SUBSTITUTED 2-(PYRROLIDINE-3-YL)ACETIC ACID DERIVATIVE, PREPARATION METHOD THEREFOR, AND USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to Chinese Patent Application No. 202311536343.5 filed on November 17, 2023; No. 202410174573.X filed on February 7, 2024; No. 202410811526.1 filed on June 21, 2024; and No. 202411250214.4 filed on September 6, 2024, the entireties of all of which are hereby incorporated by reference.

TECHNICAL FIELD

The invention relates to the field of pharmaceutical technology, and in particular, to compounds as Lp(a) inhibitors, particularly a substituted 2-(pyrrolidine-3-yl)acetic acid derivative, a preparation method therefor, and a use thereof.

BACKGROUND

Lipoprotein(a) (Lp(a)) is a lipoprotein particle synthesized in the liver, consisting of cholesterol-rich low-density lipoprotein (LDL-C)-like particles attached to apolipoprotein(a). Lp(a) levels are primarily genetically determined, vary widely across populations, and are largely unaffected by lifestyle interventions.

Lp(a) is associated with an increased risk of coronary artery diseases, ischemic stroke, aortic stenosis, heart failure, atrial fibrillation, and peripheral artery diseases. Elevated Lp(a) levels (≥30 mg/dL) are present in approximately 20% of people. The increased risk of cardiovascular diseases (CVDs) associated with Lp(a) is mainly attributed to the dual prothrombotic effects of Apo(a) [the structure of Apo(a) is similar to that of plasminogen], as well as the atherogenic effects of Apo B (apolipoprotein B) and the pro-inflammatory effects of oxidized phospholipids (OxPL). Lp(a) is not only a causative factor for atherosclerotic cardiovascular disease (ASCVD) but also for calcific aortic valve disease. Elevated Lp(a) plasma levels are an independent risk factor for CVDs.

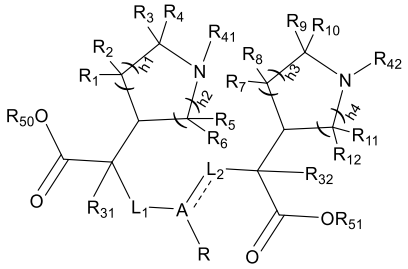
There are few approved treatment options for patients with elevated Lp(a) concentrations. Plasmapheresis can be used to filter the blood to remove LDL and Lp(a), which, however, has temporary effects and usually needs to be repeated every two weeks, and patient compliance is not

very good. To date, there are no approved drug therapies for lowering Lp(a) levels. Therefore, there is a great need to provide patients with CVDs with medicinal compounds and treatment options to lowering plasma Lp(a) levels.

SUMMARY

The purpose of the invention is to provide a novel compound for lowering a plasma Lp(a) level, a method for preparing the compound, and a use thereof in the treatment of a disease mediated by Lp(a). The novel compound is biochemically effective and physiologically active.

In a first aspect of the present invention, provided is a compound represented by the following Formula (I), or a pharmaceutically acceptable salt thereof:



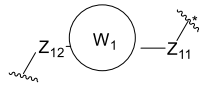
(I)

In the formula, ⎓ is a single bond or a double bond;

A is CR_X, P, P(O), N, C_{6-12} aryl, 5-14-membered heteroaryl, C_{3-8} carbocyclyl or 5-18-membered heterocyclyl; wherein the aryl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

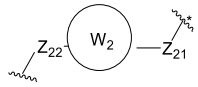
when ⎓ is a single bond, R_X is H, -OH, or C_{1-3} alkoxy;

when ⎓ is a double bond, R_X is absent;

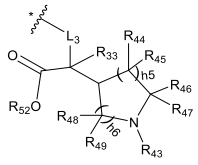
L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one

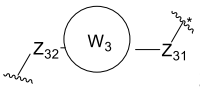
or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and 

; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; wherein the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; wherein the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $-N(C_{1-3}\text{ alkyl})_2$, $-NH(C_{1-3}\text{ alkyl})$, and $-C(O)C_{1-3}$ alkyl;

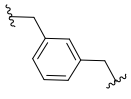
each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -O-, -S-, -NH-, -Se-, $-C_{1-4}$ alkylene-, $-C_{1-8}$ oxaalkylene-, $-C_{1-4}$ thiaalkylene-, $-C_{1-4}$ azaalkylene-, and $-C_{1-4}$ selenaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents independently selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen, oxo, thio, -CN, -OH, $-NH_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom linked thereto form C_{3-6} cycloalkyl, 3-6-membered heterocyclyl, phenyl, or 5-6-membered heteroaryl;

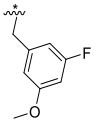
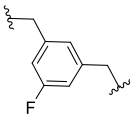
each of R_{31}, R_{32}, and R_{33} is independently selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} deuteroalkoxy;

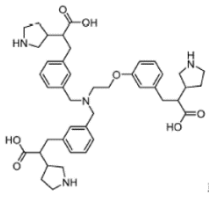
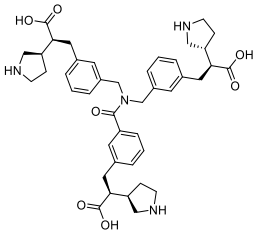
each of h1, h2, h3, h4, h5, and h6 is independently 0, 1, or 2;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, and R_{49} is independently selected from H, deuterium, -CN, -OH, $-NH_2$, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-N(C_{1-3}\text{ alkyl})_2$, and $-NH(C_{1-3}\text{ alkyl})$;

each of R_{50}, R_{51}, R_{52} is independently selected from H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, $-C_{1-3}$ alkylene-O-C_{1-6} alkyl, $-C_{1-3}$ alkylene-O-C(O)-C_{1-6} alkyl, wherein the alkyl, alkenyl, alkoxy, and alkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, -OH, $-NH_2$, -CN, oxo, C_{1-3} alkyl, and C_{1-3} alkoxy;

provided that when A is N, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, and R_{49} are all H, L_1, L_2, and L_3 are not  at the same time;

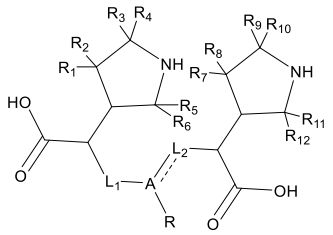
provided that when A is N, R is  , and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{41}, and R_{42} are all H, L_1 and L_2 are not  at the same time, * is the linking end of R to A;

provided that the compound is not  and  ;

a heteroatom in the heterocyclyl or heteroaryl is independently selected from O, N, or S, and the number of heteroatoms is 1, 2, 3, or 4.

In an embodiment of the compound represented by the above Formula (I), R is a group comprising L_3; L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2$O-, and -S-C(O)-.

In some embodiments, a compound represented by the following Formula (I-1-P1), or a pharmaceutically acceptable salt thereof is provided:



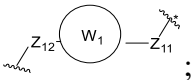
(I-1-P1)

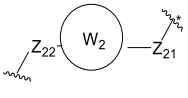
wherein ⎓ is a single bond or a double bond;

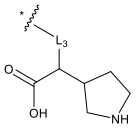
A is CR_X, P, P(O) or N;

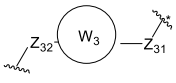
when ⎓ is a single bond; R_X is H, -OH, or C_{1-3} alkoxy;

when ⎓ is a double bond, R_X is absent;

L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

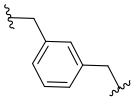
R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

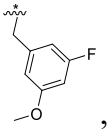
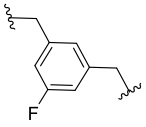
L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; wherein the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-4} alkylene-, and -C_{1-4} oxaalkylene-; wherein the alkylene and oxaalkylene are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

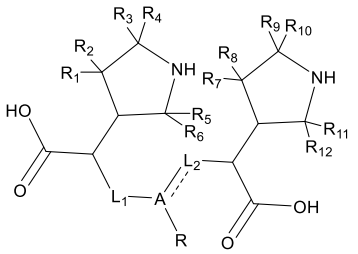
provided that when A is N, L_1, L_2, and L_3 are not  at the same time;

provided that when A is N and R is  , L_1 and L_2 are not  at the same time, and * is the linking end of R to A;

a heteroatom in the heterocyclyl or heteroaryl is independently selected from O, N, or S, and the number of heteroatoms is 1, 2, or 3.

In an embodiment of the compound represented by the above Formula (I-1-P1), R is a group comprising L_3; L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2$O-, and -S-C(O)-.

In some embodiments, a compound represented by the following formula (I-1-P2), or a pharmaceutically acceptable salt thereof is provided:



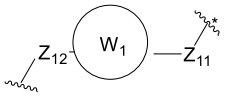
(I-1-P2)

wherein ⎓ is a single bond or a double bond;

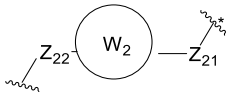
A is CR_X, P, P(O) or N;

when ⎓ is a single bond, R_X is H, -OH, or C_{1-3} alkoxy;

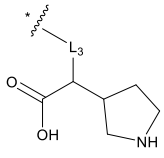
when ⎓ is a double bond, R_X is absent;

L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

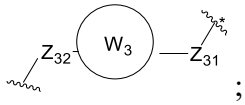
; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, 

; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

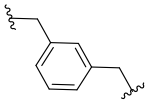
L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

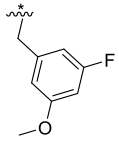
; the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

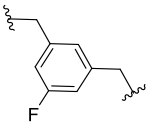
each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, 5-12-membered heterocyclyl; wherein the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-4} alkylene-, -C_{1-4} oxaalkylene-, -C_{1-4} thiaalkylene-, and -C_{1-4} azaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

provided that when A is N, L_1, L_2, and L_3 are not  at the same time;

provided that when A is N, R is 

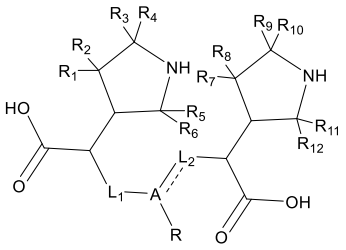
, L_1 and L_2 are not 

at the same time, wherein * is the linking end of R to A;

a heteroatom in the heterocyclyl or heteroaryl is independently selected from O, N, or S, and the number of heteroatoms is 1, 2, or 3.

In an embodiment of the compound represented by the above Formula (I-1-P2), R is a group comprising L_3; L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

In some embodiments, a compound represented by the following Formula (I-1-P3), or a pharmaceutically acceptable salt thereof is provided:



(I-1-P3)

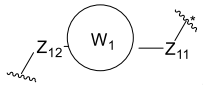
wherein ⎓ is a single bond or a double bond;

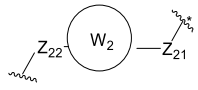
A is CR_X, P, P(O), N, C_{6-12} aryl, 5-14-membered heteroaryl, or 5-18-membered heterocyclyl; wherein the aryl, heteroaryl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

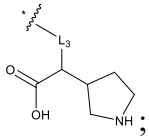
when ⎓ is a single bond; R_X is H, -OH, or C_{1-3} alkoxy;

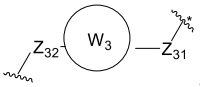
when ⎓ is a double bond, R_X is absent;

L_1 is selected from $-C_{1-3}$ alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, $-C_{1-3}$ alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, $-C_{1-3}$ alkylene-5-12-membered heteroaryl-5-12-

membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, $-NH_2$, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

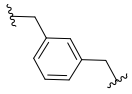
L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents

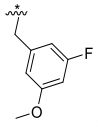
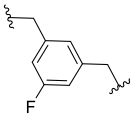
independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

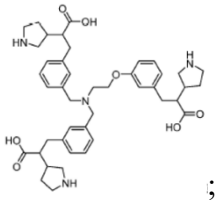
each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; wherein the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-4} alkylene-, -C_{1-4} oxaalkylene-, -C_{1-4} thiaalkylene-, and -C_{1-4} azaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

provided that when A is N, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1, L_2, and L_3 are not  at the same time;

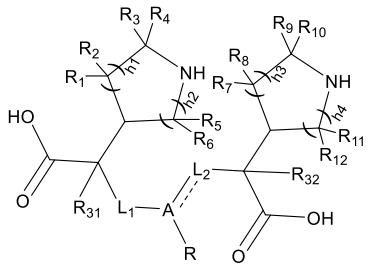
provided that when A is N, R is  , and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1 and L_2 are not  at the same time, and * is the linking end of R to A;

provided that the compound is not  ;

a heteroatom in the heterocyclyl or heteroaryl is independently selected from O, N, or S, and the number of heteroatoms is 1, 2, 3, or 4.

In an embodiment of the compound represented by the above Formula (I-1-P3), R is a group comprising L_3; L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

In some embodiments, a compound represented by the following Formula (I-1-P4), or a pharmaceutically acceptable salt thereof is provided:



(I-1-P4)

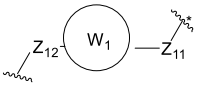
wherein ⎓ is a single bond or a double bond;

A is CR_X, P, P(O), N, C_{6-12} aryl, 5-14-membered heteroaryl, or 5-18-membered heterocyclyl; the aryl, heteroaryl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

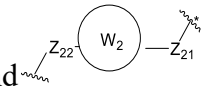
when ⎓ is a single bond, RX is H, -OH, or C_{1-3} alkoxy;

when ⎓ is a double bond, R_X is absent;

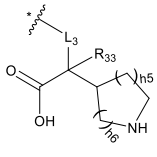
L_1 is selected from $-C_{1-3}$ alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, $-C_{1-3}$ alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, $-C_{1-3}$ alkylene-5-12-membered heteroaryl-5-12-

membered heteroaryl-C_{1-3} alkylene-, and 

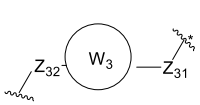
; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl isoptionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl

and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

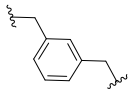
each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $-N(C_{1-3}\text{ alkyl})_2$, $-NH(C_{1-3}\text{ alkyl})$, and $-C(O)C_{1-3}$ alkyl;

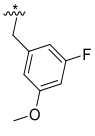
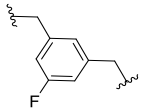
each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -O-, -S-, -NH-, -Se-, $-C_{1-4}$ alkylene-, $-C_{1-8}$ oxaalkylene-, $-C_{1-4}$ thiaalkylene-, $-C_{1-4}$ azaalkylene-, and $-C_{1-4}$selenaalkylene-; the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents independently selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen, oxo, thio, -CN, -OH, $-NH_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom linked thereto form C_{3-6} cycloalkyl, 3-6-membered heterocyclyl, phenyl, or 5-6-membered heteroaryl;

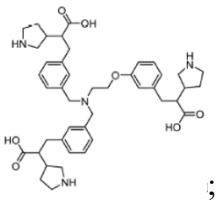
each of R_{31}, R_{32}, and R_{33} is independently selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} deuteroalkoxy;

each of h1, h2, h3, h4, h5, and h6 is independently 0, 1, or 2;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

provided that when A is N, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1, L_2, and L_3 are not  at the same time;

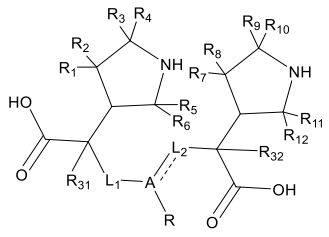
provided that when A is N, R is  , and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1 and L_2 are not  at the same time, * is the linking end of R to A;

provided that the compound is not  ;

a heteroatom in the heterocyclyl and heteroaryl is independently selected from O, N, and S, and the heteroatom number is 1, 2, 3, or 4;

In an embodiment of the compound represented by the above Formula (I-1-P4), R is a group comprising L_3; L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2$O-, and -S-C(O)-.

In some embodiments, a compound represented by the following Formula (I-2), or a pharmaceutically acceptable salt thereof is provided:

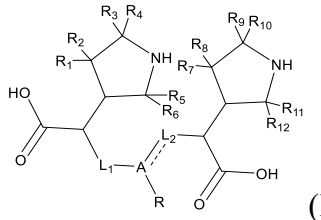
 (I-2),

wherein A, ---, L_1, L_2, R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{31}, and R_{32} are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), or Formula (I-1-P4).

In an embodiment of the compound represented by the above Formula (I-2), R is a group comprising L_3; L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example,

a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

In some embodiments, a compound represented by the following Formula (I-3), or a pharmaceutically acceptable salt thereof is provided:

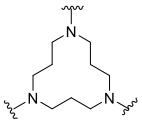
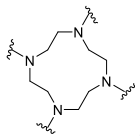


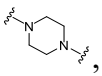
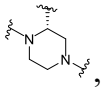
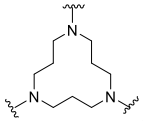
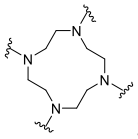
(I-3),

In the formula, A, ---, L_1, L_2, R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), or Formula (I-1-P4).

In an embodiment of the compound represented by the above Formula (I-3), R is a group comprising L_3; L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

In one embodiment of the invention, A is CR_X, P, P(O), N, phenyl, 5-6-membered heterocyclic group, or 12-membered heterocyclic group; wherein a heteroatom in the heterocyclic group is N, and the number of heteroatoms is 1, 2, 3, or 4.

In one embodiment of the invention, A is CR_X, P, P(O), N, phenyl, piperazinyl,  , or  .

In one embodiment of the invention, A is CR_X, P, P(O), N, ,  , , ,  ,  , or  ; preferably A is N, , , , or .

In one embodiment of the invention, A is CR_X, P, P(O), or N.

In one embodiment of the invention, A is N.

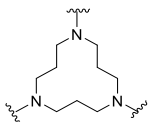
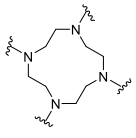
In one embodiment of the invention, A is P(O).

In one embodiment of the invention, A is selected from CR_X; R_X is H, -OH, or methoxy.

In one embodiment of the invention, A is selected from C-OH and $C\text{-}OCH_3$.

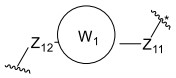
In one embodiment of the invention, A is a 6-12-membered heterocyclic group.

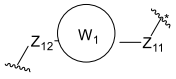
In one embodiment of the invention, A is a 6-membered heterocyclic group; preferably, A is piperazinyl; preferably , , , and .

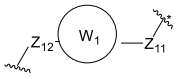
In one embodiment of the invention, A is  or  .

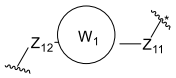
In one embodiment of the invention, A is phenyl; preferably .

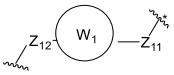
In one embodiment of the invention, R_X is H, -OH, or methoxy.

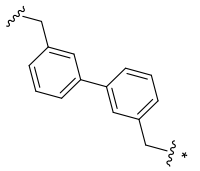
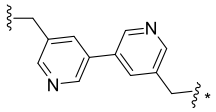
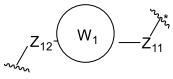
In one embodiment of the invention, L_1 is selected from -methylene-C_{6-10} aryl-C_{6-10} aryl-methylene-, -methylene-5-12-membered heteroaryl-5-12-membered heteroaryl-methylene-, and  ; wherein the methylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A.

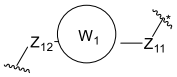
In one embodiment of the invention, L_1 is selected from -C_{1-3} alkylene-phenyl-phenyl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-6-membered heteroaryl-5-6-membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to N.

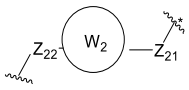
In one embodiment of the invention, L_1 is selected from -methylene-phenyl-phenyl-methylene-, -ethylene-phenyl-phenyl-ethylene-, -methylene-5-6-membered heteroaryl-5-6-membered heteroaryl-methylene-, -ethylene-5-6-membered heteroaryl-5-6-membered heteroaryl-ethylene-, and  ; wherein the methylene and ethylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A.

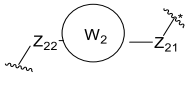
In one embodiment of the invention, L_1 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-6-membered heteroaryl-6-membered heteroaryl-methylene-, and  ; wherein the methylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A.

In one embodiment of the invention, L_1 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-pyridyl-pyridyl-methylene-, and  ; * is the linking end of L_1 to A.

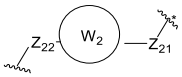
In one embodiment of the invention, L_1 is selected from  ,  , and  ; * is the linking end of L_1 to A.

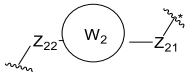
In one embodiment of the invention, L_1 is  ; * is the linking end of L_1 to A.

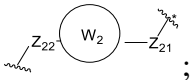
In one embodiment of the invention, L_2 is selected from -methylene-C_{6-10} aryl-C_{6-10} aryl-methylene-, -methylene-5-12-membered heteroaryl-5-12-membered heteroaryl-methylene-, and  ; wherein the methylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A.

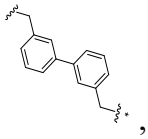
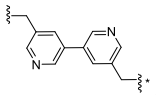
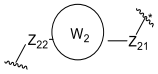
In one embodiment of the invention, L_2 is selected from -C_{1-3} alkylene-phenyl-phenyl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-6-membered heteroaryl-5-6-membered heteroaryl-C_{1-3} alkylene-, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to N.

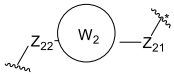
In one embodiment of the invention, L_2 is selected from -methylene-phenyl-phenyl-methylene-, -ethylene-phenyl-phenyl-ethylene-, -methylene-5-6-membered heteroaryl-5-6-membered heteroaryl-methylene-, -ethylene-5-6-membered heteroaryl-5-6-membered heteroaryl-

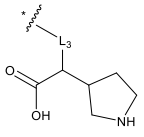
ethylene-, and  ; wherein the methylene and ethylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A.

In one embodiment of the invention, L_2 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-6-membered heteroaryl-6-membered heteroaryl-methylene-, and  ; wherein the methylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A.

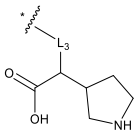
In one embodiment of the invention, L_2 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-pyridyl-pyridyl-methylene-, and  ; * is the linking end of L_2 to A.

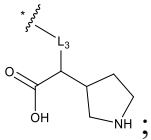
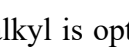
In one embodiment of the invention, L_2 is selected from  ,  , and  ; * is the linking end of L_2 to A.

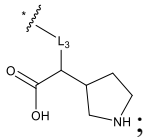
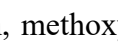
In one embodiment of the invention, L_2 is selected from  ; * is the linking end of L_2 to A.

In one embodiment of the invention, R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally

substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, $-NH_2$, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A.

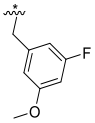
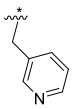
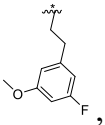
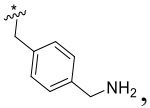
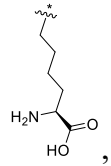
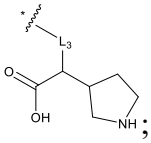
In one embodiment of the invention, R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-10-membered heteroaryl, C_{1-6} alkyl, and  ; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, and $-NH_2$; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, methoxy, and C_{1-3} aminoalkyl; and wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, $-NH_2$, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A.

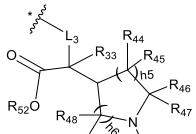
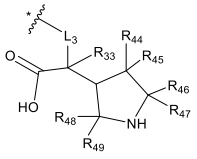
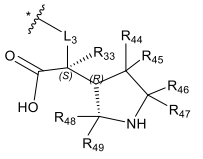
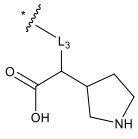
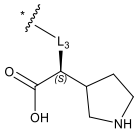
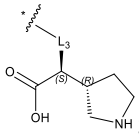
In one embodiment of the invention, R is selected from H, -methylene-phenyl, -ethylene-phenyl, -methylene-5-6-membered heteroaryl, -ethylene-5-6-membered heteroaryl, C_{1-6} alkyl, and  ; wherein the methylene and ethylene are optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, and $-NH_2$; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, methoxy, and  ; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, oxo, carboxyl, -CN, -OH, and $-NH_2$; * is the linking end of R to A.

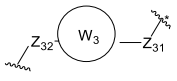
In one embodiment of the invention, R is selected from H, -methylene-phenyl, -ethylene-phenyl, -methylene-pyridinyl, -ethylene-pyridinyl, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *n*-pentyl, *n*-hexyl, and  ; wherein the phenyl and pyridinyl are optionally substituted by one or more substituents independently selected from halogen, methoxy, and  ; wherein the

methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *n*-pentyl, and *n*-hexyl are optionally substituted by one or more substituents independently selected from carboxyl and -NH_2; * is the linking end of R to A.

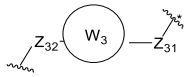
In one embodiment of the invention, R is selected from H, -C_{1-3} alkylene-phenyl, -C_{1-3} alkylene-5-6-membered heteroaryl, and C_{1-6} alkyl; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, carboxyl, -NH_2, methyl, and methoxy.

In one embodiment of the invention, R is selected from H,  ,  ,  ,  ,  , and  ; * is the linking end of R to A.

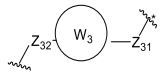
In one embodiment of the invention, R is selected from H,  ; preferably  ; preferably  ; preferably  ; preferably  ; preferably  ; wherein * is the linking end to A.

In one embodiment of the invention, L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkynylene-, -methylene-C_{6-10} aryl-C_{6-10} aryl-methylene-, -methylene-5-12-membered heteroaryl-5-12-membered heteroaryl-methylene-, and  ; wherein the alkylene, methylene, and

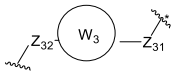
alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A.

In one embodiment of the invention, L_3 is selected from $-C_{1-6}$ alkylene-, $-C_{2-6}$ alkynylene-, -methylene-phenyl-phenyl-methylene-, -ethylene-phenyl-phenyl-ethylene-, -methylene-5-6-membered heteroaryl-5-6-membered heteroaryl-methylene-, -ethylene-5-6-membered heteroaryl-5-6-membered heteroaryl-ethylene-, and 

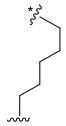
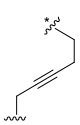
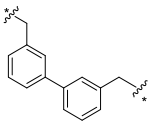
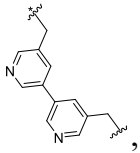
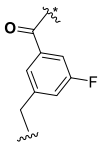
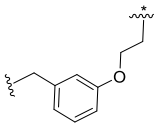
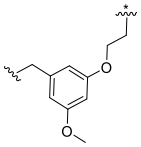
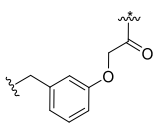
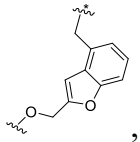
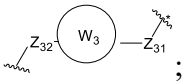
; wherein the alkylene, methylene, ethylene, and alkynylene are optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, $-NH_2$, methyl, and ethyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, methyl, ethyl, methoxy, and ethoxy; * is the linking end of L_3 to A.

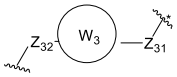
In one embodiment of the invention, L_3 is selected from $-C_{1-6}$ alkylene-, $-C_{2-6}$ alkynylene-, -methylene-phenyl-phenyl-methylene-, -methylene-6-membered heteroaryl-6-membered heteroaryl-methylene-, and 

; wherein the alkylene and methylene are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, oxo, -CN, -OH, and $-NH_2$; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, -CN, methyl, ethyl, methoxy, and ethoxy; * is the linking end of L_3 to A.

In one embodiment of the invention, L_3 is selected from methylene, ethylene, *n*-propylidene, isopropylidene, *n*-butylene, *n*-pentylene, *n*-hexylene, *n*-propynylene, *n*-butynylene, *n*-pentynylene, *n*-hexynylidene, -methylene-phenyl-phenyl-methylene-, -methylene-pyridyl-pyridyl-methylene-, and 

; * is the linking end of L_3 to A.

In one embodiment of the invention, L_3 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; * is the linking end of L_3 to A.

In one embodiment of the invention, L_3 is selected from  ; * is the linking end of L_3 to A.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, and C_{6-14} cycloalkyl; wherein the aryl, heteroaryl, and cycloalkyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from C_{6-10} aryl, 5-10-membered heteroaryl, and C_{6-10}cycloalkyl; wherein the aryl, heteroaryl, and cycloalkyl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, -CN, methyl, ethyl, methoxy, and ethoxy.

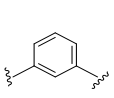
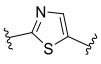
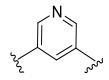
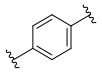
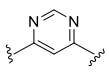
In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, 8-10-membered bicyclic heteroaryl, C_{8-10} bicyclic cycloalkyl, and 5-6-membered monocyclic heteroaryl; wherein the phenyl, naphthyl, heteroaryl, and cycloalkyl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy.

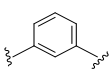
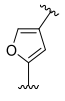
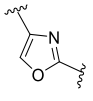
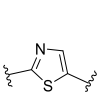
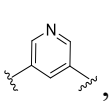
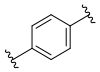
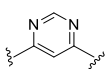
In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, 5-membered/5-membered fused heteroaryl, 5-membered/6-membered fused heteroaryl, 6-membered/5-membered fused heteroaryl, 6-membered/6-membered fused heteroaryl, 4-membered/6-membered spirocycloalkyl, 6-membered/4-membered spirocycloalkyl, 5-membered/5-membered spirocycloalkyl, 5-membered/6-membered spirocycloalkyl, 6-membered/5-membered spirocycloalkyl, 6-membered/6-membered spirocycloalkyl, and 5-6-membered monocyclic heteroaryl; wherein the phenyl, naphthyl, fused

heteroaryl, spirocycloalkyl, and monocyclic heteroaryl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, -CN, methyl, ethyl, methoxy, and ethoxy.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, 5-membered/5-membered fused heteroaryl, 5-membered/6-membered fused heteroaryl, 6-membered/5-membered fused heteroaryl, 6-membered/6-membered fused heteroaryl, 4-membered/6-membered spirocycloalkyl, 6-membered/4-membered spirocycloalkyl, and 5-6-membered monocyclic heteroaryl; wherein the phenyl, naphthyl, fused heteroaryl, spirocycloalkyl, and monocyclic heteroaryl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy.

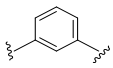
In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl and 5-6-membered monocyclic heteroaryl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}\text{ alkyl})_2$, $-NH(C_{1-3}\text{ alkyl})$, and $-C(O)C_{1-3}$ alkyl; wherein a heteroatom in the heteroaryl is O, N, or S, and the number of heteroatoms is 1 or 2.

In one embodiment of the invention, each of ring W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  , , , ,  , ,  ,  , and  ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}\text{ alkyl})_2$, $-NH(C_{1-3}\text{ alkyl})$, and $-C(O)C_{1-3}$ alkyl.

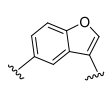
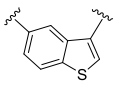
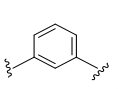
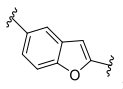
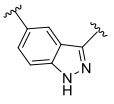
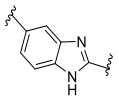
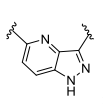
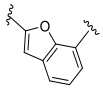
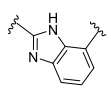
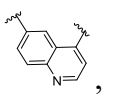
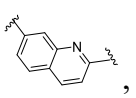
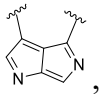
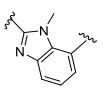
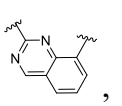
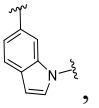
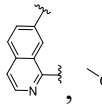
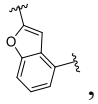
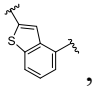
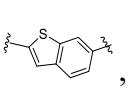
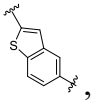
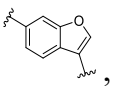
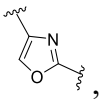
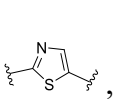
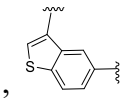
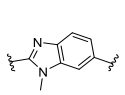
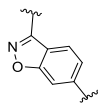
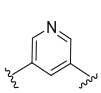
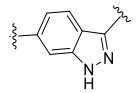
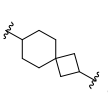
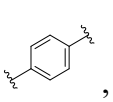
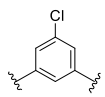
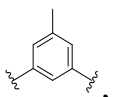
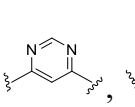
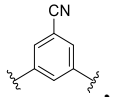
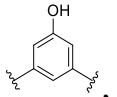
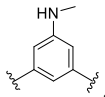
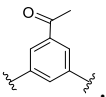
In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  ,  , ,  ,  , ,  ,  , and  ; wherein the "optionally substituted" refers to

unsubstituted or substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -CN, -OH, $-NH_2$, -CHO, methyl, ethyl, methoxy, ethoxy, $-N(CH_3)_2$, $-NH(CH_3)$, and $-C(O)CH_3$.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl and thienyl; wherein the phenyl and thienyl are optionally substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -CN, -OH, $-NH_2$, -CHO, methyl, ethyl, methoxy, ethoxy, $-N(CH_3)_2$, $-NH(CH_3)$, and $-C(O)CH_3$.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  , , and ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -CN, -OH, $-NH_2$, -CHO, methyl, ethyl, methoxy, ethoxy, $-N(CH_3)_2$, $-NH(CH_3)$, and $-C(O)CH_3$.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl; wherein the phenyl is optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy.

In one embodiment of the invention, each of W_1, W_2, and W_3 is independently selected from  ,  , , ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  , , ,  ,  ,  ,  , , ,  ,  , ,  ,  ,  ,  ,  , , ,  ,  , ,  ,  ,  ,  ,  ,  , and  .

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -O-, -S-, -NH-, -Se-, $-C_{1-4}$ alkylene-, $-C_{1-6}$ oxaalkylene-, $-C_{1-4}$ thiaalkylene-,

-C_{1-4} azaalkylene-, and -C_{1-4} selenaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen (e.g., fluorine or chlorine), oxo, thio, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom linked thereto form C_{3-6} cycloalkyl, and 3-6-membered heterocyclyl (e.g., oxetanyl); wherein a heteroatom in the heterocyclyl is O, N, or S, and the number of heteroatoms is 1 or 2.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-3} alkylene-, -C_{1-3} oxaalkylene-, -C_{1-3} thiaalkylene-, and -C_{1-3} azaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy; preferably, wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -C_{1-2} alkylene-, -C_{1-2} oxaalkylene-, -C_{1-2} thiaalkylene-, and -C_{1-2} azaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo.

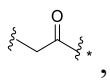
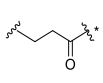
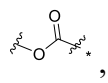
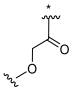
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-3} alkylene-, and -C_{1-3} oxaalkylene-; wherein the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy; preferably, the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -C_{1-2} alkylene-, -C_{1-3} oxaalkylene-, and -C_{1-3} azaalkylene-; wherein the alkylene, oxaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from oxo.

In one embodiment of the invention, when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one heteroatom

or heteroatom group is comprised, and the heteroatom or heteroatom group is selected from -O-, -S-, -Se-, -NH-, -CO-, and -C(S)-;.

In one embodiment of the invention, when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one heteroatom or heteroatom group is comprised, and the heteroatom or heteroatom group is selected from -CO- or -C(S)-.

In one embodiment of the invention, when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one group selected from  ,  , ,  , or  , preferably , is comprised; * represents the linking end to A.

In one embodiment of the invention, when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one heteroatom or heteroatom group is comprised, and the heteroatom or heteroatom group is selected from -O-, -NH-, and -CO-.

In one embodiment of the invention, when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, 1-4 heteroatoms or heteroatom groups are comprised, the heteroatom or heteroatom group is selected from -O-, -S-, -Se-, -NH-, -CO-, and -C(S)-, and the number of heteroatoms or heteroatom groups is specifically 1, 2, 3, or 4; preferably 1-3 heteroatoms or heteroatom groups are comprised, specifically 1, 2, or 3; or preferably 2-4 heteroatoms or heteroatom groups are comprised, specifically 2, 3, or 4; further preferably 2 or 3 heteroatoms or heteroatom groups are comprised; the heteroatom or heteroatom group is preferably -O-, -S-, -NH-, or -CO-; the heteroatom or heteroatom group is more preferably -O- or -CO-; preferably, the heteroatom or heteroatom group at least contains -CO- or -C(S)-.

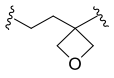
In one embodiment of the invention, Z_{21} contains a heteroatom or heteroatom group selected from -O-, -S-, -Se-, and -NH-; and Z_{31} contains a heteroatom or heteroatom group selected from -CO- and -C(S)-; and the total number of the heteroatoms or heteroatom groups in the combination of Z_{21} and Z_{31} is 1-4;

In one embodiment of the invention, when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, 1-4, preferably 1-3 and more preferably 2-3 heteroatoms or heteroatom groups are comprised, and the heteroatom or heteroatom group is selected from -O-, -NH-, and -CO-; preferably, the heteroatom or heteroatom group at least contains -CO-.

In one embodiment of the invention, Z_{11}, Z_{21}, and Z_{31} together contain 1-4 heteroatoms or heteroatom groups, wherein the heteroatoms or heteroatom groups are selected from -O-, -NH-, -CO-, and the number of heteroatoms or heteroatom groups is 1, 2, 3, and 4.

In one embodiment of the invention, Z_{11}, Z_{21}, and Z_{31} together contain 1-3 heteroatoms or heteroatom groups, wherein the heteroatoms or heteroatom groups are selected from -O-, -NH-, and -CO-, specifically 1, 2, and 3.

In one embodiment of the invention, Z_{11}, Z_{21}, and Z_{31} together contain 2-3 heteroatoms or heteroatom groups, wherein the heteroatoms or heteroatom groups are selected from -O-, -NH-, and -CO-, and the number of heteroatoms or heteroatom groups is 2 and 3; preferably, the heteroatoms or heteroatom groups contain at least -CO-.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31},and Z_{32} is independently selected from -CD_2-, -C_{1-4} alkylene-, -OC_{1-3} alkylene-, -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-2} alkylene-O-C_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, -C_{1-3} alkylene-C(S)-, -Se-C_{1-3} alkylene-,  , and ; wherein the alkylene, methylene, and ethylene are optionally substituted by one or more substituents independently selected from deuterium, fluorine, and chlorine.

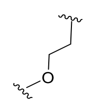
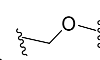
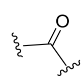
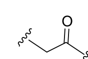
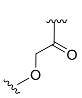
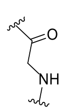
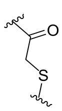
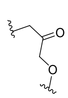
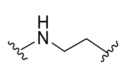
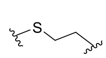
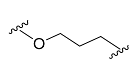
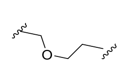
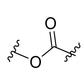
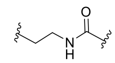
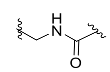
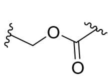
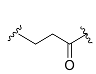
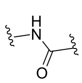
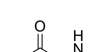
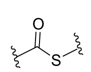
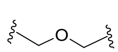
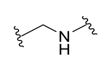
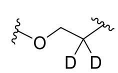
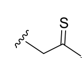
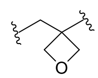
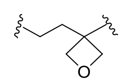
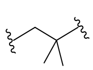
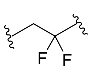
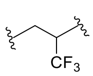
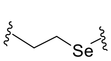
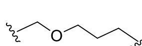
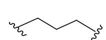
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -CD_2-, -C_{1-3} alkylene-, -OC_{1-3} alkylene-, -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-3} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-O-C_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-.

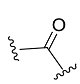
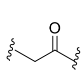
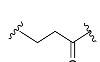
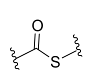
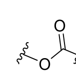
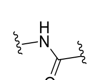
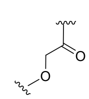
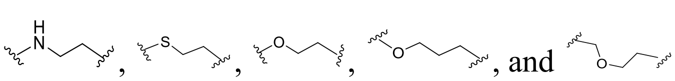
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -CD_2-, -C_{1}-$_{3}$ alkylene-, -OC_{1}-$_{3}$ alkylene-, -C(O)-, -C_{1}-$_{3}$ alkylene-C(O)-, -OC_{1}-$_{3}$ alkylene-C(O)-, -NH-C_{1}-$_{3}$ alkylene-C(O)-, -S-C_{1}-$_{3}$ alkylene-C(O)-, and -O-C_{1}-$_{3}$ alkylene-C(O)-C_{1}-$_{3}$ alkylene-.

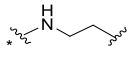
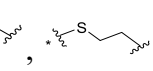
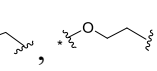
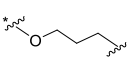
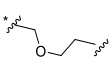
In a preferred embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -C_{1}-$_{3}$ alkylene-, -OC_{1}-$_{3}$ alkylene-, -C_{1}-$_{3}$ alkylene-C(O)-, -OC_{1}-$_{3}$ alkylene-C(O)-, -NH-C(O)-, and -O-C(O)-.

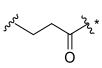
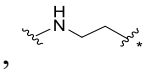
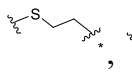
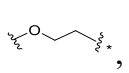
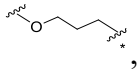
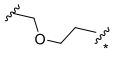
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -CD_2-, -$C_{1\text{-}2}$ alkylene-, -$OC_{1\text{-}3}$ alkylene-, -C(O)-, -$C_{1\text{-}2}$ alkylene-C(O)-, -$OC_{1\text{-}2}$ alkylene-C(O)-, -NH-$C_{1\text{-}2}$ alkylene-C(O)-, -S-$C_{1\text{-}2}$ alkylene-C(O)-, -O-$C_{1\text{-}2}$ alkylene-C(O)-$C_{1\text{-}2}$ alkylene-, -$C_{1\text{-}2}$ alkylene-O-$C_{1\text{-}2}$ alkylene-, -NH-$C_{1\text{-}2}$ alkylene-, -S-$C_{1\text{-}2}$ alkylene-, -$C_{1\text{-}2}$ alkylene-NH-C(O)-, -$C_{1\text{-}2}$ alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-.

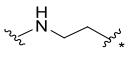
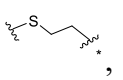
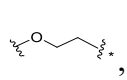
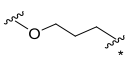
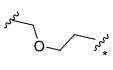
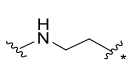
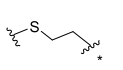
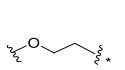
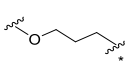
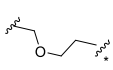
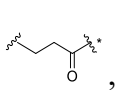
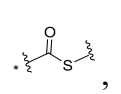
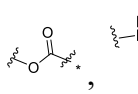
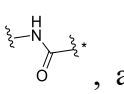
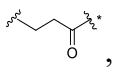
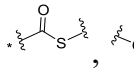
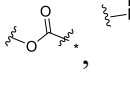
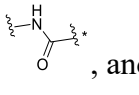
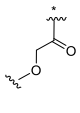
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -CD_2-, -$C_{1\text{-}2}$ alkylene-, -$OC_{1\text{-}2}$ alkylene-, -C(O)-, -$C_{1\text{-}2}$ alkylene-C(O)-, -$OC_{1\text{-}2}$ alkylene-C(O)-, -NH-$C_{1\text{-}2}$ alkylene-C(O)-, -S-$C_{1\text{-}2}$ alkylene-C(O)-, and -O-$C_{1\text{-}2}$ alkylene-C(O)-$C_{1\text{-}2}$ alkylene-.

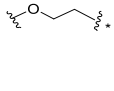
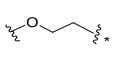
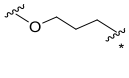
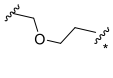
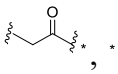
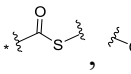
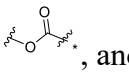
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, methylene, ethylene, -CD_2-, -O-, -S-, -NH-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from methylene, ethylene,  ,  ,  ,  ,  ,  ,  ,  .

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from methylene, ethylene, , , , , , , ,  ,  ,  ,  , and  ; * represents the linking end to A.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from methylene, ethylene, -CD_2-, , ,  , , , , ,  ,  ,  ,  , and  ; * represents the linking end to A.

In one embodiment of the invention, each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, and -CD_2, and Z_{11} is selected from methylene, ethylene, -CD_2-,  ,  ,  ,  , and  ; and Z_{21} is selected from methylene, ethylene, -CD_2-,  ,  ,  ,  , and  ; and Z_{31} is selected from , ,  ,  ,  ,  , and ; further preferably Z_{31} is selected from ,  ,  ,  ,  , and  ; * represents the linking end to A.

In one embodiment of the invention, each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, -CD_2, and Z_{11} is selected from methylene, ethylene, -CD_2-, and  ; and Z_{21} is selected from methylene, ethylene, -CD_2-,  ,  , and  ; and Z_{31} is selected from  ,  ,  , and ; * represents the linking end to A.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from methylene, ethylene, , , , , , and .

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from -CD_2- and methylene, preferably methylene.

In one embodiment of the invention, each of Z_{12}, Z_{22}, and Z_{32} is independently selected from -CD_2-, methylene, and ethylene.

In one embodiment of the invention, Z_{12}, Z_{22}, and Z_{32} are all -CD_2- or methylene, preferably methylene.

In one embodiment of the invention, Z_{11} is selected from -CD_2-, -C_{1-3} alkylene- and -OC_{1-3} alkylene-, and preferably -C_{1-3} alkylene-; preferably, Z_{11} is selected from -CD_2-, methylene, ethylene, methyleneoxy, and ethyleneoxy, and more preferably methylene.

In one embodiment of the invention, Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; preferably -OC_{1-3} alkylene-, -NH-C_{1-2} alkylene-, -S-C_{1-2} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-.

In one embodiment of the invention, Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-; preferably, Z_{31} is selected from -C(O)-, -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-, preferably -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-; and preferably -CH_2C(O)-.

In one embodiment of the invention, Z_{11} is independently selected from -OC_{1-3} alkyl-, -NH-C_{1-3} alkyl-, -S-C_{1-3} alkyl-, -Se-C_{1-3} alkyl-, and -C_{1-3} alkyl-O-C_{1-3} alkyl-; and Z_{21} is independently selected from -OC_{1-3} alkyl-, -NH-C_{1-3} alkyl-, -S-C_{1-3} alkyl-, -Se-C_{1-3} alkyl-, and -C_{1-3} alkyl-O-C_{1-3} alkyl-.

In one embodiment of the invention, Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkyl-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-.

In one embodiment of the invention, Z_{11} is selected from -CD_2, -C_{1-3} alkylene-, and -OC_{1-3} alkylene-; and Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-

C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-.

In one embodiment of the invention, Z_{11} is selected from -CD_2-, -C_{1-3} alkylene- and -OC_{1-3} alkylene-; and Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-.

In one embodiment of the invention, Z_{11} is selected from -C_{1-3} alkylene- and -OC_{1-3} alkylene-; and Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-.

In one embodiment of the invention, Z_{11} is selected from -CD_2, -C_{1-3} alkylene-, and -OC_{1-3} alkylene-*; and Z_{21} is selected from -OC_{1-3} alkylene-*, -NH-C_{1-3} alkylene-*, -S-C_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -C_{1-2} alkylene-O-C_{1-3} alkylene-*; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-3} alkylene-C(O)-*, -NH-C_{1-3} alkylene-C(O)-*, -S-C_{1-3} alkylene-C(O)-*, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-*, -C_{1-3} alkylene-NH-C(O)-*, -C_{1-3} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-3} alkylene-C(S)-*; * represents the linking end to A.

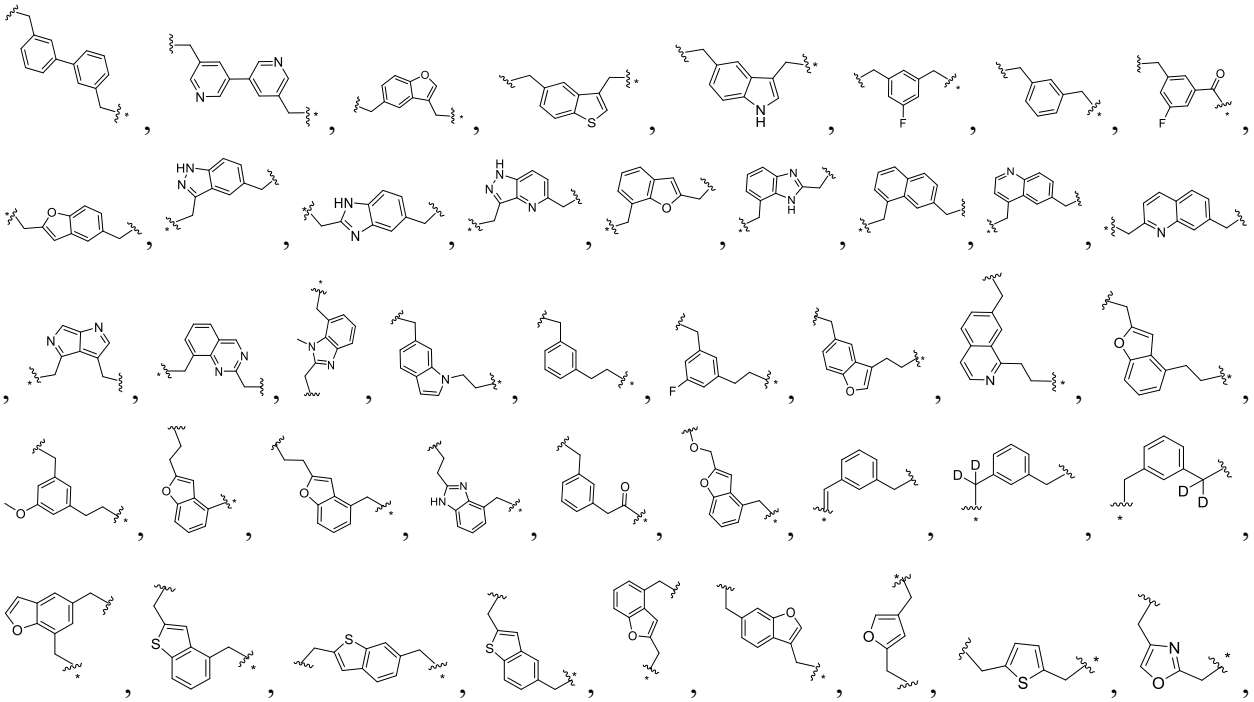
In one embodiment of the invention, Z_{11} is selected from -CD_2-, -C_{1-3} alkylene- and -OC_{1-3} alkylene-*; and Z_{21} is selected from -OC_{1-3} alkylene-*, -NH-C_{1-3} alkylene-*, -S-C_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -C_{1-2} alkylene-O-C_{1-3} alkylene-*; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-3} alkylene-C(O)-*, -NH-C_{1-3} alkylene-C(O)-*, -S-C_{1-3} alkylene-C(O)-*, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-*, -C_{1-3} alkylene-NH-C(O)-*, -C_{1-3} alkylene-O-C(O)-*, -NH-C(O)- *, -O-C(O)-*, -S-C(O)-*, and -C_{1-3} alkylene-C(S)-*; * represents the linking end to A.

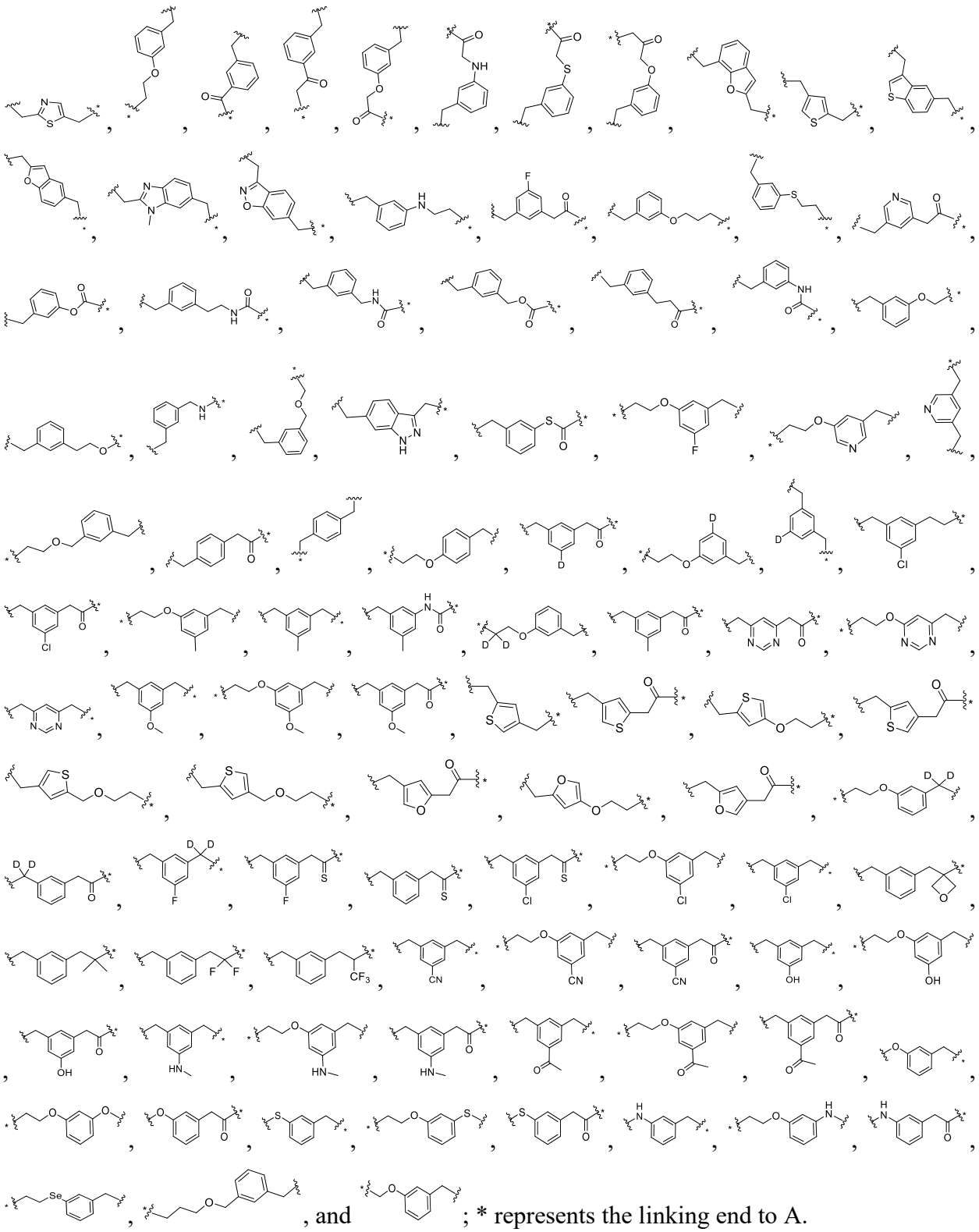
In one embodiment of the invention, Z_{11} is selected from -C_{1-3} alkylene- and -OC_{1-3} alkylene-*; and Z_{21} is selected from -OC_{1-3} alkylene-*, -NH-C_{1-3} alkylene-*, -S-C_{1-3} alkylene-*, -

Se-C_{1-3} alkylene-*, and -C_{1-2} alkylene-O-C_{1-3} alkylene-*; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-3} alkylene-C(O)-*, -NH-C_{1-3} alkylene-C(O)-*, -S-C_{1-3} alkylene-C(O)-*, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-*, -C_{1-3} alkylene-NH-C(O)-*, -C_{1-3} alkylene-O-C(O)-*, -NH-C(O)- *, -O-C(O)-*, -S-C(O)-*, and -C_{1-3} alkylene-C(S)- *; * represents the linking end to A.

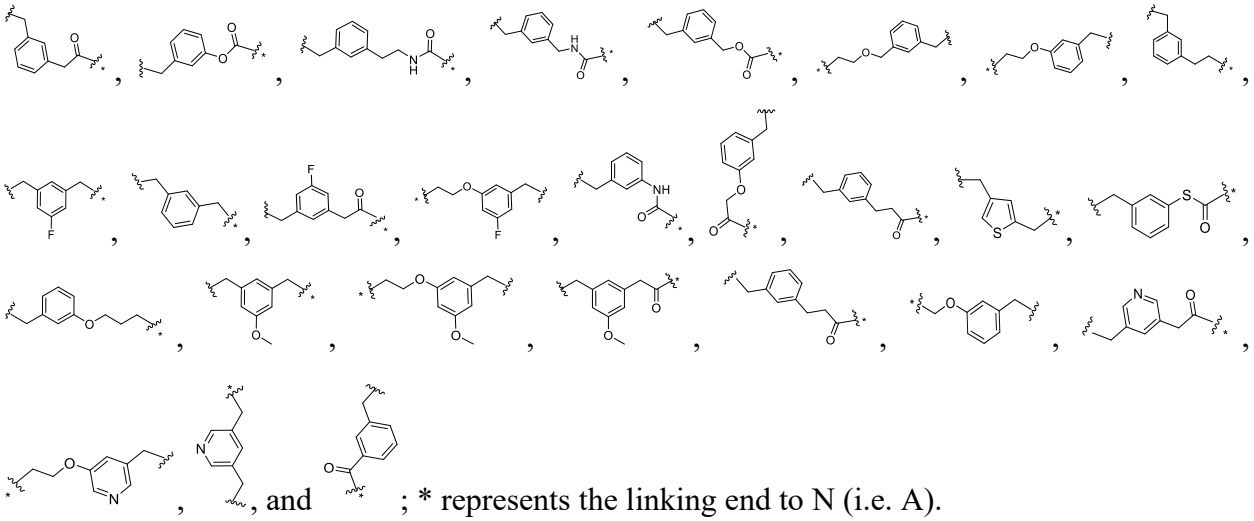
In one embodiment of the invention, Z_{11} is selected from -CD_2-, -C_{1-2} alkylene-, and -OC_{1-2} alkylene-*; and Z_{21} is selected from -OC_{1-2} alkylene-*, -NH-C_{1-2} alkylene-*, -S-C_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*; and Z_{31} is selected from -C(O)-, -C_{1-2} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -NH-C_{1-2} alkylene-C(O)-*, -S-C_{1-2} alkylene-C(O)-*, -C_{1-2} alkylene-NH-C(O)-*, -C_{1-2} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*; further preferably, Z_{31} is selected from -C_{1-2} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -NH-C_{1-2} alkylene-C(O)-*, -S-C_{1-2} alkylene-C(O)-*, -C_{1-2} alkylene-NH-C(O)-*, -C_{1-2} alkylene-O-C(O)-*, -CH_2NH-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*; further preferably, Z_{31} is selected from -C_{1-2} alkylene-C(O)-*, -OCH_2-C(O)-*, -CH_2-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, and -S-C(O)-*; further preferably, Z_{31} is selected from -CH_2C(O)-*; * represents the linking end to A.

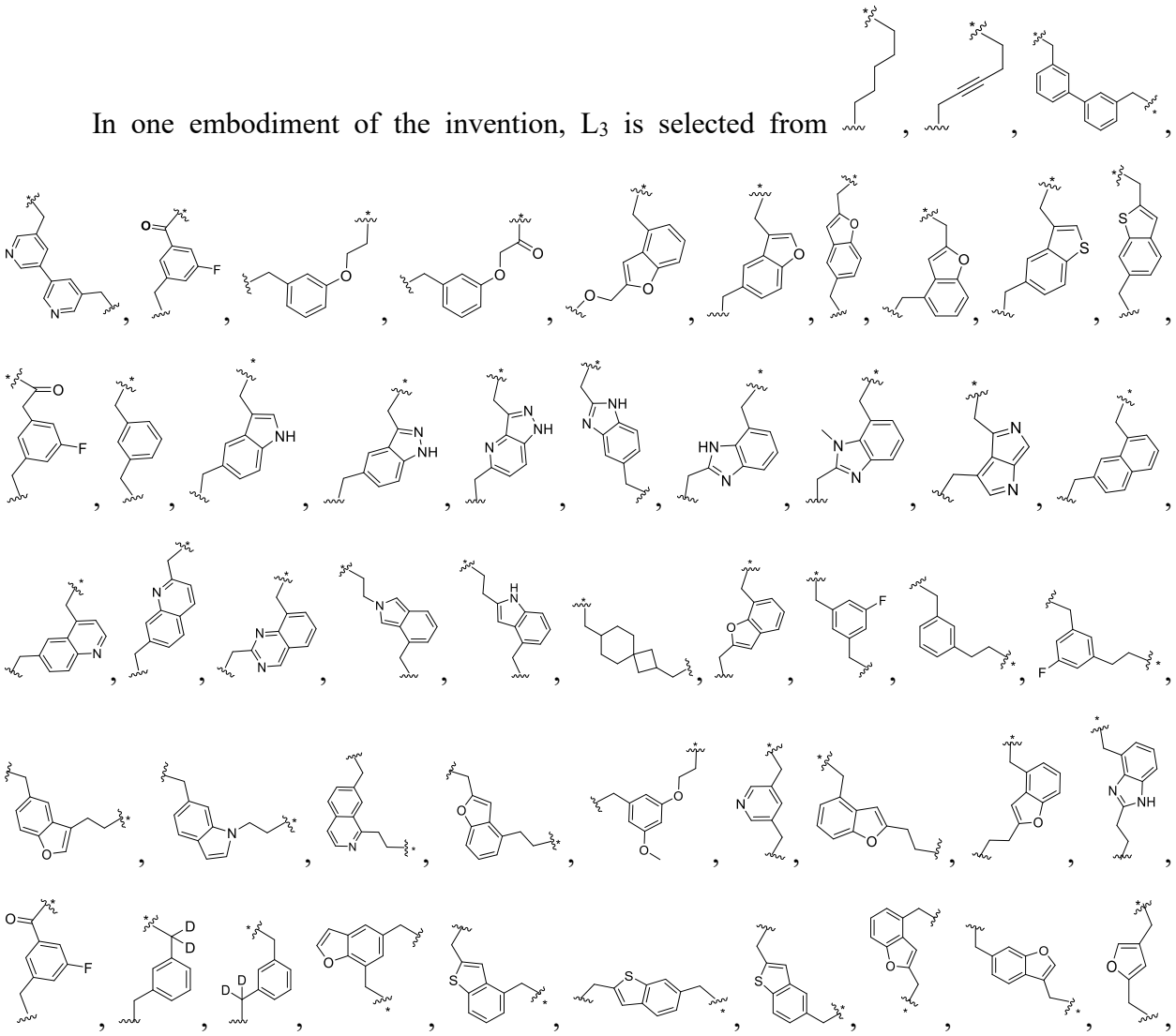
In one embodiment of the invention, each of L_1 and L_2 is independently selected from

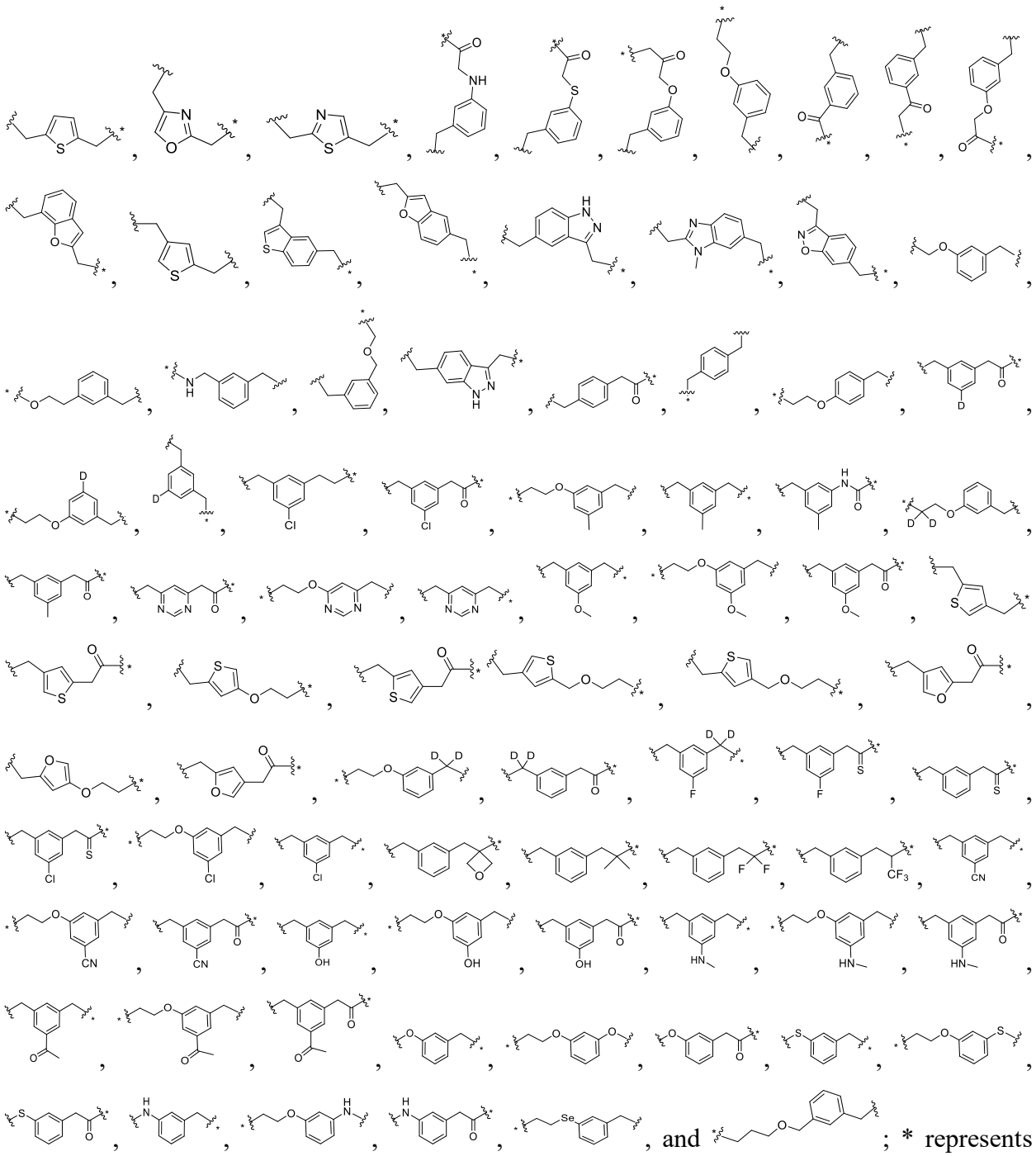




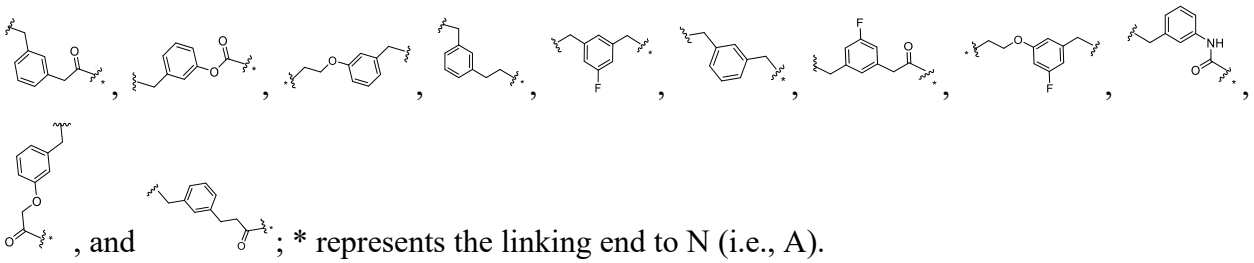
; * represents the linking end to A.

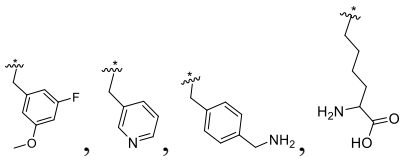
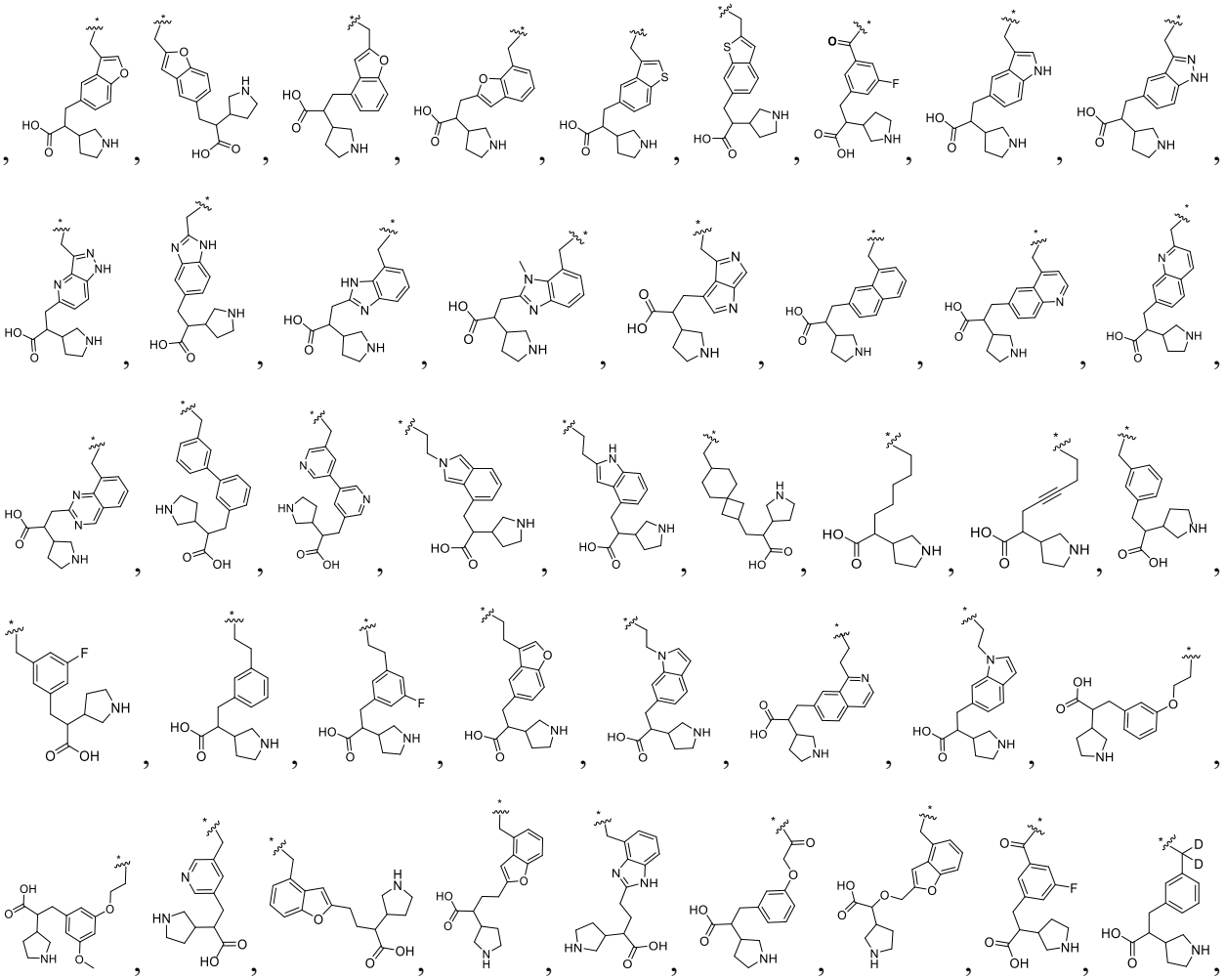
In one embodiment of the invention, each of L_1 and L_2 is independently selected from  ; * represents the linking end to N (i.e. A).

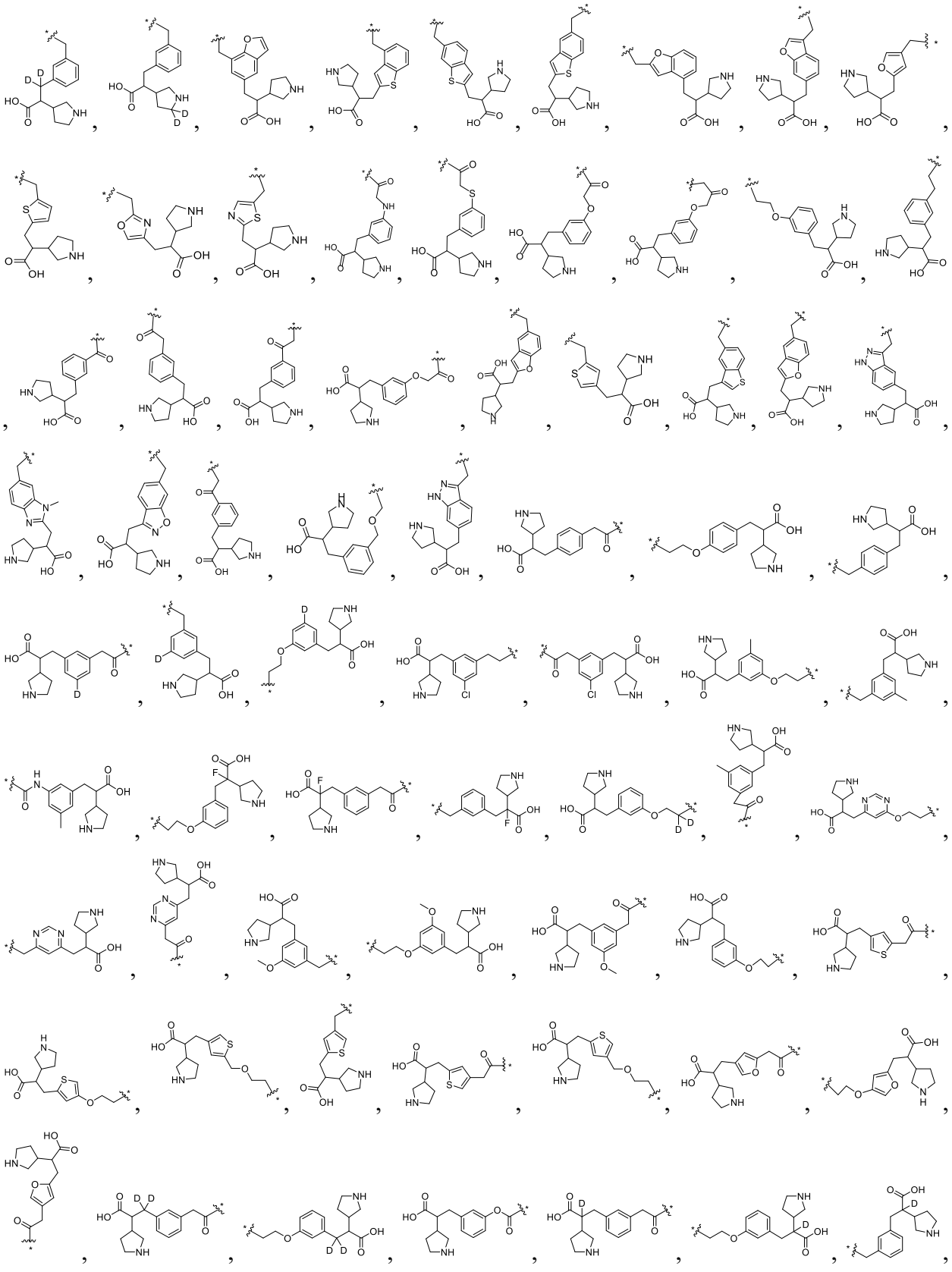
In one embodiment of the invention, L_3 is selected from 

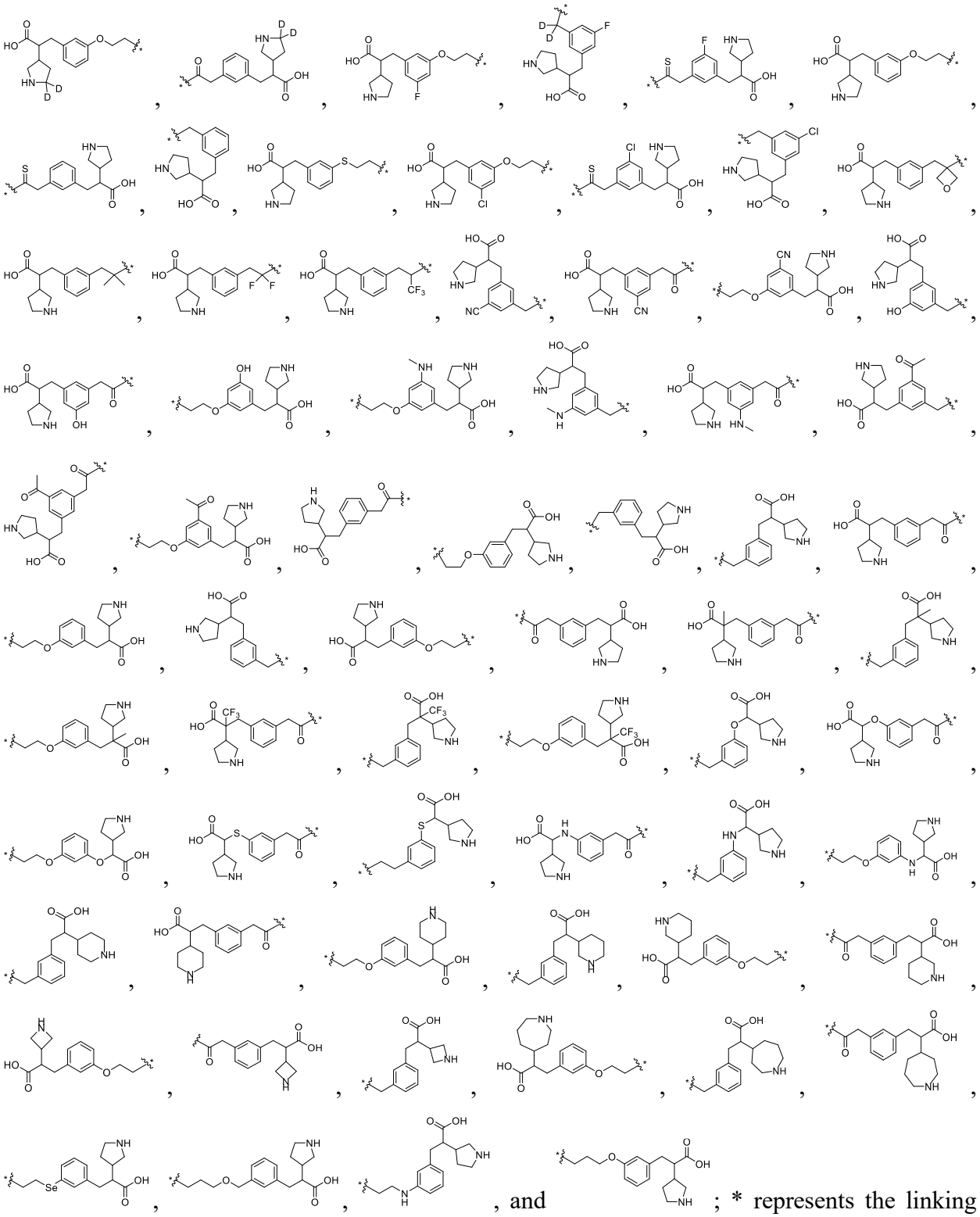


; * represents the linking end to A.

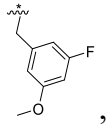
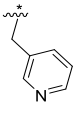
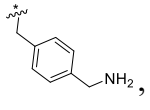
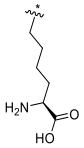
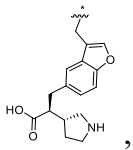
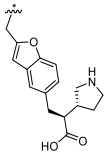
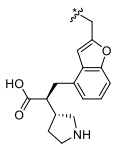
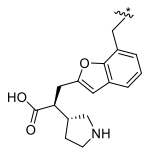
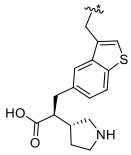
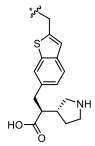
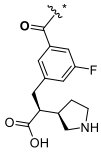
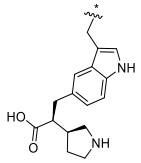
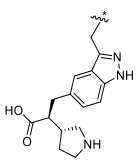
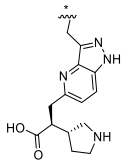
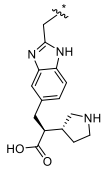
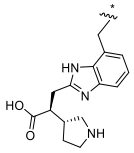
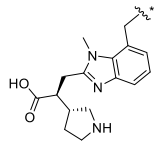
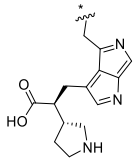
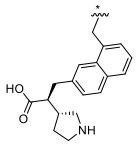
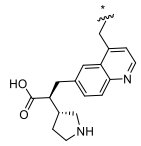
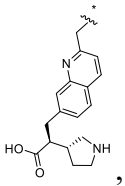
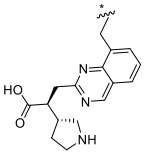
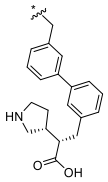
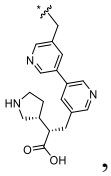
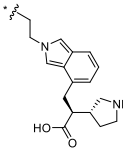
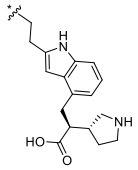
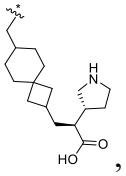
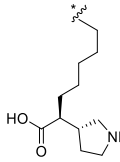
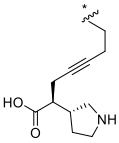
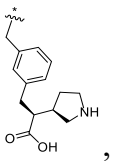
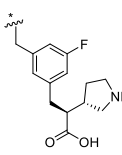
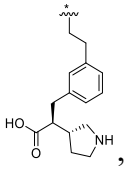
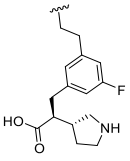
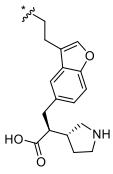
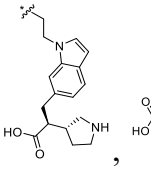
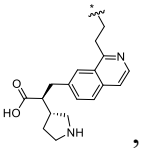
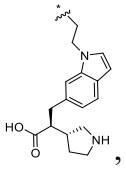
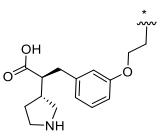
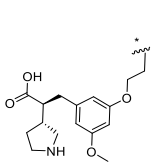
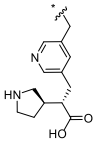
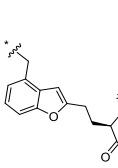
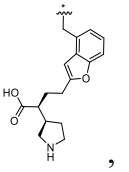
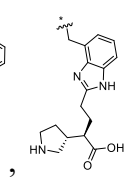
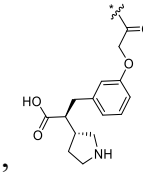
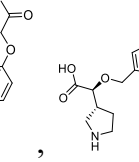
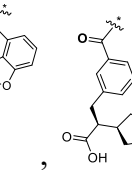
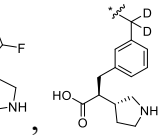
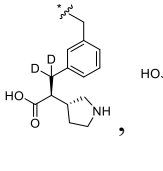
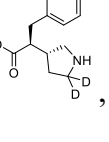
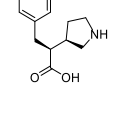
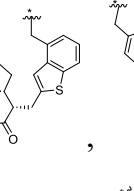
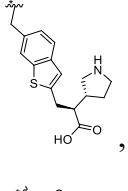
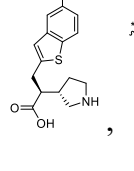
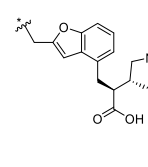
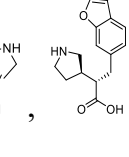
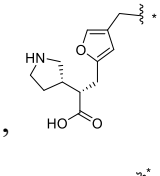
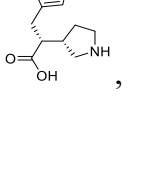
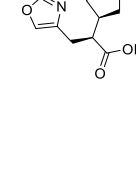
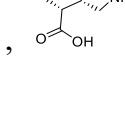
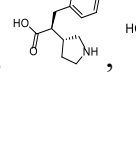
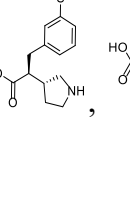
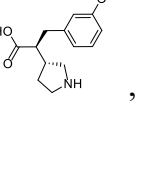
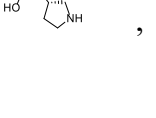
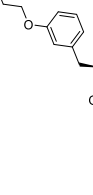
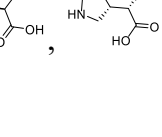
In one embodiment of the invention, each of L_1, L_2, and L_3 is independently selected from  , and ; * represents the linking end to N (i.e., A).

