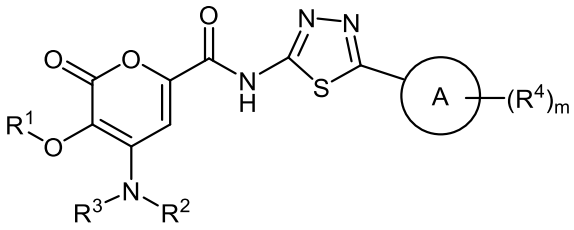
SUMMARY

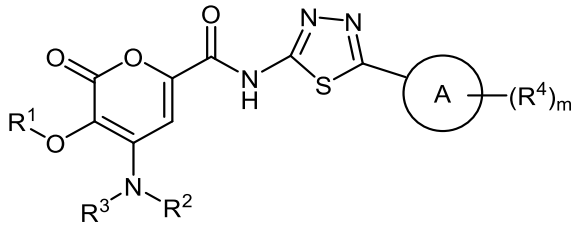
[0006] Provided herein are cGAS inhibitors of Formula (**I**):



(**I**),

or pharmaceutically acceptable salts thereof, wherein Ring A, R^1, R^2, R^3, R^4, and m are described herein.

[0006a] In one aspect, provided herein is a compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 5-membered monocyclic heteroaryl;

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -L_3-(C_3-C_6 carbocyclyl), or -L_3-(4- to 10-membered heterocyclyl), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, and heterocyclyl are independently substituted with 0, 1, 2, 3, or 4 R^{1A}; each R^{1A} is independently halogen, -OR^{1B}, -$N(R^{1B})_2$, -SR^{1B}, -$C(=O)OR^{1B}$, -$C(=O)N(R^{1C})_2$, -(C_1-C_3 alkylene)-OR^{1B}, or -(C_1-C_3 alkylene)-SR^{1B}, or two instances of R^{1A} are taken together to form =O; each R^{1B} is independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 haloalkyl, wherein the alkyl and haloalkyl are independently substituted with 0, 1, 2, 3, or 4 R^{1D}; each R^{1C} is independently hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or -OR^{1F}; each R^{1D} is independently halogen, -OR^{1F}, or -$N(R^{1F})_2$; and each R^{1F} is independently hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

L_3 of group R^1 is a bond, C_1-C_3 alkylene, or -(C_1-C_3 alkylene)-O-, wherein the alkylene is independently substituted with 0, 1, 2, 3, or 4 R^{1E}; and each R^{1E} is independently -(C_1-C_3 alkylene)-OR^{1B} or -OR^{1B}, or two instances of R^{1E} are taken together to form =O;

R^2 is hydrogen or C_1-C_6 alkyl substituted with 0, 1, 2, 3, or 4 R^{2A}, and each R^{2A} is independently halogen, -OR^{2B}, or -$N(R^{2B})_2$, wherein each R^{2B} is independently hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

or R^1 and R^2 are joined, with the atoms to which they are attached, to form a 6- or 7-membered heterocyclyl independently substituted with 0, 1, 2, 3, or 4 R^{1A};

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} carbocyclyl, or 4- to 10-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, and heterocyclyl are independently substituted with 0, 1, 2, 3, or 4 R^{3A};

or R^2 and R^3 are joined, with the atom to which they are attached, to form a 4- to 10-membered heterocyclyl independently substituted with 0, 1, 2, 3, or 4 R^{3A};

each R^{3A} is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, halogen, =O, -L_1-CN, -L_1-SOR^{3C}, -L_1-SO_2R^{3C}, -L_1-SR^{3B}, -L_1-$PO(R^{3C})_2$,-L_1-OR^{3B}, -L_1-$N(R^{3B})_2$, -L_1-$C(=O)N(R^{3B})_2$ or -L_1-$C(=O)OR^{3B}$, -L_1-(C_3-C_6 carbocyclyl), -L_1-(4- to 6-membered heterocyclyl), -L_1-($C_{6\text{-}10}$ aryl), or -L_1-(5- to 10-membered heteroaryl), or two R^{3A} groups are joined, with the atoms to which they are attached, to form C_6 aryl, 5- to 6-membered heteroaryl, C_3-C_6 carbocyclyl, or 4- to 6-membered heterocyclyl, and wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are independently substituted with 0, 1, 2, 3, or 4 R^{3D};

each R^{3B} is independently hydrogen, C_1-C_3 alkyl, C_3-C_6 carbocyclyl, or 4- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, and heterocyclyl are independently substituted with 0, 1, 2, 3, or 4 R^{3D};

each R^{3C} is independently C_1-C_3 alkyl or C_1-C_3 haloalkyl;

each R^{3D} is independently halogen, -OR^{3E}, -CN, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

each R^{3E} is independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 haloalkyl;

each R^4 is independently halogen, -CN, -L_2-OR^{4A}, -L_2-$N(R^{4B})_2$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl, wherein each R^{4A} and R^{4B} are independently hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or -$C(=O)R^{4C}$, wherein R^{4C} is C_1-C_6 alkyl or C_1-C_6 haloalkyl;

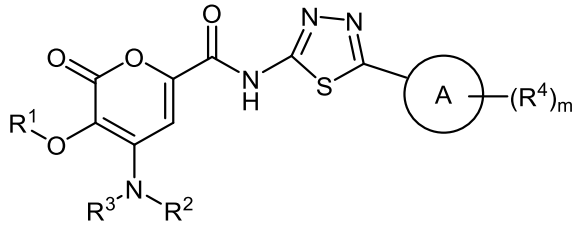
each L_1 and L_2 is independently a bond, C_1-C_3 alkylene, or C_1-C_3 haloalkylene; and

m is 0, 1 or 2.

[0006b] In another aspect, provided herein is an isotopically enriched compound of Formula (**I**) as described herein, or a pharmaceutically acceptable salt thereof, wherein the compound comprises one or more isotopically enriched atoms selected from the group consisting of deuterium, tritium, ^{19}F, ^{13}C, and ^{14}C.

[0007] Further provided are methods of preparation, methods of treatment, and pharmaceutical compositions comprising same.

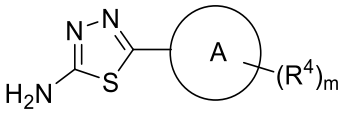
[0007a] In another aspect, provided herein is a method of preparing a compound of Formula (**I**):



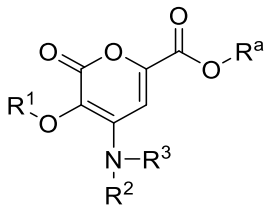
(**I**),

or a salt thereof, wherein Ring A, R^1, R^2, R^3, R^4, and m are as described herein, the method comprising:

(i) peptide coupling of a compound of Formula (**H-1**), or salt thereof, with a compound of Formula (**N**), or salt thereof:



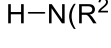
(**H-1**)



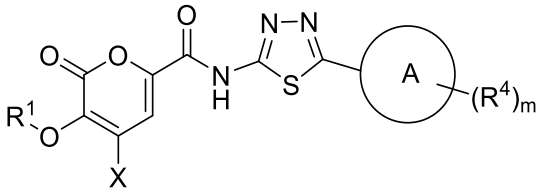
(**N**)

wherein R^a is hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl, to provide a compound of Formula (**I**), or salt thereof; or

(ii) cross-coupling of an amine of Formula (**K**), or salt thereof, with a compound of Formula (**J-1**), or salt thereof:



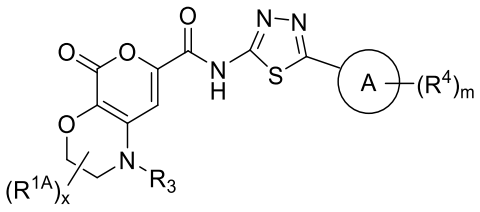
(**K**)



(**J-1**),

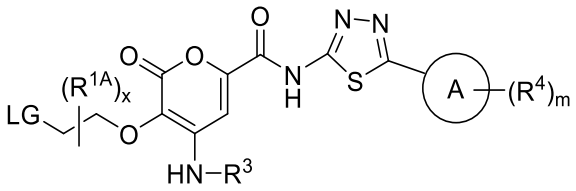
wherein X is Cl, Br, or I, to provide a compound of Formula (**I**), or salt thereof.

[0007b] In another aspect, provided herein is a method of preparing a compound of Formula (**I-BC-a**):



(**I-BC-a**), or salt thereof;

wherein Ring A, R^1, R^3, R^4, and m are as described herein, the method comprising cyclizing a compound of Formula (**P-1**):



(**P-1**), or salt thereof,

wherein LG is a leaving group.

[0007c] In another aspect, provided herein is a pharmaceutical composition comprising the compound as described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

[0007d] In another aspect, provided herein is a compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein for use in therapy.

[0007e] In another aspect, provided herein is use of a compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating a disease or disorder selected from inflammation, an autoimmune disease, a cancer, an infection, a disease or disorder of the central nervous system, a metabolic disease, a cardiovascular disease, a respiratory disease, a kidney disease, a liver disease, an ocular disease, a skin disease, a lymphatic disease, a rheumatic disease, a psychological disease, graft versus host disease, allodynia, or an cGAS-related disease in a subject that has been determined to carry a germline or somatic non-silent mutation in cGAS.

[0007f] In another aspect, provided herein is an *in vitro* method of modulating cGAS activity, comprising contacting a cell with a compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein.

DEFINITIONS

[0008] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

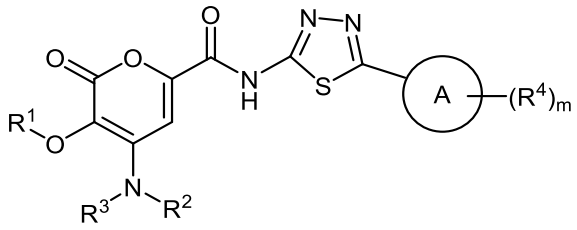
[0009] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). Compounds described herein can additionally encompasses individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0010] Unless otherwise stated, compounds described herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium,

CLAIMS

What is claimed is:

1. A compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 5-membered monocyclic heteroaryl;

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -L_3-(C_3-C_6 carbocyclyl), or -L_3-(4- to 10-membered heterocyclyl), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, and heterocyclyl are independently substituted with 0, 1, 2, 3, or 4 R^{1A}; each R^{1A} is independently halogen, -OR^{1B}, -$N(R^{1B})_2$, -SR^{1B}, -$C(=O)OR^{1B}$, -$C(=O)N(R^{1C})_2$, -(C_1-C_3 alkylene)-OR^{1B}, or -(C_1-C_3 alkylene)-SR^{1B}, or two instances of R^{1A} are taken together to form =O; each R^{1B} is independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 haloalkyl, wherein the alkyl and haloalkyl are independently substituted with 0, 1, 2, 3, or 4 R^{1D}; each R^{1C} is independently hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or -OR^{1F}; each R^{1D} is independently halogen, -OR^{1F}, or -$N(R^{1F})_2$; and each R^{1F} is independently hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

L_3 of group R^1 is a bond, C_1-C_3 alkylene, or -(C_1-C_3 alkylene)-O-, wherein the alkylene is independently substituted with 0, 1, 2, 3, or 4 R^{1E}; and each R^{1E} is independently -(C_1-C_3 alkylene)-OR^{1B} or -OR^{1B}, or two instances of R^{1E} are taken together to form =O;

R^2 is hydrogen or C_1-C_6 alkyl substituted with 0, 1, 2, 3, or 4 R^{2A}, and each R^{2A} is independently halogen, -OR^{2B}, or -$N(R^{2B})_2$, wherein each R^{2B} is independently hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

or R^1 and R^2 are joined, with the atoms to which they are attached, to form a 6- or 7-membered heterocyclyl independently substituted with 0, 1, 2, 3, or 4 R^{1A};

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} carbocyclyl, or 4- to 10-membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, and heterocyclyl are independently substituted with 0, 1, 2, 3, or 4 R^{3A};

or R^2 and R^3 are joined, with the atom to which they are attached, to form a 4- to 10-membered heterocyclyl independently substituted with 0, 1, 2, 3, or 4 R^{3A};

each R^{3A} is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, halogen, =O, -L_1-CN, -L_1-SOR^{3C}, -L_1-SO_2R^{3C}, -L_1-SR^{3B}, -L_1-$PO(R^{3C})_2$,-L_1-OR^{3B}, -L_1-$N(R^{3B})_2$, -L_1-$C(=O)N(R^{3B})_2$ or -L_1-$C(=O)OR^{3B}$, -L_1-(C_3-C_6 carbocyclyl), -L_1-(4- to 6-membered heterocyclyl), -L_1-($C_{6\text{-}10}$ aryl), or -L_1-(5- to 10-membered heteroaryl), or two R^{3A} groups are joined, with the atoms to which they are attached,

to form C_6 aryl, 5- to 6-membered heteroaryl, C_3-C_6 carbocyclyl, or 4- to 6-membered heterocyclyl, and wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are independently substituted with 0, 1, 2, 3, or 4 R^{3D};

each R^{3B} is independently hydrogen, C_1-C_3 alkyl, C_3-C_6 carbocyclyl, or 4- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, and heterocyclyl are independently substituted with 0, 1, 2, 3, or 4 R^{3D};

each R^{3C} is independently C_1-C_3 alkyl or C_1-C_3 haloalkyl;

each R^{3D} is independently halogen, -OR^{3E}, -CN, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

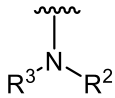
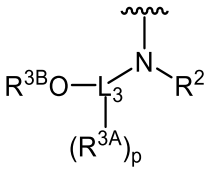
each R^{3E} is independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 haloalkyl;

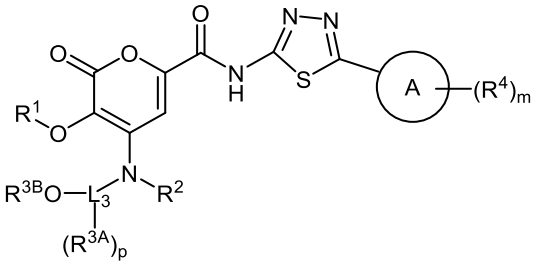
each R^4 is independently halogen, -CN, -L_2-OR^{4A}, -L_2-$N(R^{4B})_2$, C_1-C_6 alkyl, or C_1-C_6 haloalkyl, wherein each R^{4A} and R^{4B} are independently hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or -$C(=O)R^{4C}$, wherein R^{4C} is C_1-C_6 alkyl or C_1-C_6 haloalkyl;

each L_1 and L_2 is independently a bond, C_1-C_3 alkylene, or C_1-C_3 haloalkylene; and

m is 0, 1 or 2.

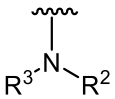
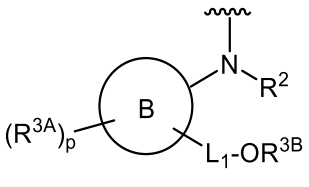
2. The compound of claim 1, wherein:

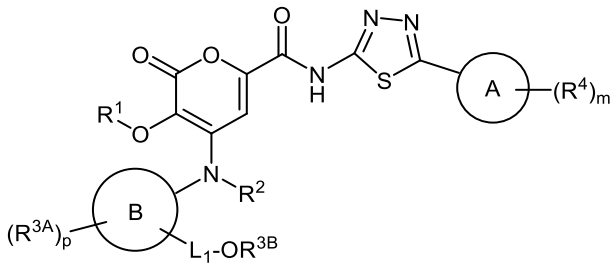
(i) the amino moiety  is a group of formula: , and the compound is of Formula (**I′**):



(**I′**),

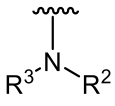
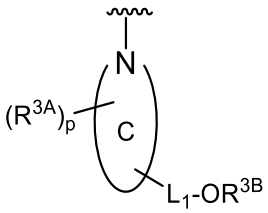
or a pharmaceutically acceptable salt thereof, wherein L_3 is C_1-C_{10} alkylene, C_2-C_{10} alkenylene, or C_2-C_{10} alkynylene, and p is 0, 1, 2, or 3; or

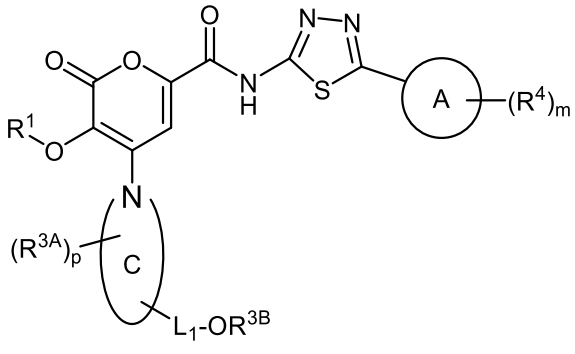
(ii) the amino moiety  is a group of formula: , and the compound is of Formula (**I″**):



(**I″**),

or a pharmaceutically acceptable salt thereof, wherein Ring B is C_3-C_{10} carbocyclyl or 4- to 10-membered heterocyclyl, and p is 0, 1, 2, or 3; or

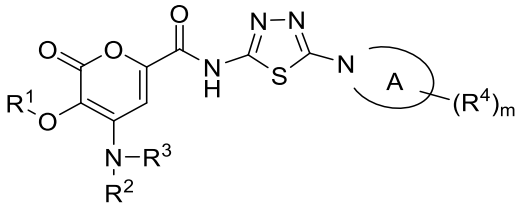
(iii) the amino moiety  is a group of formula: , and the compound is of Formula (**I‴**):



(**I‴**),

or a pharmaceutically acceptable salt thereof, wherein Ring C is a 5- to 10-membered heterocyclyl, and p is 0, 1, 2, or 3.

