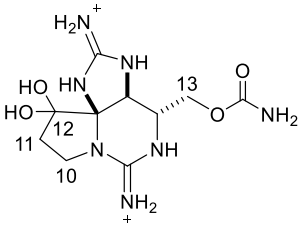
desirable. Such a drug design is challenging given the high structural homology (75-96%) of the mammalian Na_V isoforms.

[0005] There exists a need for compounds which treat pain and conditions associated with voltage-gated sodium channel function, particularly which selectively inhibit Na_V 1.7 over other Na_V isoforms.

SUMMARY

[0006] Provided herein are compounds, methods of making the compounds, pharmaceutical compositions comprising the compounds, and methods of using the compounds and compositions for the treatment of conditions modulated by voltage-gated sodium channels, in some or any examples, in the treatment of pain. The compounds are 11,13-modified, non-hydrated ketone saxitoxins. Also provided herein are methods of treating pain and/or conditions modulated by voltage-gated sodium channels in a mammal comprising administering a therapeutically or prophylactically effective amount of a 11,13-modified, non-hydrated ketone saxitoxin or composition to a mammal. In some or any examples, the mammal is a human. Also provided herein are compounds which have improved stability.

[0007] Saxitoxin has the chemical structure provided below with selected atom numbering used herein:

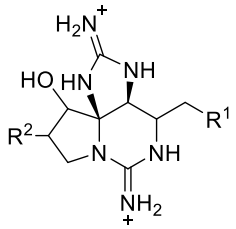


(Saxitoxin).

[0008] Compounds containing a hydrated ketone functional group at the C12 position (*i.e.* $>C(OH)_2$) can epimerize at the C11 position under certain conditions leading to a mixture of C11R and C11S diastereomers. For example, it has been shown that saxitoxinethanoic acid, a modified saxitoxin substituted with ethanoic acid at the C11 position, epimerizes at the C11 position and exists as a mixture of C11R and C11S diastereomers when synthesized (Wang *et al., Angew Chem Int Ed Engl.* 12(55): 11600-11603, 2016) and when isolated as a natural product (Arakawa *et al., Toxicon* 33(12): 1577-1584, 1995). Similarly, gonyautoxin, which is saxitoxin substituted with a sulfate at C11, has been shown to undergo epimerization when synthesized (Mulcahy *et al., J. Am. Chem. Soc.* 130(38): 12630-12631, 2008) and when

studies (34 days) in rat and monkey plasma (Example 4). Further, as described in Example 5, two compounds of Formula (I) were stable for up to two hours in cynomolgus monkey plasma at room temperature and 4 ºC. Therefore, in certain embodiments, the compounds of Formula (I), substituted with a C12 mono-hydroxyl group, represent stable saxitoxin analogs.

[0012] In one aspect, provided herein is a Compound of Formula (I):



(I)

wherein

R^1 is $-NR^{3a}R^3$, $-NR^4C(O)R^{4a}$, $-CH_2NR^4C(O)R^{4a}$, heteroaryl, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NH_3^+$, $-CH_2CH_2NH_3^+$, $-NR^5S(O)_2R^{5a}$, $-CH_2NR^5S(O)_2R^{5a}$, $-NR^6C(O)NR^{6a}R^{6b}$, $-CH_2NR^6C(O)NR^{6a}R^{6b}$, $-NR^8C(O)OR^{8a}$, or $-CH_2NR^8C(O)OR^{8a}$;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^3 is hydrogen or $C_{1\text{-}6}$alkyl;

R^{3a} is hydrogen or $C_{1\text{-}6}$alkyl;

R^4 is hydrogen or $C_{1\text{-}6}$alkyl;

R^{4a} is hydrogen; $C_{1\text{-}6}$alkyl; halo-$C_{1\text{-}6}$alkyl; amino-$C_{1\text{-}6}$alkyl; $C_{1\text{-}6}$alkylamino$C_{1\text{-}6}$alkyl; di-$C_{1\text{-}6}$alkylamino$C_{1\text{-}6}$alkyl; $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl; cycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; cycloalkylalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aralkyl where the aryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaralkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heterocyclicalkyl where the heterocyclic portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

each of the 1, 2, 3, or 4 R^{4b}, when present, is independently $C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyloxy, hydroxy, halo, halo-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, cyano, phenyl, or heteroaryl; or

2 R^{4b} groups, when on the same carbon atom, are taken together to form an oxo group, and the other 2 R^{4b}, when present, are independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group;

R^5 is hydrogen or C_{1-6}alkyl;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^6 is hydrogen or C_{1-6}alkyl;

R^{6a} is hydrogen or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, or cycloalkyl;

R^8 is hydrogen or C_{1-6}alkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl, or phenyl;

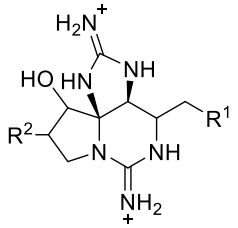
R^7 is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl; or

a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, mixture, or combination thereof.

[0013] In an example, provided herein is a Compound of Formula (P-I):



(P-I)

wherein

a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, mixture, or combination thereof.

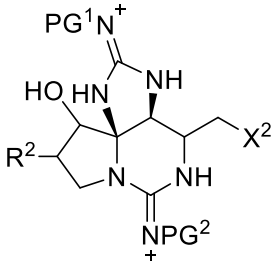
[0014] Provided herein are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating pain and/or conditions modulated by voltage-gated sodium channels which comprise a therapeutically or prophylactically effective amount of a compound provided herein, *e.g.*, of some or any of the embodiments of Formula (I), (P-I), (P-Ia), (P-Ib-1), (P-Ib-2), (P-Ic-1), (P-Ic-2), (P-Id-1), and (P-Id-2) and compounds 1-46,49-52, and 53-70. In another aspect, provided herein is a pharmaceutical composition comprising the compound as defined herein and a pharmaceutically acceptable carrier.

[0015] Provided herein is a method of treatment of pain and/or conditions modulated by voltage-gated sodium channels comprising administering to an individual in need thereof a therapeutically or prophylactically effective amount of a 11,13-modified, non-hydrated ketone saxitoxin described herein, *e.g.*, of some or any of the embodiments of Formula (I), (P-I), (P-Ia), (P-Ib-1), (P-Ib-2), (P-Ic-1), (P-Ic-2), (P-Id-1), and (P-Id-2) and compounds 1-46, 49-52, and 53-70, or administering to an individual in need thereof a pharmaceutical composition comprising a therapeutically or prophylactically effective amount of a 11,13-modified, non-hydrated ketone saxitoxin described herein, *e.g.*, of some or any of the embodiments of Formula (I), (P-I), (P-Ia), (P-Ib-1), (P-Ib-2), (P-Ic-1), (P-Ic-2), (P-Id-1), and (P-Id-2) and compounds 1-46, 49-52, and 53-70 and a pharmaceutically acceptable carrier.

[0015a] In another aspect, provided herein is a therapeutically or prophylactically effective amount of the compound as defined herein or the pharmaceutical composition as defined herein for use in the treatment of a condition associated with voltage-gated sodium channel function in a human, wherein the condition is pain or the condition is associated with pain.

[0015b] In another aspect, provided herein is use of a therapeutically or prophylactically effective amount of the compound as defined herein or the pharmaceutical composition as defined herein in the preparation of a medicament for the treatment of a condition associated with voltage-gated sodium channel function in a human wherein the condition is pain or the condition is associated with pain.

[0016] Provided herein is a compound of Formula (X)



(X);

or a salt thereof,

wherein

PG^1 is a nitrogen-protecting group;

PG^2 is a nitrogen-protecting group;

X^2 is halo (preferably Br, I), CN, or N_3;

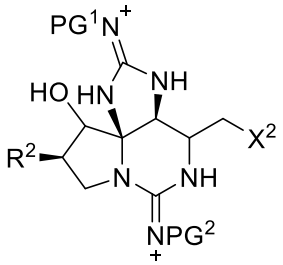
R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^7 is hydrogen or $C_{1\text{-}6}$alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl.