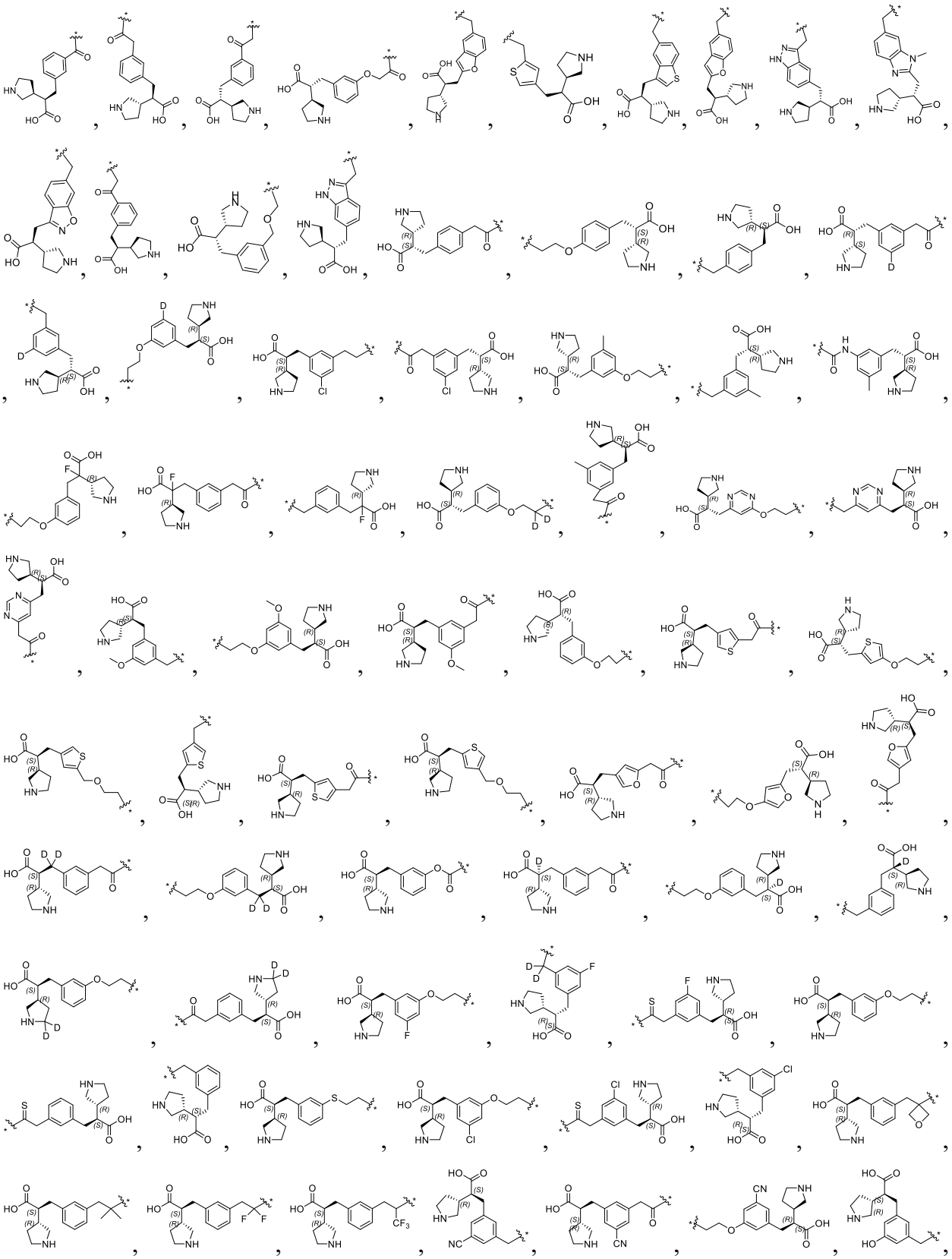
In one embodiment of the invention, R is selected from H,  , 

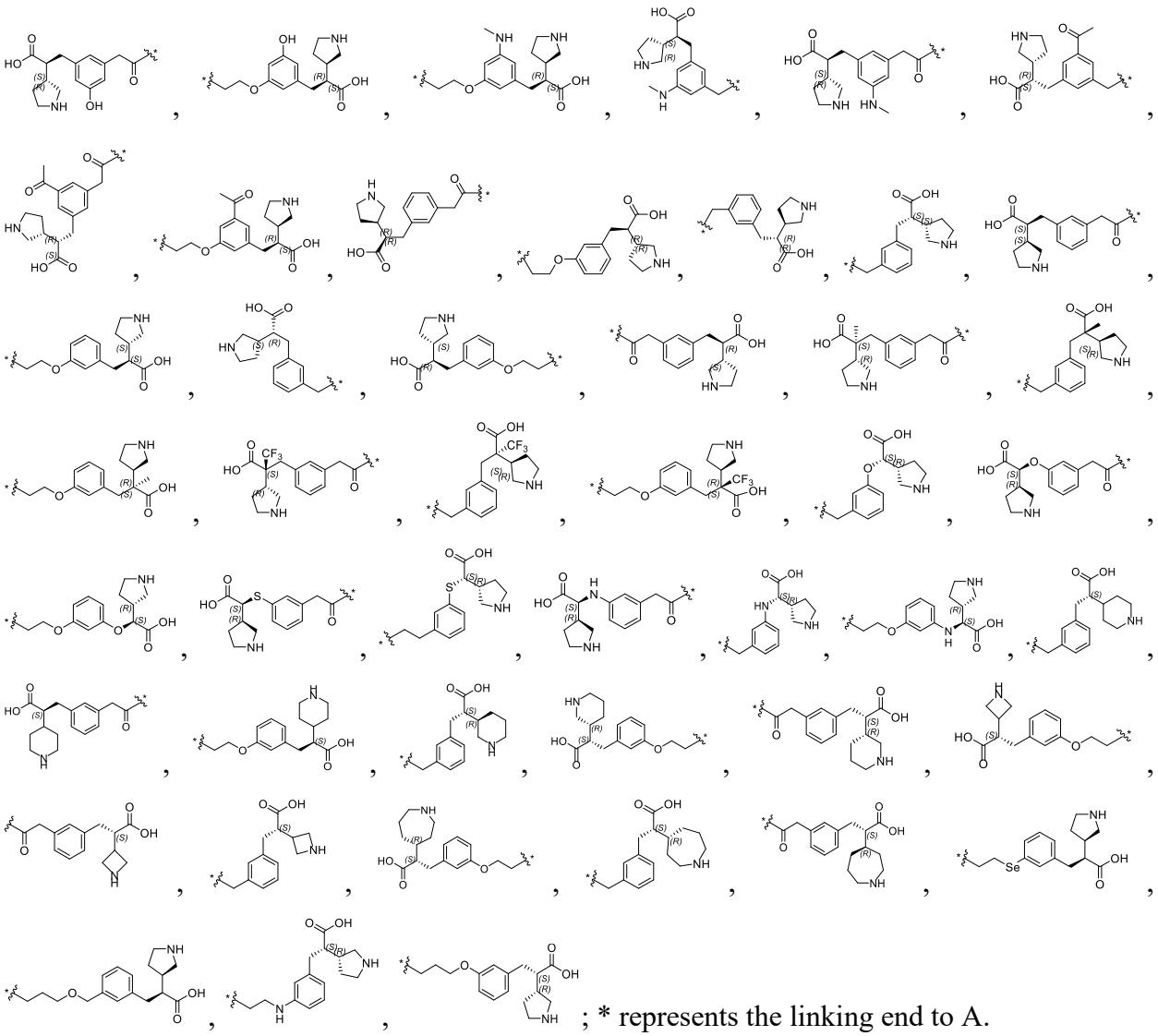




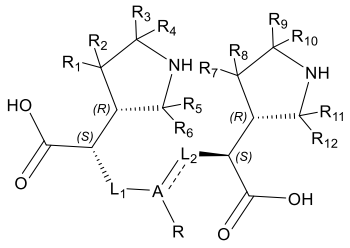
; * represents the linking end to A.

In one embodiment of the invention, R is selected from H,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , , , , .

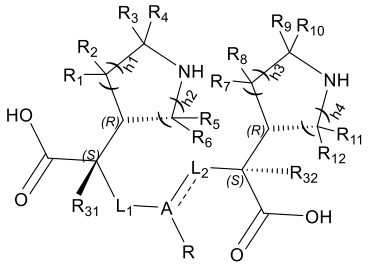



; * represents the linking end to A.

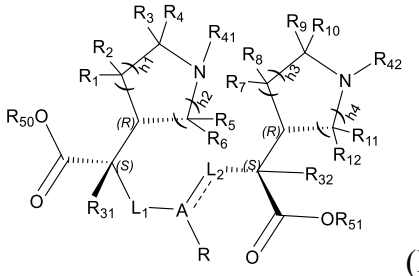
Firstly, the invention provides a compound represented by the following Formula (I'-1), Formula (I'-2), or Formula (I'-3) or a pharmaceutically acceptable salt thereof:



(I'-1),



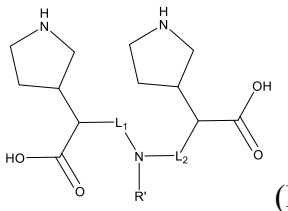
(I'-2),



(I'-3)

wherein A, L_1, L_2, R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{31}, R_{32}, R_{41}, R_{42}, R_{50}, R_{51}, h1, h2, h3, and h4 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), or Formula (I-1-P4).

In an embodiment of the compound represented by the above Formula (I'-1), (I'-2), or (I'-3), R is a group comprising L_3; and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-. The invention further provides a compound represented by the following Formula (II), or a pharmaceutically acceptable salt thereof:

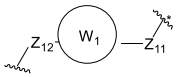


(II)

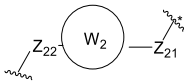
wherein L_1 and L_2 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), or Formula (I-1-P4);

R' is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, and C_{1-6} alkyl; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, R' is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-10-membered heteroaryl, and C_{1-6} alkyl; wherein the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, and -NH_2; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, methoxy, and C_{1-3} aminoalkyl; and wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy;

L_1 is 

; * represents the linking end to N;

L_2 is 

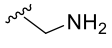
; * represents the linking end to N;

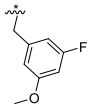
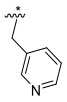
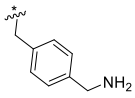
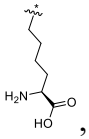
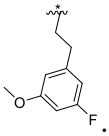
each of the rings W_1 and W_2 is independently selected from C_{6-12} aryl and 5-12-membered heteroaryl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from -C_{1-3} alkylene- and -C_{1-3} oxaalkylene-; wherein the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy.

In one embodiment of the invention, R' is selected from H, -C_{1-3} alkylene-phenyl, -methylene-5-6-membered heteroaryl, and C_{1-6} alkyl; wherein the methylene and C_{1-3} alkylene are

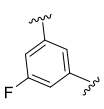
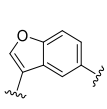
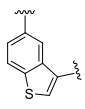
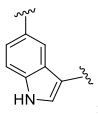
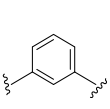
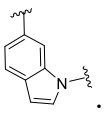
optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, oxo, carboxyl, -CN, -OH, $-NH_2$, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, R' is selected from H, -methylene-phenyl, -ethylene-phenyl, -methylene-pyridinyl, C_{1-6} alkyl; wherein the phenyl and pyridinyl are optionally substituted by one or more substituents independently selected from halogen, -CN, methoxy, and  ; wherein the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from carboxyl and $-NH_2$.

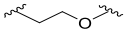
In one embodiment of the invention, R' is selected from H,  ,  ,  ,  , and  .

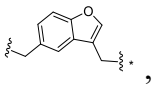
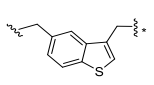
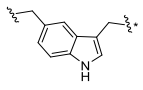
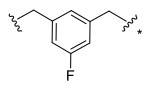
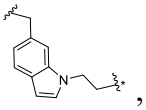
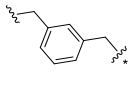
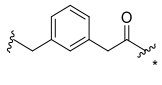
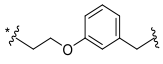
In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from phenyl and 5-12-membered heteroaryl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen and -CN.

In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from phenyl and 8-10-membered bicyclic heteroaryl; wherein the phenyl and bicyclic heteroaryl are optionally substituted by one or more substituents independently selected from halogen and -CN; wherein the heteroatoms in the bicyclic heteroaryl are independently selected from O, N, or S, and the number of heteroatoms is 1 or 2.

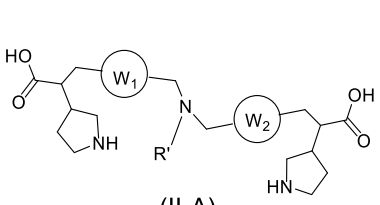
In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from  ,  ,  ,  ,  , and  .

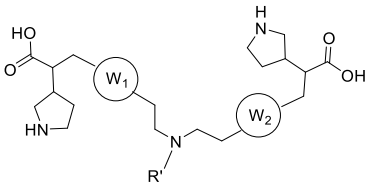
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from -C_{1-3} alkylene- and -C_{1-3} oxaalkylene-; wherein the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo.

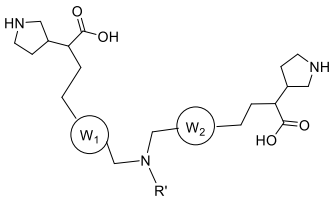
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from methylene, ethylene, , and  .

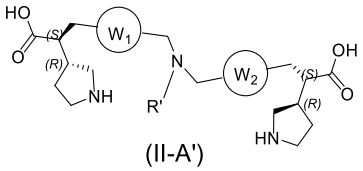
In one embodiment of the invention, each of L_1 and L_2 is independently selected from  ,  ,  ,  ,  ,  ,  , and  ; * represents the linking end to N.

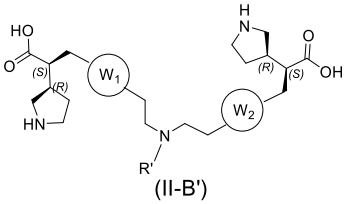
The invention further provides a compound represented by the following Formula (II-A), (II-B), (II-C), (II-A'), (II-B'), or (II-C'), or a pharmaceutically acceptable salt thereof:

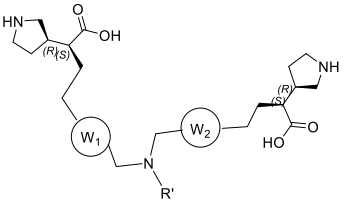

(II-A),


(II-B),


(II-C),

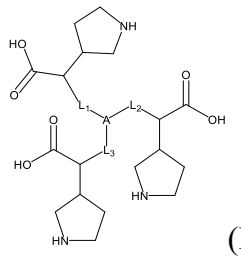

(II-A'),


(II-B'), and


(II-C'),

wherein W_1, W_2, and R' are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), or Formula (II).

The invention further provides a compound represented by the following Formula (III), or a pharmaceutically acceptable salt thereof:

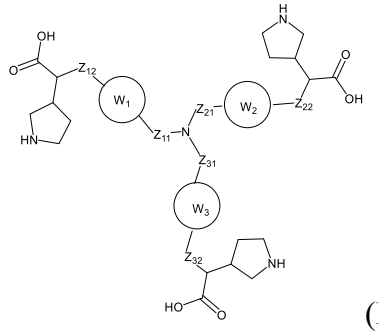


(III)

wherein A, L_1, L_2, and L_3 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), or Formula (I-1-P4).

In an embodiment of the compound represented by the above Formula (III), L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

The invention further provides a compound represented by the following Formula (III-1), or a pharmaceutically acceptable salt thereof:



(III-1)

wherein W_1, W_2, W_3, Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), or Formula (III).

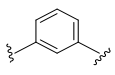
In one embodiment of the invention, each of Z_{12}, Z_{22}, and Z_{32} are independently selected from methylene and ethylene;

each of Z_{11}, Z_{21}, and Z_{31} is independently selected from a bond, -C_{1-4} alkylene-, -C_{1-6} oxaalkylene- (e.g., -C_{1-4} oxaalkylene-), -C_{1-4} thiaalkylene-, -C_{1-4} azaalkylene-, and -C_{1-4} selenaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen (e.g., flourine or chlorine), oxo, thio, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom lined thereto form C_{3-6} cycloalkyl or 3-6-membered heterocyclyl (e.g., oxetanyl); wherein a heteroatom in the heterocyclyl is O, N, or S, and the number of heteroatoms is 1;

each of the rings W_1, W_2, and W_3 is independently selected from phenyl and 5-6-membered monocyclic heteroaryl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl; wherein a heteroatom in the heteroaryl is O, N, or S, and the number of heteroatoms is 1 or 2.

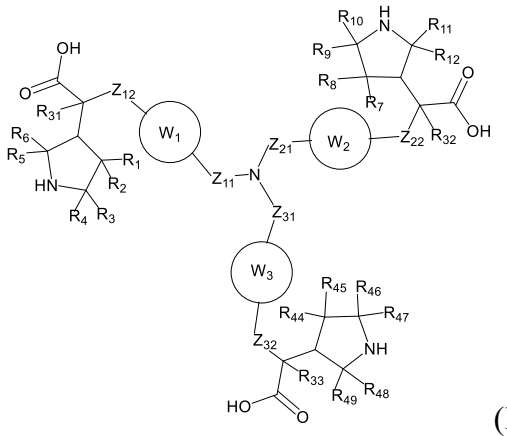
In one embodiment of the invention, Z_{12}, Z_{22}, and Z_{32} are all methylene.

In one embodiment of the invention, when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, 2 or 3 heteroatoms or heteroatom groups are comprised, and the heteroatom or heteroatom group is selected from -O-, -S-, -NH-, and -CO-. In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl and thienyl; the phenyl and thienyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from  , , and ; the groups are optionally substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy.

In an embodiment of the compound represented by the above Formula (III-1), one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

The invention further provides a compound represented by the following Formula (III-2), or a pharmaceutically acceptable salt thereof:



(III-2)

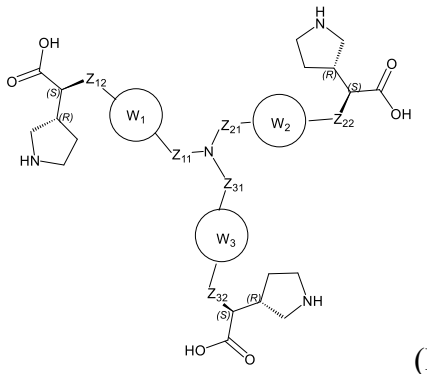
wherein W_1, W_2, W_3, Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, Z_{32}, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{31}, R_{32}, and R_{33} are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), or Formula (III-1).

In one embodiment of the invention, the heteroatom or heteroatom group in Z_{31} comprises -CO- or -C(S)-.

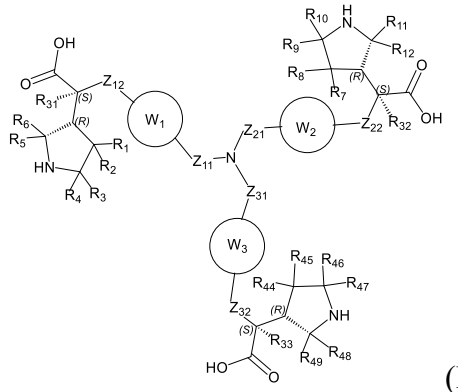
In one embodiment of the invention, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{31}, R_{32}, and R_{33} are selected from hydrogen or deuterium.

In an embodiment of the compound represented by the above Formula (III-2), one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

The invention further provides a compound represented by the following Formula (III-1-1) or Formula (III-2-1), or a pharmaceutically acceptable salt thereof:



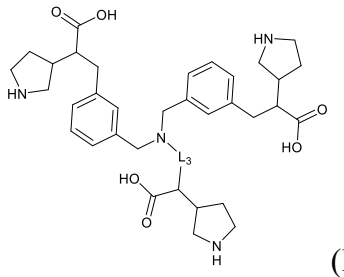
(III-1-1),



(III-2-1),

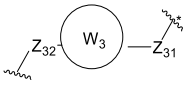
wherein W_1, W_2, W_3, Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, Z_{32}, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{31}, R_{32}, and R_{33} are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), or Formula (III-2).

The invention further provides a compound represented by the following Formula (III-A), or a pharmaceutically acceptable salt thereof:



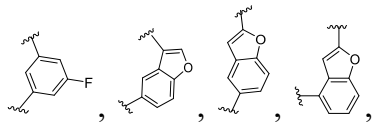
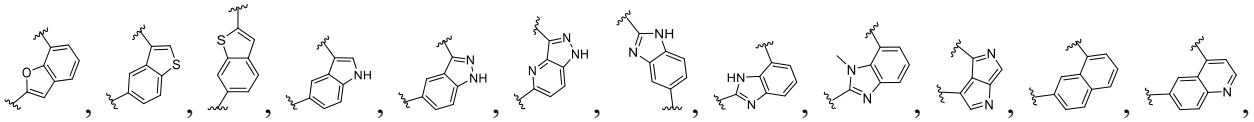
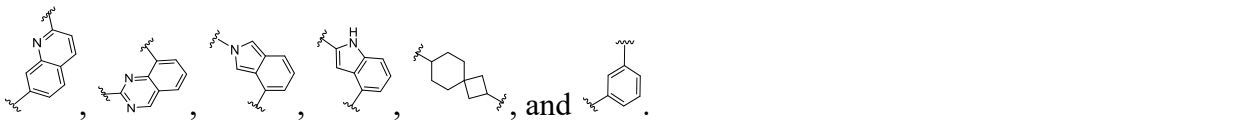
(III-A)

wherein L_3 is defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), or Formula (III-1).

In one embodiment of the invention, L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkynylene-, -methylene-phenyl-phenyl-methylene-, -methylene-6-membered heteroaryl-6-membered heteroaryl-methylene- (e.g., -methylene-pyridinyl-pyridinyl-methylene-), and  ; wherein the alkylene, methylene, and alkynylene are optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, and -NH_2; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * represents the linking end to N.

In one embodiment of the invention, the ring W_3 is selected from phenyl, naphthyl, 8-10-membered bicyclic heteroaryl, and C_{8-10} bicycloalkyl; wherein the phenyl, naphthyl, heteroaryl, and cycloalkyl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, the ring W_3 is selected from phenyl, naphthyl, 5-membered/5-membered fused heteroaryl, 5-membered/6-membered fused heteroaryl, 6-membered/5-membered fused heteroaryl, 6-membered/6-membered fused heteroaryl, 4-membered/6-membered spirocycloalkyl, and 6-membered/4-membered spirocycloalkyl; wherein the phenyl, naphthyl, fused heteroaryl, and spirocycloalkyl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy.

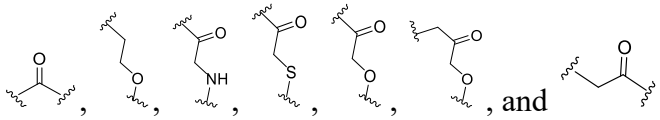
In one embodiment of the invention, W_3 is selected from  ,  ,  , and .

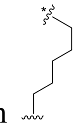
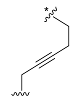
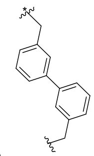
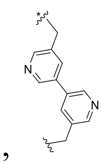
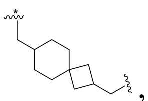
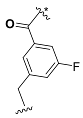
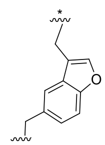
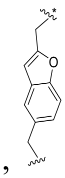
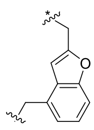
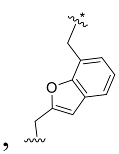
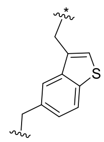
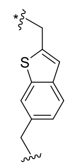
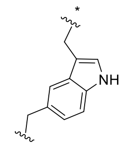
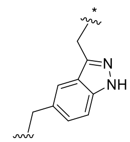
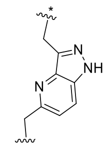
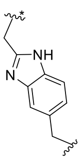
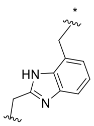
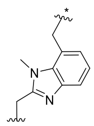
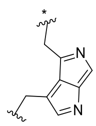
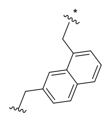
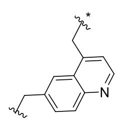
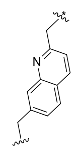
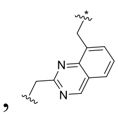
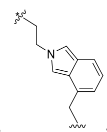
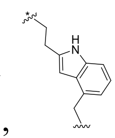
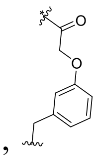
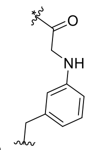
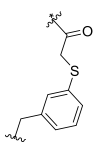
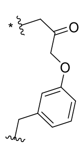
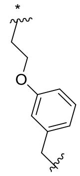
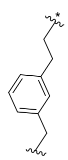
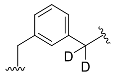
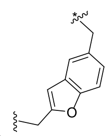
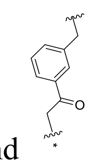
In one embodiment of the invention, each of Z_{31} and Z_{32} is independently selected from -C_{1-3} alkylene-, -C_{1-3}oxaalkylene-, -C_{1-3}thiaalkylene-, and -C_{1-3} azaalkylene-; preferably, each of Z_{31} and Z_{32} is independently selected from -C_{1-2} alkylene-, -C_{1-2} oxaalkylene-, -C_{1-2} thiaalkylene-, and -C_{1-2} azaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo.

In one embodiment of the invention, each of Z_{31} and Z_{32} is independently selected from -CD_2-, -C_{1-2} alkylene-, -OC_{1-2} alkylene-, -C(O)-, -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C_{1-2} alkylene-C(O)-, -S-C_{1-2} alkylene-C(O)-, and -O-C_{1-2} alkylene-C(O)-C_{1-2} alkylene-.

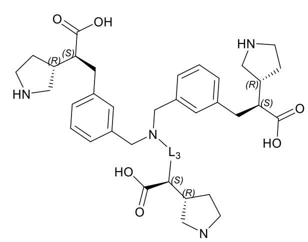
In one embodiment of the invention, each of Z_{31} and Z_{32} is independently selected from -C_{1-3} alkylene- and -C_{1-3} oxaalkylene-; wherein the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy.

In one embodiment of the invention, each of Z_{31} and Z_{32} is independently selected from -C_{1-3} alkylene-; wherein the alkylene is optionally substituted by one or more substituents independently selected from deuterium and oxo.

In one embodiment of the invention, each of Z_{31} and Z_{32} is independently selected from methylene, ethylene, -CD_2-,  , and .

In one embodiment of the invention, L_3 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; * represents the linking end to N.

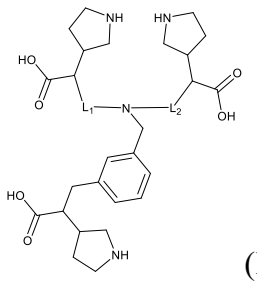
The invention further provides a compound represented by the following Formula (III-A'), or a pharmaceutically acceptable salt thereof:



(III-A')

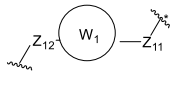
wherein L_3 is defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), or Formula (III-A).

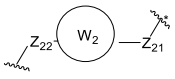
The invention further provides a compound represented by the following Formula (III-B), or a pharmaceutically acceptable salt thereof:



(III-B)

wherein L_1 and L_2 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), or Formula (III-1).

In one embodiment of the invention, L_1 is  and * represents the linking end to N.

In one embodiment of the invention, L_2 is  and * represents the linking end to N.

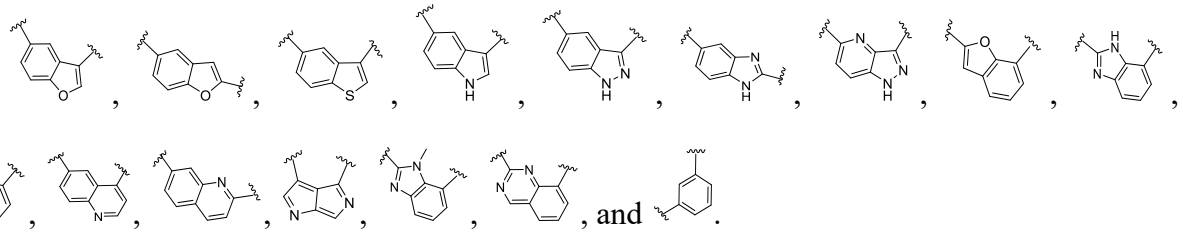
In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from C_{6-12} aryl and 5-12-membered heteroaryl; wherein the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from phenyl, C_{8-12}aryl, and 7-12-membered heteroaryl; wherein the phenyl, aryl, and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, methyl, and methoxy.

In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from phenyl, naphthyl, and 8-10-membered bicyclic heteroaryl; wherein the phenyl, naphthyl, and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from phenyl, naphthyl, 5-membered/5-membered fused heteroaryl, 5-membered/6-membered fused heteroaryl, 6-membered/5-membered fused heteroaryl, and 6-membered/6-membered fused heteroaryl; wherein the phenyl, naphthyl, and fused heteroaryl are optionally substituted by one or

more substituents independently selected from fluorine, chlorine, bromine, -CN, methyl, ethyl, methoxy, and ethoxy.

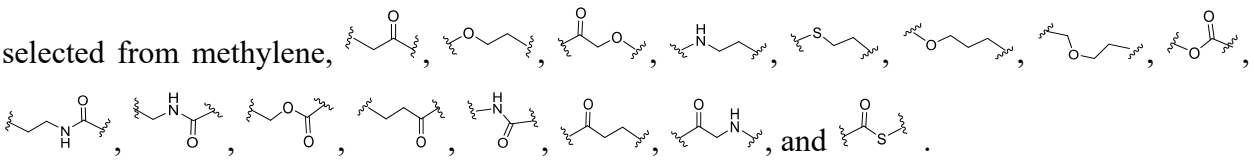
In one embodiment of the invention, each of the rings W_1 and W_2 is independently selected from  .

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from -C_{1-3} alkylene-, -C_{1-3}oxaalkylene-, -C_{1-3}thiaalkylene-, and -C_{1-3} azaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from -C_{1-3} alkylene- and -C_{1-3} oxaalkylene-; wherein the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy.

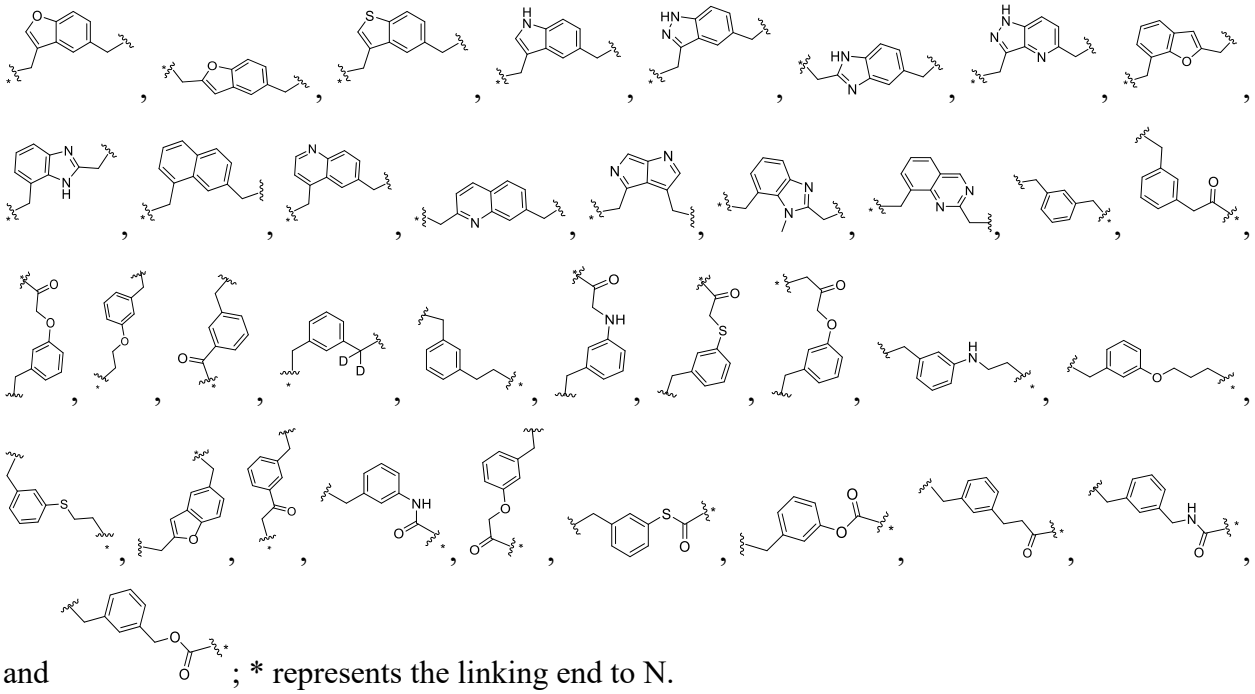
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from -C_{1-2} alkylene-, -C_{1-2} oxaalkylene-, -C_{1-2} thiaalkylene-, and -C_{1-2} azaalkylene-; wherein the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from methylene.

In a preferred embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from methylene,  .

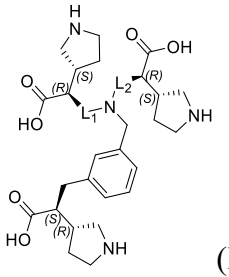
For example, L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, one and only one of Z_{11} and Z_{21} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; preferably, the double bond is for example a double bond between C and O in -C(O)-; further preferably, neither Z_{11} nor Z_{21} is methylene, or a group not containing the double bond of Z_{11} and Z_{21} contains -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11} and Z_{21} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

In one embodiment of the invention, each of L_1 and L_2 is independently selected from

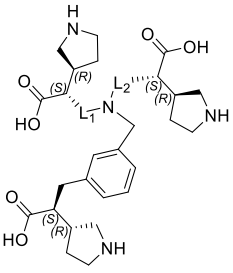


and ; * represents the linking end to N.

The invention further provides a compound represented by the following Formula (III-B') or Formula (III-B'-1), or a pharmaceutically acceptable salt thereof:



(III-B'),

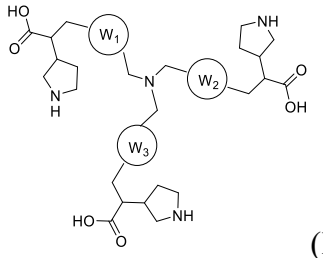


(III-B'-1),

wherein L_1 and L_2 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), or Formula (III-B).

For example, L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, one and only one of Z_{11} and Z_{21} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, neither Z_{11} nor Z_{21} is methylene, or a group not containing the double bond of Z_{11} and Z_{21} contains -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11} and Z_{21} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

The invention further provides a compound represented by the following Formula (III-C), or a pharmaceutically acceptable salt thereof:

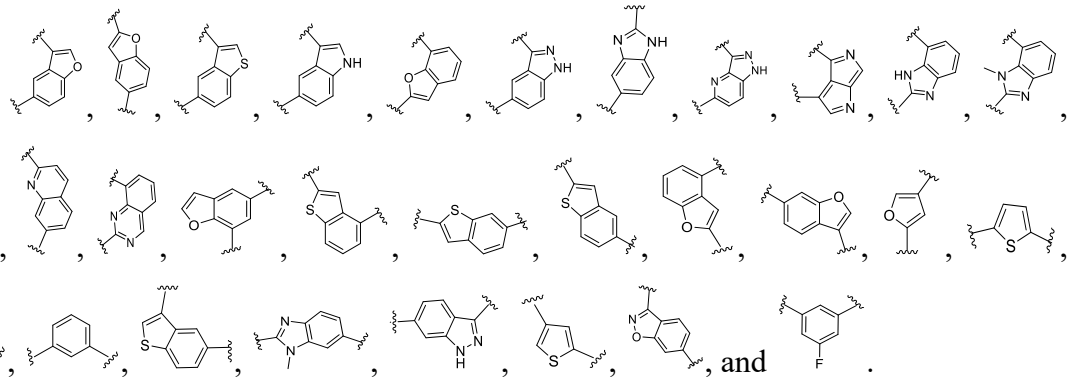


(III-C)

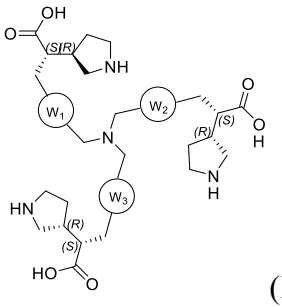
wherein W_1, W_2, and W_3 are defined as in compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), or Formula (III-1).

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, 8-10-membered bicyclic heteroaryl, and 5-6-membered

monocyclic heteroaryl; wherein the phenyl, naphthyl, and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from  .

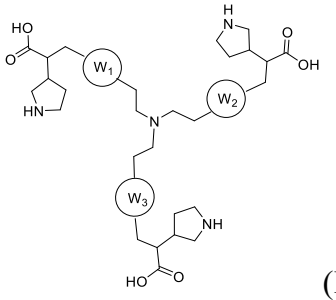
The invention further provides a compound represented by the following Formula (III-C'), or a pharmaceutically acceptable salt thereof:



(III-C')

wherein W_1, W_2, and W_3 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), or Formula (III-C).

The invention further provides a compound represented by the following Formula (III-D), or a pharmaceutically acceptable salt thereof:

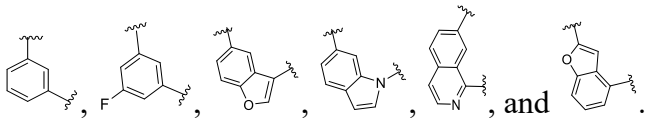


(III-D)

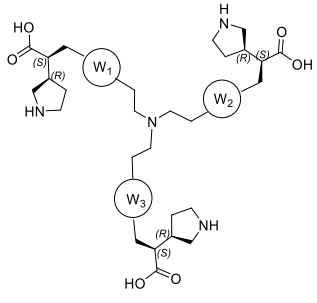
wherein W_1, W_2, and W_3 are defined as in compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), or Formula (III-1).

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, and 8-10-membered bicyclic heteroaryl; wherein the phenyl, naphthyl, and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl and 9-10-membered bicyclic heteroaryl; wherein the heteroatoms in the heteroaryl are independently selected from oxygen or N, and the number of heteroatoms is 1 or 2; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, methyl, and methoxy.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from  .

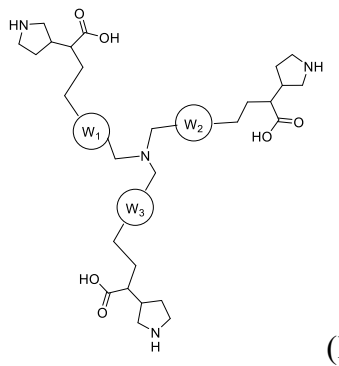
The invention further provides a compound represented by the following Formula (III-D'), or a pharmaceutically acceptable salt thereof:



(III-D')

wherein W_1, W_2, and W_3 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), or Formula (III-D).

The invention further provides a compound represented by the following Formula (III-E), or a pharmaceutically acceptable salt thereof:

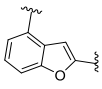
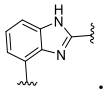


(III-E)

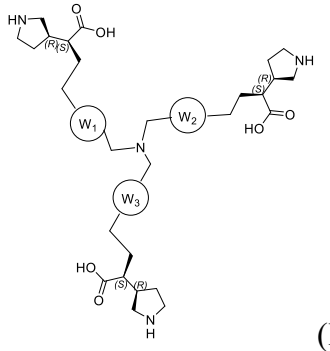
wherein W_1, W_2, and W_3 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), or Formula (III-1).

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, and 8-10-membered bicyclic heteroaryl; wherein the phenyl, naphthyl, and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from 9-membered bicyclic heteroaryl; wherein the heteroatoms in the heteroaryl are independently selected from O or N, and the number of heteroatoms is 1 or 2.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from  and  .

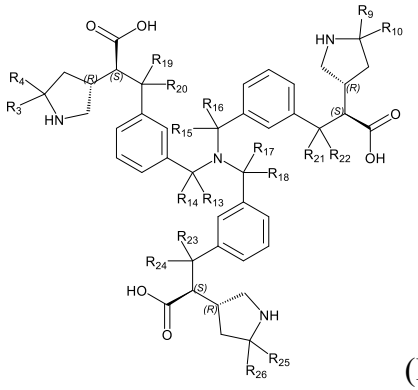
The invention further provides a compound represented by the following Formula (III-E'), or a pharmaceutically acceptable salt thereof:



(III-E')

wherein W_1, W_2, and W_3 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), or Formula (III-E).

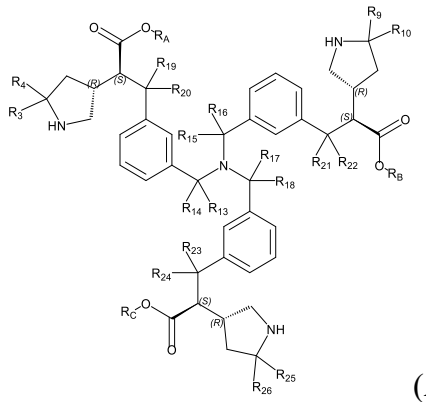
The invention further provides a compound represented by the following Formula (IV), or a pharmaceutically acceptable salt thereof:



(IV)

wherein each of R_3, R_4, R_9, R_{10}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from H and deuterium, and at least one of R_3, R_4, R_9, R_{10}, and R_{13}-R_{26} is deuterium.

The invention further provides a compound represented by the following Formula (A), or a pharmaceutically acceptable salt thereof:



(A)

wherein each of R_3, R_4, R_9, R_{10}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from H and deuterium, and at least one of R_3, R_4, R_9, R_{10}, and R_{13}-R_{26} is deuterium;

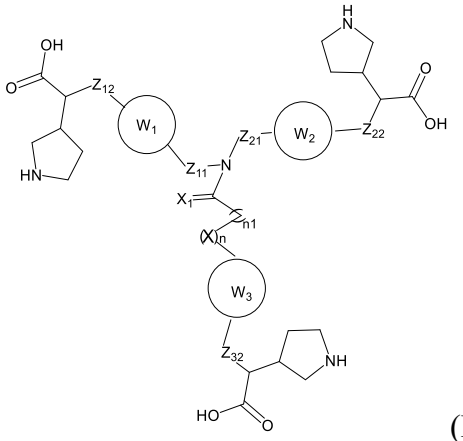
each of R_A, R_B, and R_C are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, -C_{1-3} alkylene-O-C_{1-6} alkyl, and -C_{1-3} alkylene-O-C(O)-C_{1-6} alkyl, wherein the alkyl, alkenyl, alkoxy, and alkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, -OH, -NH_2, -CN, oxo, C_{1-3} alkyl, and C_{1-3} alkoxy.

In one embodiment of the invention, each of R_A, R_B, and R_C is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, -C_{1-2} alkylene-O-C_{1-4} alkyl, -C_{1-2} alkylene-O-C(O)-C_{1-4} alkyl, wherein the alkyl, C_{1-6} alkoxy, and alkylene are optionally substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -OH, -NH_2, -CN, oxo, methyl, ethyl, *n*-propyl, isopropyl, methoxy, ethoxy, *n*-propoxy, and isopropoxy.

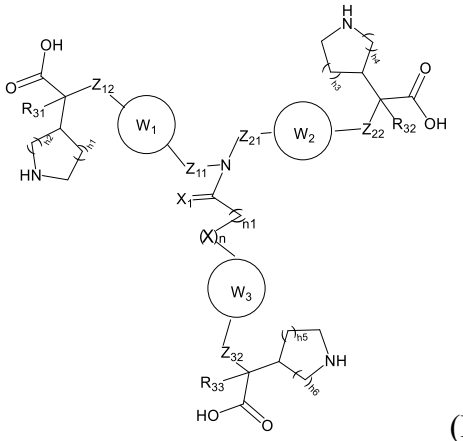
In one embodiment of the invention, each of R_A, R_B, and R_C is independently selected from C_{1-3} alkyl, -methylene-O-C_{1-4} alkyl, and -methylene-O-C(O)-C_{1-3} alkyl, wherein the methylene and alkyl are optionally substituted by one or more substituents independently selected from methyl, ethyl, *n*-propyl, and isopropyl.

In one embodiment of the invention, each of R_A, R_B, and R_C is independently selected from methyl, ethyl, and -CH_2-OC(O)-$CH(CH_3)_2$.

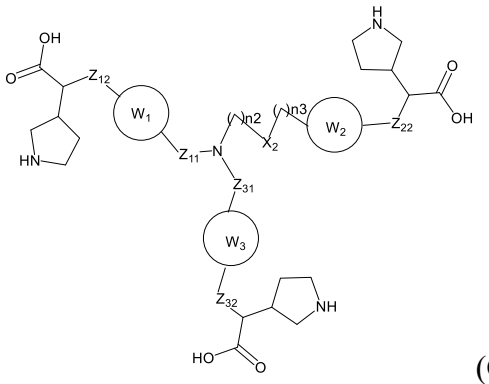
The invention further provides a compound represented by the following Formula (B), Formula (B-1), Formula (C), Formula (C-1), Formula (D), or Formula (D-1), or a pharmaceutically acceptable salt thereof:



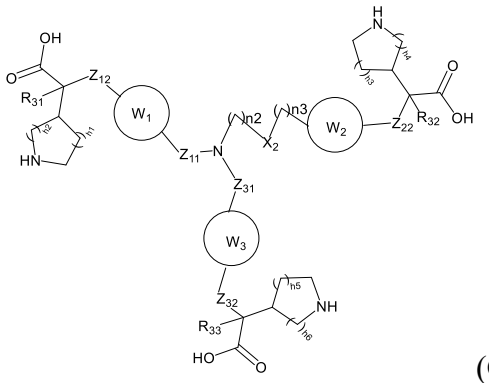
(B),



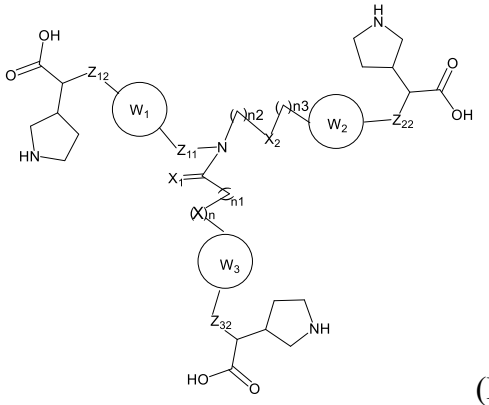
(B-1),



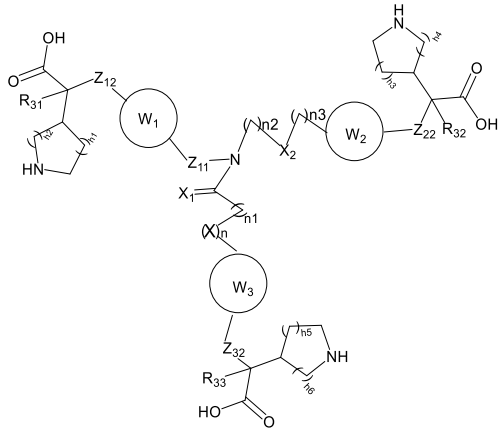
(C),



(C-1),



(D),



(D-1),

wherein Z_{11}, Z_{21}, Z_{31}, R_{31}, R_{32}, R_{33}, h1, h2, h3, h4, h5, and h6 are respectively defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), or Formula (III-B); each of X and X_2 is independently selected from O, CH_2, NH, and S, and Se, X_1 is independently selected from O and S, each of n, n1, and n3 are independently 0 or 1, and n2 is independently 0, 1, 2, or 3; each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, ethylene, and -CD_2-, or selected from methylene and ethylene;

each of the rings W_1, W_2, and W_3 is independently selected from phenyl and 5-6-membered monocyclic heteroaryl; wherein the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl; wherein a heteroatom in the heteroaryl is O, N, or S, and the number of heteroatoms is 1 or 2.

In one embodiment of the invention, each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, and -CD_2-.

In one embodiment of the invention, Z_{11} is $-CD_2-$.

In one embodiment of the invention, Z_{11} is independently selected from $-C_{1-3}$ alkylene-, $-OC_{1-3}$ alkylene-, $-NH-C_{1-3}$ alkylene-, $-S-C_{1-3}$ alkylene-, $-Se-C_{1-3}$ alkylene-, and $-C_{1-2}$ alkylene-$O-C_{1-3}$ alkylene-; preferably, Z_{11} is independently selected from $-C_{1-3}$ alkylene- and $-OC_{1-3}$ alkylene-; preferably, Z_{11} is independently selected from methylene, ethylene, methylene oxide, and ethylene oxide; preferably, Z_{11} is independently selected from methylene, and $-CD_2-$; preferably, Z_{11} is independently selected from methylene.

In one embodiment of the invention, Z_{21} is $-CD_2-$.

In one embodiment of the invention, Z_{21} is independently selected from $-C_{1-3}$ alkylene-, $-OC_{1-3}$ alkylene-, $-NH-C_{1-3}$ alkylene-, $-S-C_{1-3}$ alkylene-, $-Se-C_{1-3}$ alkylene-, and $-C_{1-2}$ alkylene-$O-C_{1-3}$ alkylene-; it is preferably selected from $-OC_{1-3}$ alkylene-, $-NH-C_{1-2}$ alkylene-, $-S-C_{1-2}$ alkylene-, and $-C_{1-2}$ alkylene-$O-C_{1-3}$ alkylene-.

In one embodiment of the invention, Z_{31} is independently selected from $-C(O)-$, $-C_{1-3}$ alkylene-$C(O)-$, $-OC_{1-3}$ alkylene-$C(O)-$, $-NH-C_{1-3}$ alkylene-$C(O)-$, $-S-C_{1-3}$ alkylene-$C(O)-$, $-O-C_{1-2}$ alkylene-$C(O)-C_{1-3}$ alkylene-, $-C_{1-3}$ alkylene-$NH-C(O)-$, $-C_{1-3}$ alkylene-$O-C(O)-$, $-NH-C(O)-$, $-O-C(O)-$, $-S-C(O)-$, and $-C_{1-3}$ alkylene-$C(S)-$; it is preferably selected from $-C(O)-$, $-C_{1-2}$ alkylene-$C(O)-$, $-OC_{1-2}$ alkylene-$C(O)-$, $-NH-C(O)-$, $-O-C(O)-$, and $-S-C(O)-$.

In one embodiment of the invention, Z_{12}, Z_{22}, and Z_{32} are all methylene.

In one embodiment of the invention, X_2 is selected from O, NH, and S; preferably, X_2 is O.

In one embodiment of the invention, n2 is 0 or 1, n3 is 0, and X_2 is CH_2.

In one embodiment of the invention, n2 is 2 or 3, n3 is 0, and X_2 is O, NH, or S; or n2 is 1 or 2, n3 is 1, and X_2 is O, NH, or S; further preferably, n2 is 2 or 3, n3 is 0, and X_2 is O; or n2 is 2, n3 is 1, and X_2 is O.

In one embodiment of the invention, n2 is 2, n3 is 0, and X_2 is O, NH, or S; preferably, n2 is 2, n3 is 0, and X_2 is O.

In one embodiment of the invention, the sum of n2 and n3 is not more than 3 (specifically 0, 1, 2, or 3); preferably the sum of n2 and n3 is not more than 2 (specifically 0, 1, or 2); preferably

the sum of n2 and n3 is 1 or 2 (i.e., n2 is 2 and n3 is 0; or n2 is 1 and n3 is 1; or n2 is 0 and n3 is 2).

In one embodiment of the invention, X_1 is O.

In one embodiment of the invention, X is CH_2.

In one embodiment of the invention, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X is O or CH_2, n is 1, and n1 is 1.

In one embodiment of the invention, X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X_1 is O, X is O or CH_2, n is 1, and n1 is 1; further preferably, X_1 is O, X is selected from O and CH_2, n is 1, and n1 is 0; or X_1 is O, X is O or CH_2, n is 1, and n1 is 1; further preferably, X_1 is O, X is selected from CH_2, n is 1, and n1 is 0.

In one embodiment of the invention, the sum of n and n1 is 0, 1, or 2; preferably the sum of n and n1 is 1 or 2 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1; or n is 1 and n1 is 1; or n is 0 and n1 is 2; or n is 2 and n1 is 0); preferably the sum of n and n1 is 1 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1).

For example, in any of the above-mentioned Formula (B) and Formula (B-1), each of Z_{11} and Z_{21} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} and Z_{21} are identical or different, and at least one of Z_{11} and Z_{21} is a group comprising -O-, -NH-, -S-, or -Se-, preferably, a group comprising -O-, e.g., *-CH_2O- or *-CH_2CH_2O-, wherein * is the linking end to N; still further preferably, Z_{11}, Z_{21}, and *-$C(X_1)$-$(CH_2)_{n1}$-$(X)_n$- each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -$CH_2C(O)$-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -$OCH_2C(O)$-, -$CH_2OC(O)$-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

For example, in any of the above-mentioned Formula (B) and Formula (B-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

each of Z_{11} and Z_{21} is independently selected from -CD_2-, -C_{1-3} alkylene- (preferably -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (preferably -OC_{1-2} alkylene-*), -SC_{1-3} alkylene-*, -NHC_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, * is the linking end to N;

X_1 is O or S, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X_1 is O or S, X is O or CH_2, n is 1, and n1 is 1; or X_1 is O or S, n is 0, and n1 is 0.

For example, in any of the above-mentioned Formula (B) and Formula (B-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, -OCH_2-*, and -OCH_2CH_2-*, wherein * is the linking end to N;

Z_{21} is independently selected from -OCH_2CH_2-*, -$CH_2OCH_2CH_2$-*, and -$OCH_2CH_2CH_2$-*, wherein * is the linking end to N;

X_1 is O, X is selected from O, CH2, NH, and S, n is 1, and n1 is 0; or X_1 is O, X is O or CH_2, n is 1, and n1 is 1.

For example, in any of the above-mentioned Formula (B) and Formula (B-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-; each of Z_{11} and Z_{21} is independently selected from -CD_2-, -C_{1-3} alkylene- (preferably -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (preferably -OC_{1-2} alkylene-*), -SC_{1-3} alkylene-*, -NHC_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, * is the linking end to N, X_1 is O or S, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 0, 1, or 2; further preferably, Z_{21} is independently selected from -OCH_2CH_2-*, -$CH_2OCH_2CH_2$-*, and -$OCH_2CH_2CH_2$-*, * is the linking end to N; further preferably, X_1 is O, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 1 or 2.

For example, in any of the above-mentioned Formula (C) and Formula (C-1), one and only one of Z_{11} and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, the group not containing a double bond of Z_{11} and Z_{31} is identical to or different from *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- (* represents the linking end to N); still further preferably, Z_{11}, -$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -

CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

For example, in any of the above-mentioned Formula (C) and Formula (C-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

Z_{11} is independently selected from -CD_2-, -C_{1-3} alkylene- (preferably -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (preferably -OC_{1-2} alkylene-*), -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, wherein * is the linking end to N;

Z_{31} is independently selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -$NHCH_2$-C(O)-*, -SCH_2-C(O)-*, -CH_2-NHC(O)-*, -C_{1-2} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*, wherein * is the linking end to N;

n2 is 2 or 3, n3 is 0, and X_2 is O, NH, or S; or n2 is 1 or 2, n3 is 1, and X_2 is O, NH, or S; or n2 is 0 or 1, n3 is 0, and X_2 is CH_2.

For example, in any of the above-mentioned Formula (C) and Formula (C-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, -OCH_2-*, and -OCH_2CH_2-*, wherein * is the linking end to N;

Z_{31} is independently selected from -C(O)-, -CH_2CH_2C(O)-*, -CH_2C(O)-*, -OCH_2C(O)-*, -NHC(O)-*, -OC(O)-*, and -SC(O)-*, wherein * is the linking end to N;

n2 is 2 or 3, n3 is 0, X_2 is O; or n2 is 1 or 2, n3 is 1, and X_2 is O; or n2 is 0 or 1, n3 is 0, and X_2 is CH_2.

For example, in any of the above-mentioned Formula (C) and Formula (C-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-; Z_{11} is independently selected from -CD_2-, -C_{1-3} alkylene- (preferably -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (preferably -OC_{1-2} alkylene-*), -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*; Z_{31} is independently selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -$NHCH_2$-C(O)-*, -SCH_2-C(O)-*, -CH_2-NHC(O)-*, -C_{1-2} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*, wherein * is the linking end to N; further preferably, Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, and -OCH_2CH_2-*, wherein * is the linking end to N; further preferably, Z_{31} is independently selected from -

$CH_2CH_2C(O)$-*, -$CH_2C(O)$-*, -$OCH_2C(O)$-*, -NHC(O)-*, -OC(O)-*, and -SC(O)-*, wherein * is the linking end to N; further preferably, X_2 is O, NH, S, or Se, and the sum of n2 and n3 is 1, 2, or 3; further preferably, X_2 is O, and the sum of n2 and n3 is 2, or 3.

For example, in any of the above-mentioned Formula (D) and Formula (D-1), Z_{11} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} is identical to or different from *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- (* represents the linking end to N); still further preferably, Z_{11}, -$C(X_1)$-$(CH_2)_{n1}$-$(X)_n$-, and -$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -$CH_2C(O)$-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -$OCH_2C(O)$-, -$CH_2OC(O)$-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

For example, in any of the above-mentioned Formula (D) and Formula (D-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

Z_{11} is independently selected from -CD_2-, -C_{1-2} alkylene-, -OC_{1-2} alkylene-*, -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, * is the linking end to N;

n2 is 2 or 3, n3 is 0, X_2 is O, NH, or S; or n2 is 1 or 2, n3 is 1, X_2 is O, NH, or S; or n2 is 0 or 1, n3 is 0, X_2 is CH_2;

X_1 is O or S, X is selected from O, CH_2, NH, and S, n is 1, n1 is 0; or X_1 is O or S, X is O or CH_2, n is 1, n1 is 1.

For example, in any of the above-mentioned Formula (D) and Formula (D-1), and each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, -OCH_2-*, and -OCH_2CH_2-*, wherein * is the linking end to N;

n2 is 2 or 3, n3 is 0, and X_2 is O; or n2 is 1 or 2, n3 is 1, and X_2 is O; or n2 is 0 or 1, n3 is 0, and X_2 is CH_2; or

X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X_1 is O, X is O or CH_2, n is 1, and n1 is 1.

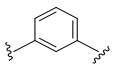
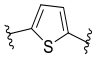
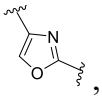
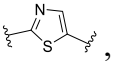
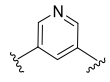
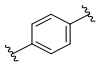
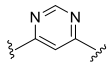
For example, in any of the above-mentioned Formula (D) and Formula (D-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

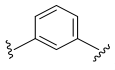
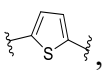
Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, and -OCH_2CH_2-*, wherein * is the linking end to N;

n2 is 2 or 3, n3 is 0, and X_2 is O; or n2 is 2, n3 is 1, and X_2 is O;

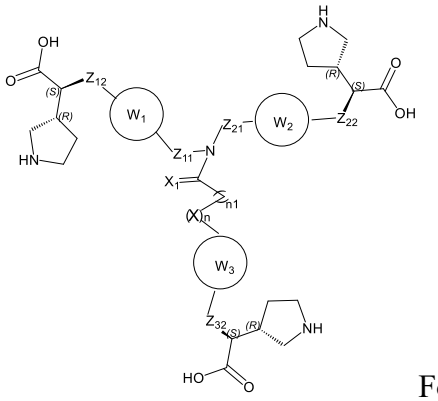
X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0.

For example, in any of the above-mentioned Formula (D) and Formula (D-1), each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, and -CD_2-; Z_{11} is independently selected from -CD_2-, -C_{1-2} alkylene-, -OC_{1-2} alkylene-*, -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, wherein * is the linking end to N; X_2 is O, NH, S, or Se, and the sum of n2 and n3 is 1, 2, or 3; X_1 is O or S, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 0, 1, or 2; further preferably, Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, and -OCH_2CH_2-*, wherein * is the linking end to N; further preferably, X_2 is O, and the sum of n2 and n3 is 2 or 3; X_1 is O, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 1 or 2.

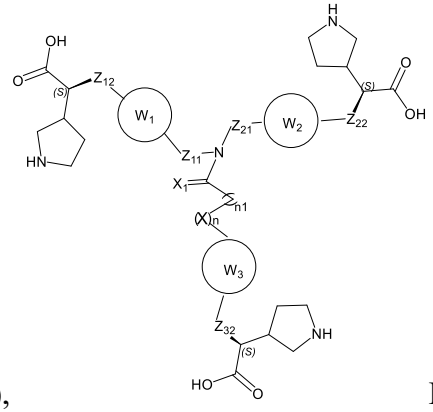
In one embodiment of the invention, each of ring W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  , ,  ,  ,  , ,  ,  , and  ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl.

In one embodiment of the invention, each of the rings W_1, W_2, and W_3 is independently selected from the following groups optionally substituted:  ,  , and ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy.

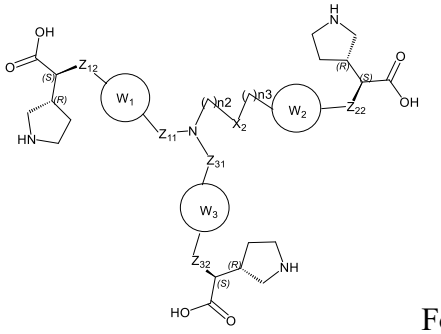
The invention further provides a compound represented by the following Formula (B-2), Formula (B-3), Formula (C-2), Formula (C-3), Formula (D-2), and Formula (D-3), or a pharmaceutically acceptable salt thereof:



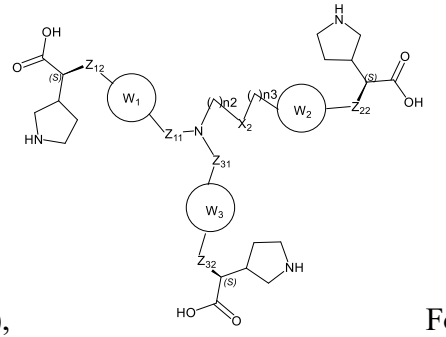
Formula(B-2),



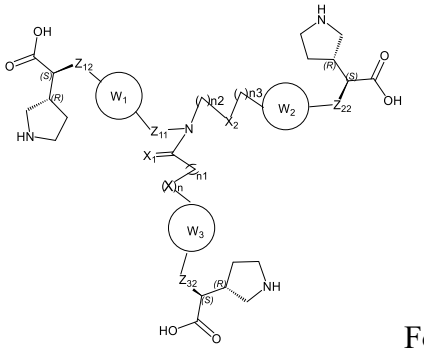
Formula(B-3),



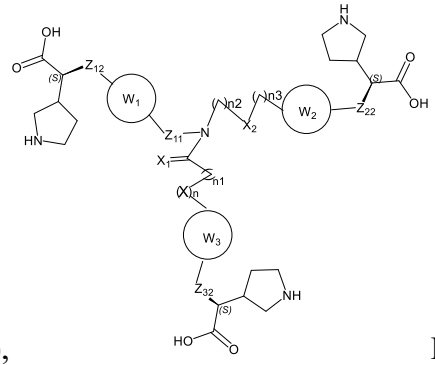
Formula(C-2),



Formula(C-3),



Formula(D-2),



Formula(D-3),

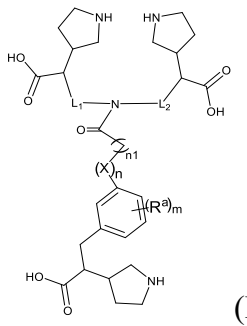
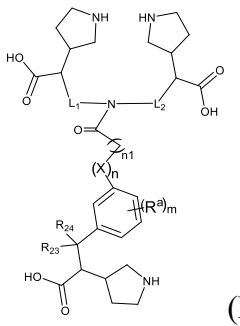
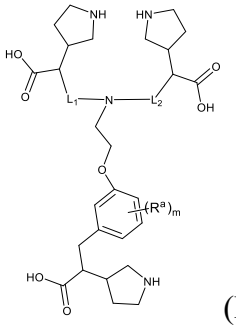
wherein Z_{11}, Z_{21}, Z_{12}, Z_{22}, Z_{32}, X, X_1, n, n1, and the rings W_1, W_2, and W_3 in Formula (B-2) and Formula (B-3) are defined as in the compound of Formula (B); Z_{11}, Z_{31}, Z_{12}, Z_{22}, Z_{32}, X_2, n2, n3, and the rings W_1, W_2, and W_3 in Formula (C-2) and Formula (C-3) are defined as in the compound of Formula (C); and Z_{11}, Z_{12}, Z_{22}, Z_{32}, X, X_1, X_2, n, n1, n2, n3, and the rings W_1, W_2, and W_3 in Formula (D-2) and Formula (D-3) are defined as in the compound of Formula (D).

For example, in any of the above-mentioned Formula (B-2) and Formula (B-3), each of Z_{11} and Z_{21} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} and Z_{21} are identical or different, and at least one of Z_{11} and Z_{21} is a group comprising -O-, -NH-, -S-, or -Se-, preferably, a group comprising -O-, e.g., *-CH_2O- or *-CH_2CH_2O-, wherein * is the linking end to N; still further preferably, Z_{11}, Z_{21}, and *-$C(X_1)$-$(CH_2)_{n1}$-$(X)_n$- each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -$CH_2C(O)$-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -$OCH_2C(O)$-, -$CH_2OC(O)$-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

For example, in any of the above-mentioned Formula (C-2) and Formula (C-3), one and only one of Z_{11} and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, the group not containing a double bond of Z_{11} and Z_{31} is identical to or different from *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- (* represents the linking end to N); still further preferably, Z_{11}, -$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$-, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -$CH_2C(O)$-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -$OCH_2C(O)$-, -$CH_2OC(O)$-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

For example, in any of the above-mentioned Formula (D-2) and Formula (D-3), Z_{11} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} is identical to or different from *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- (* represents the linking end to N); still further preferably, Z_{11}, -$C(X_1)$-$(CH_2)_{n1}$-$(X)_n$-, and -$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -$CH_2C(O)$-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -$OCH_2C(O)$-, -$CH_2OC(O)$-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

The invention further provides a compound represented by the following Formula (E), Formula (E-1) and Formula (F), or a pharmaceutically acceptable salt thereof:


(E),

(E-1),

(F)

wherein L_1 and L_2 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), Formula (III-B), Formula (B), Formula (C) or Formula (D), X is O, CH_2 or NH, R^a is deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}\text{ alkyl})_2$, $-NH(C_{1-3}\text{ alkyl})$, and $-C(O)C_{1-3}$ alkyl, n1 is 0 or 1, m is 0 or 1, and n is 0 or 1; R_{23} and R_{24} are each independently selected from H, and deuterium.

For example, in any of the above-mentioned Formula (E) and Formula (E-1), L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, and each of Z_{11} and Z_{21} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} and Z_{21} are identical or different; still further preferably, Z_{11}, Z_{21}, and $-C(O)-(CH_2)_{n1}-(X)_n-$ each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

For example, in the above-mentioned Formula (F), L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, and

one and only one of Z_{11} and Z_{21} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, the group not containing a double bond of Z_{11} and Z_{21} is identical to or different from $*-(CH_2)_2-O-$ (*represents the linking end to N); still further preferably, Z_{11} and Z_{21} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about

14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

In one embodiment of the invention, R^a is fluorine, chlorine, methyl, ethyl, methoxy and ethoxy; preferably R^a is F.

In one embodiment of the invention, m is 1.

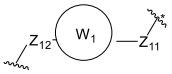
In one embodiment of the invention, X is CH_2.

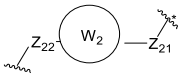
In one embodiment of the invention, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X is O or CH_2, n is 1, and n1 is 1.

In one embodiment of the invention, the sum of n and n1 is 0, 1, or 2; preferably the sum of n and n1 is 1 or 2 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1; or n is 1 and n1 is 1; or n is 0 and n1 is 2; or n is 2 and n1 is 0); preferably the sum of n and n1 is 1 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1).

For example, in any of the above-mentioned Formula (E), Formula (E-1), and Formula (F), R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy, m is 1, X is selected from O, CH_2, NH, and S, the sum of n and n1 is 0, 1, or 2.

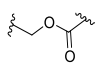
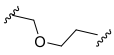
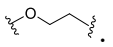
further preferably, R^a is fluorine, or methoxy, m is 1, X is selected from O, CH_2, NH, and S, the sum of n and n1 is 1 or 2.

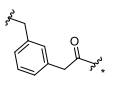
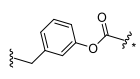
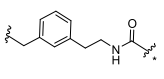
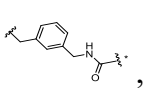
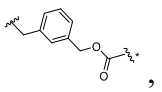
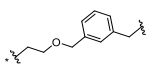
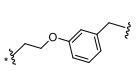
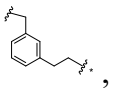
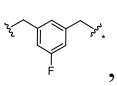
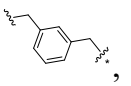
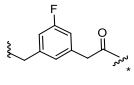
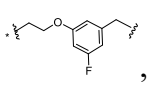
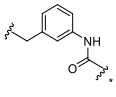
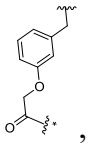
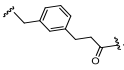
In one embodiment of the invention, L_1 is 

, L_2 is 

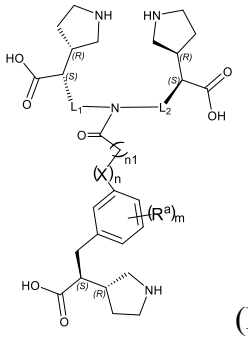
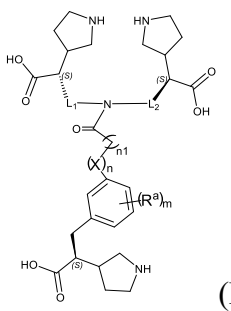
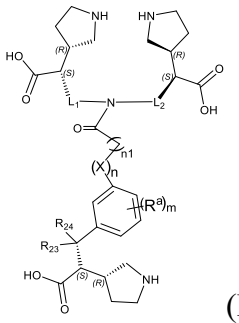
, and * represents the linking end to N; each of the rings W_1 and W_2 is independently selected from ; the phenyl is optionally substituted by one or more substituents independently selected from halogen and C_{1-3} alkoxy (preferably F and methoxy).

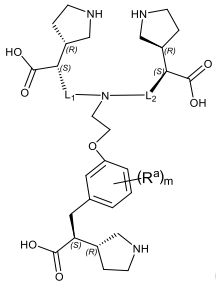
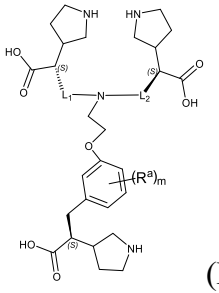
In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21} and Z_{22} is independently selected from -C_{1-2} alkylene-, -OC_{1-3} alkyl-, -NH-C_{1-2} alkylene-, -S-C_{1-2} alkylene-, -C_{1-2} alkylene-O-C_{1-2} alkylene-, -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -C_{1-2} alkylene-NH-C(O)-, -C_{1-2} alkylene-O-C(O)-, -NH-C(O)-, -NH- C_{1-2} alkyl-C(O)-, -O-C(O)-, and -S-C(O)-.

In one embodiment of the invention, each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from methylene, ethylene, , , , , , , ,  ,  , and  .

In one embodiment of the invention, each of L_1 and L_2 is independently selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; * is the linking end to N.

The invention further provides a compound represented by the following Formula (E-2), Formula (E-3), Formula (E-4),Formula (F-1), and Formula (F-2), or a pharmaceutically acceptable salt thereof:

 (E-2),  (E-3),  (E-4),

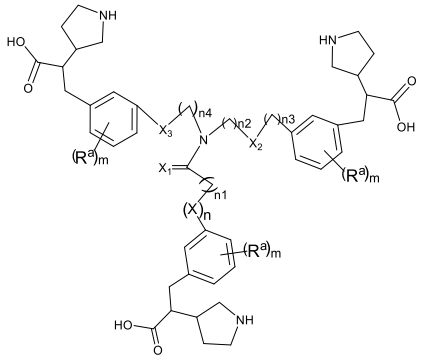
 (F-1),  (F-2)

wherein L_1, L_2, X, m, n, n1, and R^a in Formula (E-2), Formula (E-3) and Formula (E-4) are defined as in Formula (E) and Formula (E-1); R_{23} and R_{24} in Formula (E-4) are defined as in Formula (E-1); and L_1 and L_2 in Formula (F-1) and Formula (F-2) are defined as in Formula (F).

For example, in any of the above-mentioned Formula (E-2), Formula (E-3), and Formula (E-4), L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, and each of Z_{11} and Z_{21} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} and Z_{21} are identical or different; still further preferably, Z_{11}, Z_{21}, and $-C(O)-(CH_2)_{n1}-(X)_n-$ each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

For example, in any of the above-mentioned Formula (F-1) and Formula (F-2), L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, and one and only one of Z_{11} and Z_{21} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, the group not containing a double bond of Z_{11} and Z_{21} is identical to or different from $*-(CH_2)_2-O-$ (*represents the linking end to N); still further preferably, Z_{11} and Z_{21} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-.

The invention further provides a compound represented by the following Formula (G), or a pharmaceutically acceptable salt thereof:



(G),

wherein X, X_1, X_2, n, n1, n2, and n3 are defined as in the compounds of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula

(III-1), Formula (III-B), Formula (B), Formula (C), or Formula (D), m is independently 0 or 1, n4 is 0, 1, 2, or 3, X_3 is selected from O, S, CH_2, and NH; or X_3 is O, S, CH_2, NH, or CD_2, and R^a is selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}\text{ alkyl})_2$, $-NH(C_{1-3}\text{ alkyl})$, and $-C(O)C_{1-3}$ alkyl.

In one embodiment of the invention, R^a is fluorine, chlorine, methyl, ethyl, methoxy, ethoxy; preferably F and methoxy.

In one embodiment of the invention, m is 1.

In one embodiment of the invention, n4 is 0, 1, or 2, preferably 0 or 1 and more preferably 0.

In one embodiment of the invention, X_3 is O or CH_2; or X_3 is O, CH_2, or CD_2.

In one embodiment of the invention, X_3 is O and n4 is 2; or X_3 is CH_2 and n4 is 0 or 1; or X_3 is CH_2, or CD_2, n4 is 0 or 1; further preferably, X_3 is CH_2 or CD_2, n4 is 0.

For example, in the above-mentioned Formula (G), R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy; m is 1; X_2 is O, NH, S, or Se, the sum of n2 and n3 is 1, 2, or 3; X_1 is O or S, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 0, 1, or 2;

X_3 is O, and n4 is 2; or X_3 is CH_2, or CD_2, and n4 is 0 or 1.

further preferably, R^a is fluorine, chlorine, or methoxy; m is 1; X_2 is O, and the sum of n2 and n3 is 2, or 3; X_1 is O, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 1, or 2;

X_3 is O, and n4 is 2; or X_3 is CH_2 or CD_2, and n4 is 0 or 1.

For example, in the above-mentioned Formula (G), R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy; m is 1;

X_3 is O, and n4 is 2; or X_3 is CH_2 or CD_2, and n4 is 0 or 1;

n2 is 2 or 3, n3 is 0, and X_2 is O, NH, S; or n2 is 1 or 2, n3 is 1, and X_2 is O, NH, S; or n2 is 0 or 1, n3 is 0, and X_2 is CH_2;

X_1 is O or S, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X_1 is O or S, X is O or CH_2, n is 1, and n1 is 1.

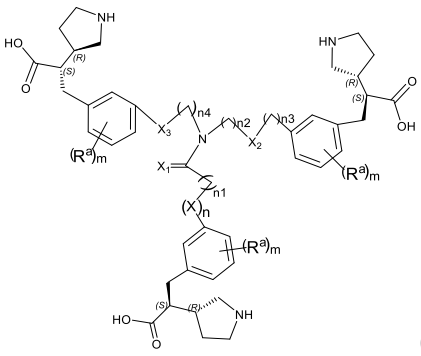
For example, in the above-mentioned Formula (G), R^a is fluorine, chlorine, or methoxy; m is 1;

X_3 is O, n4 is 2; or X_3 is CH_2 or CD_2, and n4 is 0 or 1;

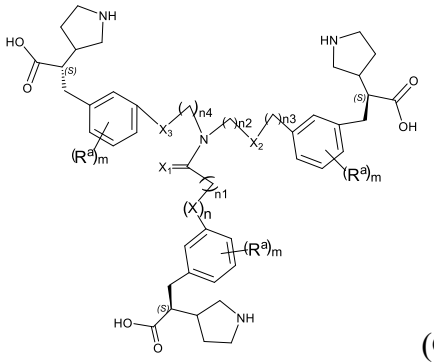
n2 is 2 or 3, n3 is 0, and X_2 is O; or n2 is 1 or 2, n3 is 1, and X_2 is O; or n2 is 0 or 1, n3 is 0, and X_2 is CH_2;

X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X_1 is O, X is O or CH_2, n is 1, and n1 is 1.

The invention further provides a compound represented by the following Formula (G-1) and Formula (G-2), or a pharmaceutically acceptable salt thereof:



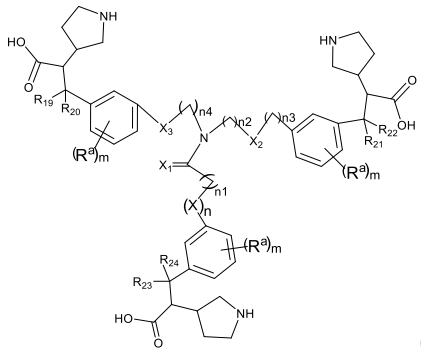
(G-1),



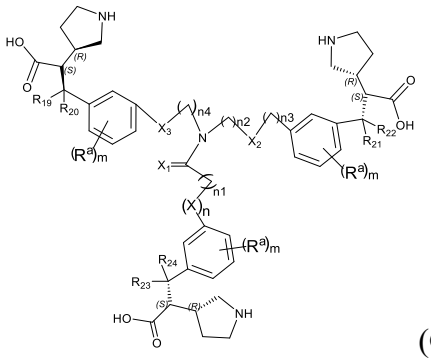
(G-2),

wherein X, X_1, X_2, X_3, n, n1, n2, n3, n4, m, and R^a are defined as in the compound of Formula (G).

The invention further provides a compound represented by the following Formula (G-3) or Formula (G-4), or a pharmaceutically acceptable salt thereof:



(G-3),

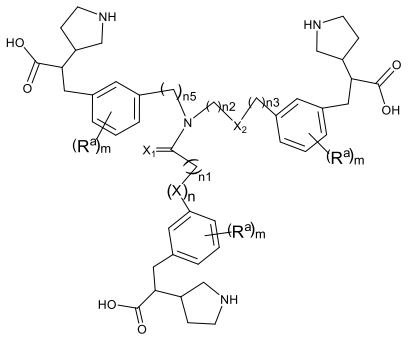


(G-4),

wherein X, X_1, X_2, X_3, n, n1, n2, n3, n4, m, and R^a are defined as in Formula (G), and R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each independently selected from hydrogen and deuterium.

For example, in any of the above-mentioned Formula (G), Formula (G-1), Formula (G-2), Formula (G-3), and Formula (G-4), *-$(CH_2)_{n4}$-X_3-, *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$-, and *-C(X_1)-$(CH_2)_{n1}$-$(X)_n$- (* represents the linking end to N) are identical to or different from each other, and they each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

The invention further provides a compound represented by the following Formula (H), or a pharmaceutically acceptable salt thereof:



(H),

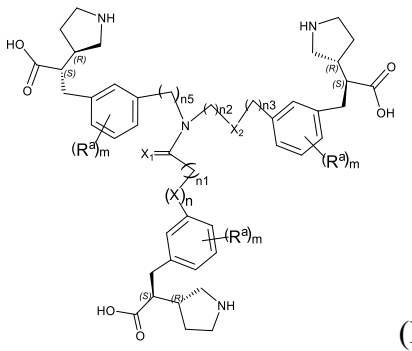
wherein X, X_1, X_2, n, n1, n2, and n3 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (III), Formula (III-1), Formula (III-B), Formula (B), Formula (C), Formula (D), or Formula (G), m is independently 0 or 1, n5 is 1, 2, 3, or 4, and R^a is selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl.

In one embodiment of the invention, R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy; preferably R^a is F or methoxy.

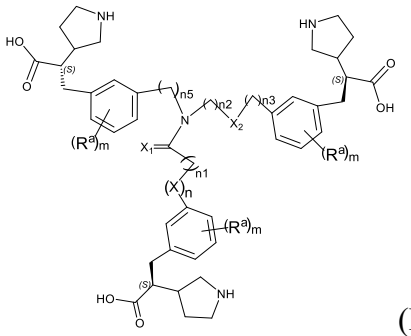
In one embodiment of the invention, m is 1.

In one embodiment of the invention, n5 is 1, 2, or 3, preferably 1 or 2 and more preferably 1.

The invention further provides a compound represented by the following Formula (H-1) and Formula (H-2), or a pharmaceutically acceptable salt thereof:



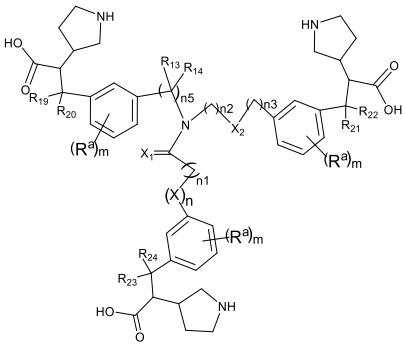
(H-1),



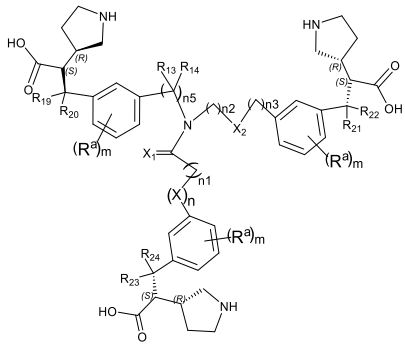
(H-2),

wherein X, X_1, X_2, n, n1, n2, n3, n5, m, and R^a are defined as in the compound of Formula (H).

The invention further provides a compound represented by the following Formula (H-3) and Formula (H-4), or a pharmaceutically acceptable salt thereof:



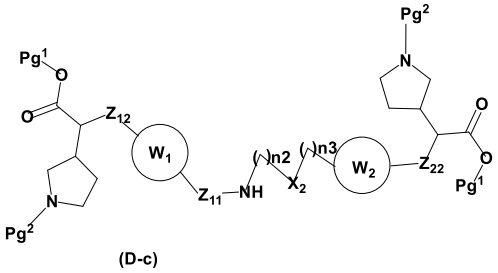
(H-3),



(H-4),

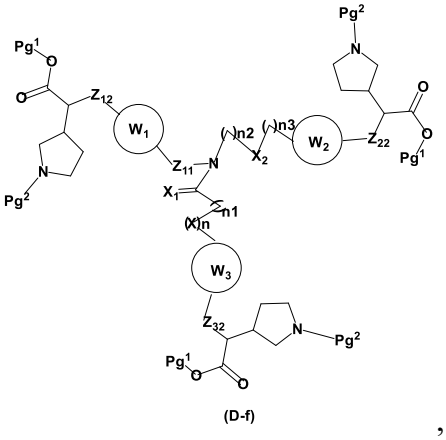
wherein X, X_1, X_2, n, n1, n2, n3, n5, m, and R^a are defined as in Formula (H), and R_{13}, R_{14}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each independently selected from hydrogen and deuterium.