3. The compound of claim 1 or 2, wherein the compound is of Formula (**I‴′**):

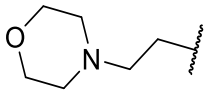


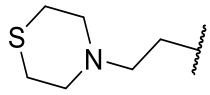
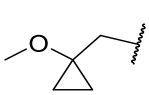
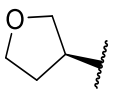
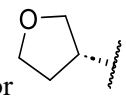
(**I‴′**),

or a pharmaceutically acceptable salt thereof, wherein the nitrogen atom of the heteroaryl Ring A is directly linked to the thiadiazole moiety.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_6 alkyl substituted with 0, 1, 2, 3, or 4 R^{1A}.

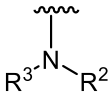
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof,

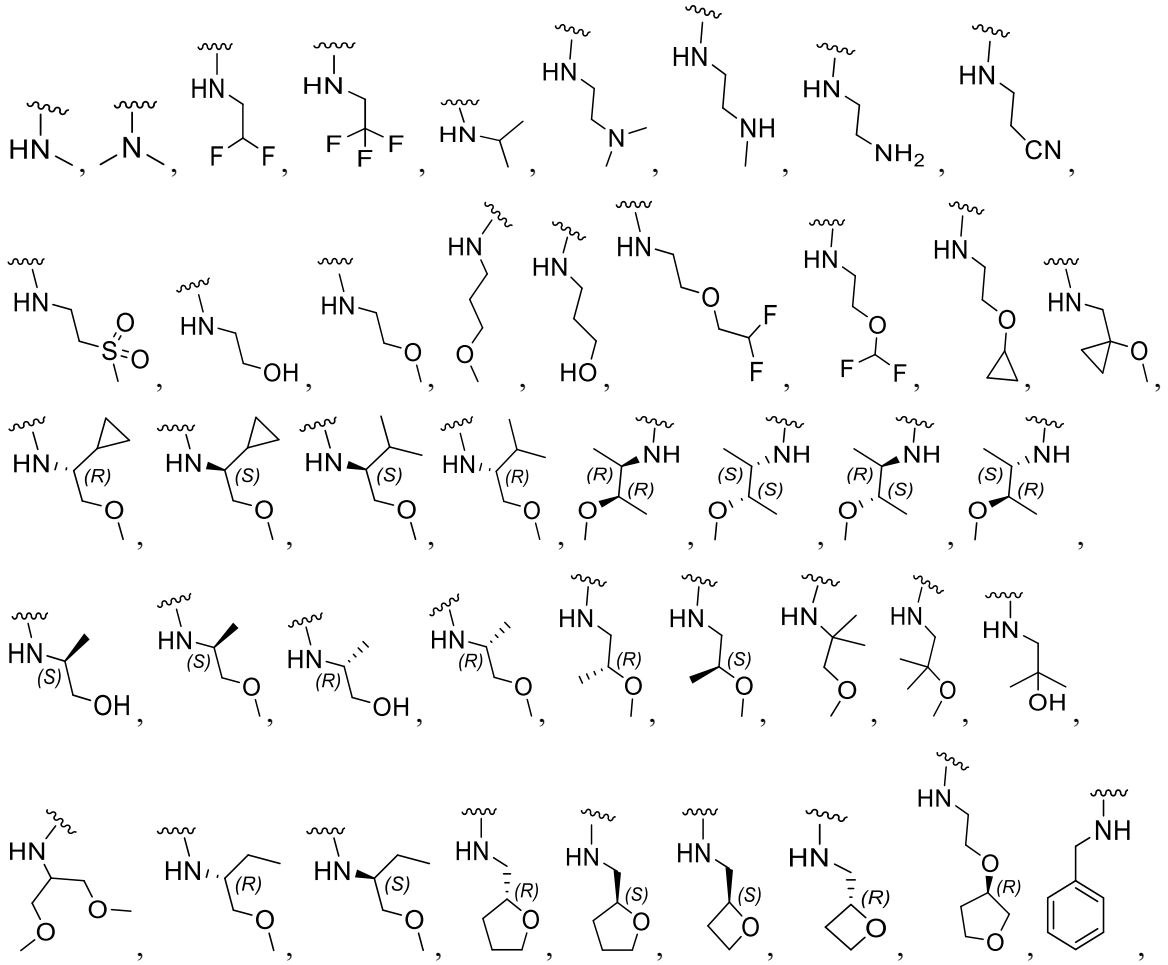
wherein R^1 is -CH_3, -CH_2-$C(CH_3)_2$-CH_2OCH_3, -CH_2CH_2OH, -$CH_2CH_2OCH_3$, ,

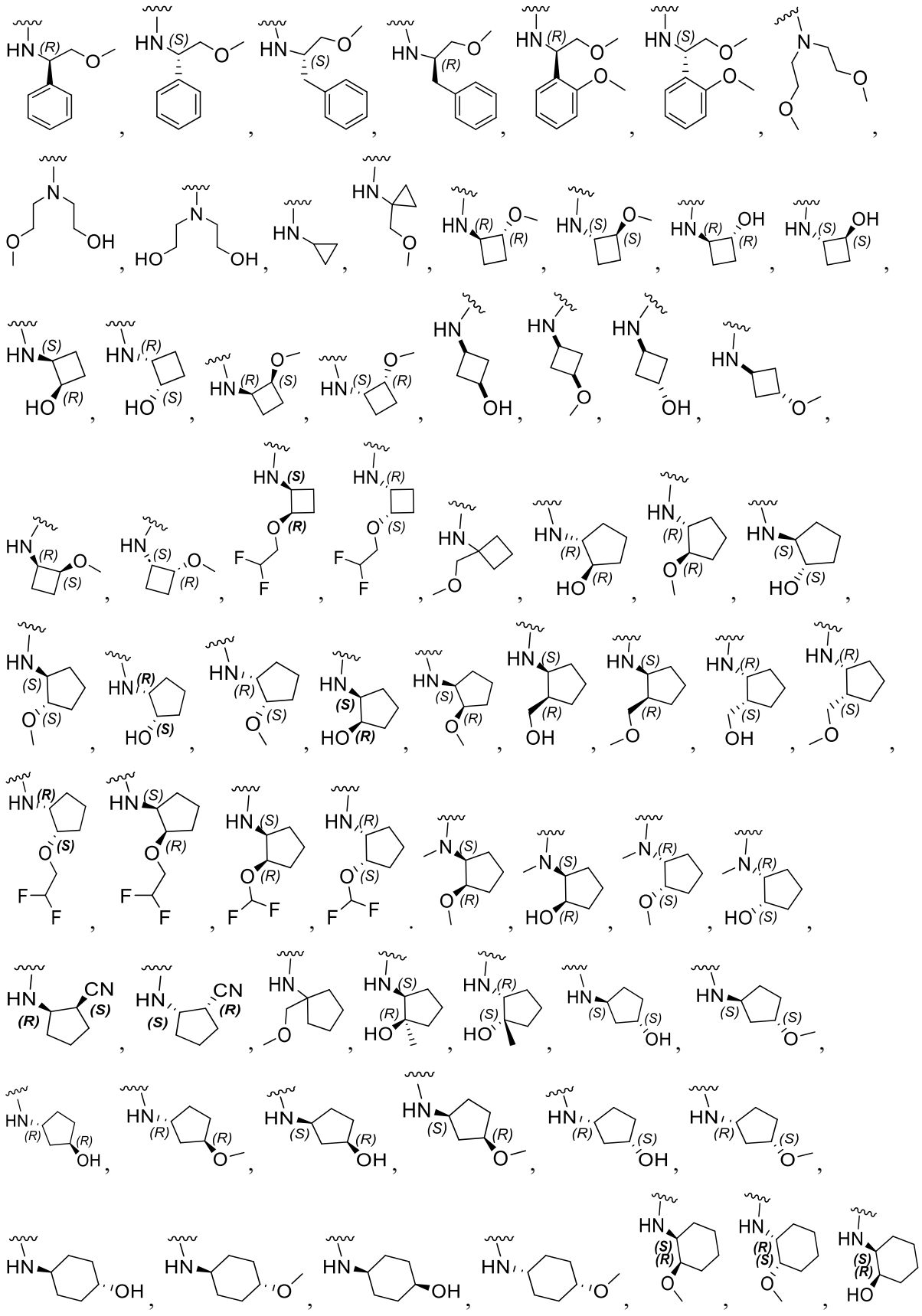
, , , or .

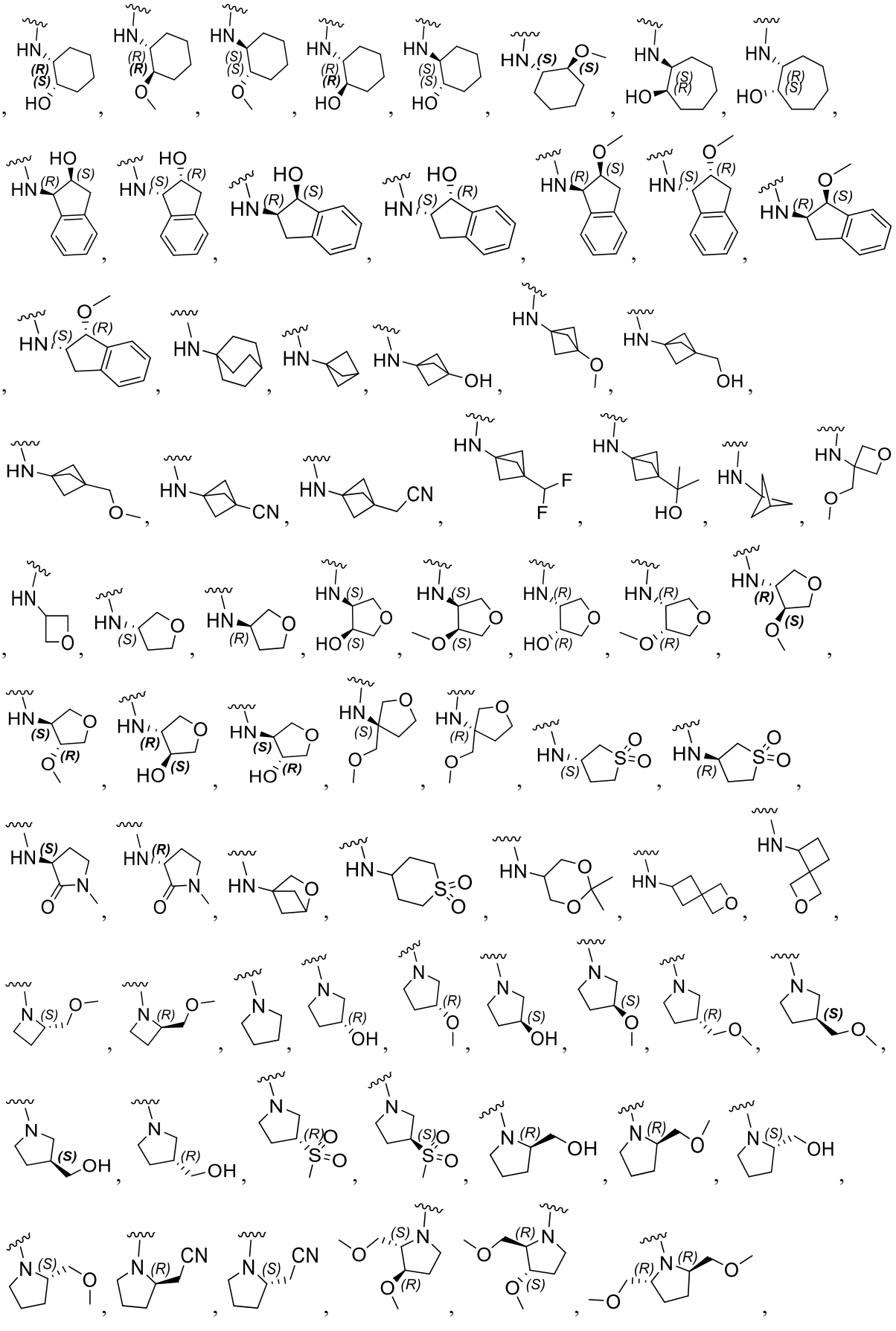
6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

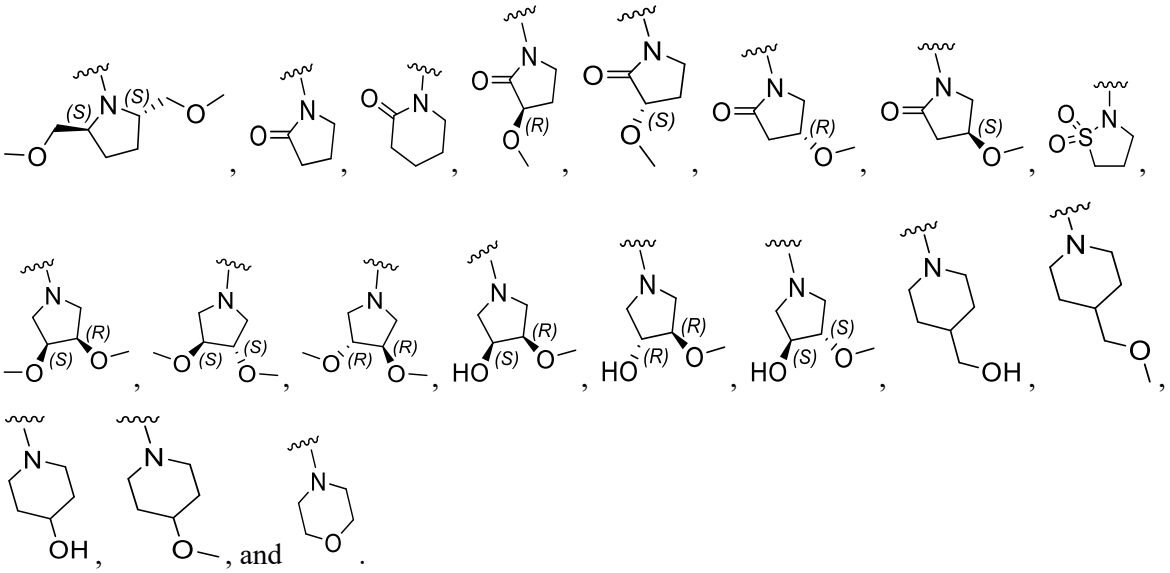
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_1-C_{10} alkyl substituted with 0, 1, 2, 3, or 4 R^{3A}.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein the amino moiety  is selected from the group consisting of:

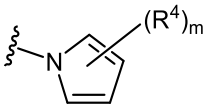
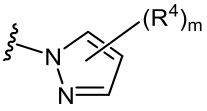
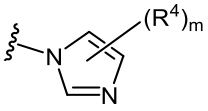


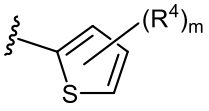
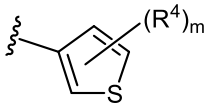
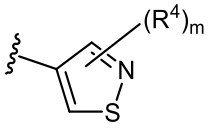


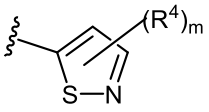
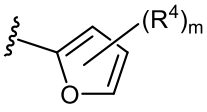
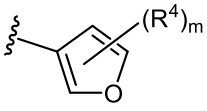


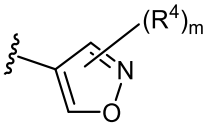
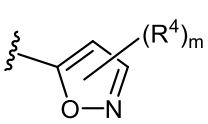
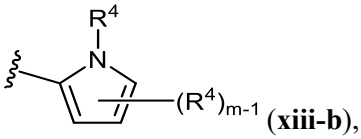


