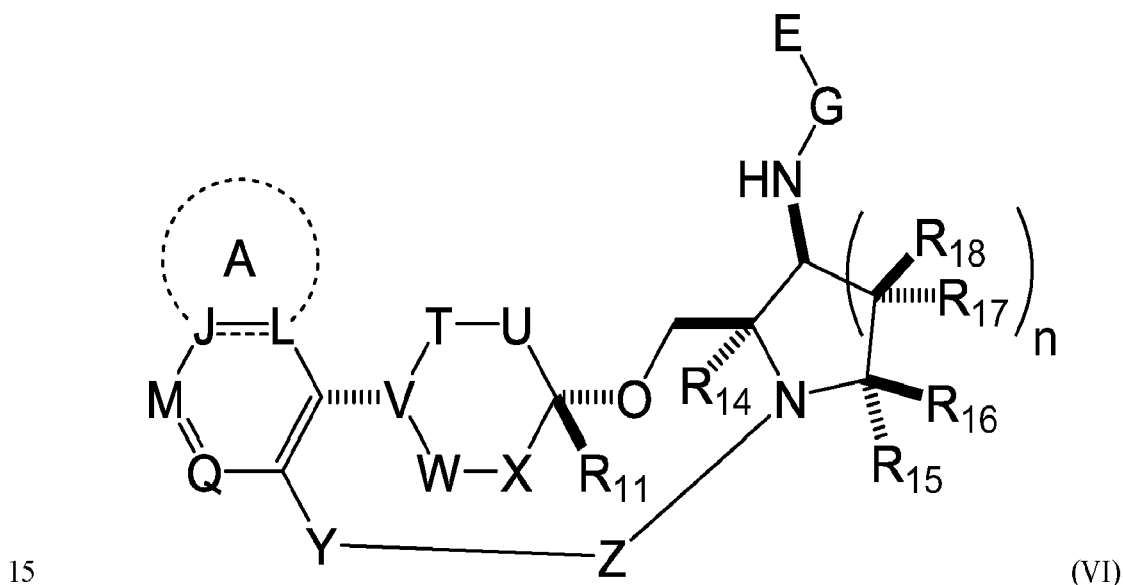
75. The compound of any one of claims 65-74, wherein V is CR₃.

25 76. The compound of any one of claims 65-75, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered

30

heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

- 5 77. The compound of any one of claims 65-75, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₃-C₈ cycloalkyl, and 4- to 10-membered heterocyclyl, wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or 4- to 10-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.
- 10 78. The compound of any one of claims 65-71, 73, and 75-77, wherein T is CR₁R₂, W is CR₄R₅, and V is CR₃.
79. The compound of any one of claims 65-78, wherein m is 2 or 3.
80. The compound of any one of claims 65-78, wherein m is 2.
81. A compound of Formula VI or a pharmaceutically acceptable salt thereof:



wherein:

- 20 fused ring A is a C₄-C₈ cycloalkyl, a 4- to 7-membered heterocyclyl, or a 5- to 8-membered heteroaryl, wherein the C₄-C₈ cycloalkyl, 4- to 7-membered heterocyclyl, or 5- to 8-membered heteroaryl is unsubstituted or substituted with one or more halogen, deuterium, hydroxyl, cyano, C₁-C₃ alkoxy, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium;

===== is a single bond or double bond;

J and L are each, independently, C or N;

M is N or CR₁₉;

Q is N or CR₂₀;

G is C(=O) or S(=O)₂;

5 n is 1, 2, or 3;

E is selected from the group consisting of H, hydroxyl, NR_aR_b, C(=O)NR_aR_b, C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, and
 10 C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkylene-NR_aR_b, C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl,
 15 C₁-C₃ alkyl, or C₁-C₃ alkoxy;

T is CR₁R₂ or O;

W is CR₄R₅ or O;

U is CR₆R₇;

X is CR₈R₉;

20 V is CR₃ or N;

Y is NR₁₀, O or absent;

Z is (CR₁₂R₁₃)_m;

R_a and R_b are each, independently, H or unsubstituted C₁-C₃ alkyl;

m is 2, 3, 4, or 5 when Y is absent; or

25 m is 1, 2, 3, or 4 when Y is NR₁₀ or O;

and further wherein:

R₁, R₂, R₄, and R₅ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

or, alternatively, R₂ and R₅ together with the carbon atoms to which they are attached,
 30 form a single bond;

R₃ is selected from the group consisting of H, deuterium, halogen, hydroxyl, and cyano;

or, alternatively, R₃ and R₁, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

or, alternatively, R₃ and R₄, together with the carbon atoms to which they are attached, form a C₃-C₅ cycloalkyl;