The invention further provides a compound represented by Formula (D-c), Formula (D-f), Formula (D- g), or Formula (D-h), or a pharmaceutically acceptable salt thereof:



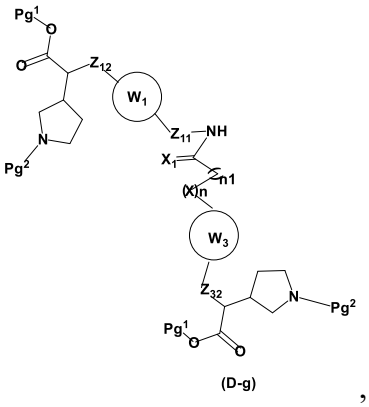
(D-c)

,

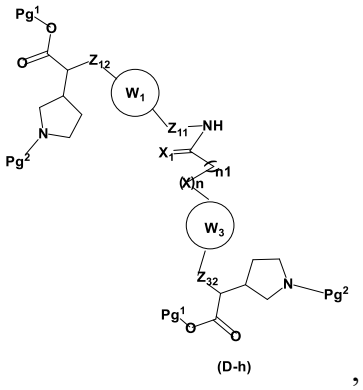


(D-f)

,



(D-g),

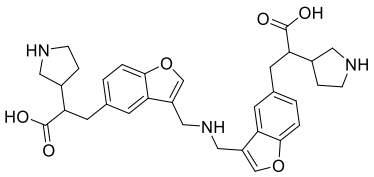
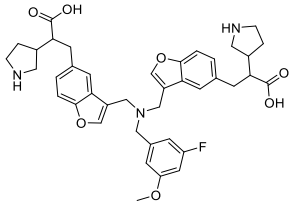


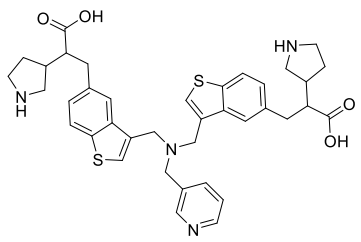
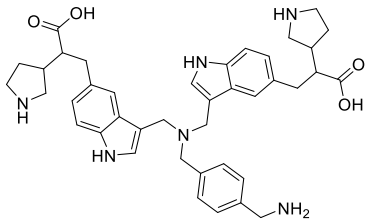
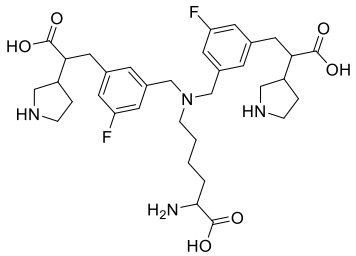
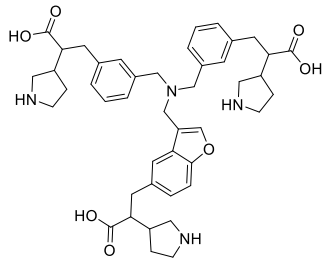
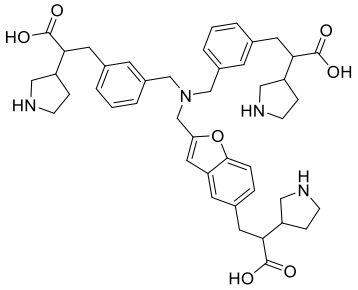
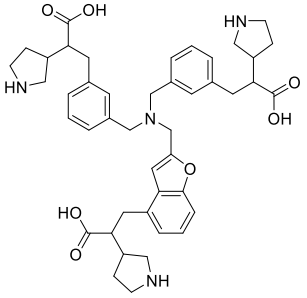
(D-h),

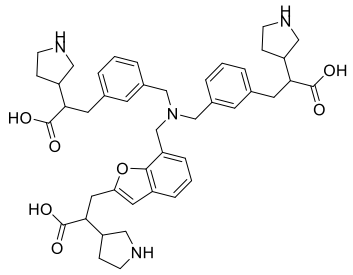
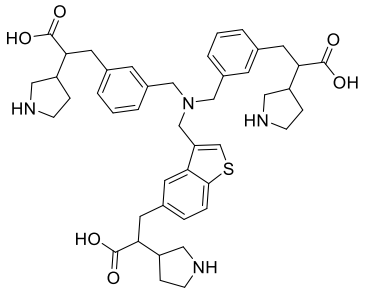
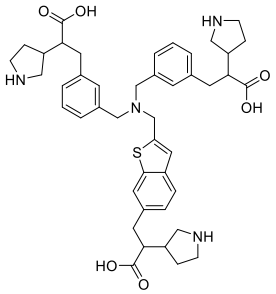
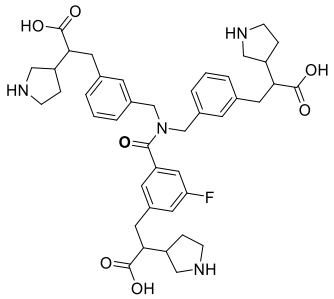
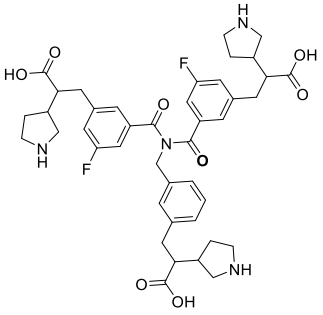
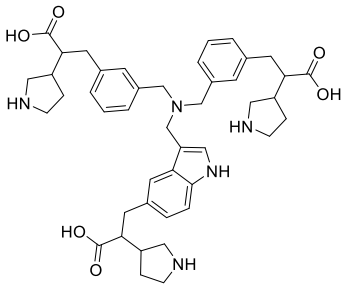
wherein Z_{11}, Z_{12}, Z_{22}, Z_{32}, X, X_1, X_2, n, n1, n2, n3, and the rings W_1, W_2, and W_3 are defined as in the compound of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), or Formula (D), each of Pg^1 and Pg^2 is independently a protecting group. Preferably, Pg^1 is independently selected from *tert*-butyl, methyl, and benzyl, Pg^2 is independently selected from *tert*-butoxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (FMOC), and andbenzyloxycarbonyl (Cbz), preferably Boc.

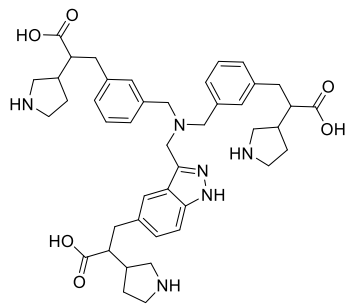
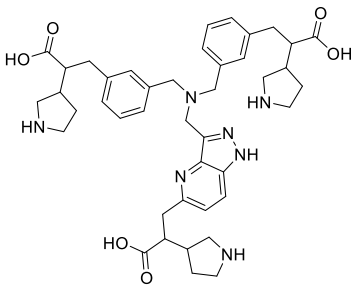
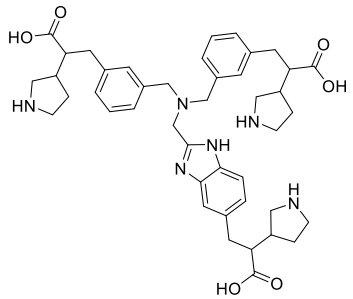
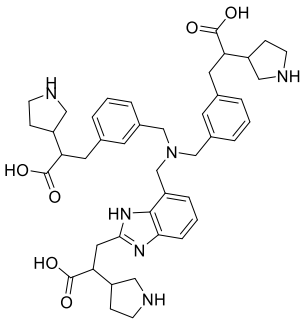
Based on the common knowledge in the field, the above specific technical features can be combined arbitrarily to obtain various preferred embodiments of the invention.

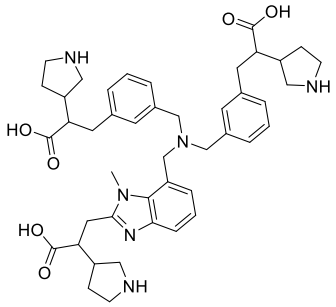
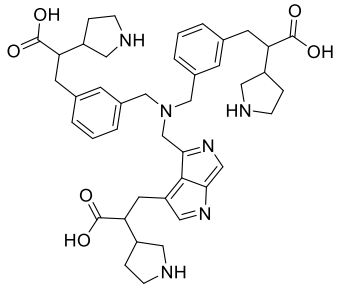
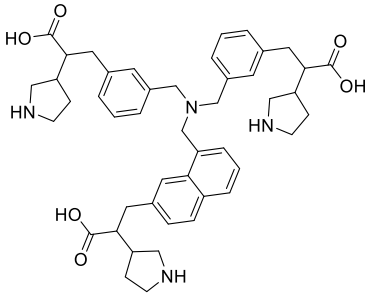
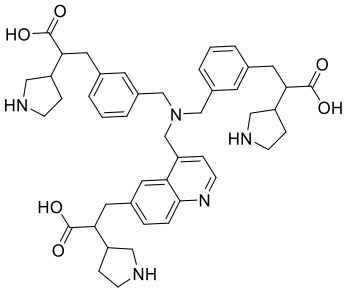
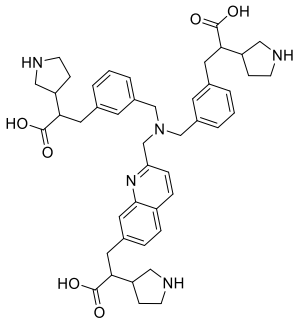
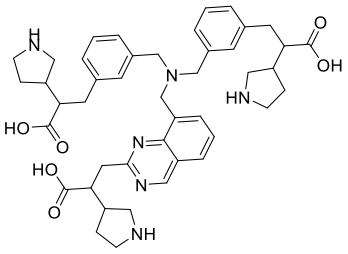
In one embodiment of the invention, the compounds of the invention or a pharmaceutically acceptable salt thereof are selected from:

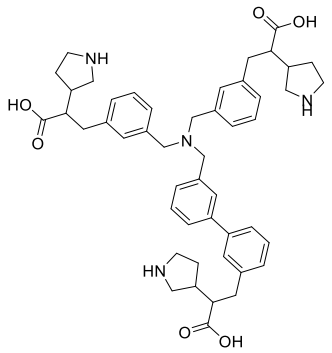
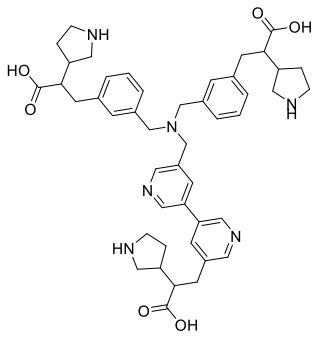
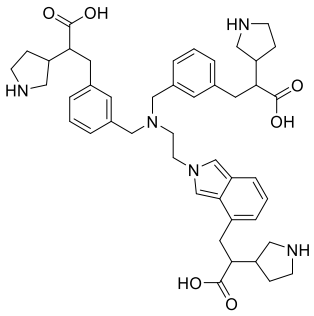
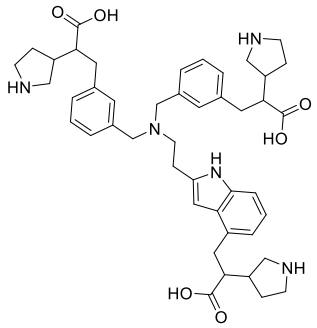
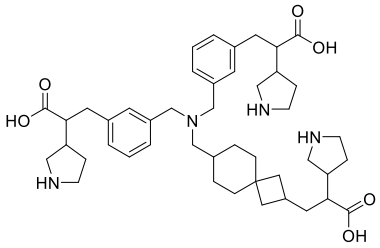
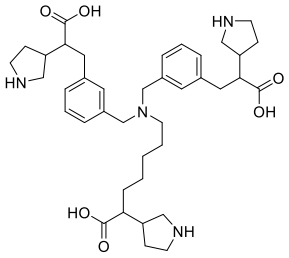
Compound No.	Compound Structure	Compound No.	Compound Structure
1-a	 3,3'-((azanediylbis(methylene))bis(benzofuran-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	2-a	 3,3'-((((3-fluoro-5-methoxybenzyl)azanediyl)bis(methylene))bis(benzofuran-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)

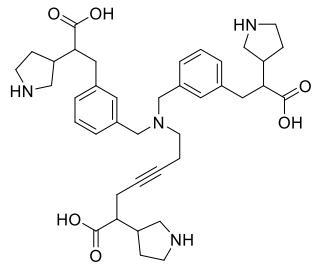
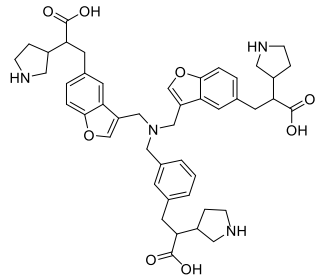
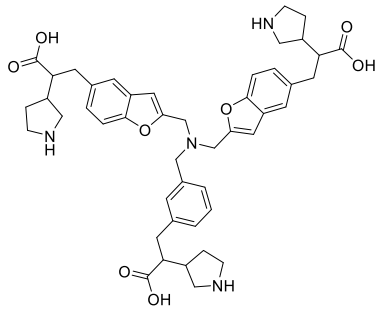
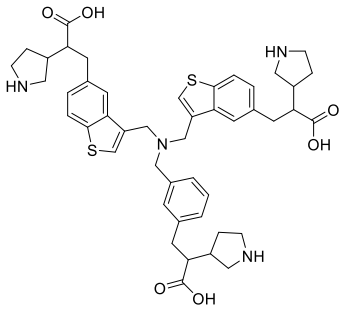
Compound No.	Compound Structure	Compound No.	Compound Structure
3-a	 3,3'-((((pyridin-3-ylmethyl)azanediyl)bis(methylene))bis(benzo[b]thiophene-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	4-a	 3,3'-((((4-(aminomethyl)benzyl)azanediyl)bis(methylene))bis(1H-indole-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
5-a	 3,3'-((((5-amino-5-carboxypentyl)azanediyl)bis(methylene))bis(5-fluoro-3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	6-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzofuran-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
7-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzofuran-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	8-a	 3,3'-(((((4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzofuran-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

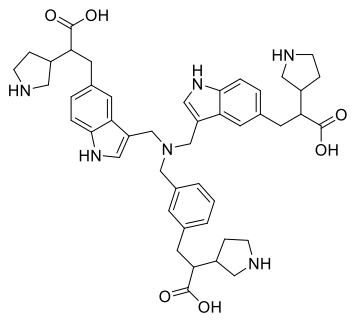
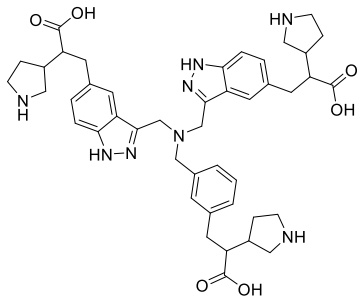
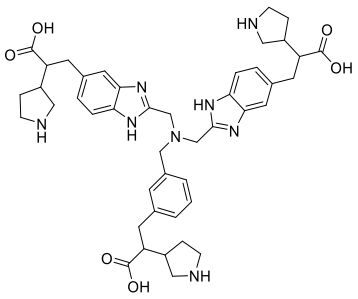
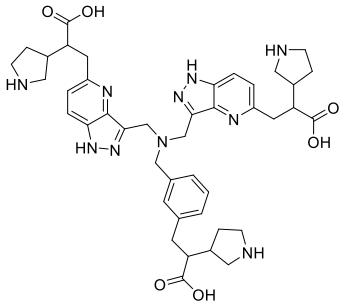
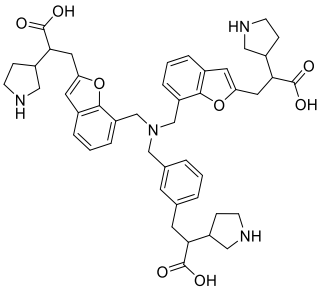
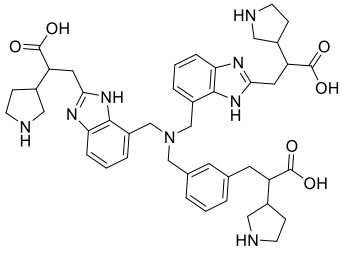
Compound No.	Compound Structure	Compound No.	Compound Structure
9-a	 3,3'-(((((2-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzofuran-7-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	10-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzo[b]thiophen-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
11-a	 3,3'-(((((6-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzo[b]thiophen-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	12-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-fluorobenzoyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
13-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(carbonyl))bis(5-fluoro-3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	14-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1H-indol-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

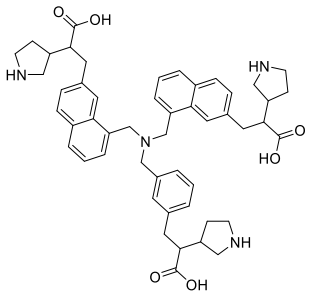
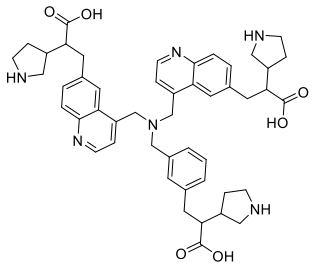
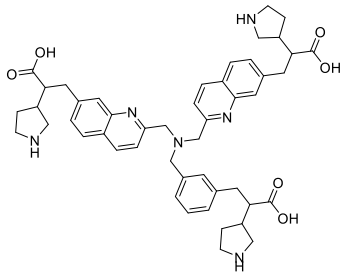
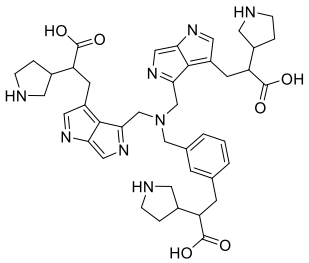
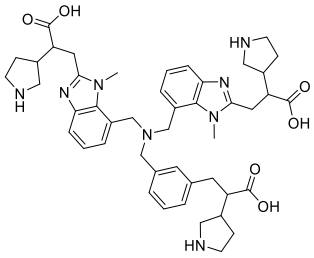
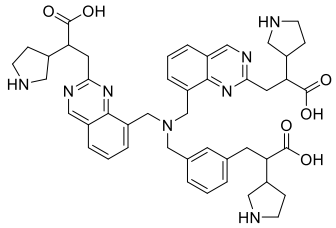
Compound No.	Compound Structure	Compound No.	Compound Structure
15-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1H-indazol-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	16-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
17-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1H-benzo[d]imidazol-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	18-a	 3,3'-(((((2-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1H-benzo[d]imidazol-7-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

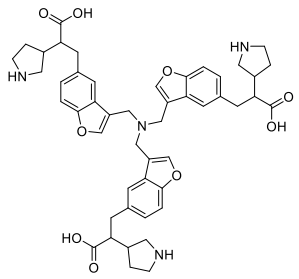
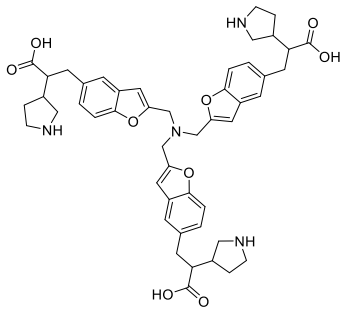
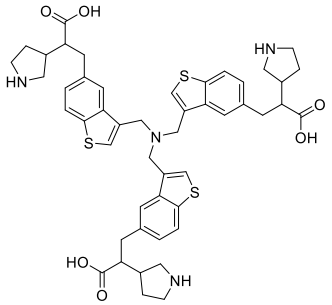
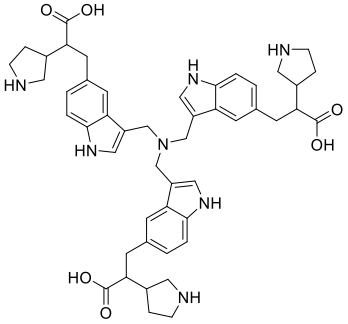
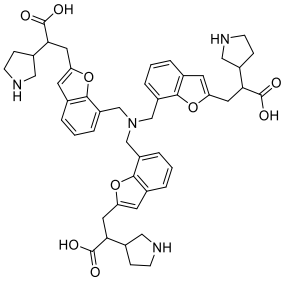
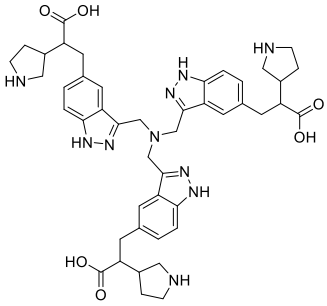
Compound No.	Compound Structure	Compound No.	Compound Structure
19-a	 3,3'-(((((2-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1-methyl-1H-benzo[d]imidazol-7-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	20-a	 3,3'-(((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)pyrrolo[3,4-b]pyrrol-4-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
21-a	 3,3'-(((((7-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)naphthalen-1-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	22-a	 3,3'-(((((6-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)quinolin-4-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
23-a	 3,3'-(((((7-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)quinolin-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	24-a	 3,3'-(((((2-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)quinazolin-8-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

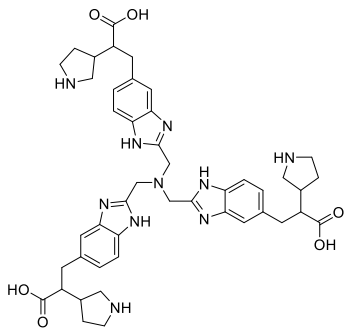
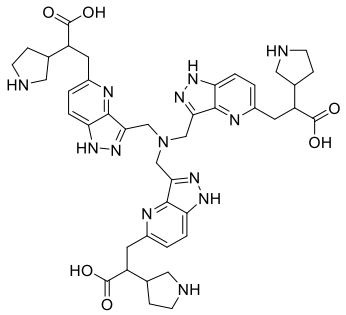
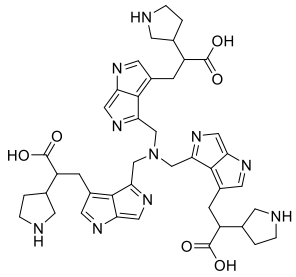
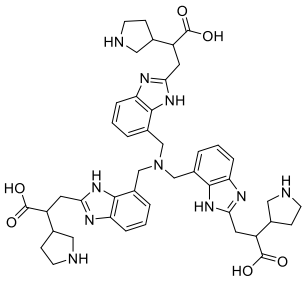
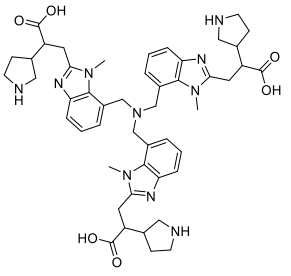
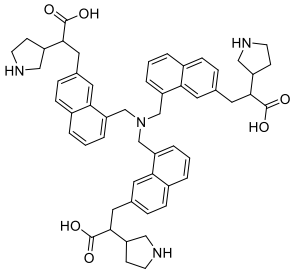
Compound No.	Compound Structure	Compound No.	Compound Structure
25-a	 3,3'-(((((3'-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-[1,1'-biphenyl]-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	26-a	 3,3'-(((((5'-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-[3,3'-bipyridin]-5-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
27-a	 3,3'-((((2-(4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-2H-isoindol-2-yl)ethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	28-a	 3,3'-((((2-(4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1H-indol-2-yl)ethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
29-a	 3,3'-(((((2-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)spiro[3.5]nonan-7-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	30-a	 3,3'-((((6-carboxy-6-(pyrrolidin-3-yl)hexyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

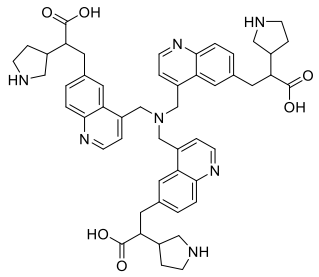
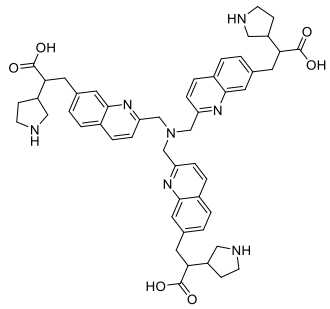
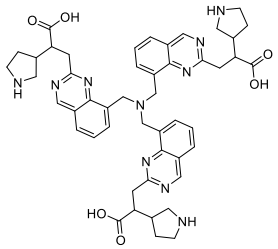
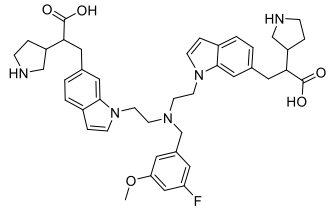
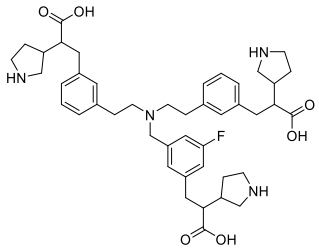
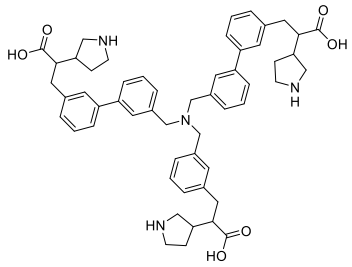
Compound No.	Compound Structure	Compound No.	Compound Structure
31-a	 3,3'-((((6-carboxy-6-(pyrrolidin-3-yl)hex-3-yn-1-yl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	32-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(benzofuran-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
33-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(benzofuran-2,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	34-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(benzo[b]thiophene-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)

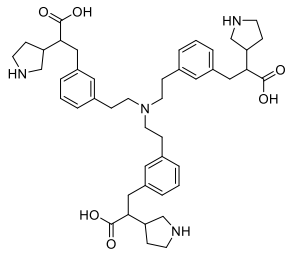
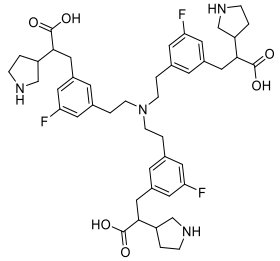
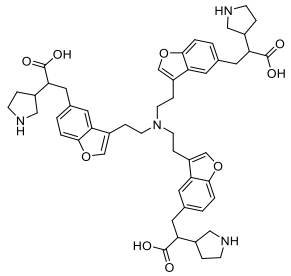
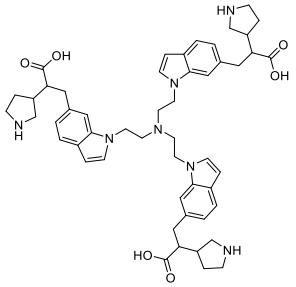
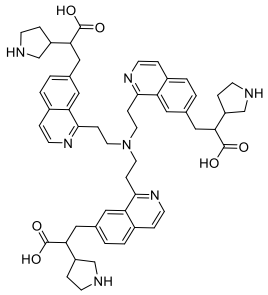
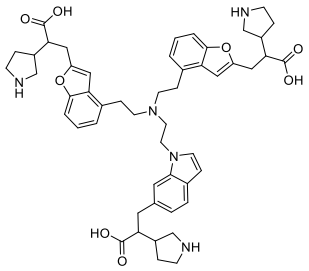
Compound No.	Compound Structure	Compound No.	Compound Structure
35-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(1H-indole-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	36-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(1H-indazole-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
37-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(1H-benzo[d]imidazole-2,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	38-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(1H-pyrazolo[4,3-b]pyridine-3,5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
39-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(benzofuran-7,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	40-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(1H-benzo[d]imidazole-7,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)

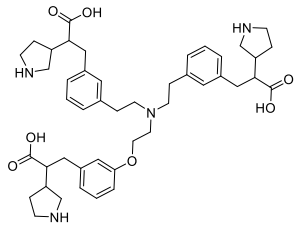
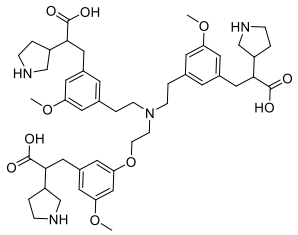
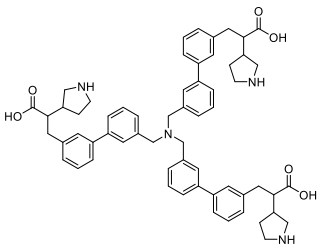
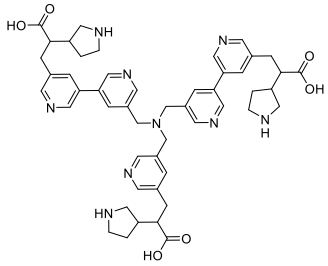
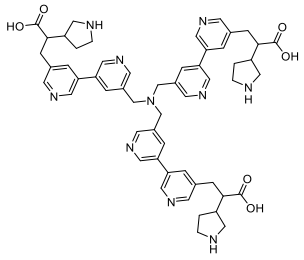
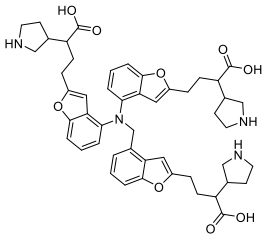
Compound No.	Compound Structure	Compound No.	Compound Structure
41-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(naphthalene-8,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	42-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(quinoline-4,6-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
43-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(quinoline-2,7-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	44-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(pyrrolo[3,4-b]pyrrole-4,3-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
45-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(1-methyl-1H-benzo[d]imidazole-7,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	46-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(quinazoline-8,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)

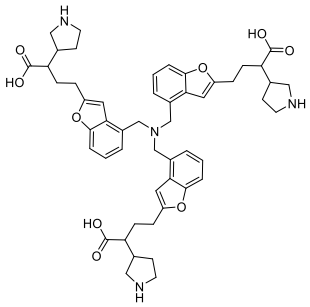
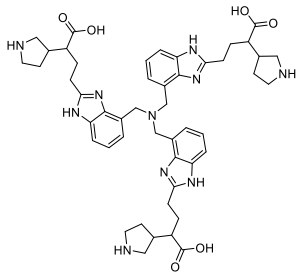
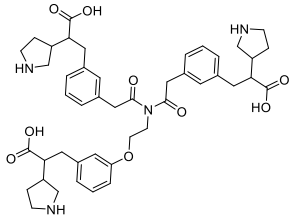
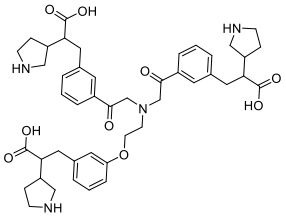
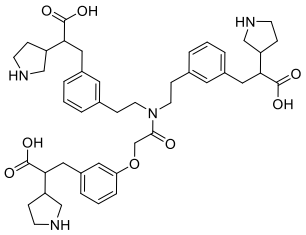
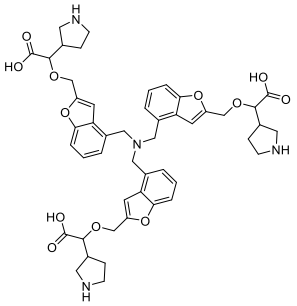
Compound No.	Compound Structure	Compound No.	Compound Structure
47-a	 3,3',3''-((nitrilotris(methylene))tris(benzofuran-3,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	48-a	 3,3',3''-((nitrilotris(methylene))tris(benzofuran-2,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
49-a	 3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-3,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	50-a	 3,3',3''-((nitrilotris(methylene))tris(1H-indole-3,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
51-a	 3,3',3''-((nitrilotris(methylene))tris(benzofuran-7,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	52-a	 3,3',3''-((nitrilotris(methylene))tris(1H-indazole-3,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)

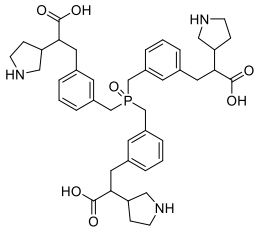
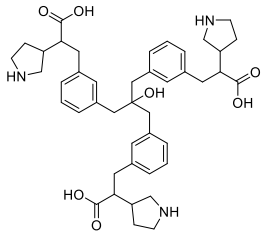
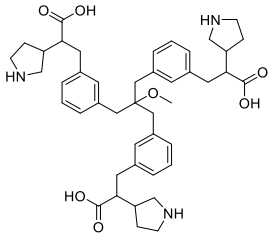
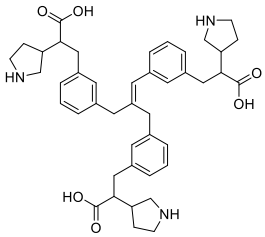
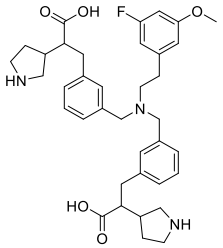
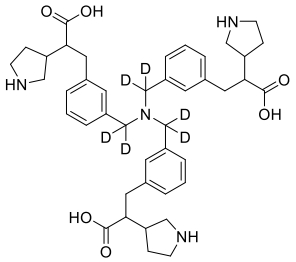
Compound No.	Compound Structure	Compound No.	Compound Structure
53-a	 3,3',3''-((nitrilotris(methylene))tris(1H-benzo[d]imidazole-2,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	54-a	 3,3',3''-((nitrilotris(methylene))tris(1H-pyrazolo[4,3-b]pyridine-3,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
55-a	 3,3',3''-((nitrilotris(methylene))tris(pyrrolo[3,4-b]pyrrole-4,3-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	56-a	 3,3',3''-((nitrilotris(methylene))tris(1H-benzo[d]imidazole-7,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
57-a	 3,3',3''-((nitrilotris(methylene))tris(1-methyl-1H-benzo[d]imidazole-7,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	58-a	 3,3',3''-((nitrilotris(methylene))tris(naphthalene-8,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)

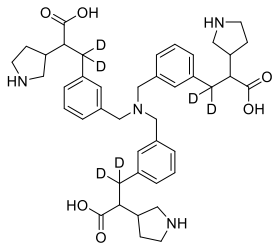
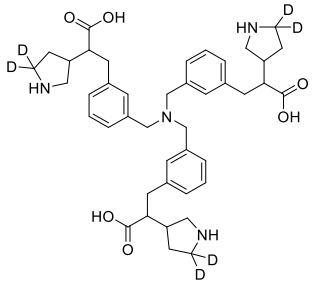
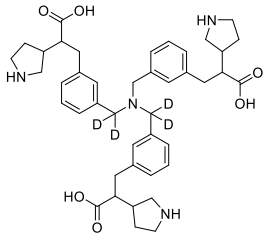
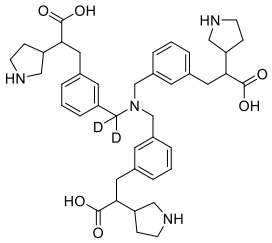
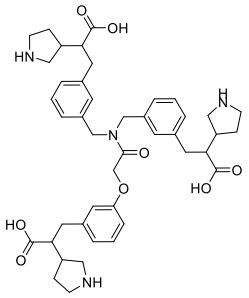
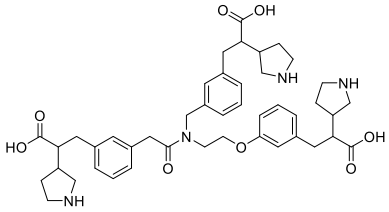
Compound No.	Compound Structure	Compound No.	Compound Structure
59-a	 3,3',3''-((nitrilotris(methylene))tris(quinoline-4,6-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	60-a	 3,3',3''-((nitrilotris(methylene))tris(quinoline-2,7-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
61-a	 3,3',3''-((nitrilotris(methylene))tris(quinazoline-8,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	62-a	 3,3'-((((3-fluoro-5-methoxybenzyl)azanediyl)bis(ethane-2,1-diyl))bis(1H-indole-1,6-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
63-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-fluorobenzyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	64-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis([1,1'-biphenyl]-3',3-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)

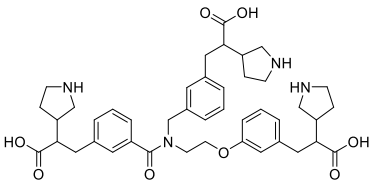
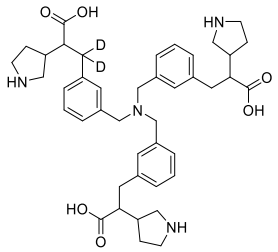
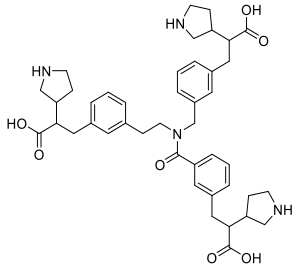
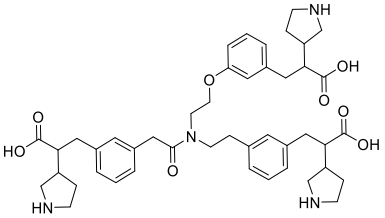
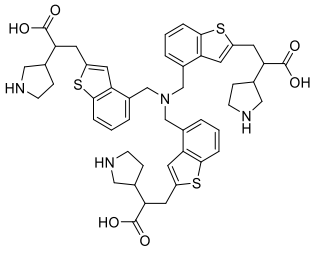
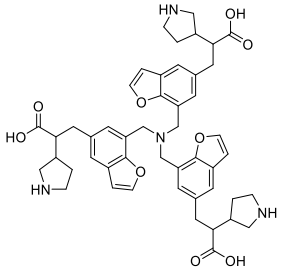
Compound No.	Compound Structure	Compound No.	Compound Structure
65-a	 3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	66-a	 3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(5-fluorobenzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
67-a	 3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(benzofuran-3,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	68-a	 3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(1H-indole-1,6-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
69-a	 3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(isoquinoline-1,7-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	70-a	 3,3'-((((2-(6-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-1H-indol-1-yl)ethyl)azanediyl)bis(ethane-2,1-diyl))bis(benzofuran-4,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)

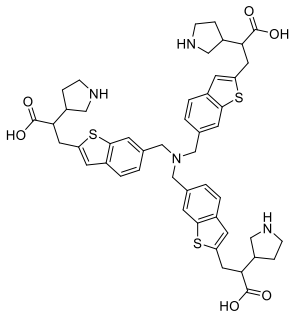
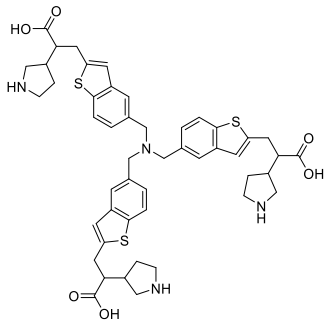
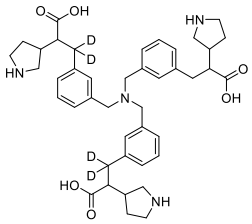
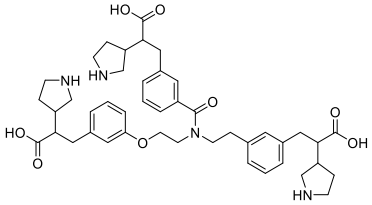
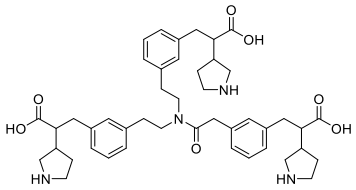
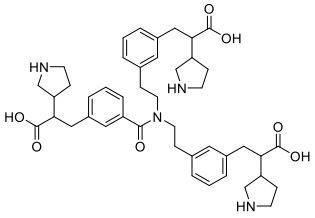
Compound No.	Compound Structure	Compound No.	Compound Structure
71-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	72-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methoxyphenoxy)ethyl)azanediyl)bis(ethane-2,1-diyl))bis(5-methoxy-3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
73-a	 3,3',3''-((nitrilotris(methylene))tris([1,1'-biphenyl]-3',3-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	74-a	 3,3'-(((((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)pyridin-3-yl)methyl)azanediyl)bis(methylene))bis([3,3'-bipyridine]-5',5-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
75-a	 3,3',3''-((nitrilotris(methylene))tris([3,3'-bipyridine]-5',5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	76-a	 4,4'-((((2-(3-carboxy-3-(pyrrolidin-3-yl)propyl)benzofuran-4-yl)methyl)azanediyl)bis(benzofuran-4,2-diyl))bis(2-(pyrrolidin-3-yl)butanoic acid)

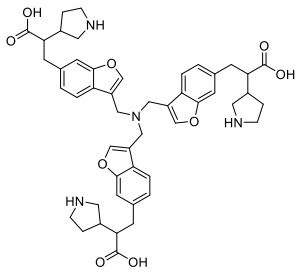
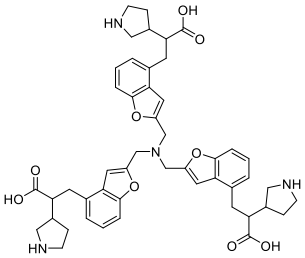
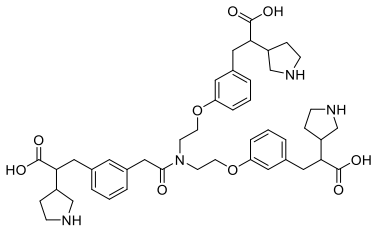
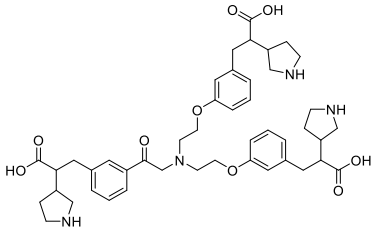
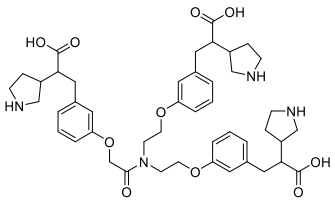
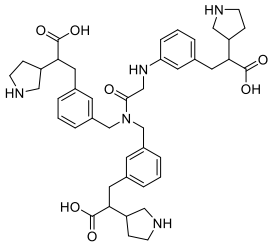
Compound No.	Compound Structure	Compound No.	Compound Structure
77-a	 4,4',4''-((nitrilotris(methylene))tris(benzofuran-4,2-diyl))tris(2-(pyrrolidin-3-yl)butanoic acid)	78-a	 4,4',4''-((nitrilotris(methylene))tris(1H-benzo[d]imidazole-4,2-diyl))tris(2-(pyrrolidin-3-yl)butanoic acid)
79-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)azanediyl)bis(2-oxoethane-2,1-diyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	80-a	 3,3'-((2,2'-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)azanediyl)bis(acetyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
81-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	82-a	 2,2',2''-((((nitrilotris(methylene))tris(benzofuran-4,2-diyl))tris(methylene))tris(oxy))tris(2-(pyrrolidin-3-yl)acetic acid)

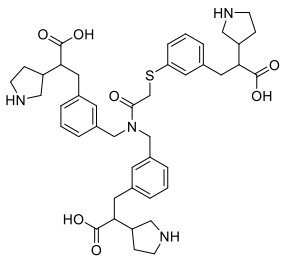
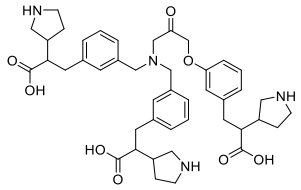
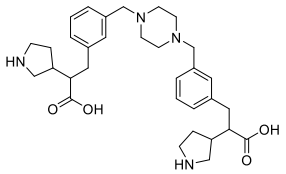
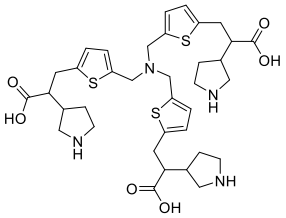
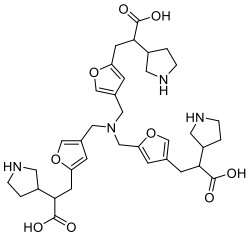
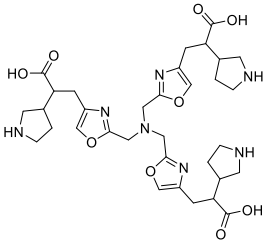
Compound No.	Compound Structure	Compound No.	Compound Structure
85-a	 3,3',3"-(((oxo-l5-phosphanetriyl)tris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	86-a	 3-[3-(3-{3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}-2-({3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}methyl)-2-hydroxypropyl)phenyl]-2-(tetrahydro-1*H*-pyrrol-3-yl)propanoic acid
87-a	 3-[3-(3-{3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}-2-({3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}methyl)-2-methoxypropyl)phenyl]-2-(tetrahydro-1*H*-pyrrol-3-yl)propanoic acid	88-a	 3-[3-(3-{3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}-2-({3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}methyl)prop-2-enyl)phenyl]-2-(tetrahydro-1*H*-pyrrol-3-yl)propanoic acid
89-a	 3,3'-((((3-fluoro-5-methoxyphenethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	90-a	 3,3',3"-((nitrilotris(methylene-d2))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)

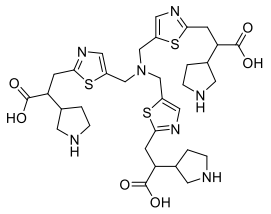
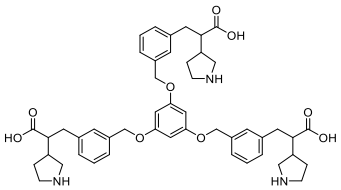
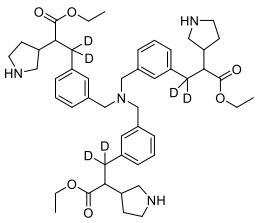
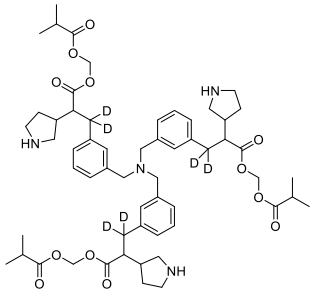
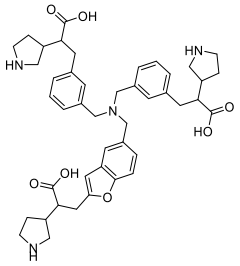
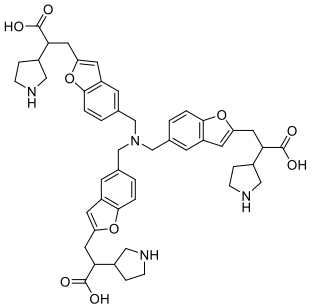
Compound No.	Compound Structure	Compound No.	Compound Structure
91-a	 3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic-3,3-d2 acid)	92-a	 3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl-5,5-d2)propanoic acid)
93-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene-d2))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	94-a	 3,3'-(((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)methyl-d2)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
95-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	96-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

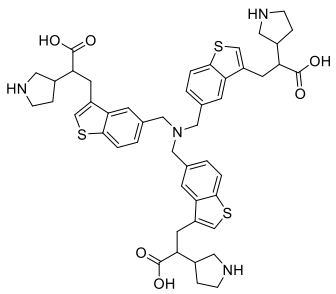
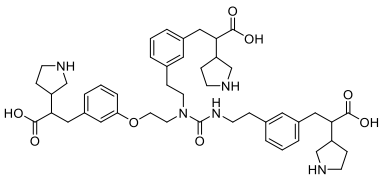
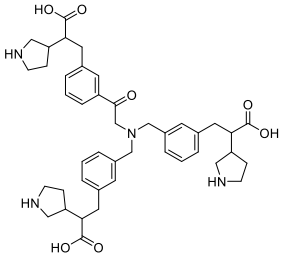
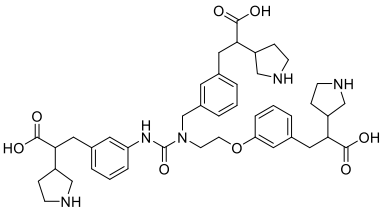
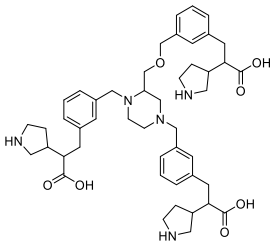
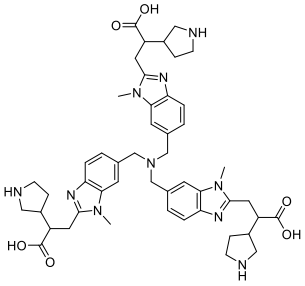
Compound No.	Compound Structure	Compound No.	Compound Structure
97-a	 3-(3-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-N-(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)benzamido)methyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	98-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl-1,1-d2)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
99-a	 3-(3-(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-N-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)benzamido)ethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	100-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenethyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
101-a	 3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-4,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	102-a	 3,3',3''-((nitrilotris(methylene))tris(benzofuran-7,5-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)

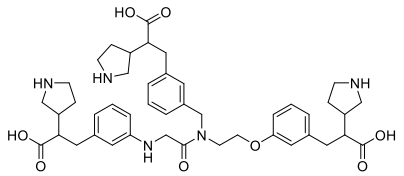
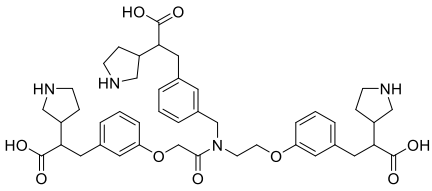
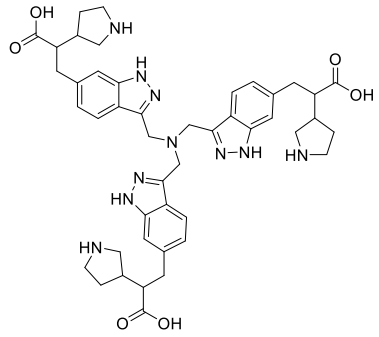
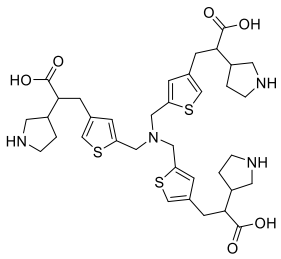
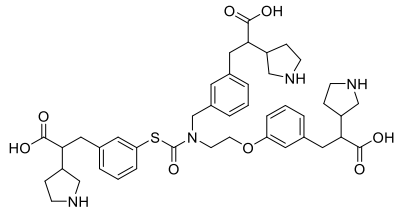
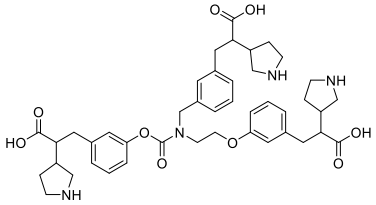
Compound No.	Compound Structure	Compound No.	Compound Structure
103-a	 3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-6,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	104-a	 3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-5,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
105-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic-3,3-d2 acid)	106-a	 3-(3-(2-(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-N-(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)benzamido)ethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
107-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	108-a	 3,3'-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzoyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

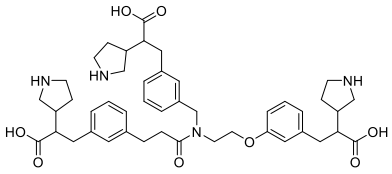
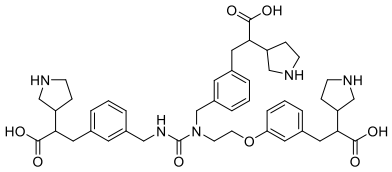
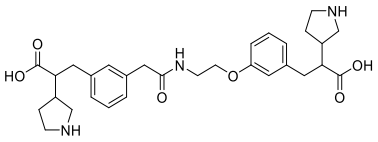
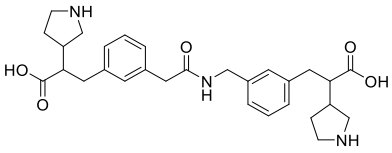
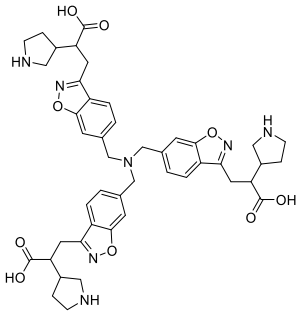
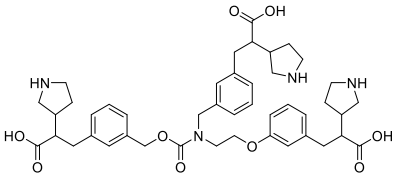
Compound No.	Compound Structure	Compound No.	Compound Structure
109-a	 3,3',3''-((nitrilotris(methylene))tris(benzofuran-3,6-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	110-a	 3,3',3''-((nitrilotris(methylene))tris(benzofuran-2,4-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
111-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	112-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)-2-oxoethyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
113-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	114-a	 3,3'-(((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)glycyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

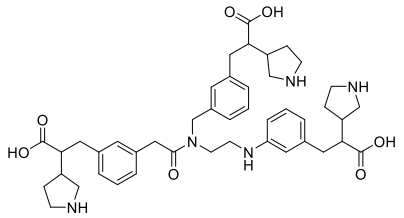
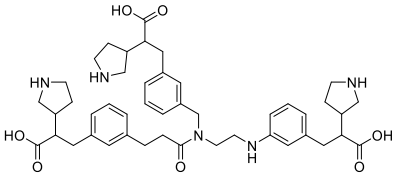
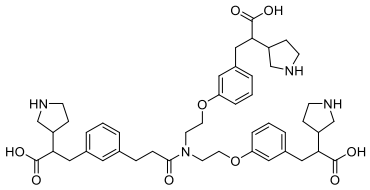
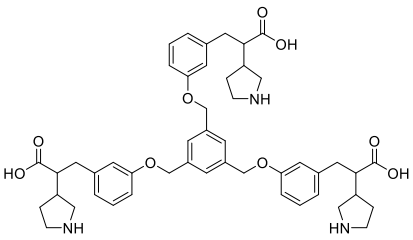
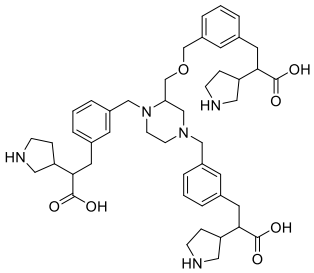
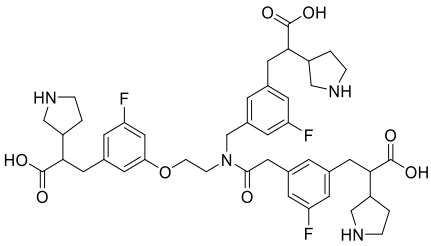
Compound No.	Compound Structure	Compound No.	Compound Structure
115-a	 3,3'-((((2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)thio)acetyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	116-a	 3,3'-((((3-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)-2-oxopropyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
117-a	 3,3'-((piperazine-1,4-diylbis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	118-a	 3,3',3''-((nitrilotris(methylene))tris(thiophene-5,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
119-a	 3,3'-(((((4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)furan-2-yl)methyl)azanediyl)bis(methylene))bis(furan-4,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	120-a	 3,3',3''-((nitrilotris(methylene))tris(oxazole-2,4-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)

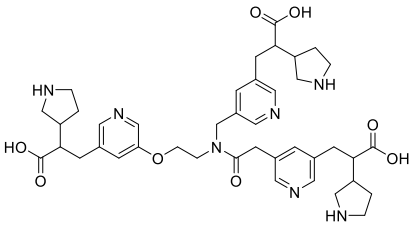
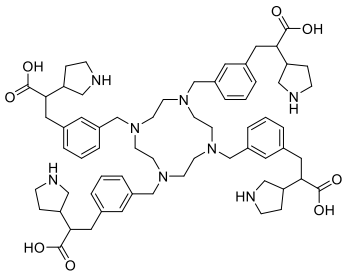
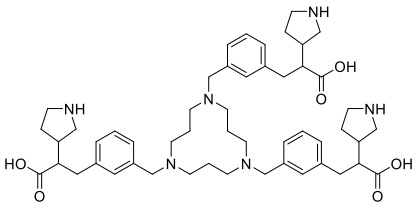
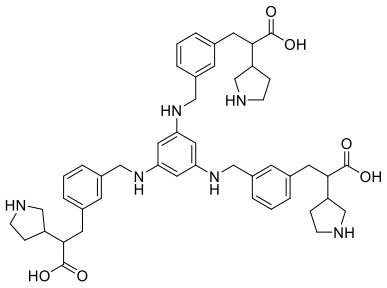
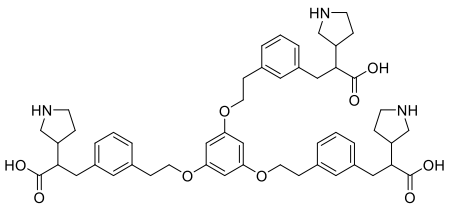
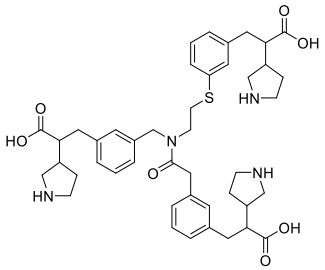
Compound No.	Compound Structure	Compound No.	Compound Structure
121-a	 3,3',3''-((nitrilotris(methylene))tris(thiazole-5,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	122-a	 3,3',3''-(((benzene-1,3,5-triyltris(oxy))tris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
123-a	 triethyl 3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoate-3',3'-d2)	124-a	 tris((isobutyryloxy)methyl) 3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoate-3',3'-d2)
126-a	 3,3'-(((((2-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzofuran-5-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	127-a	 3,3',3''-((nitrilotris(methylene))tris(benzofuran-5,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)

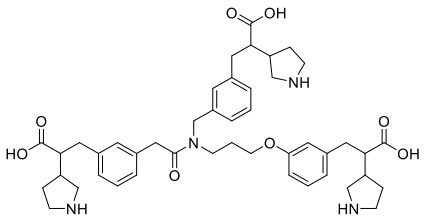
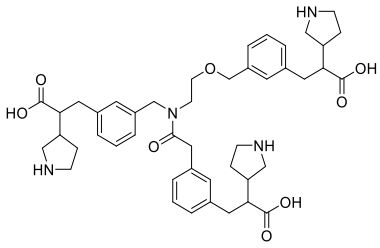
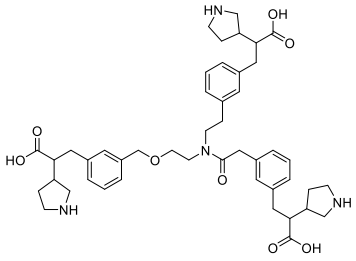
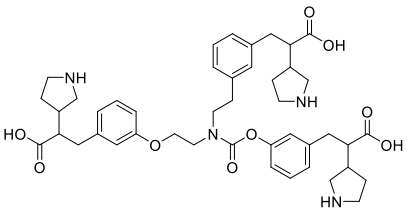
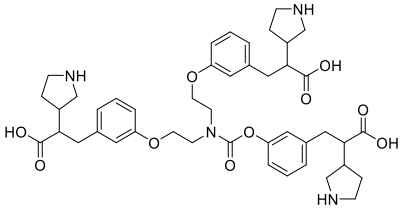
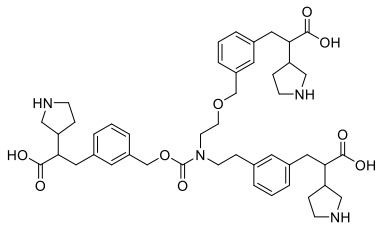
Compound No.	Compound Structure	Compound No.	Compound Structure
128-a	 3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-5,3-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	129-a	 3-(3-(2-(1,3-bis(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenethyl)ureido)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
130-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)-2-oxoethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	131-a	 3-(3-(3-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)-3-(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)ureido)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
132-a	 3,3'-(((2-(((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)methyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	133-a	 3,3',3''-((nitrilotris(methylene))tris(1-methyl-1H-benzo[d]imidazole-6,2-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)

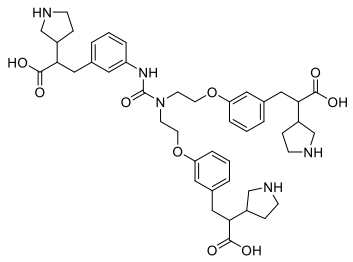
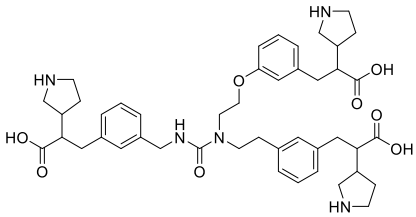
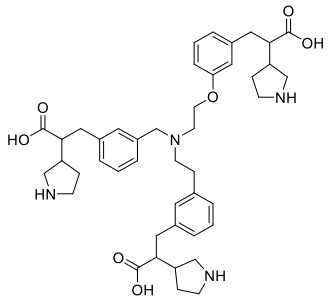
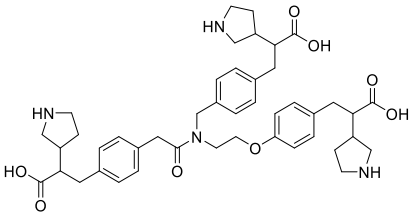
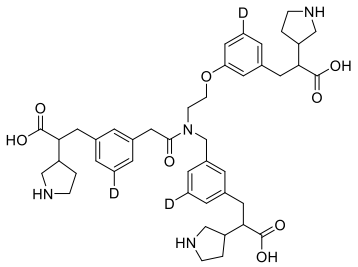
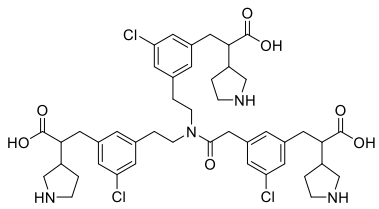
Compound No.	Compound Structure	Compound No.	Compound Structure
134-a	 3-(3-((2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)amino)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	135-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
136-a	 3,3',3''-((nitrilotris(methylene))tris(1H-indazole-3,6-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	137-a	 3,3',3''-((nitrilotris(methylene))tris(thiophene-5,3-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
138-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)thio)carbonyl)amino)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	139-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)amino)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

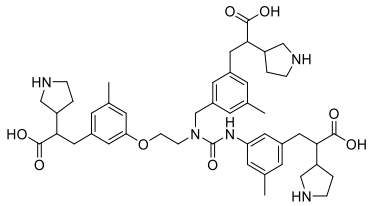
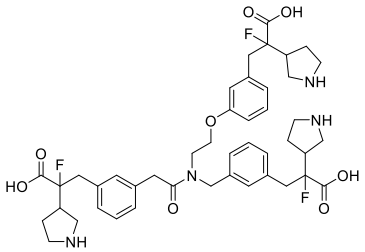
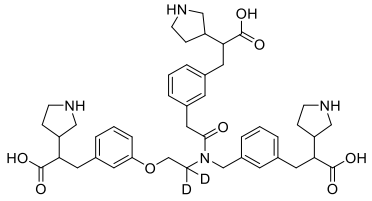
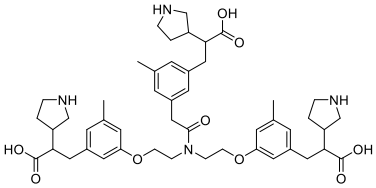
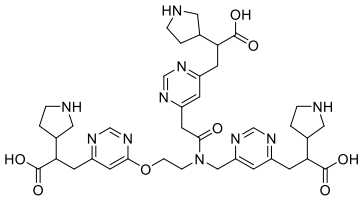
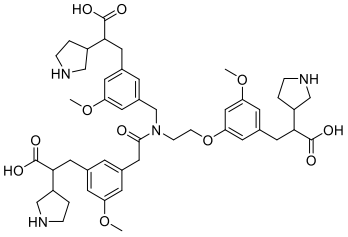
Compound No.	Compound Structure	Compound No.	Compound Structure
140-a	 3-(3-(3-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-3-oxopropyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	141-a	 3-(3-(2-(1,3-bis(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)ureido)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
142-a	 3-(3-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	143-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
144-a	 3,3',3''-((nitrilotris(methylene))tris(benzo[d]isoxazole-6,3-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	145	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)carbonyl)amino)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

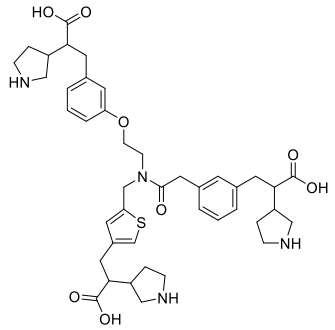
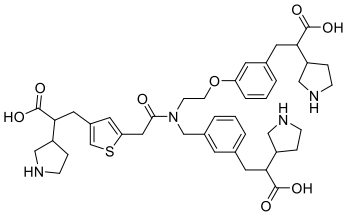
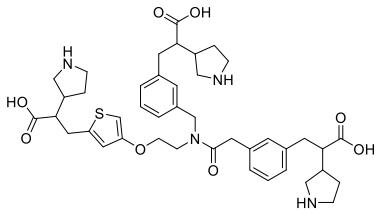
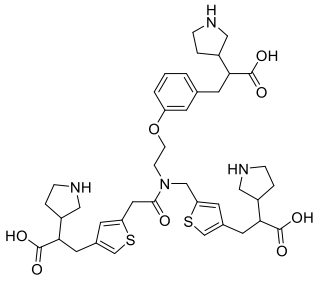
Compound No.	Compound Structure	Compound No.	Compound Structure
146-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)amino)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	147-a	 3-(3-(3-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)amino)ethyl)amino)-3-oxopropyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
148-a	 3,3'-(((((3-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)propanoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	149-a	 3,3',3''-(((benzene-1,3,5-triyltris(methylene))tris(oxy))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
150-a	 3,3'-(((2-(((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)methyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	152-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-fluorobenzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-fluorophenoxy)ethyl)amino)-2-oxoethyl)-5-fluorophenyl)-2-(pyrrolidin-3-yl)propanoic acid

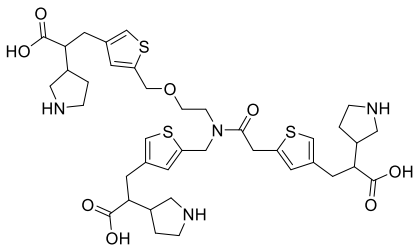
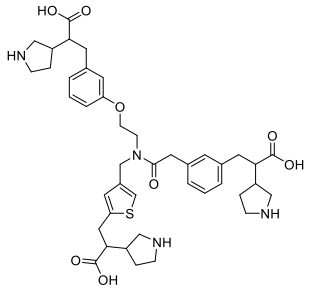
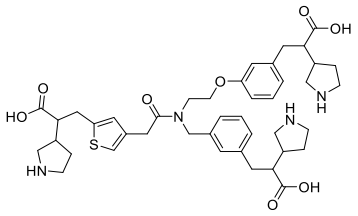
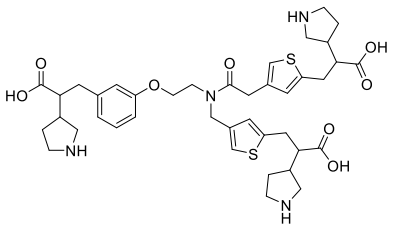
Compound No.	Compound Structure	Compound No.	Compound Structure
153-a	 3-(5-(2-(2-(5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)pyridin-3-yl)-N-((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)pyridin-3-yl)methyl)acetamido)ethoxy)pyridin-3-yl)-2-(pyrrolidin-3-yl)propanoic acid	154-a	 3,3',3",3'"-(((1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(methylene))tetrakis(benzene-3,1-diyl))tetrakis(2-(pyrrolidin-3-yl)propanoic acid)
155-a	 3,3',3"-(((1,5,9-triazacyclododecane-1,5,9-triyl)tris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	156-a	 3,3',3"-(((benzene-1,3,5-triyltris(azanediyl))tris(methylene))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)
157-a	 3,3',3"-(((benzene-1,3,5-triyltris(oxy))tris(ethane-2,1-diyl))tris(benzene-3,1-diyl))tris(2-(pyrrolidin-3-yl)propanoic acid)	158-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)thio)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

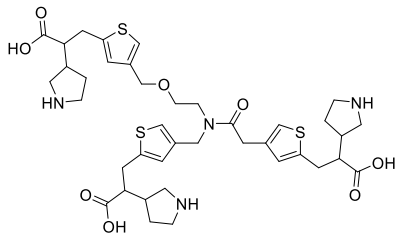
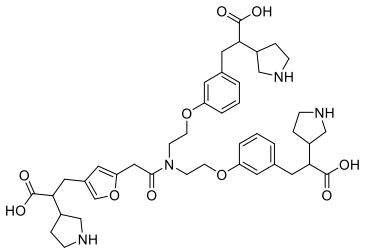
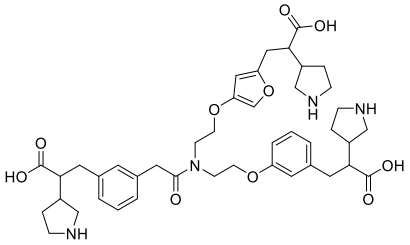
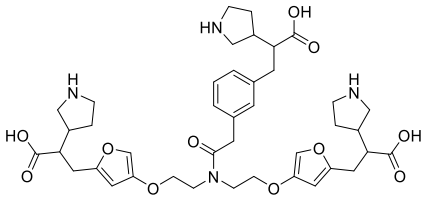
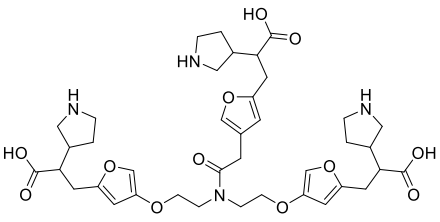
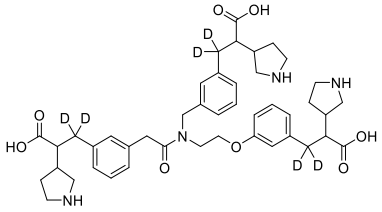
Compound No.	Compound Structure	Compound No.	Compound Structure
159-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(3-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)propyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	160-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
161-a	 3-(3-(2-((2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)ethyl)(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	162-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenethyl)((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)amino)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
163-a	 3,3'-((((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	164-a	 3-(3-(2-((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)carbonyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)ethyl)amino)ethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

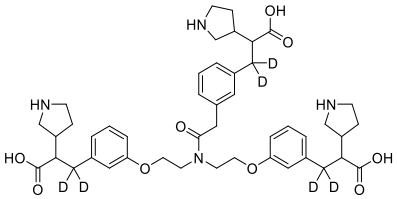
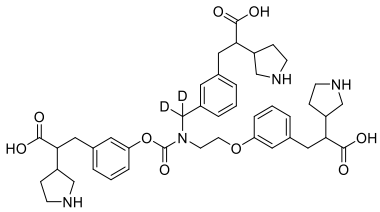
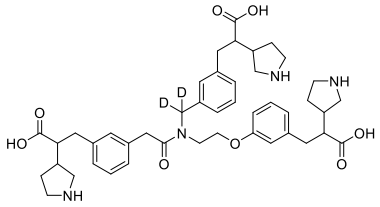
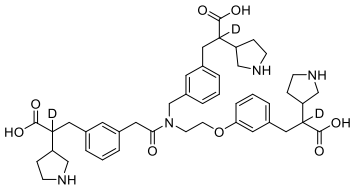
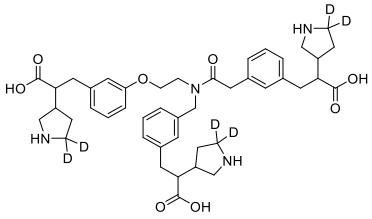
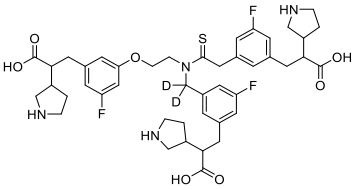
Compound No.	Compound Structure	Compound No.	Compound Structure
165-a	 3,3'-((((((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)carbamoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	166-a	 3-(3-(2-(3-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)-1-(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)ureido)ethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
167-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)ethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	168-a	 3-(4-(2-((4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
169-a	 3-(3-{[(2-{5-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]-3-deuteriophenyl}acetyl)[2-({3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]-5-deuteriophenyl}oxy)ethyl]amino]methyl}-5-deuteriophenyl)-2-(tetrahydro-1*H*-pyrrol-3-yl)propanoic acid	170-a	 3,3'-((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-chlorophenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(5-chloro-3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)

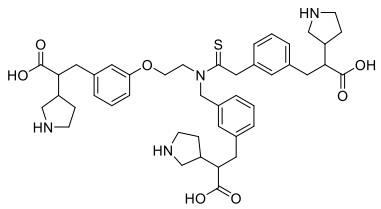
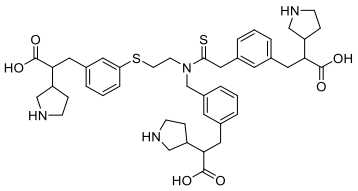
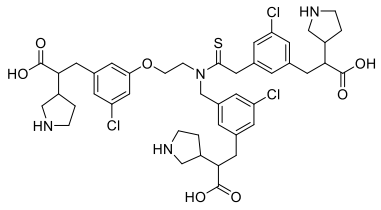
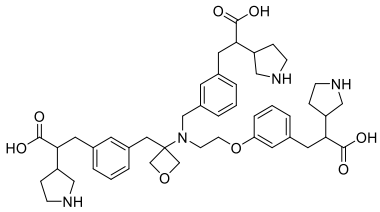
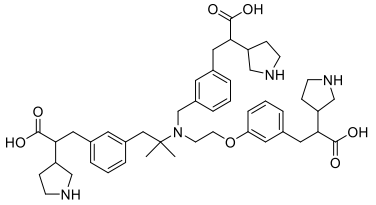
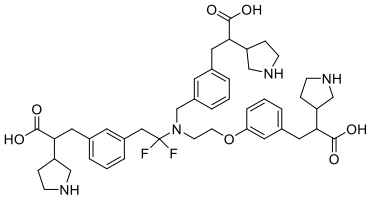
Compound No.	Compound Structure	Compound No.	Compound Structure
171-a	 3-(3-(3-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methylbenzyl)-3-(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methylphenoxy)ethyl)ureido)-5-methylphenyl)-2-(pyrrolidin-3-yl)propanoic acid	172-a	 3-(3-(2-((3-(2-carboxy-2-fluoro-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-fluoro-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-fluoro-2-(pyrrolidin-3-yl)propanoic acid
173-a	 3-[3-({2-[(2-{3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}acetyl)({3-[2-carboxy-2-(tetrahydro-1*H*-pyrrol-3-yl)ethyl]phenyl}methyl)amino]-2,2-dideuterioethyl}oxy)phenyl]-2-(tetrahydro-1*H*-pyrrol-3-yl)propanoic acid	174-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methylphenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(5-methyl-3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
175-a	 3-(6-(2-(2-(6-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)pyrimidin-4-yl)-N-((6-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)pyrimidin-4-yl)methyl)acetamido)ethoxy)pyrimidin-4-yl)-2-(pyrrolidin-3-yl)propanoic acid	176-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methoxybenzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methoxyphenoxy)ethyl)amino)-2-oxoethyl)-5-methoxyphenyl)-2-(pyrrolidin-3-yl)propanoic acid

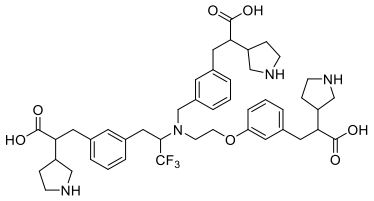
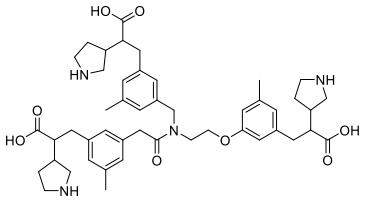
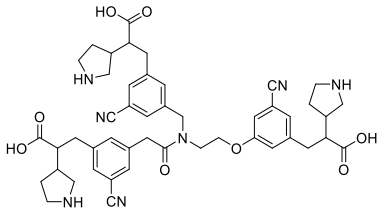
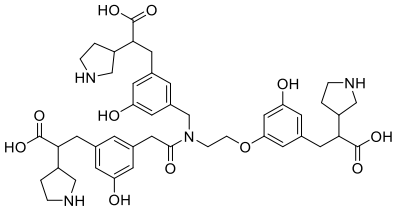
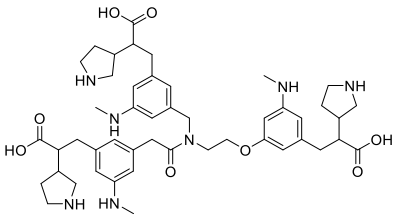
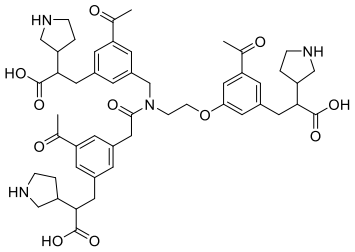
Compound No.	Compound Structure	Compound No.	Compound Structure
177-a	 3-(3-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-2-yl)methyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	178-a	 3-(5-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)thiophen-3-yl)-2-(pyrrolidin-3-yl)propanoic acid
179-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-3-yl)oxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	180-a	 3-(5-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-2-yl)methyl)amino)-2-oxoethyl)thiophen-3-yl)-2-(pyrrolidin-3-yl)propanoic acid

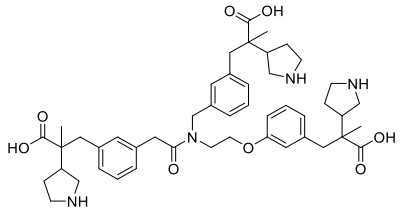
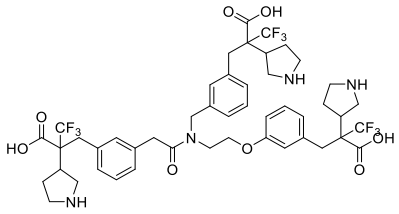
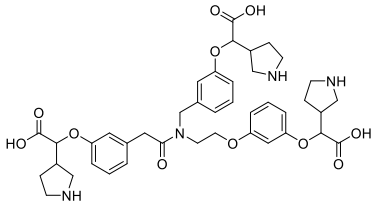
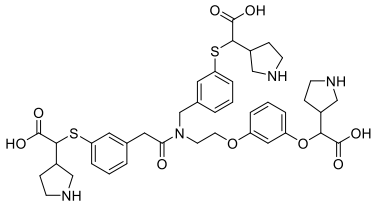
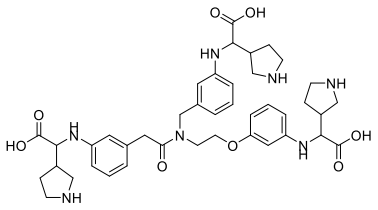
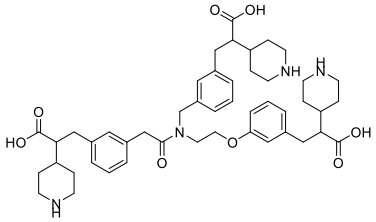
Compound No.	Compound Structure	Compound No.	Compound Structure
181-a	 3-(5-((2-(2-(4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-2-yl)-N-((4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-2-yl)methyl)acetamido)ethoxy)methyl)thiophen-3-yl)-2-(pyrrolidin-3-yl)propanoic acid	182-a	 3-(3-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-3-yl)methyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
183-a	 3-(4-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)thiophen-2-yl)-2-(pyrrolidin-3-yl)propanoic acid	184-a	 3-(4-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-3-yl)methyl)amino)-2-oxoethyl)thiophen-2-yl)-2-(pyrrolidin-3-yl)propanoic acid

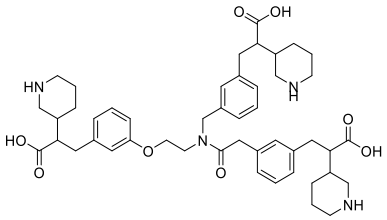
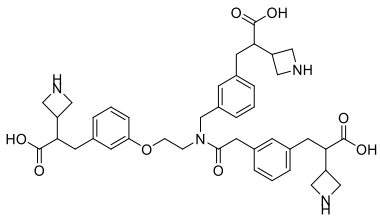
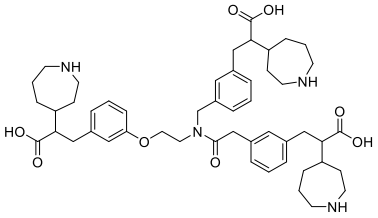
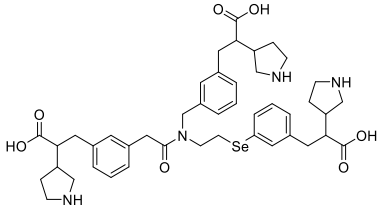
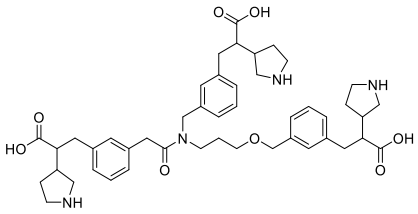
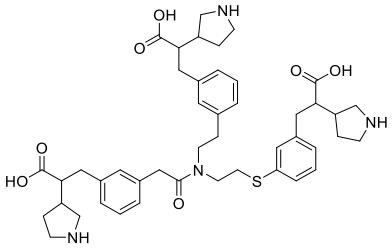
Compound No.	Compound Structure	Compound No.	Compound Structure
185-a	 3-(4-((2-(2-(5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-3-yl)-N-((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)thiophen-3-yl)methyl)acetamido)ethoxy)methyl)thiophen-2-yl)-2-(pyrrolidin-3-yl)propanoic acid	186-a	 3,3'-(((((2-(4-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)furan-2-yl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
187-a	 3-(3-(2-((2-((5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)furan-3-yl)oxy)ethyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	188-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(furan-4,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)
189-a	 3,3'-(((((2-(5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)furan-3-yl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(furan-4,2-diyl))bis(2-(pyrrolidin-3-yl)propanoic acid)	190-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl-1,1-d2)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl-1,1-d2)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic-3,3-d2 acid

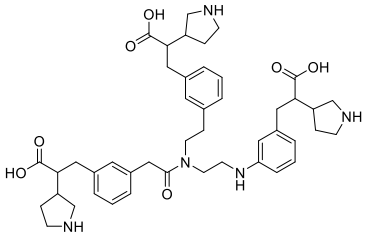
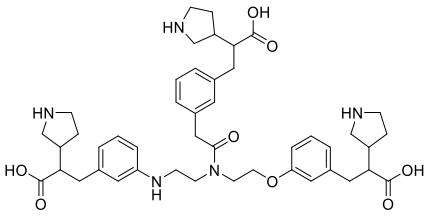
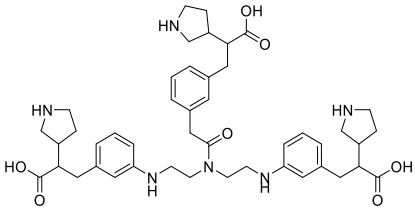
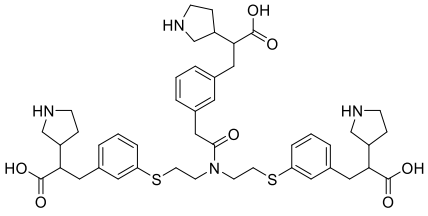
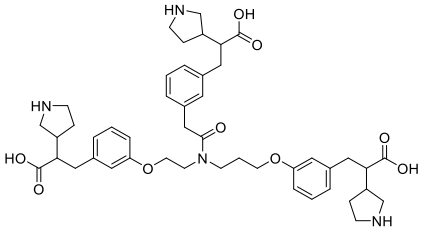
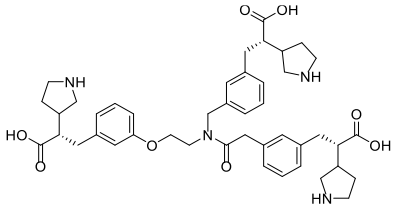
Compound No.	Compound Structure	Compound No.	Compound Structure
191-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl-1,1-d2)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic-3,3-d2 acid)	192-a	 3-(3-(2-(((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)methyl-d2)amino)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
193-a	 3-(3-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)methyl-d2)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	194-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl-2-d)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl-2-d)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic-2-d acid
195-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl-5,5-d2)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl-5,5-d2)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl-5,5-d2)propanoic acid	196-a	 3-(3-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-fluorophenoxy)ethyl)((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-fluorophenyl)methyl-d2)amino)-2-thioxoethyl)-5-fluorophenyl)-2-(pyrrolidin-3-yl)propanoic acid

Compound No.	Compound Structure	Compound No.	Compound Structure
197-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-thioxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	198-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)thio)ethyl)amino)-2-thioxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
199-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-chlorobenzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-chlorophenoxy)ethyl)amino)-2-thioxoethyl)-5-chlorophenyl)-2-(pyrrolidin-3-yl)propanoic acid	200-a	 3-(3-((3-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)oxetan-3-yl)methyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
201-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(1-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)-2-methylpropan-2-yl)amino)ethoxy)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	202-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2,2-difluoroethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

