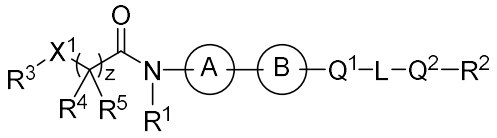
What is claimed is:

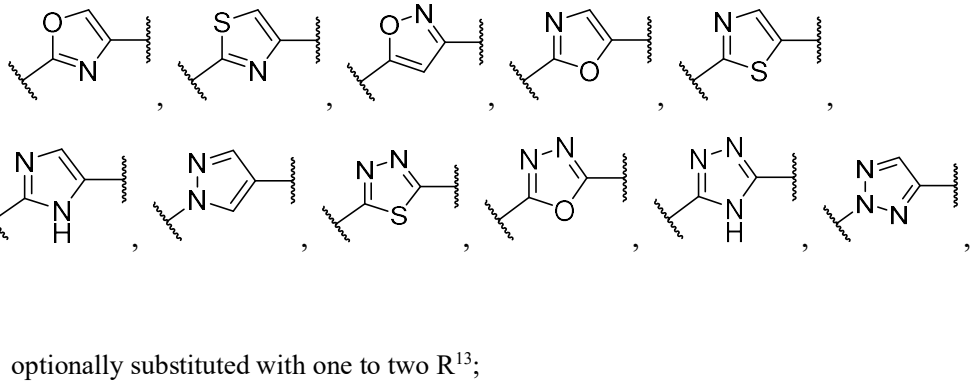
1. A compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein:

ring A is C_{3-10} cycloalkyl or heterocyclyl, provided ring A is not bicyclo[1.1.1]pentanyl or bicyclo[2.1.1]hexanyl; wherein the C_{3-10} cycloalkyl or heterocyclyl is optionally substituted with one to six R^{14};

ring B is , optionally substituted with one to two R^{13};

Q^1 and Q^2 are each independently O, S, or NR^{15};

L is a C_{1-6} alkylene linker, optionally substituted with one to three substituents independently selected from halo, cyano, nitro, $-OR^6$, $-SR^6$, $-SF_5$, $-NR^6R^7$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)OR^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^6C(O)NR^7R^8$, $-S(O)_{1-2}R^6$, $-S(O)_{1-2}NR^6R^7$, $-NR^6S(O)_{1-2}R^7$, $-NR^6S(O)_{1-2}NR^7R^8$, $-NR^6C(O)R^7$, and $-NR^6C(O)OR^7$;

z is 0 or 1;

X^1 is O, NR^9, or a bond;

R^1 is hydrogen;

R^2 is C_{1-6} haloalkyl;

R^3 is aryl or heteroaryl, each of which is optionally substituted with one to five R^{11};

R^4 and R^5 are independently hydrogen;

each of R^6, R^7, and R^8 is independently hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-S(O)_{1-2}R^{20}$, or $-S(O)_{1-2}NR^{20}R^{21}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^6, R^7, and R^8 is independently optionally substituted with one to five R^{12}; or two of R^6, R^7, and R^8 are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo, oxo, or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

R^9 is hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl, each of which, other than hydrogen, is optionally substituted with one to three R^{11};

each R^{11} is independently halo, cyano, nitro, oxo, $-OR^6$, $-SR^6$, $-SF_5$, $-NR^6R^7$, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)OR^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^6C(O)NR^7R^8$, $-S(O)_{1-2}R^6$, $-S(O)_{1-2}NR^6R^7$, $-NR^6S(O)_{1-2}R^7$, $-NR^6S(O)_{1-2}NR^7R^8$, $-NR^6C(O)R^7$, or $-NR^6C(O)OR^7$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{11} is independently optionally substituted with one to five R^{12};

each R^{12} is independently halo, cyano, nitro, oxo, $-OR^{30}$, $-SR^{30}$, $-SF_5$, $-NR^{30}R^{31}$, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)OR^{30}$, $-OC(O)R^{30}$, $-C(O)NR^{30}R^{31}$, $-OC(O)NR^{30}R^{31}$, $-NR^{30}C(O)NR^{30}R^{31}$, $-S(O)_{1-2}R^{30}$, $-S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}S(O)_{1-2}R^{31}$, $-NR^{30}S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, or $-NR^{30}C(=O)OR^{31}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{12} is independently optionally substituted with one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

each R^{13} is independently halo, cyano, nitro, oxo, $-OR^{30}$, $-SR^{30}$, $-SF_5$, $-NR^{30}R^{31}$, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)OR^{30}$, $-OC(O)R^{30}$, $-C(O)NR^{30}R^{31}$, $-OC(O)NR^{30}R^{31}$, $-NR^{30}C(O)NR^{30}R^{31}$, $-S(O)_{1-2}R^{30}$, $-S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}S(O)_{1-2}R^{31}$, $-NR^{30}S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, or $-NR^{30}C(=O)OR^{31}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{13} is independently optionally substituted with one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

each R^{14} is independently halo, cyano, $-NR^6R^7$, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl, or two R^{14} together with the atoms to which they are attached form a ring or a C=O;