R₆, R₇, R₈, R₉, and R₁₁ are each, independently, selected from the group consisting of H, hydroxyl, halogen, and deuterium;

5 R₁₀ is selected from the group consisting of H, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen;

each R₁₂ and R₁₃ is, independently, selected from the group consisting of H, halogen, deuterium, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with hydroxyl or one or more halogen; and

10 R₁₄, R₁₅, and R₁₆ are each, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen;

each R₁₇ and R₁₈ is, independently, selected from the group consisting of H, unsubstituted C₁-C₃ alkyl or C₁-C₃ alkyl substituted with one or more halogen; and

15 R₁₉ and R₂₀ are each, independently, selected from the group consisting of H, halogen, deuterium, hydroxyl, cyano, unsubstituted C₁-C₃ alkyl, and C₁-C₃ alkyl substituted with one or more halogen or deuterium.

82. The compound of claim 81, wherein n is 1.

83. The compound of claim 81, wherein n is 2.

84. The compound of any one of claims 81-83, wherein Y is O.

20 85. The compound of any one of claims 81-83, wherein Y is absent.

86. The compound of any one of claims 81-83, wherein Y is NR₁₀.

87. The compound of any one of claims 81-86, wherein T is CR₁R₂.

88. The compound of any one of claims 81-86, wherein T is O.

89. The compound of any one of claims 81-88, wherein W is CR₄R₅.

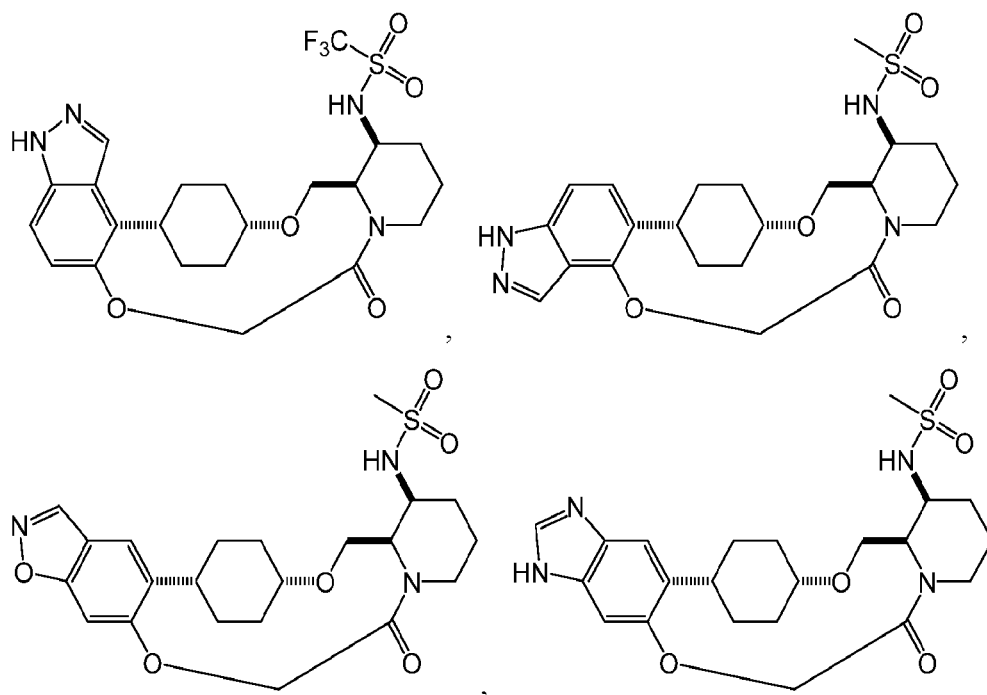
25 90. The compound of any one of claims 81-88, wherein W is O.