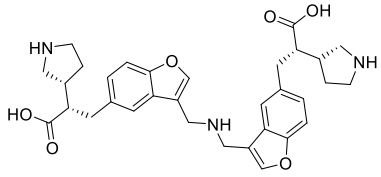
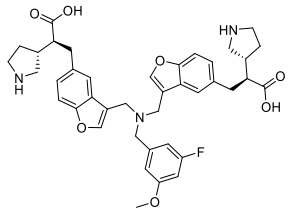
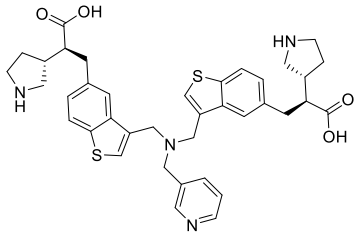
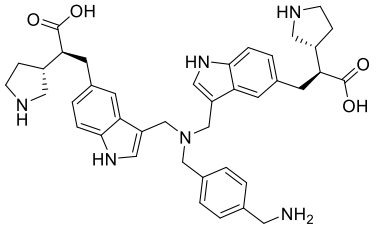
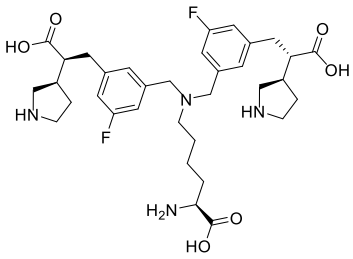
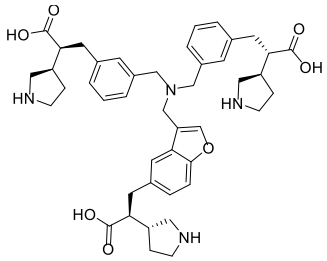
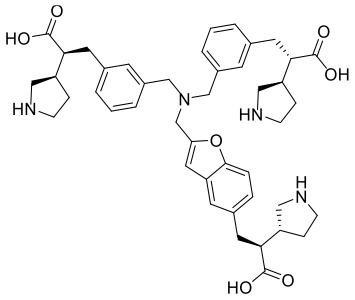
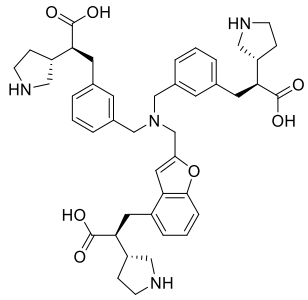
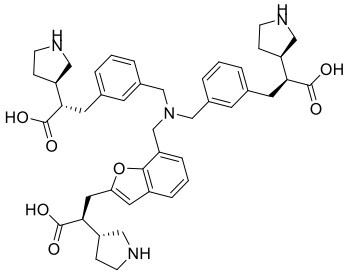
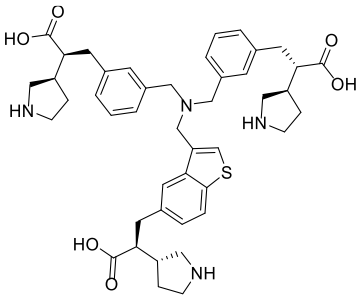
Compound No.	Compound Structure	Compound No.	Compound Structure
203-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-3,3,3-trifluoropropyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	204-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methylbenzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-methylphenoxy)ethyl)amino)-2-oxoethyl)-5-methylphenyl)-2-(pyrrolidin-3-yl)propanoic acid
205-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-cyanobenzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-cyanophenoxy)ethyl)amino)-2-oxoethyl)-5-cyanophenyl)-2-(pyrrolidin-3-yl)propanoic acid	206-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-hydroxybenzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-hydroxyphenoxy)ethyl)amino)-2-oxoethyl)-5-hydroxyphenyl)-2-(pyrrolidin-3-yl)propanoic acid
207-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-(methylamino)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)-5-(methylamino)phenoxy)ethyl)amino)-2-oxoethyl)-5-(methylamino)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	208-a	 3-(3-acetyl-5-((N-(2-(3-acetyl-5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)-2-(3-acetyl-5-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)acetamido)methyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

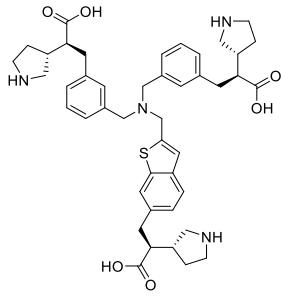
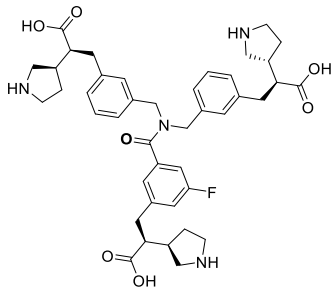
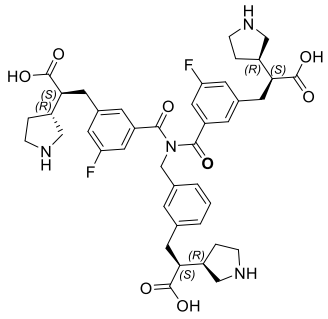
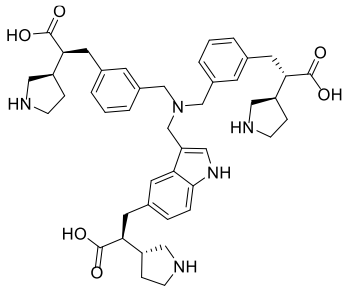
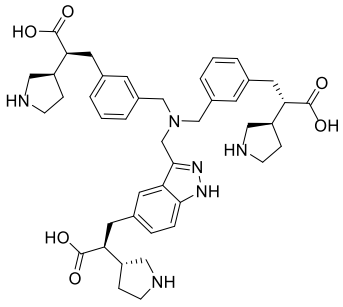
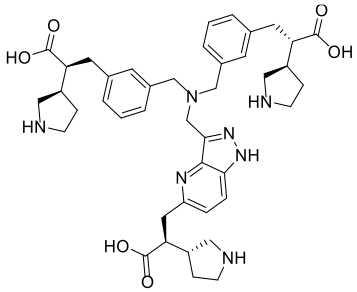
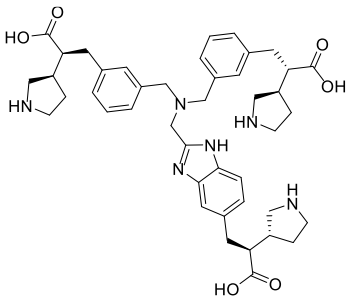
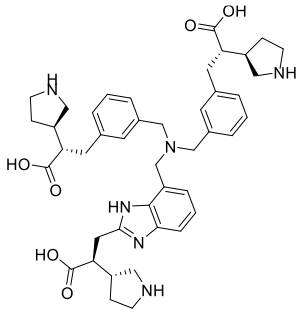
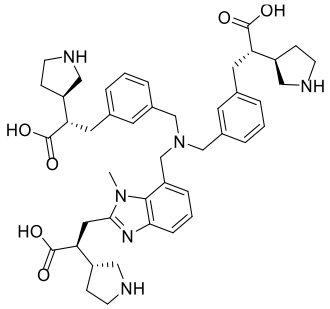
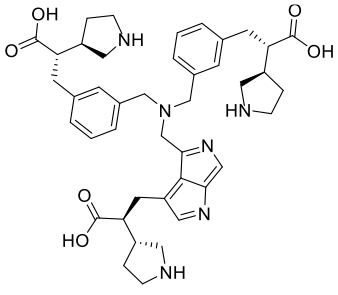
Compound No.	Compound Structure	Compound No.	Compound Structure
212-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)propyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)propyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-methyl-2-(pyrrolidin-3-yl)propanoic acid	213-a	 2-(3-(2-((3-(2-carboxy-3,3,3-trifluoro-2-(pyrrolidin-3-yl)propyl)benzyl)(2-(3-(2-carboxy-3,3,3-trifluoro-2-(pyrrolidin-3-yl)propyl)phenoxy)ethyl)amino)-2-oxoethyl)benzyl)-3,3,3-trifluoro-2-(pyrrolidin-3-yl)propanoic acid
214-a	 2-(3-(2-((3-(carboxy(pyrrolidin-3-yl)methoxy)benzyl)(2-(3-(carboxy(pyrrolidin-3-yl)methoxy)phenoxy)ethyl)amino)-2-oxoethyl)phenoxy)-2-(pyrrolidin-3-yl)acetic acid	215-a	 2-((3-(2-((2-(3-(carboxy(pyrrolidin-3-yl)methoxy)phenoxy)ethyl)(3-((carboxy(pyrrolidin-3-yl)methyl)thio)benzyl)amino)-2-oxoethyl)phenyl)thio)-2-(pyrrolidin-3-yl)acetic acid
216-a	 2-((3-(2-((3-((carboxy(pyrrolidin-3-yl)methyl)amino)benzyl)(2-(3-((carboxy(pyrrolidin-3-yl)methyl)amino)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)amino)-2-(pyrrolidin-3-yl)acetic acid	217-a	 3-(3-(2-((3-(2-carboxy-2-(piperidin-4-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(piperidin-4-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(piperidin-4-yl)propanoic acid

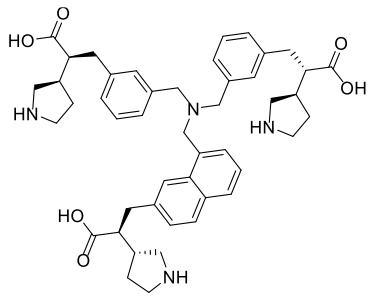
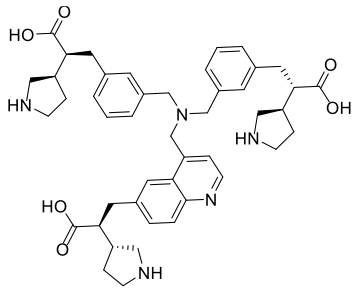
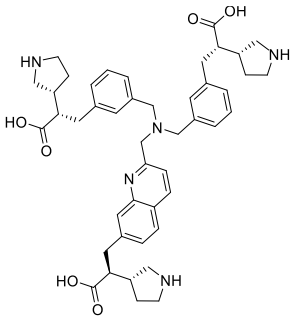
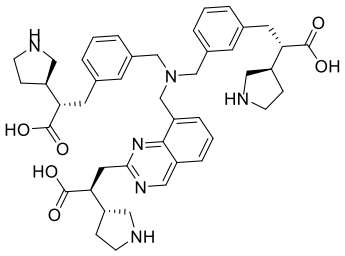
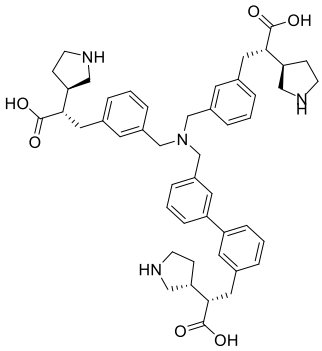
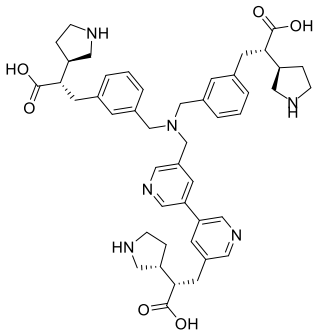
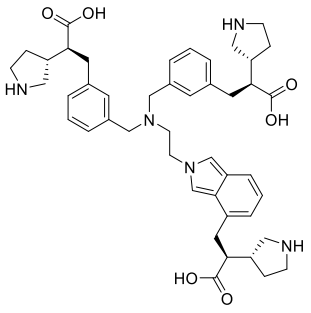
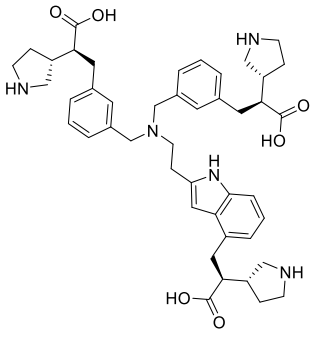
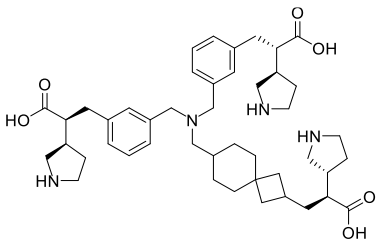
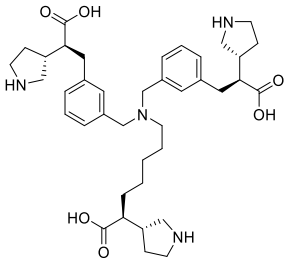
Compound No.	Compound Structure	Compound No.	Compound Structure
218-a	 3-(3-(2-((3-(2-carboxy-2-(piperidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(piperidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(piperidin-3-yl)propanoic acid	219-a	 2-(azetidin-3-yl)-3-(3-(2-((3-(2-(azetidin-3-yl)-2-carboxyethyl)benzyl)(2-(3-(2-(azetidin-3-yl)-2-carboxyethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)propanoic acid
220-a	 2-(azepan-4-yl)-3-(3-(2-((3-(2-(azepan-4-yl)-2-carboxyethyl)benzyl)(2-(3-(2-(azepan-4-yl)-2-carboxyethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)propanoic acid	221-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)selanyl)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
222-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(3-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)oxy)propyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	223-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenethyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)thio)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

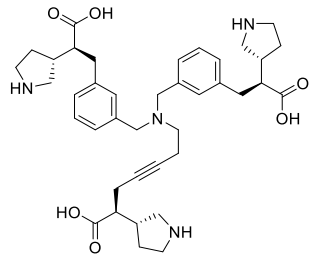
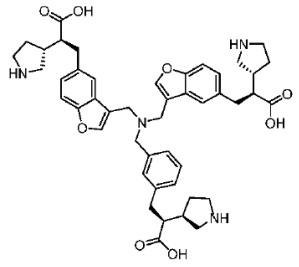
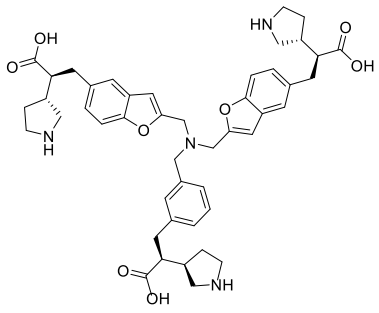
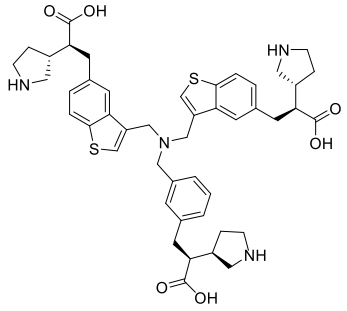
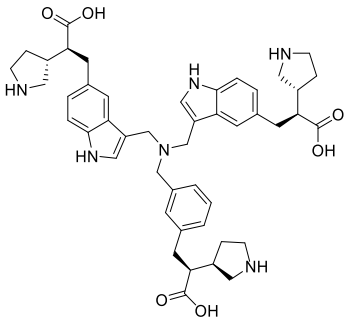
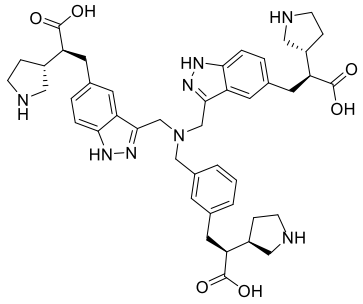
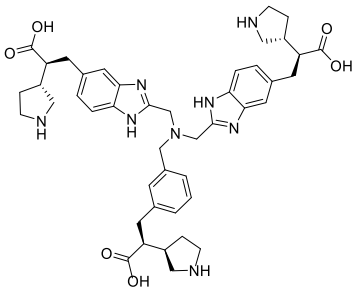
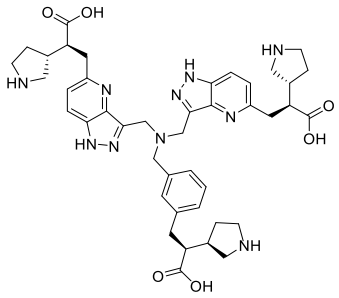
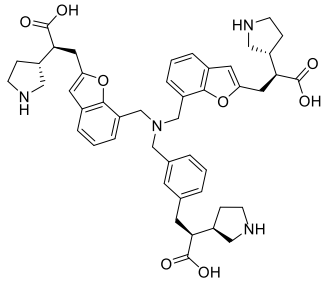
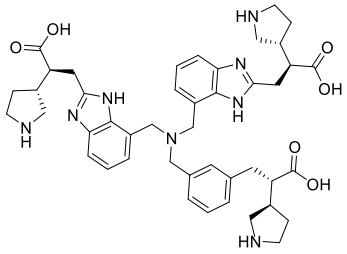
Compound No.	Compound Structure	Compound No.	Compound Structure
224-a	 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenethyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)amino)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	225-a	 3-(3-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)amino)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid
226-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(azanediyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)	227-a	 3,3'-(((((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(sulfanediyl))bis(3,1-phenylene))bis(2-(pyrrolidin-3-yl)propanoic acid)
228-a	 3-(3-(2-((2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)(3-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)propyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid	96-b	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid

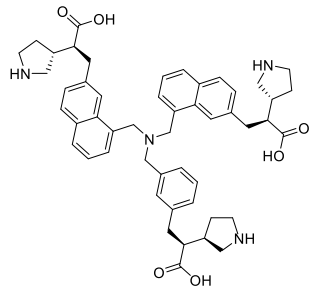
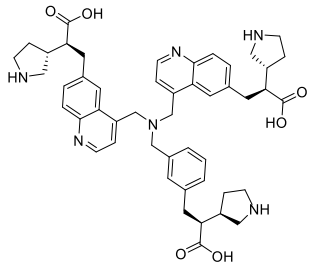
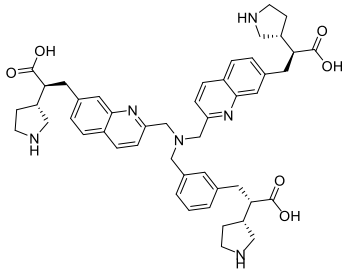
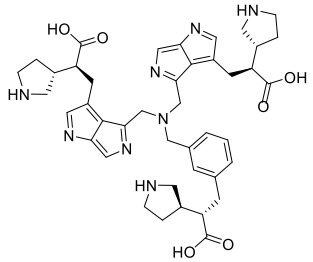
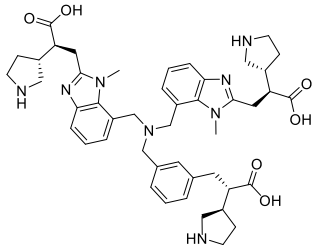
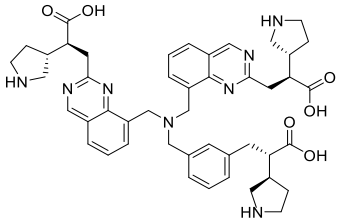
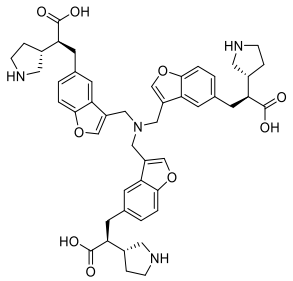
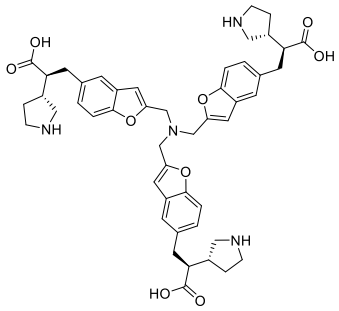
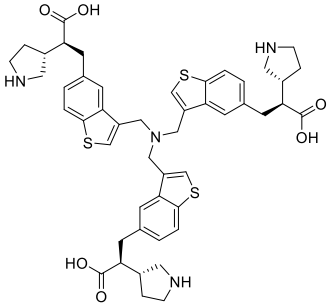
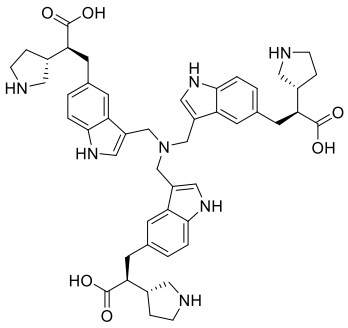
In one embodiment of the invention, the compound of the invention or a pharmaceutically acceptable salt thereof is selected from:

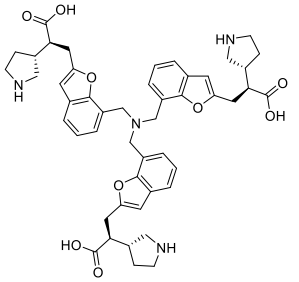
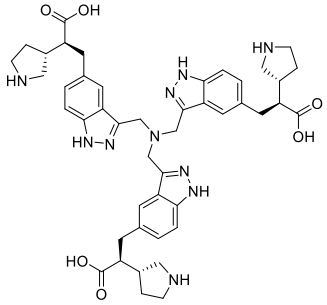
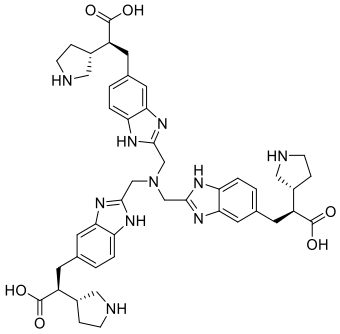
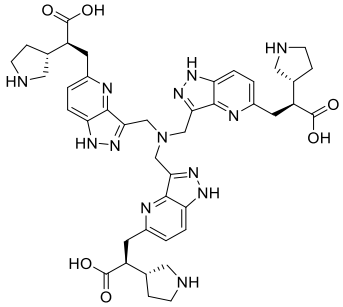
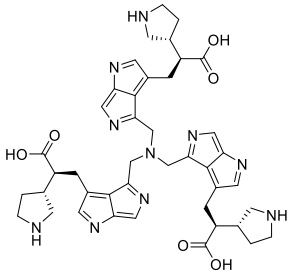
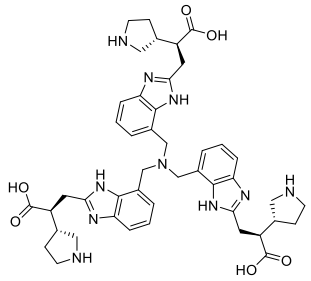
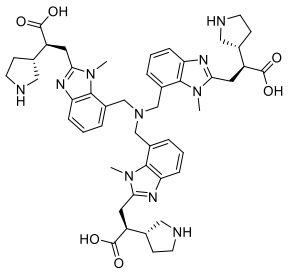
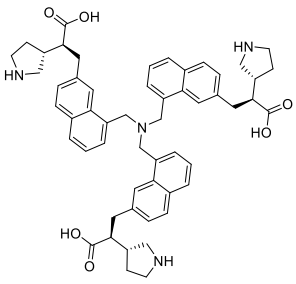
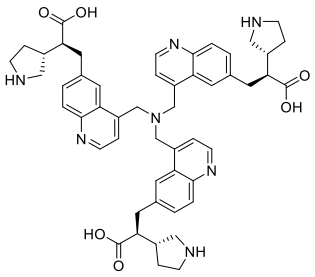
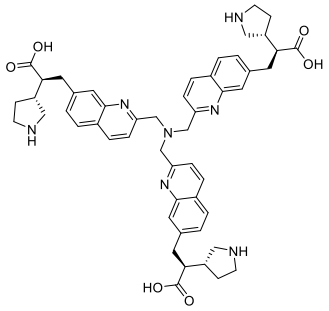
Compound No.	Structure	Compound No.	Structure
1		2	
3		4	
5		6	
7		8	
9		10	

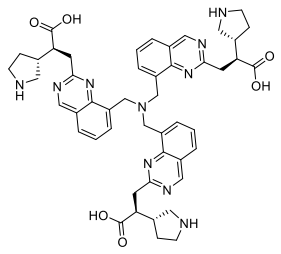
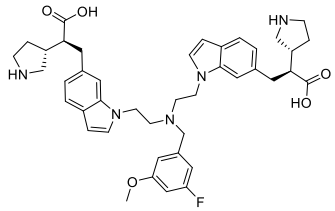
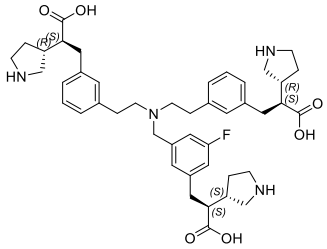
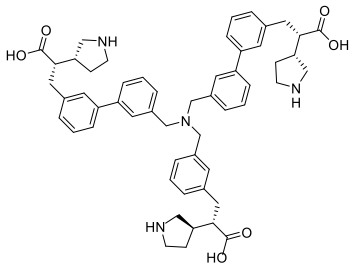
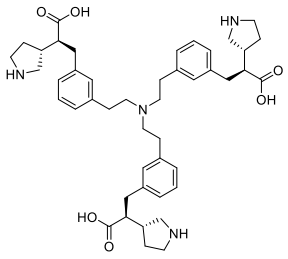
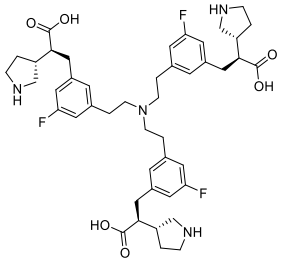
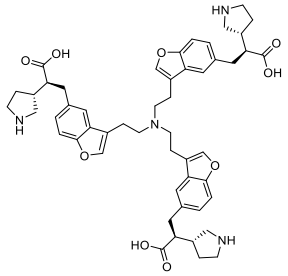
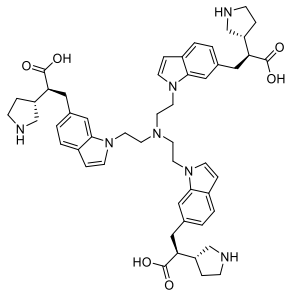
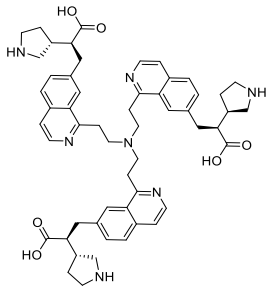
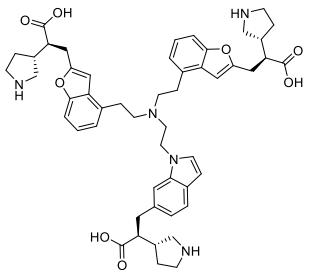
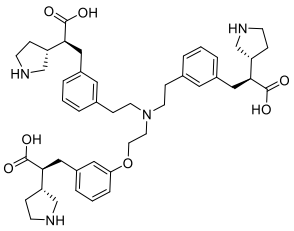
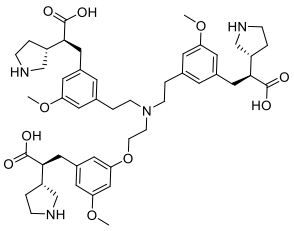
11		12	
13		14	
15		16	
17		18	
19		20	

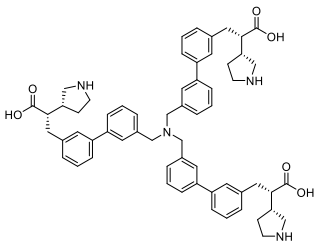
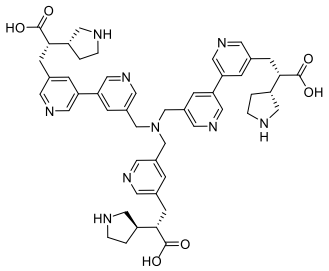
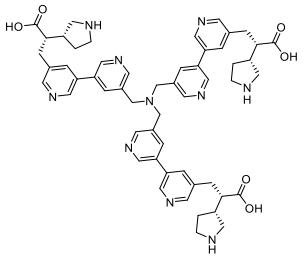
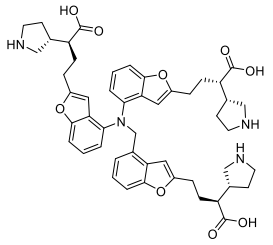
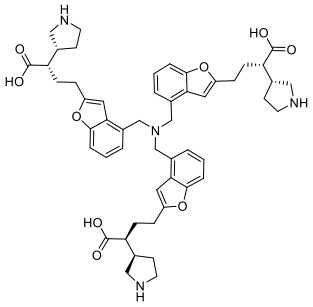
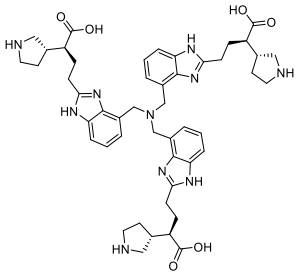
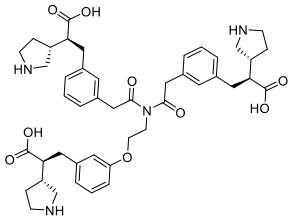
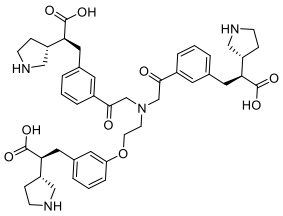
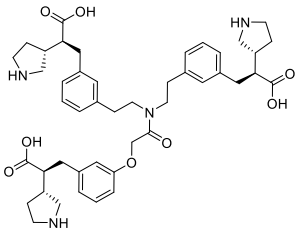
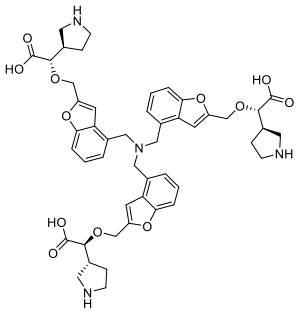
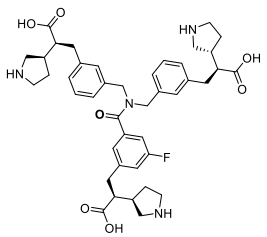
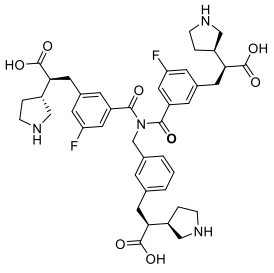
21		22	
23		24	
25		26	
27		28	
29		30	

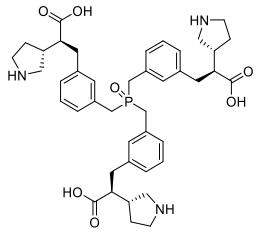
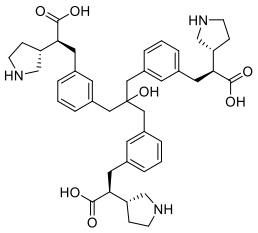
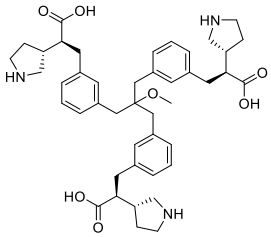
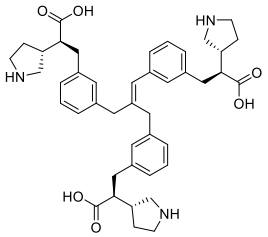
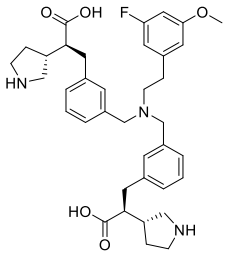
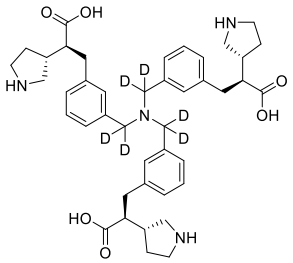
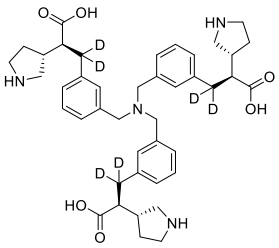
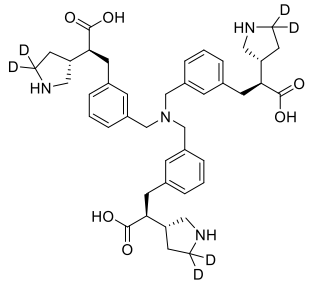
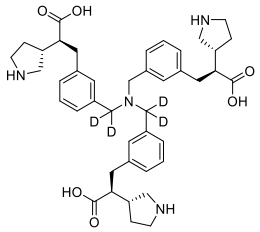
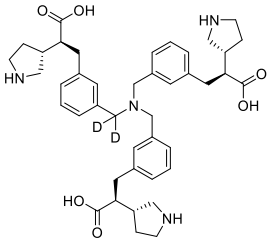
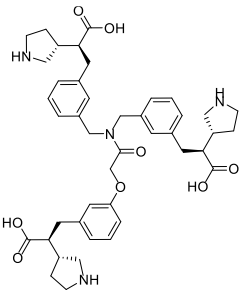
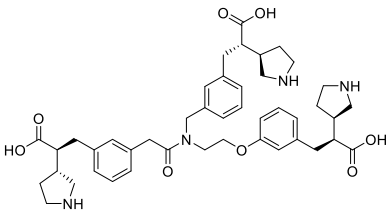
31		32	
33		34	
35		36	
37		38	
39		40	

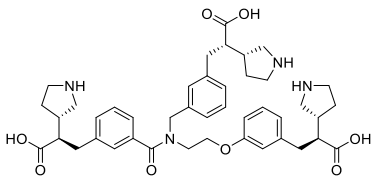
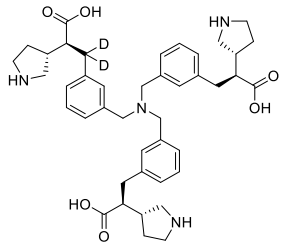
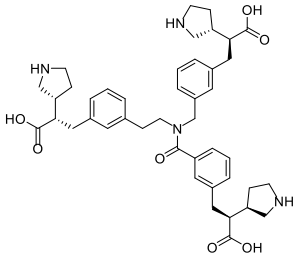
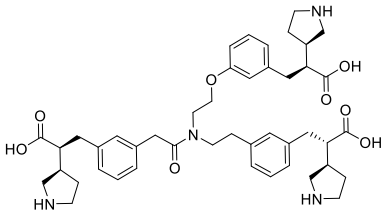
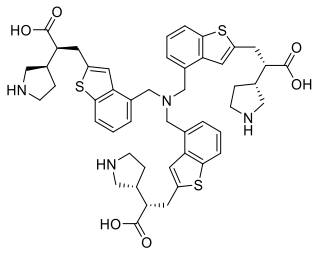
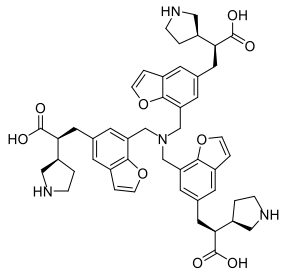
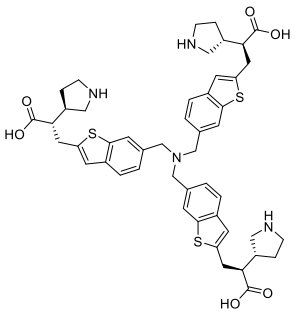
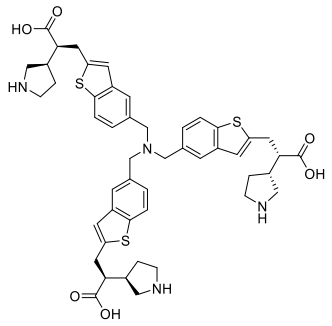
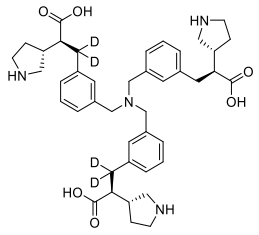
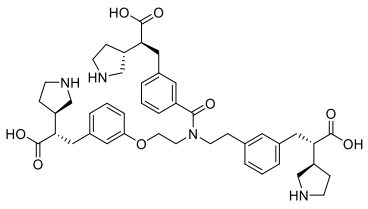
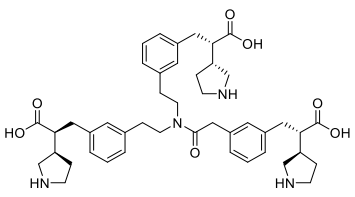
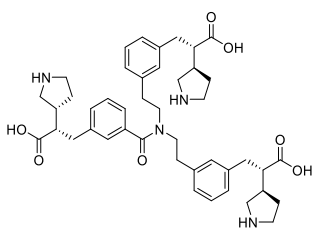
41		42	
43		44	
45		46	
47		48	
49		50	

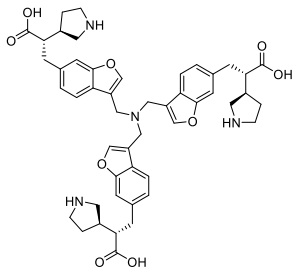
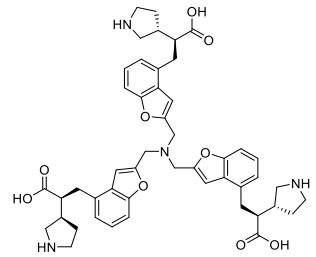
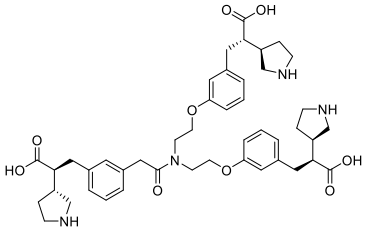
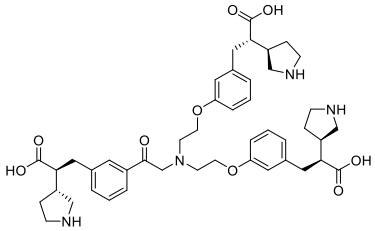
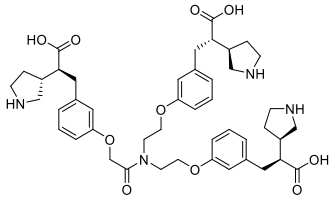
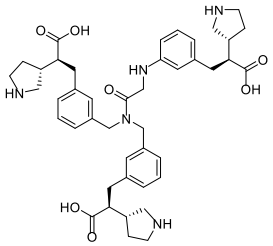
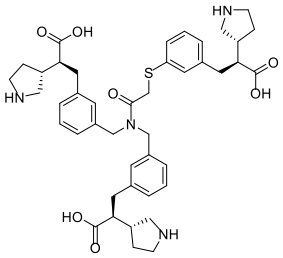
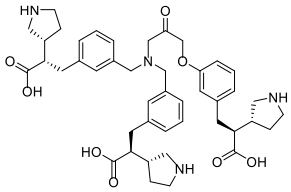
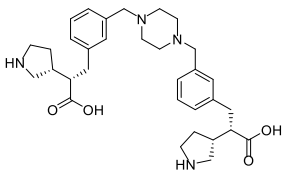
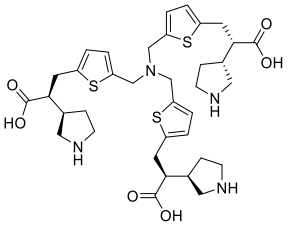
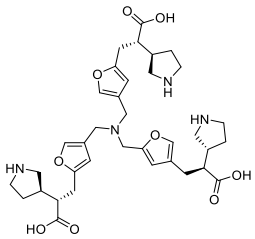
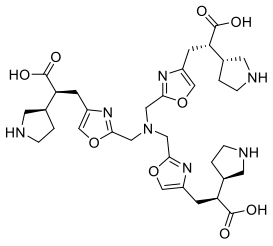
51		52	
53		54	
55		56	
57		58	
59		60	

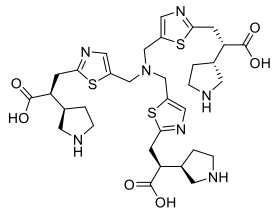
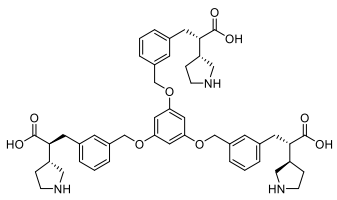
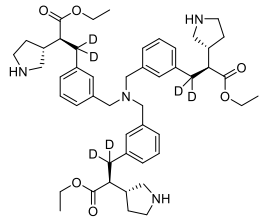
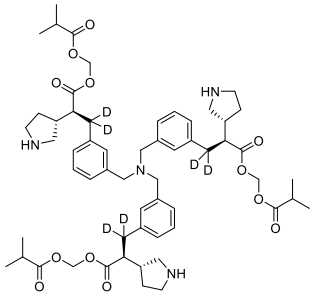
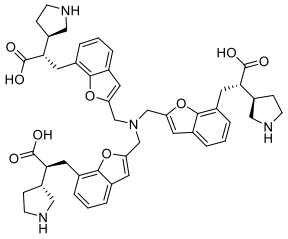
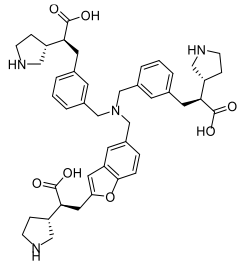
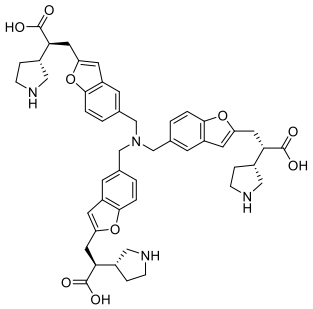
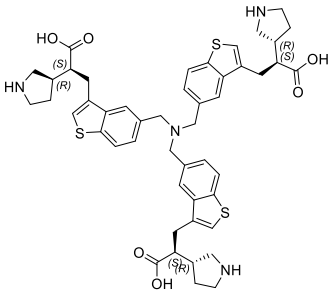
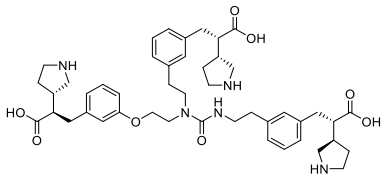
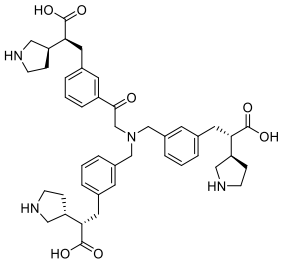
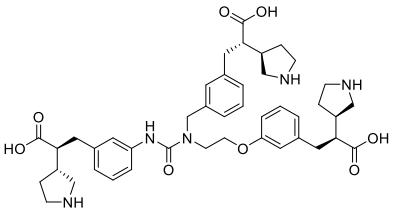
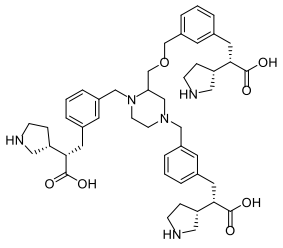
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	

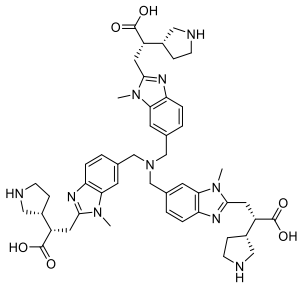
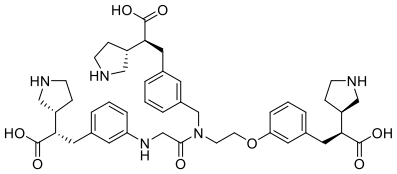
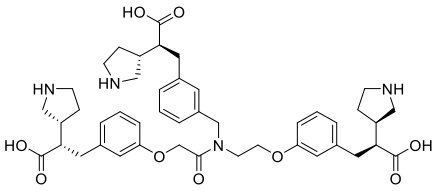
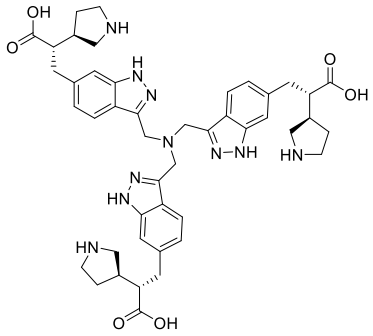
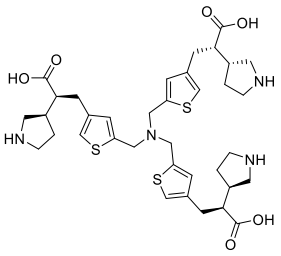
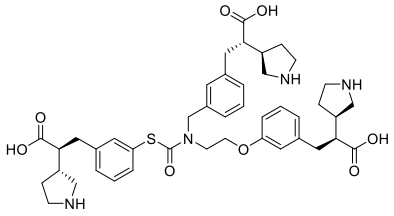
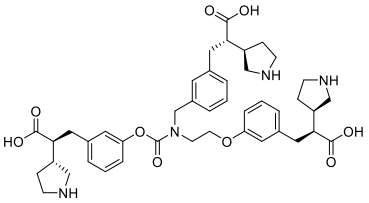
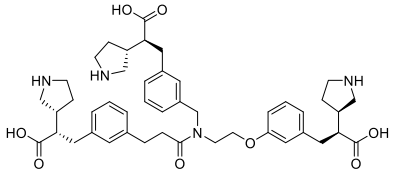
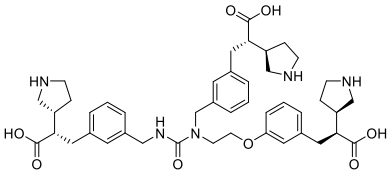
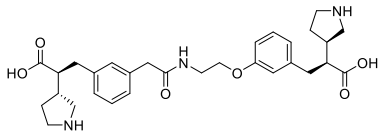
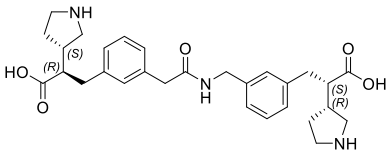
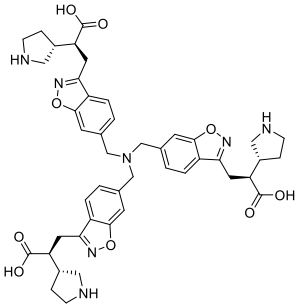
73		74	
75		76	
77		78	
79		80	
81		82	
83		84	

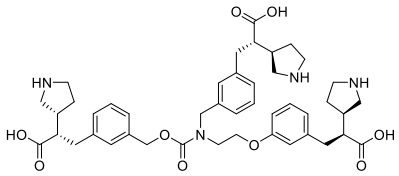
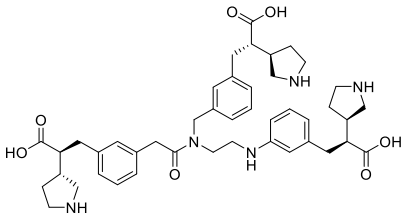
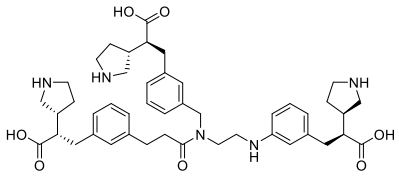
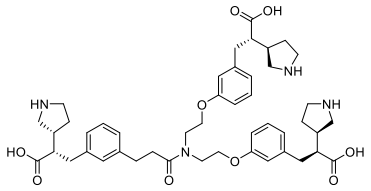
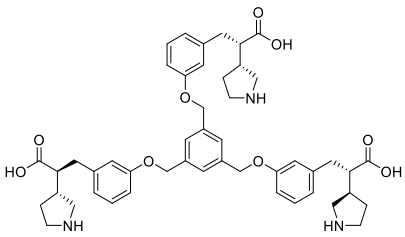
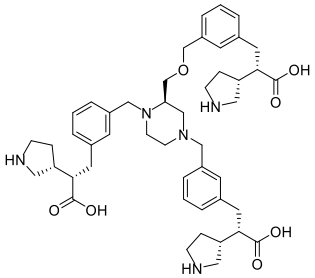
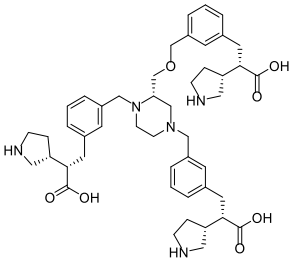
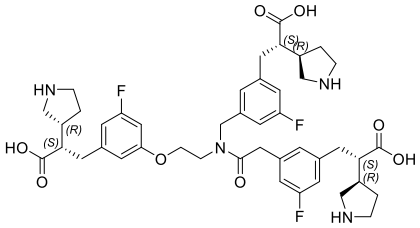
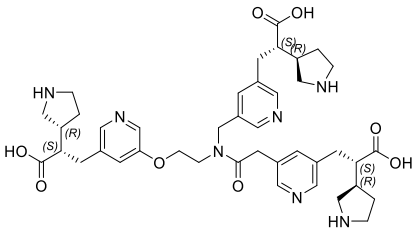
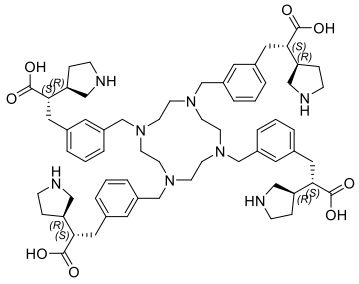
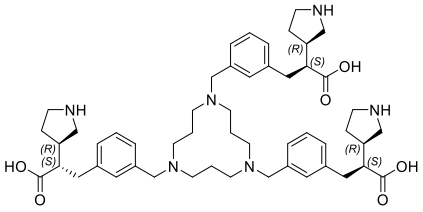
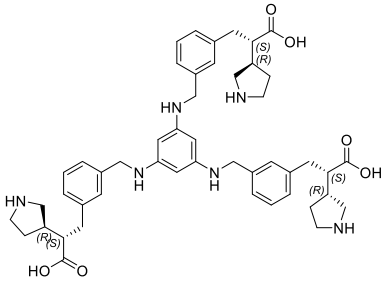
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	

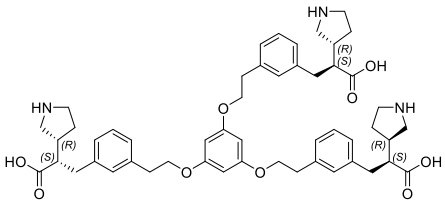
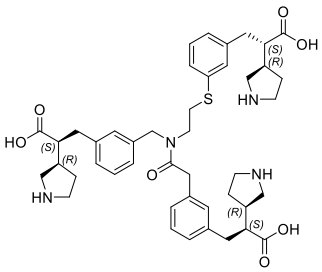
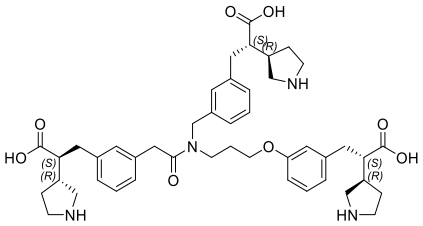
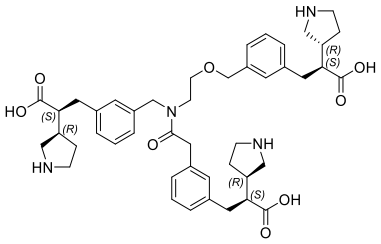
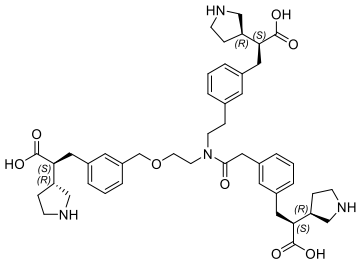
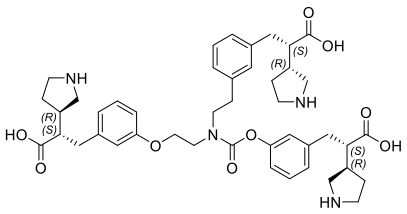
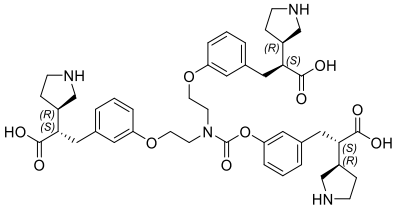
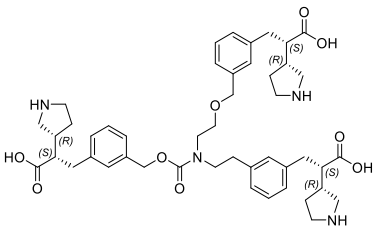
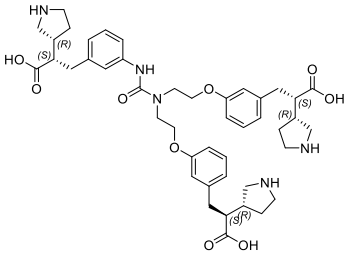
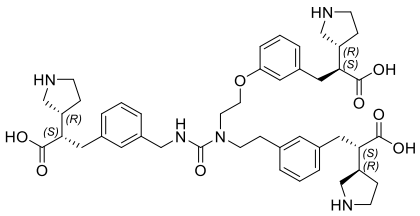
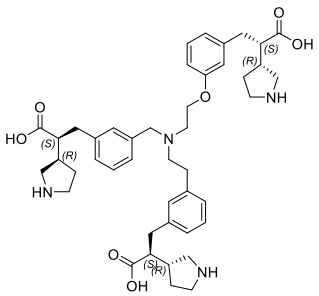
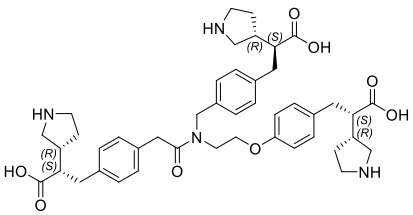
97		98	
99		100	
101		102	
103		104	
105		106	
107		108	

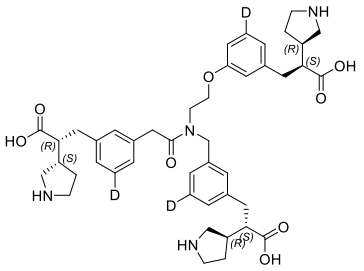
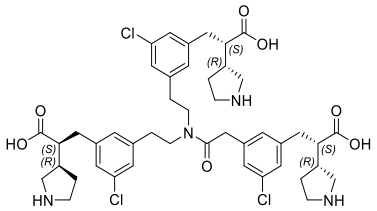
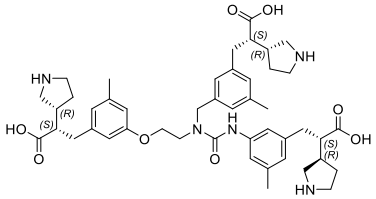
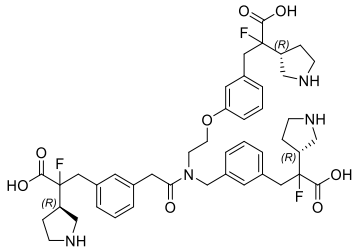
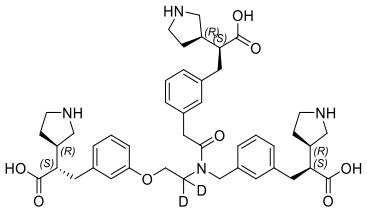
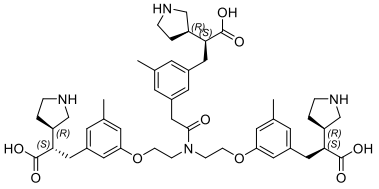
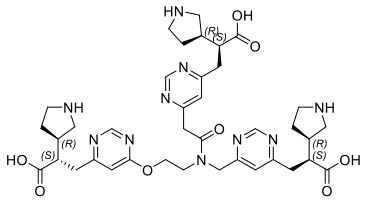
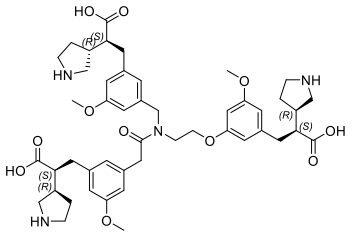
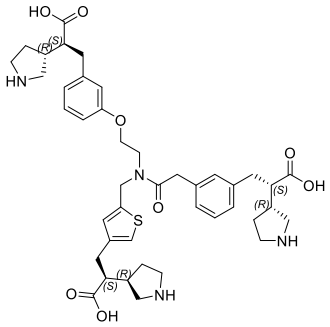
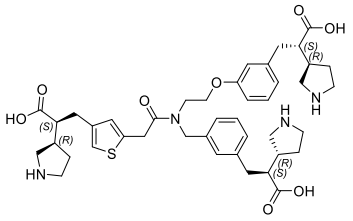
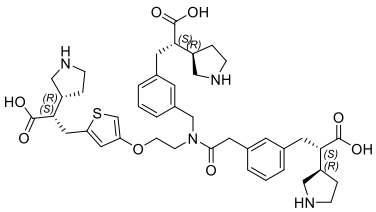
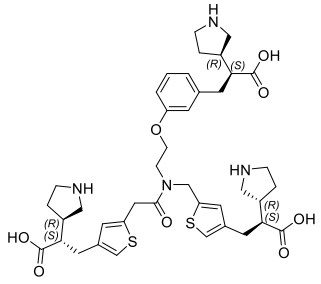
109		110	
111		112	
113		114	
115		116	
117		118	
119		120	

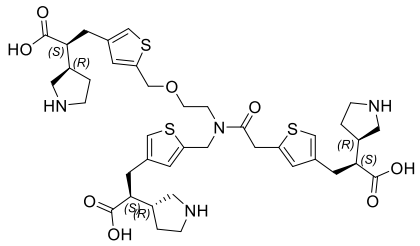
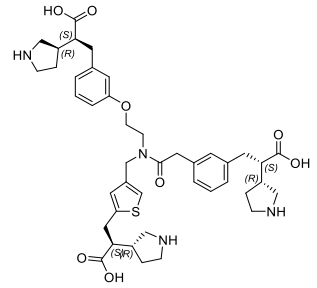
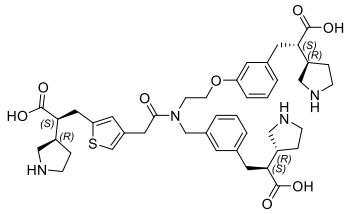
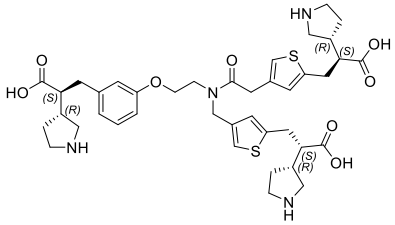
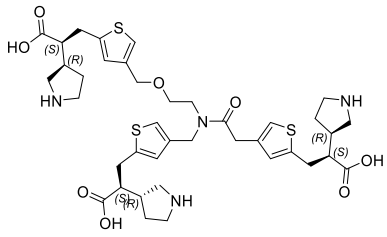
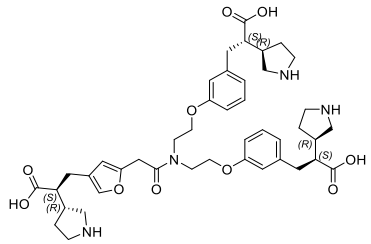
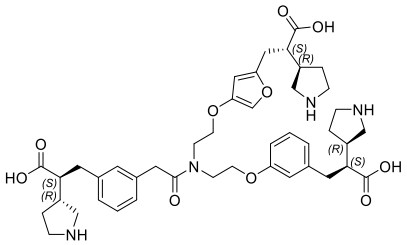
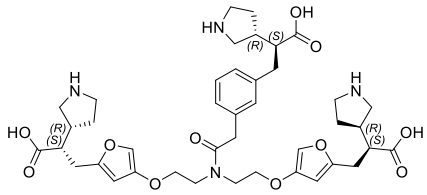
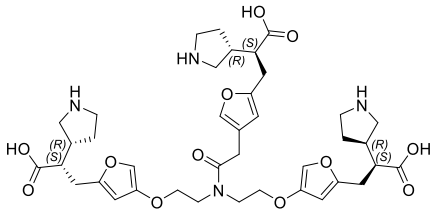
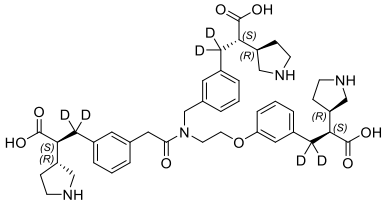
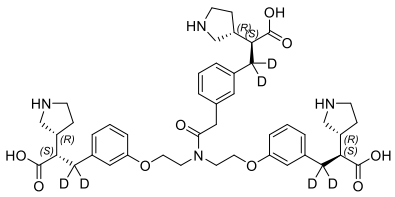
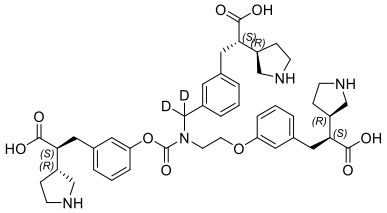
121		122	
123		124	
125		126	
127		128	
129		130	
131		132	

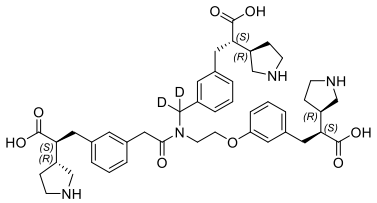
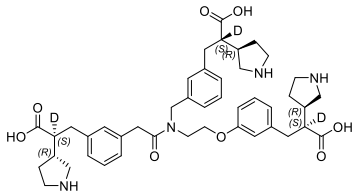
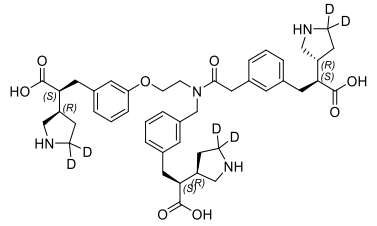
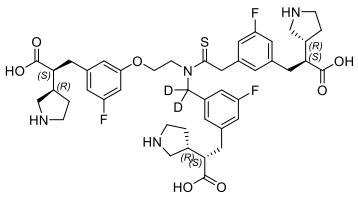
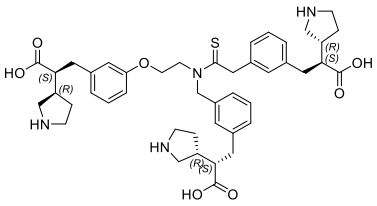
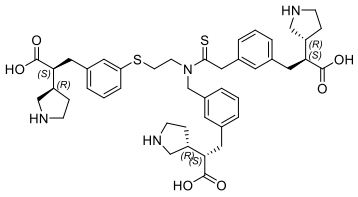
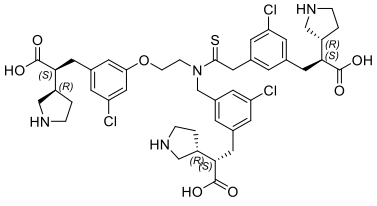
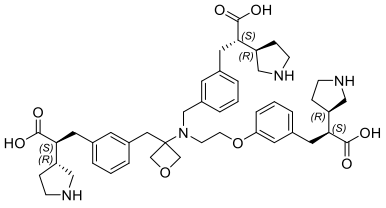
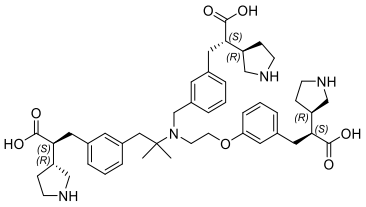
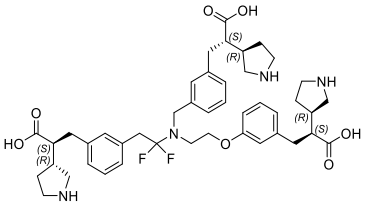
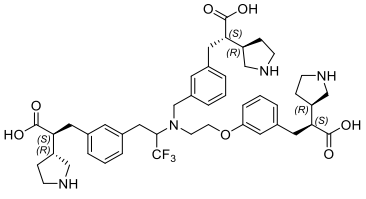
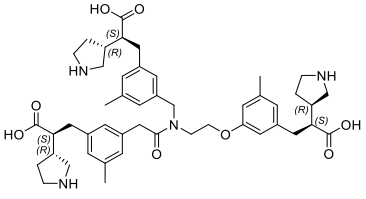
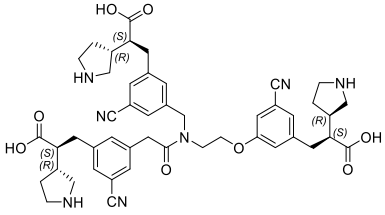
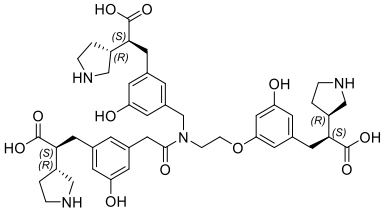
133		134	
135		136	
137		138	
139		140	
141		142	
143		144	

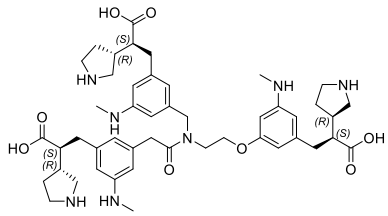
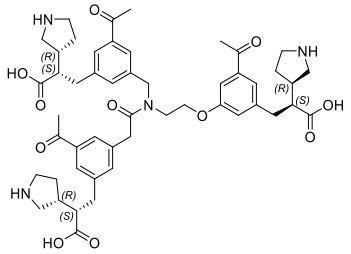
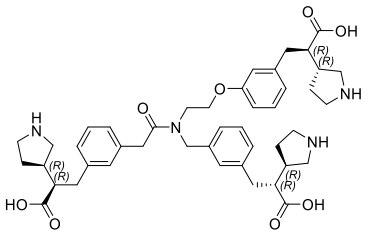
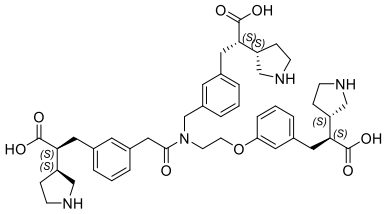
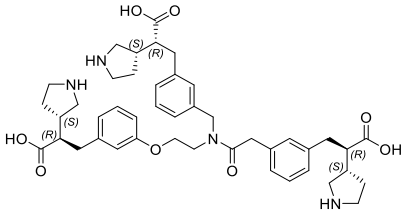
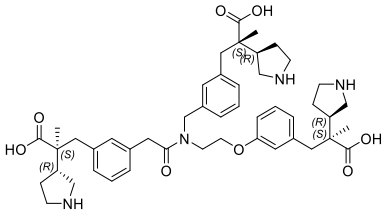
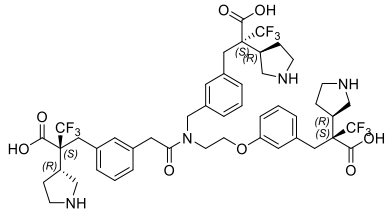
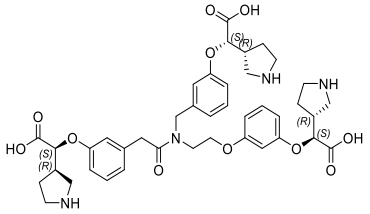
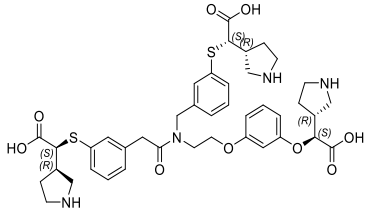
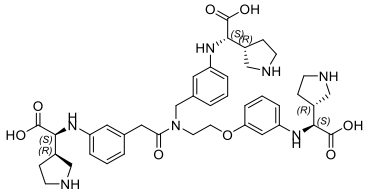
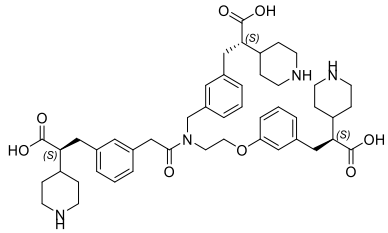
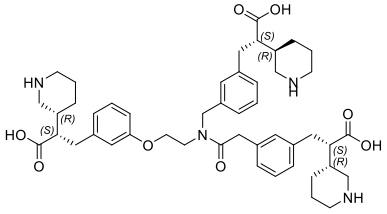
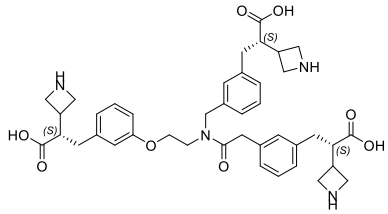
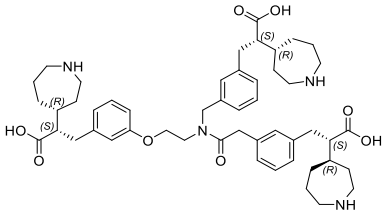
145		146	
147		148	
149		150	
151		152	
153		154	
155		156	

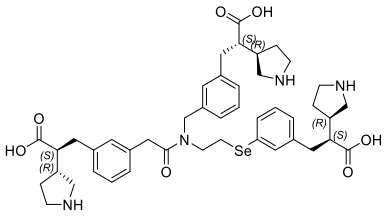
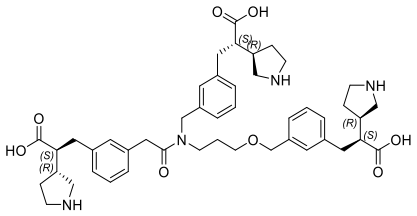
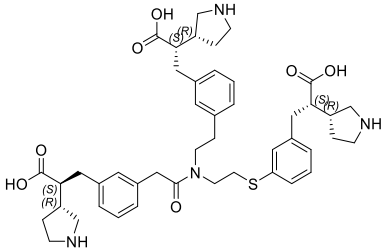
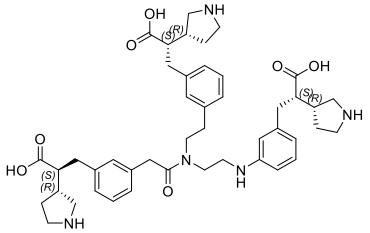
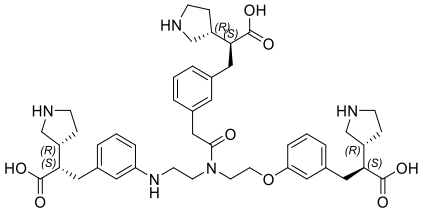
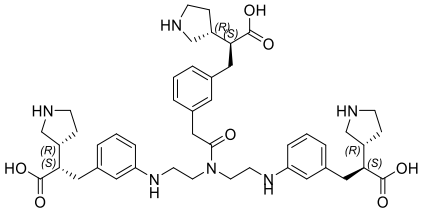
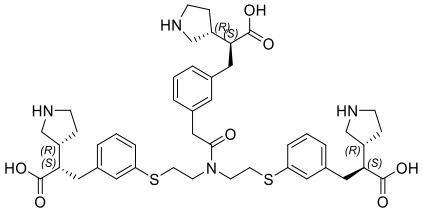
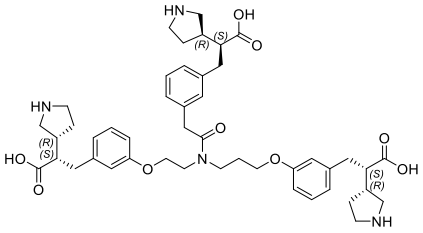
157		158	
159		160	
161		162	
163		164	
165		166	
167		168	

169		170	
171		172	
173		174	
175		176	
177		178	
179		180	

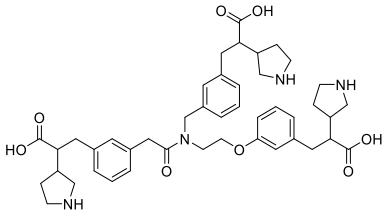
181		182	
183		184	
185		186	
187		188	
189		190	
191		192	

193		194	
195		196	
197		198	
199		200	
201		202	
203		204	
205		206	

207		208	
209		210	
211		212	
213		214	
215		216	
217		218	
219		220	

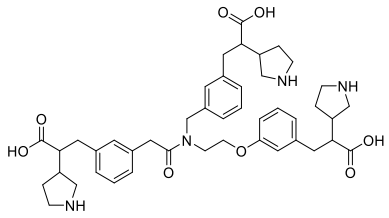
221		222	
223		224	
225		226	
227		228	

In one embodiment of the invention, the compound is 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof:



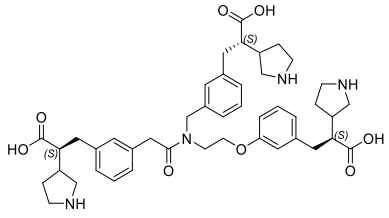
.

In one embodiment of the invention, the compound is 3-(3-(2-((3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-(2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof, in a stereoisomeric form:



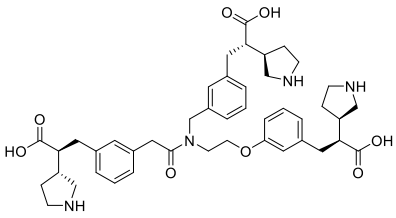
.

In one embodiment of the invention, the compound is (S)-3-(3-(2-((3-((S)-2-carboxy-2-(pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-(pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-(pyrrolidin-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof:



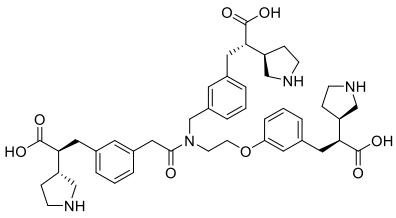
.

In one embodiment of the invention, the compound is (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof:



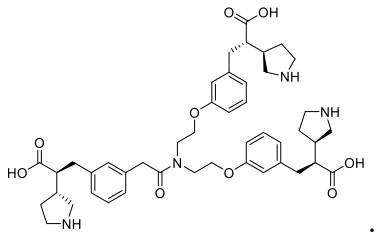
.

In one embodiment of the invention, the compound is (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid, or a deuterated derivative form thereof, or a pharmaceutically acceptable salt thereof:



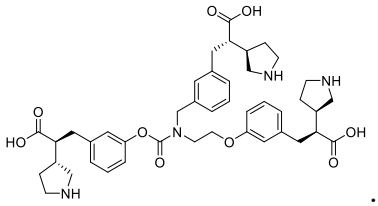
.

In one embodiment of the invention, the compound is (2S,2'S)-3,3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid), or a deuterated derivative form thereof, or a pharmaceutically acceptable salt thereof:



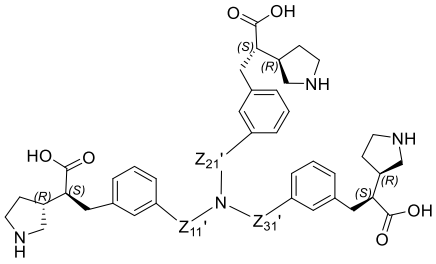
.

In one embodiment of the invention, the compound is (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid, or a deuterated derivative form thereof, or a pharmaceutically acceptable salt thereof:



.

In one embodiment of the invention, the compound of the invention or a pharmaceutically acceptable salt thereof is selected from:



, wherein * represents the linking end to N;

Compound No.	Z_{31}'	Z_{11}'	Z_{21}'
229	C(O)	CH_2	$CH_2CH_2CH_2$
230	C(O)	CH_2	*CH_2CH_2S
231	C(O)	CH_2	*CH_2CH_2NH
232	C(O)	CH_2	*$CH_2CH_2CH_2O$

233	C(O)	CH_2	*$CH_2CH_2C(O)$
234	C(O)	CH_2	*$CH_2CH_2C(S)$
235	C(O)	CH_2	*$CH_2CH_2C(O)O$
236	C(O)	CH_2	*$CH_2CH_2C(O)NH$
237	C(O)	CH_2	*$CH_2CH_2C(O)NCH_2$
238	C(O)	CH_2	*$CH_2CH_2NHC(O)$
239	C(O)	CH_2CH_2	$CH_2CH_2CH_2$
240	C(O)	CH_2CH_2	*CH_2CH_2S
241	C(O)	CH_2CH_2	*$CH_2CH_2CH_2O$
242	C(O)	*CH_2CH_2O	*CH_2CH_2O
243	C(O)	*CH_2CH_2O	*CH_2CH_2S
244	C(O)	*CH_2CH_2O	*CH_2CH_2NH
245	C(O)	*CH_2CH_2O	*$CH_2CH_2C(O)$
246	C(O)	*CH_2CH_2O	*$CH_2CH_2C(O)NH$
247	*$C(O)CH_2$	CH_2	CH_2
248	*$C(O)CH_2$	CH_2	CH_2CH_2
249	*$C(O)CH_2$	CH_2CH_2	$CH_2CH_2CH_2$
250	*$C(O)CH_2$	*CH_2CH_2O	$CH_2CH_2CH_2$
251	*$C(O)CH_2$	*CH_2CH_2O	*CH_2CH_2S
252	*$C(O)CH_2CH_2$	*CH_2CH_2O	*$CH_2CH_2CH_2S$
253	*$C(O)CH_2CH_2$	*CH_2CH_2O	*$CH_2CH_2C(O)$
254	*$C(O)CH_2CH_2$	*CH_2CH_2O	CH_2CH_2
255	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2CH_2O$
256	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2C(O)$
257	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2C(O)O$
258	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2C(O)NH$
259	*$CH_2C(O)$	CH_2	CH_2CH_2
260	*$CH_2C(O)$	CH_2	*CH_2CH_2O
261	*$CH_2C(O)$	CH_2	*CH_2CH_2NH
262	*$CH_2CH_2C(O)$	CH_2	CH_2
263	*$CH_2CH_2C(O)$	CH_2	CH_2CH_2

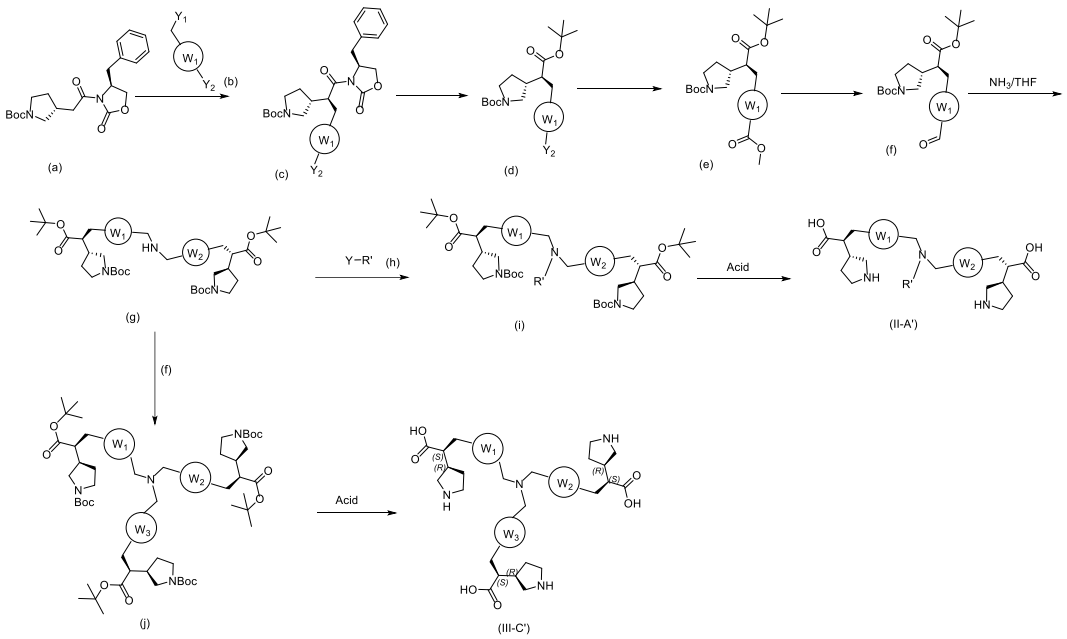
264	*$CH_2CH_2C(O)$	CH_2	*CH_2CH_2O
265	*$CH_2CH_2C(O)$	CH_2	*CH_2CH_2S
266	*CH_2CH_2O	*CH_2CH_2O	*CH_2CH_2O
267	*CH_2CH_2O	*CH_2CH_2O	*$CH_2CH_2C(O)$
268	*CH_2CH_2O	*CH_2CH_2O	*$CH_2CH_2C(O)NH$
269	*CH_2CH_2NH	CH_2	*$CH_2CH_2C(O)NCH_2$
270	*CH_2CH_2NH	CH_2	*$CH_2CH_2NHC(O)$
271	*CH_2CH_2NH	*CH_2CH_2NH	*CH_2CH_2O
272	*CH_2CH_2NH	*$CH_2CH_2NCH_2$	*$CH_2CH_2C(O)$
273	*CH_2CH_2NH	*CH_2CH_2O	*$CH_2CH_2C(O)NH$
274	*$C(O)OCH_2$	CH_2	*CH_2CH_2NH
275	*$C(O)OCH_2$	CH_2	*CH_2CH_2S
276	*$C(O)OCH_2$	CH_2CH_2	*CH_2CH_2O
277	*$C(O)OCH_2$	CH_2CH_2	*CH_2CH_2S
278	*$C(O)OCH_2$	*CH_2CH_2NH	*CH_2CH_2O
279	*$C(O)OCH_2$	*CH_2CH_2NH	*$CH_2CH_2CH_2O$
280	*$C(O)OCH_2$	CH_2	CH_2
281	*$C(O)OCH_2$	CH_2CH_2	CH_2
282	*$C(O)NHCH_2$	CH_2	*CH_2CH_2NH
283	*$C(O)NHCH_2$	CH_2CH_2	*CH_2CH_2NH
284	*$C(O)NHCH_2$	*CH_2CH_2NH	*CH_2CH_2O
285	*C(O)NH	CH_2	*CH_2CH_2S
286	*C(O)NH	CH_2CH_2	*CH_2CH_2NH
287	*C(O)NH	CH_2CH_2	*CH_2CH_2O
288	*C(O)NH	CH_2CH_2	*CH_2CH_2S
289	*C(O)NH	*CH_2CH_2NH	*CH_2CH_2O
290	*C(O)O	CH_2	*CH_2CH_2S
291	*C(O)O	CH_2CH_2	*CH_2CH_2S
292	*$C(O)CH_2O$	CH_2	*CH_2CH_2NH
293	*$C(O)CH_2O$	CH_2CH_2	*$CH_2CH_2C(O)NH$
294	*$C(O)CH_2O$	CH_2CH_2	*CH_2CH_2O

295	*C(O)CH_2O	CH_2CH_2	*CH_2CH_2NH
296	*C(O)CH_2NH	*CH_2CH_2O	*CH_2CH_2S
297	*C(O)CH_2NH	*CH_2CH_2O	*CH_2CH_2O
298	*C(O)CH_2NH	CH_2CH_2	*CH_2CH_2NH
299	CH_2	*CH_2CH_2O	*CH_2CH_2O

The invention further provides a method for preparing compounds represented by Formula(I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), Formula (I-2), Formula (I-3), Formula (I'-1), (I'-2), (I'-3), Formula (II), Formula (II-A), Formula (II-A'), Formula (II-B), Formula (II-B'), Formula (II-C), Formula (II-C'), Formula (III), Formula (III-1), Formula (III-2), Formula (III-1-1), Formula (III-2-1), Formula (III-A), Formula (III-A'), Formula (III-B), Formula (III-B'), Formula (III-B'-1), Formula (III-C), Formula (III-C'), Formula (III-D), Formula (III-D'), Formula (III-E), Formula (III-E'), Formula (IV), Formula (A), Formula (B), Formula (B-1), Formula (C), Formula (C-1), Formula (D), Formula (D-1), Formula (B-2), Formula (B-3), Formula (C-2), Formula (C-3), Formula (D-2), Formula (D-3), Formula (E), Formula (F), Formula (E-1), Formula (E-2), Formula (E-3), Formula (E-4), Formula (F-1), Formula (F-2), Formula (G), Formula (G-1), Formula (G-2), Formula (G-3), Formula (G-4), Formula (H), Formula (H-1), Formula (H-2), Formula (H-3), Formula (H-4), Formula (D-c), Formula (D-f), Formula (D- g), and Formula (D-h), or pharmaceutically acceptable salts thereof.

