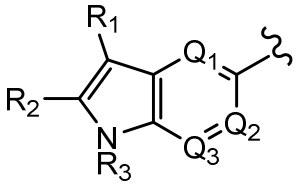
CLAIMS

1. A compound of Formula I':

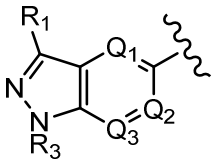
(I') TL-L_a-CE-HD

or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

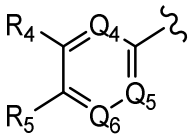
i) TL is a moiety of Formula IIa, IIb, IIIa, IIIb, IIIc, or IIId:



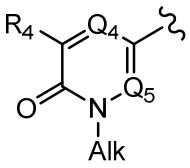
(IIa)



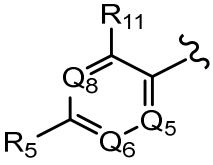
(IIb)



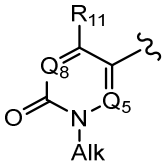
(IIIa)



(IIIb)



(IIIc)



(IIId)

wherein:

each of Q_1, Q_2, Q_3, Q_4, Q_5, Q_6, and Q_8, is independently nitrogen or -CR_b-, wherein each R_b is independently hydrogen, halogen, or lower alkyl;

R_1 is hydrogen, an optionally substituted alkyl, an optionally substituted non-aromatic carbocyclic group, an optionally substituted aryl group, an optionally substituted heterocycloalkyl group, an optionally substituted heteroaryl group, an optionally substituted (carbocyclic)alkyl group, an optionally substituted aralkyl group, an optionally substituted (heterocycloalkyl)alkyl group, an optionally substituted (heteroaryl)alkyl group, an optionally substituted amino group, an optionally substituted C-carboxy or O-carboxy group, -CN, an optionally substituted carbamoyl group, or an optionally substituted carbamoyl alkyl group, where the nitrogen of the carbamoyl or carbamoyl alkyl group is optionally a heteroatom in a ring structure;

R_2 is hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkyl, or -CN;

R_3 is hydrogen or lower alkyl;

R_4 is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted non-aromatic carbocyclic group, an optionally substituted aryl group, an optionally substituted heterocyclic group, an optionally substituted heteroaryl group, an optionally substituted

(carbocyclic)alkyl group, an optionally substituted aralkyl group, an optionally substituted (heterocycloalkyl)alkyl group, an optionally substituted (heteroaryl)alkyl group, an optionally substituted amino group, an optionally substituted sulfamoyl group, an optionally substituted carbamoyl group, or an optionally substituted carbamoyl alkyl group, where the nitrogen of the carbamoyl or carbamoyl alkyl group is optionally a heteroatom in a ring structure; and

R_5 is hydroxy, NH_2, alkylamino, alkanoylamino, or alkylsulfonylamino;

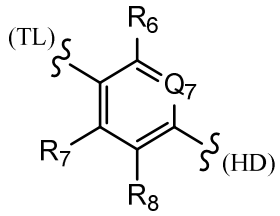
or R_4 and R_5 taken together along with the carbon atoms to which they are attached form a five- or six-membered optionally substituted non-aromatic carbocyclic group, optionally substituted aryl group, optionally substituted heterocyclic group, or optionally substituted heteroaryl group;

or R_4 and R_5 taken together along with the carbon atoms to which they are attached form a seven to eleven membered, optionally substituted spirocyclic ring or a seven to eleven membered, optionally substituted spiro-heterocyclic ring;

Alk is hydrogen or an optionally substituted alkyl; and

R_{11} is an aryl group optionally substituted with one to five substituents independently selected from lower alkyl, alkoxy, haloalkoxy, halogen, and cycloalkyl; or a heteroaryl group optionally substituted with one to five substituents independently selected from lower alkyl, alkoxy, haloalkoxy, halogen, and cycloalkyl; or a bicyclic ring system; or a bicyclic heterocyclic ring system;

ii) CE is a moiety of Formula IV

(IV) 

wherein:

each of R_6 and R_7 is independently selected from halogen, -CN, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, or cyclopropyl;

R_8 is selected from hydrogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, cyano, or halogen;

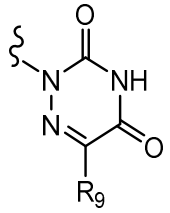
optionally R_7 and R_8 taken together, along with the carbon atoms to which they are attached, form a 4-, 5- or 6-membered non-aromatic carbocyclic, heterocycloalkyl, aryl, or heteroaryl ring

Q_7 is nitrogen or -CR_c-, wherein R_c is hydrogen, halogen, or lower alkyl;

(TL) denotes the point where the moiety of Formula IV connects to TL-L_a-; and

(HD) denotes the point where the moiety of Formula IV connects to -HD;

iii) HD is a moiety of Formula V:

(V) 

wherein:

R_9 is -$(C(R_d)_2)_n$-$N(R_d)_2$;

each R_d is independently hydrogen or optionally substituted lower alkyl;

each n is independently selected from 0, 1, 2, 3, 4, or 5;

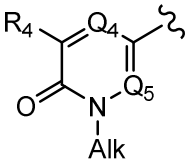
L_a is independently a bond; -$(C(R_a)_2)_z$-; oxygen; sulfur; or -NR_a-; wherein:

each R_a is independently a hydrogen or lower alkyl; and

z is 0, 1, 2, 3, 4 or 5.

2. The compound of claim 1, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

TL is a moiety of Formula IIIb:

(IIIb)  .

3. The compound of claim 2, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein R_9 is -NH_2.

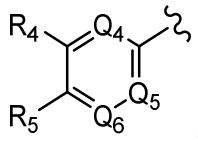
4. The compound of claim 2 or claim 3, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein Q_4 is –CH– and Q_5 is nitrogen.

5. The compound of any one of claims 2-4, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein Alk is hydrogen or C_1-C_6 alkyl optionally substituted with one to five substituents independently selected from the group consisting of hydroxy, halogen, and C_1-C_6 alkoxy.