[0016a] In another aspect, provided herein is a compound of Formula (X-4)



(X-4);

or a salt thereof,

wherein

PG^1 is a nitrogen-protecting group;

PG^2 is a nitrogen-protecting group;

X^2 is halo, CN, or N_3;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^7 is hydrogen or C_{1-6}alkyl;

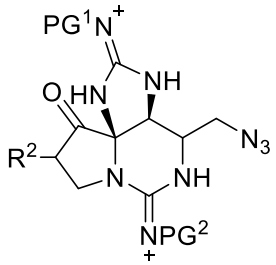
R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in

aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl.

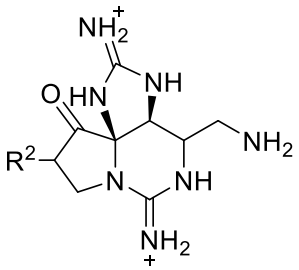
[0017] Provided herein is a method of preparing a compound of Formula (I) comprising

d) deprotecting and reducing a compound of Formula (X-1)



(X-1);

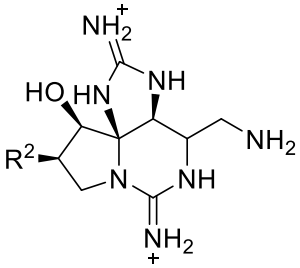
to obtain a compound of Formula (X-2):



(X-2),

or a salt thereof;

b) reducing the ketone of Formula (X-2) to obtain a compound of Formula (X-3):



(X-3);

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

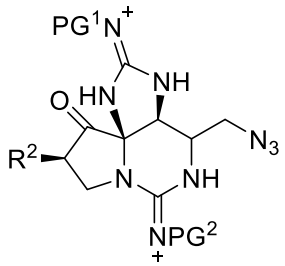
each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl;

to yield a compound of Formula I; and

d) optionally isolating the compound of Formula I.

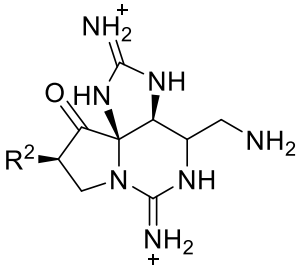
[0017a] In another aspect, provided herein is a method of preparing a compound of Formula (I) comprising

a) in a single step, deprotecting and reducing a compound of Formula (X-1)



(X-1);

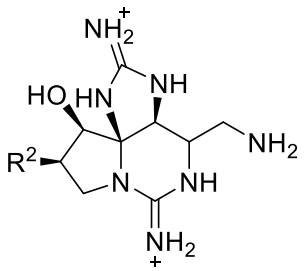
to obtain a compound of Formula (X-2):



(X-2),

or a salt thereof;

b) reducing the ketone of Formula (X-2) to obtain a compound of Formula (X-3):



(X-3);

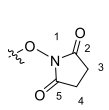
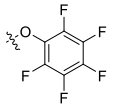
or a salt thereof;

c) coupling the compound of Formula (X-3) with a compound of Formula X^4-LG to obtain a compound of Formula I; wherein

PG^1 is a nitrogen-protecting group;

PG^2 is a nitrogen-protecting group;

X^4 is $-C(=O)R^{4a}$, $-S(O)_2R^{5a}$, $-C(O)NR^{6a}R^{6b}$, or $-C(O)OR^{8a}$;

LG is a leaving group selected from the group consisting of halo, , and , where  represents the point of attachment of LG to X^4;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^{4a} is hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkyl; di-C_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkyl; cycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; cycloalkylalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aralkyl where the aryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaralkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heterocyclicalkyl where the heterocyclic portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

each of the 1, 2, 3, or 4 R^{4b}, when present, is independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

2 R^{4b} groups, when on the same carbon atom, are taken together to form an oxo group, and the other 2 R^{4b}, when present, are independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^{6a} is hydrogen, or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or cycloalkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl or phenyl;

R^{7} is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

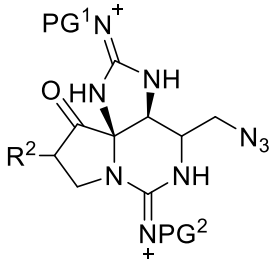
each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl;

to yield a compound of Formula I; and

d) optionally isolating the compound of Formula I.

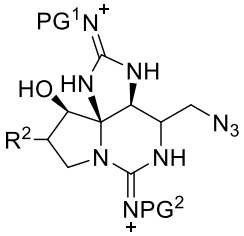
[0018] Provided herein is a method of preparing a compound of Formula (I) comprising

d) reducing the ketone in a compound of Formula (X-1)



(X-1);

to obtain a compound of Formula (X-2B):



(X-2B),

or a salt thereof;

2 R^{4b} groups, when on the same carbon atom, are taken together to form an oxo group, and the other 2 R^{4b}, when present, are independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^{6a} is hydrogen or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, or cycloalkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl, or phenyl;

R^{7} is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

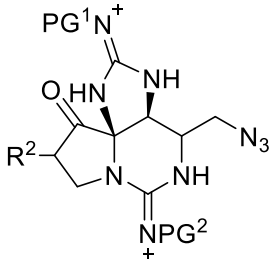
each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl;

to yield a compound of Formula I; and

d) optionally isolating the compound of Formula I.

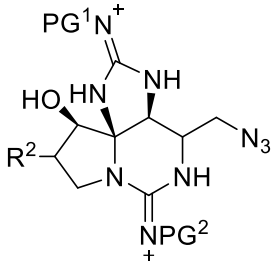
[0018a] In another aspect, provided herein is a method of preparing a compound of Formula (I) comprising

a) reducing the ketone in a compound of Formula (X-1)



(X-1);

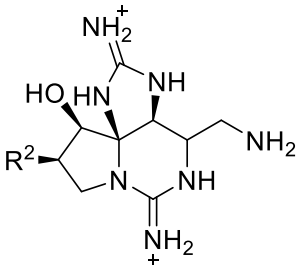
to obtain a compound of Formula (X-2B):



(X-2B),

or a salt thereof;

b) in a single step, deprotecting and reducing the compound of Formula (X-2B) to obtain a compound of Formula (X-3)



(X-3);

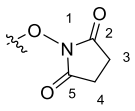
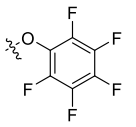
or a salt thereof;

c) coupling the compound of Formula (X-3) with a compound of Formula X^4-LG to obtain a compound of Formula I; wherein

PG^1 is a nitrogen-protecting group;

PG^2 is a nitrogen-protecting group;

X^4 is $-C(O)R^{4a}$, $-S(O)_2R^{5a}$, $-C(O)NR^{6a}R^{6b}$, or $-C(O)OR^{8a}$;

LG is a leaving group selected from the group consisting of halo, , and , where  represents the point of attachment of LG to X^4;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^{4a} is hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkyl; di-C_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkyl; cycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; cycloalkylalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aralkyl where the aryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

heteroaralkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heterocyclicalkyl where the heterocyclic portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

each of the 1, 2, 3, or 4 R^{4b}, when present, is independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

2 R^{4b} groups, when on the same carbon atom, are taken together to form an oxo group, and the other 2 R^{4b}, when present, are independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^{6a} is hydrogen, or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or cycloalkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl or phenyl;

R^{7} is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl;

to yield a compound of Formula I; and

d) optionally isolating the compound of Formula I.

BRIEF DESCRIPTION OF FIGURES

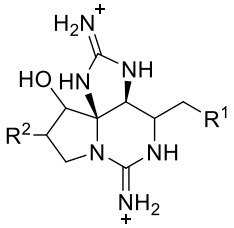
[0019] FIG. 1A is a graph of the 11S and 11R diasteromers percentage of total peak area from the high 11S standard in monkey blood:buffer as described in Example 8. The percentage of 11S and 11R from the high 11S standard is shown for the high quality control (HQC), medium quality control (MQC), and low quality control (LQC). The percentage of 11S and 11R

diastereomers is also shown for the high 11S neat material (S-neat (R) and S-neat (S)). The x-axis is time measured in minutes and the y-axis is area measured in percent.