The compounds of the general formulas mentioned can be prepared by a variety of methods, including but not limited to the following methods:

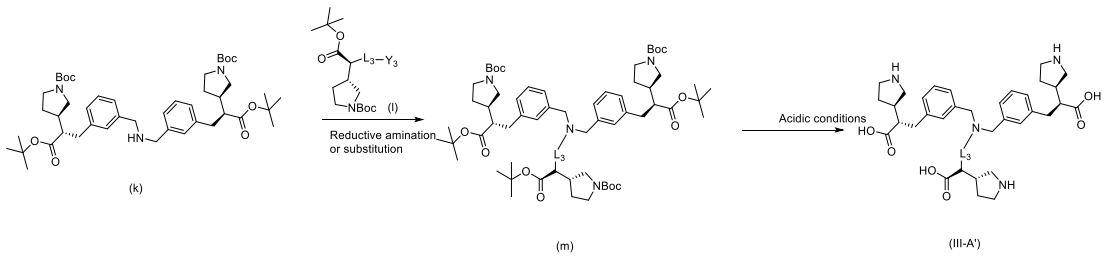
Scheme 1:



wherein each of Y_1 and Y_2 is independently halogen (i.e. fluorine, chlorine, or bromine), preferably bromine; Y is independently halogen(i.e. fluorine, chlorine, or bromine) or oxo (the "oxo" refers to = O in -C(O)H), preferably bromine or oxo (the "oxo" refers to = O in -C(O)H); R' is defined as in the compounds of Formula (II), W_1, W_2, and W_3 are defined as in the compounds of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), and Formula (I-1);

Under the action of a base, Compound (a) and Compound (b) are reacted at room temperature for 16 h to obtain Compound (c). Compound (c) is hydrolyzed under alkaline conditions of hydrogen peroxide, and then esterified to obtain Intermediate (d), which is subjected to carbonyl insertion under atmospheric pressure to obtain Intermediate (e). DIBAL-H reduction gives Intermediate (f), and Intermediate (f) is subjected to reductive amination in a tetrahydrofuran solution of ammonia to obtain Intermediate (g). The intermediate is further subjected to reductive amination or substitution reaction to obtain Intermediate (i), and deprotection under acidic conditions gives the compound of Formula (II-A'); Intermediate (g) and Intermediate (f) undergo a substitution reaction or reductive amination to give Intermediate (j) which is deprotected under acidic conditions to give a compound of Formula (III-C').

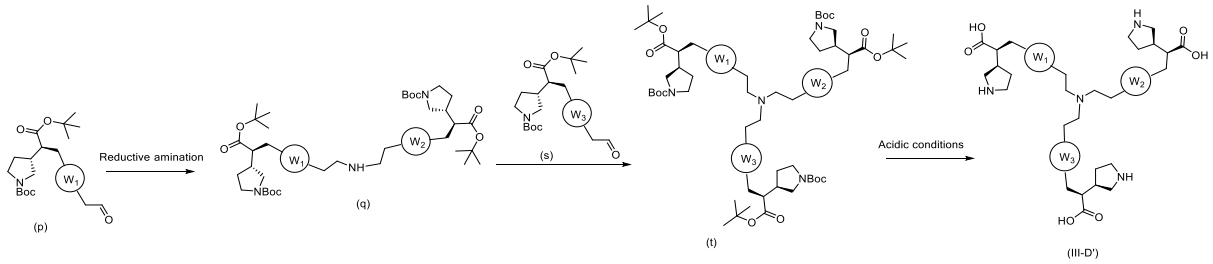
Scheme 2:



Y_3 is independently halogen (i.e., fluorine, chlorine, or bromine) or oxo (the "oxo" refers to = O in -C(O)H), preferably bromine or oxo (the "oxo" refers to = O in -C(O)H), and L_3 is defined as in the compounds of Formula (I) Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4) and Formula (I-1);

Compound (k) is synthesized according to the conditions of patent CN114008021A, and Compound (m) is obtained from Compound (k) and Compound (l) by reductive amination or substitution reaction, and then deprotected under acidic conditions to obtain a compound of Formula (III-A').

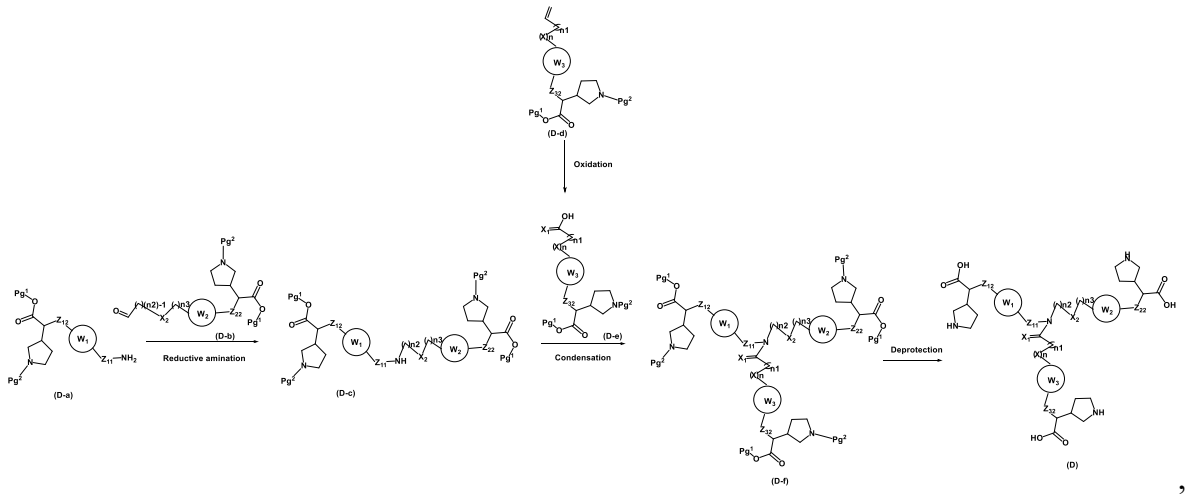
Scheme 3:



wherein W_1, W_2, and W_3 are defined as in the compounds of Formula (I) Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), and Formula (I-1);

In a tetrahydrofuran solution of ammonia, Compound (p) is obtained by reductive amination of Compound (q); Compound (q) and Compound (s) are further subjected to reductive amination to obtain Intermediate (t); Intermediate (t) is deprotected under acidic conditions to obtain a compound of Formula (III-D').

Scheme 4:



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wherein Z_{11}, Z_{12}, Z_{22}, Z_{32}, X, X_1, X_2, n, n1, n2, n3, and the rings W_1, W_2, and W_3 are defined as in compounds of Formula (I), Formula (I-1-P1), Formula (I-1-P2), Formula (I-1-P3), Formula (I-1-P4), and Formula (D), and each of Pg^1 and Pg^2 is independently a protecting group. Preferably, Pg^1 is independently selected from *tert*-butyl, methyl, and benzyl, and Pg^2 is independently selected from *tert*-butoxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (FMOC), and benzyloxycarbonyl (Cbz), preferably Boc.

The invention further provides a pharmaceutical composition comprising the compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention further provides a pharmaceutical composition comprising the compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient thereof.

In the above-mentioned pharmaceutical composition, the compound of the present invention, or a pharmaceutically acceptable salt thereof accounts for 0.1-99.9 wt% of the pharmaceutical composition, for example, 0.5 wt%, 1 wt%, 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, 9 wt%, 10 wt%, 20 wt%, 30 wt%, 40 wt%, 50 wt%, 60 wt%, 70 wt%, 80 wt%, 90 wt%, 91 wt%, 92 wt%, 93 wt%, 94 wt%, 95 wt%, 96 wt%, 97 wt%, 98 wt%, 99 wt%, 99.5 wt%, or a range formed by the combination of any two of the above-mentioned point values, and the balance is a pharmaceutically acceptable excipient.

In some embodiments of the invention, the pharmaceutical composition is used for an inhibitor of Lp(a) assembly.

In some embodiments of the invention, the pharmaceutical composition is used for a medicament for treating a cardiovascular disease (CVD).

The compounds shown in the invention, or pharmaceutically acceptable salts thereof may be carried out in pure form or in the form of a suitable pharmaceutical composition by providing any acceptable mode of administration of a medicament for similar use. The pharmaceutical composition of the invention may be prepared by combining the compound of the invention with a suitable pharmaceutically acceptable excipient. The pharmaceutical composition of the invention may be formulated as solid, semi-solid, liquid or gaseous formulations. In general, the above pharmaceutical composition may be prepared by conventional preparative methods using vehicles conventional in the field of formulations.

The invention also provides the use of the compound of the invention, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for preventing and/or treating a cardiovascular disease (CVD).

In one embodiment of the invention, provided is a use of the compound of the invention, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for preventing and/or treating a disease or condition associated with an elevated blood plasma Lp(a) level.

In one embodiment of the invention, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD), including, but not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

The term “elevated blood plasma Lp(a) level” refers to a blood plasma level equal to or above a normal level, and for human beings, “elevated blood plasma level of Lp(a)” refers to a blood plasma level equal to or above about 30 mg/dL.

In one embodiment of the present invention, for human beings, the term “elevated blood plasma Lp(a) level” refers to a blood plasma level greater than or equal to about 50 mg/dL. The compound provided herein can be used in therapy to reduce blood plasma levels of Lp(a).

The invention further provides a use of the compound of the invention, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for preventing and/or treating of a disease mediated by Lp(a).

Moreover, the invention provides a use, wherein the disease mediated by Lp(a) is a cardiovascular disease (CVD).

Furthermore, the invention provides a use, wherein the cardiovascular disease (CVD) is selected from atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

The invention further provides a method for preventing and/or treating a cardiovascular disease, comprising administering to a patient a therapeutically effective amount of the compound of the invention, or a pharmaceutically acceptable salt thereof or the pharmaceutical composition of the invention.

In one embodiment of the invention, provided is a method of preventing and/or treating a disease or condition associated with an elevated blood plasma Lp(a) level, comprising administering to a patient a therapeutically effective amount of the compound of the invention, or a pharmaceutically acceptable salt thereof or the pharmaceutical composition of the invention. In one embodiment of the invention, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD), including, but not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

The invention further provides a method for preventing and/or treating a disease mediated by Lp(a), comprising administering to a patient a therapeutically effective amount of the compound of the invention, or a pharmaceutically acceptable salt thereof or the pharmaceutical composition of the invention; preferably, the disease mediated by Lp(a) is a cardiovascular disease

(CVD), including, but not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; said ASCVD includes peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

Further, the invention provides a use or method, wherein the compound of the invention, or a pharmaceutically acceptable salt thereof may be administered in combination with another compound for treating or preventing a disease mediated by Lp(a) such as a cardiovascular disease (CVD).

The invention further provides a use of the compound of the invention or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the invention for preventing and/or treating a cardiovascular disease.

The invention further provides a use of the compound of the invention or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the invention in medicament.

The invention provides a use of the compound of the invention or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the invention in preventing and/or treating a cardiovascular disease. The invention provides a use of the compound of the invention or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the invention in preventing and/or treating a disease or condition associated with an elevated blood plasma Lp(a) level. In one embodiment of the invention, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD), including, but not limited to atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

The invention further provides a use of the compound of the invention or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the invention in preventing and/or treating a disease mediated by Lp(a); preferably, the disease mediated by Lp(a)

is a cardiovascular disease (CVD); further preferably, the cardiovascular disease (CVD) includes, but is not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

In one embodiment of the invention, provided is a use of the compound of the invention or a mixture thereof or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the invention for preventing and/or treating a disease or condition associated with an elevated blood plasma Lp(a) level. In one embodiment of the invention, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD), including, but not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

In a further aspect, this application provides a use of the compound of the invention or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the invention for preventing and/or treating a disease mediated by Lp(a); preferably, the disease mediated by Lp(a) is a cardiovascular disease (CVD); further preferably, the cardiovascular disease (CVD) is selected from atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

The compound of the invention, or a pharmaceutically acceptable salt thereof is used in combination with another compound for preventing and/or treating a cardiovascular disease to prepare a medicament for preventing and/or treating a cardiovascular disease.

In one embodiment of the invention, the cardiovascular disease is a disease or condition associated with an elevated blood plasma Lp(a) level.

In one embodiment of the invention, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD), including, but not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

The compound of the invention, or a pharmaceutically acceptable salt thereof is used in combination with another compound to prevent and/or treat a cardiovascular disease. Further, the other compound is used for preventing and/or treating a cardiovascular disease. Further, the cardiovascular disease is a disease or condition associated with an elevated blood plasma Lp(a) level. Further, the disease or condition associated with an elevated blood plasma Lp(a) level includes, but is not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, coronary artery-related diseases, aortic valve stenosis, aortic valve stenosis-related diseases, heart failure, heart failure-related diseases, atrial fibrillation, and atrial fibrillation-related diseases; the ASCVD comprises peripheral vascular disease, peripheral artery-related diseases, coronary heart disease, ischemic stroke, and ischemic stroke-related diseases.

The compound of the invention or a pharmaceutically acceptable salt thereof can be co-applied with a therapeutic method. In certain embodiments, the therapeutic method may be, but is not limited to, Lp(a) plasmapheresis. The drug or therapeutic method may be co-applied or simultaneously applied. The drug or therapeutic method may be applied sequentially or subsequently.

The invention further provides a pharmaceutical composition, comprising the compound of the invention, or a pharmaceutically acceptable salt thereof, and another compound for treating or preventing a disease mediated by Lp(a); preferably, the disease mediated by Lp(a) is for example, a cardiovascular disease (CVD).

When the compound of the invention or a pharmaceutically acceptable salt thereof is administered in combination with an additional therapeutic agent for treating a disease such as a CVD, the compound of the invention, or a pharmaceutically acceptable salt thereof may provide a more effective therapeutic effect for cardiovascular-related diseases.

Definition

The term “optional”, “arbitrary”, “optionally”, or “arbitrarily” means that the subsequently described event or circumstance may but does not necessarily occur, and that the description includes instances where the event or circumstance mentioned occurs and instances where the event or circumstance does not occur.

The “more” in “optionally substituted with one or more substituents independently selected from...” refers to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; preferably 1, 2, 3, or 4; more preferably 1 or 2.

When “about” is used to describe molecular weight, the word “about” indicates rounding.

Unless otherwise specified, the term “alkyl” refers to a monovalent saturated aliphatic hydrocarbon group, a linear or branched group comprising from 1 to 20 carbon atoms, preferably from 1 to 10 carbon atoms (i.e., C_{1-10} alkyl), further preferably from 1 to 8 carbon atoms (C_{1-8} alkyl), and more preferably from 1 to 6 carbon atoms (i.e., C_{1-6} alkyl). For example, “C_{1-6} alkyl” means that the group is an alkyl group and the number of carbon atoms on the carbon chain is between 1 to 6 (specifically 1, 2, 3, 4, 5, or 6). The examples include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, neopentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, *n*-hexyl, *n*-heptyl, and *n*-octyl.

Unless otherwise specified, the term “alkylene” refers to a monovalent saturated aliphatic hydrocarbon group, including straight or branched groups comprising 1-20 carbon atoms, preferably comprising 1-10 carbon atoms (i.e., C_{1-10} alkylene), more preferably comprising 1-8 carbon atoms (C_{1-8}alkylene), and even more preferably comprising 1-6 carbon atoms (i.e., C_{1-6} alkylene). For example, “C_{1-6} alkylene” refers to an alkylene group, and the number of carbon atoms on the carbon chain is between 1-6 (specifically 1, 2, 3, 4, 5, or 6). Examples include, but are not limited to, methylene, ethylene, *n*-propylene, *n*-pentylene, *n*-hexylene, and .

Unless otherwise specified, the term “alkenyl” refers to a straight or branched chain unsaturated aliphatic hydrocarbon group composed of carbon atoms and hydrogen atoms and with at least one double bond. Alkenyl may contain 2-20 carbon atoms, preferably 2-10 carbon atoms (i.e., C_{2-10} alkenyl), more preferably 2-8 carbon atoms (C_{2-8} alkenyl), and even more preferably 2-6 carbon atoms (i.e., C_{2-6} alkenyl), 2-5 carbon atoms (i.e., C_{2-5}alkenyl), 2-4 carbon atoms (i.e., C_{2-}

$_4$ alkenyl), 2-3 carbon atoms (i.e., C_{2-3} alkenyl), and 2 carbon atoms (i.e., C_2 alkenyl). For example, "C_{2-6} alkenyl" refers to an alkenyl group, and the number of carbon atoms on the carbon chain is between 2-6 (specifically 2, 3, 4, 5, or 6). Non-limiting examples of alkenyl groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, 1-butenyl, isobutenyl, and 1,3-butadienyl.

Unless otherwise specified, the term "alkynyl" refers to a straight or branched chain unsaturated aliphatic hydrocarbon group with at least one triple bond composed of carbon atoms and hydrogen atoms. Alkynyl may contain 2-20 carbon atoms, preferably contains 2-10 carbon atoms (i.e., C_{2-10} alkynyl), more preferably contains 2-8 carbon atoms (C_{2-8} alkynyl), even more preferably contains 2-6 carbon atoms (i.e., C_{2-6} alkynyl), 2-5 carbon atoms (i.e., C_{2-5} alkynyl), 2-4 carbon atoms (i.e., C_{2-4} alkynyl), 2-3 carbon atoms (i.e., C_{2-3} alkynyl), and 2 carbon atoms (i.e., C_2 alkynyl). For example, "C_{2-6} alkynyl" refers to an alkynyl group, and the number of carbon atoms on the carbon chain is between 2-6 (specifically 2, 3, 4, 5, or 6). Non-limiting examples of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butynyl.

Unless otherwise specified, the term "cycloalkyl" refers to a monocyclic, bicyclic or polycyclic cyclic saturated aliphatic hydrocarbon group with a specified number of carbon atoms, preferably containing 3-14 carbon atoms (i.e., C_{3-14} cycloalkyl), preferably containing 4-14 carbon atoms (i.e., C_{4-14} cycloalkyl), preferably containing 5-14 carbon atoms (i.e., C_{5-14} cycloalkyl), more preferably containing 6-14 carbon atoms (C_{6-14} cycloalkyl), and further preferably 6-12 carbon atoms (C_{6-12} cycloalkyl). The examples include, but are not limited to, cyclohexyl and spiro[3.5]nonyl.

Unless otherwise specified, the term "oxaalkyl" refers to an alkyl residue in which one or more carbons (and their associated hydrogens) are replaced by oxygen, such as "alkoxy", "alkoxyalkyl". For example, C_3oxaalkylene includes -OC_{1-3} alkoxy, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, etc. The examples include methoxy, ethoxy, propoxy and methoxypropyl. The term oxaalkyl has as its ordinary meaning as understood in the field [See Nomenclature of Organic Compounds: Principles and Practice, published by the American Chemical Society, 196, but not limited to 127(a)], that is, it refers to compounds in which the oxygen is bonded to its adjacent atom by a single bond (forming an ether bond); it does not refer to double-bond oxygen found in carbonyl groups. The terms "thiaalkyl" and "selenaalkyl" are similar to "oxaalkyl". The term "azaalkyl" refers to an alkyl group containing atomic groups "NH" or "-N(C_{1-3} alkyl)-", e.g.,

C_3azaalkylene includes -$NHCH_2CH_2CH_3$, -$CH_2NHCH_2CH_3$, -$CH_2CH_2NHCH_3$, -$CH_2CH_2N(CH_3)CH_3$, etc.

"Alkoxy" means -O-alkyl, defined hereinabove, that is, comprising 1-20 carbon atoms, preferably 1-10 carbon atoms, more preferably 1-8 carbon atoms, and even more preferably 1-6 carbon atoms (specifically 1, 2, 3, 4, 5, or 6). The examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, *tert*-butoxy, pentoxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 2,2-dimethylpropoxy, and 1-ethylpropoxy.

Unless otherwise specified, the term "halogen" or "halo/halogenated" refers to fluorine, chlorine, bromine, or iodine.

Unless otherwise specified, the term "heterocyclic/heterocyclyl" refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic hydrocarbon substituent that is nonaromatic and contains from 3 to 20 ring atoms, of which 1, 2, 3, or more ring atoms are selected from N, O, or S, and the remaining ring atoms are C. Preferably the group includes 3-12 ring atoms, further preferably 3-10 ring atoms, or 3-8 ring atoms, or 3-6 ring atoms, or 4-6 ring atoms, or 5-6 ring atoms. Heteroatoms are preferably 1-4, more preferably 1-3 (i.e., 1, 2, or 3). Examples of monocyclic heterocyclic groups include pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, dihydropyrrolidinyl, piperidinyl, piperazinyl, pyranyl, etc. Bicyclic or polycyclic heterocyclic groups include heterocyclic groups of spiro, fused, and bridged rings.

Unless otherwise specified, the term "aryl" means an aromatic carbon ring system comprising 6-16 carbon atoms, or 6-14 carbon atoms, or 6-12 carbon atoms, or a monocyclic, bicyclic and tricyclic ring of 6-10 carbon atoms, preferably 6-10 carbon atoms, and the term "aryl" may be used interchangeably with the term "aromatic ring". Examples of aryl groups may include, but are not limited to, phenyl, naphthyl, anthryl, phenanthryl, or pyrenyl.

Unless otherwise specified, the term "heteroaryl" means an aromatic monocyclic, bicyclic, or polycyclic ring system containing 5-16-membered structures, or 5-14-membered structures, 5-12-membered structures, 5-10-membered structures, 5-8-membered structures, wherein 1, 2, 3, or more ring atoms are heteroatoms and the remaining atoms are carbon, the heteroatoms are independently selected from O, N, or S, and the number of heteroatoms is preferably 1, 2, or 3. Polycyclic heteroaryl is fused heteroaryl. Examples of heteroaryl groups may include, but are not

limited to, furanyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiadiazinyl, triazinyl, phthalazinyl, quinolinyl, isoquinolinyl, pteridinyl, purinyl, indolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzoylpyridinyl, benzopyrimidinyl, quinoxalinyl, benzimidazoyl, benzophthalazinyl, pyrrolo[2,3-b]pyridinyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, and [1,2,4]triazolo[1,5-a]pyridinyl.

Unless otherwise specified, the term "fused heteroaryl" refers to an aromatic ring system formed by two or more cyclic structures sharing two adjacent atoms with each other, each ring in the fused heteroaryl being an unsaturated aromatic ring, which may comprise 5-20 ring atoms, preferably 6-14 ring atoms, more preferably 7-10 ring atoms, which comprise 1-4 cyclic heteroatoms, preferably 1-3 (i.e., 1, 2, or 3) ring heteroatoms, and the heteroatoms are independently selected from N, O, and S. Fused heteroaryl groups include bicyclic, tricyclic, tetracyclic or polycyclic fused heteroaryl, preferably bicyclic, tricyclic or tetracyclic fused heteroaryl, more preferably bicyclic or tricyclic fused heteroaryl. Examples of fused heteroaryl groups include (but are not limited to) , , , , , etc.

Unless otherwise specified, the term "pharmaceutically acceptable salt(s)" refers to salts that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of mammals, particularly humans, irritation, allergic response, etc., and are commensurate with a reasonable benefit/risk ratio, such as medically acceptable salts of amines, carboxylic acids, and other types of compounds, which are well known in the field. The salt may be prepared *in situ* during the final isolation and purification of the compounds of the invention or by reacting the free base or free acid with a suitable reagent alone.

The compounds of the present invention and pharmaceutically acceptable salts also include "stereoisomers" thereof. Unless otherwise specified, the term "stereoisomer" refers to a compound with the same chemical structure but with different spatially arranged atoms or groups. Stereoisomers include enantiomers, diastereomers, conformers (rotamers), geometric isomers (cis/trans-isomerism), atropisomers, etc. Any obtained mixtures of stereoisomers can be separated

into pure or substantially pure geometric isomers, enantiomers, and diastereomers, for example, by chromatography and/or fractional crystallization. Compounds and salts described in this specification may include one or more chiral (i.e., asymmetric) centers. To the extent a structure or chemical name in this specification does not indicate the chirality, the structure or name is intended to encompass any single stereoisomer (i.e., any single chiral isomer) corresponding to that structure or name, as well as any mixture of stereoisomers (e.g., a racemate). In some embodiments, a single stereoisomer is obtained by isolating it from a mixture of isomers (e.g., a racemate) using, for example, chiral chromatographic separation. In other embodiments, a single stereoisomer is obtained through direct synthesis from, for example, a chiral starting material.

A particular enantiomer of a compound described herein may be more active than other enantiomers of the same compound. In one embodiment, the compound, or a pharmaceutically acceptable salt thereof, is a single enantiomer being in an enantiomeric excess (%ee) of ≥ 90%, ≥ 95%, ≥ 96%, ≥ 97%, ≥ 98%, or ≥ 99%. In one aspect, the single enantiomer is present in an enantiomeric excess (%ee) of ≥ 99%.

A particular diastereoisomer of a compound described herein may be more active than other diastereoisomers of the same compound. In one embodiment, the compound, or a pharmaceutically acceptable salt thereof, is a single diastereoisomer being in a diastereomeric excess (%de) of ≥ 90% ≥ 95%, ≥ 96%, ≥ 97%, ≥ 98%, or ≥ 99%. In one aspect, the single diastereomer is present in an diastereomeric excess (%de) of ≥ 99%.

The compounds of the invention and pharmaceutically acceptable salts thereof also include "tautomers" thereof. Compounds and salts described in this specification may exist in various tautomeric forms. "Tautomers" are structural isomers that exist in equilibrium resulting from the migration of a hydrogen atom. Unless otherwise specified, the term "tautomer" refers to structural isomers with different energies that can be interconverted by low energy barriers. If tautomerism is possible (e.g. in solution), the chemical equilibrium of the tautomer can be achieved. For example, proton tautomers (also known as prototropic tautomers) include interconversion via proton migration such as keto-enol isomerization and imine-enamine isomerization. Valence tautomers include interconversions by the reorganization of some of the bonding electrons.

The compounds of the invention and pharmaceutically acceptable salts thereof also include "isotopic derivatives" thereof. Unless otherwise specified, the term "isotopic derivative" refers to

a compound of the invention that may exist in an isotopically labelled or enriched form containing one or more atoms with an atomic mass or mass number different from the atomic mass or mass number of the atom which is present in the greatest abundance in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes that are typically used as isotopic labels include isotopes of hydrogen, ^{2}H and ^{3}H; isotopes of carbon: ^{13}C and ^{14}C; isotopes of chlorine: ^{35}Cl and ^{37}Cl; isotopes of fluorine: ^{18}F; isotopes of iodine: ^{123}I and ^{125}I; isotopes of nitrogen: ^{13}N and ^{15}N; isotopes of oxygen: ^{15}O, ^{17}O and ^{18}O and isotopes of sulfur ^{35}S. These isotopically labeled compounds can be used to study the distribution of pharmaceutical molecules in tissues. Especially ^{3}H and ^{13}C, are more widely used because they are easy to label and easy to detect. Substitution of certain heavy isotopes, such as heavy hydrogen (^{2}H), enhances metabolic stability, prolongs half-life, and thus provides therapeutic advantages for dose reduction. Isotopically labeled compounds generally begin with labeled starting materials and are synthesized using known synthetic techniques like non-isotopically labeled compounds. All compounds disclosed herein, including genernal formula compounds and specific compounds, where an atom is replaced by one or more of isotopes thereof (for example a compound of Formula (I) where one or more carbon atoms is an ^{11}C or ^{13}C carbon isotope, or where one or more hydrogen atoms is a ^{2}H or ^{3}H isotope), are encompassed herein.

Unless otherwise specified, the compounds of the invention and pharmaceutically acceptable salts thereof also include “solvates” thereof. The term “solvate” refers to the physical association of a compound of the invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonds. In some cases, for example, when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid, the solvate will be able to be separated. Solvent molecules in solvates may be present in regular and/or disordered order. Solvates may contain stoichiometric or non-stoichiometric solvent molecules. “Solvate” covers the solution phase and separable solvates. The examples of solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Solvation methods are well known in the field. The term “hydrate” refers to a substance in which a water molecule binds to a cation or anion in a compound by a coordination bond or a covalent bond, or refers to a substance in which the water ion does not bind directly to a cation or anion but is present in a certain proportion at a defined position in the solid lattice.

Unless otherwise specified, the compounds of the invention and pharmaceutically acceptable salts thereof also include "prodrugs" thereof. The term "prodrug" refers to a drug that is converted *in vivo* to a parent drug. Prodrugs are usually useful as they can improve certain determined and undesirable physical or biological properties. Physical properties are usually relevant solubility (excessive or insufficient lipid or water solubility) or stability, while problematic biological characteristics include rapid metabolism or poor bioavailability, which may themselves be related to physicochemical properties, for example, they can be bioavailable through oral administration, whereas the parent compound cannot. The solubility of the prodrug in the pharmaceutical composition is also improved compared to the parent drug. An example of, but not limited to, a prodrug of the invention may be any compound of the invention administered as an ester ("prodrug") to facilitate transmission across the cell membrane, where water solubility is detrimental to mobility, but once it enters the intracellular water solubility is beneficial, which is subsequently metabolically hydrolyzed to a carboxylic acid, the active entity. Another example of a prodrug may be a short peptide (polyamino acid) bound to an acid moiety in which the peptide is metabolized to show an active moiety.

The term "oxo" refers to the replacement of two H at the same substitution position by one O to form a double bond.

The term "thio" refers to the replacement of two H at the same substitution position by one S to form a double bond.

The term "therapeutically effective amount" refers to the amount of a compound or combination of compounds that provides the intended clinical or therapeutic benefit in the subject being treated. The therapeutically effective amount will depend on the general condition of the subject being treated (e.g., weight, age, and sex), the severity of the disease, the specific compound being administered, the dosing regimen, the use of concomitant medications and other factors, and can be determined by the prescribing physician in accordance with routine practice. For example, the pharmaceutical composition can be administered at a dose appropriate for the disease to be treated (or prevented), such as administering about 0.5 μg to about 50 mg of at least one compound/kg of subject body weight, preferably about 10 μg to about 100 mg/kg of body weight/day.

The term “pharmaceutically acceptable excipient” refers to a carrier that does not cause significant irritation to an organism and does not eliminate the biological activity and properties of the administered compound. Any commonly used pharmaceutically acceptable carrier may be used, the selection of which depends on factors such as the specific mode of administration, the effect of the carrier on solubility and stability, and the nature of the dosage form and is within the ordinary skills of those skilled in the art. Examples of the pharmaceutically acceptable excipient include, but are not limited to, diluents, excipients, fillers, binders, wetting agents, disintegrants, lubricants, colorants, fragrances, absorption promoters, surfactants, adsorption carriers, etc. which are conventional in the pharmaceutical field.

Unless otherwise specified, the term “treatment” encompasses any treatment of a patient's disease, disorder, and condition, including: (a) inhibiting a disease, disorder, or condition, i.e., arresting its development; or (b) relief of symptoms of a disease, condition and condition, that is, leading to resolution of a disease or symptoms; or (c) ameliorating or eliminating a disease, disorder and condition or one or more symptoms associated with the disease.

Abbreviations used in the preparation examples, examples, and elsewhere herein are:

THF: tetrahydrofuran; Dioxane: 1,4-dioxane; FA: formic acid; PE: petroleum ether; EA: ethyl acetate; DCM: dichloromethane; TFA: trifluoroacetic acid; XPhos Pd G2: Chloro(2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)] palladium (II).

The beneficial effects of the invention are one or more of the following:

The invention designs a class of compounds with novel structures, providing a new direction for the development of drugs that reduce plasma Lp(a) levels. *In vitro* activity studies showed that the compound of the invention had strong inhibitory effects on Lp(a) assembly; the compound of the invention had good pharmacokinetic properties; safety evaluation experiments showed that the compound of the invention had excellent safety; *in vivo* pharmacodynamic experiments in mice showed that the compound of the invention significantly reduced serum Lp(a) levels and therefore could be used as a promising compound for the treatment of diseases mediated by Lp(a). In addition, the invention investigated a specific synthesis method, which is simple in process, convenient in operation, and is advantageous for large-scale industrial production and application.

DETAILED DESCRIPTION

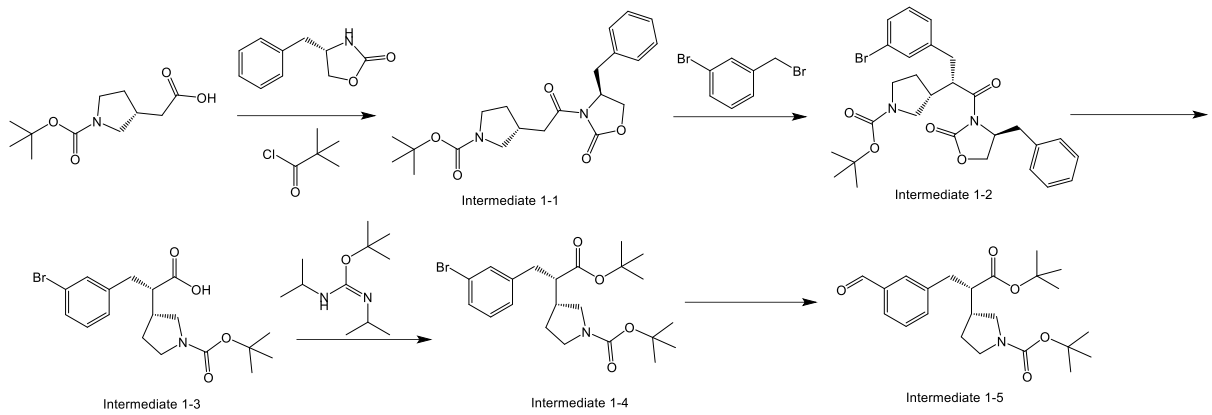
The invention is further elaborated below in conjunction with specific examples. It should be understood that these examples are intended to illustrate the invention only and not to limit the scope of the invention. Experimental methods without specific conditions are indicated in the following examples, usually under conventional conditions or as recommended by the manufacturer. All professional and scientific terms used herein have the same meaning as those familiar to professionals in the field, unless otherwise defined. In addition, any method and material similar to or equal to what has been described can be applied to the method of the invention. The preferred implementation methods and materials shown in the text are for demonstration purposes only.

The structures of the compounds of the invention are determined by nuclear magnetic resonance (NMR) or/and liquid chromatography-mass spectrometry (LC-MS) or/and high-performance liquid chromatography (HPLC). NMR was determined using Bruker 400MHz or/and Varian 400MHz; LC-MS was performed using Agilent, 1260 Infinity II-6120/6125MSD; HPLC was performed using Waters UPCC (CA-352).

The starting materials used in the examples of the invention are either known and commercially available or can be synthesized by methods known in the field or by analogy therewith.

The invention provides the methods of preparing the compounds. The compounds can be prepared by the following steps.

Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 1-5**)



Step 1: Synthesis of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (**Intermediate 1-1**)

Triethylamine (11.03 g, 109.04 mmol, 2.5 eq) was added to a solution of (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (10 g, 43.62 mmol, 1 eq) in tetrahydrofuran (150 mL) maintained at 10°C. After 5 min, pivaloyl chloride (6.57 g, 54.52 mmol, 1.25 eq) was added. After 15 min, lithium chloride (2.31 g, 54.52 mmol, 1.25 eq) and (S)-4-benzyloxazolidin-2-one (7.73 g, 43.62 mmol, 1 eq) in tetrahydrofuran (50 mL) were added. The mixture was warmed to room temperature and stirred for 24h. After 24h 1N HCl aqueous solution (50 mL) was added and the organic phase was separated from the aqueous phase. The organic phase was washed with 1N aqueous sodium hydroxide (50 mL) and saturated aqueous NaCl solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo, and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1, v/v) to give the target compound (15 g). LCMS (ESI) $[M+H]^+$ = 332.7. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 3H), 7.23-7.17 (m, 2H), 4.68 (ddd, *J* = 10.8, 7.2, 3.2 Hz, 1H), 4.26-4.16 (m, 2H), 3.68 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.48 (ddd, *J* = 11.6, 8.4, 3.6 Hz, 1H), 3.37-3.23 (m, 2H), 3.12-2.94 (m, 3H), 2.78 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.67 (dt, *J* = 14.8, 7.2 Hz, 1H), 2.17-2.06 (m, 1H), 1.63-1.55 (m, 1H), 1.46 (d, *J* = 4.4 Hz, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 1-2**)

Under nitrogen protection, a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 30.1 mL, 30.1 mmol, 1 eq) was added dropwise to a solution of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (12 g, 30.89 mmol, 1 eq) in

tetrahydrofuran (100 mL) at 0°C. The mixture was stirred at 0°C for 30 min, then a solution of 1-bromo-3-(bromomethyl)benzene (8.49 g, 33.98 mmol, 1.1 eq) in tetrahydrofuran (20 mL) was added slowly, and the reaction solution was slowly warmed to room temperature and stirred overnight. The reaction mixture was cooled using an ice-water bath, a saturated aqueous solution of ammonium chloride was added, water was added to the mixture and extracted with ethyl acetate, and then the organic layer was washed with saturated aqueous sodium chloride. The organic matter was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give the target compound (17 g). LCMS (ESI) $[M\text{-}tert\text{-butyl}+H]^+ = 501.1$.

Step 3: Synthesis of (S)-3-(3-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (**Intermediate 1-3**)

A solution of hydrogen peroxide (0.88 M in water, 3.4 mL, 32.3 mmol, 1.5 eq) was added all at once to a solution of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (12 g, 21.53 mmol, 1 eq) in tetrahydrofuran (120 mL), and cooled with an ice/water bath. A solution of lithium hydroxide monohydrate (0.77 g, 32.3 mmol, 1.5 eq) in water (10 mL) was added, and stirred for 2.5h with the reaction temperature raised to room temperature. The reaction mixture was cooled to 0°C and a solution of sodium bisulfite (4.1 g) in water (20 mL) was added, followed by adding a solution of sodium hydroxide in water (5 N) to adjust the pH of the reaction mixture to >12. Then water and methyl *tert*-butyl ether were added to separate the layers and the aqueous layer was extracted with methyl *tert*-butyl ether. The organic matter was merged and extracted with water, and then this aqueous extract was added to the main aqueous solution. The aqueous solution was stirred with methyl *tert*-butyl ether (100 mL) and the mixture was cooled to 0°C, and hydrochloric acid (5 N) was added to adjust the pH of the solution to 3; the layers were separated and the organic layer was washed with a mixture of water and saturated aqueous NaCl solution; the organic matter was dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (5.5 g). LCMS (ESI) $[M\text{-}tert\text{-butyl}+H]^+ = 341.6$.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 1-4**)

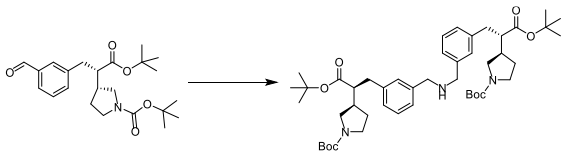
(S)-3-(3-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (5.5 g, 13.81 mmol, 1 eq) was dissolved in 2-methyltetrahydrofuran (80 mL). Under nitrogen

protection, *tert*-butyl N,N'-diisopropylcarbamimidate (13.83 g, 69.05 mmol, 5 eq) was added, and the mixture was heated to 65°C and stirred for 16h. The insoluble materials were filtered off, the filter cake was washed with methyl *tert*-butyl ether. The filtrate was concentrated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (5 g). LCMS (ESI) $[M-2\times tert\text{-butyl}+H]^+ = 343.6$.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 1-5**)

A solution of *tert*-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (3 g, 6.6 mmol, 1 eq) in toluene (25 mL) was added to a pressure vessel, followed by adding palladium acetate (148.22 mg, 0.66 mmol, 0.1 eq), *n*-butyldi(1-adamantyl)phosphine (355.07 mg, 0.99 mmol, 0.15 eq) and N,N,N',N'-tetramethylethylenediamine (1.15 g, 9.9 mmol, 1.5 eq); the mixture was stirred at 100°C for 16h under 2 MPa syngas (CO/H_2 1:1) atmosphere. The insoluble materials were filtered off through a celite pad, the filter cake was washed with ethyl acetate, and the filtrate was concentrated. Purification by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) was performed to give the target compound (3 g). LCMS (ESI) $[M-Boc]^+ = 303.8$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.72 (dd, *J* = 8.6, 4.5 Hz, 2H), 7.44 (dd, *J* = 8.5, 4.4 Hz, 2H), 3.66 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.50 (t, *J* = 8.6 Hz, 1H), 3.26 (td, *J* = 10.4, 6.9 Hz, 1H), 3.06-2.83 (m, 3H), 2.56-2.48 (m, 1H), 2.40 (dd, *J* = 16.5, 7.1 Hz, 1H), 2.01-1.90 (m, 1H), 1.68 (dt, *J* = 22.3, 10.2 Hz, 1H), 1.47 (s, 9H), 1.26 (s, 5H).

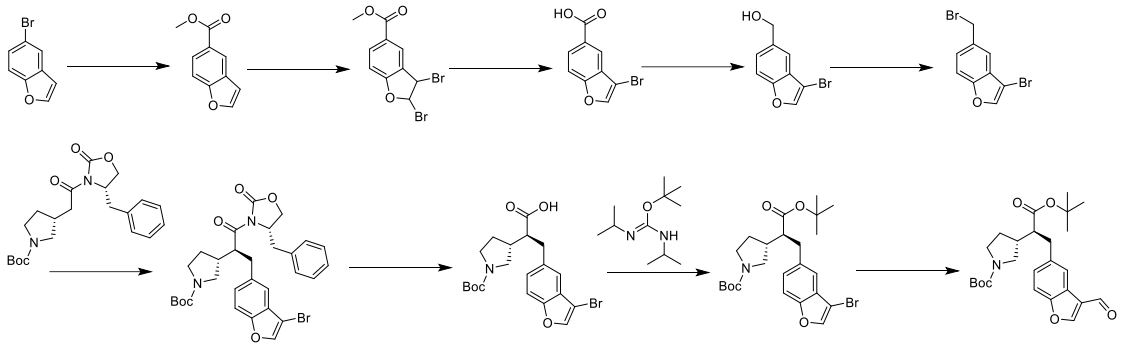
Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (**Intermediate 1-6**)



tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.6 g, 3.97 mmol, 1 eq) was dissolved in tetrahydrofuran (10 mL), ammonia methanol solution (0.62 mL, 4.36 mmol, 1.1 eq, 7 N) was added, and the mixture was stirred at room

temperature for 0.5h. Then sodium cyanoborohydride (0.49 g, 7.9.3 mmol, 2 eq) was added and the mixture was stirred at room temperature for 16h. Liquid chromatography-mass spectrometry (LCMS) showed that the reaction was completed, and the reaction solution was directly concentrated and purified by rapid chromatography (silica gel, dichloromethane:methanol = 30:1) to give the target compound (400 mg). LCMS (ESI) $[M+H]^+$ = 793.3.

Preparation of Intermediate 2



Step 1: Synthesis of methyl benzofuran-5-carboxylate

In an autoclave, 5-bromobenzofuran (20.00 g, 101.51 mmol, 1 eq), palladium acetate (2.28 g, 10.15 mmol, 0.1 eq) and triethylamine (2.05 g, 203.02 mmol, 2 eq) were added to a mixed solvent of dimethyl sulfoxide (100 mL) and methanol (100 mL), CO gas was introduced until the pressure reached 20 atmospheres, the oil bath was heated to 80°C, and the reaction was carried out for 18h. Water was added into the reaction. The mixture was extracted with ethyl acetate, the organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated, and separated through a normal phase separation column (petroleum ether:ethyl acetate = 10:1) to give the target compound (6.00 g). ^{1}HNMR (400 MHz, CD_3OD) δ 8.35 (d, J = 1.6 Hz, 1H), 8.01 (dd, J = 8.8, 1.6 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.00-6.89 (m, 1H), 3.94 (s, 3H).

Step 2: Synthesis of methyl 2,3-dibromo-2,3-dihydrobenzofuran-5-carboxylate

Methyl benzofuran-5-carboxylate (6.00 g, 34.06 mmol, 1 eq) was added in anhydrous dichloromethane (60 mL) and then bromine (6.53 g, 40.87 mmol, 1.2 eq) was added slowly dropwise at 0°C under nitrogen protection for 2h. The reaction mixture was added slowly dropwise to a solution of sodium sulfite, extracted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give the crude target compound (11.44 g,

crude). The crude compound was used directly in the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 8.00 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.15 (s, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.97 (s, 1H), 3.82 (d, *J* = 3.6 Hz, 3H).

Step 3: Synthesis of 3-bromobenzofuran-5-carboxylic acid

Methyl 2,3-dibromo-2,3-dihydrobenzofuran-5-carboxylate (11.00 g, 32.74 mmol, 1 eq) was dissolved in ethanol, an ethanol solution of potassium hydroxide (2.0 eq, 15%) was added, and the reaction was carried out at 80°C for 2h. The pH of the reaction mixture was adjusted to 2-3 with hydrochloric acid (2 M) solution. The mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to give the target compound (10.00 g, crude). The crude compound was used directly in the next step without further purification.

Step 4: Synthesis of (3-bromobenzofuran-5-yl)methanol

3-bromobenzofuran-5-carboxylic acid (10.00 g, 41.49 mmol, 1.0 eq) was dissolved in tetrahydrofuran, and a solution of borane/tetrahydrofuran (860 mg, 62.23 mmol, 1.5 eq) was added at 0°C and the reaction was carried out at 0°C for 2h. Methanol was added dropwise at low temperature to quench the reaction, and the mixture was concentrated to give the target compound (10.00 g, crude). The crude compound was used directly in the next step without further purification. LCMS (ESI) $[M\text{-}OH]^+$ = 209.2.

Step 5: Synthesis of 3-bromo-5-(bromomethyl)benzofuran

(3-bromobenzofuran-5-yl)methanol (10.00 g, 37.44 mmol, 1 eq) was dissolved in dichloromethane (100 mL), and phosphorus tribromide (11.15 g, 41.18 mmol, 1.1 eq) was slowly added dropwise at 0°C, and the reaction was carried out at 0°C for 2h. The reaction mixture was slowly poured into water, extracted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered and concentrated to give the crude target compound (10.10 g). The crude compound was used directly in the next step without further purification.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromobenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (10.25 g, 26.38 mmol, 1 eq) was dissolved in tetrahydrofuran (100 mL), and lithium

bis(trimethylsilyl)amide (5.30 g, 31.65 mmol, 1.2 eq) was slowly added dropwise at -78°C. The reaction was carried out for 1h. 3-bromo-5-(bromomethyl)benzofuran (9.00 g, 26.38 mmol, 1 eq) was dissolved in tetrahydrofuran (30 mL) and slowly added dropwise to the reaction mixture. The reaction mixture was slowly warmed to room temperature and stirred for 12h. The reaction mixture was added to saturated ammonium chloride, extracted with ethyl acetate, and the organic phases were merged. The mixture was washed with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated to give the target compound (12.00 g). The crude compound was used directly in the next step without further purification. LCMS (ESI) $[M+Na]^+ = 619.0$.

Step 7: Synthesis of (S)-3-(3-bromobenzofuran-5-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromobenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (11.00 g, 18.41 mmol, 1 eq) was dissolved in tetrahydrofuran (300 mL), lithium hydroxide (440 mg, 18.41 mmol, 1 eq) was dissolved in water (100 mL) and hydrogen peroxide (11 mL). The above were added to the reaction mixture at 0°C, and the reaction was carried out at room temperature for 2h. The reaction was quenched with sodium sulfite solution, extracted with ethyl acetate, washed with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated to give the target compound (5.50 g). The crude compound was used directly in the next step without further purification. LCMS (ESI) $[M-Boc+H]^+ = 339.0$.

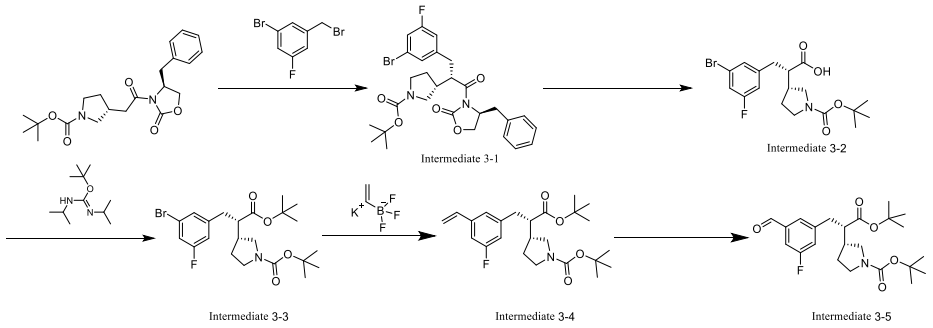
Step 8: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromobenzofuran-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(3-bromobenzofuran-5-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (5.50 g, 12.55 mmol, 1.0 eq) and *tert*-butyl N,N'-diisopropylcarbamimidate (7.54 g, 37.64 mmol, 3.0 eq) were dissolved in 2-methyltetrahydrofuran (50 mL) and heated to 80°C for 3h. The reaction mixture was extracted with ethyl acetate and water, the organic phase was washed with saturated brine, dried over sodium sulfate, concentrated, mixed, and purified by column chromatography to give the target compound (2.50 g). LCMS (ESI) $[M+Na]^+ = 516.2, 518.2$.

Step 9: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylbenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

In a high-pressure reaction vessel, *tert*-butyl (R)-3-((S)-3-(3-bromobenzofuran-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.5 g, 3.03 mmol, 1.0 eq), palladium acetate (68 mg, 0.30 mmol, 0.1 eq), [2-(dimethylamino)ethyl]dimethylamine (704 mg, 6.06 mmol, 2.0 eq), and bis(adamantan-1-yl)(butyl)phosphine (217 mg, 0.61 mmol, 0.2 eq) were added in toluene (15 mL), and H_2/CO (v/v = 1/1) was introduced until the pressure reached 1.3 MPa. The reaction was carried out at 100°C for 18h. The reaction mixture was extracted with ethyl acetate and water, washed with saturated sodium chloride solution, dried over sodium sulfate, and purified by normal phase separation (silica gel, petroleum ether:ethyl acetate = 6:1, v/v) to give the target compound (700 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.18 (d, *J* = 4.1 Hz, 1H), 7.94 (d, *J* = 6.0 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 3.71-3.34 (m, 2H), 3.23-3.13 (m, 1H), 3.02-2.77 (m, 3H), 2.45 (d, *J* = 8.6 Hz, 1H), 2.39-2.28 (m, 1H), 1.92-1.84 (m, 1H), 1.57 (d, *J* = 13.9 Hz, 1H), 1.40 (s, 9H), 1.21 (s, 9H).

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 3-5**)



Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromo-5-fluorophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 3-1)**

The target product (21.9 g) was synthesized from 1-bromo-3-(bromomethyl)-5-fluorobenzene as the starting material by referring to the method of Intermediate 1-2. LCMS (ESI) $[M\text{-}tert\text{-butyl}+H]^+$ = 521.2.

Synthesis of (S)-3-(3-bromo-5-fluorophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (**Intermediate 3-2**)

The target product (8.8 g) was synthesized by referring to the method of Intermediate 1-3. LCMS (ESI) $[M\text{-}tert\text{-butyl}+H]^+$ = 359.9.

Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromo-5-fluorophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 3-3**)

The target product (6.1 g) was synthesized by referring to the method of Intermediate 1-4. LCMS (ESI) $[M -2\times tert\text{-butyl}+H]^+ = 359.9$.

Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-vinylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 3-4)**

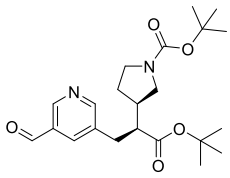
In a three-necked flask, *tert*-butyl (R)-3-((S)-3-(3-bromo-5-fluorophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (5.6 g) was dissolved in 1,4-dioxane (45 mL). Potassium vinyltrifluoroborate (8 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (922 mg), and triethylamine (3.6 g) were added in turn. Water (15 mL) was added. The mixture was heated to 75°C under nitrogen protection and stirred for 5h. LCMS showed that the reaction was completed. The insoluble materials were filtered off through diatomaceous earth, the filter cake was washed with an appropriate amount of ethyl acetate, and the filtrate was concentrated. The filtrate was separated and purified by rapid chromatography (silica gel, PE:EA = 10:1, v/v) to give the target compound (4.4 g). LCMS (ESI) $[M-2\times tert\text{-butyl}+H]^+ = 308.3$.

Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 3-5)**

In a three-necked flask, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-vinylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (4.4 g, 10.53 mmol, 1 eq) was dissolved in tetrahydrofuran (44 mL) and water (12 mL). The mixture was under nitrogen protection and then potassium osmate (388 mg, 1.05 mmol, 0.1 eq) and sodium periodate (6.76 g, 31.59 mmol, 3 eq) were added in turn under ice bath. The reaction mixture was warmed to room temperature and stirred for 3h. The insoluble materials were filtered off, the filtrate was poured into water, and then extracted with ethyl acetate. The organic phases were merged, washed with saturated NaCl aqueous solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by rapid chromatography (silica gel, PE:EA = 10:1, v/v) to give the target compound (2.7 g). LCMS (ESI) $[M-2\times tert\text{-butyl}+H]^+ = 310.0$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.97 (d, J = 1.5 Hz, 1H), 7.63 (s, 1H), 7.46 (d, J = 9.8 Hz, 1H), 3.52 (q, J = 10.5 Hz, 1H), 3.42-3.34 (m, 1H), 3.24-

3.09 (m, 1H), 3.02 (t, J = 10.0 Hz, 1H), 2.83 (q, J = 13.9 Hz, 2H), 2.59 (d, J = 8.9 Hz, 1H), 2.30 (s, 1H), 1.91-1.76 (m, 1H), 1.68-1.49 (m, 1H), 1.40 (s, 9H), 1.21 (s, 9H).

Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylpyridin-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (**Intermediate 4-1)**

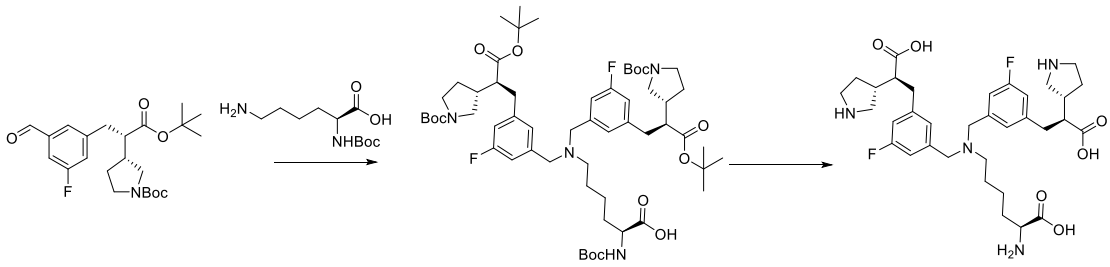


Intermediate 4-1

The target compound (320 mg) was synthesized from 3-bromo-5-(bromomethyl)pyridine instead of 1-bromo-3-(bromomethyl)benzene by referring to the method of Intermediate 1-5. LCMS (ESI) $[M+H]^+$ = 405.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.95 (d, J = 1.8 Hz, 1H), 8.71 (d, J = 1.9 Hz, 1H), 8.09 (s, 1H), 3.59-3.47 (m, 2H), 3.21-3.12 (m, 1H), 3.05 (t, J = 10.0 Hz, 1H), 2.96-2.88 (m, 1H), 2.87-2.79 (m, 1H), 2.65-2.56 (m, 1H), 2.39-2.27 (m, 1H), 1.90-1.81 (m, 1H), 1.64-1.54 (m, 1H), 1.40 (s, 9H), 1.19 (s, 9H).

Example 1 (Compound 5)

Preparation of (2S,2'S)-3,3'-(((((S)-5-amino-5-carboxypentyl)azanediyl)bis(methylene))bis(5-fluoro-3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of N^6,N^6-bis(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorobenzyl)-N2-(*tert*-butoxycarbonyl)-L-lysine

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (376 mg, 0.893 mmol, 2.2 eq) and (*tert*-butoxycarbonyl)-L-lysine

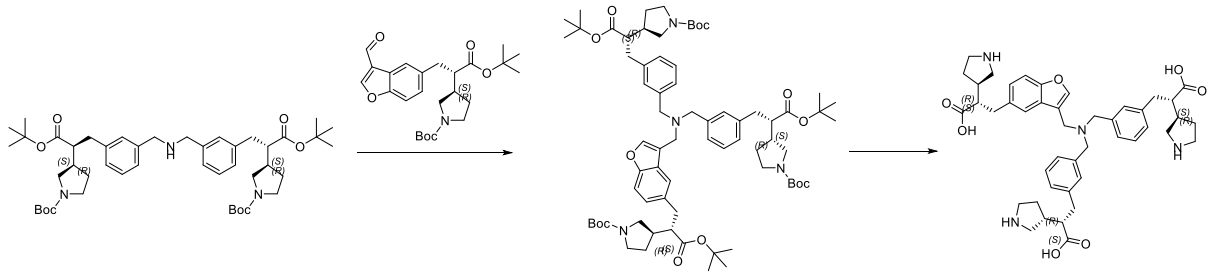
(100 mg, 0.406 mmol, 1.0 eq) were dissolved in tetrahydrofuran (2 mL), and sodium cyanoborohydride (64 mg, 1.02 mmol, 2.5 eq) and a drop of acetic acid were added. The reaction mixture was stirred at room temperature overnight. A saturated ammonium chloride solution and dichloromethane were added. The organic solvent was evaporated under reduced pressure and the residue was purified by rapid chromatography (Silica gel, DCM:MeOH = 15:1, volume ratio) to obtain the target compound (89 mg). LCMS (ESI) $[M+H]^+$ = 1057.9.

Step 2: Synthesis of (2S,2'S)-3,3'-(((((S)-5-amino-5-carboxypentyl)azanediyl)bis(methylene))bis(5-fluoro-3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

N^6,N^6-bis(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorobenzyl)-N2-(*tert*-butoxycarbonyl)-L-lysine (89 mg, 0.084 mmol, 1.0 eq) was dissolved in 1,4-dioxane (0.2 mL), and a solution of 4 M HCl (1,4-dioxane) (0.2 mL) was added. The reaction mixture was stirred at room temperature overnight. LCMS monitoring showed that the reaction was complete. The solvent was evaporated under reduced pressure, and the residue was purified by preparative-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water/acetonitrile) to obtain the target compound (9.8 mg). LCMS (ESI) $[M+H]^+$ = 645.4; ^1H NMR (400 MHz, D_2O) δ 6.97-6.86 (m, 6H), 3.78 (s, 4H), 3.64-3.57 (m, 1H), 3.51-3.42 (m, 2H), 3.40-3.31 (m, 2H), 3.23-3.13 (m, 2H), 2.97-2.87 (m, 2H), 2.77-2.68 (m, 4H), 2.66-2.53 (m, 2H), 2.45-2.33 (m, 4H), 2.10-2.00 (m, 2H), 1.81-1.53 (m, 6H), 1.32-1.17 (m, 2H).

Example 2 (Compound 6)

Preparation of (2S,2'S)-3,3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzofuran-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzofuran-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

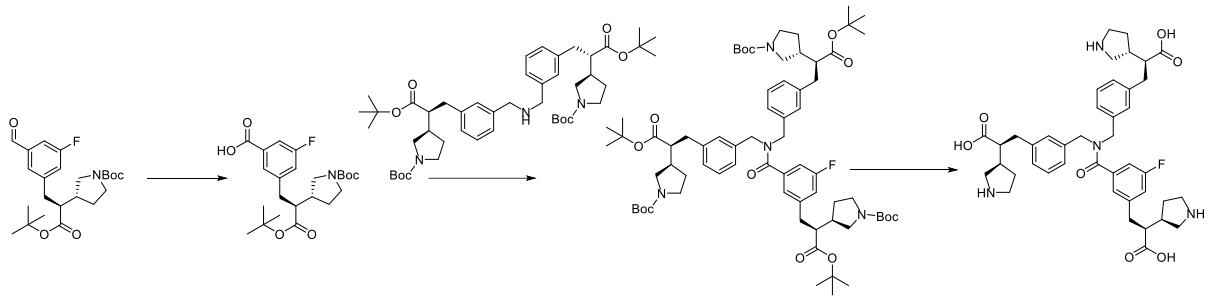
Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (50 mg, 0.063 mmol, 1.0 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylbenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (33 mg, 0.076 mmol, 1.2 eq) were dissolved in tetrahydrofuran (0.2 mL), and sodium cyanoborohydride (6 mg, 0.095 mmol, 1.5 eq) and one drop of acetic acid were added. The reaction mixture was stirred at room temperature overnight. A saturated ammonium chloride solution and dichloromethane were added. The organic phase was concentrated under reduced pressure and purified by rapid chromatography (Silica gel, DCM:MeOH = 15:1, volume ratio) to obtain the target compound (45 mg).

Step 2: Synthesis of (2S,2'S)-3,3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzofuran-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((((5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzofuran-3-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (45 mg, 0.037 mmol, 1.0 eq) was dissolved in 1,4-dioxane (0.2 mL), 4 M HCl (1,4-dioxane) solution (0.2 mL) was added, and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by preparative-HPLC (C_{18}, water/acetonitrile solution of 10mmol/L NH_4HCO_3) to obtain the target compound (13 mg). LCMS (ESI) $[M+H]^+$ = 751.5, ^{1}H NMR (400 MHz, D_2O) δ 7.45 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 9.1 Hz, 4H), 7.01 (d, *J* = 11.7 Hz, 4H), 3.53-3.44 (m, 3H), 3.32-3.18 (m, 7H), 3.12-3.05 (m, 3H), 2.83-2.67 (m, 7H), 2.65-2.54 (m, 3H), 2.38-2.27 (m, 7H), 2.03-1.96 (m, 3H), 1.68-1.60 (m, 3H).

Example 3 (Compound 12)

Preparation of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-5-fluorobenzoyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorobenzoic acid

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (50 mg), sodium hydroxide (8 mg) and potassium permanganate (30 mg) were dissolved in acetonitrile (0.5 mL) and water (0.5 mL). The reaction mixture was stirred at 60°C overnight. Water and dichloromethane were added. The organic phase was concentrated under reduced pressure and purified by rapid chromatography (Silica gel, DCM:MeOH = 30:1, volume ratio) to obtain the target compound (15 mg). LCMS (ESI) $[M\text{-}Boc+H]^+$ = 338.49.

Step 2: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorobenzoyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

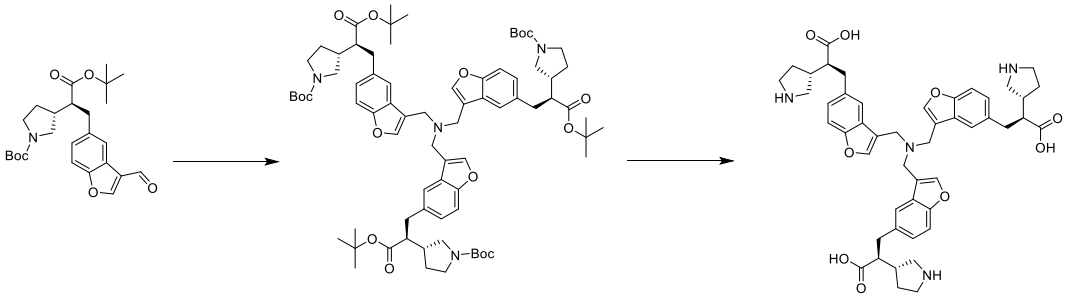
3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorobenzoic acid (15 mg) was dissolved in N,N-dimethylformamide (0.3 mL), and di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (27 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (15 mg), and *N,N*-diisopropylethylamine (14 mg) were added. The reaction mixture was stirred at room temperature overnight. Water and ethyl acetate were added. The organic phase was concentrated under reduced pressure and purified by rapid chromatography (Silica gel, DCM:MeOH = 30:1, volume ratio) to obtain the target compound (20 mg). LCMS (ESI) $[M\text{-}Boc+H]^+$ = 1111.92.

Step 3: Synthesis of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-5-fluorobenzoyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorobenzoyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (115 mg) was dissolved in 1,4-dioxane (0.2 mL), 4 M HCl (1,4-dioxane) solution (0.2 mL) was added, and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and purified by preparative-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water/acetonitrile) to obtain the target compound (39.9 mg). LCMS (ESI) $[M+H]^+$ = 743.65; ^1H NMR (400 MHz, D_2O) δ 7.30-7.18 (m, 2H), 7.16-6.93 (m, 7H), 6.92-6.81 (m, 2H), 4.60 (s, 2H), 4.41 (s, 2H), 3.42-3.23 (m, 6H), 3.20-3.06 (m, 3H), 2.88-2.60 (m, 9H), 2.45-2.24 (m, 6H), 2.11-1.93 (m, 3H), 1.75-1.53 (m, 3H).

Example 4 (Compound 47)

Preparation of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzofuran-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzofuran-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-Butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylbenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (600 mg, 1.38 mmol, 1 eq) was dissolved in isopropanol (6 mL), ammonia methanol solution (1.0 eq, 7.0 M) and sodium triacetoxyborohydride (436 mg, 2.10 mmol, 1.5 eq) were added, and the reaction was carried out at 25°C for 16h. The reaction mixture

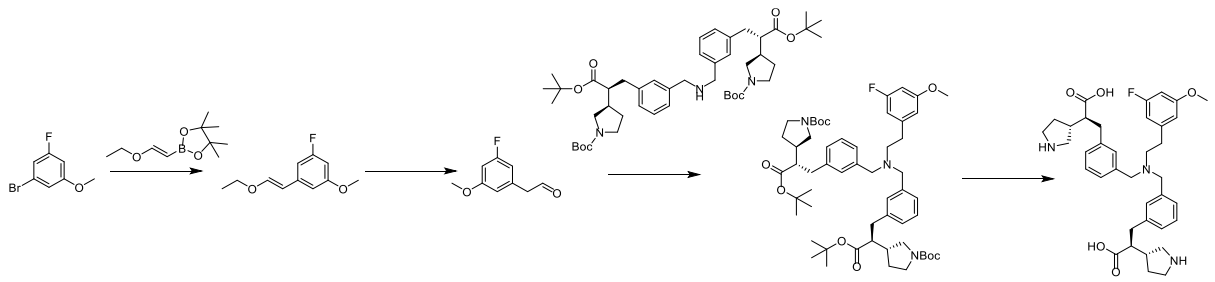
was concentrated and purified by silica gel column chromatography (Silica gel, petroleum ether/ethyl acetate = 1/1, volume ratio) to obtain the target compound (30 mg). LCMS (ESI) $[M+H]^+$ = 1322.6.

Step 2: Synthesis of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzofuran-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3"-((2S,2'S,2"S)-((nitrilotris(methylene))tris(benzofuran-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3"R)-tris(pyrrolidine-1-carboxylate) (35 mg, 0.03 mmol, 1 eq) was dissolved in hydrogen chloride dioxane solution (1 mL, 4 M) and the mixture was stirred at room temperature for 1h. The reaction mixture was concentrated, water was added, and the mixture was lyophilized to obtain the target compound (15.88 mg). LCMS (ESI) $[M+H]^+$ = 831.4; ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 3H), 7.56-7.47 (m, 6H), 7.27 (d, *J* = 8.4 Hz, 3H), 4.64 (s, 6H), 3.52-3.35 (m, 6H), 3.26-3.19 (m, 3H), 3.08-2.93 (m, 12H), 2.52 (d, *J* = 7.6 Hz, 3H), 2.16 (d, *J* = 7.2 Hz, 3H), 1.91-1.73 (m, 3H).

Example 5 (Compound 89)

Preparation of (2S,2'S)-3,3'-((((3-fluoro-5-methoxyphenethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of (E)-1-(2-ethoxyvinyl)-3-fluoro-5-methoxybenzene

Under nitrogen, in a three-necked flask, [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (1.14 g), cesium carbonate (29.32 g), 1,4-dioxane (180 mL), and water (30 mL) were added. 1-bromo-3-fluoro-5-methoxybenzene (6.15 g) and (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.54 g) were added in turn; the reaction mixture was heated to 100°C and reacted for 3h. After the reaction was completed, the reaction mixture was quenched with saturated saline

solution and extracted with ethyl acetate. After combining the organic phases, the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated, and separated by column chromatography (Silica gel, petroleum ether:ethyl acetate = 3:1, volume ratio) to obtain the target compound (3.60 g).

Step 2: Synthesis of 2-(3-fluoro-5-methoxyphenyl)acetaldehyde

(E)-1-(2-ethoxyvinyl)-3-fluoro-5-methoxybenzene (500 mg) was dissolved in HCl/dioxane (5 mL) and the mixture was stirred at room temperature for 16h. LCMS showed that the reaction was completed. The reaction mixture was concentrated directly and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1, volume ratio) to obtain the target compound (150 mg). LCMS (ESI) $[M+H]^+$ = 169.07.

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((3-fluoro-5-methoxyphenethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

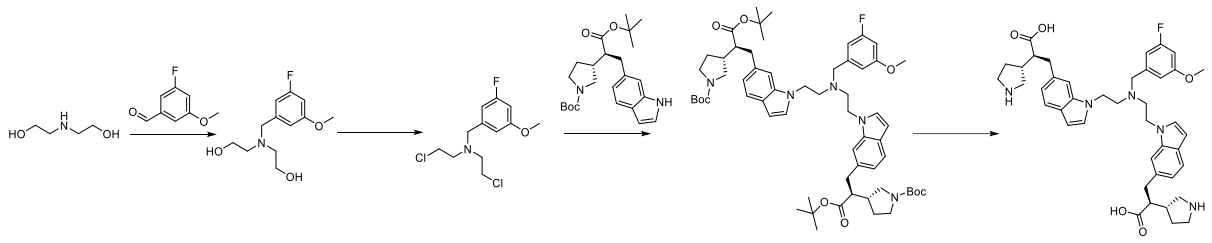
2-(3-fluoro-5-methoxyphenyl)acetaldehyde (47 mg) was dissolved in methanol (5 mL), and di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (200 mg) and two drops of acetic acid were added at room temperature. The mixture was stirred at room temperature for 16h. The reaction mixture was directly concentrated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 5:1, volume ratio) to obtain the target compound (120 mg). LCMS (ESI) $[M+H]^+$ = 944.89.

Step 4: Synthesis of (2S,2'S)-3,3'-((((3-fluoro-5-methoxyphenethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((3-fluoro-5-methoxyphenethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (120 mg) was dissolved in HCl/dioxane (5 mL) and the mixture was stirred at room temperature for 16h. The reaction mixture was concentrated directly and separated and purified by preparative-HPLC (C_{18}, 0.1%FA in water/acetonitrile) to obtain the target compound (47.46 mg). LCMS (ESI) $[M+H]^+$ = 632.4.

Example 6 (Compound 62)

Preparation of (2S,2'S)-3,3'-((((3-fluoro-5-methoxybenzyl)azanediyl)bis(ethane-2,1-diyl))bis(1H-indole-1,6-diyl))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 2,2'-((3-fluoro-5-methoxybenzyl)azanediyl)bis(ethan-1-ol)

2,2'-azanediylbis(ethan-1-ol) (2.00 g) was added in dichloromethane (30 mL), and 3-fluoro-5-methoxybenzaldehyde (4.00 g) and sodium triacetoxyborohydride (12.00 g) were added at 25°C. The reaction was carried out at 25°C for 2h, and the reaction was monitored by LCMS. The reaction mixture was extracted with dichloromethane and water. After the organic phases were concentrated under reduced pressure, the residue was purified (by reversed-phase column chromatography:acetonitrile/water = 10%) to obtain the target compound (4.00 g). LCMS (ESI) $[M+H]^+$ = 244.2.

Step 2: Synthesis of 2-chloro-N-(2-chloroethyl)-N-(3-fluoro-5-methoxybenzyl)ethan-1-amine

2,2'-((3-fluoro-5-methoxybenzyl)azanediyl)bis(ethan-1-ol) (1.50 g) was added to thionyl chloride (15 mL) and the reaction was carried out at 70°C overnight. Compounds were detected by LCMS. The thionyl chloride was concentrated under reduced pressure. The residue was triturated with ethyl acetate. The mixture was extracted with aqueous ammonium chloride solution without further purification to obtain the target compound (1.8 g, crude product) which was used in the next step without further purification.

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((3-fluoro-5-methoxybenzyl)azanediyl)bis(ethane-2,1-diyl))bis(1H-indole-1,6-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(1H-indol-6-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (0.5 g) was added in N,N-dimethylformamide (5 mL) and 2-chloro-N-(2-chloroethyl)-

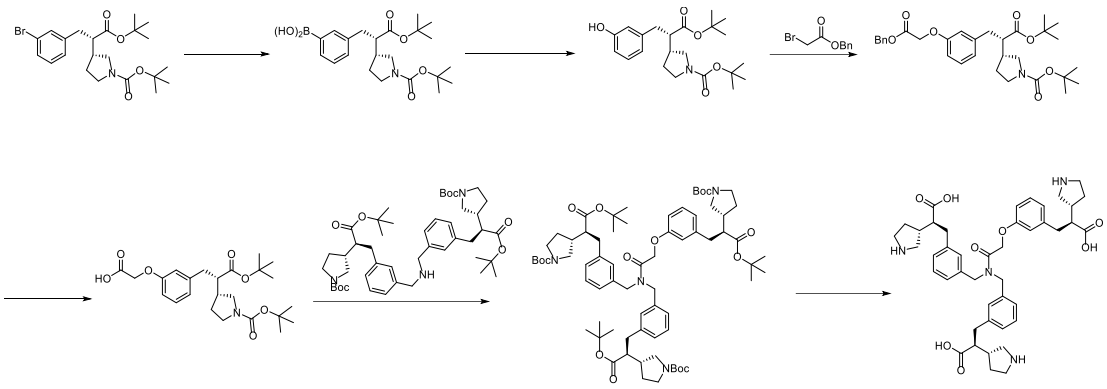
N-(3-fluoro-5-methoxybenzyl)ethan-1-amine (338 mg) and cesium carbonate (1.2 g) were added at room temperature. The reaction mixture was stirred at 100°C under nitrogen overnight. After the reaction mixture was detected by LCMS, saturated saline solution was added. The reaction mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate. After the organic phases were concentrated under reduced pressure, the residue was washed by silica gel column chromatography (pure ethyl acetate) to obtain the target compound (190 mg). LCMS (ESI) $[M+H]^+$ = 1036.6.

Step 4: Synthesis of (2S,2'S)-3,3'-((((3-fluoro-5-methoxybenzyl)azanediyl)bis(ethane-2,1-diyl))bis(1H-indole-1,6-diyl))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((3-fluoro-5-methoxybenzyl)azanediyl)bis(ethane-2,1-diyl))bis(1H-indole-1,6-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (140 mg) was added in TFA (2 mL) and the mixture was stirred at 25°C for 0.5h. LCMS detected the desired product. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in acetonitrile and purified by preparative-HPLC (FA) to obtain the target compound (13.6 mg). LCMS (ESI) $[M+H]^+$ = 725.04; ^{1}H NMR (400 MHz, MeOD-*d4*) δ 8.42 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 3.2 Hz, 2H), 6.91 (d, *J* = 7.2 Hz, 2H), 6.87-6.84 (m, 2H), 6.45-6.43 (m, 3H), 6.29 (t, *J* = 2.8 Hz, 2H), 4.07 (d, *J* = 6.2 Hz, 4H), 3.63 (d, *J* = 3.2 Hz, 3H), 3.59 (s, 2H), 3.21-3.18 (m, 4H), 3.13-3.03 (m, 6H), 2.99-2.92 (m, 2H), 2.87 (s, 2H), 2.78-2.66 (m, 2H), 2.60-2.54 (m, 2H), 2.38-2.30 (m, 2H), 2.01 (d, *J* = 24.0 Hz, 2H), 1.85-1.76 (m, 1H), 1.56 (s, 1H).

Example 7 (Compound 95)

Preparation of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of (3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)boronic acid

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.9 g, 4.18 mmol, 1 eq), (dihydroxyboranyl)boronic acid (562.29 mg, 6.27 mmol, 1.5 eq), potassium acetate (1230.7 mg, 12.54 mmol, 3 eq), 2-(dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl (199.27 mg, 0.42 mmol, 0.1 eq) and X-Phos Pd G_2 (164 mg, 0.21 mmol, 0.05 eq) were added to EtOH (20 mL). The reaction mixture was purged with nitrogen three times, and reacted at 90°C for 16h; The product was detected by LCMS, ethyl acetate (20 mL) was added to the reaction system. The mixture was filtered through diatomaceous earth, and the filtrate was evaporated under reduced pressure to obtain the target compound (2.0 g). The crude product was not further purified and directly used for the next step. LCMS[M-2×*tert*-butyl+H]$^+$ = 308.2.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)boronic acid (2000 mg, 4.77 mmol, 1 eq) was dissolved in THF (20 mL), and hydrogen peroxide (8 mL, 235.2 mmol, 49.31 eq) wad added, and the reaction mixture was stirred at 20°C for 16h. LCMS showed the desired product. A saturated solution of sodium bisulfite (20 mL) and ethyl acetate (20 mL) were added, and the mixture was extracted. The organic phase was dried over sodium sulfate, concentrated, and purified by rapid chromatography (Silica gel, PE:EtOAc = 4:1, v/v) to obtain the target compound (800 mg). LCMS (ESI) [M+H]$^+$ = 392.2.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(benzyloxy)-2-oxoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2.0 g, 5.11 mmol, 1 eq), benzyl 2-bromoacetate (2.34 g, 10.22 mmol, 2 eq) and potassium carbonate (2.12 g, 15.33 mmol, 3 eq) were added to acetonitrile (50 mL), and the mixture was reacted at 90°C for 16h; LCMS showed the desired product. Rapid chromatography (Silica gel, PE:EtOAc = 5:1, volume ratio) was used to obtain the target compound (2.5 g). LCMS (ESI) $[M+Na]^+$ = 561.9.

Step 4: Synthesis of 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetic acid

tert-butyl (R)-3-((S)-3-(3-(2-(benzyloxy)-2-oxoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2.5 g, 4.63 mmol, 1 eq) was dissolved in methanol (50 mL), followed by adding Pd/C (300 mg, 10%), and the mixture was purged with hydrogen for three times. The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The mixture was filtered, and the filtrate was concentrated to obtain the target compound (1.5 g). LCMS (ESI) $[M+Na]^+$ = 472.2.

Step 5: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

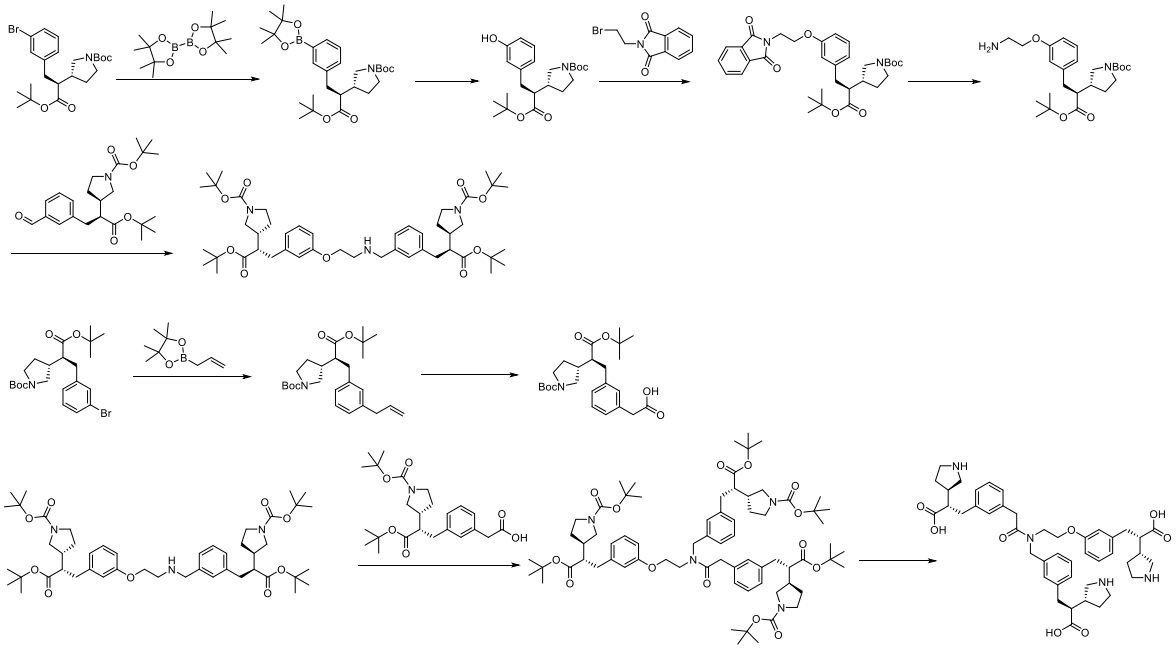
Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (88.1 mg, 0.11 mmol, 1 eq), 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetic acid (50 mg, 0.11 mmol, 1 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (41.83 mg, 0.11 mmol, 1 eq) and *N,N*-diisopropylethylamine (43.12 mg, 0.33 mmol, 3 eq) were dissolved in N,N-dimethylformamide (3 mL); the mixture was stirred at room temperature for 16h, and LCMS showed that the reaction was completed; the reaction solvent was evaporated, and the residue was purified by thin-layer silica gel plate (DCM:MeOH = 20:1, volume ratio) to obtain the target compound (100 mg). LCMS (ESI) $[M+Na]^+$ = 1245.8.

Step 6: Synthesis of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (100 mg, 0.08 mmol, 1 eq) was added to hydrochloric acid-dioxane (2 mL, 4.0 M) and reacted at room temperature for 6h. The reaction mixture was filtered and the filter cake was washed with dioxane to obtain the target compound (46 mg). LCMS (ESI) $[M+H]^+$ = 755.2. ^1H NMR (400 MHz, CD_3OD) δ 7.34-7.20 (m, 5H), 7.18-7.10 (m, 4H), 6.92-6.85 (m, 2H), 6.7-6.75 (m, 1H), 4.92 (s, 2H), 4.61 (s, 4H), 3.57 -3.40 (m, 6H), 3.34-3.21 (m, 3H), 2.99-2.81 (m, 11H), 2.78-2.72 (m, 3H), 2.56-2.49 (m, 3H), 2.29-2.15 (m, 3H), 1.87-1.81 (m, 3H).

Example 8 (Compound 96)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Preparation of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.5 g, 3.30 mmol, 1.0 eq) was dissolved in 1,4-dioxane (20 mL) in a single-necked

flask, followed by adding [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (270.0 mg, 0.33 mmol, 0.1 eq), bis(pinacolato)diboron (1.26 g, 4.95 mmol, 1.5 eq) and potassium acetate (972 mg, 9.9 mmol, 3 eq); the mixture was stirred at 90°C for 16h under nitrogen. LCMS detection showed that the reaction was completed, and the reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, PE:EtOAc = 2:1) to obtain the target compound (1.2 g). LCMS (ESI) $[M\text{-Boc}+H]^+ = 402.2$.

Step 2: Preparation of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

In a single-neck bottle, the product from the first step (1.2 g, 2.39 mmol, 1.0 eq) was dissolved in tetrahydrofuran (20 mL). Subsequently hydrogen peroxide (0.5 mL) was added, and the mixture was stirred at room temperature for 16h. LCMS detection showed that the reaction was completed, and the reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, PE:EtOAc = 1:1) to obtain the target compound (800.0 mg). LCMS (ESI) $[M\text{-}2\times tert\text{-butyl}+H]^+ = 280.0$.

Step 3: Preparation of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

In a single-neck bottle, the product from the second step (500.0 mg, 1.28 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (5 mL), followed by adding 2-(2-bromoethyl)isoindoline-1,3-dione (647.7 mg, 2.56 mmol, 2 eq), potassium carbonate (530.7 mg, 3.83 mmol, 3 eq). The mixture was stirred at 90°C for 2h. LCMS detection showed that the reaction was completed, and the reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, PE:EtOAc = 1:1) to obtain the target compound (280 mg). LCMS (ESI) $[M+H]^+ = 565.3$.