6. The compound of any one of claims 2-5, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein R_4 is C_1-C_6 alkyl; C_2-C_{10} alkenyl; a non-aromatic C_3-C_{12} carbocyclic ring; a C_6-C_{10} aryl group; a 3- to 6-membered heterocycloalkyl ring containing one to four ring heteroatoms independently selected from oxygen, sulfur, or nitrogen; a five- to ten-membered heteroaryl ring containing one to four ring heteroatoms independently selected from oxygen, sulfur, or nitrogen; a (carbocyclic)alkyl group; an aralkyl group; or a (heterocycloalkyl)alkyl group; and R_4 is optionally substituted with one to five R_g independently selected from the group consisting of hydroxy, halogen, CN, C_1-C_6 alkyl, C_6-C_{10} aryl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, and C_6-C_{10} aralkoxy, or two R_g together with the atoms to which they are attached form an aromatic or non-aromatic 3- to 6-membered ring, optionally containing one or two ring heteroatoms independently selected from oxygen, sulfur, or nitrogen, preferably wherein R_4 is C_1-C_6 alkyl, C_2-C_{10} alkenyl, a non-aromatic C_3-C_{12} carbocyclic ring, a 3- to 6-membered heterocycloalkyl ring containing one to four ring heteroatoms independently selected from oxygen, sulfur, or nitrogen, a (carbocyclic)alkyl group, an aralkyl group, or a (heterocycloalkyl)alkyl group; and R_4 is optionally substituted with one to five R_g independently selected from the group consisting of hydroxy, halogen, CN, C_1-C_6 alkyl, C_6-C_{10} aryl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, and C_6-C_{10} aralkoxy, or two R_g together with the atoms to which they are attached form an aromatic or non-aromatic 3- to 6-membered ring, optionally containing one or two ring heteroatoms independently selected from oxygen, sulfur, or nitrogen, more preferably wherein R_4 is C_1-C_6 alkyl, C_2-C_{10} alkenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, pyridazin-3(2H)-one, phenyl, naphthyl, pyridinyl, cinnolinyl, isoquinolinyl, quinolinyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, benzo[b]thiophenyl, a (cyclobutyl)alkyl group, a (cyclopentyl)alkyl group, a benzyl group, a (tetrahydrofuranyl)alkyl group, or a (tetrahydropyranyl)alkyl group; and R_4 is optionally substituted with one to five R_g independently selected from the group consisting of hydroxy, halogen, CN, C_1-C_6 alkyl, C_6-C_{10} aryl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, and C_6-C_{10} aralkoxy, or two R_g together with the atoms to which they are attached form an aromatic or non-aromatic 3- to 6-membered ring, optionally containing one or two ring heteroatoms independently selected from oxygen, sulfur, or nitrogen.

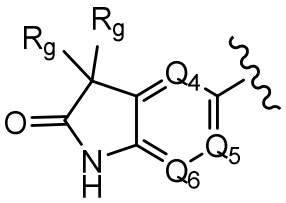
7. The compound of claim 1, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

TL is a moiety of Formula IIIa:

(IIIa)  .

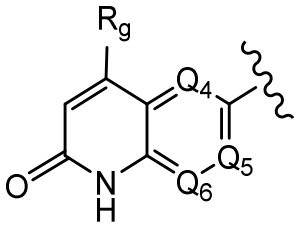
8. The compound of claim 7, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein TL is

a moiety of Formula IIIaa:

(IIIaa)  ;

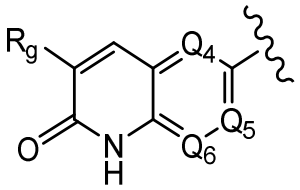
wherein each R_g is independently C_1-C_6 alkyl or the two R_g together with the atom(s) to which they are attached form a 3- to 6-membered non-aromatic carbocyclic group;

a moiety of Formula IIIab:

(IIIab)  ;

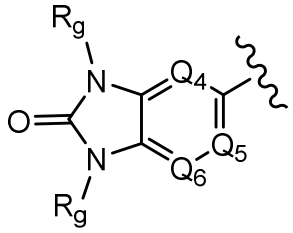
wherein R_g is C_1-C_6 alkyl;

a moiety of Formula IIIac:

(IIIac)  ;

wherein R_g is C_1-C_6 alkyl; or

a moiety of Formula IIIad:

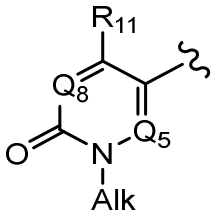


(IIIad) ;

wherein each R_g is independently hydrogen or C_1-C_6 alkyl.

9. The compound of claim 1, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

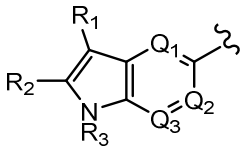
TL is a moiety of Formula IIId:



(IIId) .

10. The compound of claim 1, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

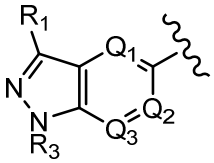
TL is a moiety of Formula IIa:



(IIa) .

11. The compound of claim 1, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

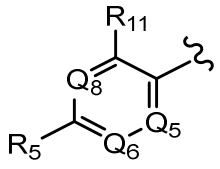
TL is a moiety of Formula IIb:



(IIb) .

12. The compound of claim 1, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

TL is a moiety of Formula IIIc:

(IIIc) 

.

13. The compound of any one of claims 1-12, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein L_a is oxygen or $–CH_2–$.

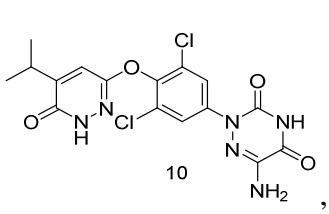
14. The compound of any one of claims 1-13, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein Q_7 is –CH–.

15. The compound of any one of claims 1-14, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein

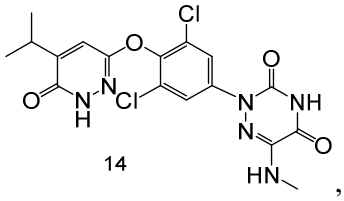
each of R_6 and R_7 is independently halogen or C_1-C_5 alkyl optionally substituted with one to five substituents independently selected from hydroxy, halogen, and C_1-C_6 alkoxy; and R_8 is hydrogen; or

R_6 is halogen or C_1-C_5 alkyl optionally substituted with one to five substituents independently selected from hydroxy, halogen, and C_1-C_6 alkoxy; and R_7 and R_8 taken together, along with the carbon atoms to which they are attached, form a 4-, 5- or 6-membered carbocyclic ring.