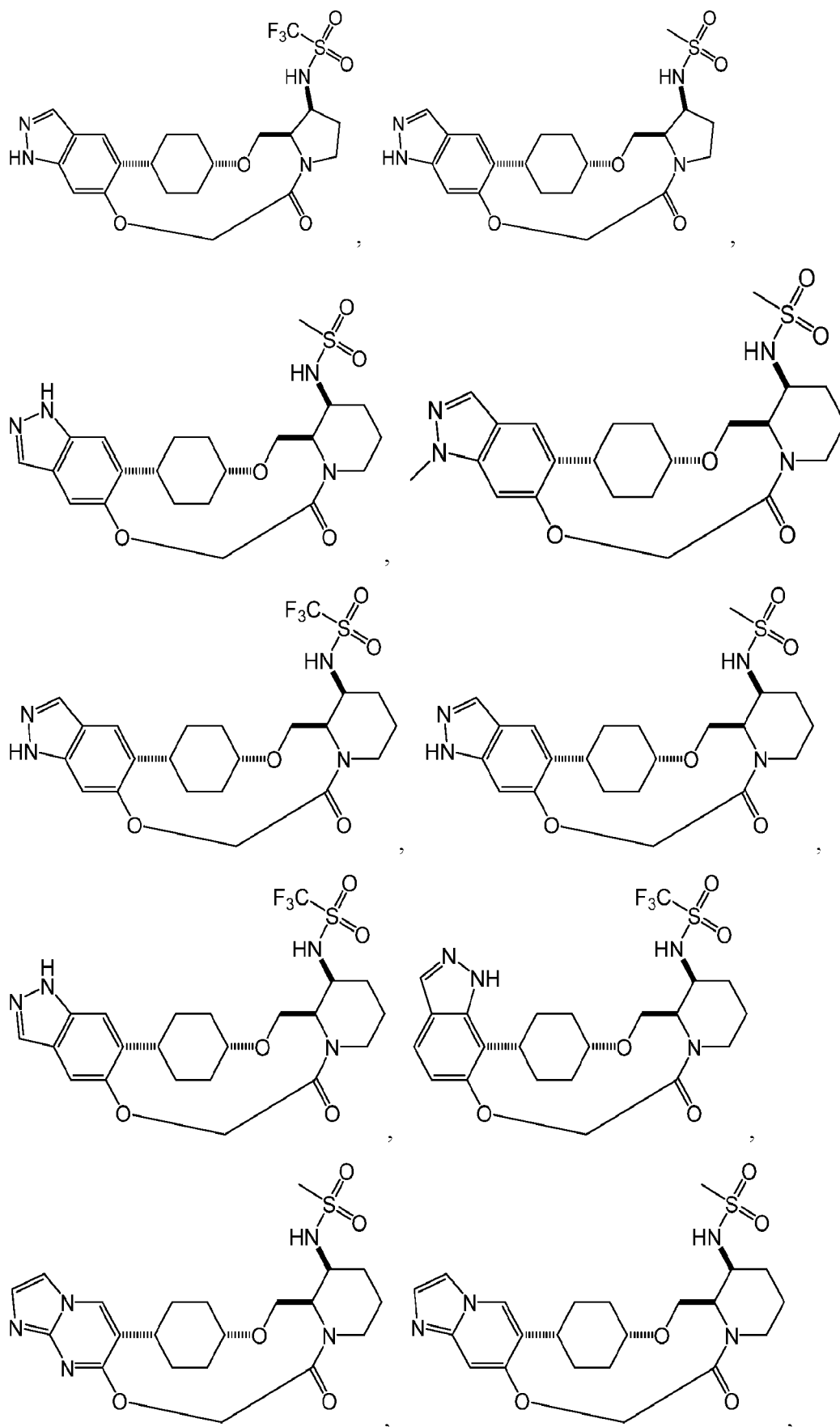
91. The compound of any one of claims 81-90, wherein V is CR₃.