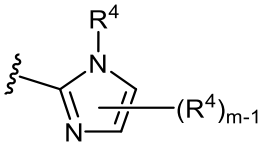
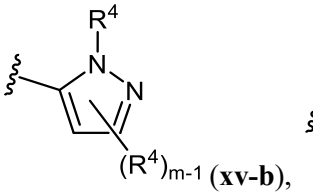
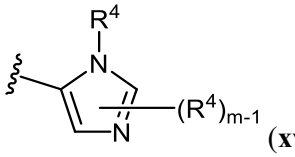
9. The compound of any one of claims 1-8, or pharmaceutically acceptable salt thereof, wherein Ring A is:

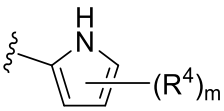
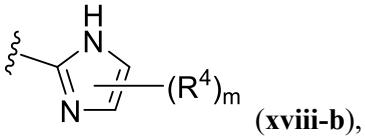
 (**i-b**),  (**ii-b**),  (**iii-b**),

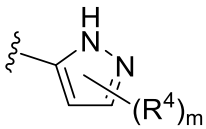
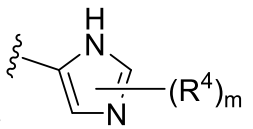
 (**iv-b**),  (**v-b**),  (**vi-b**),

 (**vii-b**),  (**viii-b**),  (**ix-b**),

 (**x-b**),  (**xii-b**),  (**xiii-b**),

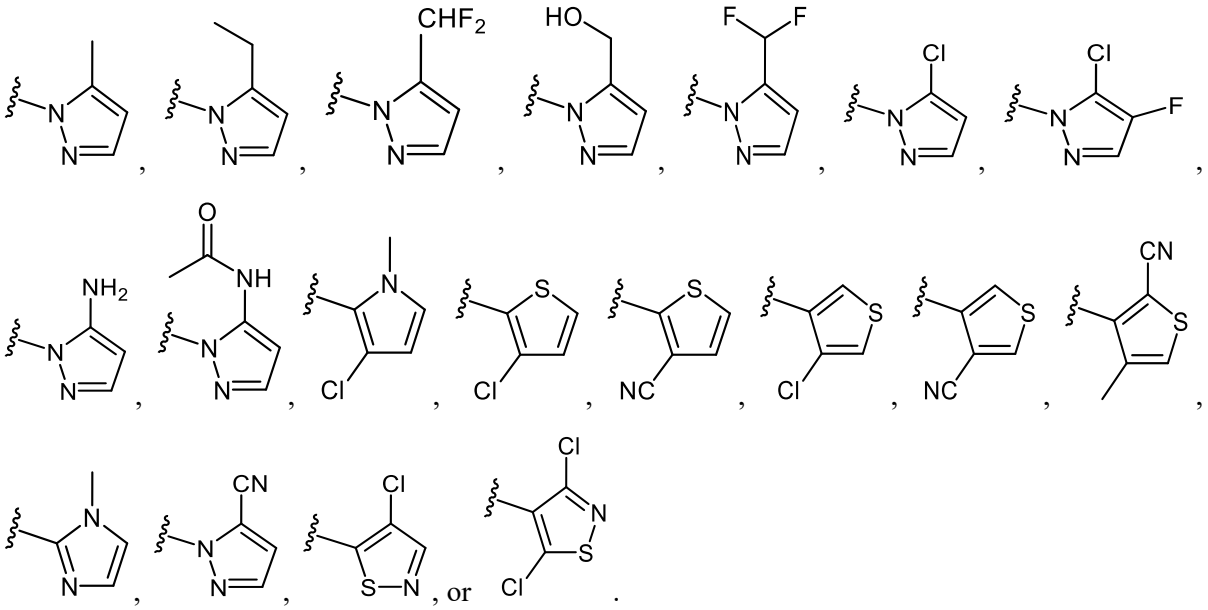
 (**xiv-b**),  (**xv-b**),  (**xvi-b**),

 (**xvii-b**),  (**xviii-b**),

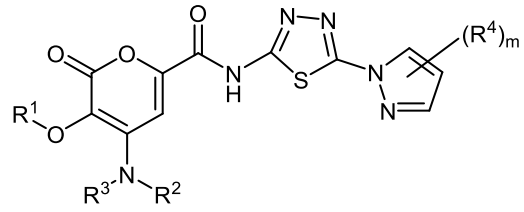
 (**xix-b**), or  (**xx-b**).

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, -Cl, -CN, $-NH_2$, or $-CH_2OH$.

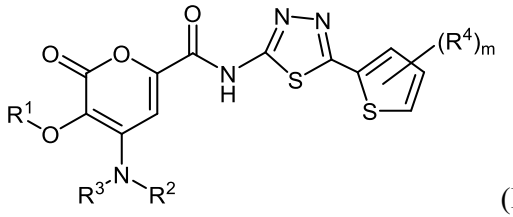
11. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein Ring A is:



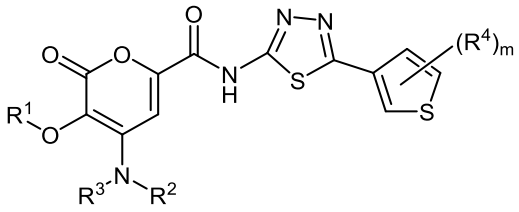
12. The compound of claim 1, wherein the compound is of Formula (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-a-1**), (**I-a-2**), (**I-a-3**), (**I-f-1**), (**I-f-2**), (**I-f-3**), (**I-BC-a**), or (**I-BC-b**):



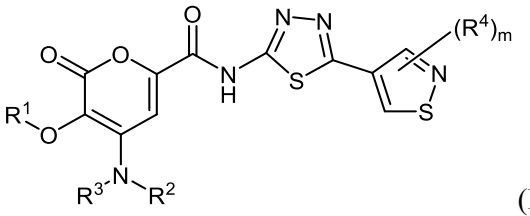
(**I-a**),



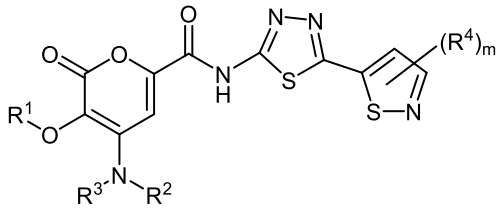
(**I-b**),



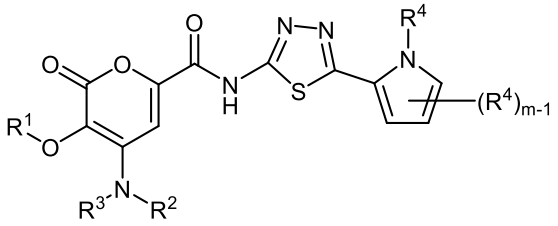
(**I-c**),



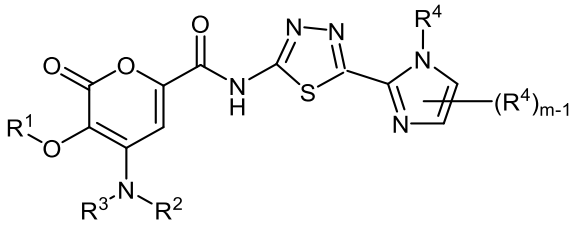
(**I-d**),



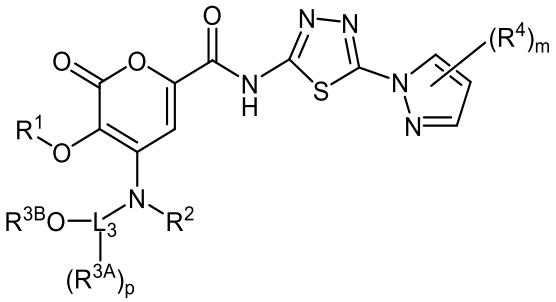
(**I-e**),



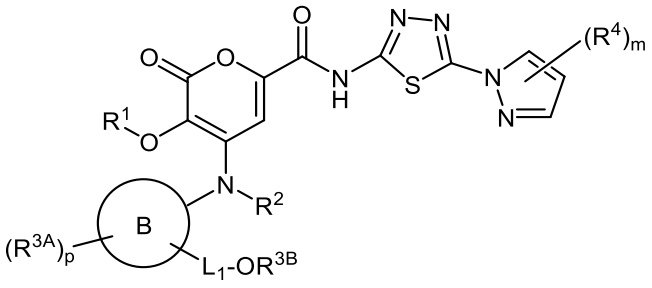
(**I-f**),



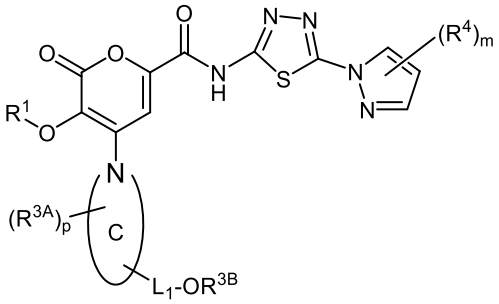
(**I-g**),



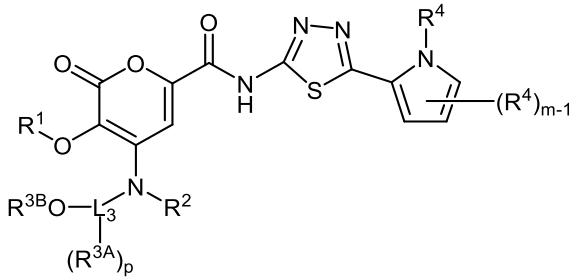
(**I-a-1**),



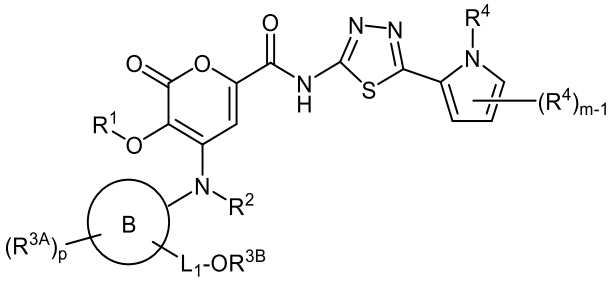
(**I-a-2**),



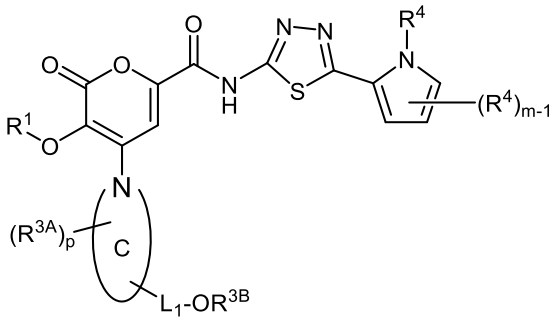
(**I-a-3**),



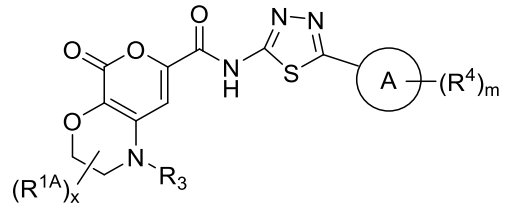
(**I-f-1**),



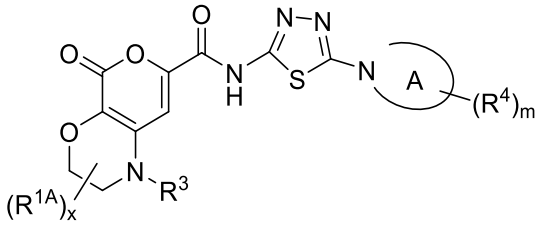
(**I-f-2**),



(**I-f-3**),



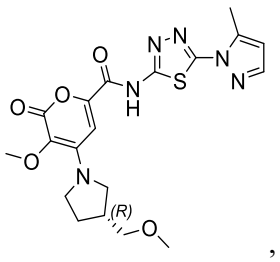
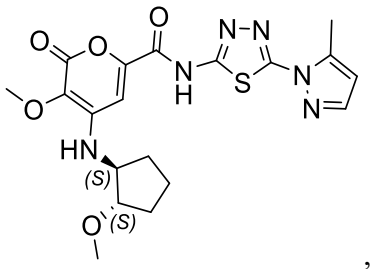
(**I-BC-a**), or

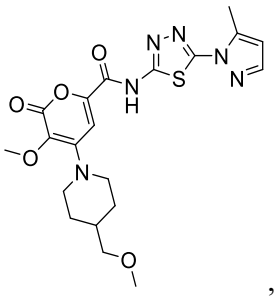
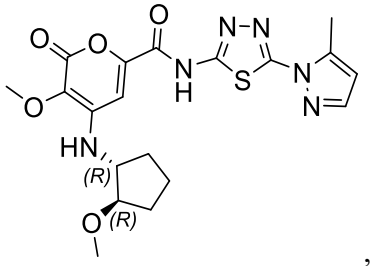


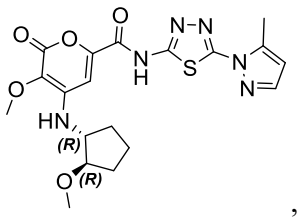
(**I-BC-b**),

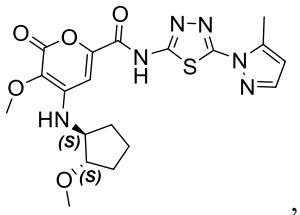
or a pharmaceutically acceptable salt thereof, wherein x is 0, 1, 2, 3, or 4.

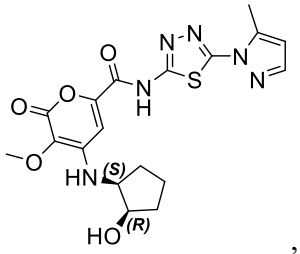
13. The compound of claim 1, wherein the compound is:

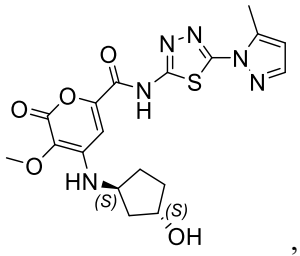
1 , 107a* ,

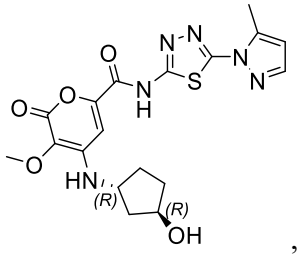
2 , 107b* ,

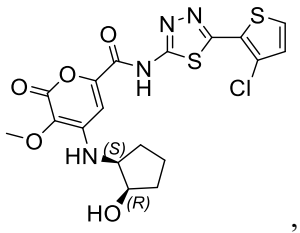
3* ,

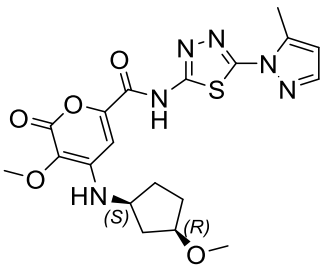
4* ,

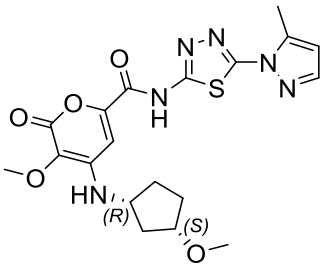
5 ,

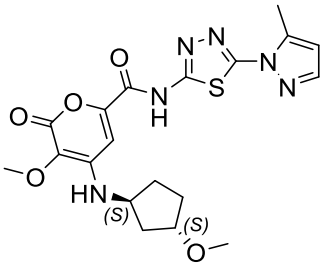
6a* ,

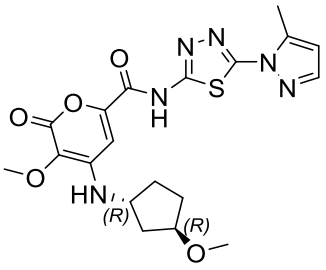
6b* ,

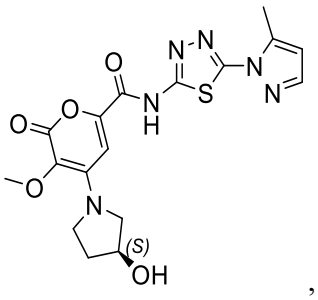
7a* ,

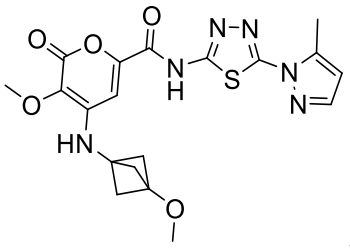
108a* ,

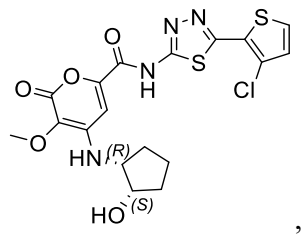
108b* ,

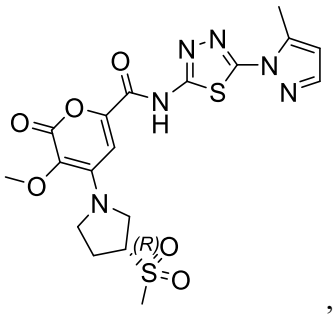
109a* ,

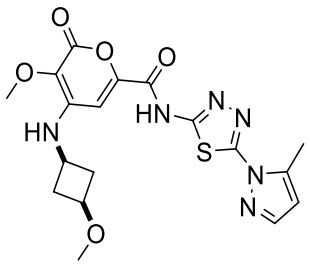
109b* ,

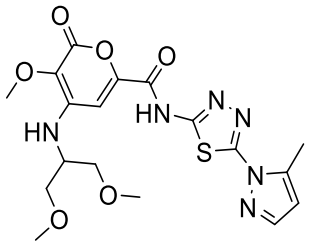
110 ,

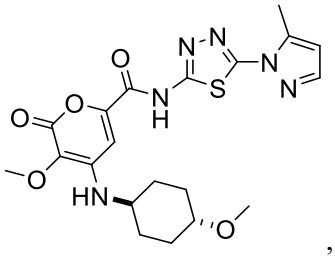
111 ,

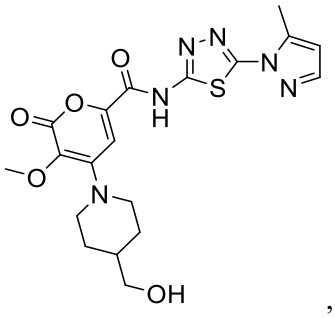
7b*  ,

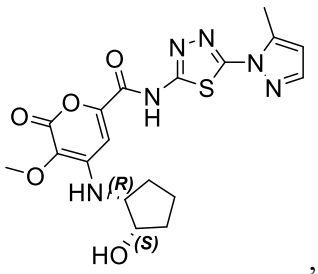
8  ,

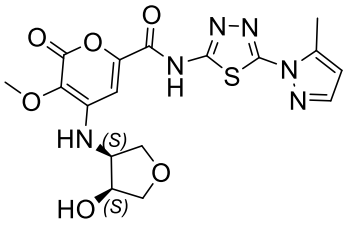
9  ,

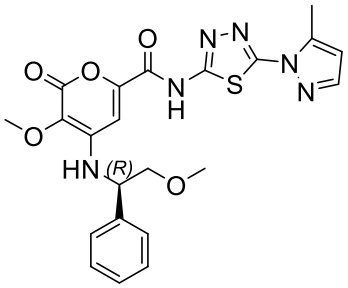
10  ,

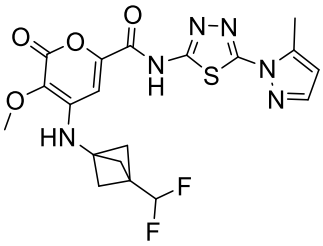
11  ,

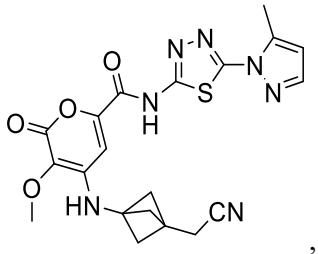
12  ,

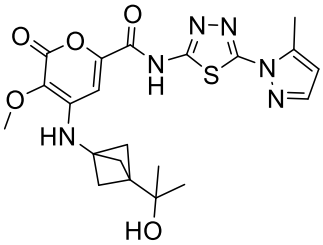
112  ,

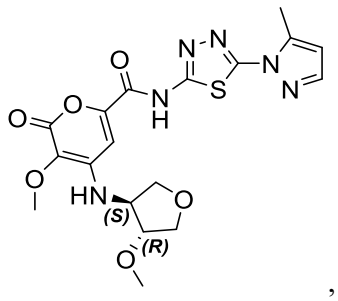
113  ,

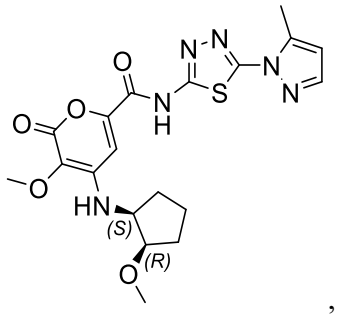
114  ,

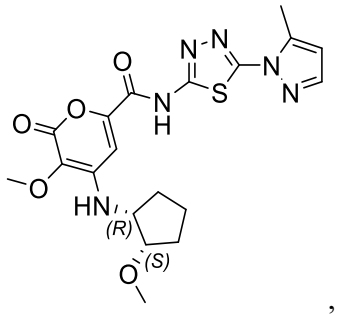
115  ,

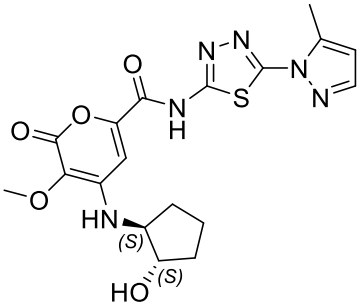
116  ,

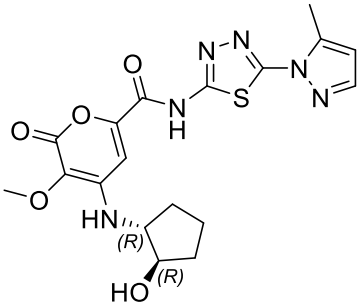
117  ,

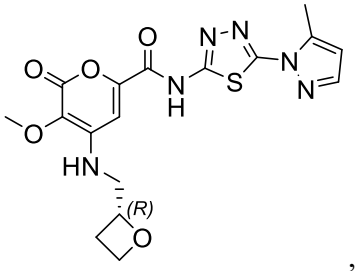
13 ,

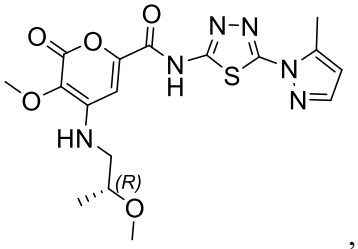
14a* ,

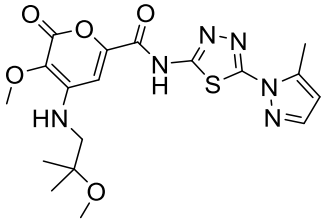
14b* ,

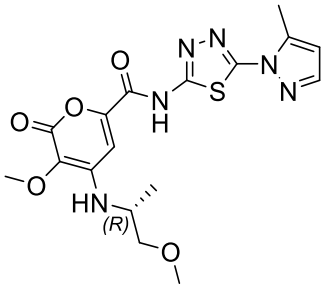
15a* ,

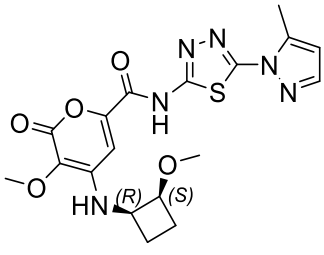
15b* ,

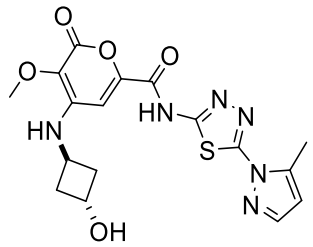
118 ,

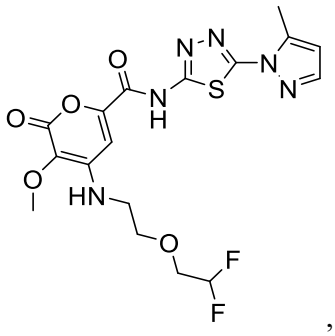
119 ,

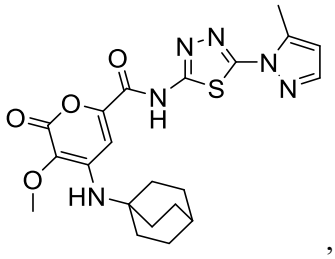
120 ,

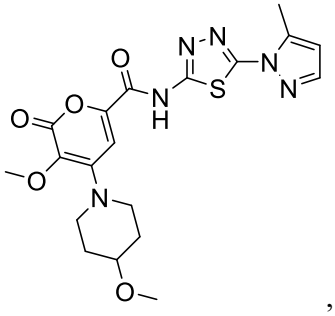
121 ,

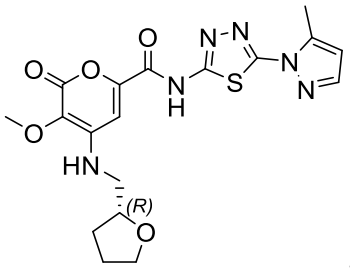
122* ,

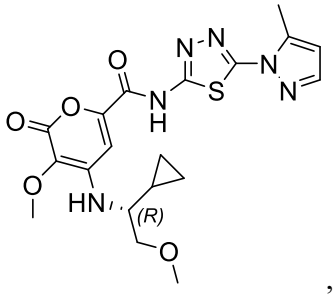
16 ,

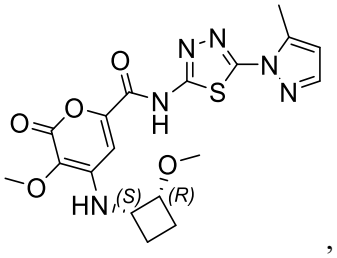
17 ,

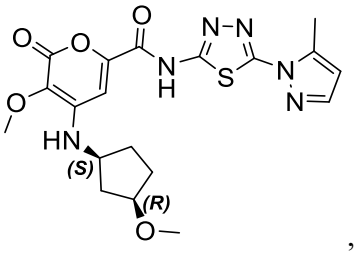
18 ,

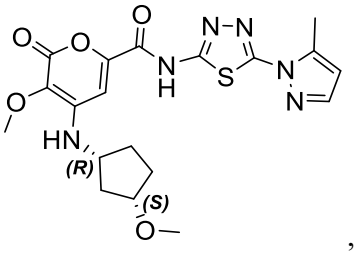
19 ,

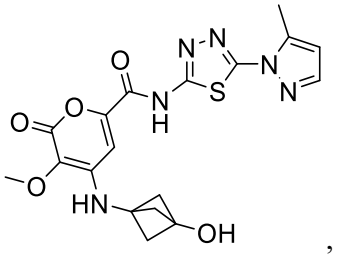
20 ,

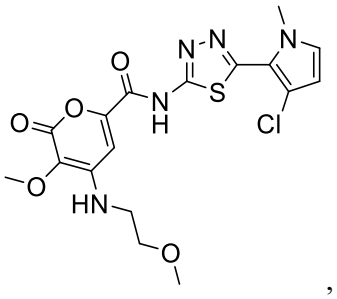
21* ,

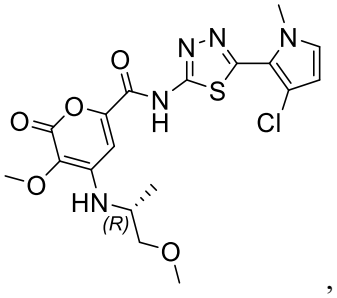
123* ,

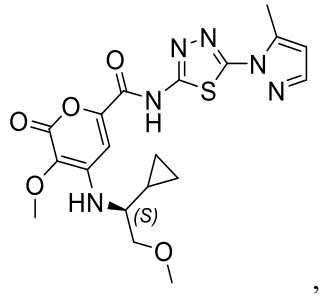
124* ,

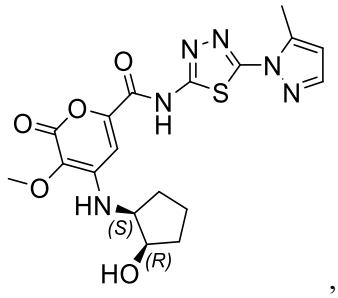
125* ,

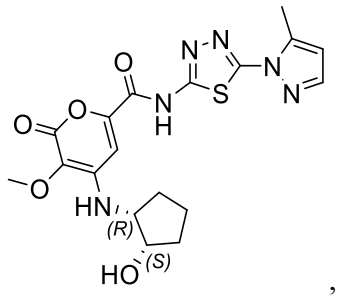
126 ,

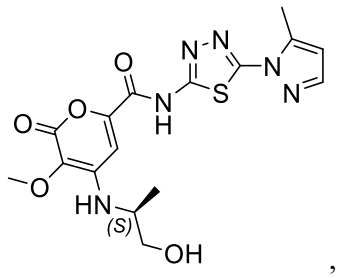
127 ,

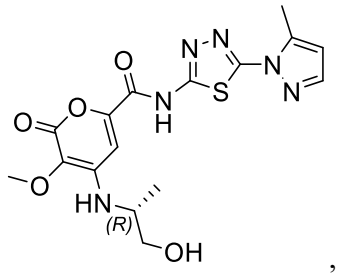
128 ,

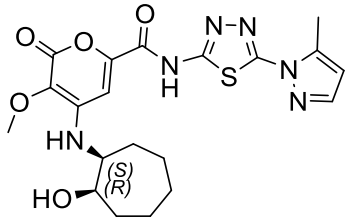
22*  ,

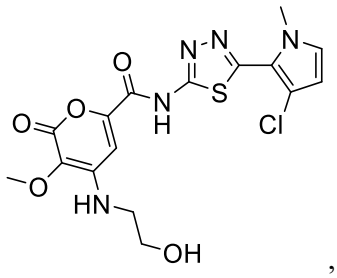
23a*  ,

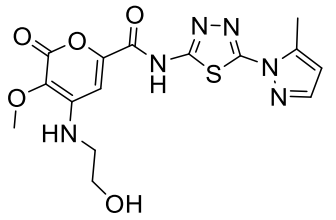
23b*  ,

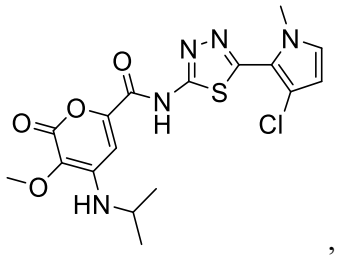
24  ,

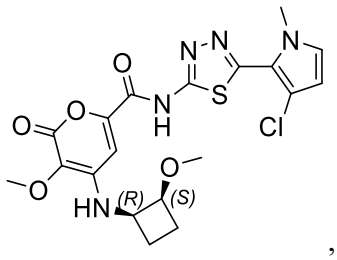
25  ,

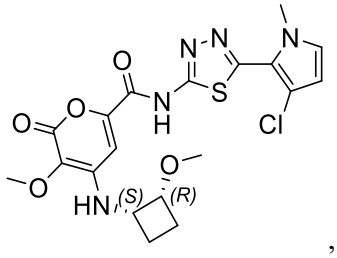
26a*  ,

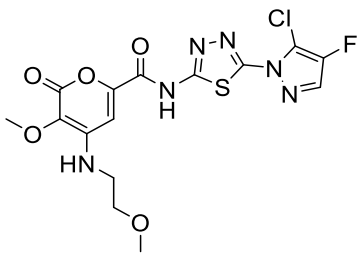
129  ,

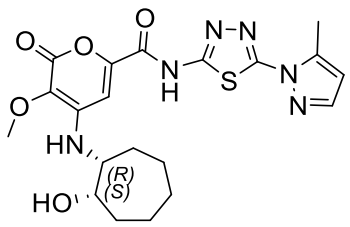
130  ,

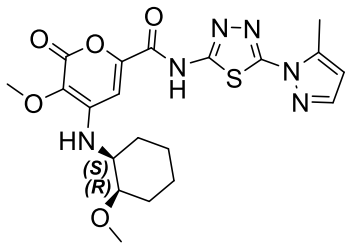
131  ,

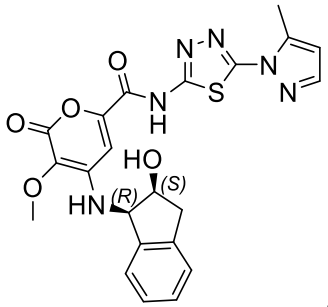
132*  ,

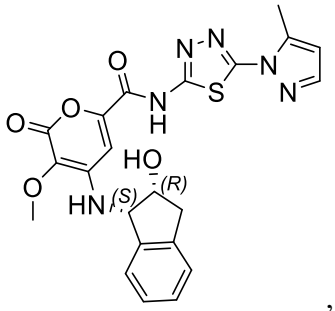
133*  ,

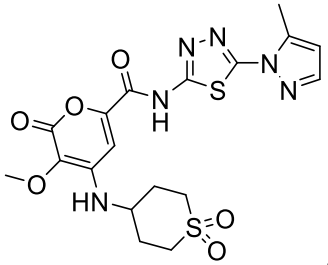
134  ,

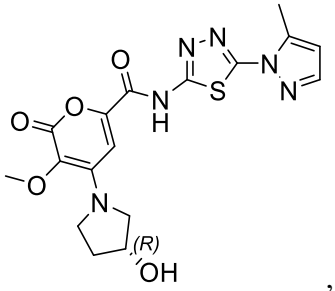