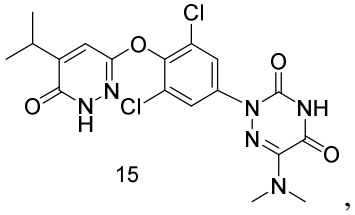
16. A compound selected from the group consisting of:



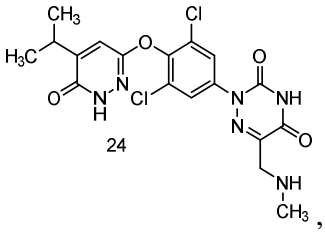
10 ,



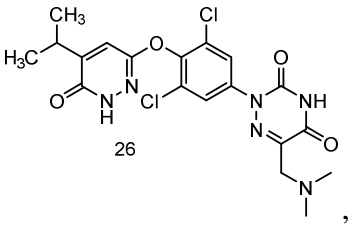
14 ,



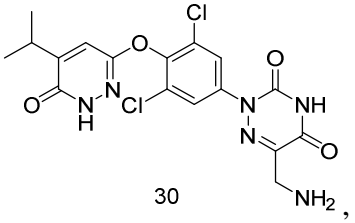
15 ,



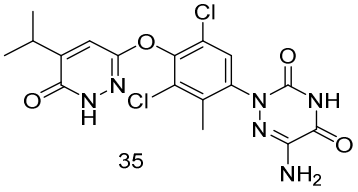
24 ,

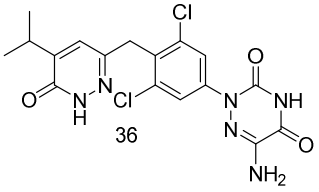


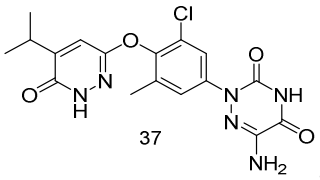
26 ,

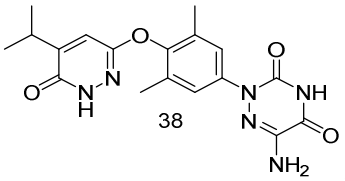


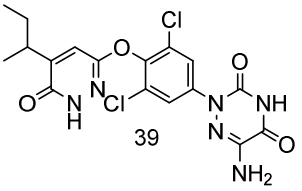
30 ,

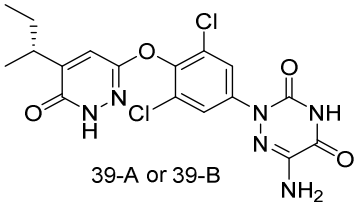

35

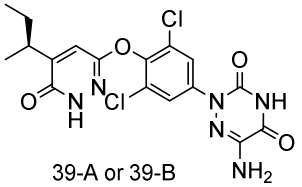

36

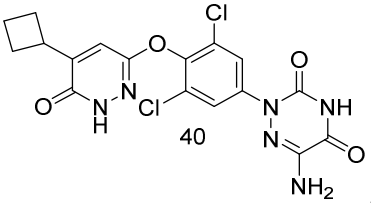

37

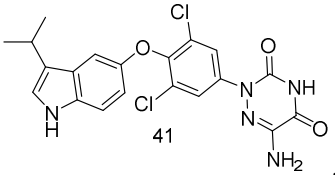

38

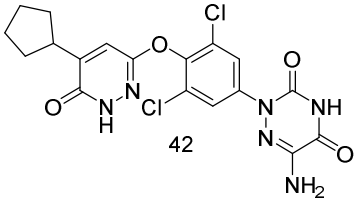

39

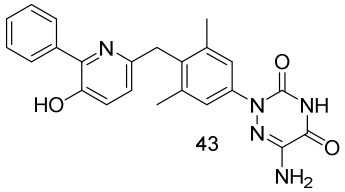

39-A or 39-B

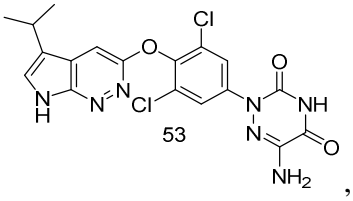

39-A or 39-B

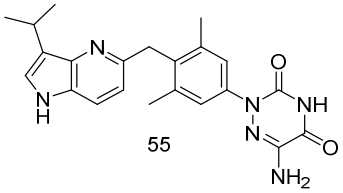

40

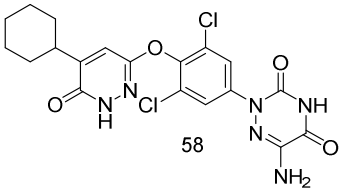

41

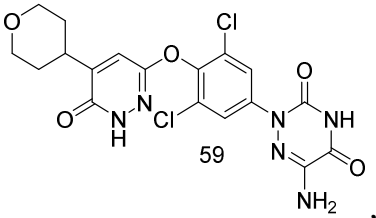

42

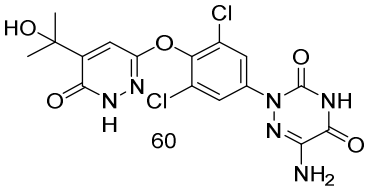

43

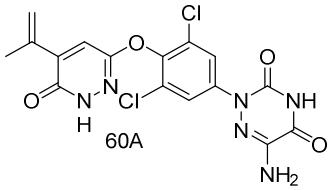

53

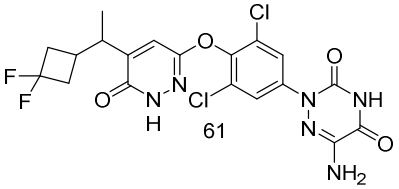

55

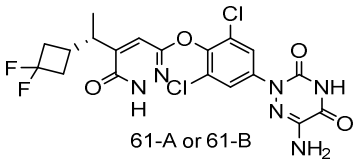

58

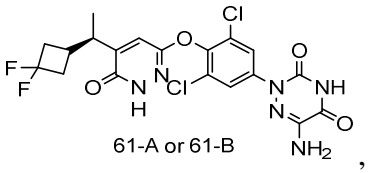

59

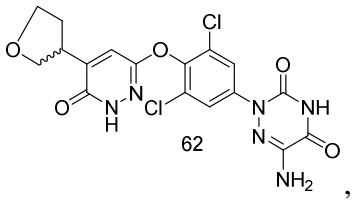

60

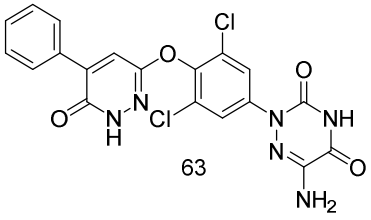

60A

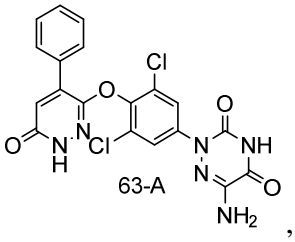

61

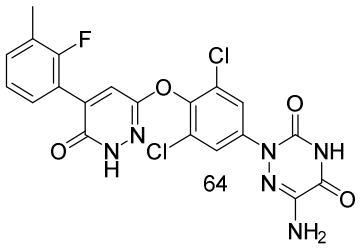

61-A or 61-B

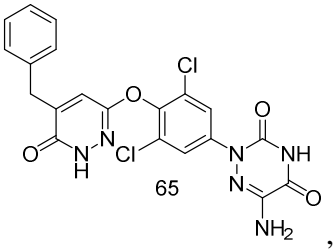

61-A or 61-B