[0020] FIG. 1B is a graph of the 11S and 11R diastereomers percentage of total peak area from the high 11R standard in monkey blood:buffer as described in Example 8. The percentage of 11S and 11R from the high 11R standard is shown for the high quality control (HQC), medium quality control (MQC), and low quality control (LQC). The percentage of 11S and

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

wherein

R^1 is $-NR^{3a}R^3$, $-NR^4C(O)R^{4a}$, $-CH_2NR^4C(O)R^{4a}$, heteroaryl, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NH_3^+$, $-CH_2CH_2NH_3^+$, $-NR^5S(O)_2R^{5a}$, $-CH_2NR^5S(O)_2R^{5a}$, $-NR^6C(O)NR^{6a}R^{6b}$, $-CH_2NR^6C(O)NR^{6a}R^{6b}$, $-NR^8C(O)OR^{8a}$, or $-CH_2NR^8C(O)OR^{8a}$;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^3 is hydrogen or C_{1-6}alkyl;

R^{3a} is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^{4a} is hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkyl; di-C_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkyl; cycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; cycloalkylalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aralkyl where the aryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaralkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heterocyclicalkyl where the heterocyclic portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

each of the 1, 2, 3, or 4 R^{4b}, when present, is independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

2 R^{4b} groups, when on the same carbon atom, are taken together to form an oxo group, and the other 2 R^{4b}, when present, are independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group;

R^5 is hydrogen or C_{1-6}alkyl;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^6 is hydrogen or C_{1-6}alkyl;

R^{6a} is hydrogen or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, or cycloalkyl;

R^8 is hydrogen or C_{1-6}alkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl, or phenyl;

R^7 is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl; or

a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, mixture, or combination thereof.

2. The Compound of claim 1

wherein

R^1 is $-NR^{3a}R^3$, $-NR^4C(O)R^{4a}$, $-CH_2NR^4C(O)R^{4a}$, heteroaryl, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2NH_3^+$, $-CH_2CH_2NH_3^+$, $-NR^5S(O)_2R^{5a}$, $-CH_2NR^5S(O)_2R^{5a}$, $-NR^6C(O)NR^{6a}R^{6b}$, $-CH_2NR^6C(O)NR^{6a}R^{6b}$, or $-NR^8C(O)OR^{8a}$, or $-CH_2NR^8C(O)OR^{8a}$;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^3 is hydrogen or C_{1-6}alkyl;

R^{3a} is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^{4a} is hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkyl; di-C_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkyl; cycloalkyl; cycloalkylalkyl; aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aralkyl where the aryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaralkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b}

groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heterocyclicalkyl where the heterocyclic portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

each R^{4b}, when present, is independently C_{1-6}alkyl, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, or phenyl;

R^5 is hydrogen or C_{1-6}alkyl;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^6 is hydrogen or C_{1-6}alkyl;

R^{6a} is hydrogen or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, or cycloalkyl;

R^8 is hydrogen or C_{1-6}alkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl or phenyl;

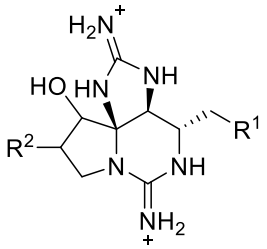
R^7 is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl; or

a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, mixture, or combination thereof.

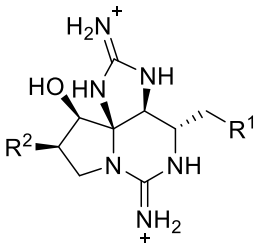
3. The Compound of claim 1 or 2, wherein the compound is according to Formula (P-Ia):

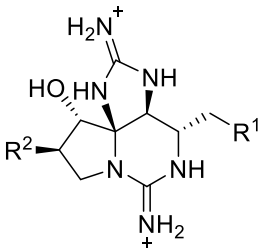


(P-Ia);

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, mixture, or combination thereof.

4. The Compound of any one of claims 1-3, wherein the compound is according to Formula (P-Ib-1) or (P-Ib-2):


(P-Ib-1);


(P-Ib-2);

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, mixture, or combination thereof.

5. The Compound of any one of claims 1-4, wherein R^1 is $-NR^{3a}R^3$ or $-NR^4C(O)R^{4a}$.

6. The Compound of any one of claims 1-4, wherein R^1 is $-NR^4C(O)R^{4a}$.

7. The Compound of any one of claims 1-6, wherein R^4 is hydrogen.

8. The Compound of any one of claims 1-7, wherein R^{4a} is aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; cycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heteroarylalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups.

9. The Compound of any one of claims 1-8, wherein R^{4a} is heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups.

10. The Compound of any one of claims 1-9, wherein R^{4a} is pyridinyl, pyrazinyl, pyrimidinyl, or pyrazinyl, where R^{4a} is optionally substituted with 1, 2, 3, or 4 R^{4b} groups.

11. The Compound of any one of claims 1-10, wherein R^{4a} is unsubstituted heteroaryl.

12. The Compound of any one of claims 1-8, wherein R^{4a} is aryl optionally substituted with 1, 2, 3 or 4 R^{4b} groups.

13. The Compound of any one of claims 1-7, wherein R^{4a} is hydrogen.

14. The Compound of any one of claims 1-7, wherein R^{4a} is $C_{1\text{-}6}$alkyl.

15. The Compound of any one of claims 1-7, wherein R^{4a} halo-$C_{1\text{-}6}$alkyl.

16. The Compound of any one of claims 1-7, wherein R^{4a} is amino-C_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkyl; or di-C_{1-6}alkylaminoC_{1-6}alkyl.

17. The Compound of any one of claims 1-7, wherein R^{4a} is C_{1-6}alkoxyC_{1-6}alkyl.

18. The Compound of any one of claims 1-7, wherein R^{4a} is cycloalkyl optionally substituted with 1 or 2 R^{4b} groups.

19. The Compound of claim 18, wherein one R^{4b} is present and R^{4b} is heteroaryl.

20. The Compound of any one of claims 1-7, wherein R^{4a} is unsubstituted cycloalkylalkyl.

21. The Compound of any one of claims 1-7, wherein R^{4a} is aralkyl where the aryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b}.

22. The Compound of any one of claims 1-8, wherein R^{4a} is heteroarylalkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups.

23. The Compound of any one of claims 1-10, 12, 18, and 21-22, wherein each R^{4b}, when present, is independently C_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyloxy, halo, halo-C_{1-6}alkyl, or C_{1-6}alkoxy.

24. The Compound of any one of claims 1-10, 12, 18, and 21-22, wherein each R^{4b}, when present, is independently C_{1-6}alkyl or hydroxy.

25. The Compound of any one of claims 1-10, 12, 18, and 21-24, wherein one R^{4b} is present.

26. The Compound of any one of claims 1-10, 12, 18, and 21-24, wherein two R^{4b} are present.

27. The Compound of any one of claims 8-10 and 22, wherein each of the 1, 2, 3, or 4 R^{4b}, when present, is independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl.

28. The Compound of any one of claims 8-10 and 22, wherein one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group.

29. The Compound of any one of claims 1-4, wherein R^1 is -$NR^{3a}R^3$.

30. The Compound of any one of claims 1-4, and 29, wherein R^{3a} and R^3 are both C_{1-6}alkyl; or R^{3a} and R^3 are both hydrogen.

31. The Compound of any one of claims 1-4, wherein R^1 is -$NR^5S(O)_2R^{5a}$.

32. The Compound of any one of claims 1-4, and 31, wherein R^5 is hydrogen.

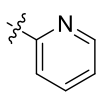
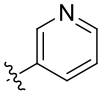
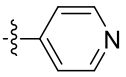
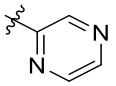
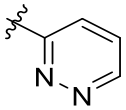
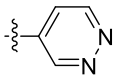
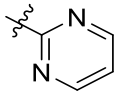
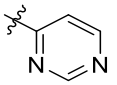
33. The Compound of any one of claims 1-4, wherein R^1 is $-NR^6C(O)NR^{6a}R^{6b}$.