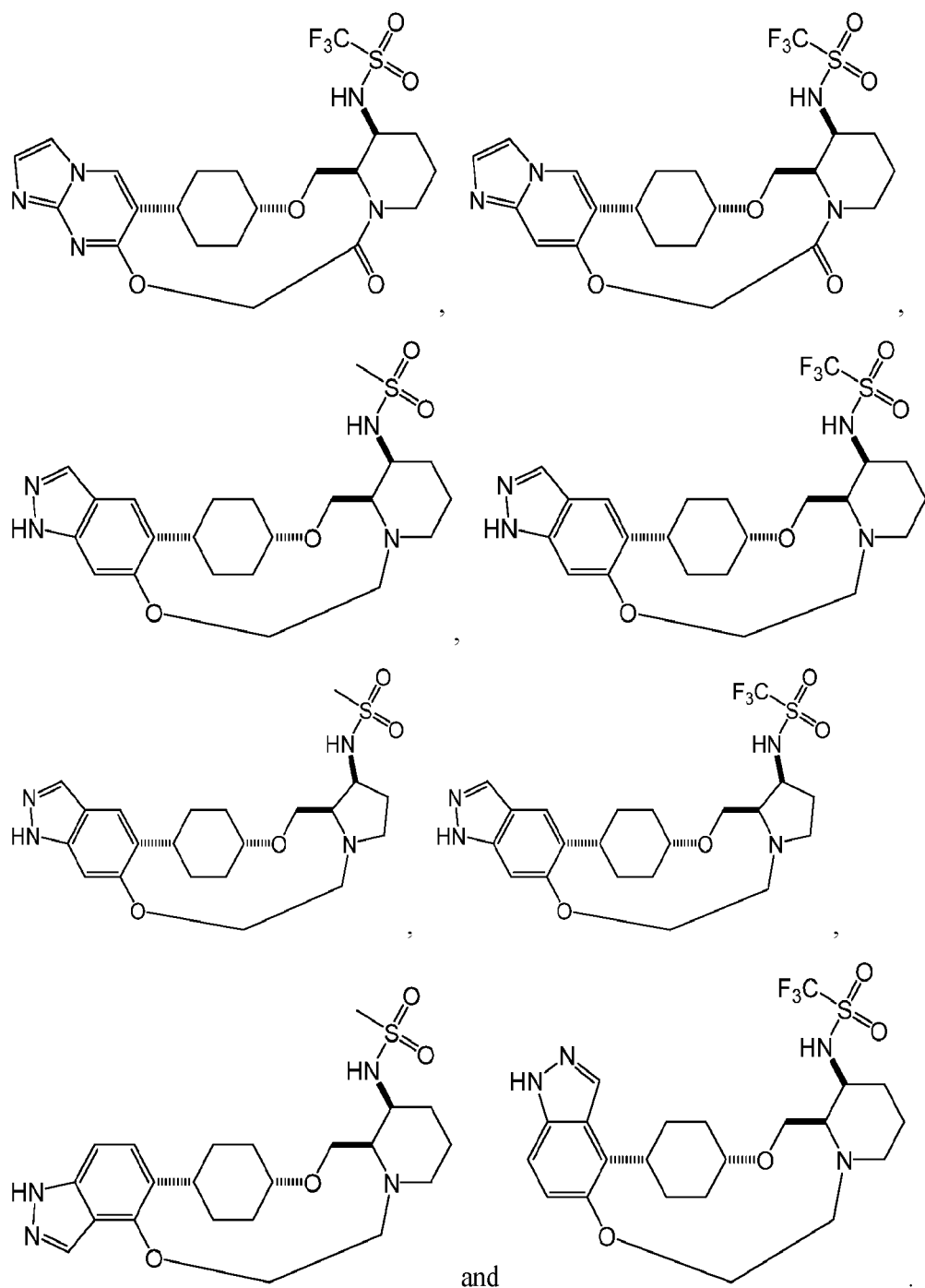
92. The compound of any one of claims 81-91, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-

30

- membered heteroaryl, and C₁-C₃ alkylene-(5- to 10-membered heteroaryl), wherein the C₁-C₃ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₈ cycloalkyl, C₁-C₃ alkylene-(C₃-C₈ cycloalkyl), 4- to 10-membered heterocyclyl, C₁-C₃ alkylene-(4- to 10-membered heterocyclyl), C₆-C₁₀ aryl, C₁-C₃ alkylene-(C₆-C₁₀ aryl), 5- to 10-membered heteroaryl, or C₁-C₃ alkylene-(5- to 10-membered heteroaryl) is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.
93. The compound of any one of claims 81-91, wherein E is selected from the group consisting of C₁-C₃ alkyl, C₃-C₈ cycloalkyl, and 4- to 10-membered heterocyclyl, wherein the C₁-C₃alkyl, C₃-C₈ cycloalkyl, or 4- to 10-membered heterocyclyl is unsubstituted or substituted with one or more halogen, hydroxyl, C₁-C₃ alkyl, or C₁-C₃ alkoxy.
94. The compound of any one of claims 81-87, 89, and 91-93, wherein T is CR₁R₂, W is CR₄R₅, and V is CR₃.
95. The compound of any one of claims 81-94, wherein m is 2 or 3.
96. The compound of any one of claims 81-94, wherein m is 2.
97. A compound or a pharmaceutically acceptable salt thereof selected from the group consisting of:







- 5 98. A pharmaceutical composition comprising a compound of any one of claims 1-97 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
99. A method of treating narcolepsy in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-97 or a pharmaceutically acceptable salt thereof, or a composition according to claim 98.

100. A method of treating cataplexy in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-97 or a pharmaceutically acceptable salt thereof, or a composition according to claim 98.
- 5 101. Use of a compound of any one of claims 1-97 or a pharmaceutically acceptable salt thereof, or a composition according to claim 98 for the manufacture of a medicament for narcolepsy.
102. Use of a compound of any one of claims 1-97 or a pharmaceutically acceptable salt thereof, or a composition according to claim 98 for the manufacture of a medicament for cataplexy.
- 10 103. A compound of any one of claims 1-97 or a pharmaceutically acceptable salt thereof, or a composition according to claim 98 for use in a method of treating narcolepsy in a subject in need thereof.
- 15 104. A compound of any one of claims 1-97 or a pharmaceutically acceptable salt thereof, or a composition according to claim 98 for use in a method of treating cataplexy in a subject in need thereof.