26b* ,

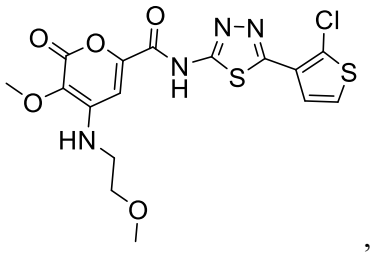
27 ,

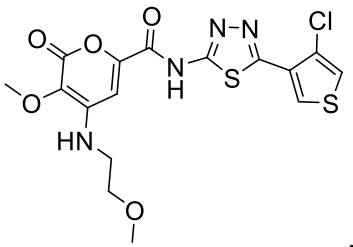
28a* ,

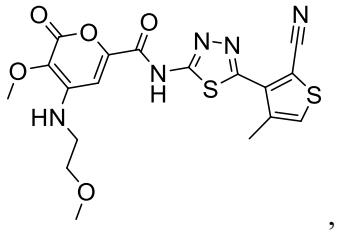
28b* ,

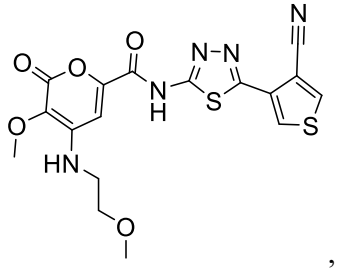
29 ,

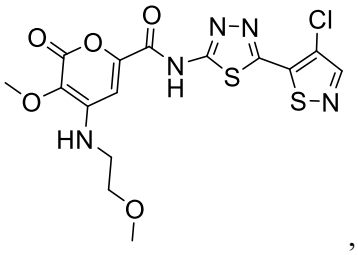
30 ,

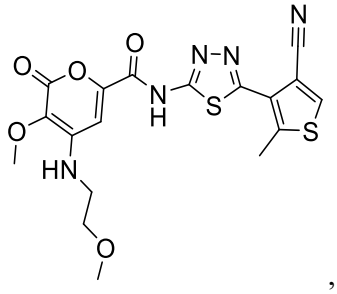
135 ,

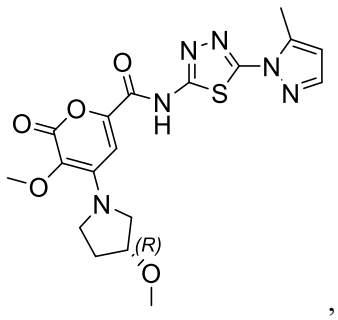
136 ,

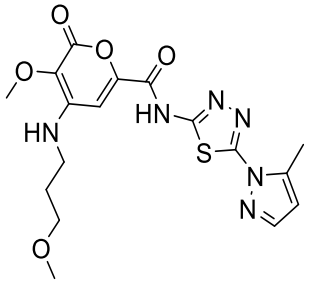
137 ,

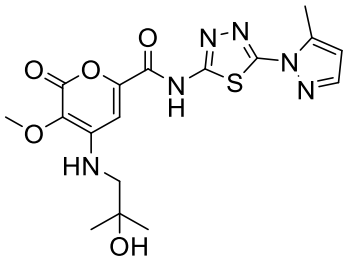
138 ,

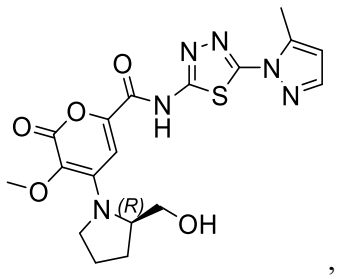
139 ,

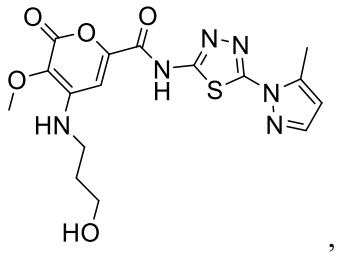
140 ,

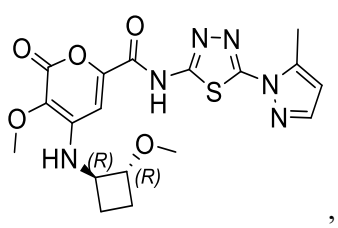
31  ,

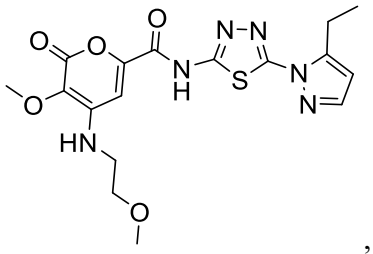
32  ,

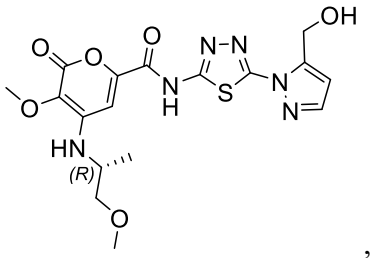
33  ,

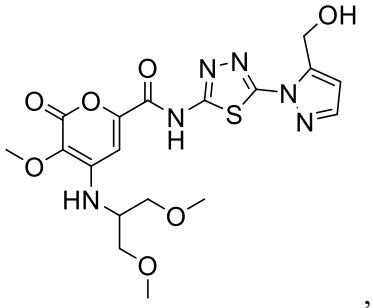
34  ,

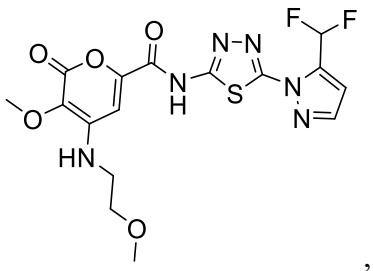
35  ,

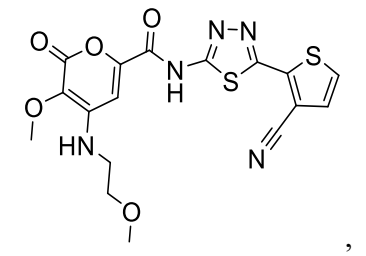
36a*  ,

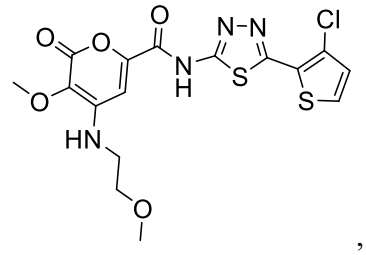
141  ,

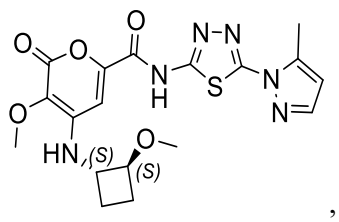
142  ,

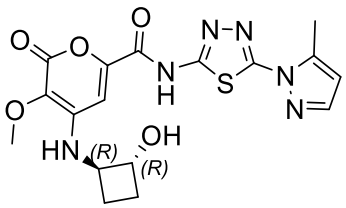
143  ,

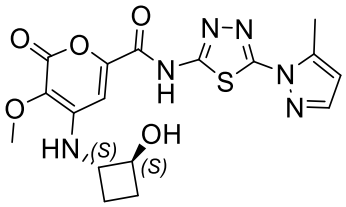
144  ,

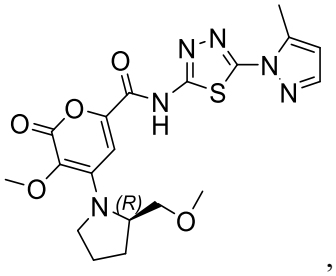
145  ,

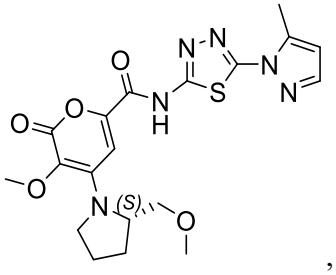
146  ,

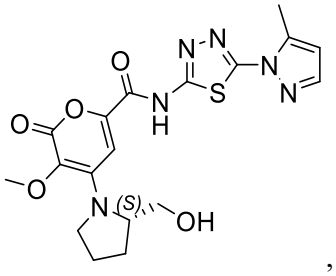
36b* ,

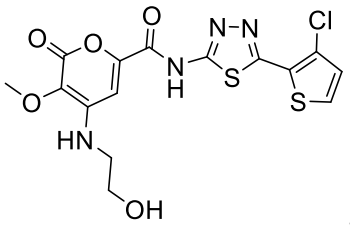
37a* ,

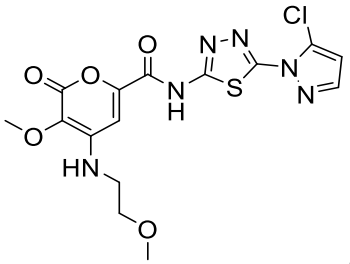
37b* ,

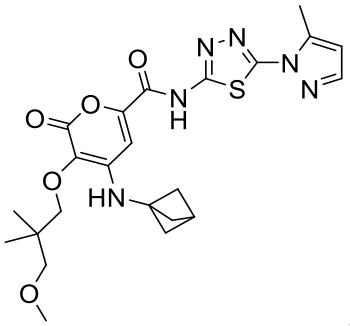
38 ,

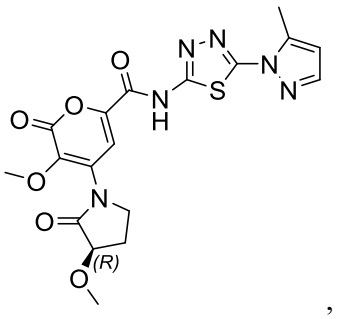
39 ,

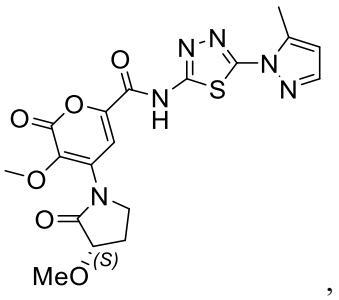
40 ,

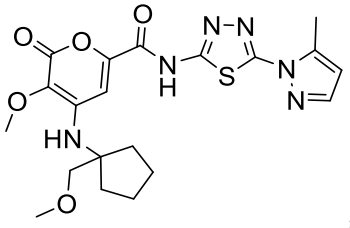
147 ,

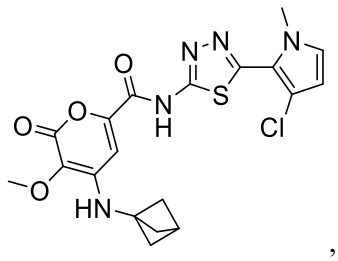
148 ,

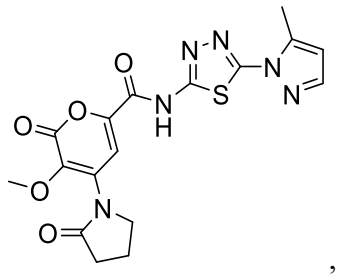
149 ,

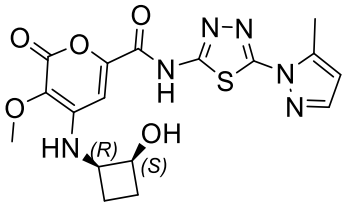
150 ,

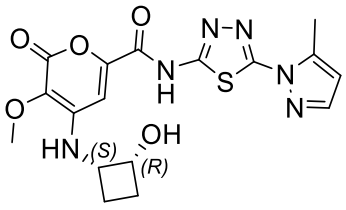
151 ,

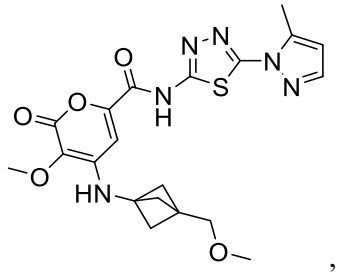
152 ,

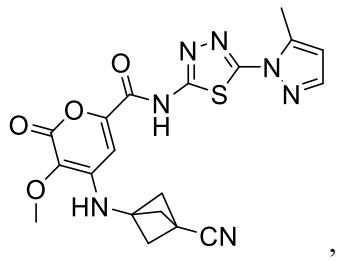
41 ,

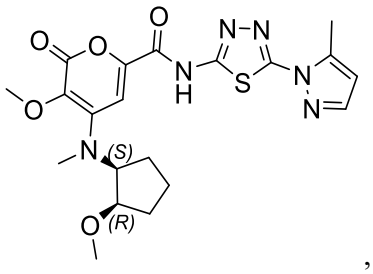
42 ,

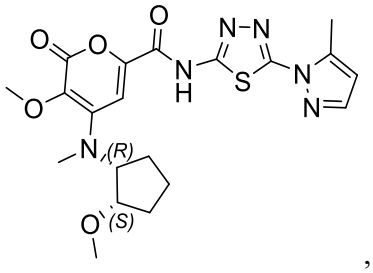
43a* ,

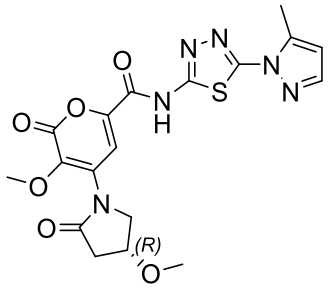
43b* ,

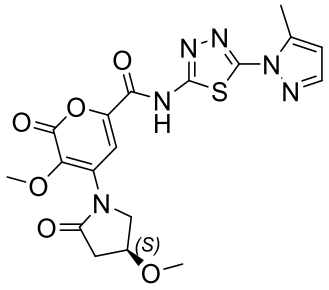
44 ,

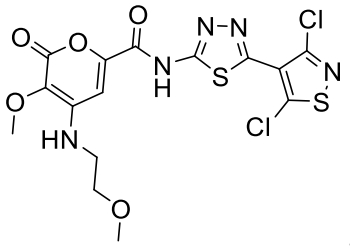
45 ,

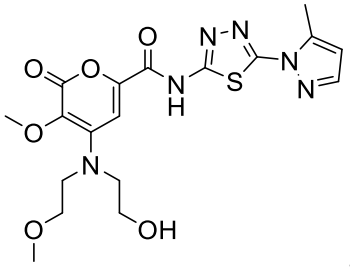
153a* ,

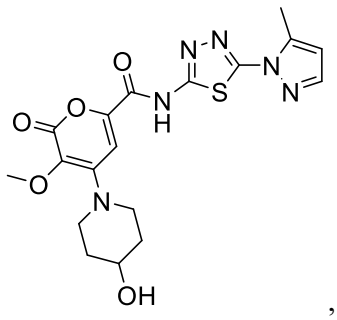
153b* ,

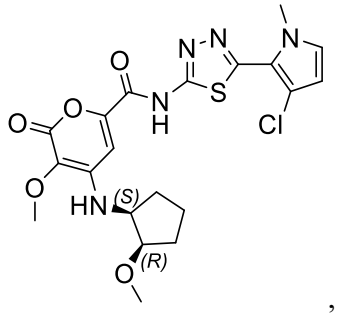
154 ,

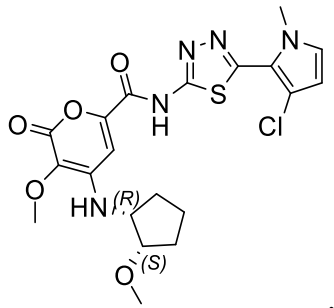
155 ,

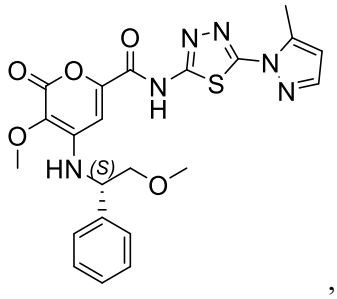
156 ,

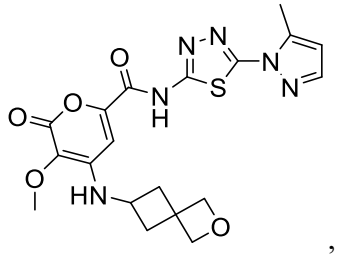
157 ,

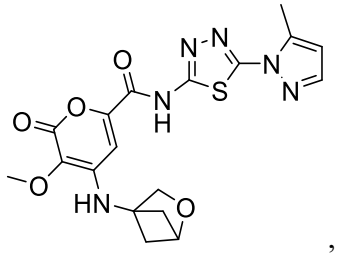
46  ,

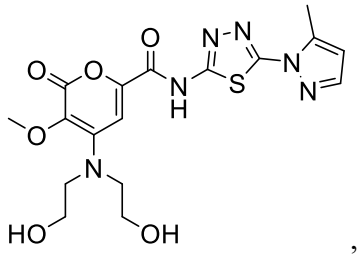
47*  ,

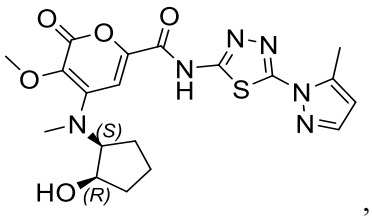
48*  ,

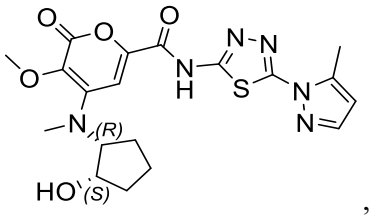
49  ,

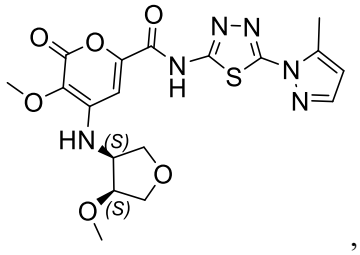
50  ,

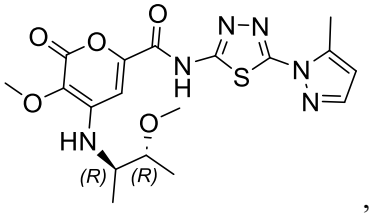
51  ,

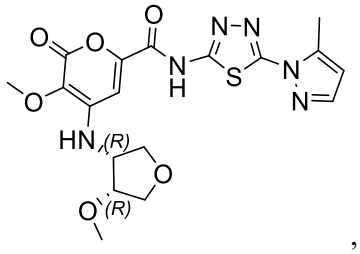
158  ,

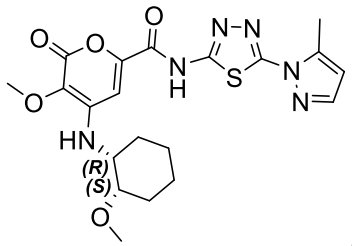
159a*  ,

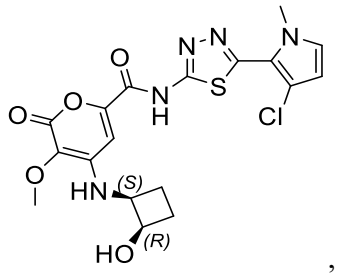
159b*  ,

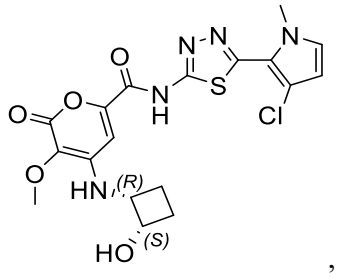
160  ,

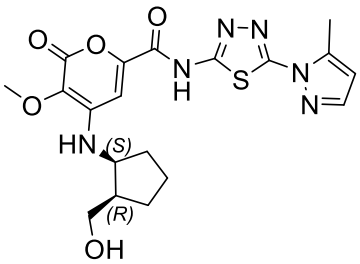
161  ,

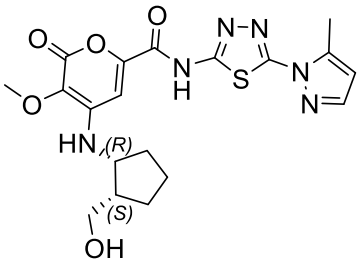
162  ,

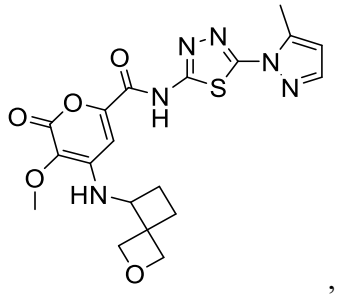
52 ,