34. The Compound of any one of claims 1-4 and 33 wherein R^6 is hydrogen.

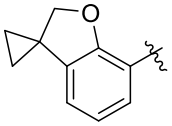
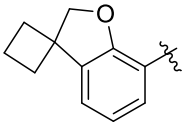
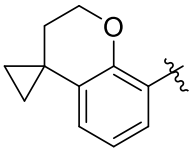
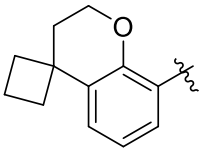
35. The Compound of any one of claims 1-4, wherein R^1 is $-NR^8C(O)OR^{8a}$.

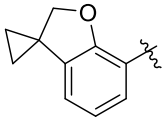
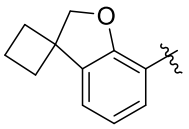
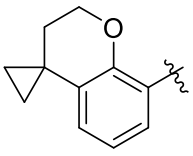
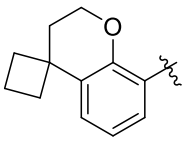
36. The Compound of any one of claims 1-4, and 35, wherein R^8 is hydrogen.

37. The Compound of any one of Claims 1-36, wherein R^7 is hydrogen.

38. The Compound of any one of claims 1-4, wherein R^1 is $-NH_2$ or $-NHC(O)R^{4a}$; and R^{4a} is , , , , , , , or , wherein  indicates the point of attachment the rest of the molecule and the R^{4a} ring is optionally substituted with 1, 2, or 3 R^{4b} groups where each R^{4b} group, when present, is independently alkyl or hydroxy.

39. The Compound of any one of Claims 1-38, wherein R^{7a} is heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}.

40. The Compound of any one of Claims 1-39, wherein the heterocyclic in R^{7a} is benzo-1,4-dioxanyl, benzodioxolyl, 2,3-dihydrobenzofuranyl, chromanyl, , , , ; each of which is optionally substituted with 1, 2, or 3 groups independently selected from halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, and phenyl.

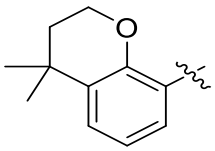
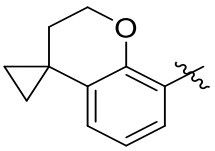
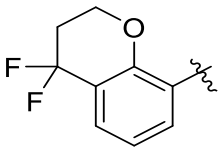
41. The Compound of any one of Claims 1-39, wherein R^{7a} is unsubstituted , unsubstituted , unsubstituted , or unsubstituted .

42. The Compound of any one of Claims 1-39, wherein the heterocyclic in R^{7a} comprises one heteroatom which is oxygen and wherein the heterocyclic is optionally substituted with 1, 2, or 3 groups independently selected from halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, and phenyl.

43. The Compound of any one of Claims 1-39, wherein the heterocyclic in R^{7a} comprises one heteroatom which is oxygen and wherein the heterocyclic is optionally substituted with one gem-di-C_{1-3}alkyl or one gem-dihalo.

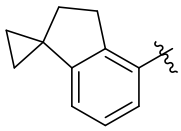
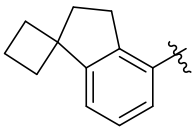
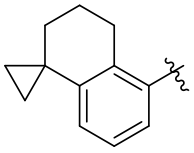
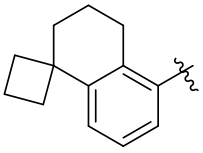
44. The Compound of any one of Claims 1-39, wherein the heterocyclic in R^{7a} is benzo-1,4-dioxanyl optionally substituted with one gem-di-C_{1-3}alkyl, cyclopropyl, or one gem-dihalo.

45. The Compound of any one of Claims 1-39, wherein R^{7a} is

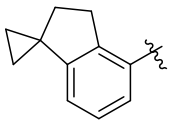
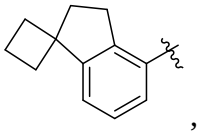
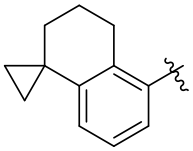
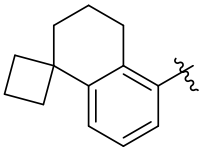

; 
, or 
.

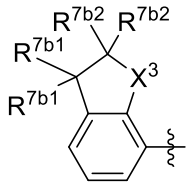
46. The Compound of any one of Claims 1-38, wherein R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}.

47. The Compound of any one of Claims 1-38, and 46, wherein the aryl in R^{7a} is phenyl, naphthyl, tetrahydronaphthyl, fluorenyl, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulenyl,


, 
, 
, 
, or indanyl; each of which is optionally substituted with 1, 2, or 3 groups independently selected from halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl, and amino.

48. The Compound of any one of Claims 1-38, and 46, wherein the aryl in R^{7a} is tetrahydronaphthyl, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulenyl, or indanyl; each of which is optionally substituted with one gem-di-C_{1-3}alkyl or one gem-di-halo.

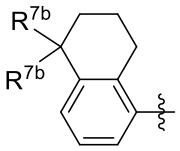
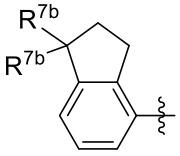
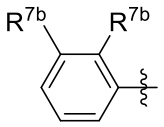
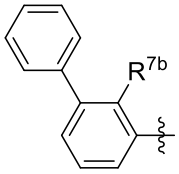
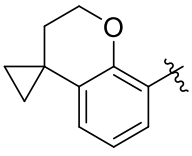
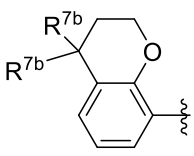
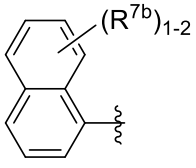
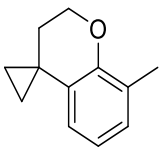
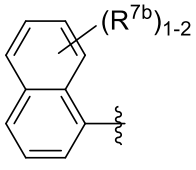
49. The Compound of any one of Claims 1-38, and 46, wherein R^{7a} is unsubstituted 6,7,8,9-tetrahydro-5*H*-benzo[7]annulenyl, unsubstituted , unsubstituted , unsubstituted , or unsubstituted .

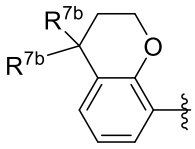
50. The Compound of any one of Claims 1-38, wherein R^{7a} is  where X^3 is -O-, -O-C(R^{7b3})(R^{7b3})-, -C(R^{7b3})(R^{7b3})-O-, -C(R^{7b3})(R^{7b3})-, -C(R^{7b3})(R^{7b3})-C(R^{7b4})(R^{7b4})-, or -C(R^{7b3})(R^{7b3})-C(R^{7b4})(R^{7b4})-C(R^{7b5})(R^{7b5})- and each R^{7b1}, R^{7b2}, R^{7b3}, R^{7b4}, and R^{7b5} is independently hydrogen, halo, or C_{1-3}-alkyl.

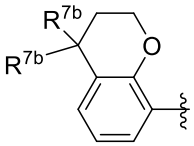
51. The Compound of Claim 50, wherein a) one R^{7b1} is methyl or ethyl and the other R^{7b1} is hydrogen, or b) the two R^{7b1} are both hydrogen, or c) the two R^{7b1} are both methyl; and each R^{7b2}, R^{7b3}, R^{7b4}, and R^{7b5} are hydrogen.

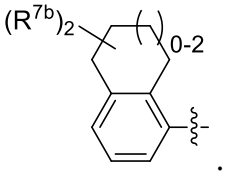
52. The Compound of Claim 50 or 51, wherein X^3 is -C(R^{7b3})(R^{7b3})-O-.