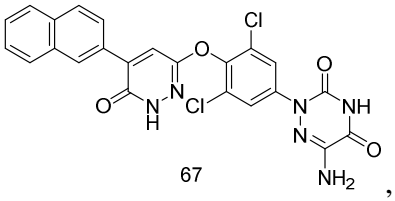

62

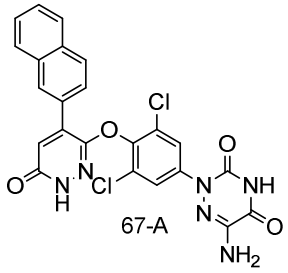

63

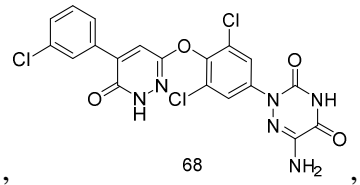

63-A

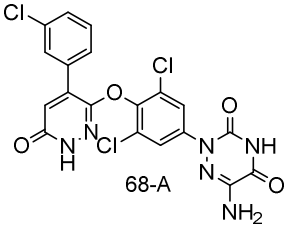

64

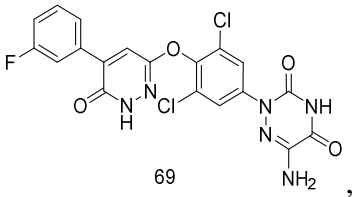

65

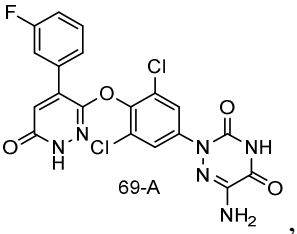

67

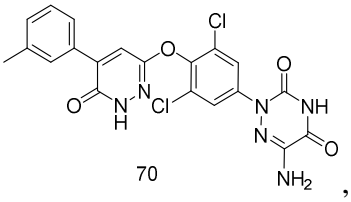

67-A

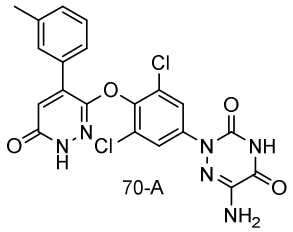

68

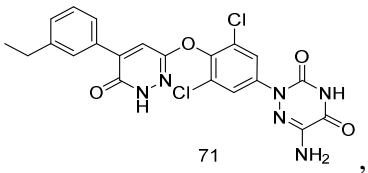

68-A

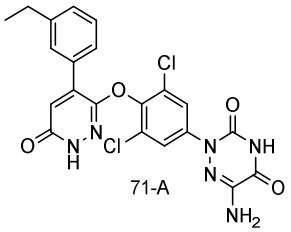

69

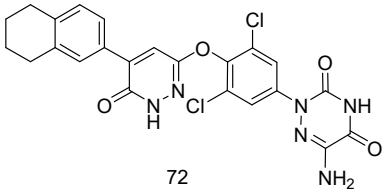

69-A

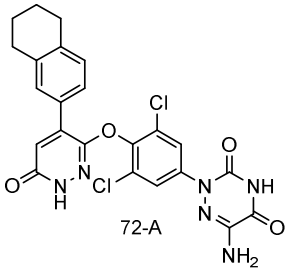

70

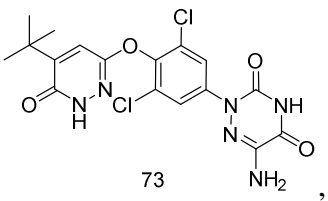

70-A

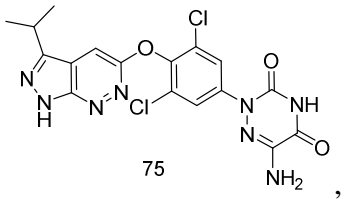

71

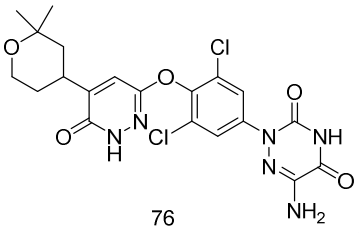

71-A

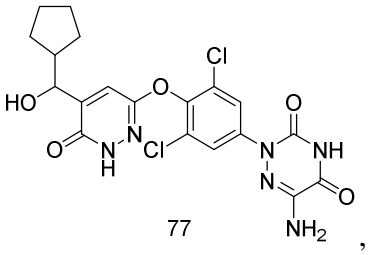

72

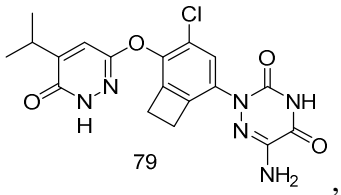

72-A

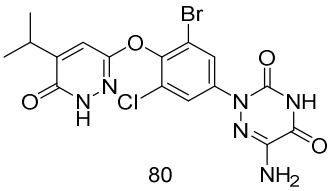

73

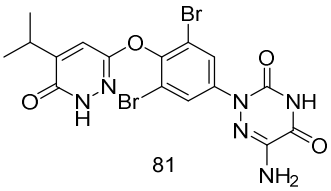

75

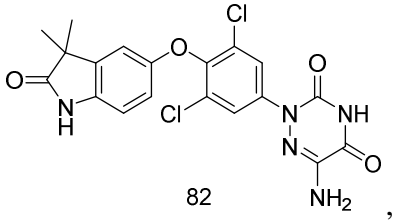

76

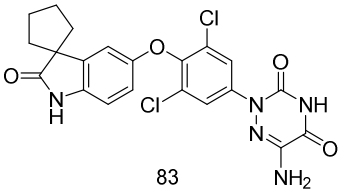

77

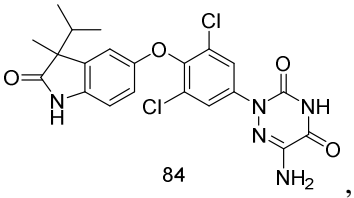

79

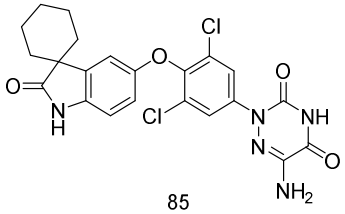

80

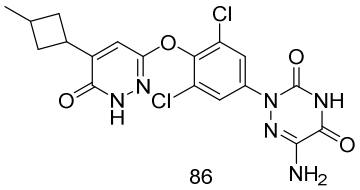

81

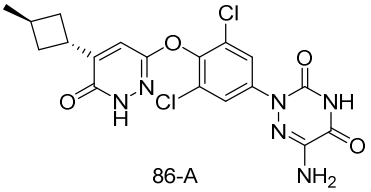

82

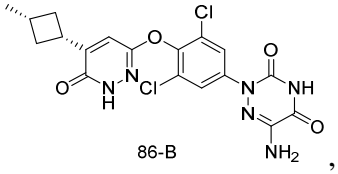

83

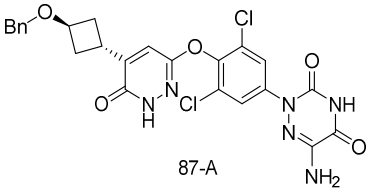

84

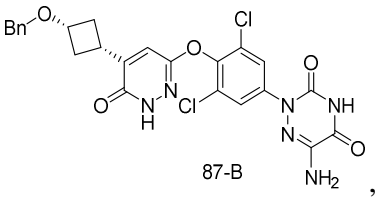

85

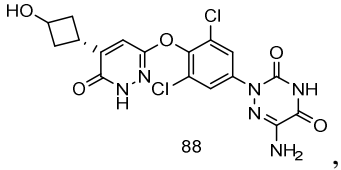

86

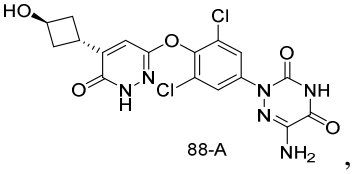

86-A

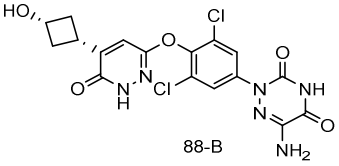