each R^{15} is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

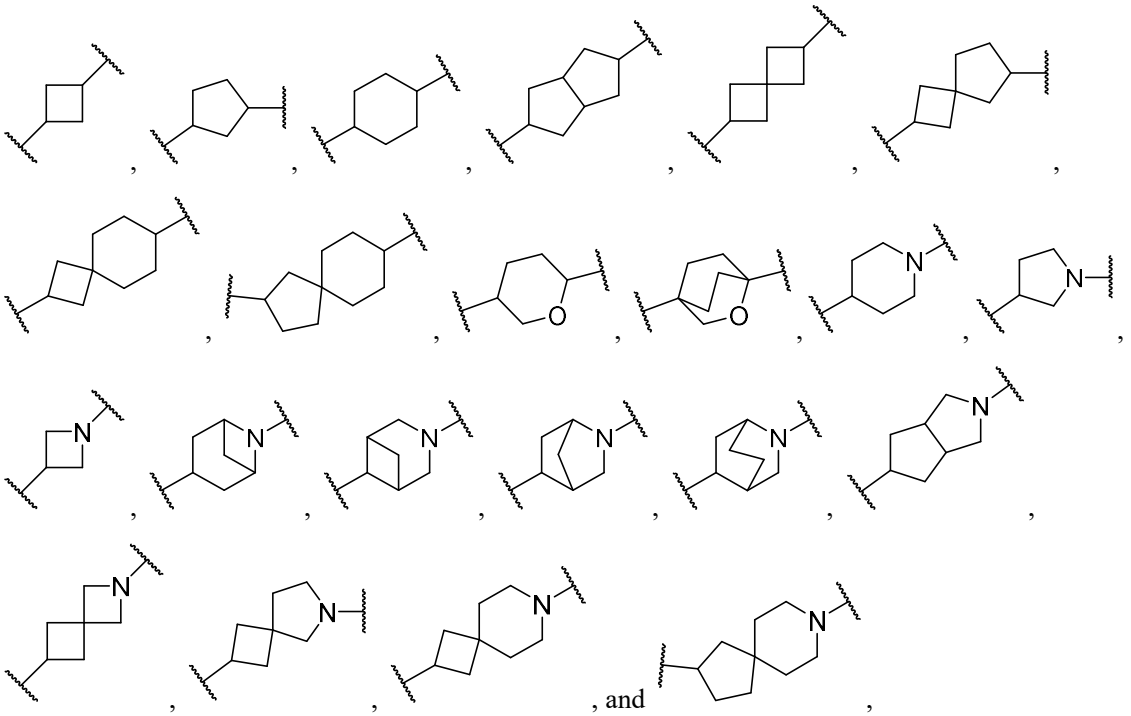
each R^{20} and R^{21} is independently hydrogen or C_{1-12} alkyl independently optionally substituted with one to three oxo, halo, hydroxyl, or amino; or R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino; and

each R^{30} and R^{31} is independently hydrogen or C_{1-12} alkyl independently optionally substituted with one to three oxo, halo, hydroxyl, or amino; or R^{30} and R^{31} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino.

2. The compound of claim 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein ring A is monocyclic cycloalkyl, fused bicyclic cycloalkyl, or spiro bicyclic cycloalkyl, wherein each is optionally substituted with one to six R^{14}.

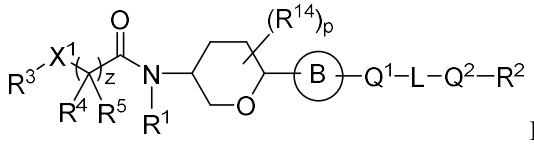
3. The compound of claim 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein ring A is heterocyclyl, wherein each is optionally substituted with one to six R^{14}.

4. The compound of claim 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein ring A is selected from



wherein each is independently optionally substituted with one to four halo.

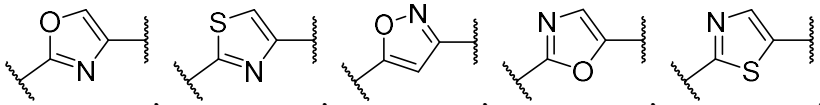
5. A compound of Formula II:

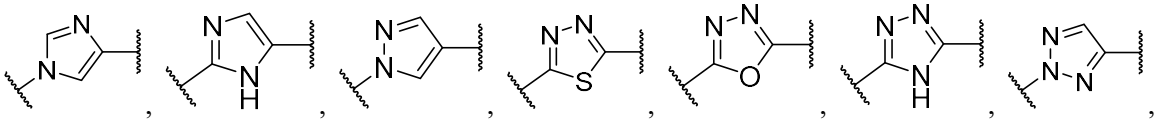


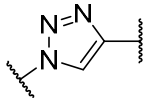
II

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein:

p is 0, 1, 2, 3, 4, 5, or 6;

ring B is 



or , wherein each is optionally substituted with one to two R^{13};

Q^1 and Q^2 are each independently O, S, or NR^{15};

L is a C_{1-6} alkylene linker, optionally substituted with one to three substituents independently selected from halo, cyano, nitro, $-OR^6$, $-SR^6$, $-SF_5$, $-NR^6R^7$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)OR^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^6C(O)NR^7R^8$, $-S(O)_{1-2}R^6R^7$, $-S(O)_{1-2}NR^6$, $-NR^6S(O)_{1-2}R^7$, $-NR^6S(O)_{1-2}NR^7R^8$, $-NR^6C(O)R^7$, and $-NR^6C(O)OR^7$;

z is 0 or 1;

X^1 is O, NR^9, or a bond;

R^1 is hydrogen;

R^2 is C_{1-6} haloalkyl;

R^3 is aryl or heteroaryl, each of which is optionally substituted with one to five R^{11};

R^4 and R^5 are independently hydrogen;

each of R^6, R^7, and R^8 is independently hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-S(O)_{1-2}R^{20}$, or $-S(O)_{1-2}NR^{20}R^{21}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^6, R^7, and R^8 is independently optionally substituted with one to five R^{12}; or two of R^6, R^7, and R^8 are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo, oxo, or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