53. The Compound of Claim 50 or 51, wherein X^3 is -C(R^{7b3})(R^{7b3})-C(R^{7b4})(R^{7b4})-.

54. The Compound of any one of claims 1-38, where R^{7a} is , , , , , , , , or .

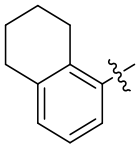
55. The Compound of Claim 54, wherein R^{7a} is  or tetrahydronaphthyl.

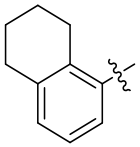
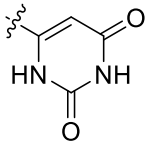
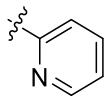
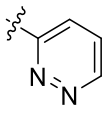
56. The Compound of claim 55, wherein R^{7a} is  and both R^{7b} are methyl.

57. The Compound of any one of claims 1-38, wherein R^{7a} is .

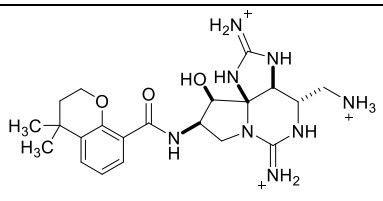
58. The Compound of claim 57, wherein both R^{7b} are hydrogen.

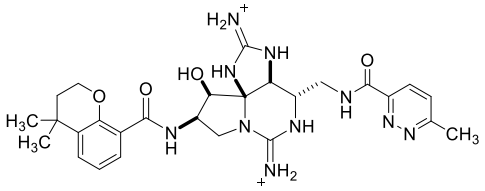
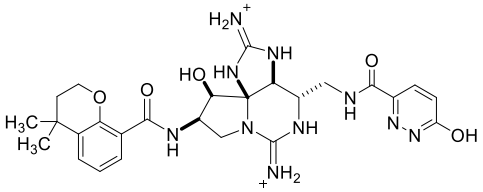
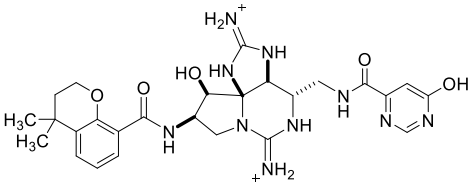
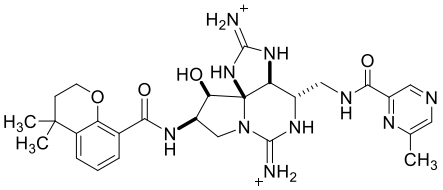
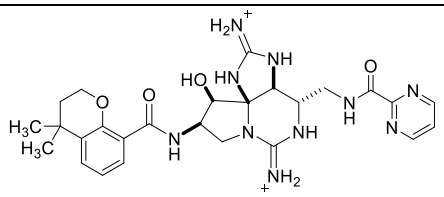
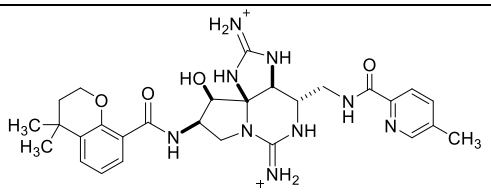
59. The Compound of claim 54 or 55, wherein a) one R^{7b} is methyl or ethyl and the other R^{7b} is hydrogen, b) the two R^{7b} are both hydrogen, or c) the two R^{7b} are both methyl.

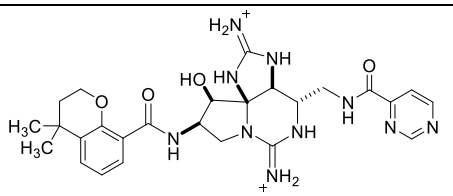
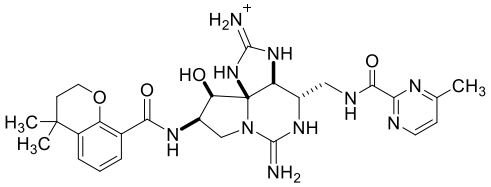
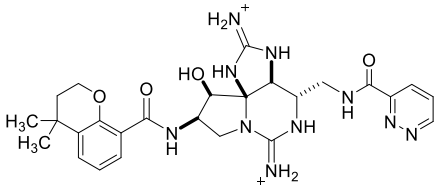
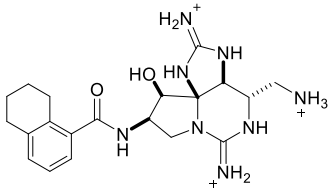
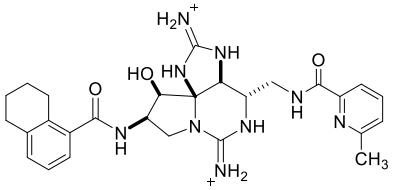
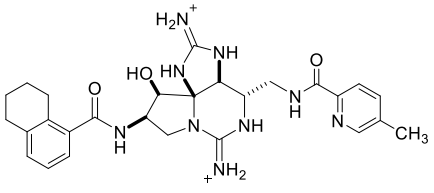
60. The Compound of claim 1, wherein R^2 is –NHC(O)R^{7a}; R^{7a} is ; R^1 is -NHC(O)R^{4a}; and R^{4a} is heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups.

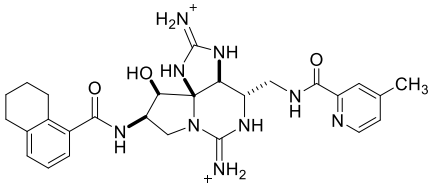
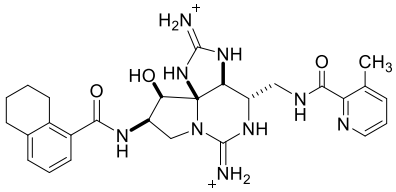
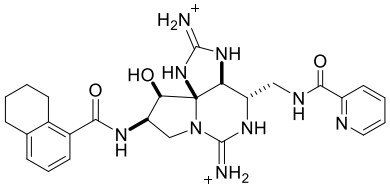
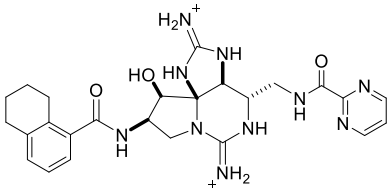
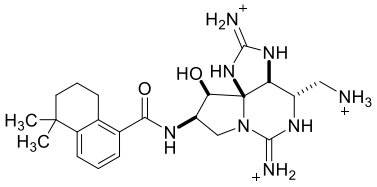
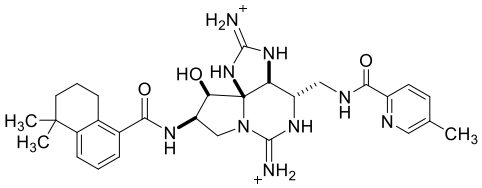
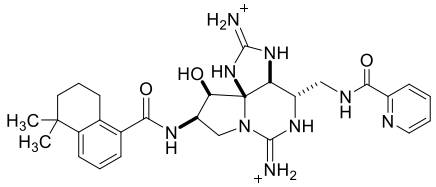
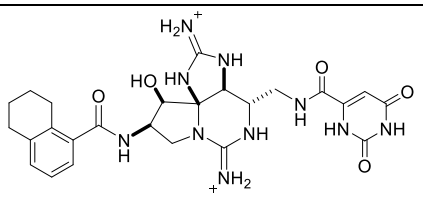
61. The Compound of claim 1, wherein R^2 is -NHC(O)R^{7a}; R^{7a} is ; R^1 is -NHC(O)R^{4a}; R^{4a} is independently selected from , , and  optionally substituted with 1, 2, 3, or 4 R^{4b} groups; and R^{4b}, when present, is $C_{1\text{-}6}$alkyl.