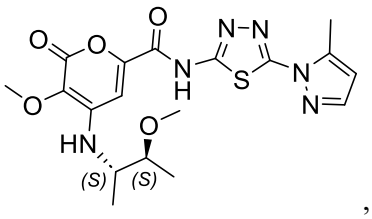
53 ,

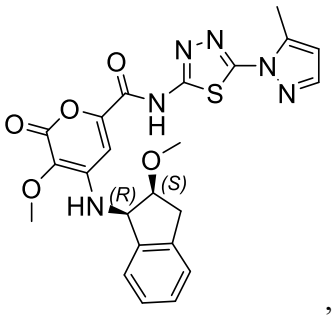
54 ,

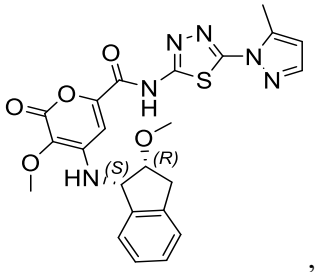
55a* ,

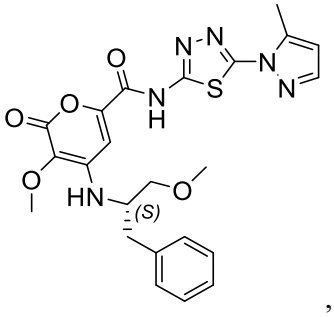
55b* ,

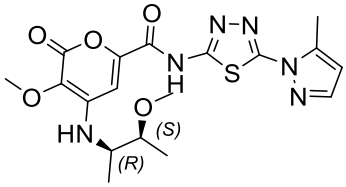
56 ,

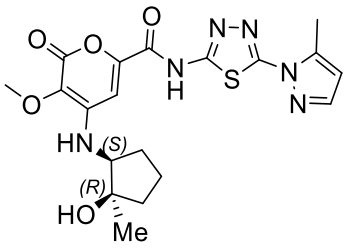
163 ,

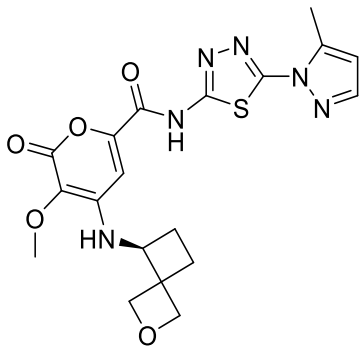
164a* ,

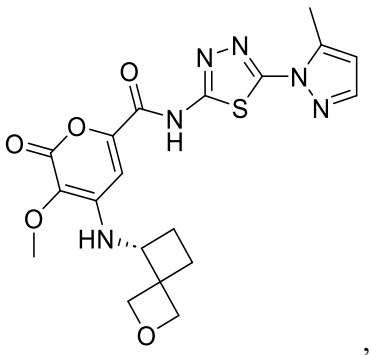
164b* ,

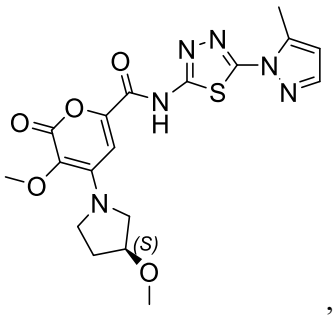
165 ,

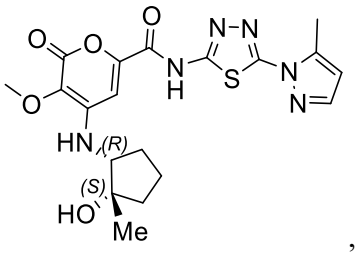
166 ,

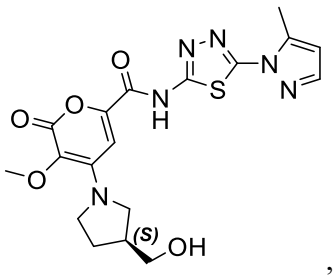
167a* ,

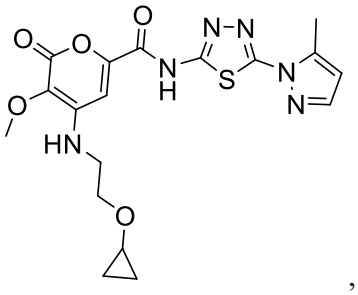
56a*  ,

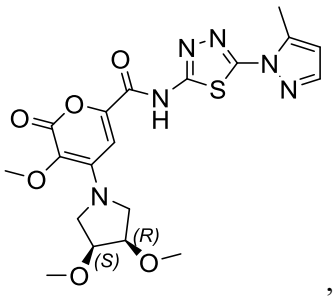
56b*  ,

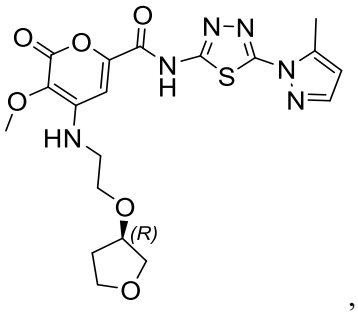
57  ,

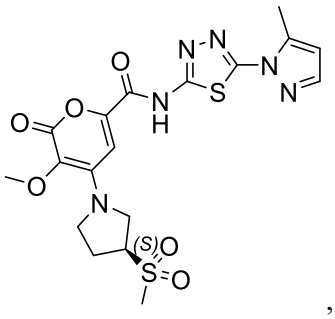
167b*  ,

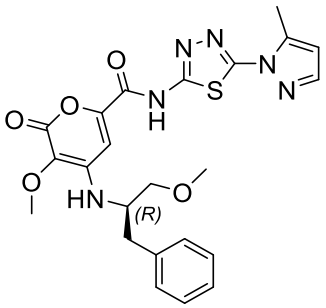
58  ,

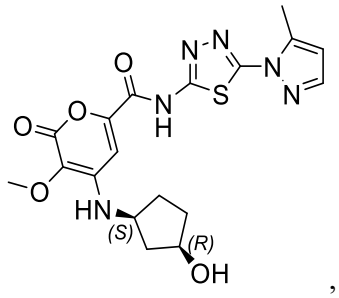
168  ,

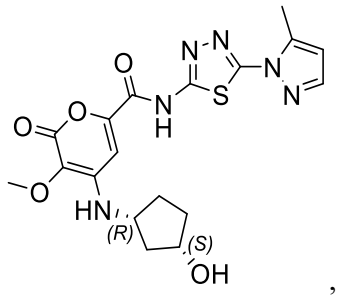
59  ,

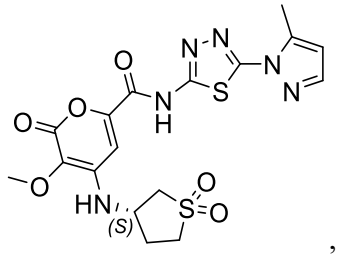
169  ,

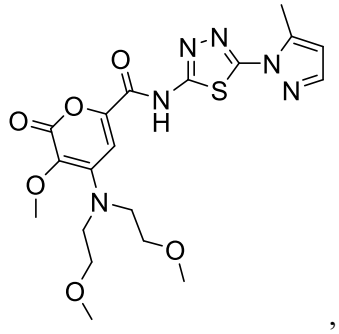
60  ,

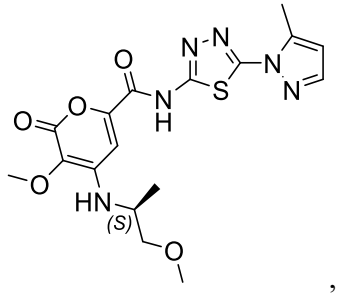
170  ,

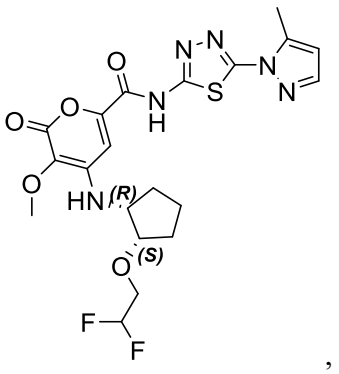
61a* ,

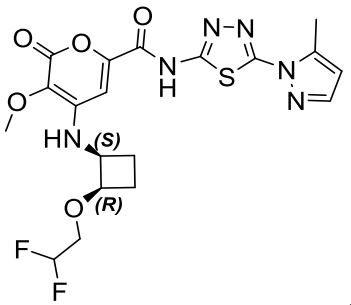
61b* ,

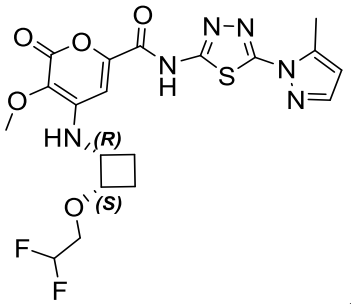
62 ,

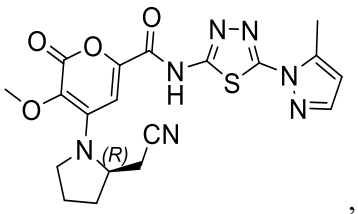
63 ,

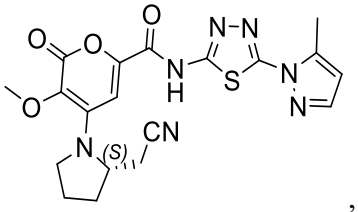
64 ,

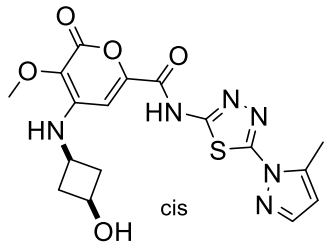
171 ,

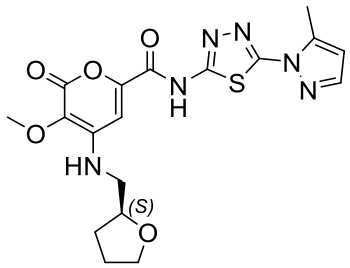
172* ,

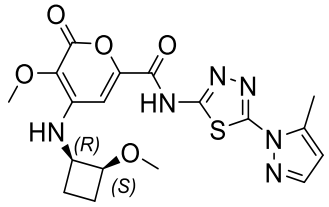
173* ,

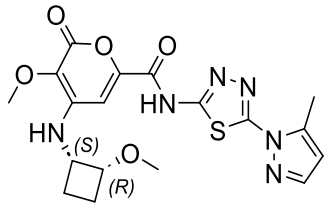
174 ,

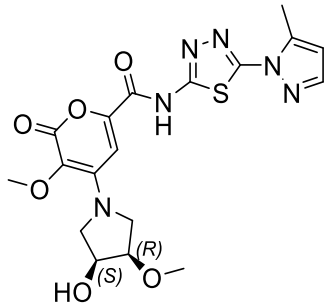
175 ,

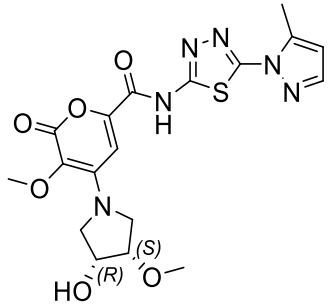
65 
,

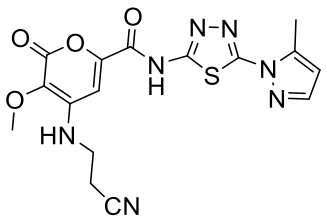
66 
,

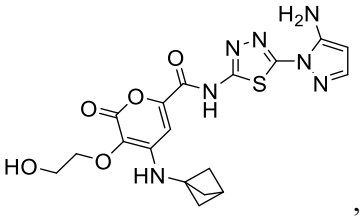
67a* 
,

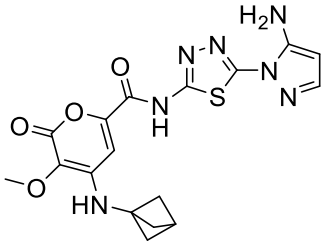
67b* 
,

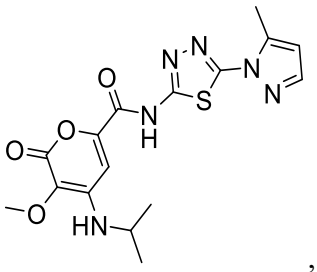
68a* 
,

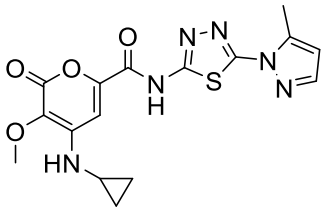
68b* 
,

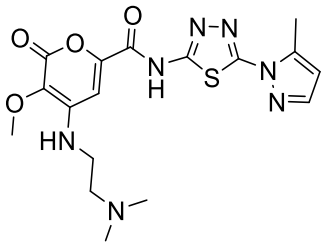
176 
,

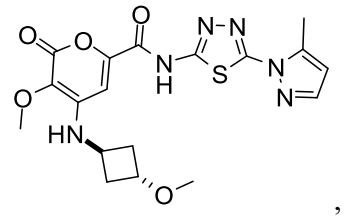
177 
,

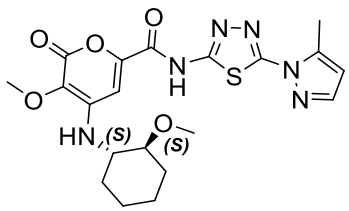
178 
,

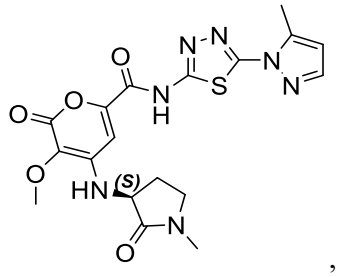
179 
,

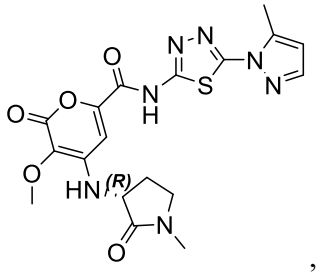
180 
,

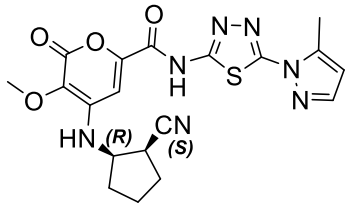
181 
,

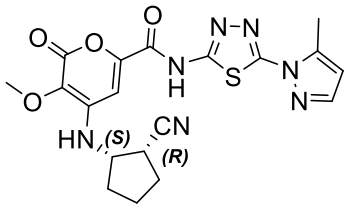
69 ,

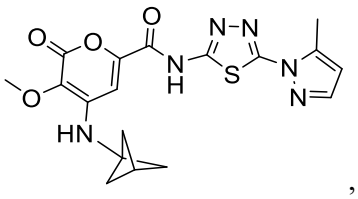
70 ,

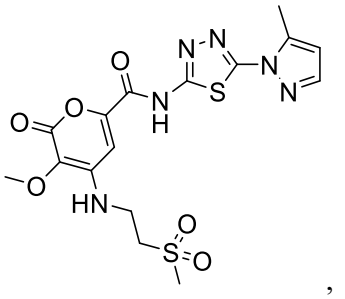
71* ,

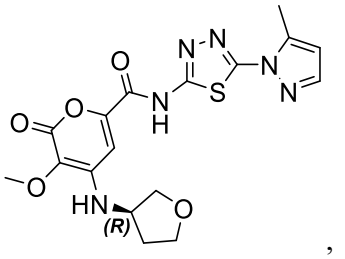
72* ,

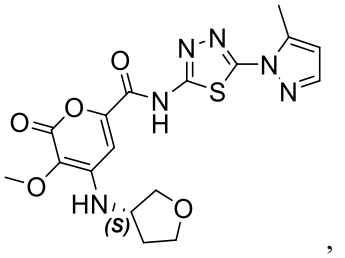
73 ,

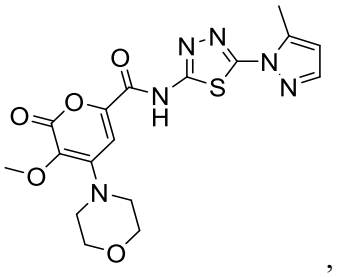
74 

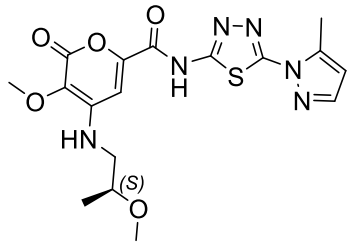
182 ,

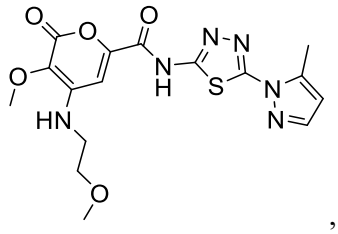
183 ,

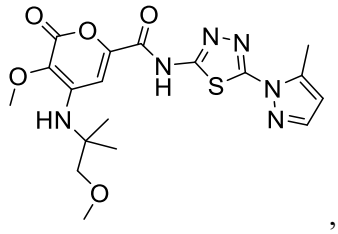
184 ,

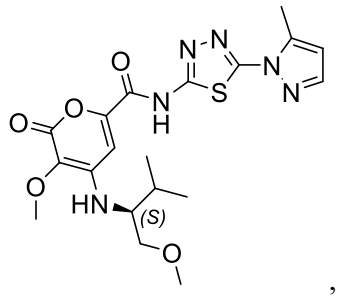
185 ,

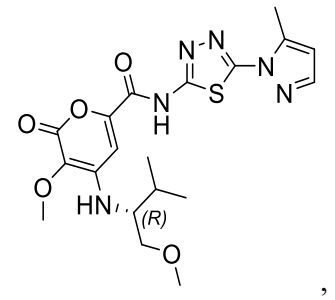
186 ,

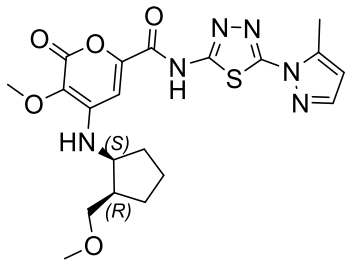
187 

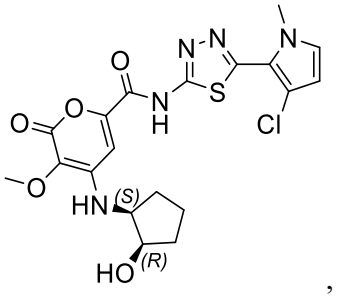
75 ,

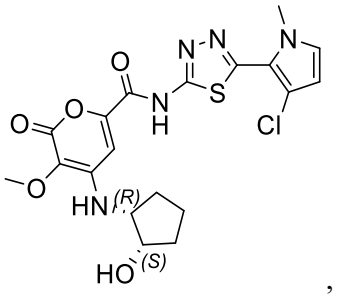
76 ,

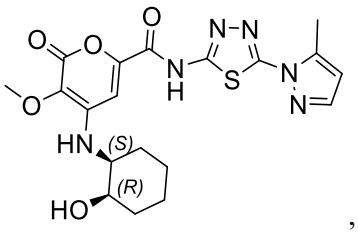
77 ,

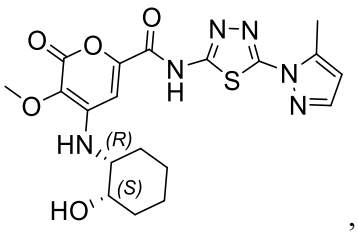
78 ,

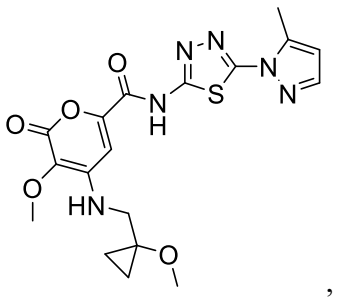
79* ,

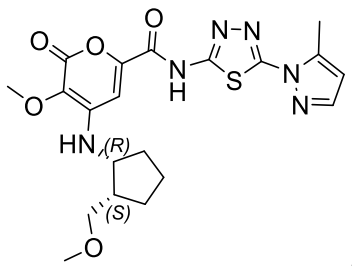
188a* ,