Step 4: Preparation of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

In a single-neck bottle, the product from the third step (280.0 mg, 0.5 mmol, 1.0 eq) was dissolved in ethanol (10 mL), followed by adding hydrazine hydrate (124 mg, 2.50 mmol, 5.0 eq). The mixture was reacted at 90°C for 16h. LCMS detection showed that the reaction was completed, and the reaction mixture was directly concentrated, separated and purified by rapid

chromatography (Silica gel, PE:EtOAc = 1:5) to obtain the target compound (160 mg). LCMS (ESI) $[M+H]^+$ = 435.3.

Step 5: Preparation of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

In a single-neck bottle, the product from the fourth step (160 mg, 0.37 mmol, 1.0 eq) was dissolved in methanol (10 mL). Subsequently, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (178.1 mg, 0.44 mmol, 1.2 eq) was added, followed by addition of sodium cyanoborohydride (23.2 mg, 0.37 mmol, 1.0 eq). The mixture was stirred at room temperature for 16h. LCMS detection showed that the reaction was completed, and the reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, PE:EtOAc = 1:5) to obtain the target compound (233 mg). LCMS (ESI) $[M+H]^+$ = 822.6.

Step 6: Preparation of *tert*-butyl (R)-3-((S)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (7.0 g, 15.4 mmol, 1.0 eq) was dissolved in 1,4-dioxane (20 mL) and water (4 mL) in a single-necked flask, followed by adding 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.2 g, 30.8 mmol, 2 eq), potassium phosphate (9.8 g, 46.2 mmol, 3 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (1.25 g, 1.54 mmol, 0.1 eq). The mixture was degassed with nitrogen for 3 times and stirred at 90°C for 16h. LCMS detection showed that the reaction was completed, and the reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, PE:EtOAc = 2:1) to obtain the target compound (5.0 g). LCMS$[M-2\times$*tert*-butyl$+H]^+$ = 304.1.

Step 7: Preparation of 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid

In a single-neck bottle, the product from the sixth step (6.0 g, 14.4 mmol, 1.0 eq) was dissolved in 1,4-dioxane (100 mL), followed by adding sodium periodate (12.3 g, 57.75 mmol, 4 eq) and potassium osmate dihydrate (532.0 mg, 1.44 mmol, 0.1 eq). The mixture was stirred at

room temperature for 16h. LCMS detection showed that the reaction was completed, and the reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, PE:EtOAc = 1:1) to obtain the target compound (500 mg). LCMS (ESI) $[M+H]^+$ = 434.2.

Step 8: Preparation of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

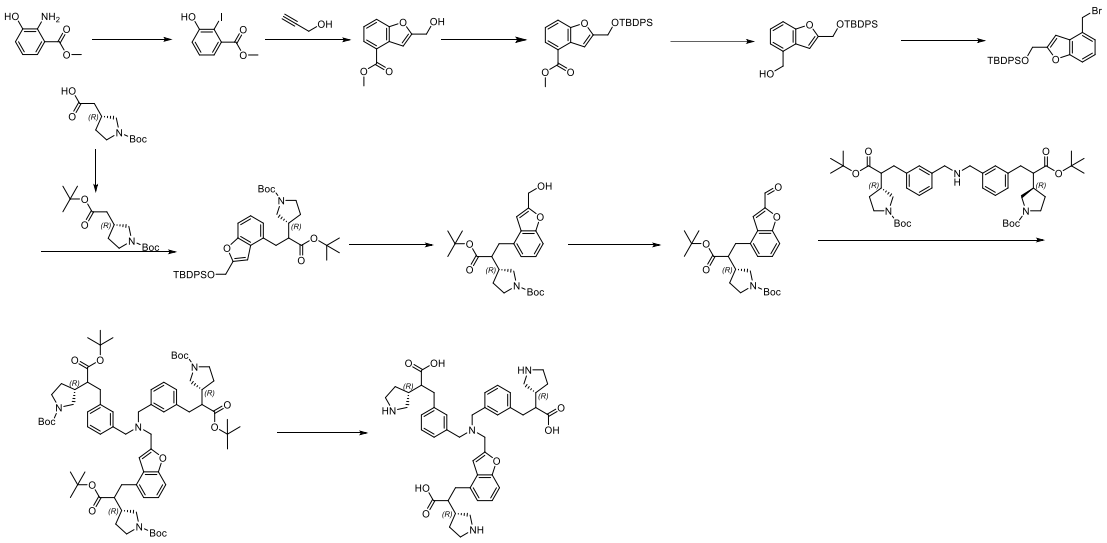
In a single-neck bottle, the product from the fifth step (70 mg, 0.0852 mmol, 1.0 eq) was dissolved in DMF (5 mL), followed by adding the product obtained in the seventh step (44.3 mg, 0.102 mmol, 1.2 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (64.7 mg, 0.17 mmol, 2.0 eq) and *N,N*-diisopropylethylamine (33.0 mg, 0.25 mmol, 3.0 eq). The mixture was stirred at room temperature for 16h, and LCMS showed the reaction was complete. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, PE:EtOAc = 1:8) to obtain the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 1237.9.

Step 9: Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

In a single-neck bottle, the product from the eighth step (70.0 mg, 0.056mmol) was dissolved in hydrochloric acid-dioxane (2 mL), and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (27.2 mg). LCMS (ESI) $[M+H]^+$ = 769.4. ^{1}H NMR (400 MHz, D_2O) δ 7.20 (dq, *J* = 30.0, 7.5 Hz, 3H), 7.11-6.86 (m, 6H), 6.81 (s, 1H), 6.69-6.59 (m, 2H), 4.59 (d, *J* = 4.6 Hz, 2H), 4.10 (t, *J* = 5.0 Hz, 1H), 4.00 (d, *J* = 5.2 Hz, 1H), 3.88 (s, 1H), 3.79 (d, *J* = 5.2 Hz, 1H), 3.69 (d, *J* = 5.2 Hz, 2H), 3.29 (dtt, *J* = 13.1, 9.3, 4.6 Hz, 6H), 3.12 (dd, *J* = 11.9, 7.9 Hz, 3H), 2.87-2.58 (m, 8H), 2.54-2.48 (m, 1H), 2.41-2.23 (m, 6H), 2.01 (s, 3H), 1.63 (dt, *J* = 22.4, 11.3 Hz, 3H).

Example 9 (Compound 8)

Preparation of 3,3'-(((((4-(2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzofuran-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of methyl 3-hydroxy-2-iodobenzoate

Methyl 2-amino-3-hydroxybenzoate (25 g, 149.65 mmol, 1 eq) was dissolved in an aqueous solution of sulfuric acid (1000 mL, 1.0 M) and cooled to 0°C. An aqueous solution (100 mL) of sodium nitrite (11.25 g, 163.0 mmol, 1.08 eq) was added and the mixture was stirred at 25°C for 20 min. An aqueous solution (100 mL) of potassium iodide (111.7 g, 672.9 mmol, 4.5 eq) was added and the mixture was stirred at 70°C for 1.5h. LCMS detection showed that the reaction was completed. Water and ethyl acetate was added to the reaction mixture, and the mixture was extracted. The organic phase was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 5:1) to obtain the target compound (20.0 g). LCMS (ESI) $[M+H]^+ = 278.9$.

Step 2: Synthesis of methyl 2-(hydroxymethyl)benzofuran-4-carboxylate

The product obtained in the first step (20.0 g, 71.94 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (200 mL), followed by adding cuprous iodide (1.37 g, 7.19 mmol, 0.1 eq), bis(triphenylphosphine)palladium(II) dichloride (5 g, 7.19 mmol, 0.1 eq), triethylamine (21.86 g, 214.55 mmol, 3.0 eq), and propargyl alcohol (6.1 g, 108.81 mmol, 1.5 eq). The reaction mixture

was stirred at 75°C for 16h under nitrogen. LCMS detection showed that the reaction was completed. Water and ethyl acetate were added to the reaction mixture and the mixture was extracted. The organic phase was washed with saturated saline, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to obtain the target compound (11 g). LCMS (ESI) $[M+H]^+$ = 207.4.

Step 3: Synthesis of methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-carboxylate

The product obtained in the second step (11.0 g, 53.38 mmol, 1.0 eq) was dissolved in dichloromethane (80 mL), followed by adding imidazole (4.5 g, 66.09 mmol, 1.5 eq) and *tert*-butyl(chloro)diphenylsilane (13.0 g, 47.30 mmol, 0.8 eq); the mixture was stirred at 25°C for 16h. LCMS detection showed that the reaction was completed. The reaction mixture was filtered, and the filtrate was directly evaporated under reduced pressure. The residue was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to obtain the target compound (12.2 g). LCMS (ESI) $[M+Na]^+$ = 467.4.

Step 4: Synthesis of (2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-yl)methanol

The product obtained in the third step (12.2 g, 27.47 mmol, 1 eq) was dissolved in tetrahydrofuran (100 mL), lithium borohydride (1.79 g, 82.41 mmol, 3.0 eq) was added at 0°C, and the mixture was stirred at 25°C for 16h. LCMS detection showed that the reaction was completed. Water and ethyl acetate were added, and the mixture was extracted. The organic phase was washed with saturated saline, dried over anhydrous sodium sulfate, filtered, concentrated and mixed. The residue was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 2:1) to obtain the target compound (7.64 g). LCMS (ESI) $[M+Na]^+$ = 439.4.

Step 5: Synthesis of ((4-(bromomethyl)benzofuran-2-yl)methoxy)(*tert*-butyl)diphenylsilane

The product of the fourth step (2.0 g, 4.81 mmol, 1.0 eq) was added to dichloromethane (20 mL), phosphorus tribromide (1.95 g, 7.21 mmol, 1.5 eq) was added at 0°C, and the mixture was stirred for 2h. TLC detection showed that the reaction was completed. Saturated ammonium chloride aqueous solution was added to quench the reaction, and the reaction mixture was extracted

with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 100:1) to obtain the target compound (1.42 g).

Step 6: Synthesis of *tert*-butyl (R)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate

(R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (25.0 g, 109.11 mmol, 1.0 eq) was dissolved in dichloromethane (200 mL), N,N'-dicyclohexylcarbodiimide (22.5 g, 109.11 mmol, 1.0 eq), *tert*-butanol (24.25 mL, 327.33 mmol, 3.0 eq) and 4-dimethylaminopyridine (13.3 g, 109.11 mmol, 1.0 eq) were added at 25°C, and the mixture was stirred for 16h after the addition. LCMS detection showed that the reaction was completed. Water and ethyl acetate were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to obtain the target compound (24.0 g).

Step 7: Synthesis of *tert*-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product obtained in the sixth step (905 mg) was dissolved in tetrahydrofuran (10 mL), and lithium bis(trimethylsilyl)amide (4.8 mL) was added slowly dropwise at 0°C, and the mixture was stirred at 0°C for 30min; the product from the fifth step (1.42 g) was dissolved in tetrahydrofuran (10 mL) and slowly added dropwise to the previous reaction mixture; the mixture was stirred at 25°C for 3h. LCMS showed that the reaction was completed. Saturated ammonium chloride aqueous solution was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 3:1) to obtain the target compound (1.67 g). LCMS (ESI) $[M+H]^+$ = 684.2.

Step 8: Synthesis of *tert*-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-(hydroxymethyl)benzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.67 g, 2.44 mmol, 1.0 eq) was dissolved in tetrahydrofuran (10 mL), and tetra-n-butylammonium fluoride (3.18 g, 12.2 mmol, 5.0 eq) was added at 25°C. The mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The mixture was filtered, and the organic phase was evaporated under reduced pressure to obtain the target compound (1.8 g). LCMS (ESI) $[M+Na]^+$ = 468.4.

Step 9: Synthesis of *tert*-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-formylbenzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product obtained in the eighth step (1.8 g, 4.04 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL), and manganese dioxide (1.75 g, 20.2 mmol, 5.0 eq) was added at 25°C; the reaction mixture was stirred at 60°C for 2h. LCMS showed the reaction was completed. After filtration, the organic phase was concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 5:1) to obtain the target compound (894 g). LCMS (ESI) $[M+Na]^+$ = 476.4.

Step 10: Synthesis of di-*tert*-butyl 3,3'-((((((4-(3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzofuran-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

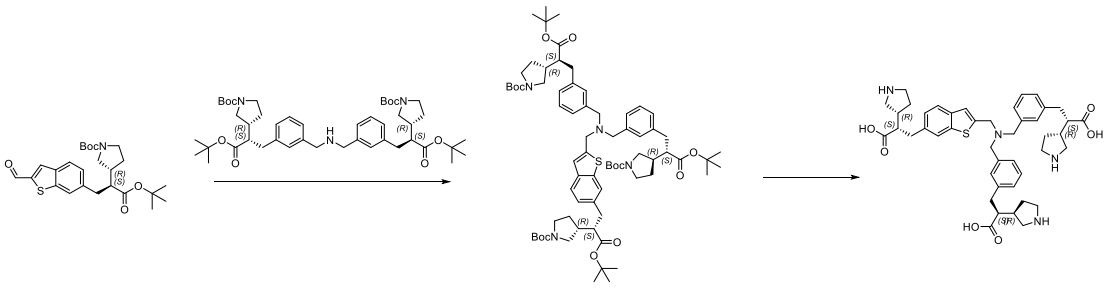
The product from the ninth step (100 mg, 0.23 mmol, 1.0 eq) was dissolved in methanol (5 mL), di-*tert*-butyl 3,3'-(((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (197.8 mg, 0.25 mmol, 1.1 eq) was added and stirred at 25°C for 30min. Sodium triacetoxyborohydride (146.2 mg, 0.69 mmol, 3.0 eq) was added and the reaction was continued for 2h. LCMS detection showed that the reaction was completed. Water and ethyl acetate were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product, which was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:1) to obtain the target compound (65 mg). LCMS (ESI) $[M+H]^+$ = 1220.1.

Step 11: Synthesis of 3,3'-(((((4-(2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzofuran-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

The product from the tenth step (65 mg) was dissolved in hydrochloric acid/1,4-dioxane (1 mL) and stirred at 25°C for 2h. LCMS detection showed the reaction was completed. After concentration, the crude product was obtained. The target compound (4 mg) was obtained by Prep-HPLC. LCMS (ESI) $[M+H]^+$ = 751.5; ^{1}H NMR (400 MHz, MeOD-*d4*)δ 7.36-7.30 (m, 3H), 7.26-7.21 (m, 4H), 7.18-7.09 (m, 4H), 6.85(s, 1H), 3.81- 3.71 (m, 2H), 3.67-3.60 (m, 4H), 3.26-2.96 (m, 14H), 2.81-2.64 (m, 5H), 2.51-2.42 (m, 2H), 2.42-2.30 (m, 3H), 2.10-2.01 (m, 3H), 1.84-1.57 (m, 3H).

Example 10 (Compound 11)

Preparation of (2S,2'S)-3,3'-(((((6-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzo[b]thiophen-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((6-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzo[b]thiophen-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

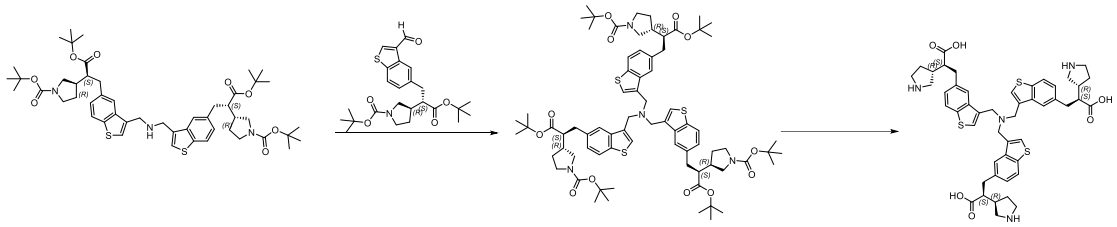
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(2-formylbenzo[b]thiophen-6-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (86.7 mg, 0.189 mmol, 1.5 eq) was dissolved in methanol (5 mL), di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (100 mg, 0.126 mmol, 1.0 eq) and sodium cyanoborohydride (15.84 mg, 0.252 mmol, 2.0 eq) were added at room temperature. The reaction mixture was stirred at room temperature for 36h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (90 g). LCMS (ESI) $[M+H]^+$ = 1235.8.

Step 2: Synthesis of (2S,2'S)-3,3'-(((((6-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzo[b]thiophen-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((((6-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzo[b]thiophen-2-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (90 mg, 0.07mmol) was dissolved in hydrochloric acid/1,4-dioxane (2 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (32.96 mg). LCMS (ESI) $[M+H]^+$ = 767.4; ^1H NMR (400 MHz, D_2O) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.70 (s, 1H), 7.43 (s, 1H), 7.30 (dd, *J* = 18.7, 7.5 Hz, 5H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.12 (s, 2H), 4.59 (s, 2H), 4.35 (s, 4H), 3.56 (ddd, *J* = 16.4, 11.8, 7.9 Hz, 3H), 3.43-3.34 (m, 3H), 3.27-3.16 (m, 3H), 3.08-2.90 (m, 5H), 2.86-2.69 (m, 5H), 2.64 (td, *J* = 9.6, 5.0 Hz, 2H), 2.51 (dq, *J* = 17.4, 8.7 Hz, 3H), 2.18-2.04 (m, 3H), 1.72 (ddd, *J* = 18.5, 13.0, 9.2 Hz, 3H).

Example 11 (Compound 49)

Preparation of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(benzo[b]thiophene-3,5-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (40 mg, 0.04 mmol, 1.0 eq) in tetrahydrofuran (5 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylbenzo[b]thiophen-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (22.36

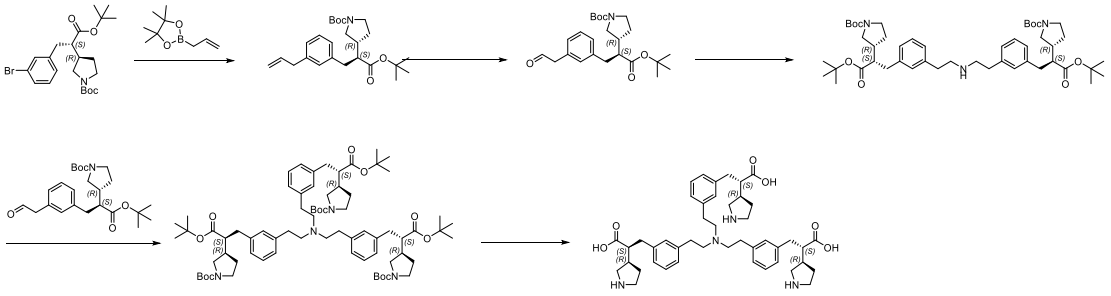
mg, 0.05 mmol, 1.1 eq) and sodium cyanoborohydride (2.74 mg, 0.04 mmol, 1.0 eq). The mixture was stirred at room temperature for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (40 mg). LCMS (ESI) $[M+H]^+$ = 1347.1.

Step 2: Synthesis of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzo[b]thiophene-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3"-((2S,2'S,2"S)-((nitrilotris(methylene))tris(benzo[b]thiophene-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3"R)-tris(pyrrolidine-1-carboxylate) (40 mg, 0.03mmol) was dissolved in hydrochloric acid/1,4-dioxane (2 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (22.36 mg). LCMS (ESI) $[M+H]^+$ = 879.0; ^{1}H NMR (400 MHz, D_2O) δ 8.08-8.00 (m, 3H), 7.92 (d, *J* = 8.3 Hz, 3H), 7.23 (dd, *J* = 8.4, 1.5 Hz, 3H), 6.47 (s, 3H), 4.86 (d, *J* = 13.7 Hz, 3H), 4.75 (s, 3H), 3.37 (ddd, *J* = 12.0, 10.0, 5.6 Hz, 6H), 3.21-3.13 (m, 3H), 2.91 (t, *J* = 11.0 Hz, 3H), 2.53 (ddd, *J* = 44.9, 11.3, 5.5 Hz, 6H), 2.42-2.24 (m, 6H), 2.05 (dtd, *J* = 13.6, 7.0, 3.3 Hz, 3H), 1.65 (dq, *J* = 13.2, 9.7 Hz, 3H).

Example 12 (Compound 65)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1500 mg, 3.3 mmol, 1.0 eq) was dissolved in 1,4-dioxane (20 mL), followed by adding 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.11 g, 6.6 mmol, 2 eq) and potassium phosphate (2.1 g, 9.9 mmol, 3 eq), and then water (4 mL); the mixture was stirred at 90°C for 16h under nitrogen. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 2:1) to obtain the target compound (900 mg). LCMS (ESI) $[M+H]^+$ = 416.3.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (900 mg, 2.17 mmol, 1.0 eq) was dissolved in 1,4-dioxane (20 mL), and sodium periodate (1.85 g, 8.66 mmol, 4 eq) and potassium osmate dihydrate (80 mg, 0.22 mmol, 0.1 eq) were added, which were stirred at room temperature for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to obtain the target compound (600 mg). LCMS (ESI) $[M+H]^+$ = 418.3.

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (400 mg, 0.96 mmol, 1.0 eq) was dissolved in methanol (10 mL), ammonia/methanol (16.31 mg, 0.96 mmol, 1.0 eq), two drops of acetic acid and sodium cyanoborohydride (71 mg, 1.15 mmol, 1.2 eq) were added, and the mixture was stirred at room temperature for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 820.6.

Step 4: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(ethane-2,1-diyl))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

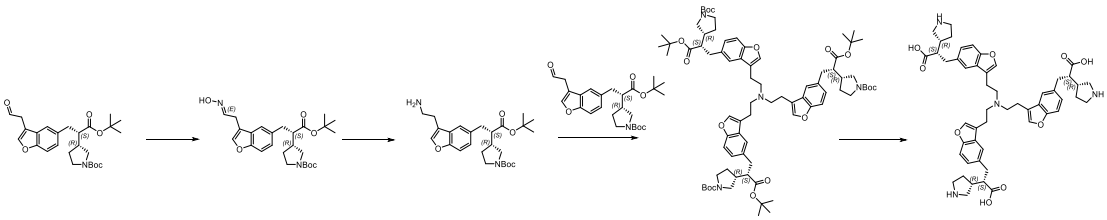
Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (100 mg, 0.12 mmol, 1.0 eq) was dissolved in methanol (5 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (51 mg, 0.12 mmol, 1.0 eq), two drops of acetic acid, and sodium cyanoborohydride (7.5 mg, 0.12 mmol, 1.0 eq). The mixture was stirred at room temperature for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (80 mg). LCMS (ESI) $[M+H]^+$ = 1221.9.

Step 5: Synthesis of (2S,2'S,2"S)-3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3"-((2S,2'S,2"S)-((nitrilotris(ethane-2,1-diyl))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3"R)-tris(pyrrolidine-1-carboxylate) (80 mg) was dissolved in hydrochloric acid/1,4-dioxane (2 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (9.7 mg). LCMS (ESI) $[M+H]^+$ = 753.7; ^1H NMR (400 MHz, D_2O) δ 7.21 (t, J = 7.5 Hz, 3H), 7.09-6.99 (m, 9H), 3.40-3.30 (m, 6H), 3.14 (ddd, J = 11.7, 9.9, 7.3 Hz, 4H), 2.96 (d, J = 7.5 Hz, 4H), 2.85 (dd, J = 11.7, 9.2 Hz, 4H), 2.78 (d, J = 9.1 Hz, 7H), 2.72-2.64 (m, 5H), 2.39 (dq, J = 14.9, 9.1, 6.8 Hz, 6H), 2.04 (td, J = 6.5, 3.6 Hz, 3H), 1.71-1.63 (m, 3H).

Example 13 (Compound 67)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(ethane-2,1-diyl))tris(benzofuran-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((E)-2-(hydroxyimino)ethyl)benzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)benzofuran-5-yl)propan-2-yl)pyrrolidine-1-carboxylate (120 mg, 0.26 mmol, 1.0 eq) was dissolved in ethanol (10 mL), and hydroxylamine hydrochloride (37 mg, 0.52 mmol, 2.0 eq) was added; the mixture was stirred at room temperature for 16h; LCMS showed the reaction was completed. The reaction mixture was filtered, and the filtrate was concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 473.2.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethyl)benzofuran-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((E)-2-(hydroxyimino)ethyl)benzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg, 0.21 mmol, 1.0 eq) was dissolved in methanol (10 mL), and Pd/C (10 mg) was added; the mixture was stirred at room temperature for 16h under a hydrogen. LCMS showed the reaction was completed. The reaction mixture was filtered and evaporated under reduced pressure. The residue was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 459.2.

Step 3: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(ethane-2,1-diyl))tris(benzofuran-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

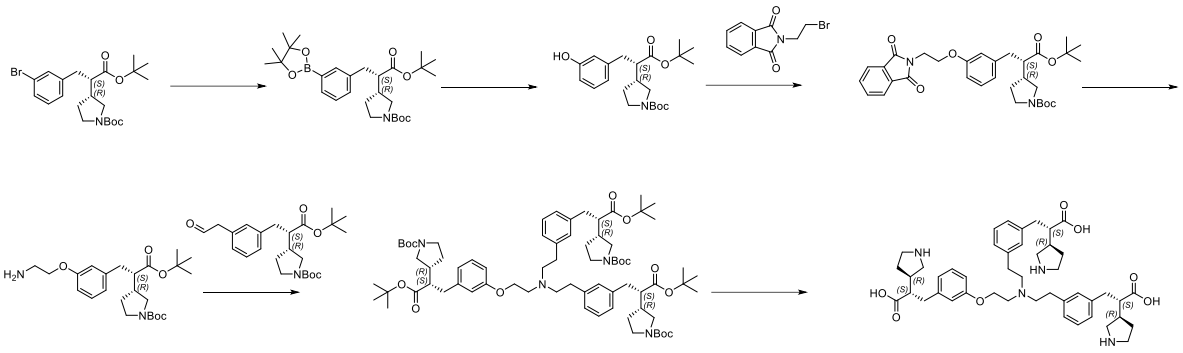
tert-butyl (R)-3-((S)-3-(3-(2-aminoethyl)benzofuran-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg, 0.22 mmol, 1.0 eq) was dissolved in methanol (10 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)benzofuran-5-yl)propan-2-yl)pyrrolidine-1-carboxylate (200 mg, 0.44 mmol, 2.0 eq) and sodium cyanoborohydride (27 mg, 0.44 mmol, 2.0 eq); the mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated after cooling and separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to obtain the target compound (100 mg).

Step 4: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(ethane-2,1-diyl))tris(benzofuran-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(ethane-2,1-diyl))tris(benzofuran-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (100 mg, 0.07mmol) was dissolved in hydrochloric acid/1,4-dioxane (4 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (6.58 mg). LCMS (ESI) $[M+H]^+ = 873.2$; ^1H NMR (400 MHz, D_2O) δ 7.26-7.14 (m, 6H), 6.94 (s, 6H), 3.17 (d, J = 33.2 Hz, 4H), 2.95 (d, J = 26.8 Hz, 5H), 2.61 (d, J = 51.5 Hz, 22H), 2.41-2.10 (m, 7H), 1.73 (dd, J = 101.8, 31.7 Hz, 3H), 1.08 (s, 1H).

Example 14 (Compound 71)

Preparation of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.5 g) was dissolved in 1,4-dioxane (20 mL), followed by adding bis(pinacolato)diboron (1.75 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (241.4 mg) and potassium acetate (972 mg), and water (4 mL); the mixture was stirred at 90°C for 16h under nitrogen. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 2:1) to obtain the target compound (1.2 g). LCMS (ESI) $[M+H\text{-}Boc]^+ = 402.2$.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (1200 mg) was dissolved in tetrahydrofuran (20 mL), followed by adding hydrogen peroxide (0.5 mL). The mixture was stirred at room temperature for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to obtain the target compound (800 mg). LCMS (ESI) $[M-2\times tert\text{-butyl}]^+$ = 280.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (500 mg) was dissolved in N,N-dimethylformamide (5 mL), followed by adding 2-(2-bromoethyl)isoindoline-1,3-dione (649 mg) and potassium carbonate (530 mg). The mixture was stirred at 90°C for 2h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to obtain the target compound (280 mg). LCMS (ESI) $[M+H]^+$ = 565.3.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (280 mg) was dissolved in ethanol (10 mL) and hydrazine hydrate (124 mg) was added. The mixture was stirred at 90°C for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:5) to obtain the target compound (160 mg). LCMS (ESI) $[M+H]^+$ = 435.3.

Step 5: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

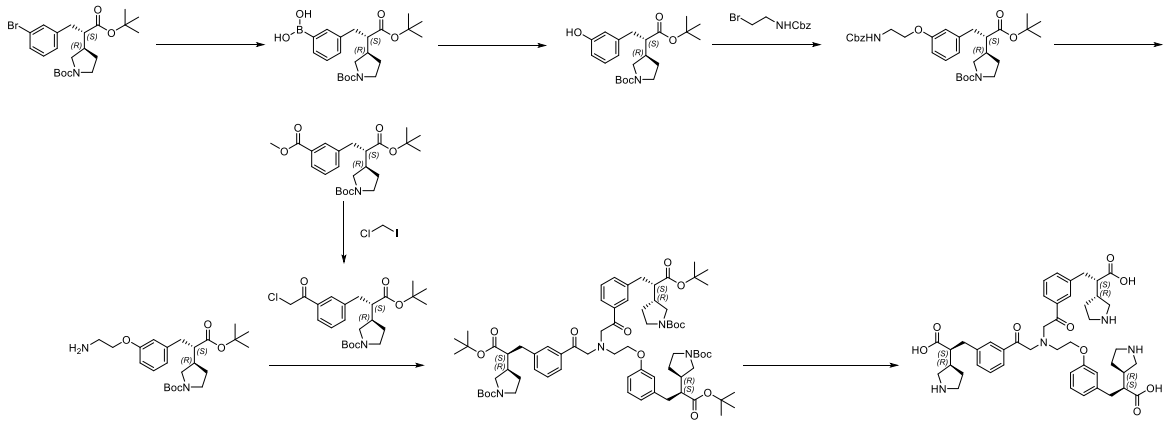
tert-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (80 mg) was dissolved in methanol (10 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (154 mg) and sodium cyanoborohydride (23 mg). The mixture was stirred at room temperature for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 1237.9.

Step 6: Synthesis of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (100 mg) was dissolved in hydrochloric acid/1,4-dioxane (2 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (27.9 mg). LCMS (ESI) $[M+H]^+$ = 769.5; ^{1}H NMR (400 MHz, D_2O) δ 7.24-7.09 (m, 4H), 7.00 (q, J = 8.0 Hz, 5H), 6.82 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 8.3 Hz, 2H), 4.17-4.06 (m, 2H), 3.39-3.28 (m, 6H), 3.17-3.03 (m, 5H), 2.90 (d, J = 9.4 Hz, 3H), 2.86-2.58 (m, 14H), 2.37 (td, J = 17.0, 15.4, 6.6 Hz, 6H), 2.02 (s, 3H), 1.66 (dd, J = 14.2, 6.5 Hz, 3H).

Example 15 (Compound 80)

Preparation of (2S,2'S)-3,3'-((2,2'-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)azanediyl)bis(acetyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of (3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)boronic acid

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1900 mg, 4.18 mmol, 1 eq), (dihydroxyboranyl)boronic acid (562.29 mg, 6.27 mmol, 1.5 eq), potassium acetate (1230.7 mg, 12.54 mmol, 3 eq), dicyclohexyl[2',4',6'-tri(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphine (199.27 mg, 0.42 mmol, 0.1 eq) and XPhos Pd G2 (164 mg, 0.21 mmol, 0.05 eq) were added in ethanol (20 mL). The reaction mixture was purged with nitrogen three times and stirred at 90°C for 16h. LCMS showed the reaction was completed. After the addition of ethyl acetate, the mixture was filtered through diatomaceous earth. The filtrate was evaporated under reduced pressure to obtain the target compound (2000 mg), which was used in the next step directly.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)boronic acid (2000 mg, 4.77 mmol, 1 eq) was dissolved in tetrahydrofuran (30 mL) and hydrogen peroxide (8 mL) was added. The mixture was stirred at 20°C for 16h; LCMS detection showed that the reaction was completed, saturated sodium bisulfite solution and ethyl acetate were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 4:1) to obtain the target compound (800 mg). LCMS (ESI) $[M+H]^+$ = 392.2.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2 g, 5.11 mmol, 1 eq), benzyl (2-bromoethyl)carbamate (2.64 g, 10.22 mmol, 2 eq) and potassium carbonate (2.12 g, 15.33 mmol, 3 eq) were added in acetonitrile (50 mL) and stirred at 90°C for 16h; LCMS showed the reaction was completed. The reaction mixture was directly purified by column chromatography (petroleum ether:ethyl acetate = 7:1) to obtain the target compound (3 g). LCMS (ESI) $[M+H]^+$ = 569.0.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (3 g, 5.27 mmol, 1 eq) was dissolved in methanol (50 mL), palladium (300 mg, 10%) was added, and the mixture was exchanged with hydrogen three times; the mixture was stirred at 25°C for 16h. LCMS detection showed that the reaction was completed. The reaction mixture was filtered, and the filtrate was concentrated to obtain the target compound (2 g). LCMS (ESI) $[M+H]^+$ = 435.4

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-chloroacetyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (700 mg, 1.614 mmol, 1 eq) was dissolved in anhydrous tetrahydrofuran (10 mL) and cooled to -78°C. Lithium diisopropylamide (1.0M, 2.42 mL, 2.42 mmol, 1.5 eq) was added to the mixture and stirred at -78°C for 1h. Chloroiodomethane (854.03 mg, 4.84 mmol, 3 eq) was added to the mixture and stirred at -78°C for another 2h. LCMS detection showed that the reaction was completed. Saturated ammonium chloride aqueous solution and ethyl acetate were added to the reaction mixture and the reaction mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 4:1) to obtain the target compound (100 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 352.4.

Step 6: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((2,2'-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)azanediyl)bis(acetyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

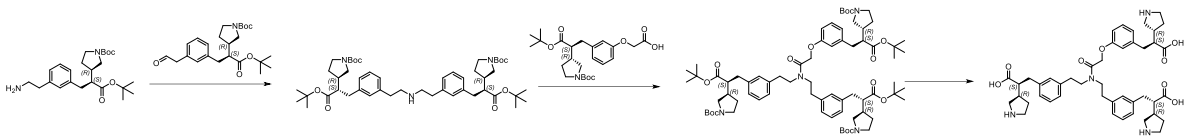
tert-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (192.2 mg, 0.44 mmol, 2 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-chloroacetyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg, 0.22 mmol, 1 eq) were dissolved in acetonitrile (3 mL), anhydrous potassium carbonate (91.1 mg, 0.66 mmol, 3 eq) was added, and the mixture was stirred at 60°C for 2h; LCMS detection showed that the reaction was completed. The reaction mixture was directly concentrated, and purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:1) to obtain the target compound (50 mg). LCMS (ESI) $[M+H]^+$ = 1265.3.

Step 7: Synthesis of (2S,2'S)-3,3'-((2,2'-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)azanediyl)bis(acetyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((2,2'-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)azanediyl)bis(acetyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (50 mg, 0.04 mmol, 1 eq) was added in hydrochloric acid/1,4-dioxane (2 mL, 4.0 M) at 0°C, the mixture was stirred at 25°C for 6h; LCMS showed the reaction was completed. The reaction mixture was concentrated to obtain a crude product, which was purified by Prep-HPLC to obtain the target compound (6 mg). LCMS (ESI) $[M-H]^-$ = 795.6; ^{1}H NMR (400 MHz, DMSO) δ7.90 (s, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.53-6.45 (m, 2H), 5.34 (s, 3H), 4.46 (s, 2H), 3.92 (s, 2H), 3.34-2.69 (m, 25H), 2.41-2.32 (m, 3H), 2.03-1.95 (m, 3H), 1.69-1.62 (m, 3H).

Example 16 (Compound 81)

Preparation of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate))

tert-butyl (R)-3-((S)-3-(3-(2-aminoethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg) was dissolved in methanol (10 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (100 mg) and sodium cyanoborohydride (15 mg). The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated after cooling and separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to obtain the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 820.6.

Step 2: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

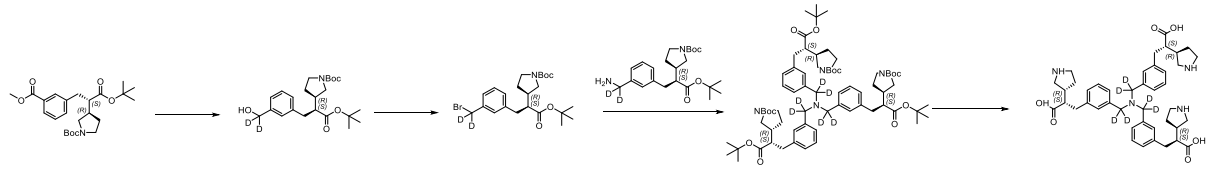
Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (10 mL) was added in 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetic acid (82 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (93 mg) and *N,N*-diisopropylethylamine (47 mg); The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried, filtered, and concentrated to obtain a crude product, which was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (70 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1152.0.

Step 3: Synthesis of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)) (70 mg) was dissolved in hydrochloric acid/1,4-dioxane (4 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (13.41 mg). LCMS (ESI) $[M+H]^+$ = 783.1; ^1H NMR (400 MHz, D_2O) δ 7.21 (td, *J* = 7.7, 2.0 Hz, 2H), 7.14-6.99 (m, 7H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.57 (t, *J* = 2.1 Hz, 1H), 6.08 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.14-4.04 (m, 2H), 3.63-3.55 (m, 2H), 3.41-3.26 (m, 7H), 3.14 (dddd, *J* = 25.2, 23.0, 11.2, 4.0 Hz, 4H), 2.87-2.63 (m, 12H), 2.60-2.54 (m, 1H), 2.43-2.25 (m, 6H), 2.10-1.98 (m, 3H), 1.66 (td, *J* = 12.8, 11.1, 7.5 Hz, 3H).

Example 17 (Compound 90)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene-d_2))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(hydroxymethyl-d_2)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.2 g, 2.77 mmol, 1 eq) was dissolved in a mixture of tetrahydrofuran (14.4 mL) and deuterated methanol (4.2 mL) and deuterated sodium borohydride (695.19 mg, 16.61 mmol, 6 eq) was added batchwise under nitrogen. The reaction mixture was stirred at 70°C for 3h. LCMS showed the reaction was completed. The reaction mixture was cooled to room temperature, followed by addition of deuterium oxide (5 mL). The reaction mixture was stirred for 10 min. Water and ethyl acetate were added to the reaction mixture and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2:1) to obtain the target compound (600 mg). LCMS (ESI) $[M+Na]^+$ = 430.2.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(hydroxymethyl-d_2)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (600 mg, 1.47 mmol, 1 eq) was dissolved in dichloromethane (5 mL) and cooled to 0°C. Triphenylphosphine (1158.47 mg, 4.42 mmol, 3 eq) and N-bromosuccinimide (786.09 mg, 4.42 mmol, 3 eq) were added. The mixture was stirred at room temperature for 2h. LCMS detection showed that the reaction was completed. Water and dichloromethane were added, and the reaction mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3:1) to obtain the target compound (400 mg). LCMS (ESI) $[M+Na]^+$ = 492.7.

Step 3: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene-d_2))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(3-(aminomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (30 mg, 0.07 mmol, 1 eq), *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (69.43 mg, 0.15 mmol, 2 eq) and potassium carbonate (30.6 mg, 0.22 mmol, 3 eq) were added in acetonitrile (1 mL), heated to 60°C and stirred for 4h. LCMS detection showed that the reaction was completed and the reaction mixture was filtered. The filtrate was directly purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3:1) to obtain the target compound (55 mg). LCMS (ESI) $[M+H]^+$ = 1185.8.

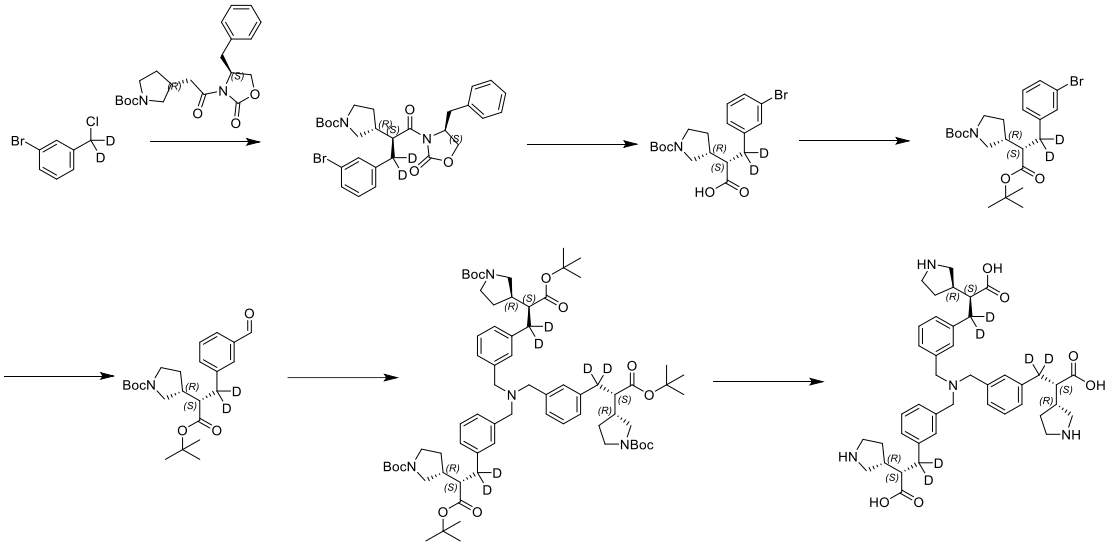
Step 4: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene-d_2))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene-d_2))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (50 mg, 0.04 mmol, 1 eq) was added in hydrochloric acid/1,4-dioxane (3.0 mL, 4 M) and stirred at 25°C for 2h. LCMS detection showed that the reaction was completed and the reaction mixture was filtered. The filter cake was lyophilized with acetonitrile and water to obtain the target compound (25.84 mg). LCMS (ESI) $[M-H]^-$ = 715.5; ^{1}H NMR (400 MHz, D_2O) δ 7.38-7.27 (m,

6H), 7.1-7.11 (m, 6H), 3.61-3.51 (m, 3H), 3.38-3.33 (m, 3H), 3.28-3.16 (m, 3H), 3.07-2.98 (m, 3H), 2.91-2.87 (m, 3H), 2.84-2.74 (m, 3H), 2.68-2.58 (m, 3H), 2.53-2.47 (m, 3H), 2.15-2.09 (m, 3H), 1.78-1.65 (m, 3H).

Example 18 (Compound 91)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic-3,3-d2 acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

Under ice bath and nitrogen, a solution of lithium bis(trimethylsilyl)amide (7.08 mL, 7.08 mmol, 1.1 eq, 1.0 M) was added dropwise to a solution of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (2.5 g, 6.44 mmol, 1 eq) in tetrahydrofuran (30 mL). The mixture was stirred at 0°C for 30min; a solution of 1-bromo-3-(chloromethyl-d_2)benzene (1.47 g, 7.08 mmol, 1.1 eq) in tetrahydrofuran (2 mL) was slowly added dropwise, and after the addition, the reaction temperature was slowly raised to room temperature and the mixture was stirred for 16h. LCMS showed the reaction was completed, the reaction mixture was cooled with an ice-water bath, saturated aqueous ammonium chloride solution and water were added, and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to obtain a crude product. The crude product was purified

by column chromatography to obtain the target compound (3.1 g). LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+$ = 503.2.

Step 2: Synthesis of (S)-3-(3-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic-3,3-d2 acid

A solution of hydrogen peroxide (275 mg, 8.1 mmol, 1.5 eq) was added to a solution of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (3 g, 5.28 mmol, 1 eq) in tetrahydrofuran (120 mL) and cooled with an ice bath, followed by adding a solution (10 mL) of lithium hydroxide (192 mg, 8.1 mmol, 1.5 eq). The reaction mixture was stirred at 25°C for 2.5h. LCMS showed the reaction was completed, the reaction mixture was cooled to 0°C, and a solution (5 mL) of sodium bisulfite (1 g) and sodium hydroxide solution (5N) were added to adjust the pH of the reaction mixture to >12. The mixture was extracted with water and methyl *tert*-butyl ether, and the organic phase was discarded. The aqueous phase was acidified to pH3 with hydrochloric acid solution (5N) and extracted with methyl *tert*-butyl ether. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the target compound (1.8 g). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 300.20.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

(S)-3-(3-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic-3,3-d2 acid (1.8 g, 4.5 mmol, 1 eq) was dissolved in 2-methyltetrahydrofuran (50 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (4.5 g, 22.5 mmol, 5 eq) was added, and the mixture was heated to 65°C and stirred for 16h under nitrogen, LCMS showed the reaction was completed, the insoluble matter was filtered, the filter cake was washed with methyl *tert*-butyl ether, and the filtrate was concentrated to obtain a crude product. The crude product was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to obtain the target compound (0.6 g). LCMS (ESI) $[M+H\text{-}2\times tert\text{-butyl}]^+$ = 344.16.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (0.6 g, 1.31 mmol, 1 eq) was dissolved in *N*,*N*-dimethylformamide (4 mL), followed by adding palladium acetate (59 mg, 0.26 mmol, 0.2 eq), 1,4-bis(diphenylphosphino)butane (112 mg, 0.26 mmol, 0.2 eq), N-formylsaccharin (691 mg, 3.296 mmol, 2.5 eq), sodium carbonate (418 mg, 3.94 mmol, 3 eq) and triethylsilane (305 mg, 2.63 mmol, 2 eq); under nitrogen, the mixture was heated to 75°C and stirred for 16h. The LCMS showed the reaction was completed. The insoluble matter was filtered, the filter cake was washed with methyl *tert*-butyl ether. The filtrate was concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to obtain the target compound (165 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 306.35.

Step 5: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl-1,1-d_2))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (160 mg, 0.39 mmol, 1 eq) was dissolved in tetrahydrofuran (5 mL), to which ammonia methanol (0.018 mL, 0.13 mmol, 0.33 eq, 7.0 M), sodium cyanoborohydride (61 mg, 0.97 mmol, 2.5 eq) and one drop of acetic acid were added. The reaction mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The reaction was quenched with saturated ammonium chloride solution, extracted with ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was purified by column chromatography to obtain the product (40 mg). LCMS (ESI) $[M+H]^+$ = 1186.02.

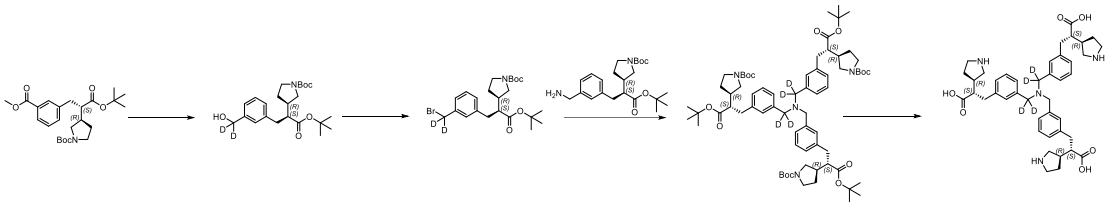
Step 6: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic-3,3-d2 acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl-1,1-d_2))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (30 mg, 0.03 mmol, 1 eq) was dissolved in 1,4-dioxane (1 mL), and hydrochloric acid/1,4-dioxane (1 mL, 4.0 M) was added; the mixture was stirred at room temperature overnight, and the reaction was monitored by LCMS until completion. The solvent was evaporated under reduced pressure, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN)

to obtain the target compound (4.5 mg). LCMS (ESI) $[M+H]^+$ = 717.63; ^{1}H NMR (400 MHz, D_2O) δ 8.37 (s, 2H), 7.40-7.25 (m, 6H), 7.24-7.09 (m, 6H), 4.19 (s, 6H), 3.56-3.43 (m, 3H), 3.40-3.29 (m, 3H), 3.26-3.13 (m, 3H), 3.00-2.87 (m, 3H), 2.49-2.30 (m, 6H), 2.15-1.97 (m, 3H), 1.75-1.59 (m, 3H).

Example 19 (Compound 93)

Preparation of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene-*d*$_2$))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(hydroxymethyl-*d*$_2$)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.2 g, 2.77 mmol, 1 eq) was dissolved in a mixture of tetrahydrofuran (14.4 mL) and deuterated methanol (4.2 mL) and deuterated sodium borohydride (695.19 mg, 16.61 mmol, 6 eq) was added batchwise under nitrogen; the reaction mixture was stirred at 70°C for 3h. LCMS showed the reaction was completed. The reaction mixture was cooled to room temperature, followed by addition of deuterium oxide (5 mL). The reaction mixture was stirred for 10 min. Water and ethyl acetate were added to the reaction mixture and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to obtain the target compound (600 mg). LCMS (ESI) $[M+Na]^+$ = 430.2.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl-*d*$_2$)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(hydroxymethyl-*d*$_2$)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (600 mg, 1.47 mmol, 1 eq) was dissolved in dichloromethane (5 mL) and cooled to 0°C. Triphenylphosphine (1158.47 mg, 4.42 mmol, 3 eq) and N-bromosuccinimide

(786.09 mg, 4.42 mmol, 3 eq) were added under ice bath. The mixture was continued to be stirred at room temperature for 2h; LCMS detection showed that the reaction was completed. Water and dichloromethane were added, and the reaction mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to obtain the target compound (400 mg). LCMS (ESI) $[M+Na]^+$ = 491.7.

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)azanediyl)bis(methylene-d_2))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

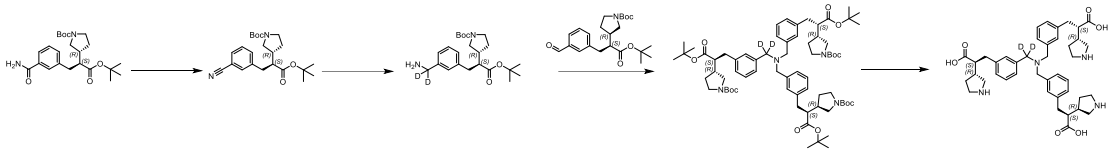
tert-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (40 mg, 0.1 mmol, 1 eq), *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (93.03 mg, 0.2 mmol, 2 eq) and potassium carbonate (41 mg, 0.3 mmol, 3 eq) were added in acetonitrile (1 mL) and stirred at 60°C for 4h. LCMS detection showed that the reaction was completed and the reaction mixture was filtered to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 3:1) to obtain the target compound (60 mg). LCMS (ESI) $[M+Na]^+$ = 1205.6.

Step 4: Synthesis of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene-d_2))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)azanediyl)bis(methylene-d_2))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (70 mg, 0.06 mmol, 1 eq) was added to hydrochloric acid/1,4-dioxane (3 mL, 4.0 M). The mixture was stirred at 25°C for 2h. LCMS showed the reaction was completed. The reaction mixture was filtered and lyophilized with acetonitrile and water to obtain the target compound (41.67 mg). LCMS (ESI) $[M+H]^+$ = 715.2. ^{1}H NMR (400 MHz, D_2O) δ 7.41-7.26(m, 6H), 7.15-7.11(m, 6H), 4.25-421(m, 2H), 3.59-353(m, 3H), 3.39-3.34(m, 3H), 3.27-3.17(m, 3H), 3.08-2.98(m, 3H), 2.92-2.87(m, 3H), 2.85-2.64(m, 6H), 2.53-2.48(m, 3H), 2.21-2.02(m,3H), 1.78-1.63(m, 3H).

Example 20 (Compound 94)

Preparation of (2S,2'S)-3,3'-(((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)methyl-d_2)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-cyanophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Oxalyl chloride (365 mg) was added in acetonitrile (10 mL), the temperature of the reaction mixture was reduced to 0°C under nitrogen and N, N-dimethylformamide (262 mg) was added. After stirring for 40min, a solution of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-carbamoylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.0 g) in N,N-dimethylformamide (10 mL) was added and the mixture was stirred for 3h. TLC showed the reaction was completed. Triethylamine (1 mL) was added and the solvent was evaporated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to obtain the target compound (500 mg). LCMS (ESI) $[M+Na]^+$ = 423.2.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(aminomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-cyanophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (190 mg) was dissolved in deuterated methanol (2 mL), cooled to 0°C, and anhydrous nickel chloride (30.74 mg) and deuterated sodium borohydride (107.68 mg) were added; under nitrogen, the temperature was raised to 15°C, and the mixture was stirred for 16h; LCMS detection showed the reaction was completed. Deuterium oxide (1 mL) was added to quench the reaction, and the mixture was stirred for ten min and extracted with ethyl acetate and water. The organic phase was evaporated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (dichloromethane:methanol = 10:1) to obtain the target product (90 mg). LCMS (ESI) $[M+H]^+$ = 407.2.

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)methyl-d_2)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

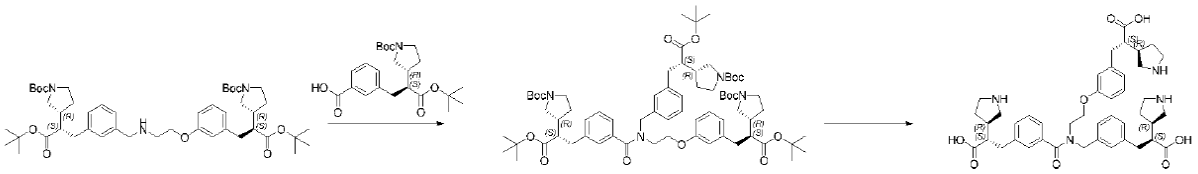
tert-butyl (R)-3-((S)-3-(3-(aminomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (90 mg) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (223.31 mg) were dissolved in isopropanol (3 mL), sodium triacetoxyborohydride (232.03 mg) was added, and the mixture was stirred at 15°C for 16h; LCMS detection showed that the reaction was completed. The reaction mixture was extracted with water and ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to obtain the target compound (150 mg). LCMS (ESI) $[M+Na]^+$ = 1203.6.

Step 4: Synthesis of (2S,2'S)-3,3'-(((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)methyl-d_2)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)methyl-d_2)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (150 mg) was added to hydrochloric acid/1,4-dioxane (5 mL, 4.0 M). The mixture was stirred at 25°C for 3h. The reaction mixture was filtered and lyophilized with acetonitrile and water to obtain the target compound (74 mg). LCMS (ESI) $[M-H]^+$ = 711.42; ^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 3H), 7.45-7.34 (m, 9H), 4.37-4.25 (m, 4H), 3.61-3.53 (m, 3H), 3.50-3.42 (m, 3H), 3.32-3.26 (m, 3H), 3.22-3.13 (m, 3H), 3.10-2.98 (m, 6H), 2.95-2.84 (m, 3H), 2.67-2.58 (m, 3H), 2.26-2.17 (m, 3H), 1.94-1.79 (m, 3H).

Example 21 (Compound 97)

Preparation of (S)-3-(3-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-N-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)benzamido)methyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)benzamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (70 mg) was dissolved in N,N-dimethylformamide (5 mL), and 3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzoic acid (43 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (32 mg) and *N,N*-diisopropylethylamine (17 mg) were added. The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to obtain the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 1223.9.

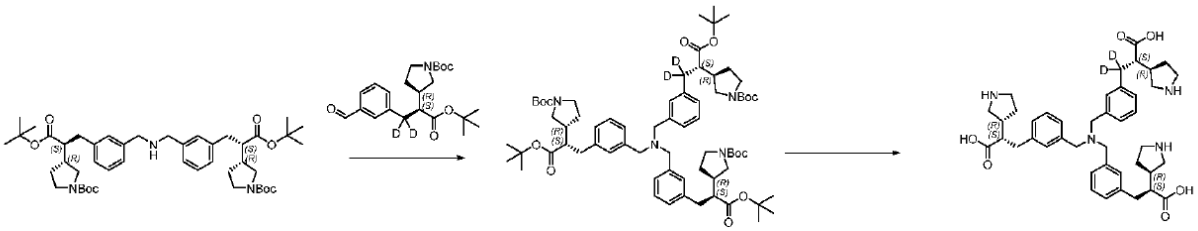
Step 2: Synthesis of (S)-3-(3-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-N-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)benzamido)methyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)benzamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (70 mg) was dissolved in hydrochloric acid/1,4-dioxane (2 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by preparative chromatography to obtain the target compound (15.41 mg). LCMS (ESI) $[M+H]^+$ = 755.4; ^{1}H NMR (400 MHz, D_2O) δ 7.32-7.15 (m, 4H), 7.14-6.97 (m, 3H), 6.94-6.74 (m, 3H), 6.71-6.49 (m, 2H), 4.53 (d, *J* = 14.7 Hz, 2H), 4.26 (d, *J* = 5.5 Hz, 1H), 4.06 (d, *J* = 15.0 Hz, 1H), 3.94 (s, 1H), 3.82-3.67 (m, 2H),

3.32 (dt, *J* = 23.6, 8.8 Hz, 5H), 3.13 (dt, *J* = 18.8, 9.5 Hz, 3H), 2.73 (dtd, *J* = 41.0, 21.0, 9.8 Hz, 9H), 2.34 (t, *J* = 11.9 Hz, 6H), 2.02 (d, *J* = 9.2 Hz, 3H), 1.72-1.55 (m, 3H).

Example 22 (Compound 98)

Preparation of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl-1,1-d_2)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

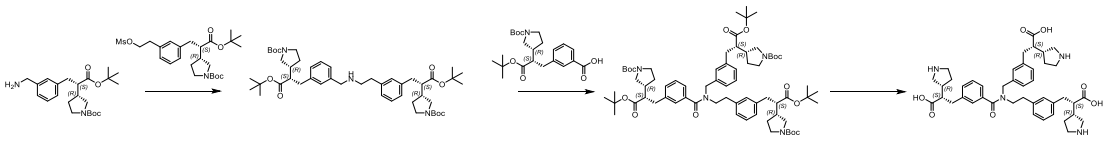
Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (117 mg, 0.15 mmol, 1 eq), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (60 mg, 0.15 mmol, 1 eq) and a drop of acetic acid were dissolved in tetrahydrofuran (2 mL) and stirred at room temperature for 0.5h. Sodium cyanoborohydride (18 mg, 0.30 mmol, 2 eq) was added; the mixture was stirred at room temperature for 16h. LCMS detection showed that the reaction was completed. The reaction mixture was concentrated, and ethyl acetate was added. The mixture was washed with saturated sodium bicarbonate solution and saturated saline solution successively, and separated. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was separated and purified by rapid chromatography (Silica gel, dichloromethane:methanol = 40:1) to obtain the target compound (120 mg). LCMS (ESI) $[M+H]^+$ = 1181.99.

Step 2: Synthesis of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl-1,1-d_2)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (110 mg, 0.09 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/1,4-dioxane (2 mL, 4.0 M) was added, and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to obtain the target compound (33 mg). LCMS (ESI) $[M+H]^+$ = 713.62; ^{1}H NMR (400 MHz, D_2O) δ 7.27 (t, J = 7.5 Hz, 3H), 7.23-6.89 (m, 9H), 3.59 (s, 6H), 3.40-3.28 (m, 6H), 3.17-3.09 (m, 3H), 2.88-2.69 (m, 7H), 2.47-2.32 (m, 6H), 2.10-1.97 (m, 3H), 1.72-1.58 (m, 3H).

Example 23 (Compound 99)

Preparation of (S)-3-(3-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-N-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)benzamido)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg) was dissolved in acetonitrile (10 mL), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((methylsulfonyl)oxy)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (122 mg) was added, and the mixture was stirred at 75ºC overnight; LCMS showed the reaction was completed. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to obtain the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 806.79.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-N-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-

(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)benzamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

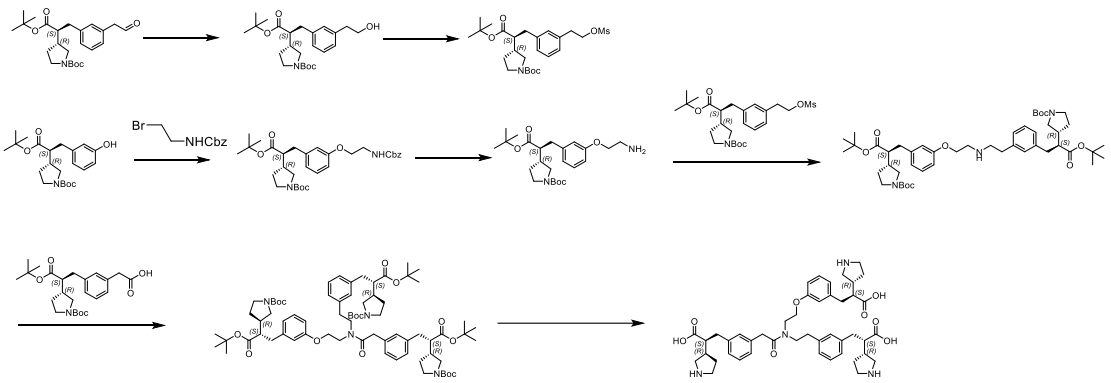
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (70 mg) and 3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzoic acid (44 mg) were dissolved in *N*,*N*-dimethylformamide (0.5 mL), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (50 mg) and triethylamine (34 mg) were added, and the reaction mixture was stirred at room temperature for 16h. TLC monitoring showed that the reaction was completed, ethyl acetate and water were added, and the mixture was extracted and separated. The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography to obtain the target compound (75 mg). LCMS (ESI) $[M+H\text{-Boc}]^+ = 1107.97$.

Step 3: Synthesis of (S)-3-(3-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-N-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)benzamido)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-N-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)benzamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (75 mg) was dissolved in 1,4-dioxane (2 mL), and hydrochloric acid/1,4-dioxane (4.0M, 2 mL) was added; the mixture was stirred at room temperature for 16h; The solvent was evaporated under reduced pressure, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to obtain the target compound (17 mg). LCMS (ESI) $[M+H]^+ = 739.4$; ^1H NMR (400 MHz, D_2O) δ 7.33-6.83 (m, 10H), 6.82-6.59 (m, 2H), 3.70-3.07 (m, 12H), 3.02-2.50 (m, 12H), 2.46-2.28 (m, 6H), 2.10-1.99 (m, 3H), 1.74-1.59 (m, 3H).

Example 24 (Compound 100)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenethyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-hydroxyethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (300 mg) was dissolved in ethanol (10 mL), and sodium borohydride (55 mg) was added; the mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and purified by column chromatography to obtain the target compound (280 mg). LCMS (ESI) $[M+H]^+ = 420.3$.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((methylsulfonyl)oxy)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-hydroxyethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (280 mg) was dissolved in dichloromethane (6 mL), methanesulfonic anhydride (116 mg) and triethylamine (135 mg) were added; the mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The crude product was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to obtain the target compound (300 mg). LCMS (ESI) $[M+H]^+ = 498.2$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2000 mg) was dissolved in N,N-dimethylformamide (20 mL), benzyl (2-bromoethyl)carbamate (3956 mg) and potassium carbonate (3530 mg) were added. The mixture was stirred at 90°C for 16h under nitrogen. LCMS showed the reaction was completed. Water was

added to the reaction mixture, it was extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The product was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 2:1) to obtain the target compound (1500 mg). LCMS (ESI) $[M+H]^+$ = 569.3.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1500 mg) was dissolved in methanol (10 mL), and Pd/C (150 mg) was added; the mixture was stirred at room temperature for 16h under a hydrogen (hydrogen balloon). LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to obtain the target compound (1100 mg). LCMS (ESI) $[M+H]^+$ = 435.3.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (175 mg) was dissolved in acetonitrile (5 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((methylsulfonyl)oxy)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg) and potassium carbonate (156 mg). The reaction mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated after cooling and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (280 mg). LCMS (ESI) $[M+H]^+$ = 836.6.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

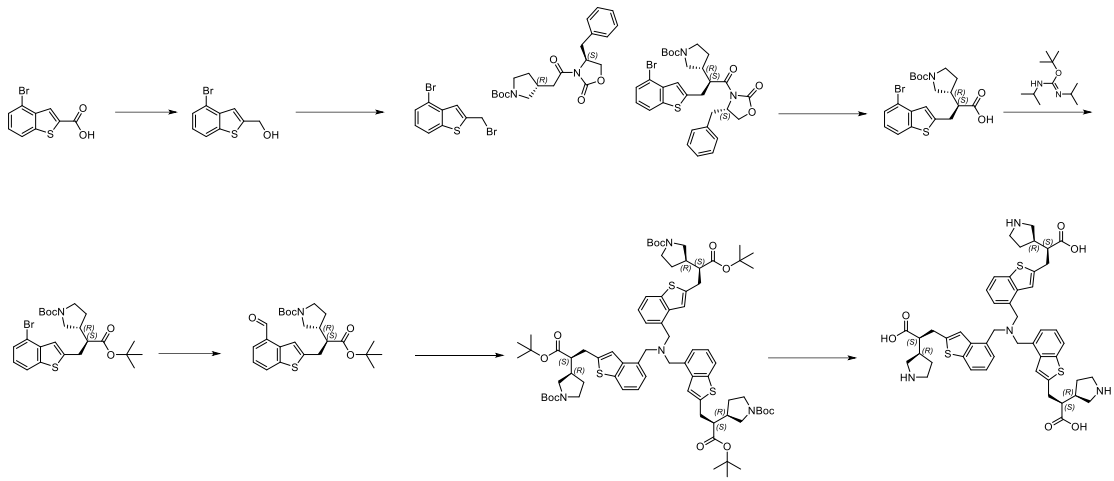
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (140 mg) was dissolved in N,N-dimethylformamide (10 mL), followed by adding 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (80 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (64 mg), and *N,N*-diisopropylethylamine (32 mg). The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. Water and ethyl acetate were added to the reaction mixture. The mixture was extracted, and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The product was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 1251.8.

Step 7: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenethyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (70 mg) was dissolved in hydrochloric acid/1,4-dioxane (4.0M, 4 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to give the target compound (19.18 mg). LCMS (ESI) $[M+H]^+$ = 783.4; ^{1}H NMR (400 MHz, D_2O) δ 7.20-7.08 (m, 2H), 7.07-6.98 (m, 2H), 6.96-6.81 (m, 4H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.64 (dt, *J* = 6.7, 2.8 Hz, 2H), 6.61-6.54 (m, 1H), 4.49 (s, 2H), 4.08 (t, *J* = 5.2 Hz, 1H), 3.79 (d, *J* = 5.6 Hz, 1H), 3.63-3.50 (m, 3H), 3.43 (d, *J* = 5.3 Hz, 1H), 3.30-3.18 (m, 5H), 3.14-2.97 (m, 5H), 2.75-2.49 (m, 10H), 2.33-2.16 (m, 6H), 1.94 (qq, *J* = 6.6, 3.8 Hz, 3H), 1.65-1.47 (m, 3H).

Example 25 (Compound 101)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzo[b]thiophene-4,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of (4-bromobenzo[b]thiophen-2-yl)methanol

4-bromobenzo[b]thiophene-2-carboxylic acid (10 g, 38.9 mmol, 1.0 eq) was dissolved in THF (100 mL), followed by the slow addition of a solution of borane/THF (58.3 mL, 110 mmol, 1.5 eq, 1.0 M) at 0°C. The mixture was heated to 60°C under nitrogen protection and stirred for 3h. LCMS showed the reaction was completed. It was quenched with methanol, the reaction mixture was filtered, water was added to the filtrate, it was extracted with ethyl acetate, the organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, and the target compound (4.0 g) was obtained by column chromatography (petroleum ether:ethyl acetate = 5:1). LCMS (ESI) $[M+H]^+$ = 242.6.

Step 2: Synthesis of 4-bromo-2-(bromomethyl)benzo[b]thiophene

(4-bromobenzo[b]thiophen-2-yl)methanol (4.0 g, 16.45 mmol, 1 eq) and hydrogen bromide (24 mL, 40%) were added to dichloromethane (32 mL). Under nitrogen protection, it was heated to 46°C and stirred for 18h. LCMS showed the reaction was completed. Water and dichloromethane were added to the reaction mixture which was extracted and separated. The organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was subjected to column chromatography (petroleum ether = 100%) to give the target compound (3.7 g).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(4-bromobenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (7.16 g, 18.43 mmol, 1.2 eq) was dissolved in tetrahydrofuran (70 mL), lithium bis(trimethylsilyl)amide (8.3 mL, 23.04 mmol, 1.5 eq) was added at 0°C and stirred for 0.5h, and 4-bromo-2-(bromomethyl)benzo[b]thiophene (4.7 g, 15.36 mmol, 1.0 eq) was added and stirred for 2h. LCMS showed the reaction was completed. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target product (3.7 g). LCMS (ESI) $[M+H\text{-Boc}]^+ = 513.4$.

Step 4: Synthesis of (S)-3-(4-bromobenzo[b]thiophen-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(4-bromobenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (8.5 g, 13.85 mmol, 1.0 eq) was added in tetrahydrofuran (90 mL), followed by adding the aqueous solution of hydrogen peroxide (22.4 mL, 30%) and lithium hydroxide (664 mg, 27.7 mmol, 2.0 eq) at 0°C. The reaction mixture was warmed to room temperature and incubated for 2h. LCMS showed the reaction was completed. It was quenched with sodium sulfate decahydrate. The pH was adjusted to 5-6 with dilute hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (6.0 g). LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+ = 398.3$

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(4-bromobenzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(4-bromobenzo[b]thiophen-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (6 g, 13.2 mmol, 1.0 eq) was added in 2-methyltetrahydrofuran (70 mL), followed by adding *tert*-butyl N,N'-diisopropylcarbamimidate (10.58 g, 52.82 mmol, 4.0 eq). The mixture was stirred at 70°C for 3h under nitrogen protection. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phase was washed with saturated sodium carbonate solution and saturated sodium chloride

solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 9:1) to give the target compound (5.3 g). LCMS(ESI) $[2M+Na]^+$ = 1041.2.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(4-bromobenzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2.2 g, 4.31 mmol, 1.0 eq) was dissolved in toluene (25 mL), followed by adding palladium acetate (193.53 mg, 0.862 mmol, 0.2 eq), N,N,N',N'-tetramethylethylenediamine (901.52 mg, 7.758 mmol, 1.8 eq), and *n*-butyldi(1-adamantyl)phosphine (309.06 mg, 0.862 mmol, 0.2 eq). The reaction mixture was charged with hydrogen and carbon monoxide (1:1 = 1.6 MPa:1.6 MPa), heated to 110°C, and stirred for 48h. LCMS showed the reaction was completed. the reaction mixture was concentrated directly and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (1.3 g). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 360.2

Step 7: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-4,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (300 mg) was dissolved in methanol (5 mL), followed by adding acetic acid (3 drops), ammonia methanol solution (3.3 mg), and sodium cyanoborohydride (241 mg). LCMS showed the reaction was completed. The reaction mixture was concentrated directly and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 1347.9.

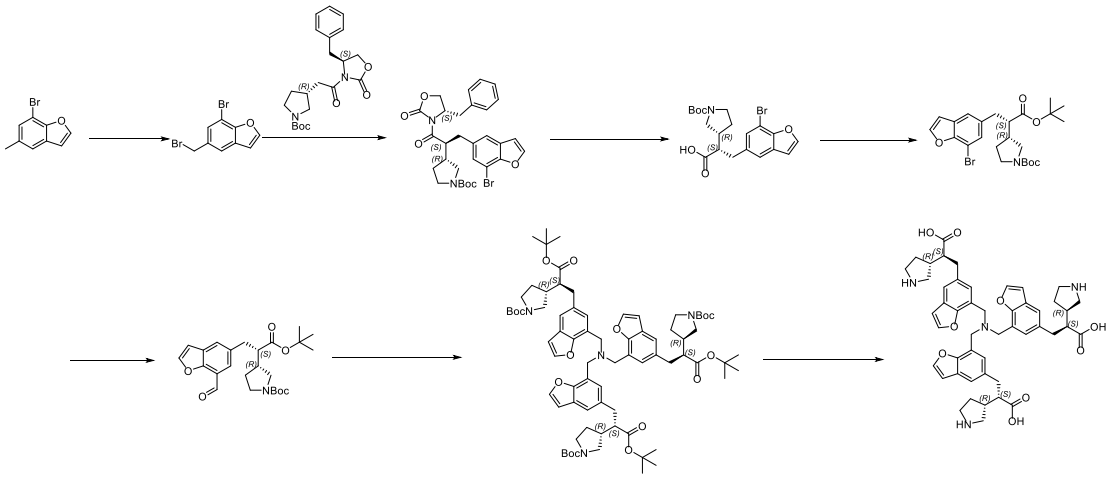
Step 8: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-4,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-4,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (90 mg) was added in the solution of hydrochloric acid/1,4-dioxane (4 mL, 4 M) and stirred at room temperature, and the mixture was stirred for 6h. After filtration, acetonitrile and water were

added, and the mixture was lyophilized to give the target compound (31 mg). LCMS (ESI) $[M+H]^+$ = 879.2; ^1H NMR (400 MHz, D_2O) δ 8.06-8.04 (m, 3H), 7.59-7.57 (m, 3H), 7.47-7.43 (m, 3H), 7.39-7.21 (m, 3H), 5.29(s, 3H),4.92-4.91(m, 3H), 4.75-4.72(m, 3H), 3.51-3.46 (m, 3H), 3.43-3.37 (m, 3H), 3.27-3.17 (m, 12H), 2.98-2.93 (m, 3H), 2.72-2.70 (m, 3H), 2.49-2.41(m, 6H), 2.12-2.07 (m, 3H), 1.76-1.70 (m, 3H).

Example 26 (Compound 102)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzofuran-7,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 7-bromo-5-(bromomethyl)benzofuran

7-bromo-5-methylbenzofuran (10 g, 47.3 mmol, 1.0 eq) was dissolved in carbon tetrachloride (100 mL), followed by adding benzoyl peroxide (1.15 g, 4.73 mmol, 0.1 eq) and N-bromosuccinimide (16.8 g, 94.6 mmol, 2.0 eq). The reaction was maintained at 25°C for 16h. LCMS showed the reaction was completed. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated. The mixture was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 20:1) to give the title compound (11.5 g).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(7-bromobenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (11.5 g, 29.6 mmol, 1.0 eq) was dissolved in tetrahydrofuran (100 mL) and cooled to -78°C with dry ice-ethanol bath, followed by adding lithium bis(trimethylsilyl)amide (40 mL, 1.0M, 1.35 eq). The reaction mixture was stirred at -78°C for 30min. 7-bromo-5-(bromomethyl)benzofuran (8.6 g, 29.6 mmol, 1.0 eq) was dissolved in tetrahydrofuran (20 mL), and the solution was slowly added dropwise to the above reaction mixture. The reaction mixture was stirred at 25°C for 16h. LCMS showed the reaction was completed. The reaction mixture was added with saturated ammonium chloride aqueous solution (50 mL) and extracted with ethyl acetate (100mL×3). The organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered. The filtrate was rotary-evaporated to dryness and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (7.5 g). LCMS (ESI) $[M+Na]^+$ = 619.2.

Step 3: Synthesis of (S)-3-(7-bromobenzofuran-5-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(7-bromobenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (7.5 g, 12.6 mmol, 1.0 eq) was dissolved in tetrahydrofuran (80 mL) and cooled to 0°C in an ice-water bath, followed by adding hydrogen peroxide (8 mL). Lithium hydroxide (603 mg, 25.2 mmol, 2.0 eq) was dissolved in water (15 mL), and the solution was slowly added dropwise to the above reaction mixture. After the addition was completed, the solution was allowed to gradually return to 25°C and stirred for 16h. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give the target compound (5.6 g). LCMS (ESI) $[M-tert\text{-butyl}]^+$ = 382.2.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(7-bromobenzofuran-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(7-bromobenzofuran-5-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (5.6 g, 12.8 mmol, 1.0 eq) was dissolved in 2-methyltetrahydrofuran (50 mL), followed by adding *tert*-butyl N,N'-diisopropylcarbamimidate (7.7 g, 38.4 mmol, 3.0 eq). The reaction mixture was stirred at 65°C for 16h. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give a crude product, which was separated and purified by rapid

chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (3.85 g). LCMS (ESI) $[M+Na]^+$ = 516.3.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(7-formylbenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(7-bromobenzofuran-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2.0 g, 4.06 mmol, 1.0 eq) was dissolved in toluene (20 mL), followed by adding palladium acetate (91.6 mg, 0.406 mmol, 0.1 eq), N,N,N',N'-tetramethylethylenediamine (849.4 mg, 7.31 mmol, 1.8 eq), and *n*-butyldi(1-adamantyl)phosphine (294.1 mg, 0.81 mmol, 0.2 eq). The mixture was charged with carbon monoxide to 1.2 MPa and then hydrogen to 2.4 MPa, heated to 110°C, and stirred for 48h. TLC showed the reaction was completed. The reaction mixture was filtered, concentrated, separated, and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (1.3 g). LCMS (ESI) $[M+Na]^+$ = 466.4.

Step 6: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzofuran-7,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(7-formylbenzofuran-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg, 0.451 mmol, 1.0 eq) was dissolved in methanol (2 mL), followed by adding ammonia methanol solution (0.1 mL, 7.0 M) and sodium cyanoborohydride (84 mg, 1.354 mmol, 3.0 eq) at 25°C. The mixture was stirred at 25 for 16h. LCMS showed the reaction was completed. Water and ethyl acetate was added. The mixture was extracted and separated. The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give the crude product, which was purified by chromatography (petroleum ether:ethyl acetate = 2:1) to give the target compound (110 mg). LCMS (ESI) $[M+H]^+$ = 1299.2.

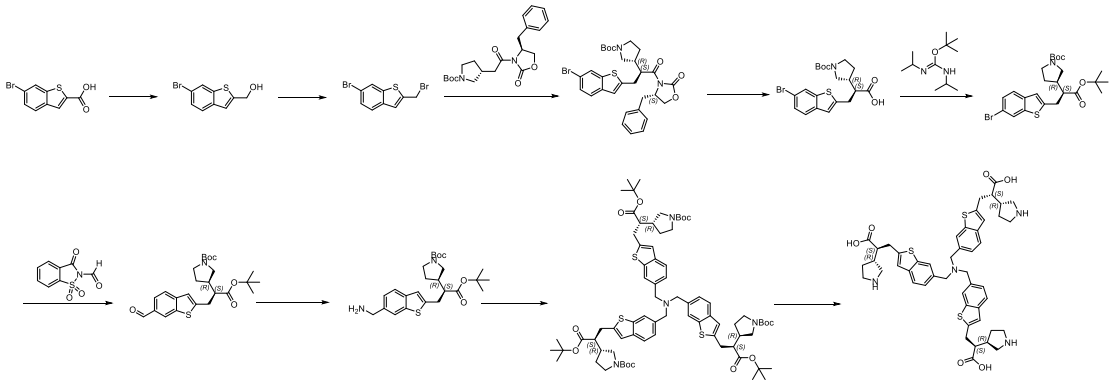
Step 7: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzofuran-7,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzofuran-7,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (110 mg) was dissolved in hydrochloric acid/1,4-dioxane (5 mL) and stirred at 25°C for 3h. LCMS

showed the reaction was completed. The reaction mixture was filtered to give the target compound (35.98 mg). LCMS (ESI) $[M+Na]^+ = 853.3$; ^{1}HNMR(EN1298-248-P):(400MHz, D_2O) δ 7.48-7.52 (m, 6H), 7.0 (s, 3H), 6.79 (d, J = 4.8 Hz, 3H), 4.77 (s, 6H), 3.56-3.50 (m, 3H),3.36-3.25 (m, 3H), 3.15-3.22 (m, 3H), 2.97-3.03 (m, 3H), 2.79-2.92 (m, 6H), 2.67-2.54 (m, 3H), 2.50-2.38 (m, 3H), 2.11-2.05 (m, 3H), 1.68-1.63 (m, 3H).

Example 27 (Compound 103)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzo[b]thiophene-6,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of (6-bromobenzo[b]thiophen-2-yl)methanol

6-bromobenzo[b]thiophene-2-carboxylic acid (5 g, 19.45mmol) was dissolved in tetrahydrofuran (40 mL), followed by adding a solution of borane/tetrahydrofuran (58.34 mL, 3.0 eq, 3.0 M) at room temperature. The mixture was stirred at room temperature for 16h. TLC showed the reaction of starting material was completed. The reaction mixture was added with a saturated solution of sodium bicarbonate slowly under ice-water bath. The mixture was extracted and separated. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (4.0 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23-8.18 (m, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.48 (dd,J = 8.5, 1.9 Hz, 1H), 7.27 (q, J = 1.1 Hz, 1H), 5.70 (s, 1H), 4.73 (s, 2H).

Step 2: Synthesis of 6-bromo-2-(bromomethyl)benzo[b]thiophene

(6-bromobenzo[b]thiophen-2-yl)methanol (4 g, 16.45mmol) was dissolved in dichloromethane (20 mL), followed by adding phosphorus tribromide (4454 mg, 16.45mmol) at

room temperature. The mixture was stirred at room temperature for 16h. TLC showed the reaction of starting material was completed. The reaction mixture was added with a saturated solution of sodium bicarbonate slowly under ice-water bath. The mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (3.8 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28-8.23(m, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.57-7.50 (m, 2H), 5.09 (d, J = 0.7 Hz, 2H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(6-bromobenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

A solution of lithium bis(trimethylsilyl)amide (7.45 mL, 7.45 mmol, 1.2 eq, 1.0 M in THF) was added dropwise to the solution of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (2.653 g, 6.83 mmol, 1.1 eq) in tetrahydrofuran (20 mL) under ice-bath and nitrogen protection. The mixture was stirred at 0°C for 30min. Then a solution of 6-bromo-2-(bromomethyl)benzo[b]thiophene (1.9 g, 6.21 mmol, 1.0 eq) in tetrahydrofuran (10 mL) was added slowly. The reaction temperature was increased slowly to room temperature and stirred for 16h. The reaction mixture was cooled with an ice-water bath. Saturated ammonium chloride aqueous solution was added. The mixture was added with water and extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (2 g). LCMS (ESI) [M+H-*tert*-butyl] = 557.07.

Step 4: Synthesis of (S)-3-(6-bromobenzo[b]thiophen-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

A solution of hydrogen peroxide (333 mg, 9.78 mmol, 3.0 eq) was added once to the solution of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(6-bromobenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2 g, 3.26 mmol, 1.0 eq) in tetrahydrofuran (20 mL) and cooled with an ice/water bath, followed by adding a solution of lithium hydroxide monohydrate (274 mg, 6.52 mmol, 2.0 eq). The reaction temperature was increased to room temperature, and the mixture was stirred for 16h. LCMS showed the reaction was completed. The reaction mixture was cooled to 0°C. The sodium hydrogen sulfite (300 mg) aqueous solution (10 mL) and sodium hydroxide (5N) aqueous solution were added. The pH of

the reaction mixture was adjusted to >12. Water (20 mL) and methyl *tert*-butyl ether (50 mL) were added. The mixture was extracted and separated. The organic phase was discarded; the mixture was cooled to 0°C, the pH of the mixture was adjusted to 3 by the addition of hydrochloric acid (5N), it was extracted with methyl *tert*-butyl ether, and the organic phase was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (1.2 g). LCMS (ESI) $[M+H-tert\text{-butyl}]^+ = 397.8$.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(6-bromobenzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(6-bromobenzo[b]thiophen-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (1.2 g, 2.64 mmol, 1 eq) was dissolved in 2-methyltetrahydrofuran (20 mL), followed by adding *tert*-butyl N,N'-diisopropylcarbamimidate (2.645 g, 13.2 mmol, 5 eq). It was heated to 65°C under nitrogen protection and stirred for 16h. LCMS showed the reaction was completed. The insoluble matter was filtered. The filter cake was washed with methyl *tert*-butyl ether, the filtrate was concentrated, separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (1 g). LCMS (ESI) $[M+H-2\times tert\text{-butyl}]^+ = 397.8$.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(6-bromobenzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (900 mg, 1.76 mmol, 1.0 eq) and N,N-dimethylformamide (10 mL) were added in a microwave tube, followed by adding N-formylsaccharin (745 mg, 3.53 mmol, 2.0 eq), palladium acetate (40 mg, 0.18 mmol, 0.1 eq), 1,4-bis(diphenylphosphino)butane (75 mg, 0.18 mmol, 0.1 eq), triethylsilane (410 mg, 3.53 mmol, 2.0 eq), and sodium carbonate (561 mg, 5.29 mmol, 3.0 eq). Nitrogen was replaced 3 times. The mixture was stirred at 70°C for 16h. LCMS showed the reaction was completed. The insoluble matter was filtered through diatomaceous earth. The filter cake was washed with ethyl acetate. The filtrate was concentrated, separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (400 mg). LCMS (ESI) $[M-tert\text{-butyl-Boc}]^+ = 303.9$.