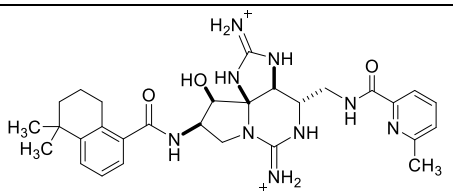
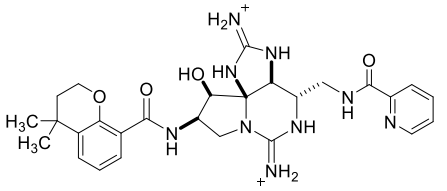
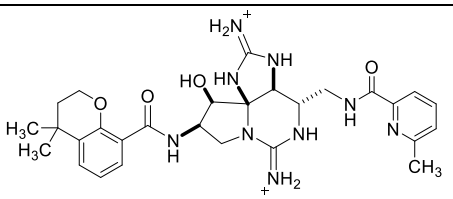
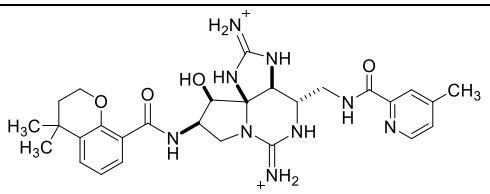
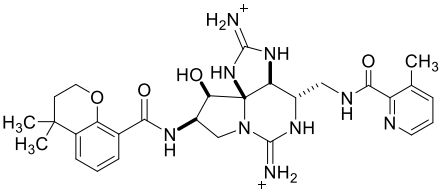
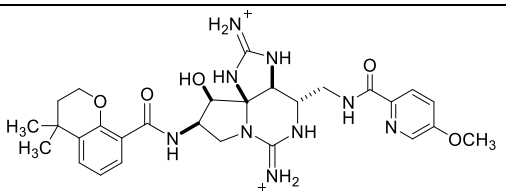
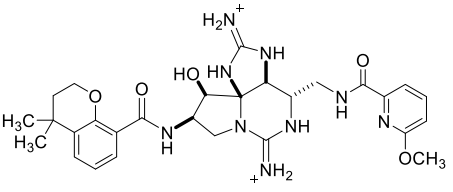
62. The Compound of claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, mixture, or combination thereof, selected from the group consisting of:

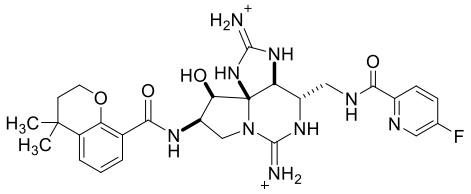
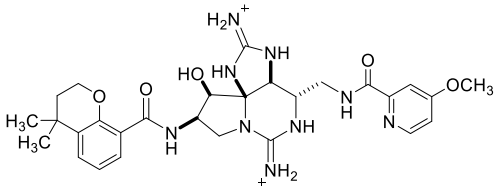
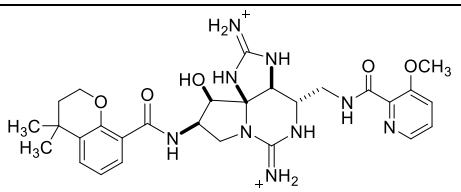
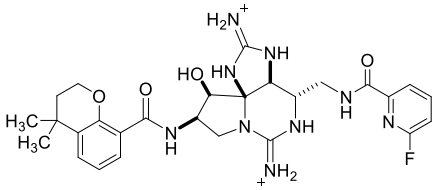
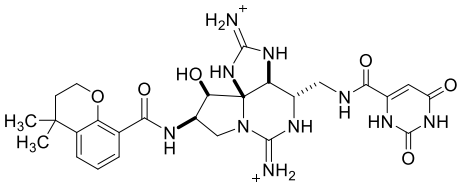
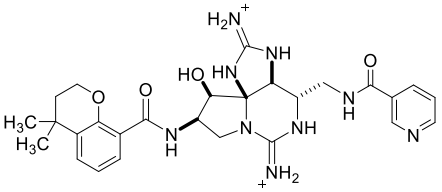
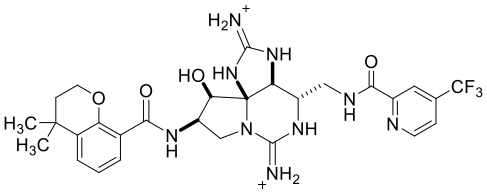
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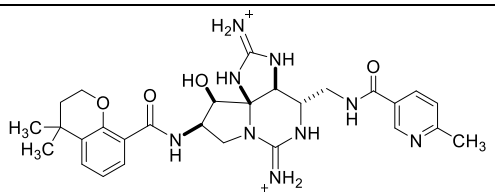
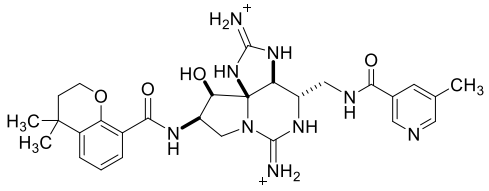
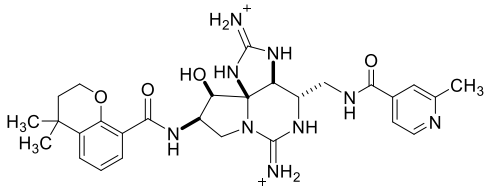
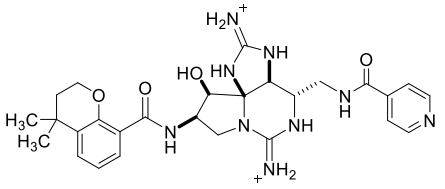
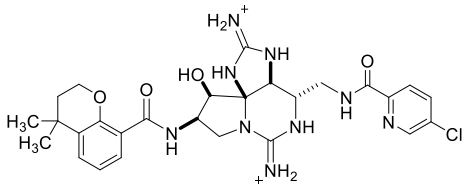
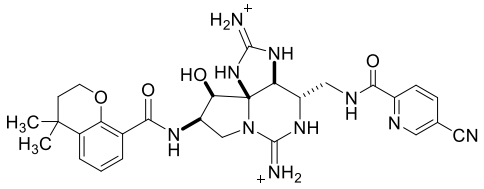
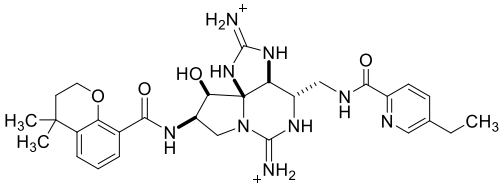
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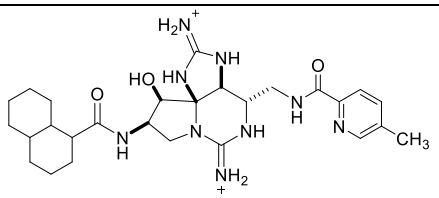
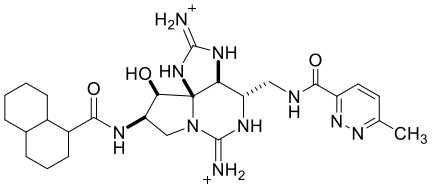
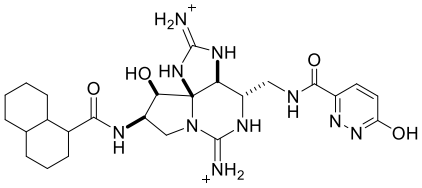
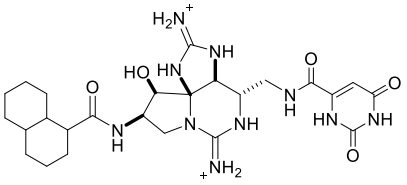
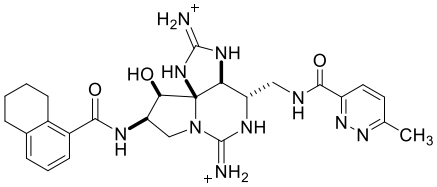
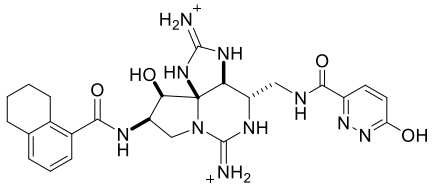
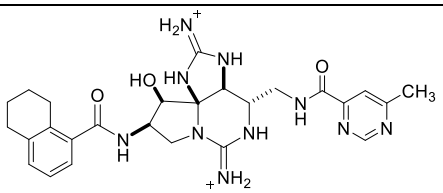
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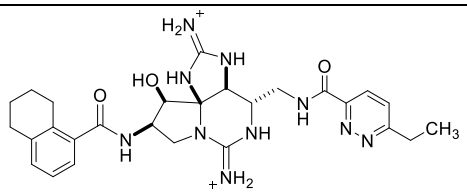
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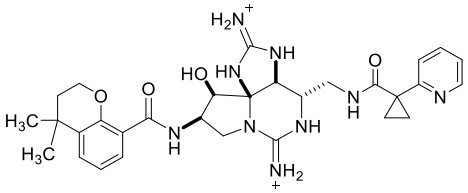
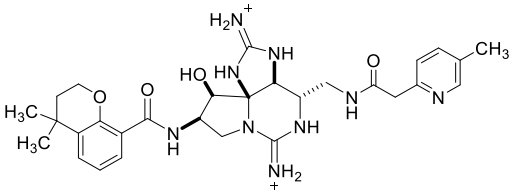
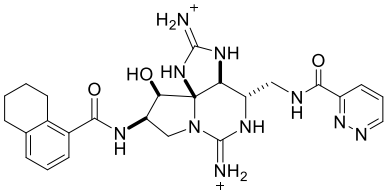
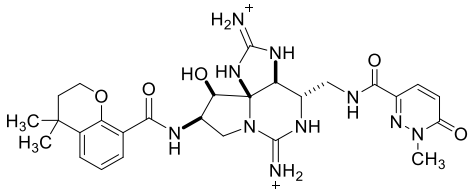
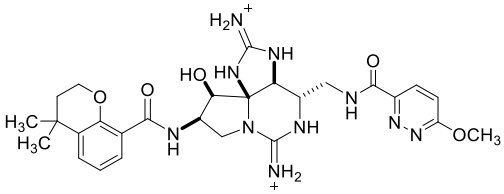
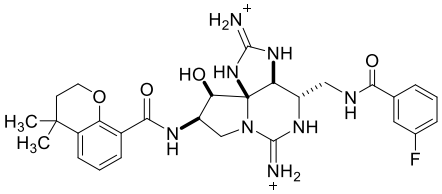
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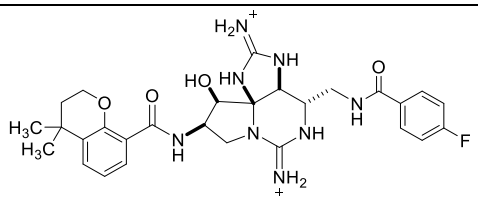
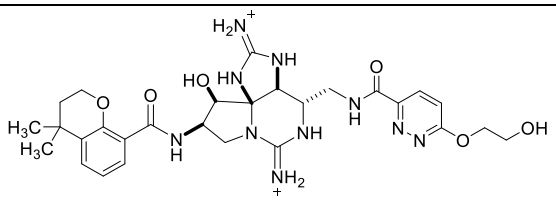
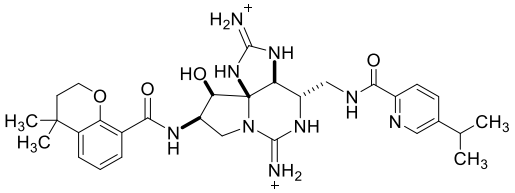
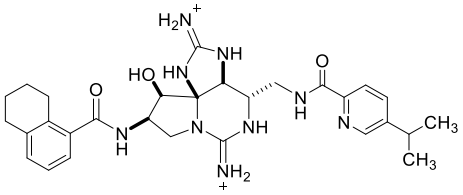
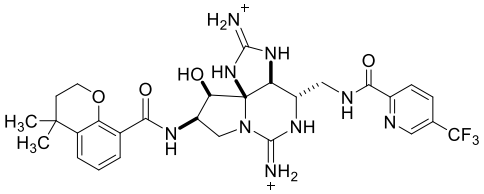
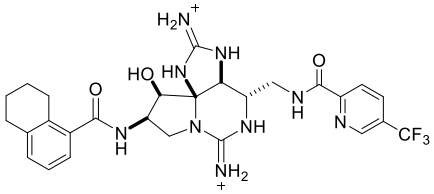
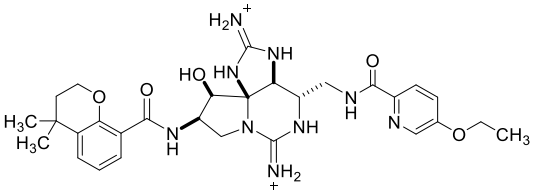
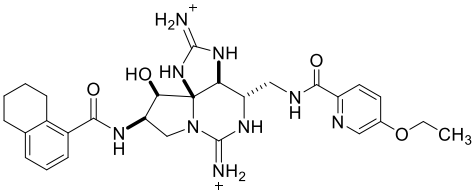
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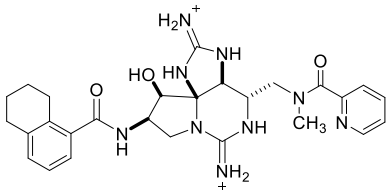
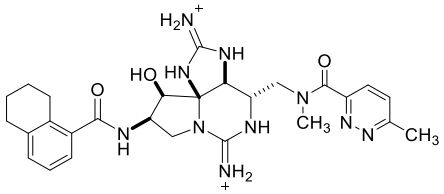
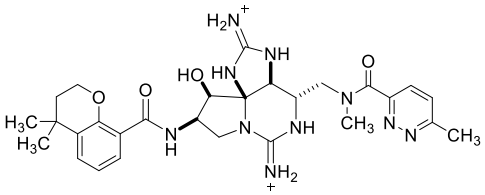
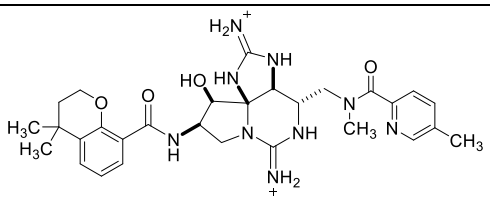
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63. A pharmaceutical composition comprising the compound of any one of claims 1-62 and a pharmaceutically acceptable carrier.