R^9 is hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl, each of which, other than hydrogen, is optionally substituted with one to three R^{11};

each R^{11} is independently halo, cyano, nitro, oxo, $-OR^6$, $-SR^6$, $-SF_5$, $-NR^6R^7$, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)OR^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^6C(O)NR^7R^8$, $-S(O)_{1-2}R^6$, $-S(O)_{1-2}NR^6R^7$, $-NR^6S(O)_{1-2}R^7$, $-NR^6S(O)_{1-2}NR^7R^8$, $-NR^6C(O)R^7$, or $-NR^6C(O)OR^7$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{11} is independently optionally substituted with one to five R^{12};

each R^{12} is independently halo, cyano, nitro, oxo, $-OR^{30}$, $-SR^{30}$, $-SF_5$, $-NR^{30}R^{31}$, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)OR^{30}$, $-OC(O)R^{30}$, $-C(O)NR^{30}R^{31}$, $-OC(O)NR^{30}R^{31}$, $-NR^{30}C(O)NR^{30}R^{31}$, $-S(O)_{1-2}R^{30}$, $-S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}S(O)_{1-2}R^{31}$, $-NR^{30}S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, or $-NR^{30}C(=O)OR^{31}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{12} is independently optionally substituted with one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

each R^{13} is independently halo, cyano, nitro, oxo, $-OR^{30}$, $-SR^{30}$, $-SF_5$, $-NR^{30}R^{31}$, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{30}$, $-C(O)OR^{30}$, $-OC(O)OR^{30}$, $-OC(O)R^{30}$, $-C(O)NR^{30}R^{31}$, $-OC(O)NR^{30}R^{31}$, $-NR^{30}C(O)NR^{30}R^{31}$, $-S(O)_{1-2}R^{30}$, $-S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}S(O)_{1-2}R^{31}$, $-NR^{30}S(O)_{1-2}NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, or $-NR^{30}C(=O)OR^{31}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{13} is independently optionally

substituted with one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

each R^{14} is independently halo, cyano, $-NR^6R^7$, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl, or two R^{14} together with the atoms to which they are attached form a ring or a C=O;

each R^{15} is independently hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

each R^{20} and R^{21} is independently hydrogen or C_{1-12} alkyl independently optionally substituted with one to three oxo, halo, hydroxyl, or amino; or R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino; and

each R^{30} and R^{31} is independently hydrogen or C_{1-12} alkyl independently optionally substituted with one to three oxo, halo, hydroxyl, or amino; or R^{30} and R^{31} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^2 is $-CHF_2$, $-CF_3$, or $-CH_2CF_3$.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein Q^1 is O.

8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein Q^2 is O.

9. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein Q^1 is NR^{15} and Q^2 is O.

10. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein Q^1 and Q^2 are each O.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein L is an ethylene linker, optionally substituted with one to three halo.

12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein L is $-CH_2CH_2-$.

13. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein the moiety $-Q^1-L-Q^2-R^2$ is $-OCH_2CH_2OCF_3$.

14. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein the moiety $-Q^1-L-Q^2-R^2$ is $-NR^{15}CH_2CH_2OCF_3$.

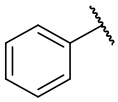
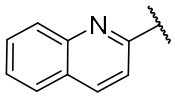
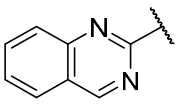
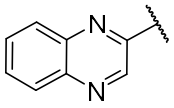
15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein X^1 is O.

16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is aryl optionally substituted with one to five R^{11}.

17. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is heteroaryl optionally substituted with one to five R^{11}.

18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is aryl or heteroaryl, each of which is optionally substituted with one to five substituents independently selected from halo, cyano, $C_{1\text{-}12}$ haloalkyl, and $C_{1\text{-}12}$ haloalkoxy.

19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is aryl or heteroaryl, each of which is optionally substituted with chloro, fluoro, $-CF_3$, or a combination thereof.

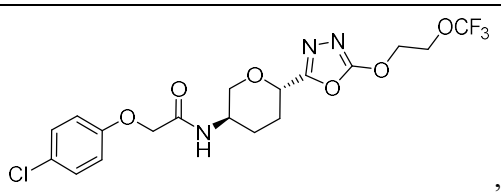
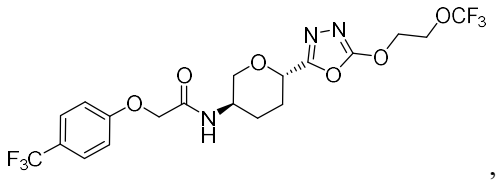
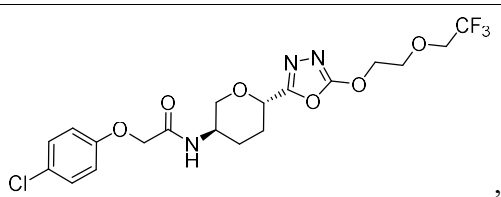
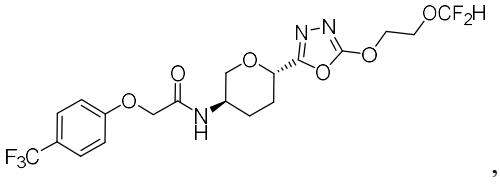
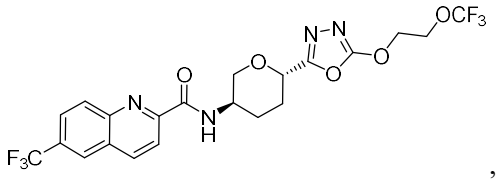
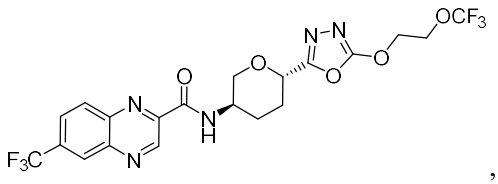
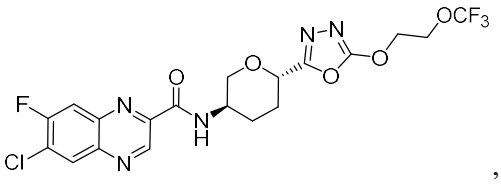
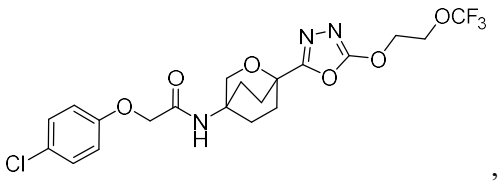
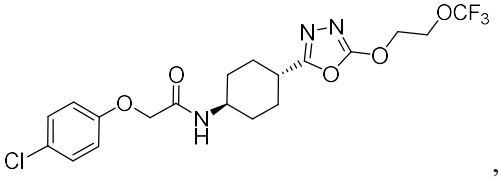
20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is , , , or , each of which is optionally substituted with one to five R^{11}.