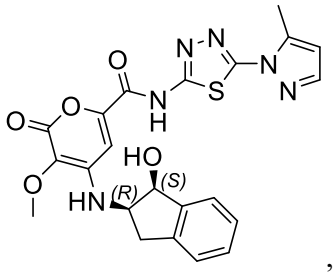
188b* ,

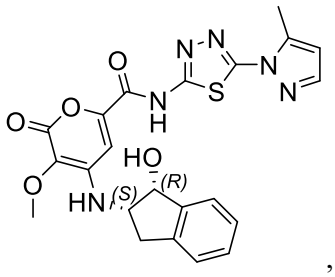
189a* ,

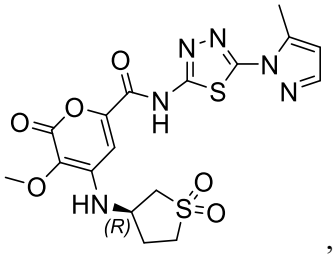
189b* ,

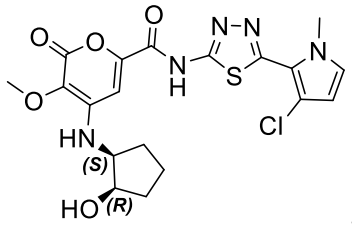
190 ,

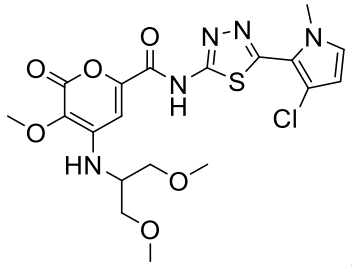
80*  ,

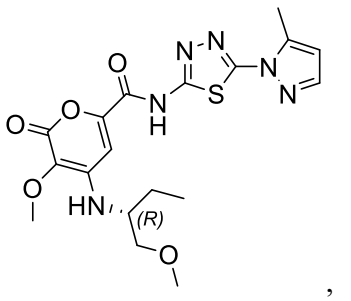
81a*  ,

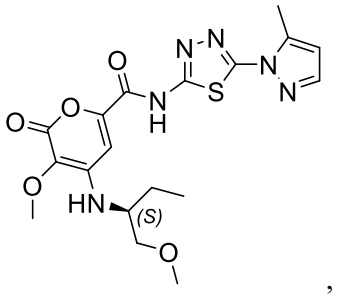
81b*  ,

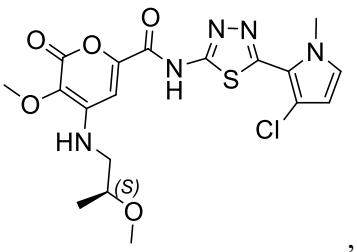
82  ,

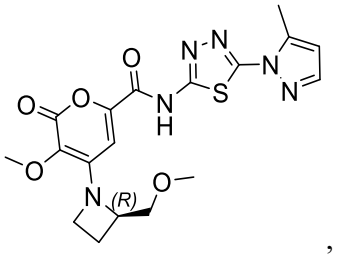
83  ,

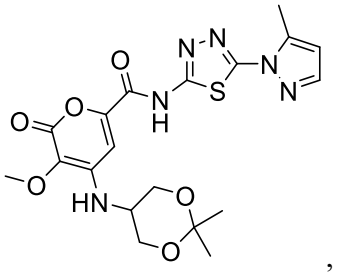
84  ,

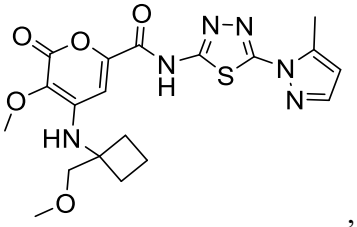
191*  ,

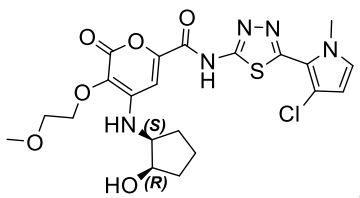
192*  ,

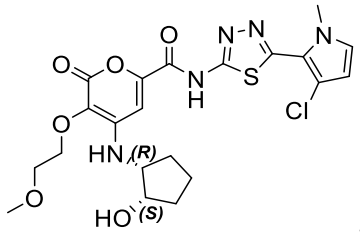
193  ,

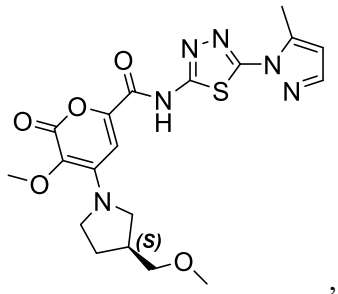
194  ,

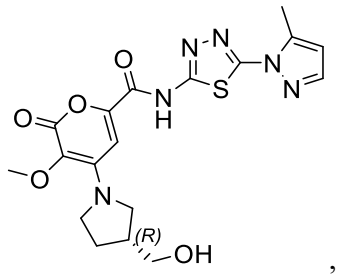
195  ,

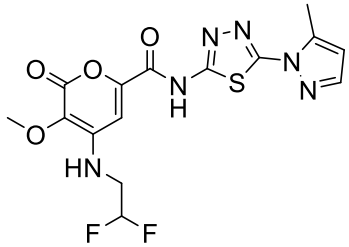
196  ,

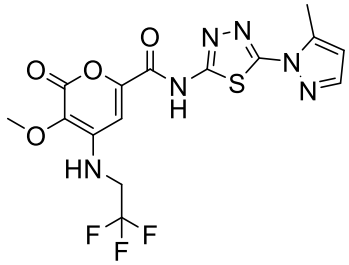
85 ,

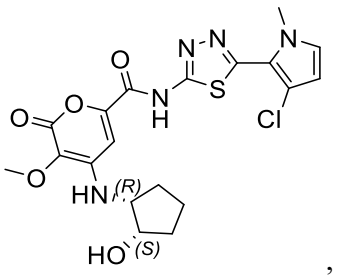
86 ,

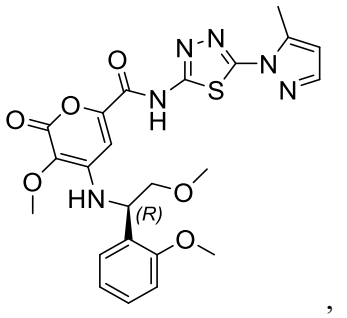
87 ,

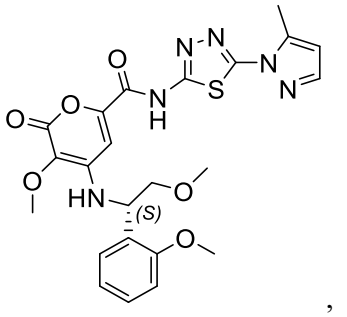
88 ,

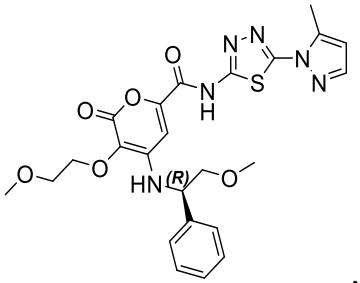
89 ,

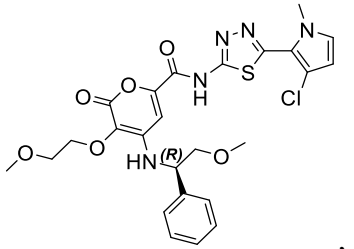
90 ,

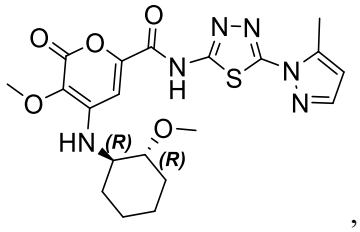
197 ,

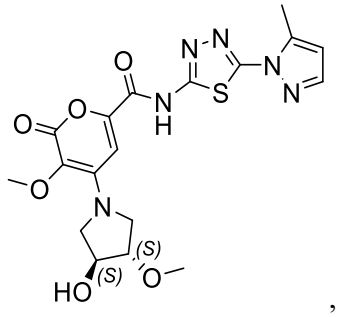
198* ,

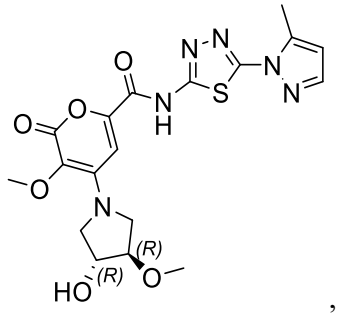
199* ,

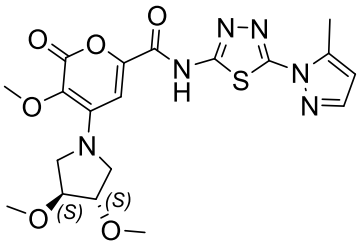
200 ,

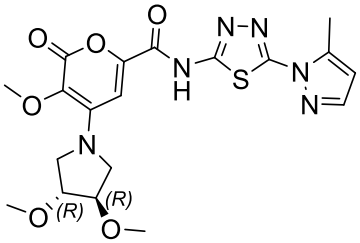
201 ,

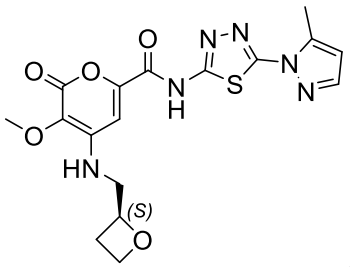
202 ,

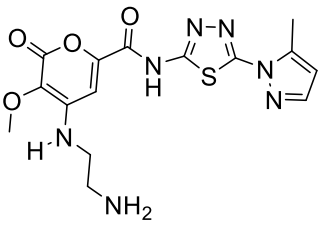
91a* ,

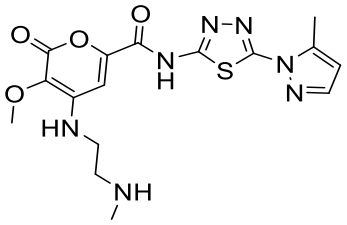
91b* ,

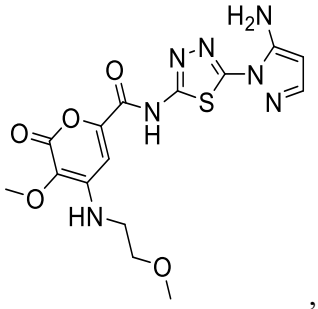
92a* ,

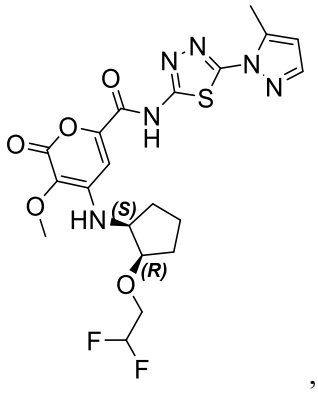
92b* ,

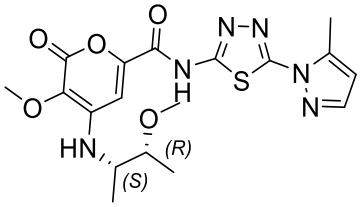
93 ,

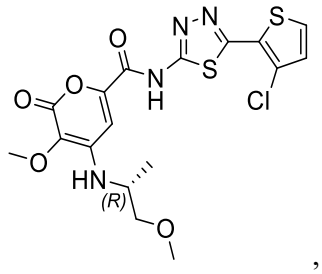
203 ,

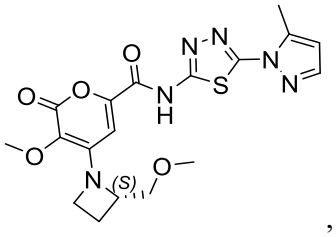
204 ,

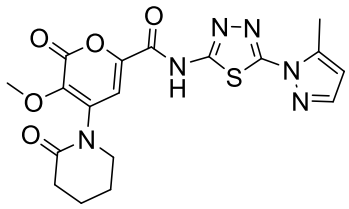
205 ,

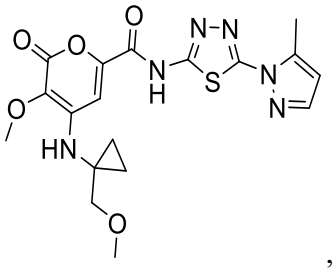
206 ,

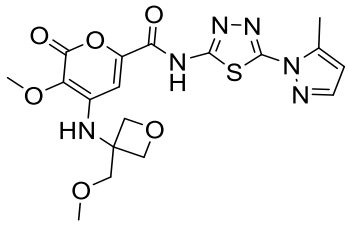
207 ,

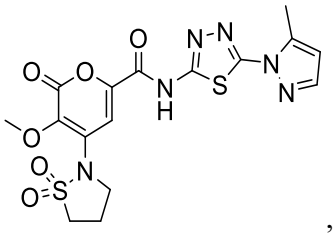
94 ,

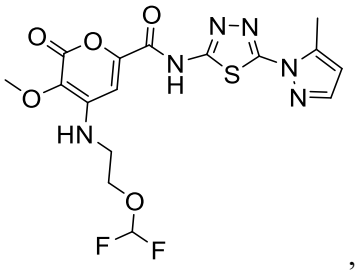
95 ,

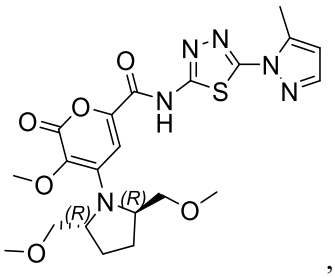
96 ,

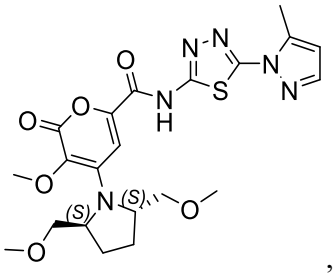
97 ,

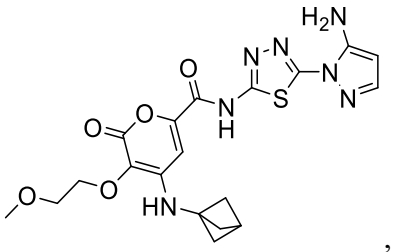
98 ,

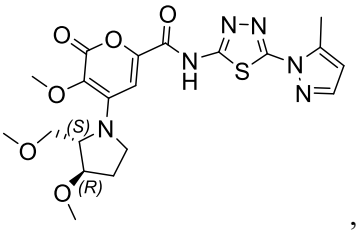
99 ,

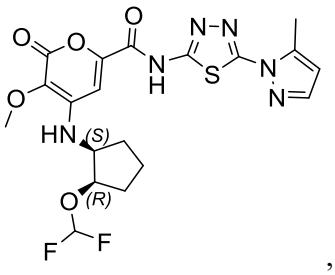
208 ,

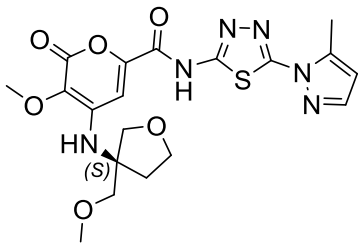
209a* ,

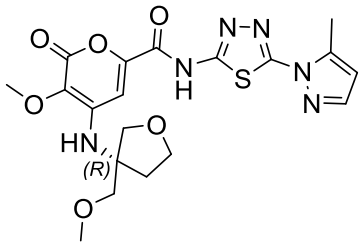
209b* ,

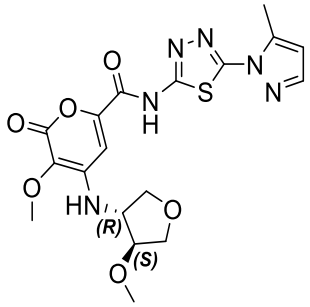
210 ,

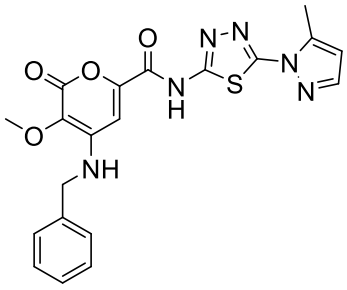
211 ,

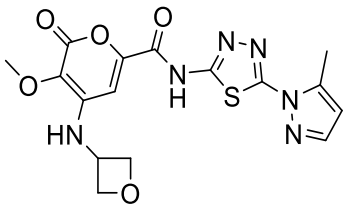
212 ,

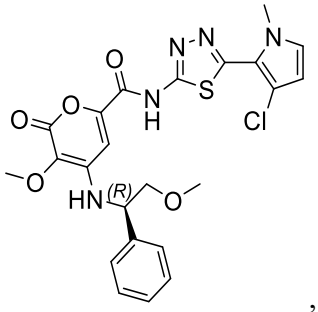
100* ,

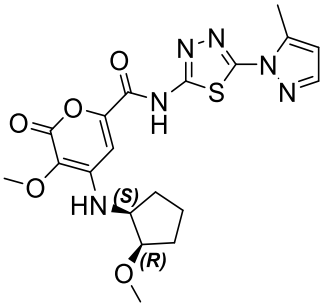
101* ,

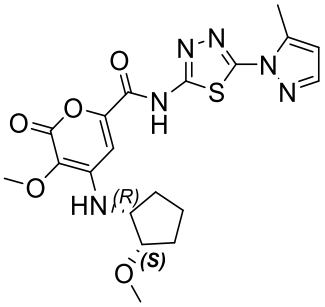
102 ,

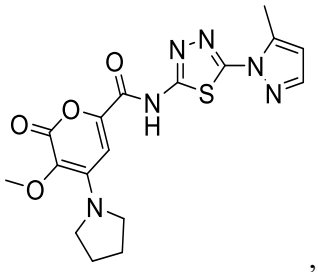
103 ,

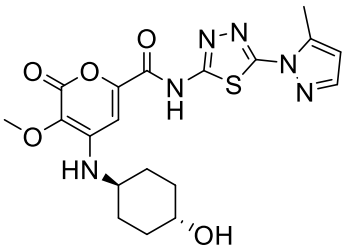
104 ,

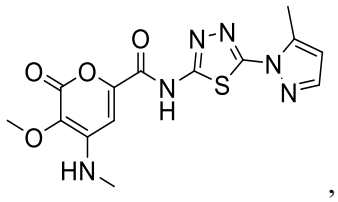
213 ,

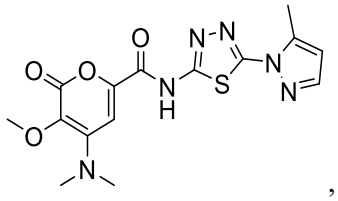
214* ,

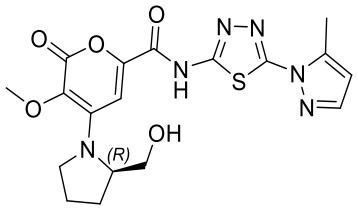
215* ,

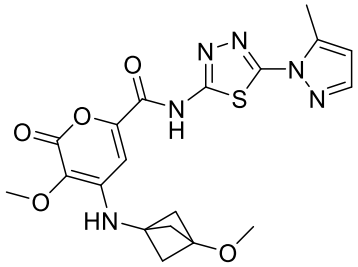
216 ,

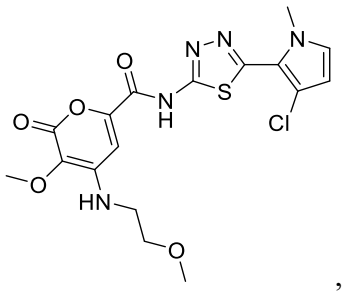
217 ,

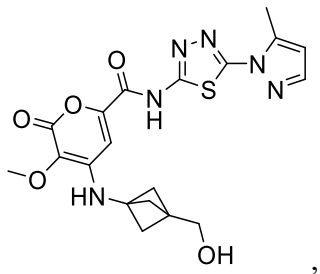
105 ,