64. The pharmaceutical composition of claim 63, wherein the composition is an oral or injectable composition.

65. The pharmaceutical composition of claim 64, wherein the injectable composition is a subcutaneously injectable composition.

66. A therapeutically or prophylactically effective amount of the compound of any one of claims 1-62 or the pharmaceutical composition of any one of claims 63-65 for use in the treatment of a condition associated with voltage-gated sodium channel function in a human, wherein the condition is pain or the condition is associated with pain.

67. The compound or pharmaceutical composition for use of claim 66, wherein the condition is selected from the group consisting of erythromelalgia, diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain syndrome, trigeminal

neuralgia, multiple sclerosis, arthritis, osteoarthritis, postherpetic neuralgia, cancer pain, cluster headache, migraine, sciatica, endometriosis, fibromyalgia, postsurgical pain, subacute pain, chronic pain, pain and/or discomfort associated with dry eye syndrome, pain associated with (acute) corneal injuries or abrasions, acute ocular pain, chronic ocular pain, pain associated with corneal infections, pain associated with Parkinson's disease, pain associated with ALS, pain associated with ocular surgery, epilepsy, Parkinson's disease, a mood disorder, psychosis, amyotropic lateral sclerosis, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder.

68. The compound or pharmaceutical composition for use of claim 66, wherein the condition is selected from the group consisting of acute pain, subacute pain, and post-surgical pain.

69. The compound or pharmaceutical composition of claim 66, wherein the condition is ocular pain.

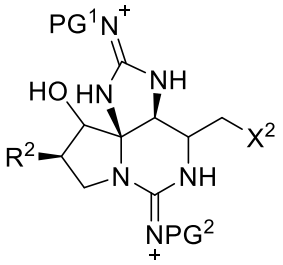
70. Use of a therapeutically or prophylactically effective amount of the compound of any one of claims 1-62 or the pharmaceutical composition of any one of claims 63-65 in the preparation of a medicament for the treatment of a condition associated with voltage-gated sodium channel function in a human wherein the condition is pain or the condition is associated with pain.