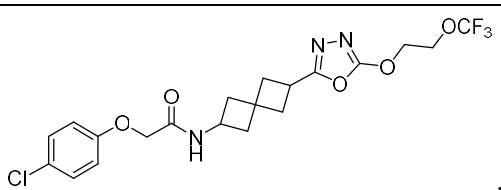
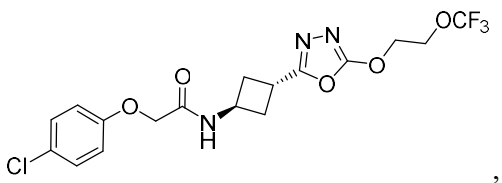
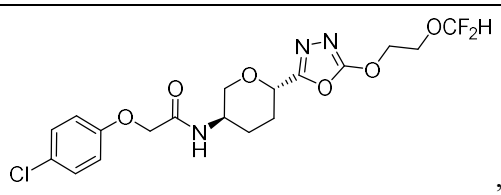
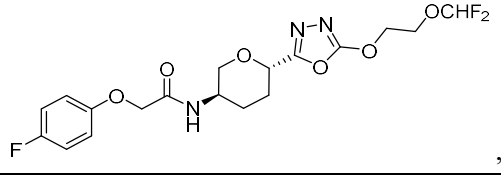
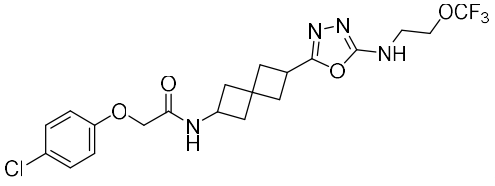
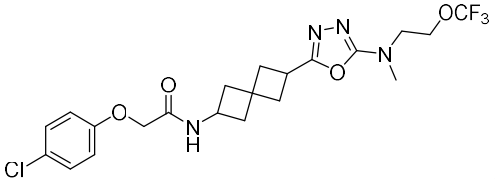
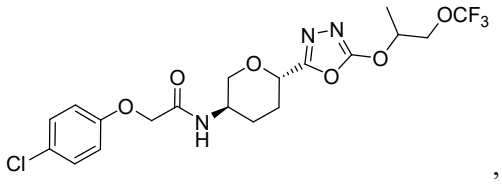
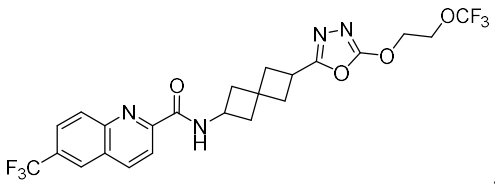
21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is phenyl optionally substituted with one to five R^{11}.

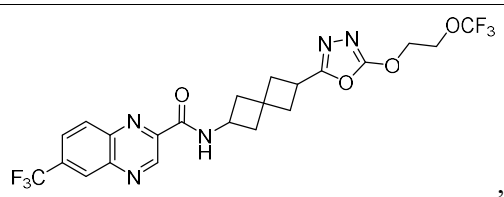
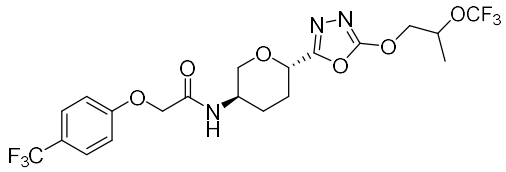
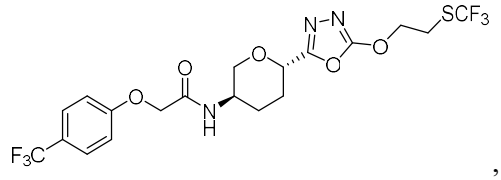
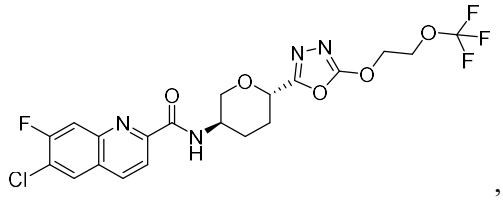
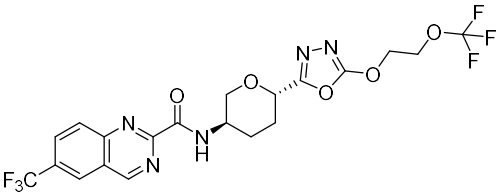
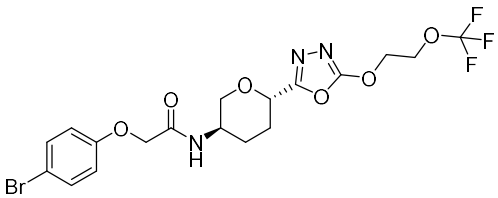
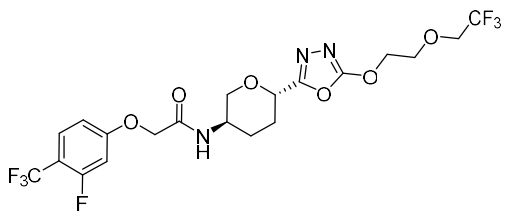
22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is phenyl optionally substituted with one to five substituents independently selected from halo, cyano, $C_{1\text{-}12}$ haloalkyl, and $C_{1\text{-}12}$ haloalkoxy.