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(6-(aminomethyl)benzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(170 mg, 0.37 mmol, 1.0 eq) was added in ammonia methanol solution (1.5 mL, 7.0 M) and stirred at room temperature for 0.5h, followed by adding sodium cyanoborohydride (160 mg, 2.59 mmol, 7.0 eq). The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by rapid chromatography (silica gel, dichloromethane:methanol = 30:1) to give the target compound (50 mg). LCMS (ESI) $[M+H]^+$ = 461.0.

Step 8: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-6,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(6-(aminomethyl)benzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (50 mg) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg) were dissolved in methanol (5 mL) and stirred at room temperature for 0.5h, followed by adding sodium cyanoborohydride (13 mg). The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated, diluted with ethyl acetate, washed with saturated sodium bicarbonate solution and saturated saline solution successively, dried over anhydrous sodium sulfate, and filtered. The organic phase was concentrated, separated and purified by rapid chromatography (silica gel, dichloromethane:methanol = 40:1) to give the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 1347.2.

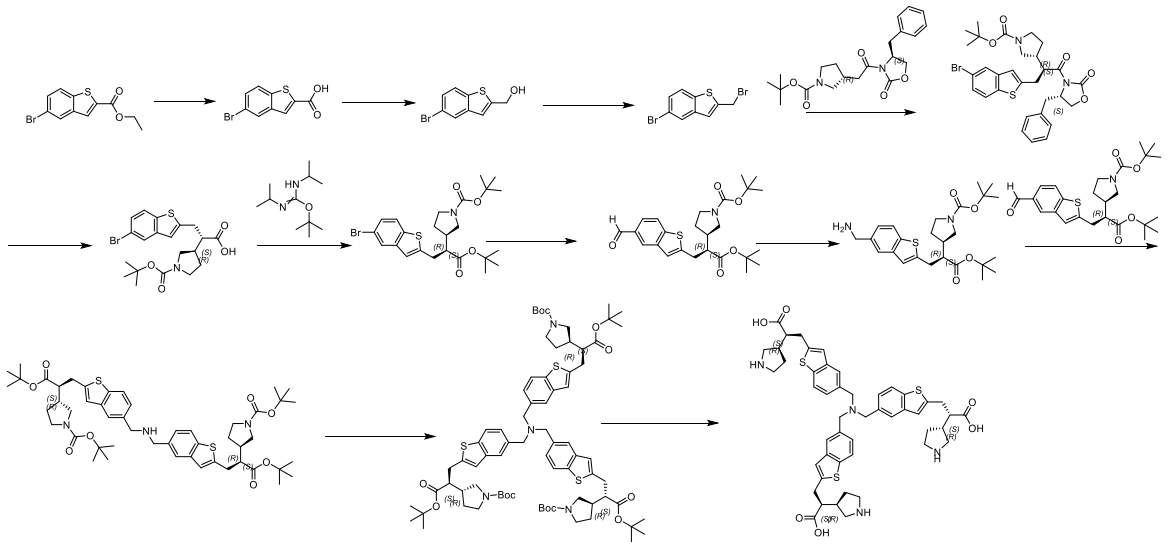
Step 9: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-6,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-6,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (70 mg) was added in hydrochloric acid/1,4-dioxane (3 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly. The concentrate was separated and purified by Prep-HPLC to give the target compound (31.90 mg). LCMS (ESI) $[M+H]^+$ = 879.0; ^{1}H NMR (400 MHz, D_2O) δ 7.56 (d, *J* = 8.3 Hz, 3H), 7.53-7.46 (m, 3H), 7.13-7.03 (m, 6H), 4.29 (s, 6H), 3.56 (dd, *J* = 11.8, 7.9 Hz, 3H), 3.39 (ddd, *J* = 11.9,

8.5, 3.4 Hz, 3H), 3.23-3.02 (m, 12H), 2.83 (dt, *J* = 9.6, 4.6 Hz, 3H), 2.56 (q, *J* = 8.5 Hz, 3H), 2.14 (dtd, *J* = 13.7, 7.1, 3.4 Hz, 3H), 1.80-1.70 (m, 3H).

Example 28 (Compound 104)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzo[b]thiophene-5,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 5-bromobenzo[b]thiophene-2-carboxylic acid

Ethyl 5-bromobenzo[b]thiophene-2-carboxylate (4.5 g) was dissolved in a mixed solution of THF (10 mL) and water (10 mL), followed by adding lithium hydroxide (2.0 g). The mixture was stirred at room temperature for 3h. The pH of the reaction mixture was adjusted to 3 with dilute hydrochloric acid (1.0 M) solution. The mixture was filtered to give the target compound (3.5 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 1.9 Hz, 1H), 8.08 (s, 1H), 8.04 (d, J = 8.7 Hz, 1H), 7.65 (dd, J = 8.7, 2.0 Hz, 1H).

Step 2: Synthesis of (5-bromobenzo[b]thiophen-2-yl)methanol

5-bromobenzo[b]thiophene-2-carboxylic acid (200 mg) was dissolved in THF (15.0 mL). The reaction mixture was cooled to 0°C. A solution of BH_3 in THF (1.0 M, 2.33 mL) was added dropwise. Then the reaction was stirred for 2h. Methanol was added to quench the reaction. The reaction mixture was concentrated to give the crude product. Ethyl acetate was added to the crude product and filtered. The filtrate was concentrated to give the target compound (1.6 g). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.01 (d, J = 1.8 Hz, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.43 (dd, J = 8.5, 1.8 Hz, 1H), 7.25 (s, 1H), 5.72 (t, J = 5.7 Hz, 1H), 4.75 (d, J = 5.8 Hz, 2H).

Step 3: Synthesis of 5-bromo-2-(bromomethyl)benzo[b]thiophene

(5-bromobenzo[b]thiophen-2-yl)methanol (2.5 g) was dissolved in DCM (20 mL), followed by adding HBr (15 mL, 48%) at room temperature. The reaction mixture was heated to 45°C and stirred for 16h. TLC showed the reaction of starting material was completed. The reaction mixture was slowly quenched with saturated sodium bicarbonate solution in an ice-water bath and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (2.7 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 1.9 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.52 (dd, J = 8.6, 1.9 Hz, 2H), 5.10 (s, 2H).

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (609 mg) was dissolved in anhydrous THF (10 mL). The reaction mixture was cooled to 0°C. Lithium bis(trimethylsilyl)amide (1.83 mL, 1.0 M) was added dropwise at 0°C. The mixture was stirred for 30min at the same temperature. A solution of 5-bromo-2-(bromomethyl)benzo[b]thiophene (400 mg) in THF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 16h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated ammonium chloride aqueous solution at 0°C in an ice-water bath, extracted with ethyl acetate, dried, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (900 mg). LCMS (ESI) $[M+H-Boc]^+$ = 513.13.

Step 5: Synthesis of (S)-3-(5-bromobenzo[b]thiophen-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg) was

dissolved in THF (10 mL). The reaction mixture was cooled to 0°C. H_2O_2/H_2O (47.5 mg) was added and stirred for 15 min. The mixture was stirred for another 3h. LCMS showed the reaction was completed. The reaction mixture was quenched with the sodium bisulfite (75 mg) aqueous solution slowly in an ice-water bath. The pH was adjusted to 3. The mixture was extracted with ethyl acetate, dried, filtered, and concentrated to give the target compound (148 mg, crude product) which was used directly in the next step. LCMS (ESI) $[M+Na]^+ = 476.19$

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-bromobenzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromobenzo[b]thiophen-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (250 mg) was dissolved in 2-methyltetrahydrofuran (10 mL), followed by adding *tert*-butyl N,N'-diisopropylcarbamimidate (551 mg). The mixture was stirred at room temperature for 15 min. The reaction mixture was stirred at 65°C overnight. TLC showed the reaction was completed. The reaction mixture was filtered. The filter cake was washed with *tert*-butyl ether. The merged filtrates were concentrated to give the crude product, which was separate and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (140 mg). LCMS (ESI) $[M+H]^+ = 510.12$.

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(5-bromobenzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (240 mg), palladium acetate (21.1 mg), 1,4-bis(diphenylphosphino)butane (40 mg), N-formylsaccharin (298 mg), sodium carbonate (242 mg), and triethylsilane (82 mg) were dissolved in DMF (5 mL). The reaction mixture was heated to 75°C and stirred for 16h under nitrogen protection. LCMS showed the reaction was completed. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target product (100 mg). LCMS (ESI) $[M+H]^+ = 460.2$.

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-(aminomethyl)benzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (50 mg) was dissolved in methanol (2 mL), followed by adding ammonia methanol (0.19 mL, 7 M). The mixture was stirred at room temperature for 30min. sodium cyanoborohydride (47.1 mg) was added and stirred at 60°C for 1.5h under microwave irradiation. LCMS showed the reaction was completed. The reaction mixture was filtered. The filtrate was concentrated, separated and purified by reversed-phase column chromatography (C_{18}, water:acetonitrile = 40%) to give the target compound (30 mg). LCMS (ESI) $[M+H]^+$ = 461.36.

Step 9: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(benzo[b]thiophene-5,2-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(5-(aminomethyl)benzo[b]thiophen-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (20 mg) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (20 mg) were dissolved in THF (3.0 mL). The mixture was stirred at room temperature for 3h under nitrogen protection. Then, sodium cyanoborohydride (5.65 mg) was added to the reaction mixture to continue stirring for 13h. LCMS showed the reaction was completed. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (20 mg). LCMS (ESI) $[M+H]^+$ = 904.26.

Step 10: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-5,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(benzo[b]thiophene-5,2-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (20 mg), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (10 mg), and one drop of acetic acid were dissolved in THF (3.0 mL). The mixture was stirred at room temperature for 3h under nitrogen protection. sodium cyanoborohydride (3.0 mg) was added. The mixture was stirred for another 13h. Water was added to the reaction mixture to quench the reaction. The mixture was extracted, dried, filtered, and

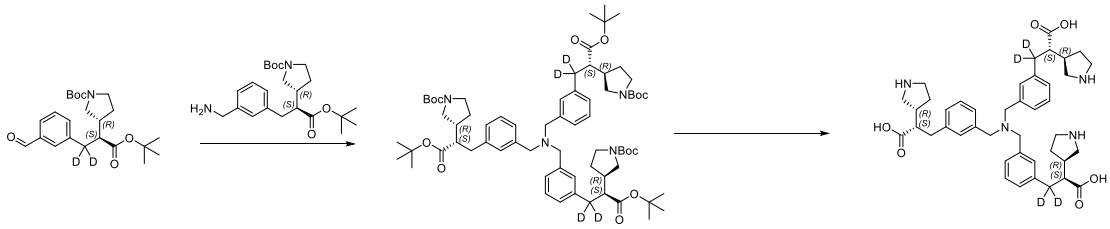
concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (20 mg). LCMS (ESI) $[M+H]^+$ = 1347.80

Step 11: Synthesis of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzo[b]thiophene-5,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3"-((2S,2'S,2"S)-((nitrilotris(methylene))tris(benzo[b]thiophene-5,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3"R)-tris(pyrrolidine-1-carboxylate) (20 mg) was dissolved in dichloromethane (4 mL), followed by adding trifluoroacetic acid (17.1 mg). The reaction was maintained at room temperature overnight. The reaction mixture was concentrated, and the crude product was separated and purified by Prep-HPLC to give the target compound (5 mg). LCMS(ESI)$(M+H)^+$ = 879.1; ^{1}H NMR (400 MHz, D_2O)δ7.62 (d,J = 8.3 Hz, 3H), 7.40 (s, 3H), 6.98 (d,J = 8.2 Hz, 3H), 6.92 (s, 3H),4.29 (s, 6H), 3.54-3.41 (m, 3H), 3.36-3.24 (m, 3H), 3.20 -2.90 (m, 14H), 2.75-2.62 (m, 3H), 2.51-2.38 (m, 3H), 2.11-1.98 (m, 3H), 1.73 -1.59 (m, 3H).

Example 29 (Compound 105)

Preparation of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic-3,3-d2 acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl-1,1-d_2))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (48 mg, 0.12 mmol, 1 eq) was added a solution of *tert*-butyl (R)-3-

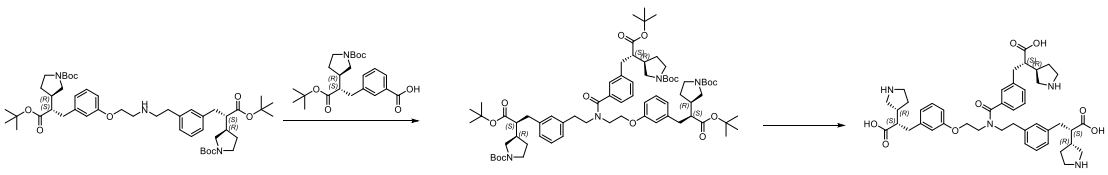
((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (110 mg, 0.27 mmol, 2.2 eq) in tetrahydrofuran (1 mL), followed by the dropwise addition of one drop of acetic acid. The mixture was stirred at room temperature for 0.5h. sodium cyanoborohydride (18 mg, 0.3 mmol, 2.5 eq) was added. The reaction mixture was stirred at room temperature overnight. TLC showed the reaction was completed. Saturated ammonium chloride solution was added to quench the reaction. The mixture was extracted and separated with ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was purified by column chromatography to give the target compound. LCMS (ESI) $[M+H]^+$ = 1184.81.

Step 2: Synthesis of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic-3,3-d2 acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl-1,1-d_2))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (60 mg, 0.05 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), followed by adding hydrochloric acid/1,4-dioxane (2 mL). The mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation to dryness, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the target compound (61 mg). LCMS (ESI) $[M+H]^+$ = 715.68; ^{1}H NMR (400 MHz, D_2O) δ 7.29-7.21 (m, 3H), 7.20-7.05 (m, 9H), 3.72-3.41 (m, 6H), 3.37-3.23 (m, 6H), 3.18-3.04 (m, 3H), 2.89-2.64 (m, 5H), 2.44-2.27 (m, 6H), 2.13-1.94 (m, 3H), 1.72-1.57 (m, 3H).

Example 30 (Compound 106)

Preparation of (S)-3-(3-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-N-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)benzamido)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)carbamoyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

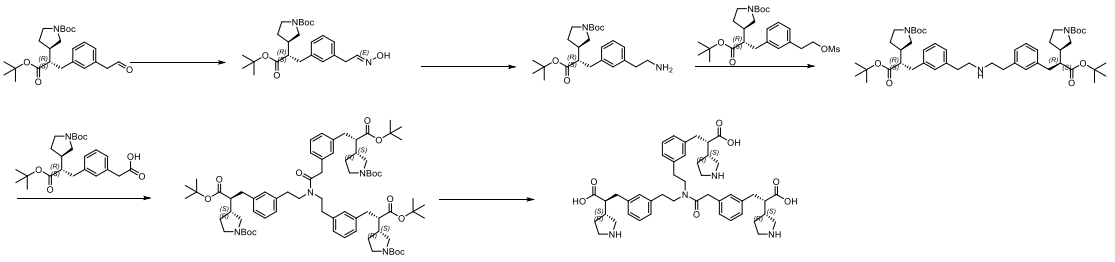
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (120 mg, 0.14 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (10 mL), followed by adding 3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzoic acid (72 mg, 0.17 mmol, 1.2 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (109 mg, 0.29 mmol, 2.0 eq), and *N,N*-diisopropylethylamine (56 mg, 0.43 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 1237.9.

Step 2: Synthesis of (S)-3-(3-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-N-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)benzamido)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)carbamoyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (70 mg, 0.06mmol) was dissolved in hydrochloric acid/1,4-dioxane (4 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to give the target compound (11.7 mg). LCMS (ESI) $[M+H]^+$ = 769.5; ^{1}H NMR (400 MHz, D_2O) δ 7.31-6.91 (m, 7H), 6.89-6.65 (m, 4H), 6.49 (d, *J* = 85.2 Hz, 1H), 4.35 (s, 1H), 4.12 (t, *J* = 5.3 Hz, 1H), 4.01 (t, *J* = 5.3 Hz, 1H), 3.96-3.73 (m, 2H), 3.55 (dt, *J* = 29.9, 6.6 Hz, 3H), 3.43-3.26 (m, 6H), 3.20-3.08 (m, 3H), 2.86-2.62 (m, 9H), 2.47-2.23 (m, 6H), 2.07 (s, 3H), 1.67 (d, *J* = 12.1 Hz, 3H).

Example 31 (Compound 107)

Preparation of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((E)-2-(hydroxyimino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (1000 mg) was dissolved in ethanol (20 mL), followed by adding hydroxylamine hydrochloride (250 mg). The mixture was stirred at room temperature for 16h under nitrogen protection. LCMS showed the reaction was completed. The reaction mixture was added with water, extracted with ethyl acetate, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (900 mg). LCMS (ESI) $[M+H]^+$ = 433.3

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the first step (900 mg) was dissolved in methanol (10 mL), followed by adding Pd/C (150 mg). The mixture was stirred at room temperature for 16h under hydrogen. LCMS showed the reaction was completed. The reaction mixture was directly concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (600 mg). LCMS (ESI) $[M+H]^+$ = 419.3

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

The product from the second step (219 mg) was dissolved in acetonitrile (10 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((methylsulfonyl)oxy)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg) and potassium carbonate (78 mg). The reaction mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (240 mg). LCMS (ESI) $[M+H]^+$ = 820.6.

Step 4: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

The product from the third step (120 mg) was dissolved in N,N-dimethylformamide (10 mL), followed by adding 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (70 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (56 mg), and *N,N*-diisopropylethylamine (28 mg). The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 1235.8

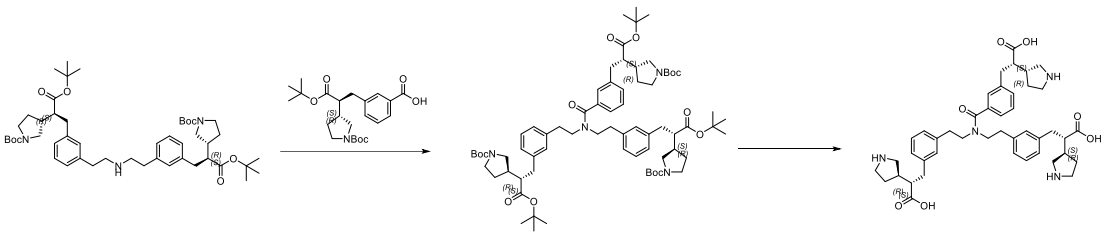
Step 5: Synthesis of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

The product from the fourth step (70 mg) was dissolved in hydrochloric acid/1,4-dioxane (4 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to give the target compound (29.99 mg). LCMS (ESI) $[M+H]^+$ = 767.4; ^{1}H NMR (400 MHz, D_2O) δ 7.27-7.14 (m, 3H), 7.12-7.02 (m, 3H), 6.99-6.91 (m, 4H), 6.75-6.68 (m, 2H), 3.49 (dt, *J* = 11.1, 7.6 Hz, 4H), 3.43-3.31 (m, 4H), 3.25 (t, *J* = 6.4 Hz, 2H), 3.21-3.05 (m, 5H), 3.00-2.92 (m, 3H),

2.86-2.73 (m, 8H), 2.65 (q, *J* = 7.2, 6.7 Hz, 5H), 2.50-2.37 (m, 3H), 2.10 (d, *J* = 7.6 Hz, 3H), 1.70 (dq, *J* = 12.9, 3.5 Hz, 3H).

Example 32 (Compound 108)

Preparation of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzoyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzoyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(ethane-2,1-diyl))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (120 mg) was dissolved in N,N-dimethylformamide (10 mL), followed by adding 3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzoic acid (74 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (111 mg), and *N,N*-diisopropylethylamine (57 mg). The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 1221.9

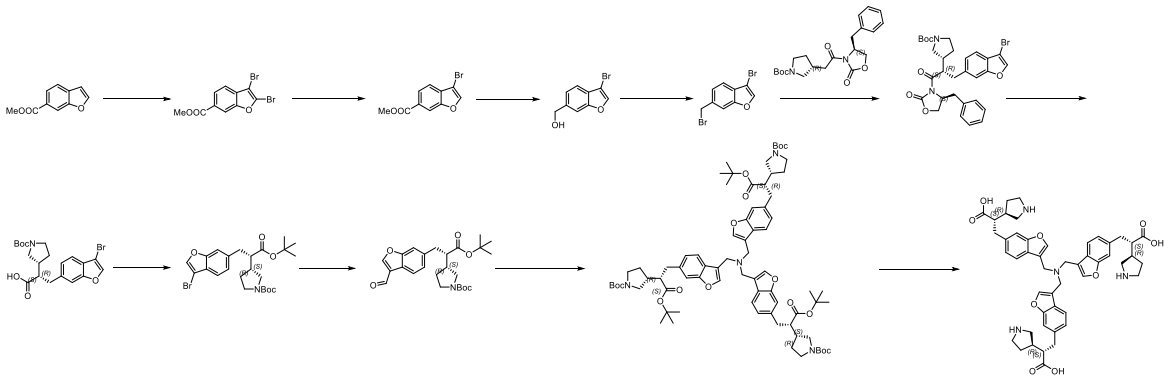
Step 2: Synthesis of (2S,2'S)-3,3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzoyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzoyl)azanediyl)bis(ethane-2,1-diyl))bis(3,1-

phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (70 mg) was dissolved in hydrochloric acid/1,4-dioxane (4 mL) and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to obtain the target compound (8.41 mg). LCMS (ESI) $[M+H]^+$ = 753.5; ^1H NMR (400 MHz, D_2O) δ 7.26 (t, *J* = 7.5 Hz, 1H), 7.17-7.13 (m, 4H), 7.09 (dd, *J* = 7.6, 4.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.72-6.61 (m, 2H), 6.48 (d, *J* = 3.8 Hz, 1H), 6.30 (s, 1H), 3.76 (dq, *J* = 20.4, 6.8 Hz, 2H), 3.39-3.26 (m, 8H), 3.19-3.08 (m, 3H), 2.95 (t, *J* = 6.9 Hz, 2H), 2.86-2.77 (m, 4H), 2.68 (dd, *J* = 13.8, 7.0 Hz, 3H), 2.58 (q, *J* = 5.0 Hz, 3H), 2.48-2.22 (m, 7H), 2.04 (td, *J* = 6.3, 3.5 Hz, 3H), 1.72-1.60 (m, 3H).

Example 33 (Compound 109)

Preparation of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzofuran-3,6-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of methyl 2,3-dibromobenzofuran-6-carboxylate

Methyl benzofuran-6-carboxylate (5.0 g, 28.4 mmol, 1 eq) was dissolved in dichloromethane (50 mL), followed by adding bromine (5.1 g, 31.2 mmol, 1.1 eq). The mixture was stirred at -10°C for 1h. TLC showed the reaction was completed. A saturated solution of $Na_2S_2O_3$ was added. The mixture was extracted with dichloromethane. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (8.0 g). LCMS (ESI) $[M+H]^+$ = 332.6.

Step 2: Synthesis of methyl 3-bromobenzofuran-6-carboxylate

Methyl 2,3-dibromobenzofuran-6-carboxylate (8 g, 23.95 mmol, 1 eq) was dissolved in a mixed solvent of THF (100 mL) and MeOH (20 mL), followed by adding cesium carbonate (15.61

g, 47.91 mmol, 2 eq). The mixture was stirred at room temperature for 2.5h. TLC showed the reaction was completed. The mixture was filtered. The filtrate was added with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated to give the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 10:1) and slurried to give the target compound (6.4 g). LCMS (ESI) $[M+H]^+$ = 254.9.

Step 3: Synthesis of (3-bromobenzofuran-6-yl)methanol

Methyl 3-bromobenzofuran-6-carboxylate (6.4 g, 25.09 mmol, 1 eq) was dissolved in THF (80 mL), followed by adding lithium borohydride (2732.53 mg, 125.46 mmol, 5 eq) under nitrogen protection. The mixture was stirred at 30°C for 6h. LCMS showed the reaction was completed. Water was added. The mixture was extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. The crude product was slurried by the mixed solvent (petroleum ether:ethyl acetate = 10:1) to give the target compound (5.6 g).

Step 4: Synthesis of 3-bromo-6-(bromomethyl)benzofuran

(3-bromobenzofuran-6-yl)methanol (5.6 g, 24.70 mmol, 1 eq) was dissolved in dichloromethane (100 mL), followed by adding hydrobromic acid aqueous solution (20 mL, 40 %); the tube was sealed and stirred at 45°C for 16h; TLC (petroleum ether 100 %) showed the reaction was completed. Saturated sodium carbonate solution (150 mL) was added to neutralize. The mixture was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give the target compound (5.4 g).

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromobenzofuran-6-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (5.31 g, 13.66 mmol, 1.1 eq) was dissolved in tetrahydrofuran (50 mL). The mixture was cooled to 0°C in an ice bath, and lithium bis(trimethylsilyl)amide (16.14 mL, 16.14 mmol, 1.3 eq, 1.0 M) was added dropwise. Then, the mixture was stirred for 30 min, and a solution of 3-bromo-6-(bromomethyl)benzofuran (3.6 g, 12.42 mmol, 1.0 eq) in tetrahydrofuran (20 mL) was added slowly dropwise. The reaction mixture was stirred at 25°C under nitrogen protection for

16h. LCMS showed the reaction was completed. The reaction mixture was poured into saturated ammonium chloride aqueous solution and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated. The residue was purified by column chromatography (dichloromethane:methanol = 98:2) to give the target compound (5.4 g). LCMS (ESI) $[M+Na]^+ = 619.3$

Step 6: Synthesis of (S)-3-(3-bromobenzofuran-6-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromobenzofuran-6-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (5.3 g, 8.87 mmol, 1 eq) was dissolved in tetrahydrofuran (50 mL). The mixture was cooled to 0°C in an ice-water bath. An aqueous solution (20 mL) of hydrogen peroxide (20 mL, 176.4 mmol, 19.89 eq, 30% content) and lithium hydroxide (320 mg, 13.31 mmol, 1.5 eq) was added. The reaction mixture was stirred under nitrogen protection for 16h. LCMS showed the reaction was completed. Saturated sodium sulfite solution was added. The mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (5.0 g). LCMS (ESI) $[M+H-tert\text{-butyl}]^+ = 382.10$

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromobenzofuran-6-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(3-bromobenzofuran-6-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (4.9 g, 11.18 mmol, 1 eq) was dissolved in 2-methyltetrahydrofuran (50 mL), followed by adding *tert*-butyl N,N'-diisopropylcarbamimidate (6.72 g, 33.54 mmol, 3 eq). The reaction mixture was raised to 70°C and stirred for 3h under nitrogen protection. LCMS showed the reaction was completed. The reaction mixture was cooled to room temperature and filtered with celite. The filtrate was rotary-evaporated to dryness for column chromatography (petroleum ether:ethyl acetate = 90:10) to give the target compound (2.1 g). LCMS (ESI) $[M+Na]^+ = 516.0$.

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylbenzofuran-6-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromobenzofuran-6-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.03 mmol, 1.0 eq) was dissolved in toluene (20 mL), followed

by adding palladium acetate (45.9 mg, 0.203 mmol, 0.1 eq), N,N,N',N'-tetramethylethylenediamine (424.6 mg, 3.65 mmol, 1.8 eq), and *n*-butyldi(1-adamantyl)phosphine (145.6 mg, 0.406 mmol, 0.2 eq). The reaction system was charged with carbon monoxide to 1.2 MPa and then hydrogen to 2.4 MPa. The mixture was raised to 110°C and stirred for 48h. TLC showed the reaction was completed. The mixture was filtered. The filtrate was concentrated, separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (570 mg). LCMS (ESI) $[M+Na]^+$ = 466.4.

Step 9: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzofuran-3,6-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

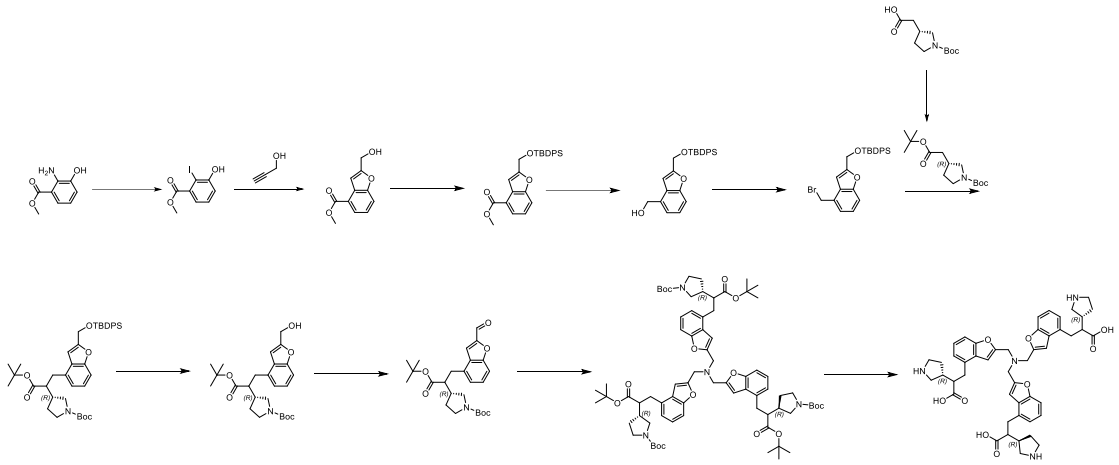
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylbenzofuran-6-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (150 mg, 0.34 mmol, 1.0 eq) was dissolved in methanol (2 mL), followed by adding ammonia methanol solution (0.1 mL, 7mol/L), sodium cyanoborohydride (62 mg, 1.02 mmol, 3.0 eq) at 25°C, and 2 drops of acetic acid. The mixture was raised to 60°C and stirred for 3h. LCMS showed the formation of a product. Water was added. The mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to give the target compound (42 mg). LCMS (ESI) $[M+H]^+$ = 1300.1.

Step 10: (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzofuran-3,6-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzofuran-3,6-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (42 mg, 0.03 mmol, 1.0 eq) was dissolved in hydrochloric acid/1,4-dioxane (3 mL, 4.0 M) and stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was filtered to give the target compound (2 mg). LCMS (ESI) $[M+H]^+$ = 831; ^{1}HNMR(EN1298-249-P):(400MHz, D_2O) δ 7.21-7.27 (m, 6H), 7.03-6.98 (m, 3H), 6.85-6.88 (m, 3H), 4.73 (s, 6H), 3.38-3.21 (m, 6H), 3.17-3.27 (m, 4H), 2.89-2.81 (m, 9H), 2.62-2.58 (m, 3H), 2.48-2.52 (m, 3H), 2.26-2.21 (m, 2H), 1.68-1.73 (m, 3H).

Example 34 (Compound 110)

Preparation of 3,3',3"-((nitrilotris(methylene))tris(benzofuran-2,4-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of methyl 3-hydroxy-2-iodobenzoate

Methyl 2-amino-3-hydroxybenzoate (25 g) was dissolved in a mixed solution of sulfuric acid (90 mL) and water (910 mL). The mixture was cooled to 0°C. Sodium nitrite (11.25 g, formulated as a 25 mL aqueous solution) was added. Then, the reaction mixture was warmed to room temperature and stirred for 20 min. Potassium iodide (111.7 g, formulated as a 100 mL aqueous solution) was added, the temperature was raised to 70°C, and the mixture was stirred for 1.5h. LCMS showed the reaction was completed. Water was added to the reaction mixture. The mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product. The crude product was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (20 g). LCMS (ESI) $[M+H]^+$ = 279.2.

Step 2: Synthesis of methyl 2-(hydroxymethyl)benzofuran-4-carboxylate

Methyl 3-hydroxy-2-iodobenzoate (20.0 g) was dissolved in N,N-dimethylformamide (200 mL), followed by adding copper iodide (1.37 g), bis(triphenylphosphine)palladium(II) dichloride (5 g), triethylamine (21.86 g), and propargyl alcohol (6.1 g). The reaction mixture was heated to 75°C and stirred for 16h under nitrogen protection. LCMS showed the reaction was completed. Water and ethyl acetate were added. The mixture was extracted and separated. The organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered, and

concentrated. The residue was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (11.0 g). LCMS (ESI) $[M+H]^+$ = 207.4.

Step 3: Synthesis of methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-carboxylate

Methyl 2-(hydroxymethyl)benzofuran-4-carboxylate(11.0 g) was dissolved in dichloromethane (80 mL), followed by adding imidazole (4.5 g) and *tert*-butyl(chloro)diphenylsilane (13.0 g). The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The mixture was filtered. The filtrate was concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (12.2 g). LCMS (ESI) $[M+Na]^+$ = 467.2.

Step 4: Synthesis of (2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-yl)methanol

Methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-carboxylate (12.2 g) was dissolved in tetrahydrofuran (100 mL), followed by adding lithium borohydride (1.79 g) at 0°C. Then, the reaction mixture was brought to room temperature and stirred for 16h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, and concentrated. The residue was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (7.64 g). LCMS (ESI) $[M+Na]^+$ = 439.4.

Step 5: Synthesis of ((4-(bromomethyl)benzofuran-2-yl)methoxy)(*tert*-butyl)diphenylsilane

(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-yl)methanol (2.0 g) was dissolved in dichloromethane (20 mL), followed by adding phosphorus tribromide (1.95 g) at 0°C. The reaction mixture was stirred for 2h. TLC showed the reaction was completed. The reaction was quenched with saturated ammonium chloride aqueous solution. The mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, separated and purified

by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 100:1) to give the target compound (1.42 g). LCMS (ESI) $[M+H]^+$ = 479.10.

Step 6: Synthesis of *tert*-butyl (R)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate

(R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (25.0 g) was dissolved in dichloromethane (200 mL), followed by adding N,N'-dicyclohexylcarbodiimide (22.5 g), *tert*-butyl alcohol (24.25 mL), and 4-dimethylaminopyridine (13.3 g) at room temperature. The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. Water and ethyl acetate were added. The mixture was extracted and separated. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (24.0 g). LCMS (ESI) $[M+H]^+$ = 286.5.

Step 7: Synthesis of *tert*-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate (905 mg) was dissolved in tetrahydrofuran (10 mL), followed by the dropwise addition of lithium bis(trimethylsilyl)amide (4.8 mL, 1.0 M) at 0°C. Then, the mixture was stirred at this temperature for 30min. A solution of ((4-(bromomethyl)benzofuran-2-yl)methoxy)(*tert*-butyl)diphenylsilane (1.42 g) in tetrahydrofuran (10 mL) was added dropwise to the reaction system. After the addition, the reaction mixture was warmed to room temperature and stirred for 3h. LCMS showed the reaction was completed. The reaction was quenched with saturated ammonium chloride aqueous solution. The mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate. The residue was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (1.67 g). LCMS (ESI) $[M+H]^+$ = 684.2.

Step 8: Synthesis of *tert*-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-(hydroxymethyl)benzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)benzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.67 g) was dissolved in tetrahydrofuran (10

mL), followed by adding di-tetra-n-butylammonium fluoride (3.19 g) at room temperature. The mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction was quenched with saturated ammonium chloride aqueous solution. The mixture was extracted with ethyl acetate and separated. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product (1.8 g). LCMS (ESI) $[M+Na]^+ = 468.4$.

Step 9: Synthesis of *tert*-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-formylbenzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-(hydroxymethyl)benzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.8 g) was dissolved in dichloromethane (10 mL), followed by adding manganese dioxide (1.76 g) at room temperature. The reaction mixture was heated to 60°C and stirred for 3h. LCMS showed the reaction was completed. The reaction mixture was filtered. The filtrate was concentrated. The residue was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (894 mg). LCMS (ESI) $[M+Na]^+ = 466.4$.

Step 10: Synthesis of tri-*tert*-butyl 3,3',3''-(((nitrilotris(methylene))tris(benzofuran-2,4-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (3R)-3-(1-(*tert*-butoxy)-3-(2-formylbenzofuran-4-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg) was dissolved in methanol (2 mL), followed by adding ammonia methanol solution (0.01 mL, 7 mol/L) and sodium cyanoborohydride (84.8 mg) at room temperature. Two drops of acetic acid were added, and the temperature was raised to 60°C. The mixture was stirred for 3h. The reaction was detected by LCMS until a product was formed. The product was separated and purified by silica gel plate (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (32 mg). LCMS (ESI) $[M+H]^+ = 1299.5$.

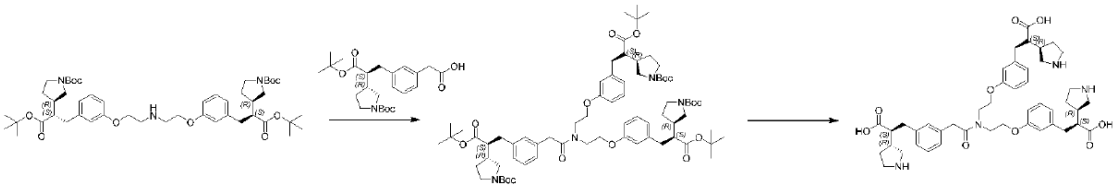
Step 11: Synthesis of 3,3',3''-((nitrilotris(methylene))tris(benzofuran-2,4-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-(((nitrilotris(methylene))tris(benzofuran-2,4-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (32 mg) was dissolved in hydrochloric acid/1,4-dioxane (5 mL) and stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was filtered to give the target compound

(4.41 mg). LC-MS:$[M+H]^+$ = 831.5; ^{1}HNMR:(400MHz, D_2O) δ 7.21-7.26 (m, 6H), 7.03-6.98 (m, 3H), 6.86-6.82 (m, 3H), 4.73 (s, 6H), 3.49-3.42 (m, 1H),3.38-3.24 (m, 6H), 3.20-3.25 (m, 3H), 2.89-2.81 (m, 9H), 2.62-2.59 (m, 3H), 2.51-2.47 (m, 3H), 2.27-2.21 (m, 3H), 1.72-1.68 (m, 3H).

Example 35 (Compound 111)

Preparation of (2S,2'S)-3,3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((azanediylbis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (100 mg, 0.12 mmol, 1 eq) was dissolved in ethyl acetate (2 mL), followed by adding 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (52.74 mg, 0.12 mmol, 1 eq), 1-propylphosphonic anhydride (116.11 mg, 0.18 mmol, 1.5 eq, 50% content), and *N,N*-diisopropylethylamine (47.16 mg, 0.36 mmol, 3 eq). The reaction was maintained at 50°C for 16h under nitrogen protection. The reaction mixture was concentrated, separated and purified by rapid chromatography (silica gel, tetrahydrofuran:petroleum ether = 1:3) to give the target compound (75 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1167.5.

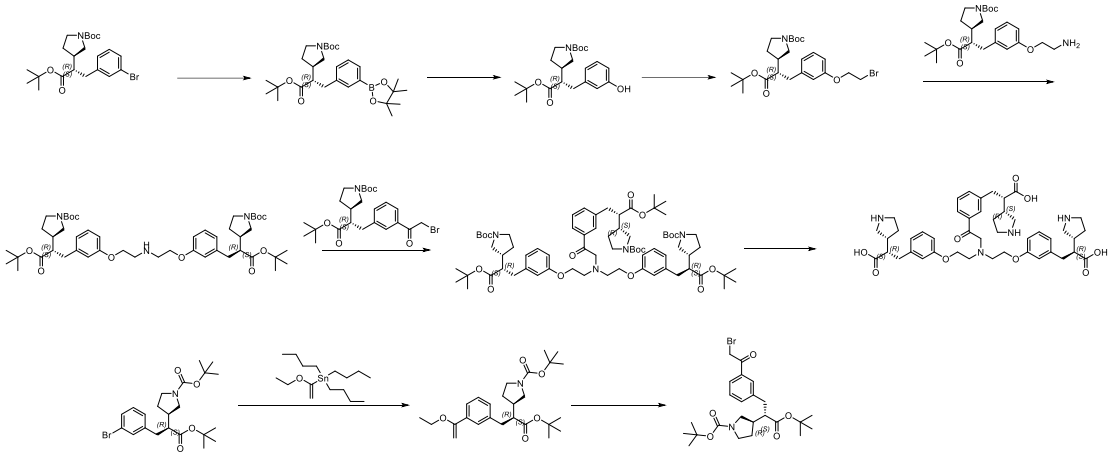
Step 2: Synthesis of (2S,2'S)-3,3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

The product from the first step (75 mg, 0.06 mmol, 1 eq) was dissolved in dioxane (2 mL), followed by adding hydrochloric acid/1,4-dioxane (2 mL). The reaction was maintained at room

temperature for 2h under nitrogen protection. The reaction mixture was concentrated, separated and purified by Prep-HPLC (0.1% NH_4HCO_3 in water, acetonitrile) to give the target compound (15.11 mg). LCMS (ESI) $[M+H]^+$ = 799.3; ^{1}H NMR (400 MHz, D_2O) δ 7.23-6.96 (m, 6H), 6.95-6.76 (m, 4H), 6.70-6.64 (m, 1H), 6.60-6.56 (m, 1H), 4.56-4.44 (m, 2H), 4.00 (t, *J* = 5.2 Hz, 1H), 3.93-3.84 (m, 1H), 3.67-3.57 (m, 2H), 3.41-3.25 (m, 6H), 3.19-3.08 (m, 3H), 2.90-2.48 (m, 13H), 2.42-2.25 (m, 6H), 2.10-1.94 (m, 3H), 1.72-1.57 (m, 3H).

Example 36 (Compound 112)

Preparation of (2S,2'S)-3,3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)-2-oxoethyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (10 g, 22.01 mmol, 1.0 eq) was dissolved in 1,4-dioxane (100 mL), followed by adding bis(pinacolato)diboron (11.18 g, 44.02 mmol, 2 eq), potassium acetate (6.48 g, 66.03 mmol, 3 eq), and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (1.61 g,2.2 mmol, 0.1 eq). The reaction mixture was heated to 90°C for 18h under nitrogen protection. After the reaction was completed, the mixture was filtered and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (10 g). LCMS (ESI) $[M+Na]^+$ = 524.0; ^{1}HNMR(400 MHz, DMSO-d_6) δ 7.51 (s, 1H), 7.49 (d, *J* = 6.9 Hz, 1H), 7.33-7.24 (m, 2H), 3.56-3.48 (m, 1H), 3.37-

3.34 (m, 1H), 3.14-3.13 (m, 1H), 3.00 (t, *J* = 10.0 Hz, 1H), 2.73 (d, *J* = 10.2 Hz, 2H), 2.29 (d, *J* = 8.1 Hz, 1H), 1.83 (d, *J* = 5.7 Hz, 1H), 1.67-1.50 (m, 2H), 1.28 (s, 12H), 1.23 (s, 9H), 1.16 (s, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (8 g, 15.95 mmol, 1 eq) was dissolved in methanol (80 mL), followed by slow addition of hydrogen peroxide (18.09.53 mmol, 10 eq, 30% content) in an ice bath. The mixture was stirred at room temperature for 1h. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (4.8 g). LCMS (ESI) $[M+Na]^+$ = 414.0.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-bromoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

In a sealed vessel, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (500 mg, 1.28 mmol, 1 eq) was dissolved in acetonitrile (10 mL) solution, followed by adding 1,2-dibromoethane (1.2 g, 6.39 mmol, 5 eq) and potassium carbonate (529.54 mg, 3.83 mmol, 3 eq). The mixture was heated to 70°C and stirred for 18h. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give the crude product, which was separated and purified by rapid chromatography (petroleum ether:ethyl acetate = 5:1) to give the target compound (300 mg). LCMS (ESI) $[M+Na]^+$ = 520.1; ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.18 (d, *J* = 7.9 Hz, 1H), 6.82-6.75 (m, 3H), 4.29-4.28 (m, 2H), 3.79 (t, *J* = 5.4 Hz, 2H), 3.57-3.43 (m, 1H), 3.38-3.36 (m, 2H), 3.21-3.08 (m, 1H), 2.99 (t, *J* = 10.0 Hz, 1H), 2.70-2.68 (m, 2H), 2.33-2.21 (m, 1H), 1.90-1.78 (m, 1H), 1.64-1.51 (m, 1H), 1.40 (s, 9H), 1.24 (s, 9H).

Step 4: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((azanediylbis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

In a sealed vessel, *tert*-butyl (R)-3-((S)-3-(3-(2-bromoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(300 mg, 0.6 mmol, 1 eq) was dissolved in acetonitrile (5 mL), *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (261.55 mg, 0.6 mmol, 1 eq) and potassium carbonate (249.55 mg, 1.81 mmol, 3 eq) were added; the mixture was heated to 90°C and the reaction was maintained for 18h under nitrogen protection. The reaction mixture was diluted with water, extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue was purified by rapid chromatography (ethyl acetate:petroleum ether = 2:1) to give the target compound (180 mg). LCMS (ESI) $[M+H]^+$ = 852.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23-7.21 (m, 2H), 6.87-6.80 (m, 6H), 4.31-4.20 (m, 4H), 3.64-3.59 (m, 2H), 3.55-3.47 (m, 4H), 3.19-3.11 (m, 2H), 2.99 (d, J = 7.0 Hz, 2H), 2.72 (d, J = 8.2 Hz, 4H), 2.34-2.17 (m, 3H), 2.01 (d, J = 8.2 Hz, 1H), 1.88-1.81 (m, 2H), 1.78-1.75 (m, 1H), 1.64-1.52 (m, 3H), 1.40 (s, 18H), 1.25 (s, 18H).

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(1-ethoxyvinyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (400 mg, 0.88 mmol, 1 eq) was dissolved in dioxane (8 mL), tributyl(1-ethoxyvinyl)stannane (635.81 mg, 1.76 mmol, 2 eq) and bis(triphenylphosphine)palladium(II) dichloride (61.79 mg, 0.09 mmol, 0.1 eq) were added; the mixture was heated to 100°C and stirred for 1h under nitrogen. After the reaction mixture was cooled to room temperature, a saturated solution of potassium fluoride and dichloromethane were added, and then stirred the mixture for 0.5h. The mixture was extracted with dichloromethane, the organic phases were merged, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give the crude product (350 mg). LCMS (ESI) $[M+Na]^+$ = 468.2.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-bromoacetyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(1-ethoxyvinyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(350 mg, 0.79 mmol, 1 eq) was dissolved in tetrahydrofuran (10 mL) and water (0.4 mL), N-bromosuccinimide (139.8 mg, 0.79 mmol, 1 eq) was added, and the mixture was stirred at 25°C for 30min under nitrogen. The reaction mixture was quenched with water and

extracted with ethyl acetate. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was purified by rapid chromatography (Silica gel, petroleum ether:dichloromethane = 5:1) to give the target compound (220 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 396.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88-7.82 (m, 2H), 7.53-7.45 (m, 2H), 4.94-4.86 (m, 2H), 3.58-3.49 (m, 1H), 3.40-3.36 (m, 1H), 3.21-3.11 (m, 1H), 3.02 (t, J = 10.0 Hz, 1H), 2.87-2.79 (m, 2H), 2.60-2.54 (m, 1H), 2.34-2.26 (m, 1H), 1.89-1.82 (m, 1H), 1.61-1.60 (m, 1H), 1.41 (s, 9H), 1.21 (s, 9H).

Step 7: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)-2-oxoethyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((azanediylbis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (44 mg) was dissolved in acetonitrile (2 mL), *tert*-butyl (R)-3-((S)-3-(3-(2-bromoacetyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (25.63 mg) and potassium carbonate (42.82 mg) were added; the mixture was heated to 60°C and stirred for 2h under nitrogen. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was purified by TLC silica gel plate (ethyl acetate:petroleum ether = 1:5) to give the target compound (40 mg). LCMS (ESI) $[M+H]^+$ = 1266.9.

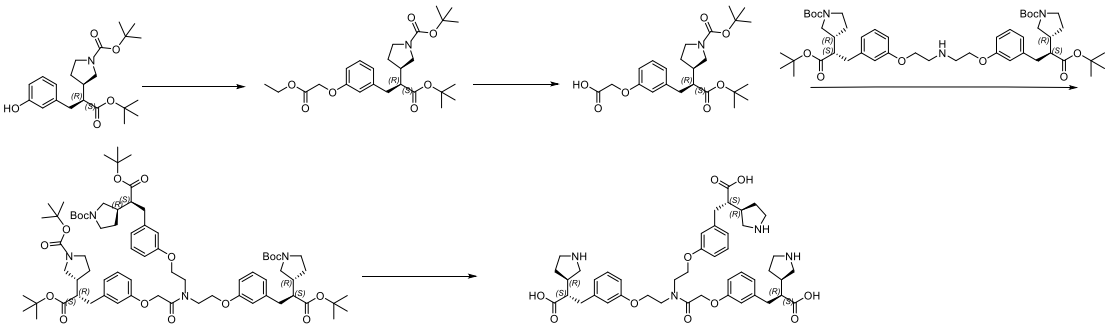
Step 8: Synthesis of (2S,2'S)-3,3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)-2-oxoethyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)-2-oxoethyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (27 mg) was dissolved in 1,4-dioxane (0.5 mL), and hydrochloric acid-1,4-dioxane (0.5 mL, 4 M) was added; the mixture was stirred at 20°C for 2h under nitrogen. After the reaction was completed, the reaction mixture was concentrated and purified by reversed-phase preparation (0.1% ammonia water-acetonitrile system) to give the target compound (16 mg).

LCMS (ESI) $[M+H]^+$ = 799.3; ^{1}H NMR (400 MHz, D_2O) δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.56 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 2H), 6.78 (d, *J* = 6.8 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 2H), 6.54 (s, 2H), 4.95 (s, 2H), 4.34-4.27 (m, 4H), 3.76-3.60 (m, 4H), 3.53-3.46 (m, 1H), 3.43-3.31 (m, 5H), 3.21-3.12 (m, 3H), 2.93-2.80 (m, 3H), 2.75-2.69 (m, 2H), 2.68-2.53 (m, 4H), 2.43-2.32 (m, 6H), 2.08-2.00 (m, 3H), 1.70-1.60 (m, 3H).

Example 37 (Compound 113)

Preparation of (2S,2'S)-3,3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-ethoxy-2-oxoethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (400 mg, 1.02 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (10 mL), and ethyl bromoacetate (256 mg, 1.54 mmol, 1.5 eq) and potassium carbonate (432 mg, 3.06 mmol, 3.0 eq) were added; the mixture was stirred at room temperature for 24h, and LCMS showed the reaction was completed. The reaction mixture was concentrated to give a crude product, which was purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 478.0.

Step 2: Synthesis of 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetic acid

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-ethoxy-2-oxoethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (300 mg, 0.63 mmol, 1.0 eq) was dissolved in tetrahydrofuran/water (3:1, 12 mL), lithium hydroxide monohydrate (27 mg, 0.63 mmol, 1.0 eq) was added, and the

mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The crude product was purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (200 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 394.0.

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((azanediylbis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (100 mg, 0.12 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (10 mL). Then 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetic acid (58 mg, 0.13 mmol, 1.1 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (89 mg, 0.23 mmol, 2.0 eq) and *N,N*-diisopropylethylamine (46 mg, 0.35 mmol, 3.0 eq) were added. The reaction mixture was stirred at room temperature for 6h. LCMS showed the reaction was completed. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (80 mg). LCMS (ESI) $[M+H]^+$ = 1183.2.

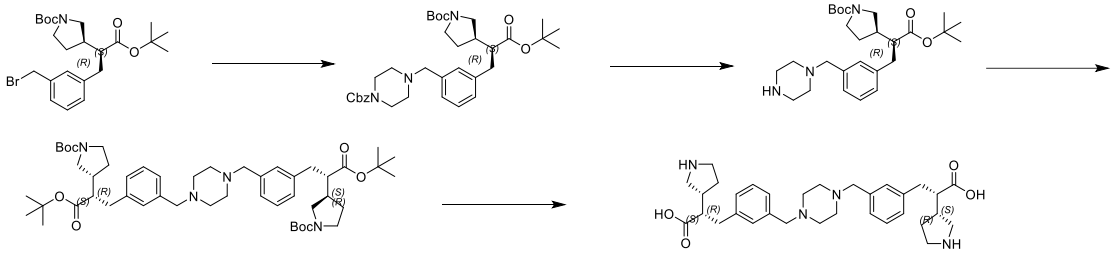
Step 4: Synthesis of (2S,2'S)-3,3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (80 mg, 0.06mmol) was dissolved in dichloromethane (4 mL), trifluoroacetic acid (1 mL) were added. Then the mixture was stirred at room temperature for 30h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and purified by preparative chromatography to give the target compound (48.19 mg). LCMS (ESI) $[M+H]^+$ = 815.0; ^{1}H NMR (400 MHz, D_2O) δ 7.16 (dt, *J* = 22.4, 7.9 Hz, 2H), 7.03 (t, *J* = 7.9 Hz,

1H), 6.83-6.73 (m, 4H), 6.72-6.62 (m, 4H), 6.57 (t, *J* = 2.0 Hz, 1H), 4.92 (s, 2H), 4.24 (t, *J* = 4.9 Hz, 2H), 4.12 (t, *J* = 5.0 Hz, 2H), 3.76 (q, *J* = 5.1, 4.2 Hz, 4H), 3.45 (dt, *J* = 11.7, 8.4 Hz, 2H), 3.32 (dddd, *J* = 23.3, 11.7, 8.6, 3.4 Hz, 4H), 3.16 (dddd, *J* = 19.6, 7.4, 6.0, 4.1 Hz, 3H), 2.93 (td, *J* = 12.4, 10.1 Hz, 2H), 2.81-2.55 (m, 10H), 2.44 (p, *J* = 8.2 Hz, 2H), 2.30 (q, *J* = 8.3 Hz, 1H), 2.09 (dp, *J* = 12.5, 3.8 Hz, 2H), 1.99 (ddt, *J* = 13.7, 7.1, 3.5 Hz, 1H), 1.74-1.63 (m, 2H), 1.61-1.50 (m, 1H).

Example 38 (Compound 117)

Preparation of (2S,2'S)-3,3'-((piperazine-1,4-diylbis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of benzyl 4-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)piperazine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (30 mg) and benzyl piperazine-1-carboxylate (15.6 mg) were dissolved in N,N-dimethylformamide (3 mL), cesium carbonate (42 mg) was added; the mixture was stirred for 3h at room temperature, quenched with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated to give the crude product, which was purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 2:1) to give the target product (30 mg). LCMS (ESI) $[M+H]^+$ = 608.1.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(piperazin-1-ylmethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

benzyl 4-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)piperazine-1-carboxylate (30 mg) and Pd/C (69.5 mg) were dissolved in methanol (5.0 mL), and the reaction mixture was replaced with hydrogen balloon three times and

stirred at room temperature overnight. The reaction mixture was filtered and concentrated to give the target compound (23 mg). LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+ = 418.3$.

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((piperazine-1,4-diylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

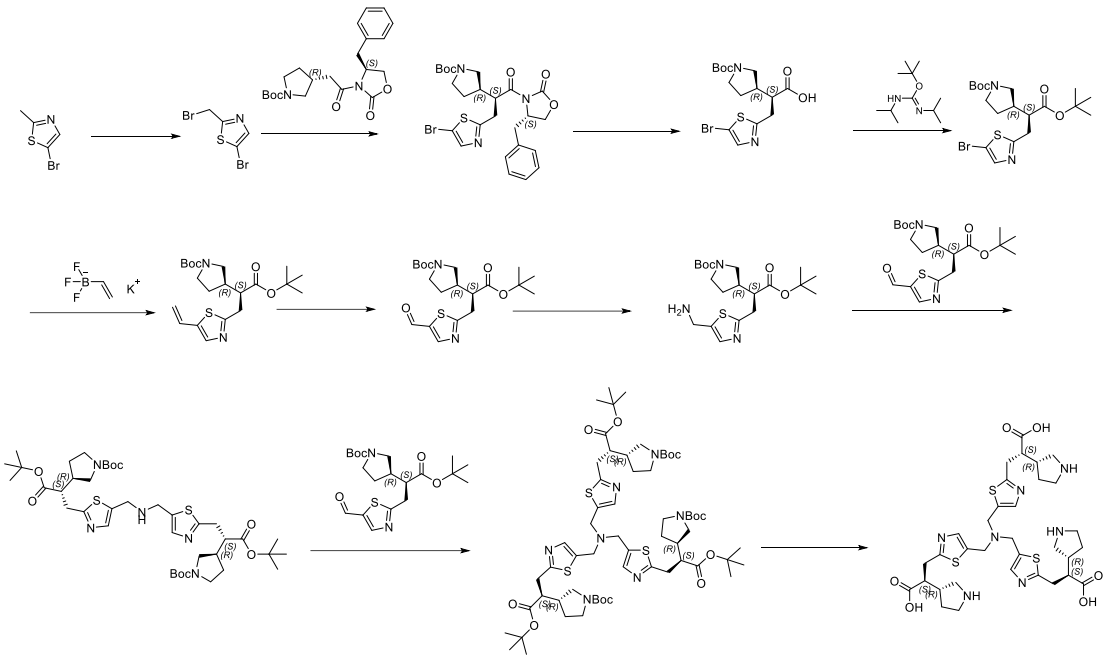
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(piperazin-1-ylmethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (23 mg), *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (26 mg) and cesium carbonate (32.8 mg) were dissolved in N,N-dimethylformamide (3.0 mL). The mixture was stirred overnight at room temperature, quenched with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 2:1) to give the target product (36 mg). LCMS (ESI) $[M+H]^+ = 861.1$.

Step 4: Preparation of (2S,2'S)-3,3'-((piperazine-1,4-diylbis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((piperazine-1,4-diylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (36 mg) was dissolved in dichloromethane (4 mL), and trifluoroacetic acid (47.9 mg) was added. The mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The reaction mixture was concentrated to give a crude product, which was purified by Prep-HPLC to give the target product (18 mg). LCMS(ESI)$(M+H)^+ = 549.0$; ^{1}H NMR (400 MHz, D_2O)δ7.28-7.21 (m, 2H), 7.15-7.09 (m, 6H), 3.49 (s, 4H), 3.46-3.41 (m, 2H), 3.36-3.3 (m, 3H), 3.2-3.13 (m,3H), 2.91-2.86 (m, 3H), 2.78-2.68 (m, 5H), 2.78-2.67 (m, 6H), 2.44-2.35 (m, 3H), 1.72-1.61 (m, 3H).

Example 39 (Compound 121)

Preparation of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(thiazole-5,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 5-bromo-2-(bromomethyl)thiazole

5-bromo-2-methylthiazole (4.5 g, 25.27 mmol, 1 eq) was dissolved in carbon tetrachloride (90 mL). Benzoyl peroxide (0.31 g, 1.26 mmol, 0.05 eq) and N-bromosuccinimide (4.95 g, 27.8 mmol, 1.1 eq) were added at room temperature. The reaction mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. The reaction mixture was filtered, and the filtrate was concentrated and purified by column chromatography (petroleum ether:ethyl acetate = 10:1) to give the target compound (2.7 g). LCMS (ESI) $[M+H]^+$ = 257.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 4.67 (s, 2H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (2.42 g, 6.22 mmol, 0.8 eq) was dissolved in anhydrous tetrahydrofuran (20 mL). Cooling to 0°C in an ice-water bath, lithium bis(trimethylsilyl)amide (11.67 mL, 11.67 mmol, 1.5 eq, 1.0 M) was added to the mixture, which was stirred at 0°C for 30min. A solution of 5-bromo-2-(bromomethyl)thiazole (2 g, 7.78 mmol, 1 eq) in tetrahydrofuran (10 mL) was added slowly at this temperature. After the addition was completed, the mixture was warmed gradually to room temperature and stirred for 16h. LCMS showed the reaction was completed. A saturated solution of ammonium chloride was added, and the mixture was extracted with ethyl acetate. The organic

phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was rotary-evaporated to dryness. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to give the target compound (1.0 g). LCMS (ESI) $[M+H]^+$ = 564.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.36-7.27 (m, 3H), 7.22-7.17 (m, 2H), 4.74-4.63 (m, 1H), 4.58-4.49 (m, 1H), 4.18-4.13 (m, 2H), 3.73-3.55 (m, 1H), 3.54-3.42 (m, 2H), 3.31-3.18 (m, 3H), 3.13-3.02 (m, 1H), 2.65-2.47 (m, 2H), 2.01-1.93 (m, 1H), 1.81-1.68 (m, 1H), 1.46 (s, 9H).

Step 3: Synthesis of (S)-3-(5-bromothiazol-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(6 g, 10.63 mmol, 1 eq) was dissolved in tetrahydrofuran (60 mL). The mixture was cooled to 0°C in an ice-water bath, and hydrogen peroxide (7.2 g, 212.58 mmol, 20 eq) was added; lithium hydroxide (509.13 mg, 21.26 mmol, 2 eq) was dissolved in water (20 mL) and the mixture was slowly added dropwise to the above reaction system. After the addition was completed, the mixture was warmed gradually to room temperature and stirred for 3h. LCMS showed the reaction was completed. A saturated solution of anhydrous sodium sulfite was added to quench the reaction. An aqueous solution of sodium hydroxide was added, and the mixture was extracted with ethyl acetate. The organic phase was discarded; the aqueous phase was adjusted to pH = 5 with an aqueous solution of hydrochloric acid (1 N). Ethyl acetate was added, and the mixture was extracted and separated. The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was rotary-evaporated to dryness to give the target compound (4 g). LCMS (ESI) $[M+H]^+$ = 405.1.

Step 4: *tert*-butyl (R)-3-((S)-3-(5-bromothiazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromothiazol-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid(4 g) was dissolved in anhydrous 2-methyltetrahydrofuran (40 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (4.23 g) was added at room temperature, and the reaction mixture was stired at 70°C for 3h. LCMS showed the reaction was completed. The reaction mixture was filtered, and the filter cake was washed with methyl *tert*-butyl ether. The filtrate was merged and evaporated to dryness to give the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (3.8 g). LCMS (ESI) $[M+H]^+$ =

461.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 3.69-3.44 (m, 2H), 3.32-3.21 (m, 2H), 3.09-2.97 (m, 2H), 2.80-2.71 (m, 1H), 2.44-2.32 (m, 1H), 2.01-1.93 (m, 1H), 1.77-1.66 (m, 1H), 1.46 (s, 9H), 1.40 (s, 9H).

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(5-vinylthiazol-2-yl)propan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(5-bromothiazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2 g) was dissolved in tetrahydrofuran (30 mL) and water (6 mL), potassium vinyltrifluoroborate (2.76 g), potassium phosphate (2.75 g) and $Pd(dppf)Cl_2$ (317.7 mg) were added at room temperature. The mixture was stirred at 80°C for 3h under nitrogen. LCMS showed the reaction was completed. The reaction mixture was diluted with water and extracted with ethyl acetate, the organic phase was dried, filtered, and the filtrate was rotary-evaporated to dryness. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (1.4 g). LCMS (ESI) $[M+H]^+$ = 409.2.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(5-vinylthiazol-2-yl)propan-2-yl)pyrrolidine-1-carboxylate (1.4 g, 3.43 mmol, 1 eq) was dissolved in dichloromethane (30 mL) and methanol (3 mL). Cooling to -70°C with a dry ice-acetone bath, sufficient oxygen was introduced into the reaction solution. Oxygen was converted to ozone using an ozone generator, and the mixture was stirred at -70°C for 10 min. TLC plate showed that the starting material was basically consumed. The reaction was quenched with dimethyl sulfide, and the mixture was rotary-evaporated to dryness. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (900 mg). LCMS (ESI) $[M+H]^+$ = 411.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.28 (s, 1H), 3.71-3.49 (m, 2H), 3.44-3.34 (m, 1H), 3.31-3.23 (m, 1H), 3.18-3.11 (m, 1H), 3.09-3.00 (m, 1H), 2.87-2.79 (m, 1H), 2.47-2.35 (m, 1H), 2.03-1.95 (m, 1H), 1.79-1.67 (m, 1H), 1.46 (s, 9H), 1.39 (s, 9H).

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-(aminomethyl)thiazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (300 mg, 0.73 mmol, 1 eq) was dissolved in ammonia methanol solution (6 mL, 7 M), glacial acetic acid (0.1 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 0.5h, and sodium cyanoborohydride (451.36 mg, 7.3 mmol, 10 eq) was added. The reaction mixture was heated to 80°C and stirred for 1h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness, and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 1/4) to give the target compound (150 mg). LCMS (ESI) $[M+H]^+$ = 412.2.

Step 8: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(thiazole-5,2-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(5-(aminomethyl)thiazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (150 mg, 0.36 mmol, 1 eq) was dissolved in isopropanol (2 mL). *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (295.58 mg, 0.72 mmol, 2 eq) and glacial acetic acid (0.05 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 2h, then sodium cyanoborohydride (225.35 mg, 3.64 mmol, 10 eq) was added. The reaction mixture was heated to 75°C and stirred for 16h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness, and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 1/4) to give the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 806.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (s, 2H), 3.80 (s, 4H), 3.56-3.45 (m, 3H), 3.20-3.10 (m, 5H), 2.98-2.92 (m, 2H), 2.71-2.63 (m, 3H), 2.35-2.22 (m, 3H), 1.90-1.81 (m, 2H), 1.66-1.58 (m, 2H), 1.39 (s, 18H), 1.32 (s, 18H).

Step 9: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(thiazole-5,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(thiazole-5,2-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (90 mg, 0.11 mmol, 1 eq) was dissolved in ethanol (3 mL), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (91.67 mg, 0.22 mmol, 2 eq) and glacial acetic acid (0.05 mL) were added at room temperature. The reaction mixture was stirred at room

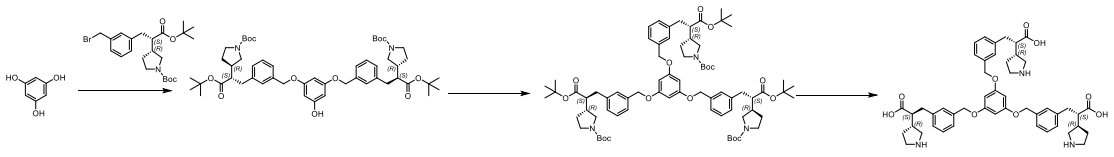
temperature for 8h, then sodium cyanoborohydride (69.03 mg, 1.12 mmol, 10 eq) was added, and the reaction mixture was heated to 75°C and stirred for 16h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness, and the crude product was purified by reversed-phase column chromatography (0.03% TFA in H_2O/ACN) to give the target compound (45 mg). LCMS (ESI) $[M/2+H]^+$ = 601.3; ^1H NMR (400 MHz, DMSO-d_6) δ 7.52 (s, 3H), 3.57 (s, 6H), 3.52-3.49 (m, 3H), 3.38-3.32 (m, 3H), 3.21-3.12 (m, 6H), 3.10-3.03 (m, 3H), 2.98-2.91 (m, 3H), 2.72-2.65 (m, 3H), 2.37-2.27 (m, 3H), 1.92-1.84 (m, 3H), 1.66-1.57 (m, 3H), 1.39 (s, 27H), 1.30 (s, 27H).

Step 10: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(thiazole-5,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(thiazole-5,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (45 mg, 0.04 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL). Hydrochloric acid/1,4-dioxane (2 mL, 4 M) solution was added at room temperature. The mixture was stirred at room temperature for 5h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness, and the crude product was purified by prep-HPLC (30 mmol NH_4HCO_3 in H_2O/ACN) to give the target compound (18.02 mg). LCMS (ESI) $[M+H]^+$ = 732.2; ^1H NMR (400 MHz, D_2O) δ 7.44 (s, 3H), 3.79 (s, 6H), 3.44-3.32 (m, 6H), 3.22-3.13 (m, 6H), 3.08-3.00 (m, 3H), 2.95-2.87 (m, 3H), 2.63-2.55 (m, 3H), 2.48-2.36 (m, 3H), 2.13-2.03 (m, 3H), 1.77-1.66 (m, 3H).

Example 40 (Compound 122)

Preparation of (2S,2'S,2''S)-3,3',3''-(((benzene-1,3,5-triyltris(oxy))tris(methylene))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((5-hydroxy-1,3-phenylene)bis(oxy))bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

benzene-1,3,5-triol (10 mg), *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (74.2 mg), and potassium carbonate (33 mg) were dissolved in DMF (5.0 mL). The reaction mixture was heated to 55°C and stirred for 48h. The reaction mixture was then quenched by the addition of water dropwise, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give a crude product, which was separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (20 mg). LCMS (ESI) $[M+H]^+$ = 901.1.

Step 2: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-(((benzene-1,3,5-triyltris(oxy))tris(methylene))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

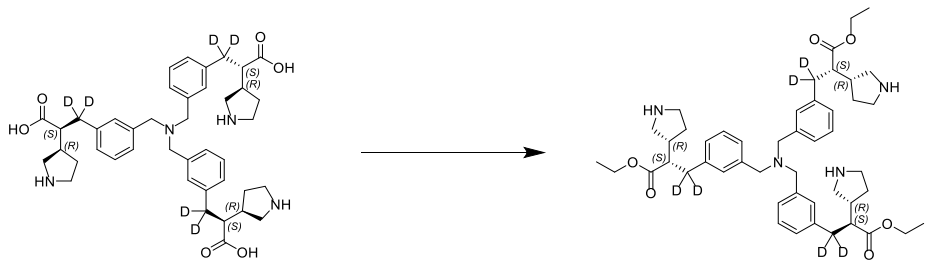
Di-*tert*-butyl 3,3'-((2S,2'S)-((((5-hydroxy-1,3-phenylene)bis(oxy))bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (20 mg), *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (11 mg) and potassium carbonate (9.1 mg) were dissolved in toluene (3.0 mL). The mixture was heated to 120°C under nitrogen protection and the reaction was maintained for 3h under microwave irradiation. LCMS showed the reaction was completed. The reaction mixture was concentrated and separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:1) to give the product (18 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1188.3.

Step 3: Synthesis of (2S,2'S,2''S)-3,3',3''-(((benzene-1,3,5-triyltris(oxy))tris(methylene))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-(((benzene-1,3,5-triyltris(oxy))tris(methylene))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (18 mg) was dissolved in dichloromethane (4 mL). Trifluoroacetic acid (16.0 mg) was added, and the mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The reaction mixture was concentrated to give a crude product, which was separated and purified by Prep-HPLC to give the target product (2 mg). LCMS(ESI)$(M+H)^+$ = 820.2; ^{1}H NMR (400 MHz, D_2O)δ7.31-6.98(m, 12H), 6.02 (s, 3H), 4.62 (s, 6H), 3.32-3.20 (m, 3H), 3.19-2.97 (m, 6H), 2.64 (dd,J = 22.0, 11.8 Hz, 6H), 2.46 (dd,J = 12.3, 4.0 Hz, 3H), 2.38-2.17 (m, 6H), 2.02-1.85 (m, 3H), 1.60 (td,J = 18.8, 10.7 Hz, 3H).

Example 41 (Compound 123)

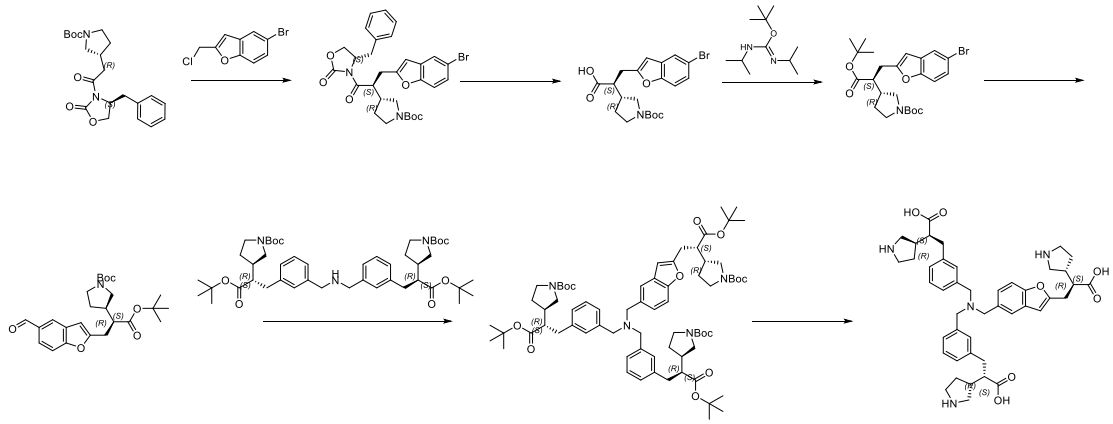
Preparation of triethyl 3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))(2S,2'S,2''S)-tris(2-((R)-pyrrolidin-3-yl)propanoate-3',3'-d_2)



(2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic-3,3-d2 acid) (92 mg, 0.128 mmol, 1 eq) was dissolved in ethanol (4 mL), and concentrated sulfuric acid (1 mL) was added. The mixture was stirred at 75°C overnight, and LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation to dryness, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the target compound (61 mg). LCMS (ESI) $[M+H]^+$ = 801.71; ^{1}H NMR (400 MHz, D_2O) δ 7.40-7.25 (m, 6H), 7.24-7.02 (m, 6H), 4.14 (s, 6H), 3.88-3.78 (m, 6H), 3.62-3.55 (m, 3H), 3.41-3.34 (m, 3H), 3.25-3.17 (m, 3H), 3.06-2.91 (m, 6H), 2.83-2.72 (m, 6H), 2.60-2.51 (m, 3H), 2.13-2.03 (m, 3H), 1.72-1.61 (m, 3H), 0.88 (t, J = 7.1 Hz, 9H).

Example 42 (Compound 126)

Preparation of (2S,2'S)-3,3'-(((((2-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzofuran-5-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzofuran-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection and ice bath, a solution of lithium bis(trimethylsilyl)amide (0.57 mL, 0.57 mmol, 1.1 eq, 1.0 M in THF) was added dropwise to *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (200 mg, 0.51 mmol, 1 eq) in tetrahydrofuran (5 mL). The mixture was stirred at 0°C for 30 min, and then a solution of 5-bromo-2-(chloromethyl)benzofuran (139 mg, 0.57 mmol, 1.1 eq) in tetrahydrofuran (1 mL) was added dropwise. The reaction temperature was slowly raised to room temperature and the mixture was stirred for 16h. The reaction mixture was cooled with an ice bath, and saturated aqueous ammonium chloride solution and water were added. The mixture was extracted with ethyl acetate, and the organic phase was washed with saturated aqueous sodium chloride solution, dried, filtered, and concentrated to give a crude product, which was purified by column chromatography to give the target compound (240 mg). LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+ = 541.19$.

Step 2: Synthesis of (S)-3-(5-bromobenzofuran-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

A solution of hydrogen peroxide (4 mL, 3.51 mmol, 1.5 eq, 0.88 M in H_2O) was added dropwise to a solution of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzofuran-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.4 g, 2.34 mmol, 1 eq) in tetrahydrofuran (30 mL), and the mixture was cooled in an ice bath. A solution of lithium hydroxide (84 mg, 3.51 mmol, 1.5 eq) in water (1 mL) was added. The reaction temperature was raised to room temperature and the mixture was stirred for 3h; LCMS showed the reaction was completed. The reaction mixture was cooled to 0°C, a solution of sodium bisulfite (1 g) in water (5 mL) and an aqueous solution of sodium hydroxide (5N) were added to raise the pH of the reaction mixture to >12. Water and methyl *tert*-butyl ether were added, the mixture was extracted and separated, and the organic phase was discarded. The hydrochloric acid solution (5N) was added into aqueous phase to adjust the pH to 3. The mixture was extracted with methyl *tert*-butyl ether, the organic phase was washed with water, saturated sodium chloride aqueous solution in turn, dried over anhydrous sodium sulfate, filtered and concentrated to give the target compound (0.8 g). LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+ = 382.16$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-bromobenzofuran-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromobenzofuran-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (870 mg, 1.98 mmol, 1 eq) was dissolved in 2-methyltetrahydrofuran (10 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (1983 mg, 9.9 mmol, 5 eq) was added, and the mixture was heated to 65°C and stirred for 16h under nitrogen protection. LCMS showed the reaction was completed. The insoluble matter was filtered, the filter cake was washed with methyl *tert*-butyl ether. The filtrate was concentrated, and separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (0.8 g). LCMS (ESI) $[M+H-2\times tert\text{-butyl}]^+ = 382.17$.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzofuran-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(5-bromobenzofuran-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (598 mg, 1.21 mmol, 1 eq) was dissolved in *N*,*N*-dimethylformamide (3 mL). Palladium acetate (54 mg, 0.24 mmol, 0.2 eq), 1,4-bis(diphenylphosphino)butane (103 mg, 0.24 mmol, 0.2 eq), N-formylsaccharin (638 mg, 3.02 mmol, 2.5 eq), sodium carbonate (320 mg, 3.02 mmol, 2.5 eq) and triethylsilane (211 mg, 1.81 mmol, 1.5 eq) were added; under nitrogen protection, the mixture was heated to 75°C and stirred for 16h. LCMS showed the reaction was completed. The insoluble matter was filtered, and the filter cake was washed with methyl *tert*-butyl ether. The filtrate was concentrated, and separated and purified by rapid column chromatography (Silica gel, PE:EA = 10:1) to give the target compound (0.3 g).LCMS (ESI) $[M+H\text{-Boc-}tert\text{-butyl}]^+ = 288.24$.

Step 5: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((2-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzofuran-5-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzofuran-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (30 mg, 0.07 mmol, 1 eq) and di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (55 mg, 0.07 mmol, 1 eq) were dissolved in

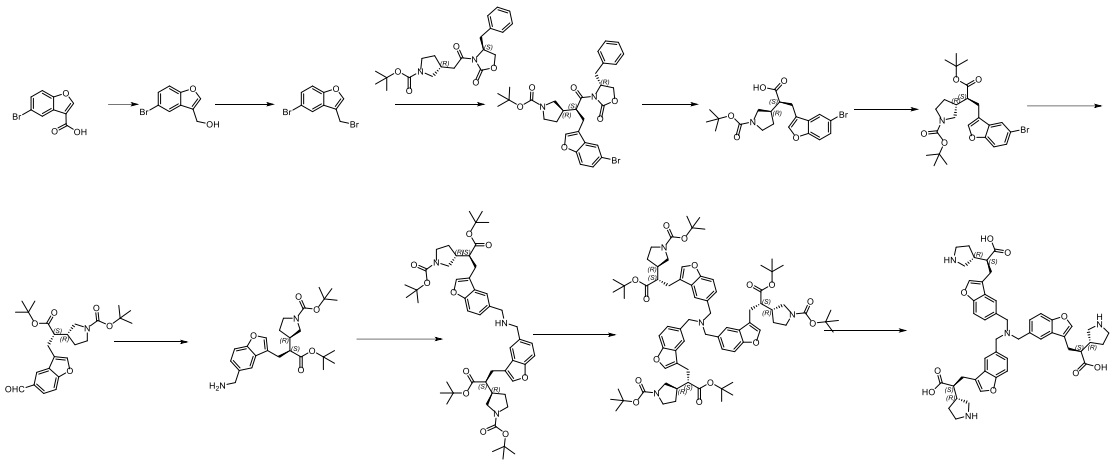
tetrahydrofuran, sodium cyanoborohydride (8 mg) and a drop of acetic acid was added. The mixture was stirred overnight at room temperature. LCMS showed the reaction was completed. The reaction was quenched with saturated ammonium chloride solution, the mixture was extracted and separated with ethyl acetate and water, and the organic phase was dried over anhydrous sodium sulfate and concentrated to give a crude product, which was purified by column chromatography to give the target compound (48 mg). LCMS(ESI) $[(M+H\text{-}Boc)/2]^+ = 560.66$.

Step 6: Synthesis of (2S,2'S)-3,3'-(((((2-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzofuran-5-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-(((((2-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzofuran-5-yl)methyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (35 mg, 0.03 mmol, 1 eq) was dissolved in 1,4-dioxane (1 mL), hydrochloric acid/1,4-dioxane (4 M, 1 mL) was added. The mixture was stirred at room temperature overnight, and LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation to dryness, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the target compound (12 mg). LCMS (ESI) $[M+H]^+ = 751.60$; ^1H NMR (400 MHz, D_2O) δ 7.44 (s, 1H), 7.41-7.36 (m, 1H), 7.28-7.22 (m, 2H), 7.19-7.07 (m, 7H), 6.50 (s, 1H), 3.81-3.54 (m, 6H), 3.49-3.28 (m, 6H), 3.25-3.07 (m, 3H), 2.98-2.58 (m, 10H), 2.48-2.32 (m, 5H), 2.13-1.98 (m, 3H), 1.75-1.59 (m, 3H).

Example 43 (Compound 127)

Preparation of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzofuran-5,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of (5-bromobenzofuran-3-yl)methanol

5-bromobenzofuran-3-carboxylic acid (2 g, 8.3 mmol, 1 eq) was dissolved in tetrahydrofuran (30 mL). Under ice bath, borane/tetrahydrofuran solution (12.45 mL, 12.45 mmol, 1 M, 1.5 eq) was added dropwise. After the addition, the mixture was slowly warmed to room temperature and stirred for 12h; TLC (petroleum ether/ethyl acetate = 3/1) showed the reaction of starting material was completed. The reaction mixture was quenched with methanol, and the solvent was removed by rotary-evaporation and concentration. The residue was purified by column chromatography (ethyl acetate/petroleum ether = 0-30%) to give the target compound (1.5 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 2.1 Hz, 1H), 7.53 (dt, J = 8.7, 0.7 Hz, 1H), 7.41 (dd, J = 8.7, 2.1 Hz, 1H), 6.75 (q, J = 0.9 Hz, 1H), 5.53 (t, J = 5.9 Hz, 1H), 4.57 (dd, J = 5.9, 0.9 Hz, 2H).

Step 2: Preparation of 5-bromo-3-(bromomethyl)benzofuran

(5-bromobenzofuran-3-yl)methanol (1 g, 4.4 mmol, 1 eq) was dissolved in tetrahydrofuran (20 mL). Phosphorus tribromide (1.19 g, 4.4 mmol, 1 eq) was added in batches under ice bath. After the addition, the mixture was warmed to room temperature and stirred for 2h; TLC (petroleum ether/ethyl acetate) = 6/1 showed the reaction of starting material was completed. The reaction mixture was concentrated to remove the solvent, and the residue was purified by column chromatography (ethyl acetate/petroleum ether = 0-10%) to give the target compound (1.2 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.49 (dd, J = 9.1, 2.5 Hz, 1H), 7.02 (s, 1H), 4.92 (s, 2H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzofuran-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (2.41 g, 6.21 mmol, 1.2 eq) was dissolved in tetrahydrofuran (25 mL), lithium bis(trimethylsilyl)amide (7.24 mL, 7.24 mmol, 1.4 eq, 1.0 M) was added dropwise under ice bath. After the addition, the mixture was stirred under ice bath for 0.5h, and then a solution of 5-bromo-3-(bromomethyl)benzofuran (1.5 g, 5.17 mmol, 1 eq) in tetrahydrofuran (15 mL) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The reaction mixture was quenched with an ice-cold saturated ammonium chloride solution, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by column chromatography (ethyl acetate/petroleum ether = 0-50%) to give the target compound (2.1 g).LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+$ = 541.1.