86-B

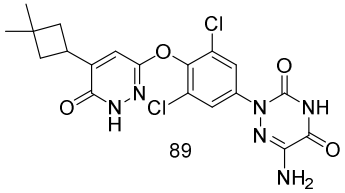

87-A

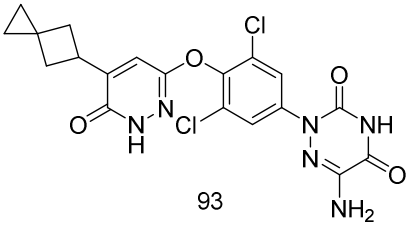

87-B

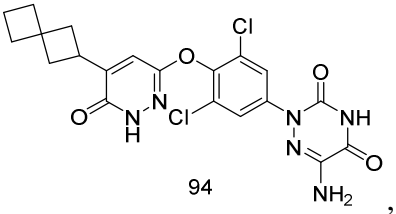

88

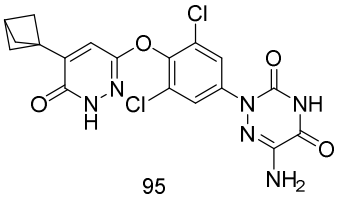

88-A

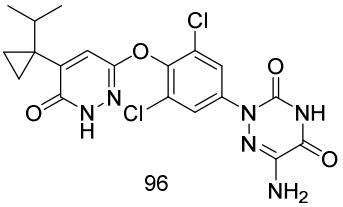

88-B

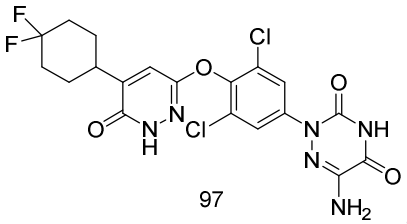

89

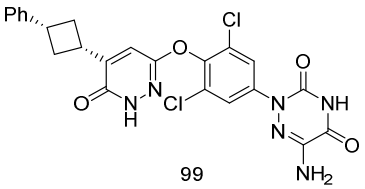

93

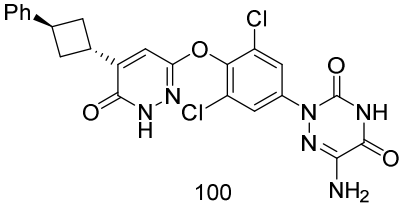

94

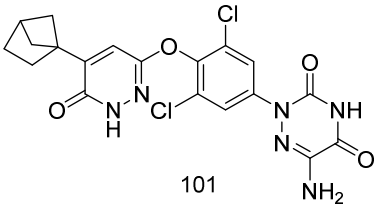

95 ,

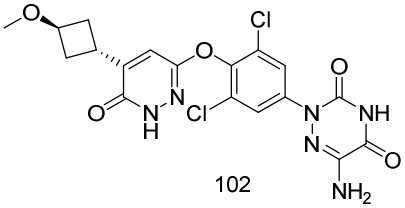

96 ,

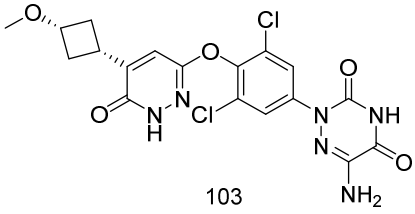

97 ,

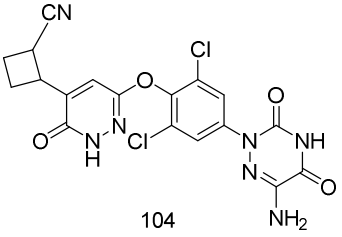

99 ,

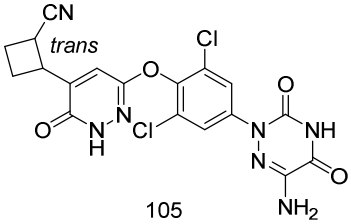

100 ,

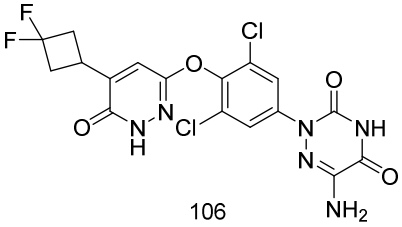

101 ,

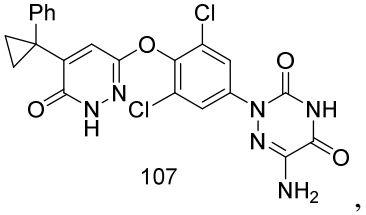

102 ,

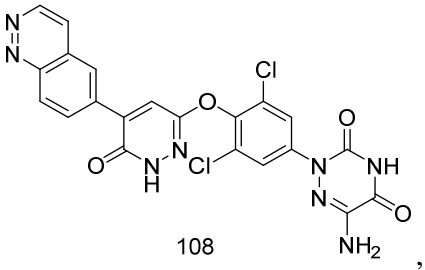

103 ,

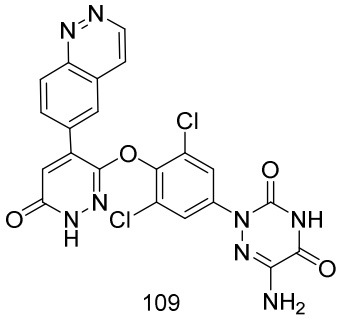

104 ,

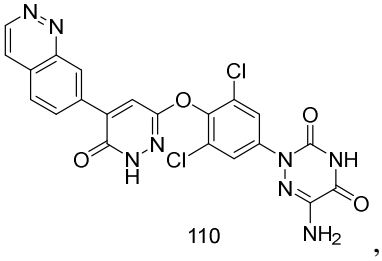

105 ,

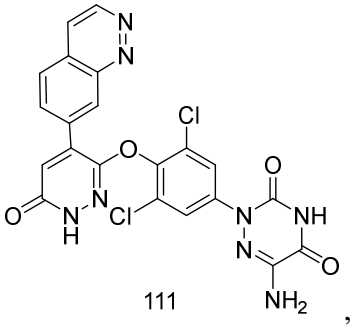

106 ,

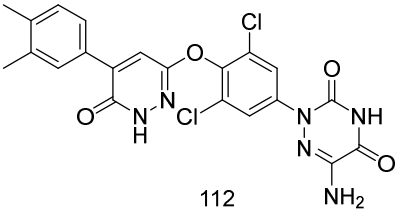

107 ,

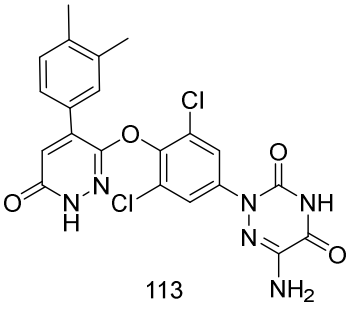

108 ,

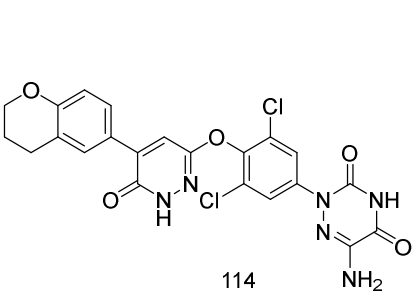

109 ,

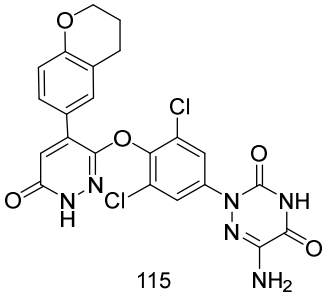

110 ,

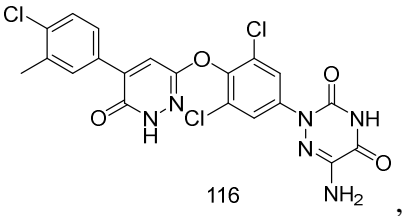

111 ,

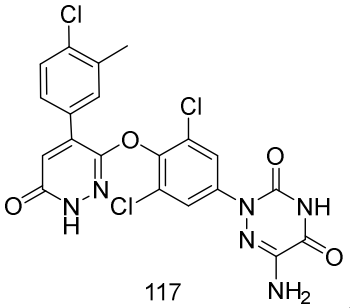

112 ,

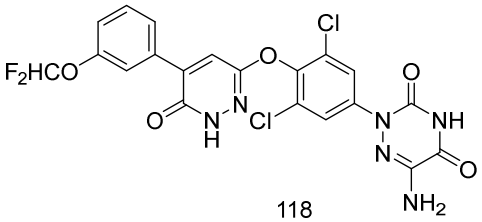

113 ,

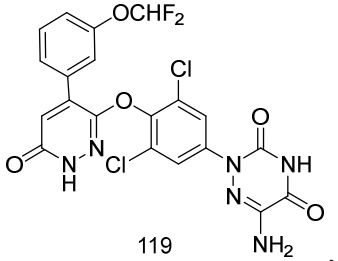

114 ,

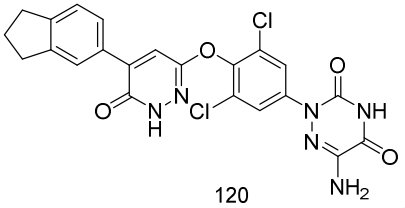

115 ,

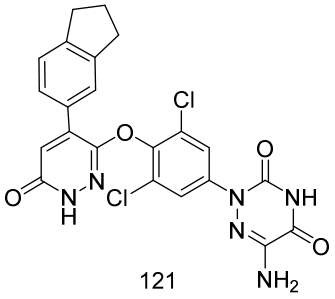

116 ,