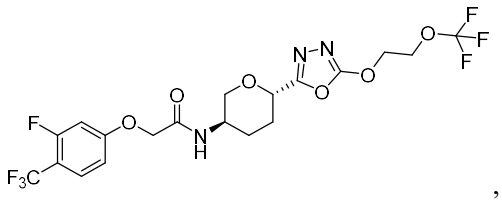
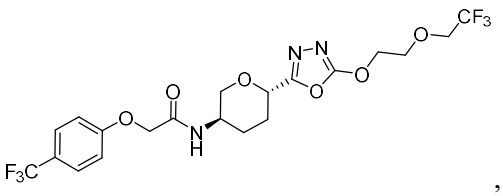
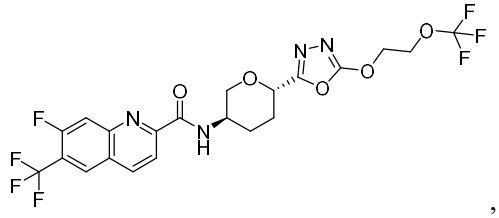
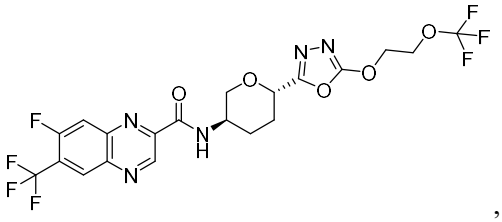
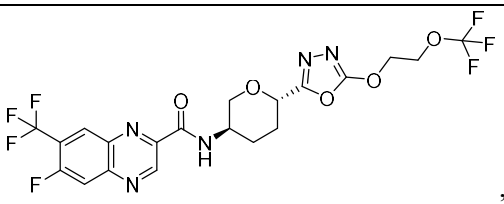
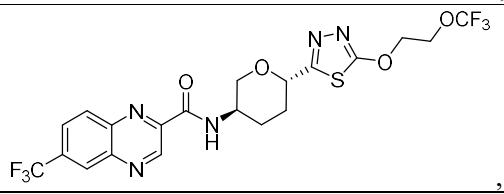
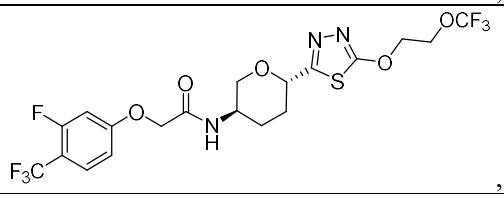
23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof, wherein R^3 is phenyl substituted with chloro, fluoro, bromo, $-CF_3$, or a combination thereof.

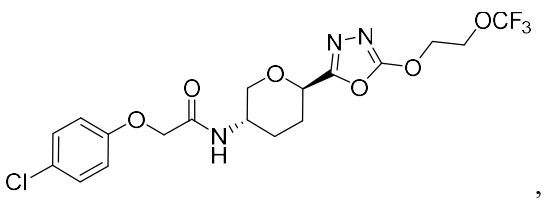
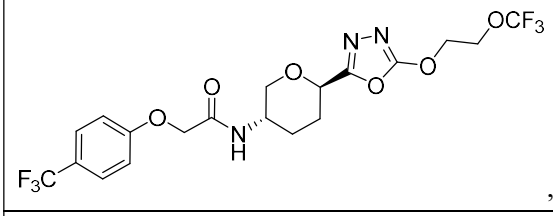
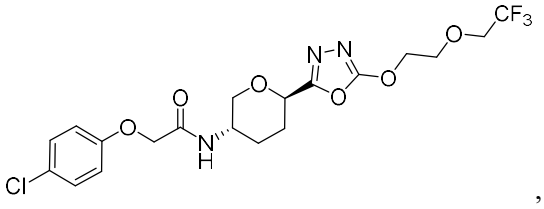
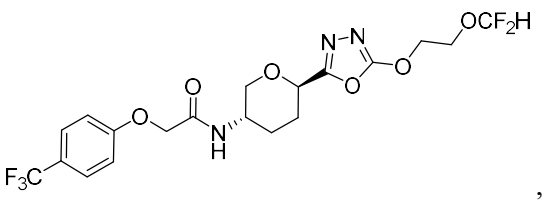
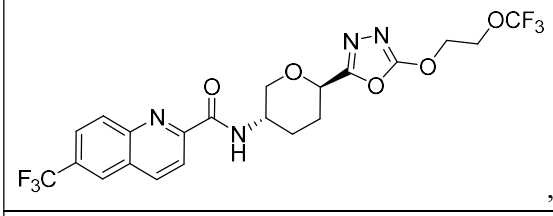
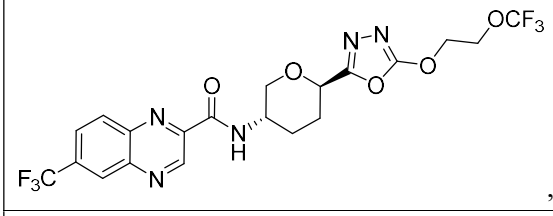
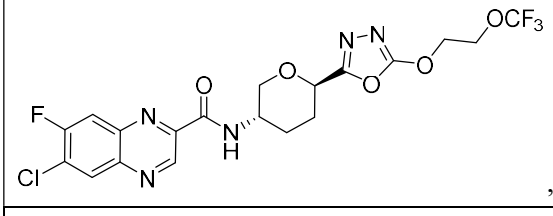
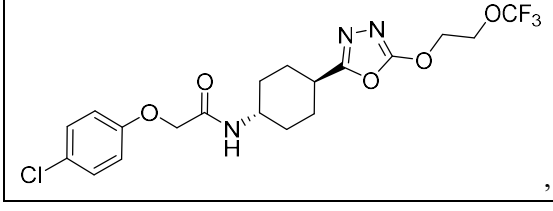
24. A compound or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof selected from:

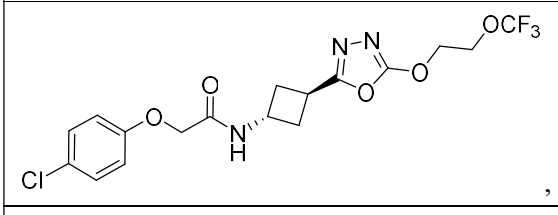
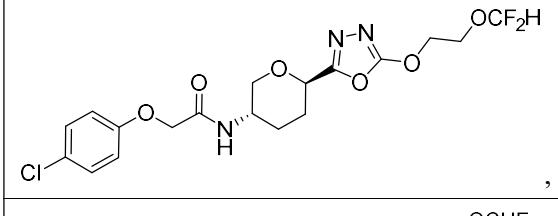
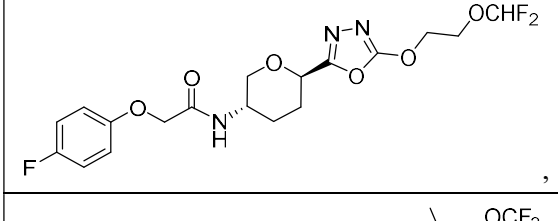
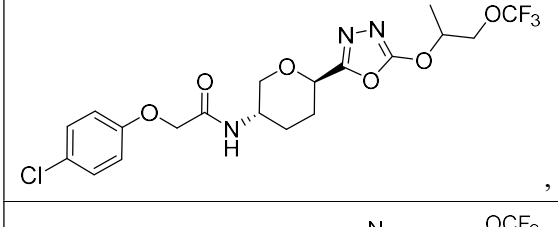
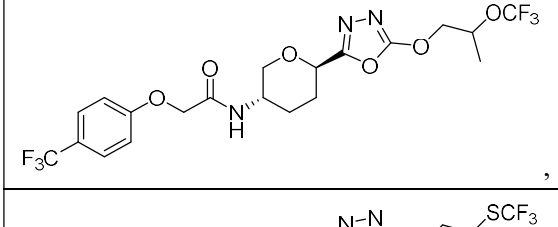
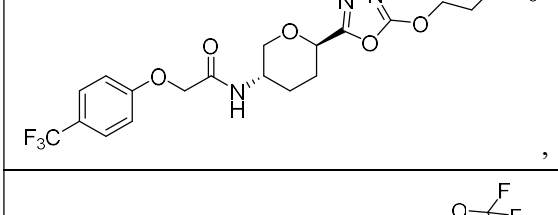
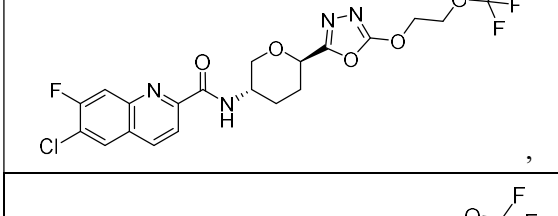
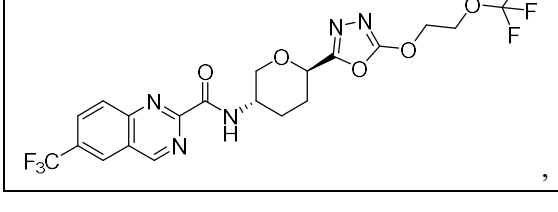
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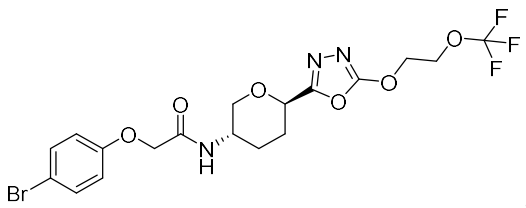
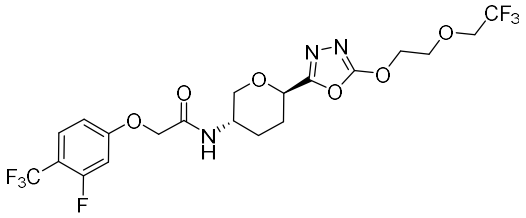
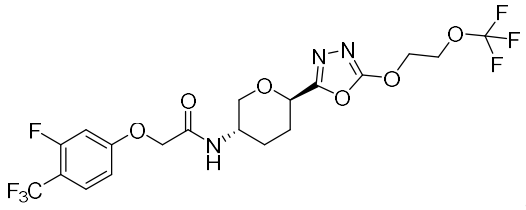
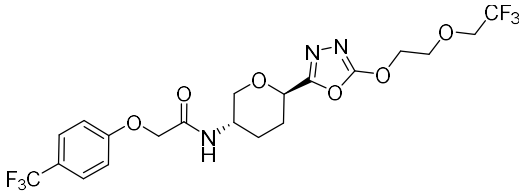
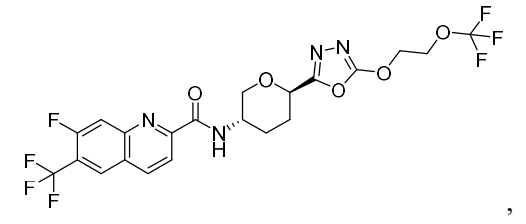
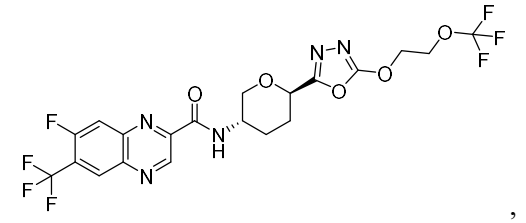
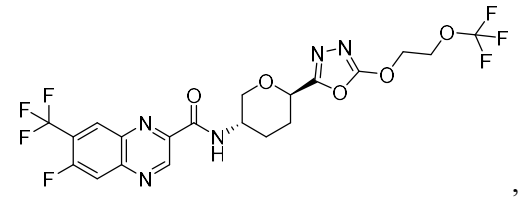
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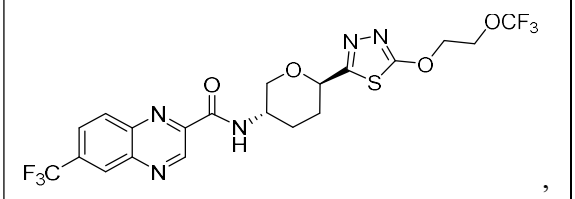
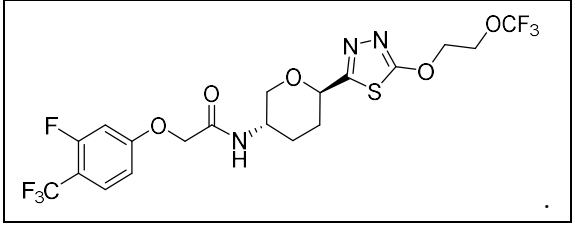
Ex.	Structure
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Ex.	Structure
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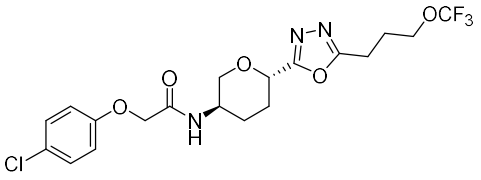
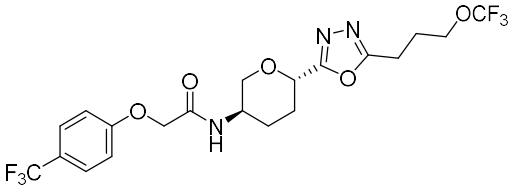
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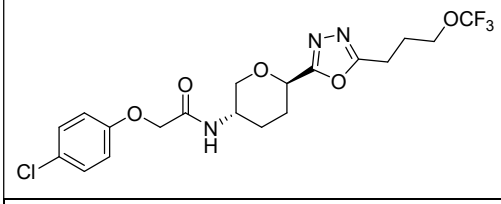
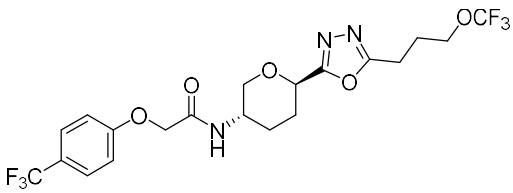
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25. A compound or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof selected from:

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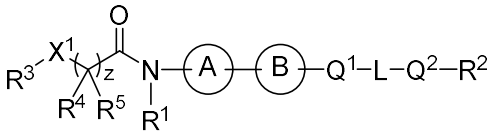
26. A pharmaceutical composition comprising a compound of any one of claims 1-25, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, and a pharmaceutically acceptable carrier.

27. The use of a compound of any one of claims 1-25, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, for the manufacture of a medicament for treating a neurodegenerative disease, treating cancer or treating cognitive impairment.

28. The use of a compound of any one of claims 1-25, or a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof, for the manufacture of a medicament for treating Alexander's disease, Alper's disease, Alzheimer's disease, amyotrophic lateral sclerosis, ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Bovine spongiform encephalopathy (BSE), Canavan disease, Cockayne syndrome, Corticobasal degeneration,

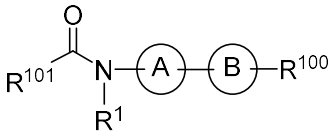
Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Straussler-Scheinker syndrome, Huntington's disease, HIV-associated dementia, Kennedy's disease, Krabbe's disease, kuru, Lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple sclerosis, Multiple System Atrophy, narcolepsy, Neuroborreliosis, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, primary lateral sclerosis, Prion diseases, Refsum's disease, Sandhoffs disease, Schilder's disease, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, vanishing white matter (VWM) disease, insulin resistance, or Tabes dorsalis.

29. A method of preparing a compound of Formula I, or a salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof:

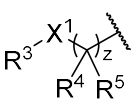
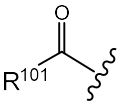


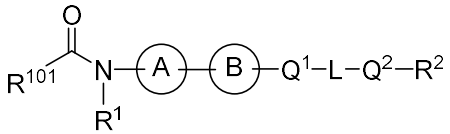
I

comprising contacting a compound of Formula 1:



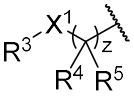
1

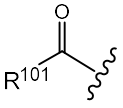
wherein R^{100} is halo and R^{101} is the moiety  or  is a nitrogen protecting group; with a compound of Formula H-Q^1-L-Q^2-R^2, under conditions suitable to provide a compound of Formula 2:

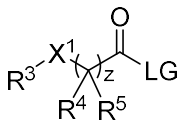


2

wherein:

a) when R^{101} is the moiety , the method provides the compound of Formula I, or a salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof; and

b) when  is a nitrogen protecting group, the method further comprises removing the nitrogen protecting group and contacting the compound of Formula 2 with a compound of Formula 3:



3

wherein LG is a leaving group, under conditions suitable to provide the compound of Formula I, or a salt, isotopically enriched analog, stereoisomer, or mixture of stereoisomers thereof; and

ring A is cycloalkyl or heterocyclyl, provided ring A is not bicyclo[1.1.1]pentane or bicyclo[2.1.1]hexane; wherein each is optionally substituted with one to six R^{14};

ring B is a 5- or 6-membered heteroaryl or phenyl; wherein each is optionally substituted with one to three R^{13};