71. The use of claim 70, wherein the condition is selected from the group consisting of erythromelalgia, diabetic peripheral neuropathy, paroxysmal extreme pain disorder, complex regional pain syndrome, trigeminal neuralgia, multiple sclerosis, arthritis, osteoarthritis, postherpetic neuralgia, cancer pain, cluster headache, migraine, sciatica, endometriosis, fibromyalgia, postsurgical pain, subacute pain, chronic pain, pain and/or discomfort associated with dry eye syndrome, pain associated with (acute) corneal injuries or abrasions, acute ocular pain, chronic ocular pain, pain associated with corneal infections, pain associated with Parkinson's disease, pain associated with ALS, pain associated with ocular surgery, epilepsy, Parkinson's disease, a mood disorder, psychosis, amyotropic lateral sclerosis, glaucoma, ischemia, a spasticity disorder, and obsessive compulsive disorder.

72. The use of claim 70, wherein the condition is selected from the group consisting of acute pain, subacute pain, and post-surgical pain.

73. The use of claim 70, wherein the condition is ocular pain.

74. A compound of Formula (X-4)



(X-4);

or a salt thereof,

wherein

PG^1 is a nitrogen-protecting group;

PG^2 is a nitrogen-protecting group;

X^2 is halo, CN, or N_3;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

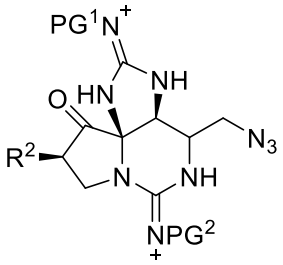
R^7 is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl.

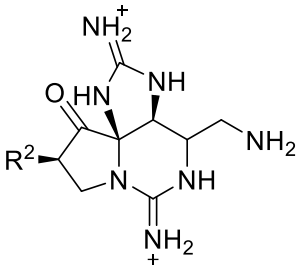
75. A method of preparing a compound of Formula (I) comprising

a) in a single step, deprotecting and reducing a compound of Formula (X-1)



(X-1);

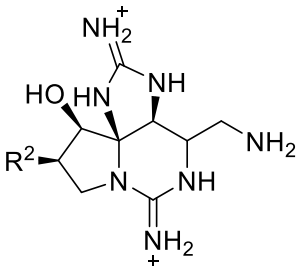
to obtain a compound of Formula (X-2):



(X-2),

or a salt thereof;

b) reducing the ketone of Formula (X-2) to obtain a compound of Formula (X-3):



(X-3);

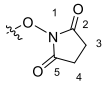
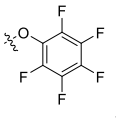
or a salt thereof;

c) coupling the compound of Formula (X-3) with a compound of Formula X^4-LG to obtain a compound of Formula I; wherein

PG^1 is a nitrogen-protecting group;

PG^2 is a nitrogen-protecting group;

X^4 is $-C(=O)R^{4a}$, $-S(O)_2R^{5a}$, $-C(O)NR^{6a}R^{6b}$, or $-C(O)OR^{8a}$;

LG is a leaving group selected from the group consisting of halo, , and , where  represents the point of attachment of LG to X^4;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^{4a} is hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkyl; di-C_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkyl; cycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; cycloalkylalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aralkyl where the aryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

heteroaralkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heterocyclicalkyl where the heterocyclic portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

each of the 1, 2, 3, or 4 R^{4b}, when present, is independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

2 R^{4b} groups, when on the same carbon atom, are taken together to form an oxo group, and the other 2 R^{4b}, when present, are independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^{6a} is hydrogen, or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or cycloalkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl or phenyl;

R^{7} is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

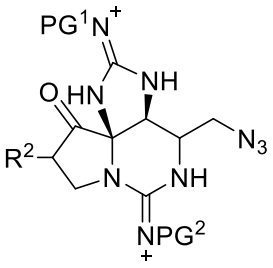
each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl;

to yield a compound of Formula I; and

d) optionally isolating the compound of Formula I.

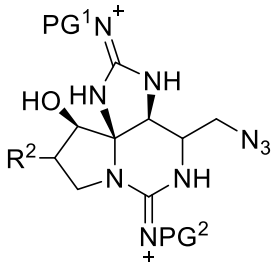
76. A method of preparing a compound of Formula (I) comprising

a) reducing the ketone in a compound of Formula (X-1)



(X-1);

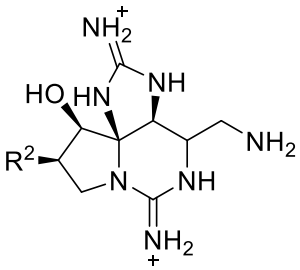
to obtain a compound of Formula (X-2B):



(X-2B),

or a salt thereof;

b) in a single step, deprotecting and reducing the compound of Formula (X-2B) to obtain a compound of Formula (X-3)



(X-3);

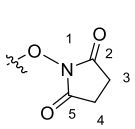
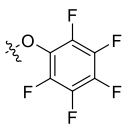
or a salt thereof;

c) coupling the compound of Formula (X-3) with a compound of Formula X^4-LG to obtain a compound of Formula I; wherein

PG^1 is a nitrogen-protecting group;

PG^2 is a nitrogen-protecting group;

X^4 is $-C(O)R^{4a}$, $-S(O)_2R^{5a}$, $-C(O)NR^{6a}R^{6b}$, or $-C(O)OR^{8a}$;

LG is a leaving group selected from the group consisting of halo, , and ,

where  represents the point of attachment of LG to X^4;

R^2 is $-NR^7C(O)R^{7a}$, $-NR^7S(O)_2R^{7a}$, or $-NR^7C(O)OR^{7a}$;

R^{4a} is hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylaminoC_{1-6}alkyl; di-C_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkoxyC_{1-6}alkyl; cycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; cycloalkylalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; aralkyl where the aryl portion is

optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocycloalkyl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaryl optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heteroaralkyl where the heteroaryl portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{4b} groups; or heterocyclicalkyl where the heterocyclic portion is optionally substituted with 1, 2, 3, or 4 R^{4b} groups;

each of the 1, 2, 3, or 4 R^{4b}, when present, is independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

2 R^{4b} groups, when on the same carbon atom, are taken together to form an oxo group, and the other 2 R^{4b}, when present, are independently C_{1-6}alkyl, hydroxyC_{1-6}alkyloxy, hydroxy, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, cyano, phenyl, or heteroaryl; or

one pair of two R^{4b} groups are present on one carbon, the second pair of two R^{4b} are present on another carbon, and each pair of R^{4b} are taken together to form an oxo group;

R^{5a} is heterocycloalkyl, amino, C_{1-6}alkylamino, or di- C_{1-6}alkylamino;

R^{6a} is hydrogen, or C_{1-6}alkyl;

R^{6b} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or cycloalkyl;

R^{8a} is hydrogen, C_{1-6}alkyl, cycloalkyl or phenyl;

R^{7} is hydrogen or C_{1-6}alkyl;

R^{7a} is aryl optionally substituted with 1, 2, 3, or 4 R^{7b}; heterocyclic optionally substituted with 1, 2, 3, or 4 R^{7b}; or biphenyl optionally substituted with 1, 2, 3, or 4 R^{7b}; and

each R^{7b}, when present, is independently halo, C_{1-6}alkyl, halo-C_{1-6}alkyl, aryl-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, aryloxy, nitro, C_{1-6}alkylthio, halo-C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, halo-C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, halo-C_{1-6}alkylsulfonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, -C(O)(heterocycloalkyl), phenyl, or cyano; where the aryl in aryloxy and aryl-C_{1-6}alkyl are optionally substituted with 1, 2, or 3 groups independently selected from C_{1-6}alkyl, halo, and halo-C_{1-6}alkyl;

to yield a compound of Formula I; and

d) optionally isolating the compound of Formula I.