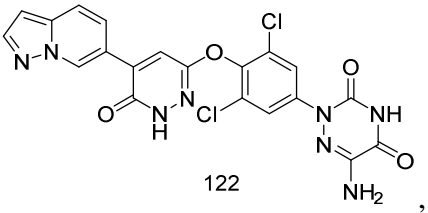

117 ,

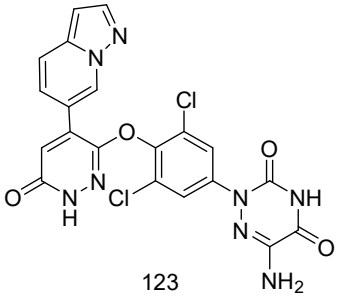

118 ,

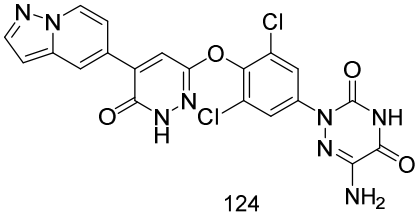

119 ,

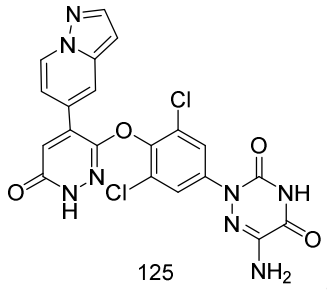

120 ,

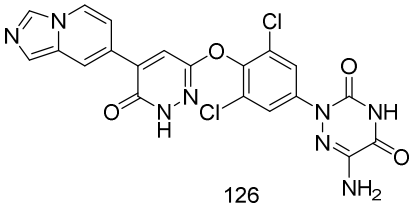

121 ,

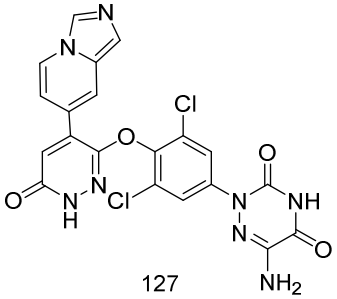

122 ,

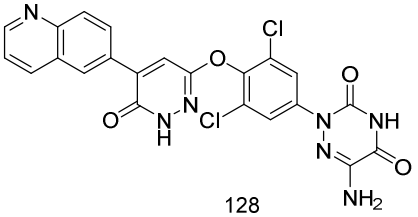

123 ,

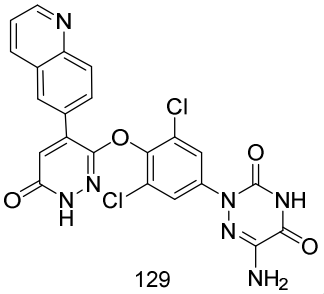

124 ,

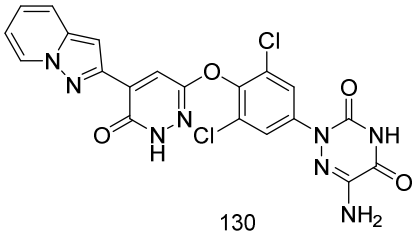

125 ,

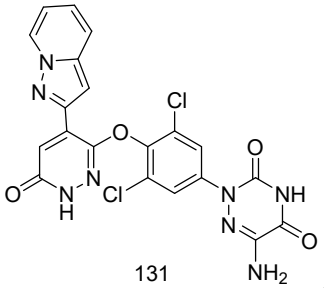

126 ,

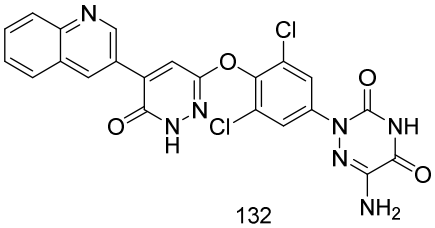

127 ,

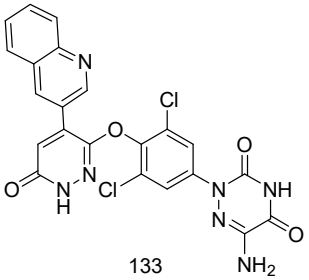

128 ,

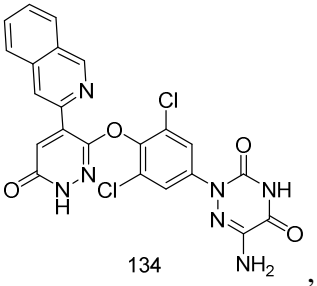

129 ,

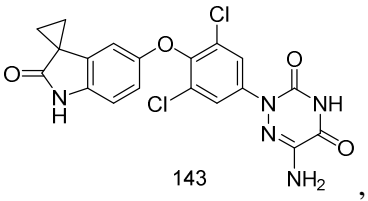

130 ,

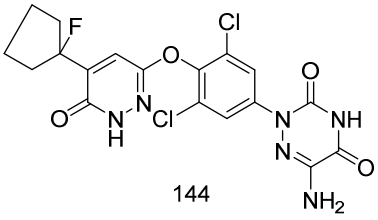

131 ,

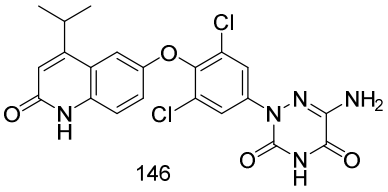

132 ,

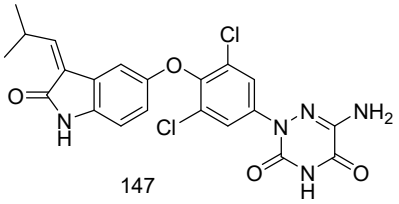

133 ,

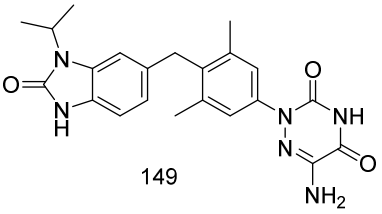

134 ,

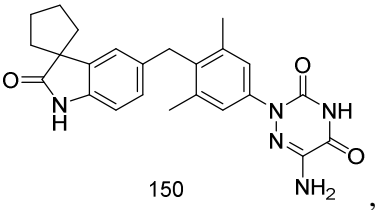

143 ,

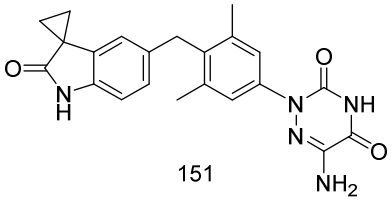

144 ,

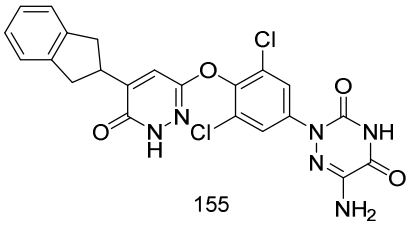

146 ,

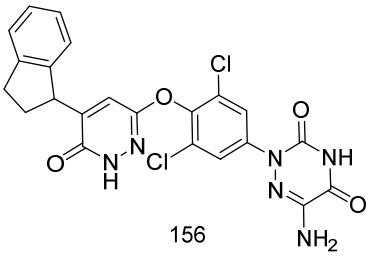

147 ,

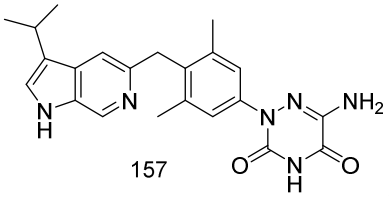

149 ,

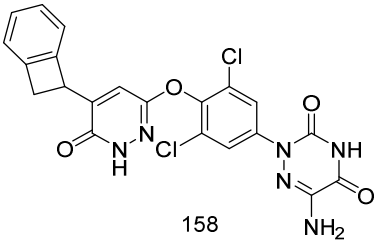

150 ,

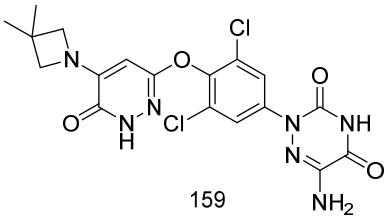

151 ,

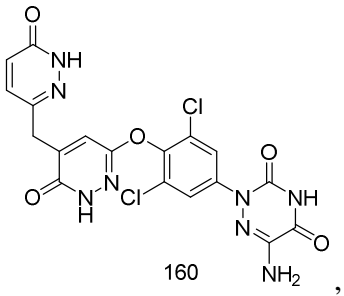
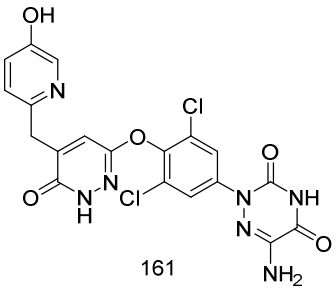
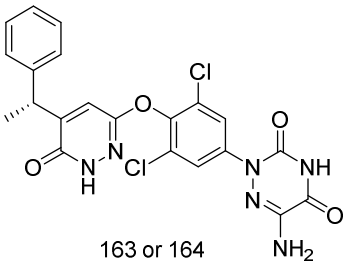
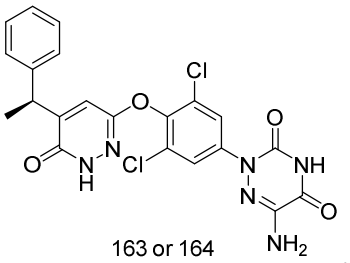
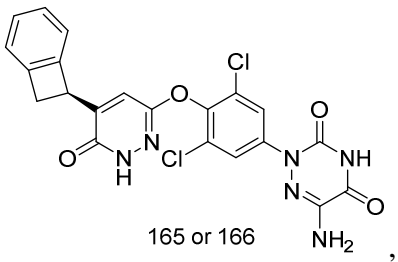