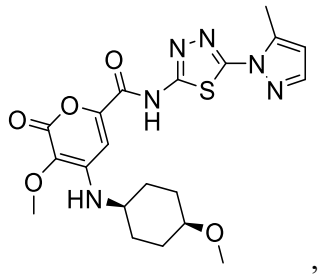
106 ,

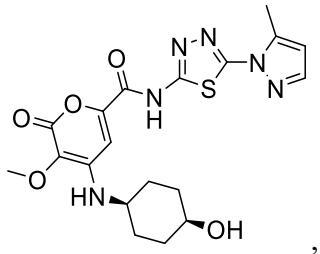
174-OH ,

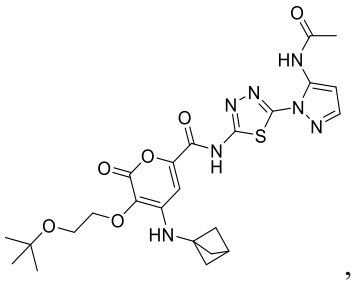
126-OMe ,

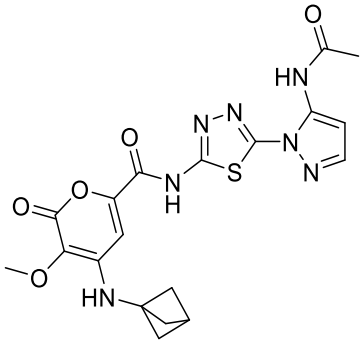
129-OMe ,

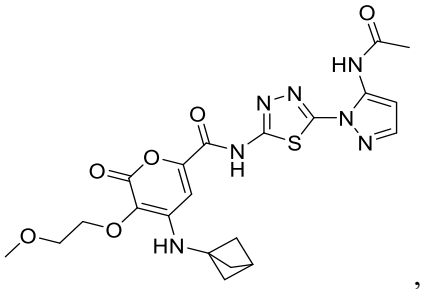
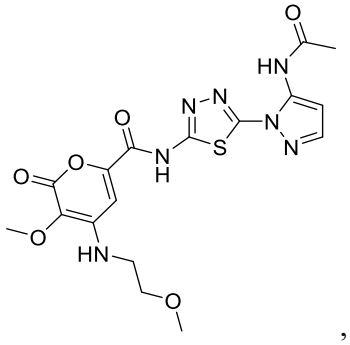
218 ,

219 ,

220 ,

177-Ac-OtBu ,

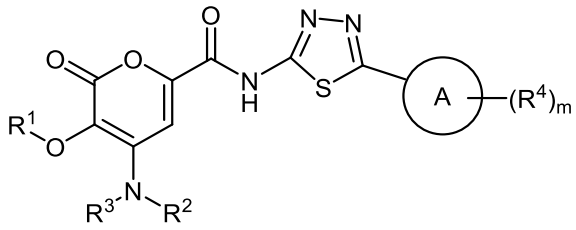
178-Ac ,

210-Ac  , 205-Ac  ,

or a pharmaceutically acceptable salt thereof.

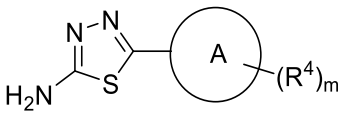
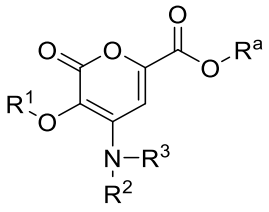
14. An isotopically enriched compound of Formula (**I**) of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein the compound comprises one or more isotopically enriched atoms selected from the group consisting of deuterium, tritium, ^{19}F, ^{13}C, and ^{14}C.

15. A method of preparing a compound of Formula (**I**):

 (**I**),

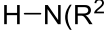
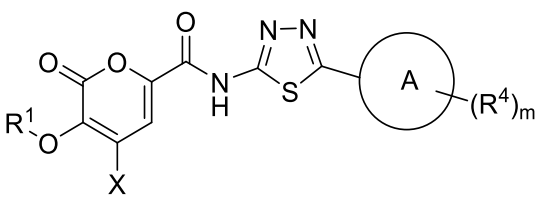
or a salt thereof, wherein Ring A, R^1, R^2, R^3, R^4, and m are defined in any one of claims 1-14, the method comprising:

(i) peptide coupling of a compound of Formula (**H-1**), or salt thereof, with a compound of Formula (**N**), or salt thereof:

 (**H-1**)  (**N**)

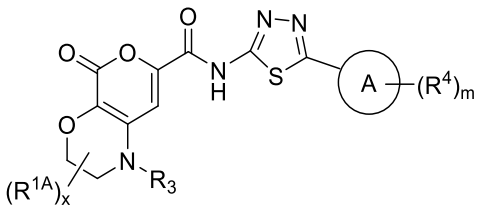
wherein R^a is hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl, to provide a compound of Formula (**I**), or salt thereof; or

(ii) cross-coupling of an amine of Formula (**K**), or salt thereof, with a compound of Formula (**J-1**), or salt thereof:

 (**K**)  (**J-1**),

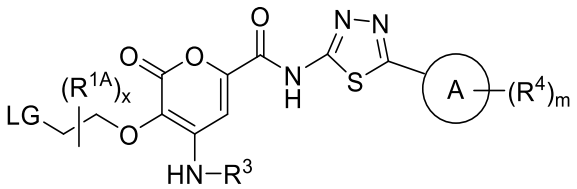
wherein X is Cl, Br, or I, to provide a compound of Formula (**I**), or salt thereof.

16. A method of preparing a compound of Formula (**I-BC-a**):



(**I-BC-a**), or salt thereof;

wherein Ring A, R^1, R^3, R^4, and m are defined in any one of claims 1-14, the method comprising cyclizing a compound of Formula (**P-1**):



(**P-1**), or salt thereof,

wherein LG is a leaving group.

17. A pharmaceutical composition comprising the compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

18. A compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 17 for use in therapy.

19. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 17, in the manufacture of a medicament for treating a disease or disorder selected from inflammation, an autoimmune disease, a cancer, an infection, a disease or disorder of the central nervous system, a metabolic disease, a cardiovascular disease, a respiratory disease, a kidney disease, a liver disease, an ocular disease, a skin disease, a lymphatic disease, a rheumatic disease, a psychological disease, graft versus host disease, allodynia, or an cGAS-related disease in a subject that has been determined to carry a germline or somatic non-silent mutation in cGAS.

20. An *in vitro* method of modulating cGAS activity, comprising contacting a cell with a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 17.