Q^1 and Q^2 are each independently O, S, or NR^{15};

L is a C_{1-6} alkylene linker, optionally substituted with one to three substituents independently selected from halo, cyano, nitro, $-OR^6$, $-SR^6$, $-SF_5$, $-NR^6R^7$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)OR^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^6C(O)NR^7R^8$, $-S(O)_{1-2}R^6$, $-S(O)_{1-2}NR^6R^7$, $-NR^6S(O)_{1-2}R^7$, $-NR^6S(O)_{1-2}NR^7R^8$, $-NR^6C(O)R^7$, and $-NR^6C(O)OR^7$;

z is 0 or 1;

X^1 is O, NR^9, or a bond;

R^1 is hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl, each of which, other than hydrogen, is optionally substituted with one to three R^{11};

R^2 is C_{1-6} haloalkyl;

R^3 is hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which, other than hydrogen, is optionally substituted with one to five R^{11};

R^4 and R^5 are independently hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, or C_{2-12} alkynyl, each of which, other than hydrogen, is independently optionally substituted with one to five R^{11};

or R^3 and R^4, together with the atoms to which they are attached, join to form a C_{3-10} cycloalkyl, or heterocyclyl, each of which is optionally substituted with one to five R^{11};

or R^4 and R^5, together with the atoms to which they are attached, join to form a C_{3-10} cycloalkyl, or heterocyclyl, each of which is optionally substituted with one to five R^{11};

each of R^6, R^7, and R^8 is independently hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)NR^{20}R^{21}$, $-S(O)_{1-2}R^{20}$, or $-S(O)_{1-2}NR^{20}R^{21}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^6, R^7, and R^8 is independently optionally substituted with one to five R^{12}; or two of R^6, R^7, and R^8 are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo, oxo, or C_{1-12} alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

R^9 is hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, or heterocyclyl, each of which, other than hydrogen, is optionally substituted with one to three R^{11};

each R^{11} is independently halo, cyano, nitro, oxo, $-OR^6$, $-SR^6$, $-SF_5$, $-NR^6R^7$, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^6$, $-C(O)OR^6$,

-OC(O)OR^6, -OC(O)R^6, -C(O)NR^{6}R^7, -OC(O)NR^{6}R^7, -NR^{6}C(O)NR^{7}R^8, -S(O)$_{1-2}$R^6, -S(O)$_{1-2}$NR^{6}R^7, -NR^{6}S(O)$_{1-2}$R^7, -NR^{6}S(O)$_{1-2}$NR^{7}R^8, -NR^{6}C(O)R^7, or -NR^{6}C(O)OR^7, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{11} is independently optionally substituted with one to five R^{12};

each R^{12} is independently halo, cyano, nitro, oxo, -OR^{30}, -SR^{30}, -SF$_5$, -NR^{30}R^{31}, C$_{1-12}$ alkyl, C$_{2-12}$ alkenyl, C$_{2-12}$ alkynyl, C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, heteroaryl, -C(O)R^{30}, -C(O)OR^{30}, -OC(O)OR^{30}, -OC(O)R^{30}, -C(O)NR^{30}R^{31}, -OC(O)NR^{30}R^{31}, -NR^{30}C(O)NR^{30}R^{31}, -S(O)$_{1-2}$R^{30}R^{31}, -S(O)$_{1-2}$NR^{30}, -NR^{30}S(O)$_{1-2}$R^{31}, -NR^{30}S(O)$_{1-2}$NR^{30}R^{31}, -NR^{30}C(O)R^{31}, or -NR^{30}C(=O)OR^{31}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{12} is independently optionally substituted with one to three halo or C$_{1-12}$ alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

each R^{13} is independently halo, cyano, nitro, oxo, -OR^{30}, -SR^{30}, -SF$_5$, -NR^{30}R^{31}, C$_{1-12}$ alkyl, C$_{2-12}$ alkenyl, C$_{2-12}$ alkynyl, C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, heteroaryl, -C(O)R^{30}, -C(O)OR^{30}, -OC(O)OR^{30}, -OC(O)R^{30}, -C(O)NR^{30}R^{31}, -OC(O)NR^{30}R^{31}, -NR^{30}C(O)NR^{30}R^{31}, -S(O)$_{1-2}$R^{30}, -S(O)$_{1-2}$NR^{30}R^{31}, -NR^{30}S(O)$_{1-2}$R^{31}, -NR^{30}S(O)$_{1-2}$NR^{30}R^{31}, -NR^{30}C(O)R^{31}, or -NR^{30}C(=O)OR^{31}, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl of R^{13} is independently optionally substituted with one to three halo or C$_{1-12}$ alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino;

each R^{14} is independently halo, cyano, -NR^{6}R^7, C$_{1-6}$ alkyl, C$_{1-6}$ alkoxy, or C$_{1-6}$ haloalkyl, or two R^{14} together with the atoms to which they are attached form a ring or a C=O;

each R^{15} is independently hydrogen, C$_{1-6}$ alkyl, or C$_{1-6}$ haloalkyl;

each R^{20} and R^{21} is independently hydrogen or C$_{1-12}$ alkyl independently optionally substituted with one to three oxo, halo, hydroxyl, or amino; or R^{20} and R^{21} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo or C$_{1-12}$ alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino; and

each R^{30} and R^{31} is independently hydrogen or C$_{1-12}$ alkyl independently optionally substituted with one to three oxo, halo, hydroxyl, or amino; or R^{30} and R^{31} are taken together with the atoms to which they are attached to form heterocyclyl independently optionally substituted by one to three halo or C$_{1-12}$ alkyl independently optionally substituted by one to three oxo, halo, hydroxyl, or amino.

30. The method of claim 29, wherein LG is -OH, C$_{1-6}$ alkoxy, or halo.