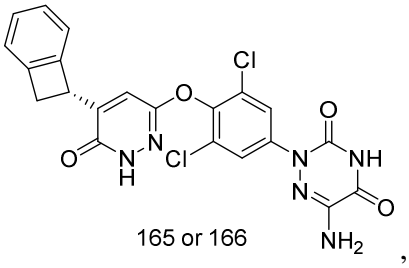
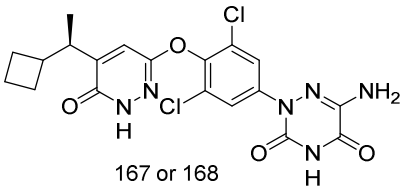
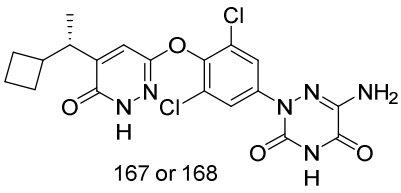
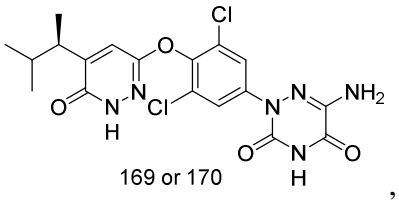
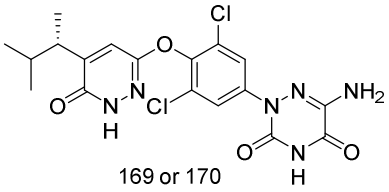
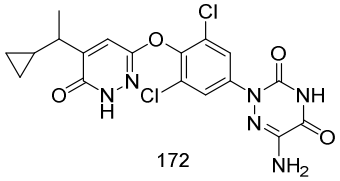
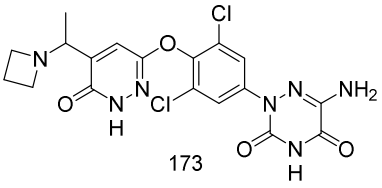

155 ,


156 ,


157 ,


158 ,


159 ,


160 ,

161 ,

163 or 164 ,

163 or 164 ,

165 or 166 ,

165 or 166 ,

167 or 168 ,

167 or 168 ,

169 or 170 ,

169 or 170 ,

172 , and

173 ; or

a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising the compound of any one of claims 1-16, or the stereoisomer or the tautomer thereof, or the pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

18. Use of the compound of any one of claims 1-16, or the stereoisomer or the tautomer thereof, or the pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disorder or disease selected from non-alcoholic steatohepatitis (NASH), obesity, hyperlipidemia, hypercholesterolemia, diabetes, liver steatosis, atherosclerosis, cardiovascular diseases, hypothyroidism, and thyroid cancer.

19. Use of the composition of claim 17 for the manufacture of a medicament for the treatment of a disorder or disease selected from non-alcoholic steatohepatitis (NASH), obesity,

hyperlipidemia, hypercholesterolemia, diabetes, liver steatosis, atherosclerosis, cardiovascular diseases, hypothyroidism, and thyroid cancer.

20. Use of the compound of any one of claims 1-16, or the stereoisomer or the tautomer thereof, or the pharmaceutically acceptable salt thereof, for the manufacture of a medicament for selectively modulating the activity of a thyroid hormone receptor beta (THR-β) in a patient suffering from a disease or disorder selected from non-alcoholic steatohepatitis (NASH), obesity, hyperlipidemia, hypercholesterolemia, diabetes, liver steatosis, atherosclerosis, cardiovascular diseases, hypothyroidism, and thyroid cancer.

21. Use of the composition of claim 17 for the manufacture of a medicament for selectively modulating the activity of a thyroid hormone receptor beta (THR-β) in a patient suffering from a disease or disorder selected from non-alcoholic steatohepatitis (NASH), obesity, hyperlipidemia, hypercholesterolemia, diabetes, liver steatosis, atherosclerosis, cardiovascular diseases, hypothyroidism, and thyroid cancer.

22. A compound of any one of claims 1-16, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, for use in treating a disorder or disease is selected from non-alcoholic steatohepatitis (NASH), obesity, hyperlipidemia, hypercholesterolemia, diabetes, liver steatosis, atherosclerosis, cardiovascular diseases, hypothyroidism, and thyroid cancer.

23. A compound of any one of claims 1-16, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof, for use in selectively modulating the activity of a thyroid hormone receptor beta (THR-β).