Step 4: Synthesis of (S)-3-(5-bromobenzofuran-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzofuran-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2.1 g, 3.51 mmol, 1 eq) was dissolved in tetrahydrofuran (30 mL), and hydrogen peroxide solution (239.07 mg, 7.03 mmol, 2 eq, 30% content) was added under ice bath, and the mixture was stirred for 5min after the addition, and then an aqueous solution (3 mL) of lithium hydroxide (126.26 mg, 5.27 mmol, 1.5 eq) was added dropwise. After the addition, the mixture was slowly warmed to room temperature and stirred for 2h. LCMS showed the reaction was completed. Potassium bisulfate solution was added to quench the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the target compound (2 g, crude product). LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+$ = 382.0.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-bromobenzofuran-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromobenzofuran-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (2 g, 4.56 mmol, 1 eq) and *tert*-butyl N,N'-diisopropylcarbamimidate (4.57 g, 22.81 mmol, 5 eq) were dissolved in 2-methyltetrahydrofuran (40 mL), and the mixture was heated to 65°C and

stirred overnight. LCMS showed the reaction of starting material was completed. The mixture was filtered, washed with 2-methyltetrahydrofuran, and the filtrate was concentrated to give a crude product, which was separated by column chromatography (ethyl acetate/petroleum ether = 0-30%) to give the target compound (1.1 g). LCMS (ESI) $[M+H\text{-}tert\text{-butylx2}]^+$ = 382.0.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzofuran-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(5-bromobenzofuran-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.1 g, 2.22 mmol, 1 eq), 1,4-bis(diphenylphosphino)butane (189.76 mg, 0.44 mmol, 0.2 eq), sodium carbonate (589.52 mg, 5.56 mmol, 2.5 eq), N-formylsaccharin (1.41 g, 6.67 mmol, 3 eq), triethylsilane (388.05 mg, 1.5 eq) and palladium acetate (99.9 mg, 0.44 mmol, 0.2 eq) were added to N,N-dimethylformamide (30 mL). Under nitrogen protection, the mixture was heated to 75°C and stirred for 12h. LCMS showed the reaction of starting material was completed. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with saturated brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated to give a crude product, which was then separated by column chromatography (ethyl acetate/petroleum ether = 0-60%) to give the target compound (700 mg).LCMS (ESI) $[M+H\text{-Boc-}tert\text{-butyl}]^+$ = 288.0.

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-(aminomethyl)benzofuran-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzofuran-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (150 mg, 0.34 mmol, 1 eq) was added to a solution of ammonia in methanol (7 M, 3 mL), and an appropriate amount of 4A molecular sieve was added. The mixture was stirred at room temperature for 40 min, and sodium cyanoborohydride (146.37 mg, 2.37 mmol, 7 eq) was added to the reaction system. The reaction was heated at 70°C by microwave for 1h. LCMS showed the reaction of starting material was completed. The solvent was removed by rotary-evaporation, and the residue was separated by column chromatography (methanol/dichloromethane = 0-10%) to give the target compound (70 mg). LCMS (ESI) $[M+H]^+$ = 445.38.

Step 8: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(benzofuran-5,3-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(5-(aminomethyl)benzofuran-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (70 mg, 0.16 mmol, 1 eq) and *tert*-butyl (R)-3-((S)-1-(5-formylbenzofuran-3-yl)-4,4-dimethyl-3-oxopentan-2-yl)pyrrolidine-1-carboxylate (106.45 mg, 0.24 mmol, 1.5 eq) were dissolved in tetrahydrofuran (5 mL), a drop of acetic acid was added dropwise, and the mixture was stirred at room temperature for 2h. sodium cyanoborohydride (19.79 mg, 0.32 mmol, 2 eq) was added, and the mixture was stirred for another 12h. LCMS showed the reaction of starting material was completed. The solvent was removed by rotary-evaporation, and the residue was separated by column chromatography (methanol/dichloromethane = 0-10%) to give the target compound (150 mg, crude). LCMS (ESI) $[M+H]^+$ = 872.1.

Step 9: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzofuran-5,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(benzofuran-5,3-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (150 mg, 0.17 mmol, 1 eq) and *tert*-butyl (R)-3-((S)-1-(5-formylbenzofuran-3-yl)-4,4-dimethyl-3-oxopentan-2-yl)pyrrolidine-1-carboxylate (114.43 mg, 0.26 mmol, 1.5 eq) were dissolved in tetrahydrofuran (8 mL). One drop of acetic acid was added dropwise, and the mixture was stirred at room temperature for 2h. sodium cyanoborohydride (21.27 mg, 0.34 mmol, 2 eq) was added. The mixture was stirred at room temperature for 12h. LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation, and the residue was separated by column chromatography (methanol/dichloromethane = 0-10%) to give the target compound (150 mg). LCMS (ESI) $[M+H]^+$ = 1299.2.

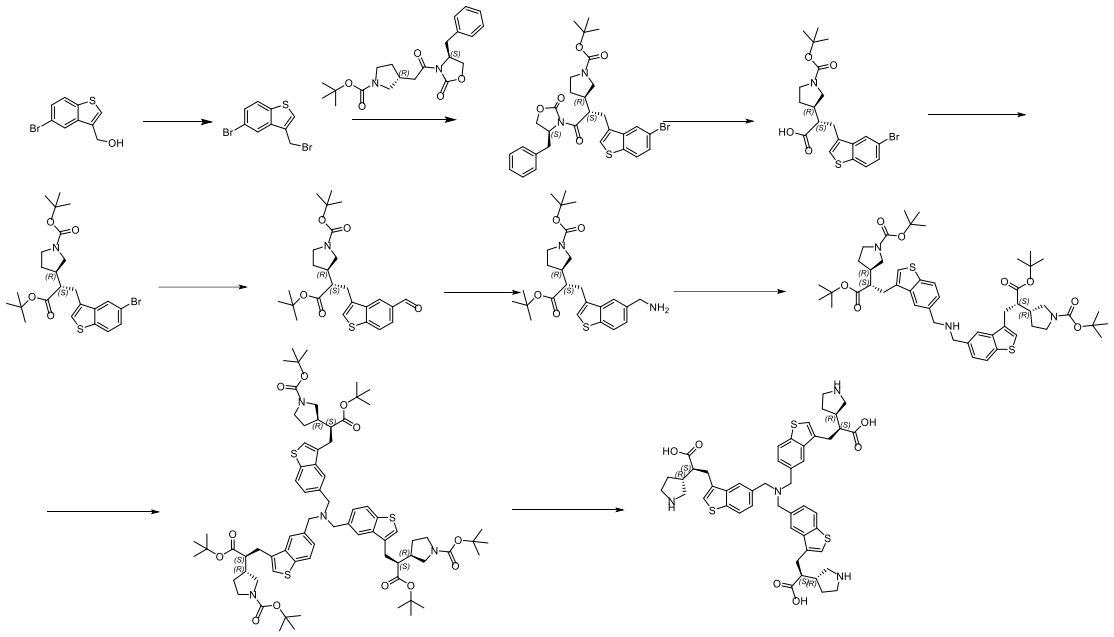
Step 10: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzofuran-5,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzofuran-5,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (100 mg, 0.08 mmol, 1 eq) was dissolved in dichloromethane (5 mL), and trifluoroacetic acid (91.22 mg, 0.8 mmol, 10 eq) was added dropwise. After the addition, the mixture was stirred at room temperature for 12h. LCMS showed the reaction of starting material was completed. The

solvent was removed by rotary-evaporation, and the residue was dissolved in acetonitrile, filtered, and the filtrate was separated and purified by Prep-HPLC (C_{18}, 0.1%FA in water, MeCN) to give the target compound (7.02 mg). LCMS (ESI) $[M+H]^+$ = 831.1; ^{1}H NMR (400 MHz, D_2O) δ 6.99 (s, 6H), 6.68 (s, 3H), 6.06 (s, 3H), 3.10 (s, 6H), 2.75 (d, J = 71.9 Hz, 11H), 2.45 (s, 4H), 2.24 (s, 5H), 1.96 (s, 3H), 1.71 (s, 4H), 1.44 (s, 3H).

Example 44 (Compound 128)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(benzo[b]thiophene-5,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 5-bromo-3-(bromomethyl)benzo[b]thiophene

(5-bromobenzo[b]thiophen-3-yl)methanol(900 mg, 3.7 mmol, 1 eq) was dissolved in tetrahydrofuran (10 mL). Phosphorus tribromide (1.0 g, 3.7 mmol, 1 eq) was added in batches under ice bath. After the addition, the mixture was slowly warmed to room temperature and stirred for 2h. TLC (petroleum ether/ethyl acetate) = 8/1 showed the reaction of starting material was completed. The reaction mixture was concentrated to give a crude product, which was purified by column chromatography (ethyl acetate/petroleum ether = 0-10%) to give the target compound (1 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.58 (dd, J = 8.5, 2.0 Hz, 1H), 5.04 (s, 2H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzo[b]thiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate(1.42 g, 3.65 mmol, 1.2 eq) was dissolved in tetrahydrofuran (25 mL), lithium bis(trimethylsilyl)amide (711.93 mg, 4.25 mmol, 1 M, 1.4 eq) was added dropwise under ice bath. After the addition, the mixture was stirred under ice bath for 30min. A solution of 5-bromo-3-(bromomethyl)benzo[b]thiophene (930 mg, 3.04 mmol, 1 eq) in tetrahydrofuran (15 mL) was slowly added to the reaction mixture. The temperature of the reaction system was slowly warmed to room temperature and the mixture was stirred for 2h; LCMS showed the reaction of starting material was completed. The reaction mixture was completely quenched with a saturated ammonium chloride ice water solution, extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give a crude product, which was purified by column chromatography (ethyl acetate/petroleum ether = 0-30%) to give the target compound (1.3 g).LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+$ = 557.1

Step 3: Synthesis of (S)-3-(5-bromobenzo[b]thiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromobenzo[b]thiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.2 g, 1.96 mmol, 1 eq) was dissolved in tetrahydrofuran (40 mL), a hydrogen peroxide solution (119.73 mg, 3.52 mmol, 1.8 eq, 30% content) was added dropwise under ice bath, followed by dropwise addition of a solution of lithium hydroxide (70.26 mg, 2.93 mmol, 1.5 eq) in water (10 mL). After the addition, the mixture was continually stirred for 2h. LCMS showed the reaction of starting material was completed. The reaction mixture was quenched with a potassium bisulfate solution, extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (1.2 g, crude product).LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+$ = 398.0.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-bromobenzo[b]thiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromobenzo[b]thiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (1.2 g, 2.64 mmol, 1 eq) was dissolved in 2-methyltetrahydrofuran (30 mL), and

tert-butyl N,N'-diisopropylcarbamimidate (2.12 g, 10.56 mmol, 4 eq) was added; under nitrogen, the reaction mixture was heated to 65°C and stirred for 12h. LCMS showed the reaction of starting material was completed, the solvent was removed by concentration, and the residue was purified by column chromatography (ethyl acetate/petroleum ether = 0-30%) to give the target compound (500 mg). LCMS (ESI) $[M+H-tert\text{-butyl}*2]^+ = 398.0$.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(5-bromobenzo[b]thiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (500 mg, 0.98 mmol, 1 eq), 1,4-bis(diphenylphosphino)butane (83.54 mg, 0.2 mmol, 0.2 eq), sodium carbonate (259.54 mg, 2.45 mmol, 2.5 eq), N-formylsaccharin (827.42 mg, 3.92 mmol, 4 eq), triethylsilane (170.84 mg, 1.47 mmol, 1.5 eq) and palladium acetate (43.98 mg, 0.2 mmol, 0.2 eq) were added to N,N-dimethylformamide (15 mL), under nitrogen, the mixture was heated to 75°C and stirred for 12h; LCMS showed the reaction of starting material was completed. The reaction mixture was poured into water, extracted with ethyl acetate and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give a crude product, which was purified by column chromatography (ethyl acetate/petroleum ether = 0-70%) to give the target compound (170 mg). LCMS (ESI) $[M+H-Boc]^+ = 360.0$.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-(aminomethyl)benzo[b]thiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (60 mg, 0.13 mmol, 1 eq) was added to ammonia methanol solution (2 mL, 7 M) with an appropriate amount of 4A molecular sieve, and the mixture was stirred at room temperature for 40 min. sodium cyanoborohydride (56.5 mg, 0.91 mmol, 7 eq) was added. The reaction was carried out under microwave irradiation at 70°C for 1h. LCMS showed the reaction of starting material was completed. The reaction mixture was concentrated to give a crude product, which was purified by column chromatography (methanol/dichloromethane = 0-10%) to give the target compound (35 mg). LCMS (ESI) $[M+H]^+ = 461.0$.

Step 7: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(benzo[b]thiophene-5,3-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(5-(aminomethyl)benzo[b]thiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (30 mg, 0.07 mmol, 1 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (48.26 mg, 0.11 mmol, 1.5 eq) were dissolved in tetrahydrofuran (3 mL), and a drop of acetic acid was added dropwise. The reaction mixture was stirred at room temperature for 2h. sodium cyanoborohydride (8.66 mg, 0.14 mmol, 2 eq) was added, and the mixture was stirred for 12h; LCMS showed the reaction of starting material was completed. The reaction mixture was concentrated to give a crude product, which was purified by column chromatography (methanol/dichloromethane = 0-10%) to give the target compound (40 mg). LCMS (ESI) $[M+H]^+$ = 904.1.

Step 8: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-5,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(benzo[b]thiophene-5,3-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (40 mg, 0.04 mmol, 1 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylbenzo[b]thiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (30.5 mg, 0.07 mmol, 1.5 eq) were dissolved in tetrahydrofuran (4 mL), a drop of acetic acid was added dropwise, and the reaction mixture was stirred at room temperature for 2h. sodium cyanoborohydride (4.1 mg, 0.07 mmol, 1.5 eq) was added, and the mixture was stirred for 12h; LCMS showed the reaction of starting material was completed. The reaction mixture was concentrated to remove the solvent and give a crude product, which was purified by column chromatography (methanol/dichloromethane = 0-10%) to give the target compound (20 mg). LCMS (ESI) $[M+H]^+$ = 1347.1.

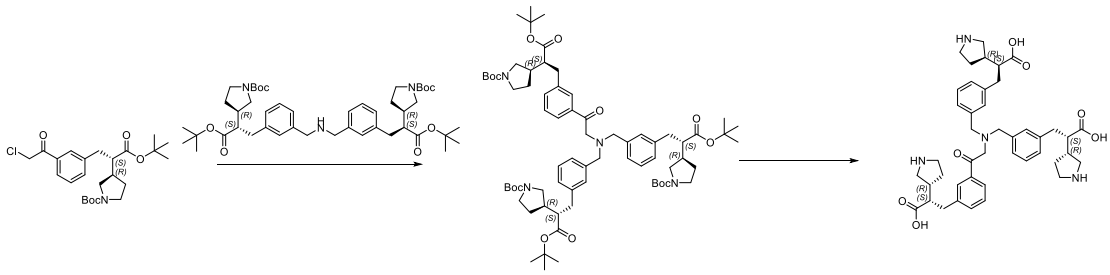
Step 9: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzo[b]thiophene-5,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[b]thiophene-5,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

(20 mg, 0.01mmol) was dissolved in dichloromethane (5 mL), and trifluoroacetic acid (11.4 mg, 0.1 mmol, 10 eq) was added dropwise. After the addition, the reaction mixture was stirred at room temperature for 12h. LCMS showed the reaction of starting material was completed. The reaction mixture was concentrated to remove the solvent, and the residue was dissolved in acetonitrile, filtered, and separated and purified by Prep-HPLC (C_{18}, 0.1%FA in water, MeCN) to give the target compound (1.64 mg). LCMS (ESI) $[M+H]^+$ = 879.0; ^1H NMR (400 MHz, D_2O) δ 8.16-7.57 (m, 3H), 7.53-6.56 (m, 9H), 3.41-2.70 (m, 15H), 2.56-1.95 (m, 12H), 1.93-1.33 (m, 9H).

Example 45 (Compound 130)

Preparation of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)-2-oxoethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)-2-oxoethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

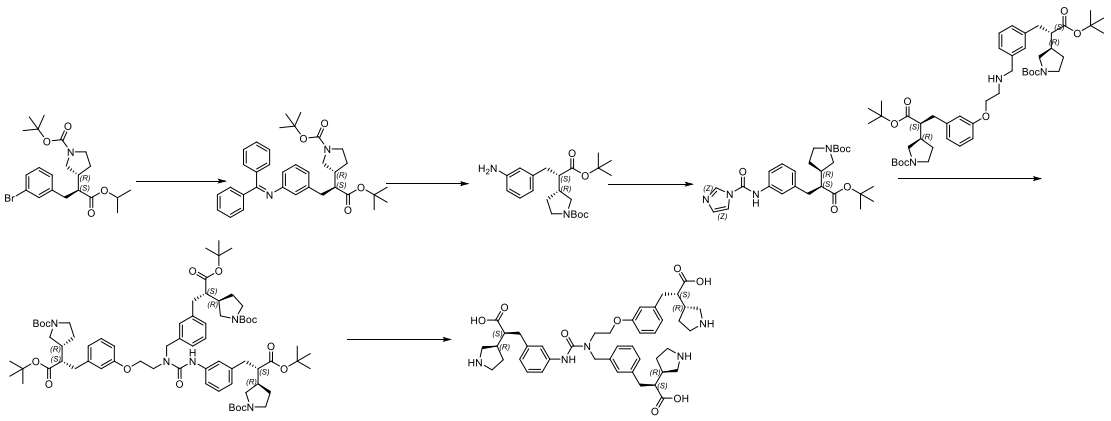
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-chloroacetyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(120 mg, 0.27 mmol, 1.0 eq) was dissolved in DMF (5 mL), followed by adding di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (252.35 mg, 0.32 mmol, 1.2 eq) and potassium carbonate (110 mg, 0.8 mmol, 3.0 eq). The mixture was stirred at 105°C for 24h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 1207.2.

Step 2: Synthesis of (2S,2'S)-3,3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)-2-oxoethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Di-*tert*-butyl 3,3'-((2S,2'S)-((((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)-2-oxoethyl)azanediyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (100 mg, 0.08mmol) was dissolved in hydrochloric acid/1,4-dioxane (2 mL), and the mixture was stirred at room temperature for 36h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and separated and purified by preparative chromatography to give the target compound (45.78 mg).LCMS (ESI) $[M+H]^+$ = 739.1; 1H NMR (400 MHz, Deuterium oxide) δ 7.52-7.38 (m, 3H), 7.31 (t, J = 7.7 Hz, 1H), 7.21 (t, J = 7.4 Hz, 2H), 7.14-7.05 (m, 5H), 3.83 (d, J = 5.3 Hz, 2H), 3.70 (d, J = 5.0 Hz, 3H), 3.55-3.02 (m, 10H), 3.01-2.62 (m, 8H), 2.61-2.52 (m, 2H), 2.45-2.27 (m, 6H), 2.03 (dt, J = 6.5, 3.6 Hz, 3H), 1.71-1.58 (m, 3H).

Example 46 (Compound 131)

Preparation of (S)-3-(3-(3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)-3-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)ureido)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((diphenylmethylene)amino)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-isopropoxy-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(150 mg, 0.34 mmol, 1 eq), sodium *tert*-butoxide (50 mg, 0.51 mmol, 1.5 eq), 1,1'-binaphthalene-2,2'-bis(diphenylphosphine) (15 mg, 0.02 mmol, 0.07 eq) and tris(dibenzylideneacetone)dipalladium(0) (9 mg, 0.01 mmol, 0.03 eq) were added in 1,4-dioxane (2 mL), followed by adding benzophenone imine (75 mg, 0.41 mmol, 1.2 eq). The reaction mixture was stirred at 90°C for 4h under nitrogen. LCMS showed the reaction of starting material was completed. The reaction mixture was cooled to room temperature and extracted with ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by column chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (162 mg). LCMS (ESI) $[M+H]^+$ = 555.50.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-aminophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the first step (400 mg, 0.72 mmol, 1 eq) was dissolved in THF (10 mL), and citric acid (276 mg, 1.44 mmol, 2 eq) was added. The mixture was stirred overnight at room temperature, and LCMS showed the reaction was completed. The reaction mixture was concentrated and purified by column chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to give the target product (250 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 291.0.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(1H-imidazole-1-carboxamido)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the second step (15 mg, 0.04 mmol, 1 eq) and N,N'-carbonyldiimidazole (6.85 mg, 0.044 mmol, 1.1 eq) were dissolved in DCM (0.5 mL), and then triethylamine (7.77 mg, 0.08 mmol, 2 eq) was added. The mixture was stirred at room temperature for 2h, and LCMS showed the reaction of starting material was completed. The solvent was removed to dryness, and the crude product was directly used in the next step.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((1-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)ureido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

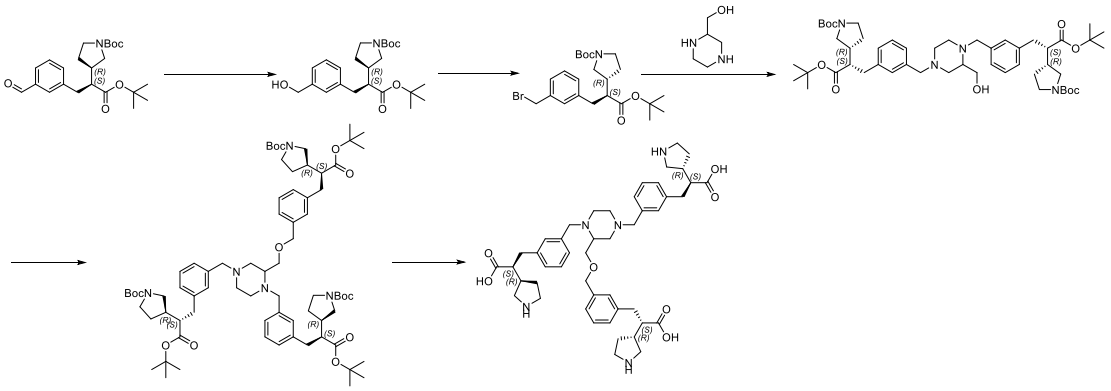
The product from the third step (45 mg, 0.09 mmol, 1 eq), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(75 mg, 0.09 mmol, 1 eq) was dissolved in THF (1 mL), and triethylamine (18 mg, 0.18 mmol, 2 eq) was added. The mixture was stirred overnight at room temperature, and LCMS showed the reaction was completed. Ethyl acetate and water were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to give the target product (60 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1138.95.

Step 5: Synthesis of (S)-3-(3-(3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)-3-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)ureido)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the fourth step (90 mg, 0.07 mmol, 1 eq) was dissolved in dioxane (2 mL), and hydrochloric acid/1,4-dioxane (2 mL, 4.0 M) was added in ice bath; the mixture was stirred at room temperature for 24h. LCMS showed the reaction was completed. The solvent was removed to dryness, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the target compound (10.7 mg). LCMS (ESI) $[M+H]^+$ = 770.64; ^{1}H NMR (400 MHz, D_2O) δ 7.40-7.25 (m, 6H), 7.24-7.02 (m, 6H), 4.14 (s, 6H), 3.88-3.78 (m, 6H), 3.62-3.55 (m, 3H), 3.41-3.34 (m, 3H), 3.25-3.17 (m, 3H), 3.06-2.91 (m, 6H), 2.83-2.72 (m, 6H), 2.60-2.51 (m, 3H), 2.13-2.03 (m, 3H), 1.72-1.61 (m, 3H), 0.88 (t, J = 7.1 Hz, 9H).

Example 47 (Compound 132)

Preparation of (2S,2'S)-3,3'-(((2-(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)methyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(hydroxymethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2 g, 4.96 mmol, 1 eq) was dissolved in methanol (20 mL), and sodium borohydride (0.56 g, 14.87 mmol, 3 eq) was added. The reaction mixture was stirred at 0°C for 1h. After the reaction was completed, water (40 mL) was added to quench the reaction mixture, followed by extraction with ethyl acetate (30mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (1.8 g). LCMS (ESI) $[M+Na]^+$ = 428.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (t, J = 7.7 Hz, 1H), 7.15-7.10 (m, 2H), 7.03 (d, J = 7.4 Hz, 1H), 5.13 (t, J = 5.6 Hz, 1H), 4.45 (d, J = 5.4 Hz, 2H), 3.57-3.42 (m, 1H), 3.39-3.32 (m, 1H), 3.20-3.08 (m, 1H), 2.98 (t, J = 9.7 Hz, 1H), 2.80-2.68 (m, 2H), 2.48-2.41 (m, 1H), 2.34-2.20 (m, 1H), 1.88-1.78 (m, 1H), 1.64-1.51 (m, 1H), 1.40 (s, 9H), 1.24 (s, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from first step (2.2 g, 5.42 mmol, 1 eq) was dissolved in dichloromethane (30 mL), and triphenylphosphine (2.14 g, 8.14 mmol, 1.5 eq) and carbon tetrabromide (2.7 g, 8.14 mmol, 1.5 eq) were added at 0°C; the reaction mixture was stirred at 0°C for 1h under nitrogen protection. After the reaction was completed, water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated, and the crude product was purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give the target compound (1.7 g). LCMS (ESI) $[M+Na]^+$ = 490.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29-7.24 (m, 3H), 7.17-7.10 (m, 1H), 4.65 (s, 2H),

3.57-3.48 (m, 1H), 3.39-3.32 (m, 2H), 3.19-3.10 (m, 1H), 2.99 (t, *J* = 10.0 Hz, 1H), 2.78-2.66 (m, 2H), 2.34-2.24 (m, 1H), 1.89-1.79 (m, 1H), 1.63-1.54 (m, 1H), 1.40 (s, 9H), 1.22 (s, 9H).

Step 3: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((2-(hydroxymethyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

Piperazin-2-ylmethanol(40 mg, 0.34 mmol, 1 eq) was dissolved in acetonitrile (3 mL), and the product from the second step (477.79 mg, 1.02 mmol, 3 eq) and *N,N*-diisopropylethylamine (0.16 mL, 1.02 mmol, 3 eq) were added; the mixture was stirred at 70°C for 18h under nitrogen. The reaction mixture was concentrated to give a crude product, which was separated and purified by rapid chromatography (Silica gel, tetrahydrofuran:petroleum ether = 1:1) to give the target compound (120 mg). LCMS (ESI) $[M+H]^+$ = 891.4.

Step 4: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((2-(((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)oxy)methyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (63.07 mg, 0.13 mmol, 1.5 eq) was dissolved in dichloromethane (5 mL), and silver oxide (16.64 mg, 0.07 mmol, 0.8 eq), tetrabutylammonium iodide (16.58 mg, 0.04 mmol, 0.5 eq) and the product from the third step (80 mg, 0.09 mmol, 1 eq) were added; the mixture was stirred at 25°C for 18h under nitrogen protection. The reaction mixture was filtered, concentrated, and purified by TLC silica gel plate (ethyl acetate:petroleum ether = 1:1) to give the target product (35 mg). LCMS (ESI) $[M+H]^+$ = 1279.0.

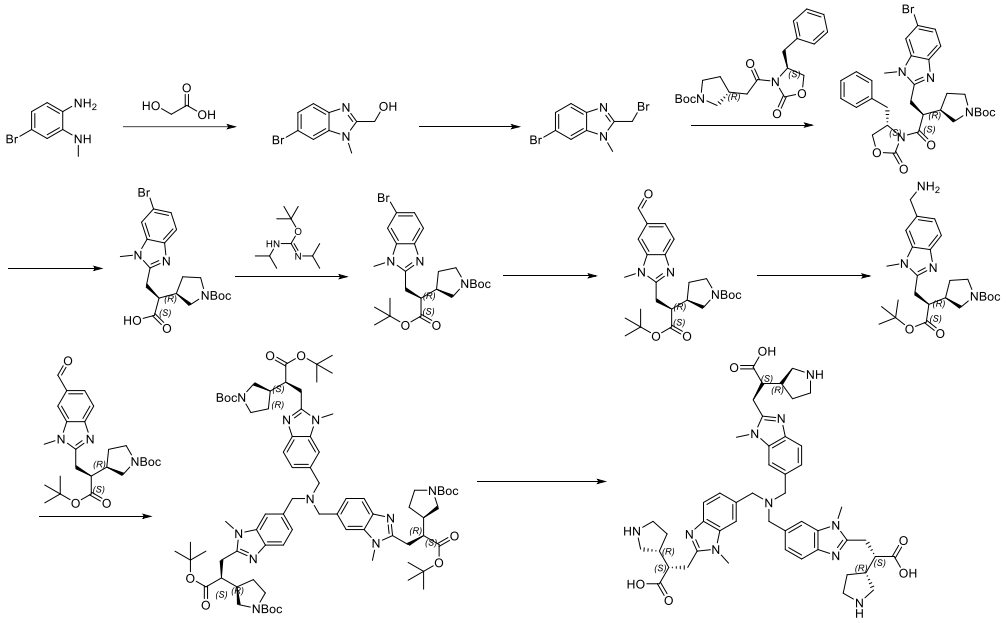
Step 5: Synthesis of (2S,2'S)-3,3'-(((2-(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)methyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

The product from the fourth step (30 mg, 0.02 mmol, 1 eq) was dissolved in dioxane (1 mL), and hydrochloric acid/1,4-dioxane (1 mL, 4 M) was added; the mixture was stirred at 25°C for 3h under nitrogen. The reaction mixture was concentrated and purified by reversed-phase preparation (acetonitrile/ammonium bicarbonate system) to give the target compound (2.12 mg).

LCMS (ESI) $[M+H]^+$ = 810.4; ^1H NMR (400 MHz, D_2O) δ 7.28-7.20 (m, 3H), 7.16-7.09 (m, 7H), 7.07-7.01 (m, 2H), 4.46 (s, 2H), 3.96 (t, *J* = 13.0 Hz, 1H), 3.79-3.66 (m, 1H), 3.57-3.50 (m, 1H), 3.50-3.43 (m, 2H), 3.42-3.26 (m, 6H), 3.20-3.09 (m, 4H), 2.90-2.80 (m, 3H), 2.80-2.59 (m, 10H), 2.59-2.52 (m, 1H), 2.43-2.31 (m, 6H), 2.19-2.09 (m, 2H), 2.06-1.99 (m, 3H), 1.71-1.58 (m, 3H).

Example 48 (Compound 133)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(1-methyl-1H-benzo[d]imidazole-6,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid):



Step 1: Synthesis of (6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)methanol

5-bromo-N1-methylbenzene-1,2-diamine(25 g, 124.34 mmol, 1.0 eq) was dissolved in water (160 mL), hydrochloric acid (110 mL, 6 M) and 2-hydroxyacetic acid(47.28 g, 621.7 mmol, 5.0 eq) were added. The reaction mixture was stirred at 100°C for 2h. After the reaction was completed, the mixture was cooled to room temperature and adjusted to pH = 9 with ammonia water. The mixture was filtered, and the filter cake was washed with water and dried to give the target compound (22 g). LCMS (ESI) $[M+H]^+$ = 241.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 1.7 Hz, 1H), 7.35 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.87 (s, 2H), 3.78 (s, 3H).

Step 2: Synthesis of 6-bromo-2-(bromomethyl)-1-methyl-1H-benzo[d]imidazole

(6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)methanol (22 g, 91.26 mmol, 1.0 eq) was dissolved in dichloromethane (500 mL), and phosphorus tribromide (247.02 g, 912.56 mmol, 10.0 eq) was slowly added in batches under ice bath; the reaction mixture was reacted at room temperature for 16h. The reaction system was poured into water to quench, and the pH was adjusted to 9 with aqueous sodium carbonate solution. Dichloromethane (1 L) was added for extraction and separation, the organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give the target compound (22 g). LCMS (ESI) $[M+H]^+$ = 302.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.6 Hz, 1H), 7.48 (s, 1H), 7.37 (dd, *J* = 8.6, 1.1 Hz, 1H), 4.65 (s, 2H), 3.79 (s, 3H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate(5.0 g, 12.87 mmol, 1 eq) was dissolved in tetrahydrofuran (70 mL), and lithium bis(trimethylsilyl)amide (18.02 mL, 18.02 mmol, 1.4 eq) was added dropwise at 0°C under nitrogen protection, and the mixture was stirred at 0°C for 1h; 6-bromo-2-(bromomethyl)-1-methyl-1H-benzo[d]imidazole (5.87 g, 19.31 mmol, 1.5 eq) was dissolved in tetrahydrofuran. Under ice bath, the mixture was added dropwise to the reaction system, which was stirred at room temperature for 2h. The reaction mixture was quenched with aqueous ammonium chloride solution (200 mL). The mixture was extracted with ethyl acetate, and the organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness, and the crude product was separated and purified by rapid chromatography (silica gel, petroleum ether/tetrahydrofuran = 3/1) to give the target compound (6.4 g). LCMS (ESI) $[M+H]^+$ = 611.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 1.8 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.23-7.17 (m, 6H), 4.64 (s, 2H), 4.28 (t, *J* = 8.3 Hz, 1H), 4.06 (d, *J* = 8.7 Hz, 1H), 3.74 (s, 3H), 3.51-3.30 (m, 3H), 3.16-3.06 (m, 2H), 3.02 (t, *J* = 10.2 Hz, 1H), 2.89-2.80 (m, 1H), 2.77-2.67 (m, 1H), 2.56-2.47 (m, 1H), 1.93-1.84 (m, 1H), 1.82-1.65 (m, 1H), 1.36 (s, 9H).

Step 4: Synthesis of (S)-3-(6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (6.5 g, 10.63 mmol, 1.0 eq) was dissolved in tetrahydrofuran (80 mL), a solution of hydrogen peroxide (13 mL) was added under ice bath. Lithium hydroxide (381.85 mg, 15.94 mmol, 1.5 eq) was dissolved in water and then added dropwise to the reaction system under ice bath; the mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. Sodium sulfite was added to quench the reaction mixture, and aqueous sodium carbonate was added to adjust the pH = 10. The mixture was extracted with ethyl acetate. The aqueous phase was retained, and its pH was adjusted to 4 with dilute hydrochloric acid (1 M). The mixture was extracted with dichloromethane (100mL×3), and the organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give the target product (3.6 g). LCMS (ESI) $[M+H]^+$ = 452.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.33 (dd, J = 8.5, 1.6 Hz, 1H), 3.78 (s, 3H), 3.51-3.35 (m, 2H), 3.25-3.12 (m, 2H), 3.08-2.95 (m, 3H), 2.47-2.36 (m, 1H), 2.00-1.92 (m, 1H), 1.69 (dd, J = 21.2, 10.7 Hz, 1H), 1.38 (d, J = 9.6 Hz, 9H).

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (3.2 g, 7.07 mmol, 1.0 eq) was dissolved in 2-methyltetrahydrofuran (20 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (4.25 g, 21.22 mmol, 3.0 eq) was added, and the mixture was stirred at 65°C for 16h under nitrogen protection. The mixture was diluted with tetrahydrofuran, filtered, and the filter cake was washed with acetonitrile. The filtrate was concentrated and separated and purified by rapid chromatography (silicon dioxide, petroleum ether/ethyl acetate = 3/1) to give the target compound (2.7 g). LCMS (ESI) $[M+H]^+$ = 508.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 1.8 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.27 (dd, J = 8.5, 1.9 Hz, 1H), 3.73 (s, 3H), 3.58-3.45 (m, 1H), 3.42-3.34 (m, 1H), 3.25-3.06 (m, 2H), 3.05-2.87 (m, 3H), 2.44-2.32 (m, 1H), 1.96-1.86 (m, 1H), 1.78-1.61 (m, 1H), 1.39 (d, J = 7.1 Hz, 9H), 1.27 (s, 9H).

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formyl-1-methyl-1H-benzo[d]imidazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(6-bromo-1-methyl-1H-benzo[d]imidazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (400 mg, 0.79 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (5 mL). Sodium carbonate (251.2 mg, 2.37 mmol, 3.0 eq), N-formylsaccharin (417.1 mg, 1.98 mmol, 2.5 eq), 1,4-bis(diphenylphosphino)butane palladium(II) dichloride (95 mg, 0.16 mmol, 0.2 eq) and triethylsilane (183.72 mg, 1.58 mmol, 2.0 eq) were added sequentially; after replacing with nitrogen, the reaction mixture was reacted at 75°C for 16h. The mixture was diluted with water, extracted with ethyl acetate, and the organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness. The crude product was separated and purified by rapid chromatography (silicon dioxide, petroleum ether/tetrahydrofuran = 1/1) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 458.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.13 (d, J = 0.8 Hz, 1H), 7.74 (dd, J = 8.3, 1.4 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 3.85 (s, 3H), 3.60-3.47 (m, 1H), 3.42-3.36 (m, 1H), 3.25-3.12 (m, 2H), 3.11-2.94 (m, 3H), 2.46-2.35 (m, 1H), 1.97-1.88 (m, 1H), 1.80-1.62 (m, 1H), 1.40 (d, J = 7.4 Hz, 9H), 1.27 (s, 9H).

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(6-(aminomethyl)-1-methyl-1H-benzo[d]imidazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formyl-1-methyl-1H-benzo[d]imidazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg, 0.22 mmol, 1.0 eq) was dissolved in methanol (2 mL) and ammonia methanol (2 mL, 7 M), and a drop of acetic acid was added; the reaction mixture was stirred at room temperature for 2h, sodium cyanoborohydride (68.01 mg, 1.1 mmol, 5 eq) was added, and the mixture was stirred at 80°C for 2h. LCMS showed the reaction was completed and quenched with water. After concentration, the residue was purified by reversed-phase column chromatography (0.1% formic acid in water) to give the target compound (60 mg). LCMS (ESI) $[M+H]^+$ = 459.2.

Step 8: Synthesis of tri-*tert*-butyl 3,3',3"-((2S,2'S,2"S)-((nitrilotris(methylene))tris(1-methyl-1H-benzo[d]imidazole-6,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3"R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(6-(aminomethyl)-1-methyl-1H-benzo[d]imidazol-2-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (50 mg, 0.11 mmol, 1.0 eq) was dissolved in ethanol (3 mL), and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formyl-1-methyl-1H-

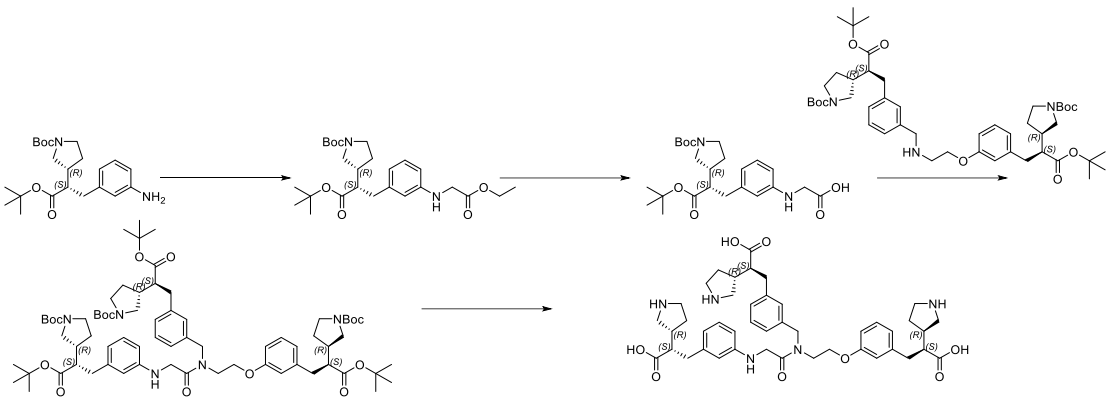
benzo[d]imidazol-2-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (99.78 mg, 0.22 mmol, 2.0 eq) was added. One drop of acetic acid was added dropwise; the reaction mixture was stirred at room temperature for 2h, sodium cyanoborohydride (67.41 mg, 1.09 mmol, 10 eq) was added, and the mixture was stirred at 70°C for 5h, and then stirred at room temperature for 13h. The reaction mixture was quenched with water, and the mixture was concentrated, purified by reverse phase column chromatography (0.1% ammonium bicarbonate in water) to give the target compound (40 mg). LCMS (ESI) $[M+H]^+$ = 1341.7.

Step 9: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(1-methyl-1H-benzo[d]imidazole-6,2-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(1-methyl-1H-benzo[d]imidazole-6,2-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (40 mg, 0.029 mmol, 1.0 eq) was dissolved in 1,4-dioxane (2 mL), and hydrochloric acid/1,4-dioxane (2 mL, 4 M) was added; the reaction mixture was stirred at room temperature for 2h. After the reaction was completed, the mixture was concentrated to dryness, dissolved in water, adjusted to pH = 7 with sodium hydroxide aqueous solution (1 M). After concentration, the mixture was purified by high pressure liquid chromatography (0.1% NH_4HCO_3 / CH_3CN) to give the target compound (23 mg). LCMS (ESI) $[M+H]^+$ = 873.4; ^1H NMR (400 MHz, D_2O) δ 7.31 (d, *J* = 8.1 Hz, 3H), 6.77 (d, *J* = 11.5 Hz, 6H), 3.36 (s, 9H), 3.30-3.10 (m, 12H), 3.08-3.00 (m, 3H), 2.91 (dd, *J* = 16.5, 10.4 Hz, 3H), 2.75-2.67 (m, 3H), 2.62-2.51 (m, 6H), 2.37-2.25 (m, 3H), 2.04-1.94 (m, 3H), 1.63 (dq, *J* = 12.7, 9.7 Hz, 3H).

Example 49 (Compound 134)

Preparation of (S)-3-(3-((2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)amino)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-ethoxy-2-oxoethyl)amino)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-aminophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(100 mg) was dissolved in DMF (0.2 mL), ethyl bromoacetate (51 mg) and potassium carbonate (70 mg) were added; the reaction mixture was stirred at 50°C overnight, and LCMS showed the reaction was completed. Ethyl acetate and water were added, the mixture was extracted, and the organic phase was dried over anhydrous sodium sulfate and purified by column chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (60 mg). LCMS (ESI) $[M+H\text{-}Boc]^+ = 377.3$.

Step 2: Synthesis of (3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)glycine

The product from the first step (85 mg) was dissolved in tetrahydrofuran (0.3 mL)and H_2O (0.3 mL), followed by adding lithium hydroxide (13 mg). The reaction mixture was stirred overnight at room temperature. LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation to dryness, and the residue was purified by column chromatography (Silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (60 mg). LCMS (ESI) $[M+H\text{-}Boc]^+ = 349.3$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)-2-oxoethyl)amino)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

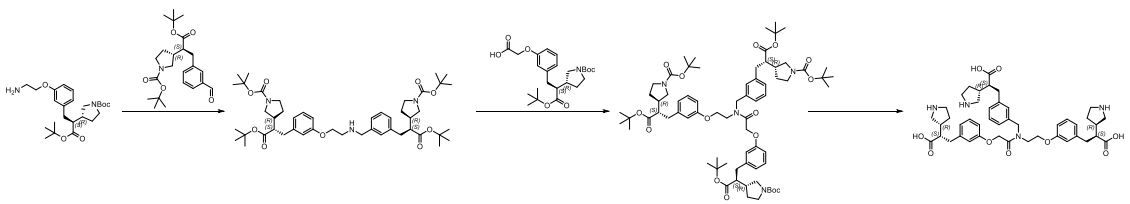
The product from the second step (60 mg) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (110 mg) were dissolved in N,N-dimethylformamide (0.5 mL), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (76 mg) and triethylamine (41 mg) were added; the reaction mixture was stirred overnight at room temperature, and LCMS showed the reaction was completed. Ethyl acetate and water were added, and the mixture was extracted and separated. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by column chromatography (Silica gel, petroleum ether:ethyl acetate = 5:1) to give the target product (105 mg). LCMS (ESI) $[M+H\text{-}Boc]^+ = 1152.97$.

Step 4: Synthesis of (S)-3-(3-((2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)amino)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the third step (105 mg) was dissolved in 1,4-dioxane (3 mL), and hydrochloric acid/1,4-dioxane (4.0M, 3 mL) was added; the mixture was stirred at room temperature overnight, and LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation to dryness, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the target compound (6 mg). LCMS (ESI) $[M+H]^+ = 784.62$; ^1H NMR (400 MHz, D_2O) δ 7.32-6.93 (m, 6H), 6.87-6.36 (m, 6H), 4.68-4.53 (m, 4H), 4.18-4.04 (m, 2H), 3.91-3.74 (m, 2H), 3.41-3.08 (m, 9H), 2.88-2.46 (m, 9H), 2.43-2.25 (m, 6H), 2.13-1.93 (m, 3H), 1.73-1.55 (m, 3H).

Example 50 (Compound 135)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg) was dissolved in methanol (3 mL). *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (93 mg) and sodium cyanoborohydride (7 mg) were added at room temperature. The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:5) to give the target compound (90 mg). LCMS (ESI) $[M+H]^+$ = 822.77.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)-N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the first step (100 mg) was dissolved in DMF (5 mL), followed by adding 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)acetic acid (66 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (93 mg) and *N,N*-diisopropylethylamine (47 mg). The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (120 mg). LCMS (ESI) $[M+H]^+$ = 1253.75.

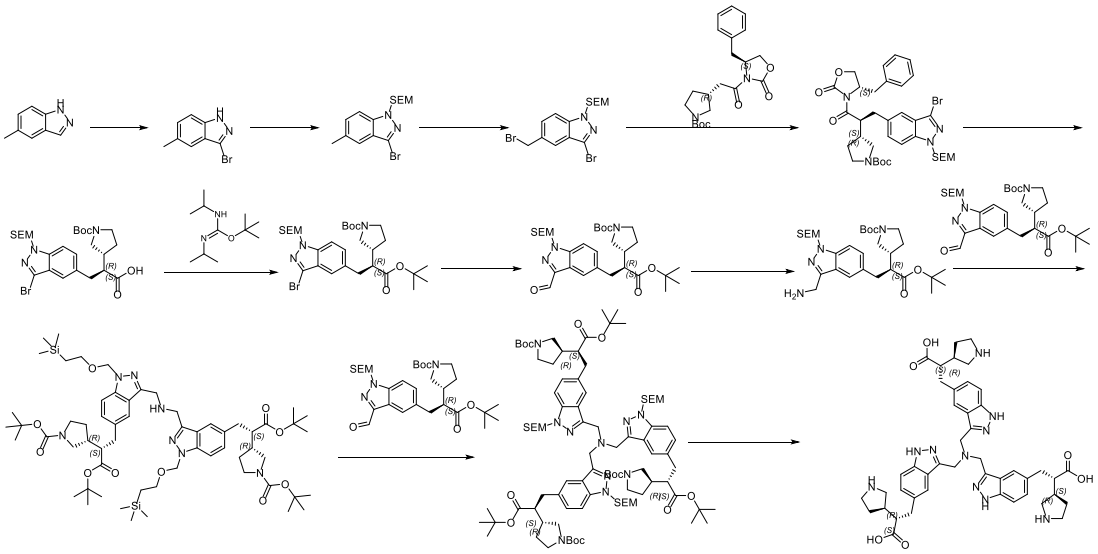
Step 3: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the second step (120 mg) was dissolved in dichloromethane (5 mL), and trifluoroacetic acid (2 mL) was added; the mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to give the target compound (52.91 mg). LCMS (ESI)

$[M+H]^+$ = 785.2; ^1H NMR (400 MHz, D_2O) δ 7.28-6.93 (m, 6H), 6.85-6.48 (m, 6H), 5.02 (s, 1H), 4.65 (d, *J* = 16.5 Hz, 2H), 4.51 (d, *J* = 15.7 Hz, 1H), 4.13-3.96 (m, 2H), 3.71 (q, *J* = 9.9, 7.7 Hz, 2H), 3.45-3.19 (m, 6H), 3.18-3.05 (m, 3H), 2.83-2.53 (m, 8H), 2.52-2.19 (m, 7H), 2.01 (dtd, *J* = 12.1, 6.4, 5.7, 3.0 Hz, 3H), 1.72-1.53 (m, 3H).

Example 51 (Compound 52)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(1H-indazole-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 3-bromo-5-methyl-1H-indazole

5-methyl-1H-indazole (24 g, 181.6 mmol, 1.0 eq) was dissolved in acetonitrile (240 mL), and sodium 4,5,6,7-tetrachloro-2',4',5',7'-tetraiodo-3H-spiro[isobenzofuran-1,9'-xanthene]-3',6'-bis(olate) (1.76 g, 1.82 mmol, 0.01 eq) and N-bromosuccinimide (35.55 g, 199.76 mmol, 1.1 eq) were added at room temperature; the reaction mixture was stirred at room temperature for 2h. LCMS showed the reaction of starting material was completed. The reaction mixture was concentrated, and the crude product was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (37 g). LCMS (ESI) $[M+H]^+$ = 211.0; ^1H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.41 (s, 1H), 7.38-7.32 (m, 1H), 2.50 (s, 3H).

Step 2: Synthesis of 3-bromo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole

3-bromo-5-methyl-1H-indazole (19 g, 90.02 mmol, 1.0 eq) was dissolved in tetrahydrofuran (200 mL), and sodium hydride (4.14 g, 180.04 mmol, 2.0 eq) was added at 0°C. The mixture was stirred for 30min. Then [2-(chloromethoxy)ethyl]trimethylsilane (22.51 g, 135.03 mmol, 1.5 eq) was added at 0°C, and the reaction mixture was stirred at 0°C for 1.5h. LCMS showed the reaction of starting material was completed. Saturated ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The crude product was separated and purified by column chromatography (petroleum ether:ethyl acetate = 10:1) to give the target compound (25 g). LCMS (ESI) $[M+H]^+$ = 340.9; ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.51 (d, *J* = 8.6 Hz, 1H), 7.46 (s, 1H), 7.39-7.35 (m, 1H), 5.72 (s, 2H), 3.64-3.59 (m, 2H), 2.55 (s, 3H), 0.94-0.93 (m, 2H), 0.10-0.08 (m, 9H).

Step 3: Synthesis of 3-bromo-5-(bromomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole

N-bromosuccinimide (25.24 g, 141.8 mmol, 1.1 eq) and 2-[2-(1-cyano-1-methylethyl)diazen-1-yl]-2-methylpropanenitrile (2.12 g, 12.89 mmol, 0.1 eq) were sequentially added to a solution of 3-bromo-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (44 g, 128.91 mmol, 1.0 eq) in carbon tetrachloride (200 mL), and the reaction mixture was heated to 80°C under nitrogen protection and stirred for 16h. LCMS showed the reaction was completed. After the reaction mixture was cooled to room temperature, the mixture was filtered to remove the filter residue. The filtrate was concentrated, and the crude product was separated and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 200:1-100:1) to give the target compound (14 g). LCMS (ESI) $[M+H]^+$ = 418.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, *J* = 8.7 Hz, 1H), 7.69 (s, 1H), 7.57 (dd, *J* = 8.8, 1.5 Hz, 1H), 5.69 (s, 2H), 4.86 (s, 2H), 3.50-3.45 (m, 2H), 0.77-0.72 (m, 2H), -0.15--0.17 (m, 9H).

Step 4: *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate(5 g, 12.87 mmol, 1.0 eq) was dissolved in anhydrous tetrahydrofuran (70 mL), and the reaction mixture was replaced with nitrogen. Under nitrogen protection, the mixture was cooled to -5°C in an ice-salt bath. Lithium bis(trimethylsilyl)amide (19.31 mL, 19.31 mmol, 1.5 eq) was

slowly added to the above solution; after the addition was completed, the mixture was stirred at -5°C for 1h. A solution of 3-bromo-5-(bromomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (6.49 g, 15.45 mmol, 1.2 eq) in tetrahydrofuran (10 mL) was slowly added dropwise to the reaction mixture. After the addition was completed, the reaction mixture was warmed to room temperature and stirred for 15h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated ammonium chloride solution, diluted with water, and extracted with ethyl acetate. The merged organic phases were washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was separated and purified by column chromatography (tetrahydrofuran/petroleum ether = 0~25%) to give the target compound (6.2 g). LCMS (ESI) $[M+Na]^+$ = 749.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 8.7 Hz, 1H), 7.53-7.43 (m, 2H), 7.11 (t, J = 7.4 Hz, 1H), 7.02-6.95 (m, 2H), 6.67-6.59 (m, 2H), 5.74-5.67 (m, 2H), 4.69-4.60 (m, 1H), 4.42-4.29 (m, 1H), 4.28-4.18 (m, 1H), 4.03-3.94 (m, 1H), 3.51-3.42 (m, 3H), 3.17-2.91 (m, 5H), 2.74-2.66 (m, 1H), 2.45-2.30 (m, 2H), 1.98-1.87 (m, 1H), 1.72-1.58 (m, 1H), 1.41-1.36 (m, 9H), 0.78-0.70 (m, 2H), -0.14 (s, 9H).

Step 5: Synthesis of (S)-3-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (3 g, 4.12 mmol, 1.0 eq) was dissolved in tetrahydrofuran (50 mL), hydrogen peroxide (9.34 g, 82.4 mmol, 20 eq, 30% content) was added, and a solution of lithium hydroxide monohydrate (0.35 g, 8.24 mmol, 2.0 eq) in water (5 mL) was added dropwise to the reaction mixture. After the addition was completed, the reaction mixture was stirred at 25°C for 16h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated sodium sulfate solution (20 mL), and the pH was adjusted to around 12 with sodium hydroxide solution. The mixture was washed with ethyl acetate, and the aqueous phase was adjusted to a pH of about 4 with hydrochloric acid (3 M), and extracted with ethyl acetate again. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (3.3 g). This intermediate was used directly in the next step without further purification. LCMS (ESI) $[M+Na]^+$ = 590.1.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (3.2 g, 5.63 mmol, 1.0 eq) was dissolved in 2-methyltetrahydrofuran (30 mL). *tert*-butyl N,N'-diisopropylcarbamimidate(5.64 g, 28.14 mmol, 5 eq) was added, and the reaction mixture was stirred at 70°C for 3h under nitrogen protection. After cooled to room temperature, the reaction mixture was filtered to remove the filter residue. The filter cake was fully washed with methyl *tert*-butyl ether. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (tetrahydrofuran/petroleum ether = 0%~20%) to give the target compound (2 g).LCMS (ESI) $[M+Na]^+$ = 646.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, J = 8.7 Hz, 1H), 7.42-7.33 (m, 2H), 5.69 (s, 2H), 3.61-3.51 (m, 1H), 3.47 (t, J = 7.9 Hz, 2H), 3.30-3.25 (m, 1H), 3.20-3.10 (m, 1H), 3.06-2.98 (m, 1H), 2.94-2.78 (m, 2H), 2.60-2.52 (m, 1H), 2.36-2.24 (m, 1H), 1.89-1.78 (m, 1H), 1.65-1.52 (m, 1H), 1.39 (s, 9H), 1.16 (s, 9H), 0.79-0.71 (m, 2H), -0.14 (s, 9H).

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1 g, 1.6 mmol, 1.0 eq) and sodium carbonate (339.34 mg, 3.2 mmol, 2.0 eq) were dissolved in *N,N*-dimethylformamide (15 mL), followed by adding triethylsilane (279.21 mg, 2.4 mmol, 1.5 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (117.46 mg, 0.16 mmol, 0.1 eq); the reaction mixture was stirred at 80°C for 16h under a carbon monoxide. LCMS showed the reaction was completed. After the reaction mixture was cooled to room temperature, water was added for dilution, and the mixture was extracted with ethyl acetate. The organic phase was washed with water and saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by column chromatography (tetrahydrofuran/petroleum ether = 0%~25%) to give the target compound (0.8 g). LCMS (ESI) $[M+Na]^+$ = 596.2.

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(aminomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg, 0.35 mmol, 1.0 eq) was dissolved in a solution of ammonia methanol (7 M, 5 mL), one drop of glacial acetic acid was added dropwise, and the reaction mixture was stirred at 25°C for 15 min. sodium cyanoborohydride (215.51 mg, 3.49 mmol, 10 eq) was added to the reaction mixture, which was heated to 80°C in a sealed tube and stirred for 16h. LCMS showed the reaction was completed. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was separated and purified by reversed-phase column (0.1% aqueous formic acid/acetonitrile = 62%) to give the target compound (130 mg). LCMS (ESI) $[M+H]^+$ = 575.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 2H), 7.82-7.75 (m, 2H), 7.45 (d, J = 8.3 Hz, 1H), 5.86-5.78 (m, 2H), 4.55-4.39 (m, 2H), 3.68-3.62 (m, 2H), 3.48-3.43 (m, 2H), 3.30-3.21 (m, 1H), 3.10 (t, J = 9.9 Hz, 1H), 3.00-2.90 (m, 2H), 2.71-2.62 (m, 1H), 2.46-2.35 (m, 1H), 2.01-1.90 (m, 1H), 1.76-1.62 (m, 1H), 1.49 (s, 9H), 1.33-1.25 (m, 9H), 0.94-0.85 (m, 2H), 0.03--0.04 (m, 9H).

Step 9: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-3,5-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(3-(aminomethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (80 mg, 0.14 mmol, 1.0 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(119.78 mg, 0.21 mmol, 1.5 eq) were dissolved in ethanol (4 mL), one drop of glacial acetic acid was added, and the reaction mixture was stirred at 25°C for 30min. sodium cyanoborohydride (86.05 mg, 1.39 mmol, 10 eq) was added to the reaction mixture, which was heated to 60°C and stirred for 3.5h. LCMS showed the reaction was completed. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was separated and purified by reversed-phase column chromatography (0.1% aqueous trifluoroacetic acid/acetonitrile = 72%) to give the target compound (80 mg). LCMS (ESI) $[M+H]^+$ = 1132.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s,

1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 16.9 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 5.88 (s, 2H), 5.76 (s, 2H), 4.84 (s, 2H), 4.79-4.67 (m, 2H), 3.67-3.55 (m, 6H), 3.47 (t, *J* = 9.3 Hz, 2H), 3.32-3.23 (m, 2H), 3.16-3.08 (m, 2H), 3.01-2.89 (m, 4H), 2.72-2.64 (m, 2H), 2.47-2.37 (m, 2H), 2.02-1.91 (m, 2H), 1.74-1.65 (m, 2H), 1.51 (s, 18H), 1.29 (d, *J* = 10.3 Hz, 18H), 0.93-0.86 (m, 4H), 0.02--0.04 (m, 18H).

Step 10: Synthesis of tri-*tert*-butyl 3,3',3"-((2S,2'S,2"S)-((nitrilotris(methylene))tris(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3"R)-tris(pyrrolidine-1-carboxylate)

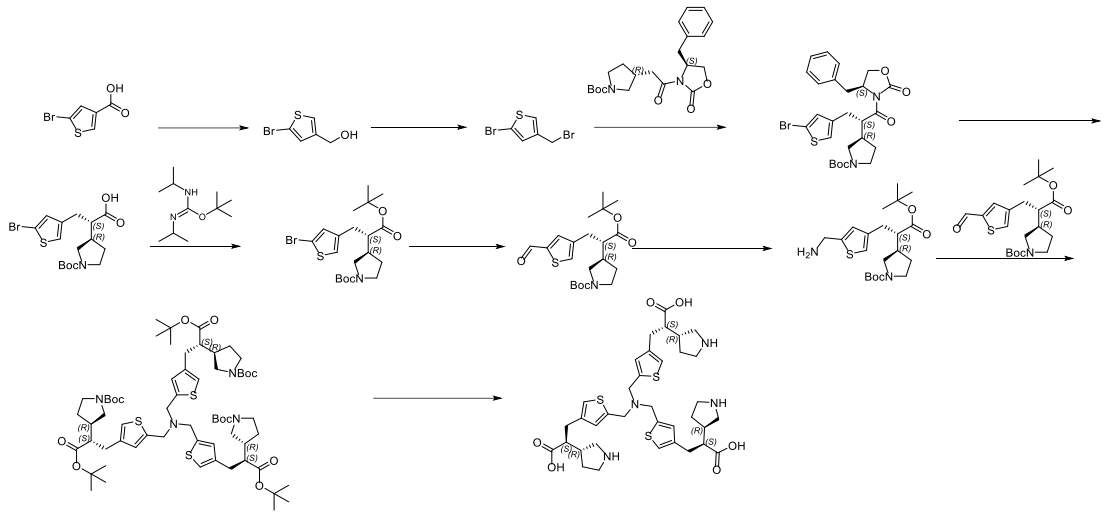
Di-*tert*-butyl 3,3'-((2S,2'S)-((azanediylbis(methylene))bis(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-3,5-diyl))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (50 mg) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(50.66 mg) were dissolved in ethanol (2 mL), a small drop of glacial acetic acid was added, and the reaction mixture was stirred at 35°C for 6h. sodium cyanoborohydride (27.3 mg) was added to the reaction mixture, which was heated to 70°C and stirred for 10h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure. The obtained residue was separated and purified by reversed-phase column chromatography (0.1% formic acid in water/acetonitrile = 0~100%) to remove impurities, and the system (0.1% formic acid in water/methanol = 100%) was changed to give the target compound (30 mg). LCMS (ESI) $[M/2+H]^+$ = 846.0.

Step 11: Synthesis of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(1H-indazole-3,5-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3"-((2S,2'S,2"S)-((nitrilotris(methylene))tris(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-3,5-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3"R)-tris(pyrrolidine-1-carboxylate) (70 mg) was dissolved in hydrochloric acid/1,4-dioxane (4M, 3 mL), and the reaction mixture was stirred at room temperature for 4h. LCMS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure, and the residue was separated and purified by preparative chromatography (0.1% ammonium bicarbonate aqueous solution/acetonitrile) to give the target compound (3.7 mg). LCMS (ESI) $[M+H]^+$ = 831.1.

Example 52 (Compound 137)

Preparation of (2S,2'S,2"S)-3,3',3"-((nitrilotris(methylene))tris(thiophene-5,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of (5-bromothiophen-3-yl)methanol

5-bromothiophene-3-carboxylic acid(12 g) was dissolved in tetrahydrofuran (150 mL). Borane/tetrahydrofuran (173.87 mL) was added dropwise at 0°C, and the reaction mixture was stirred at room temperature for 3h. After the reaction was completed, methanol (30 mL) was added to the reaction mixture to quench the reaction, water (300 mL) was added for dilution, and the mixture was extracted with ethyl acetate (300mL×3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to give the target compound (10.5 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32-7.28 (m, 1H), 7.12 (d, J = 1.6 Hz, 1H), 5.18 (t, J = 5.8 Hz, 1H), 4.41-4.38 (m, 2H).

Step 2: Synthesis of 2-bromo-4-(bromomethyl)thiophene

(5-bromothiophen-3-yl)methanol (21 g) was dissolved in dichloromethane (200 mL). Phosphorus tribromide (47.91 g) was added under ice bath, and the reaction was maintained at room temperature for 2h. LCMS showed the reaction of starting material was completed. The reaction mixture was poured into water to quench and extracted with dichloromethane (300 mL x 3). The organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was

purified by silica gel column chromatography (petroleum ether 100%) to give the target product (22 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.5 Hz, 1H), 7.07 (d, *J* = 1.7 Hz, 1H), 4.40 (s, 2H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate(5 g) was dissolved in tetrahydrofuran (60 mL), lithium bis(trimethylsilyl)amide (16.73 mL) was added dropwise under nitrogen protection and ice bath, and the mixture was stirred for 1h; 2-bromo-4-(bromomethyl)thiophene (4.94 g) was dissolved in tetrahydrofuran. Under ice bath, the mixture was added dropwise to the reaction system, which was stirred at room temperature for 6h. The reaction mixture was quenched with aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, and the organic phases were merged and washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude product was separated and purified by rapid chromatography (silica gel, petroleum ether/ethyl acetate = 3/1) to give the target compound (3.8 g).LCMS (ESI) $[M+Na]^+$ = 585.0/587.0; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.28-7.21 (m, 4H), 7.11 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 6.7 Hz, 2H), 4.67 (s, 1H), 4.29 (t, *J* = 8.2 Hz, 1H), 4.25-4.15 (m, 1H), 4.14-4.07 (m, 1H), 3.50-3.37 (m, 1H), 3.33-3.27 (m, 1H), 3.18-3.02 (m, 1H), 3.00-2.89 (m, 2H), 2.86-2.73 (m, 2H), 2.65 (td, *J* = 13.3, 7.6 Hz, 1H), 2.45-2.31 (m, 1H), 1.94-1.84 (m, 1H), 1.69-1.52 (m, 1H), 1.39 (s, 9H).

Step 4: Synthesis of (S)-3-(5-bromothiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (3.8 g) was dissolved in tetrahydrofuran (40 mL), hydrogen peroxide solution (7.6 mL) was added under ice bath. Dissolved in water, lithium hydroxide (242.26 mg) was added dropwise to the mixture under ice bath, and the mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was quenched with sodium sulfite and extracted with dichloromethane. The merged organic phases were washed with saturated sodium chloride aqueous solution, dried over

anhydrous sodium sulfate, filtered and concentrated to dryness to give the target product (3.8 g). LCMS (ESI) $[M+Na]^+$ = 426.0.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-bromothiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromothiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (3.8 g, 70% purity) was dissolved in 2-methyltetrahydrofuran (40 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (6.59 g) was added. The reaction mixture was stirred at 70°C for 16h under nitrogen protection. LCMS showed the reaction of starting material was completed. The mixture was diluted with acetonitrile (50 mL), filtered, the filter cake was washed with acetonitrile, and the filtrate was concentrated to give a crude product, which was separated and purified by rapid chromatography (silicon dioxide, petroleum ether/ethyl acetate = 5/1) to give the target product (2.5 g). LCMS (ESI) $[M+H]^+$ = 460.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (s, 1H), 7.13 (d, J = 3.3 Hz, 1H), 3.57-3.48 (m, 1H), 3.43-3.39 (m, 1H), 3.20 (dt, J = 10.6, 8.3 Hz, 1H), 3.00 (t, J = 10.0 Hz, 1H), 2.83-2.69 (m, 2H), 2.55-2.50 (m, 1H), 2.37-2.25 (m, 1H), 1.93-1.85 (m, 1H), 1.69-1.54 (m, 1H), 1.45 (s, 9H), 1.34 (s, 9H).

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(5-bromothiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2.4 g) was dissolved in N,N-dimethylformamide (30 mL), followed by adding sodium carbonate (1.1 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (382.45 mg) and triethylsilane (1.21 g); after replacing with carbon monoxide gas, the reaction mixture was stirred at 80°C for 16h under a carbon monoxide. LCMS showed the reaction was completed. The reaction mixture was quenched with water, extracted with ethyl acetate, and the organic phases were merged and washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude product was separated and purified by rapid chromatography (silica gel, petroleum ether/ethyl acetate = 3/1) to give the target compound (1.5 g). LCMS (ESI) $[M+Na]^+$ = 432.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (d, J = 1.2 Hz, 1H), 7.89 (s, 1H), 7.80 (s, 1H), 3.56-3.44 (m, 1H), 3.39-3.33 (m, 1H), 3.21-3.10 (m, 1H), 2.98 (t, J = 9.9 Hz, 1H), 2.87-2.74 (m, 2H), 2.61-2.54 (m, 1H), 2.34-2.22 (m, 1H), 1.90-1.81 (m, 1H), 1.65-1.52 (m, 1H), 1.40 (s, 9H), 1.26 (s, 9H).

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-(aminomethyl)thiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (600 mg) was dissolved in ammonia methanol (10 mL, 7 M), one drop of acetic acid was added, and the mixture was stirred at room temperature for 2h. sodium cyanoborohydride (452.92 mg) was added, and the reaction mixture was stirred at 70°C for 4h. LCMS showed the reaction of starting material was completed. The reaction mixture was quenched with water, concentrated, and purified by reversed-phase column chromatography (0.1% ammonia water) to give the target product (240 mg). LCMS (ESI) $[M+H]^+$ = 411.2.

Step 8: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(thiophene-5,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(5-(aminomethyl)thiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (290 mg) was dissolved in ethanol (8 mL), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(723.18 mg) was added, a drop of acetic acid was added dropwise, and the mixture was stirred at room temperature for 4h. sodium cyanoborohydride (436.73 mg) was added and the mixture was stirred at 70°C for 16h. LCMS showed the reaction of starting material was completed. The reaction mixture was quenched with water and concentrated. The residue was purified by reversed-phase column chromatography (0.1% trifluoroacetic acid) to give the target product (400 mg). LCMS (ESI) $[M+H]^+$ = 1196.9.

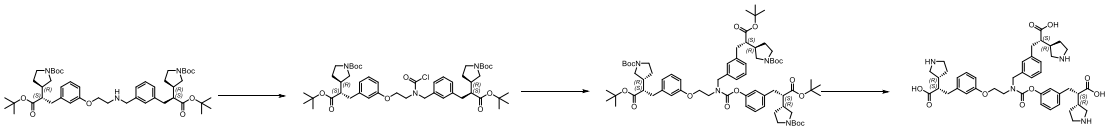
Step 9: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(thiophene-5,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(thiophene-5,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (400 mg) was dissolved in 1,4-dioxane (5 mL), hydrochloric acid/1,4-dioxane (5 mL, 4 M) was added, and the reaction mixture was stirred at room temperature for 16h. After the reaction was completed, the mixture was concentrated to dryness, dissolved in water, adjusted to pH = 7 with sodium carbonate aqueous solution (1 M). After concentration, the mixture was purified by high pressure liquid chromatography (0.1%NH_4HCO_3) to give the target compound (178.81 mg). LCMS (ESI) $[M+H]^+$

= 729.3; ^{1}H NMR (400 MHz, D_2O) δ 6.95 (s, 3H), 6.80 (s, 3H), 3.67 (s, 6H), 3.30 (ddd, *J* = 11.2, 7.2, 2.8 Hz, 6H), 3.12 (ddd, *J* = 11.6, 10.2, 7.3 Hz, 3H), 2.79-2.71 (m, 6H), 2.61 (dd, *J* = 14.3, 5.1 Hz, 3H), 2.42-2.25 (m, 6H), 2.03 (tdd, *J* = 10.1, 6.9, 3.4 Hz, 3H), 1.65 (dq, *J* = 12.9, 9.5 Hz, 3H).

Example 53 (Compound 139)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(98.65 mg, 0.12 mmol, 1 eq) was dissolved in tetrahydrofuran (2 mL), and triphosgene (35.61 mg, 0.12 mmol, 1 eq) and *N,N*-diisopropylethylamine (155.09 mg, 1.2 mmol, 10 eq) were added at 0°C; the reaction mixture was stirred at 0°C for 0.5 h under nitrogen protection. LCMS showed the formation of the product, and the reaction mixture was directly used for the next step. LCMS (ESI) $[M+H\text{-}Boc]^+$ = 784.4.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)carbonyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the first step (100 mg, 0.11 mmol, 1 eq) was dissolved in tetrahydrofuran (3 mL), and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (44.26 mg, 0.11 mmol, 1 eq) and 4-dimethylaminopyridine (1.38 mg, 0.01 mmol, 0.1 eq) were added; the mixture was stirred at 50°C for 3h under nitrogen protection.

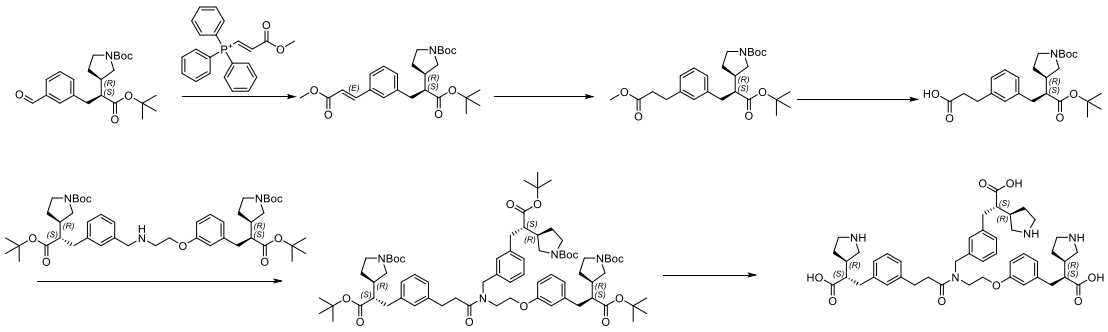
The reaction mixture was concentrated and purified by column chromatography (petroleum ether:ethyl acetate = 4:1) to give the target product (100 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1139.0.

Step 3: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the second step (100 mg, 0.08 mmol, 1 eq) was dissolved in dioxane (2 mL), followed by adding hydrochloric acid-1,4-dioxane (4.0M, 2 mL). The reaction mixture was stirred at room temperature for 2h under nitrogen protection. After concentration, the reaction mixture was separated and purified by Prep-HPLC (0.1% NH_4HCO_3 in water, MeCN) to give the target compound (35.08 mg). LCMS (ESI) $[M+H]^+$ = 771.2; ^1H NMR (400 MHz, D_2O) δ 7.33-7.06 (m, 7H), 6.92-6.86 (m, 1H), 6.85-6.76 (m, 2H), 6.72 (d, *J* = 12.9 Hz, 2H), 4.69-4.66 (m, 1H), 4.56 (s, 1H), 4.17 (d, *J* = 4.7 Hz, 2H), 3.77 (d, *J* = 40.3 Hz, 2H), 3.40-3.24 (m, 6H), 3.19-3.08 (m, 3H), 2.85-2.56 (m, 9H), 2.43-2.27 (m, 6H), 2.09-1.96 (m, 3H), 1.72-1.58 (m, 3H).

Example 54 (Compound 140)

Preparation of (S)-3-(3-(3-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-3-oxopropyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(3-methoxy-3-oxopropyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(600 mg) was dissolved in dichloromethane (15 mL), and (3-methoxy-3-oxoprop-1-en-1-yl)triphenylphosphonium(994.32 mg) was added at 0°C; under nitrogen, the mixture was heated to room temperature and stirred for 16h. The reaction mixture was concentrated and purified

by column chromatography (petroleum ether:ethyl acetate = 5:1) to give the target product (650 mg). LCMS (ESI) $[M+H]^+$ = 460.3.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((E)-3-methoxy-3-oxoprop-1-en-1-yl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the first step (650 mg) was dissolved in methanol (10 mL), followed by adding Pd/C (75.03 mg); the reaction mixture was stirred at room temperature for 2h under hydrogen (balloon pressure). The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated to give the target product (600 mg). LCMS (ESI) $[M+H]^+$ = 462.3; ^{1}HNMR(400 Hz, $CDCl_3$) δ 7.21-7.15 (m, 1H), 7.05-6.97 (m, 3H), 3.67 (s, 3H), 3.59-3.41 (m, 1H), 3.30-3.19 (m, 1H), 3.08-2.94 (m, 1H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.85-2.72 (m, 2H), 2.60 (t, *J* = 7.9 Hz, 2H), 2.53-2.43 (m, 1H), 2.41-2.30 (m, 1H), 1.98-1.90 (m, 1H), 1.71-1.57 (m, 2H), 1.47 (s, 9H), 1.27 (s, 9H).

Step 3: Synthesis of 3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)propanoic acid

The product from the second step (600 mg) was dissolved in a mixture of tetrahydrofuran (3 mL), water (1.5 mL) and methanol (1.5 mL), and lithium hydroxide (46.7 mg) was added; the reaction mixture was stirred at room temperature for 2h. The pH of the mixture was adjusted to 5 with hydrochloric acid aqueous solution (1.0 M). The mixture was separated, the organic phases were merged, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give the target product (500 mg). LCMS (ESI) $[M+H]^+$ = 448.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.8 Hz, 1H), 7.09-7.01 (m, 3H), 3.50-3.36 (m, 2H), 3.19 (dd, *J* = 17.6, 10.7 Hz, 1H), 2.96-2.87 (m, 3H), 2.81-2.67 (m, 2H), 2.67-2.61 (m, 2H), 2.52-2.43 (m, 1H), 2.39-2.27 (m, 1H), 2.02-1.93 (m, 1H), 1.64-1.53 (m, 1H), 1.45 (s, 9H), 1.37 (s, 9H).

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)propanamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the third step (70 mg) was dissolved in ethyl acetate (4 mL), followed by adding *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-

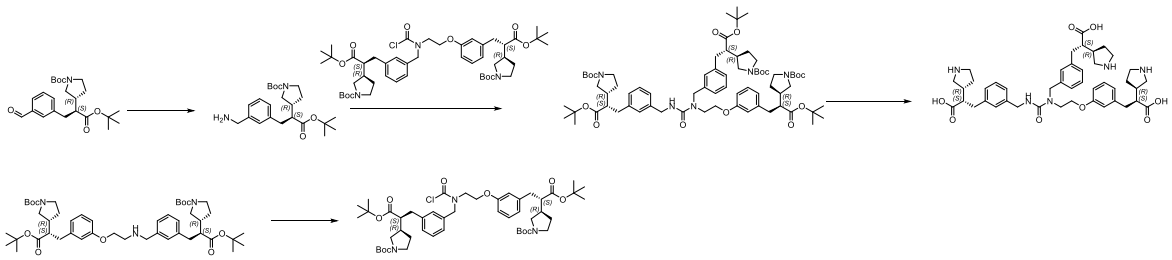
butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (128.58 mg), Propylphosphonic anhydride (76.3 mg), and *N,N*-diisopropylethylamine (60.64 mg); the reaction mixture was stirred at 50°C for 3h under nitrogen protection. LCMS showed the reaction was completed. The reaction mixture was concentrated to give a crude product, which was purified by rapid chromatography (Silica gel, tetrahydrofuran:petroleum ether = 1:3) to give the target compound (100 mg). LCMS (ESI) $[M+H]^+$ = 1151.0.

Step 5: Synthesis of (S)-3-(3-(3-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-3-oxopropyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the fourth step (100 mg) was dissolved in dioxane (2 mL), followed by adding hydrochloric acid-1,4-dioxane (4.0M, 2 mL); the mixture was stirred at room temperature for 2h under nitrogen. LCMS showed the reaction was completed. The reaction mixture was concentrated and separated and purified by Prep-HPLC (0.1% NH_4HCO_3 in acetonitrile) to give the target compound (23.8 mg). LCMS (ESI) $[M+H]^+$ = 783.3; ^1H NMR (400 MHz, D_2O) δ 7.23-6.96 (m, 6H), 6.95-6.76 (m, 4H), 6.70-6.64 (m, 1H), 6.60-6.56 (m, 1H), 4.56-4.44 (m, 2H), 4.00 (t, *J* = 5.2 Hz, 1H), 3.93-3.84 (m, 1H), 3.67-3.57 (m, 2H), 3.41-3.25 (m, 6H), 3.19-3.08 (m, 3H), 2.90-2.48 (m, 13H), 2.42-2.25 (m, 6H), 2.10-1.94 (m, 3H), 1.72-1.57 (m, 3H).

Example 55 (Compound 141)

Preparation of (S)-3-(3-(2-(1,3-bis(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)ureido)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1 g) was dissolved in ammonia methanol solution (7 M, 10 mL), and glacial acetic acid (0.1 mL) was added at room temperature. The reaction mixture was stirred at 40°C for 5h; sodium cyanoborohydride (153 mg) was added, and the reaction mixture was heated to 70°C and stirred for 3h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness, and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 1/4) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 405.3.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (300 mg) was dissolved in tetrahydrofuran (10 mL), triethylamine (364.28 mg) and triphosgene (106.83 mg) were added at 0°C; the mixture was stirred at 0°C for 1h. LCMS showed the reaction was completed. Water was added to the mixture, which was extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give the target compound (250 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 784.4.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(1,3-bis(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)ureido)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

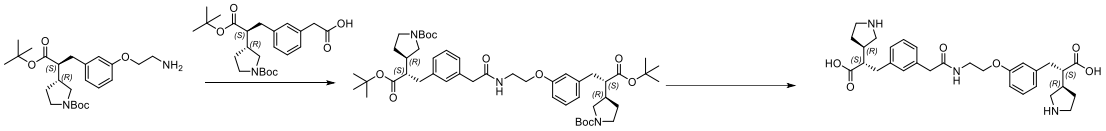
The product from the second step (200 mg) was dissolved in tetrahydrofuran (5 mL), and triethylamine (68.64 mg), 4-dimethylaminopyridine (13.81 mg) and *tert*-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (109.76 mg) were added at room temperature; the reaction mixture was stirred at 50°C for 16h. LCMS showed the reaction was completed, and the reaction mixture was rotary-evaporated to dryness to give a crude product, which was purified by column chromatography (PE/EA = 3/1) to give the target compound (100 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1152.5.

Step 4: Synthesis of (S)-3-(3-(2-(1,3-bis(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)ureido)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-3-(3-(2-(1,3-bis(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)ureido)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/1,4-dioxane (4 M, 2 mL) was added at room temperature; the reaction mixture was stirred at 30°C for 3h. LCMS showed the reaction was completed, the reaction mixture was rotary-evaporated to dryness, and the crude product was purified by Pre-HPLC (30 mmol NH_4HCO_3 in H_2O/ACN) to give the target compound (41 mg). LCMS (ESI) $[M+H]^+$ = 784.3; ^1H NMR (400 MHz, D_2O) δ 7.21-7.12 (m, 3H), 7.07-6.99 (m, 5H), 6.97 (s, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.61-6.55 (m, 2H), 4.51 (s, 2H), 4.27 (s, 2H), 4.08-4.01 (m, 2H), 3.70-3.62 (m, 2H), 3.39-3.24 (m, 6H), 3.19-3.07 (m, 3H), 2.86-2.77 (m, 1H), 2.74-2.56 (m, 7H), 2.54-2.47 (m, 1H), 2.39-2.25 (m, 6H), 2.07-1.95 (m, 3H), 1.70-1.55 (m, 3H).

Example 56 (Compound 142)

Preparation of (S)-3-(3-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of :*tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(220 mg) was dissolved in ethyl acetate (3 mL). 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid(263 mg), 1-propylphosphonic acid anhydride (644 mg, 50% in ethyl acetate) and *N,N*-diisopropylethylamine (196 mg) were added at room temperature. The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was

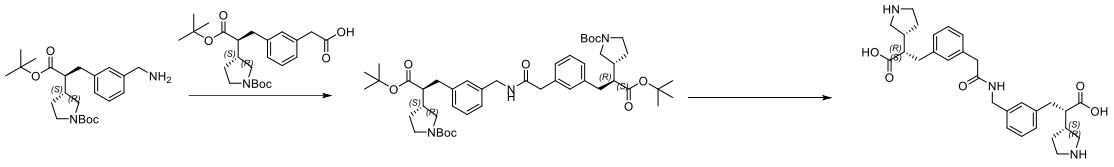
concentrated directly and separated and purified by rapid chromatography (Silica gel, petroleum ether:EtOAc = 1:8) to give the target compound (280 mg). LCMS (ESI) $[M+H]^+$ = 850.2.

Step 2: Synthesis of (S)-3-(3-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the first step (280 mg) was dissolved in ethyl acetate (5 mL), followed by adding hydrogen chloride-ethyl acetate (4.0M, 10 mL). The mixture was stirred at room temperature for 24h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to give the target compound (129.85 mg). LCMS (ESI) $[M+H]^+$ = 538.1; ^{1}H NMR (400 MHz, D_2O) δ 7.19 (t, *J* = 8.1 Hz, 2H), 7.07 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.03 (dd, *J* = 4.5, 2.7 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.75-6.69 (m, 2H), 4.05 (t, *J* = 5.2 Hz, 2H), 3.49 (d, *J* = 7.8 Hz, 4H), 3.41 (dd, *J* = 11.7, 7.1 Hz, 1H), 3.37-3.28 (m, 3H), 3.21-3.11 (m, 2H), 2.87 (dd, *J* = 11.7, 9.3 Hz, 1H), 2.79-2.57 (m, 5H), 2.43-2.27 (m, 4H), 2.04 (ddt, *J* = 17.9, 13.1, 5.7 Hz, 2H), 1.65 (ddq, *J* = 18.1, 13.0, 9.3 Hz, 2H).

Example 57 (Compound 143)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (260 mg) was dissolved in DMF (5 mL), followed by adding 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (307 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (489 mg) and *N,N*-diisopropylethylamine (249 mg). The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated

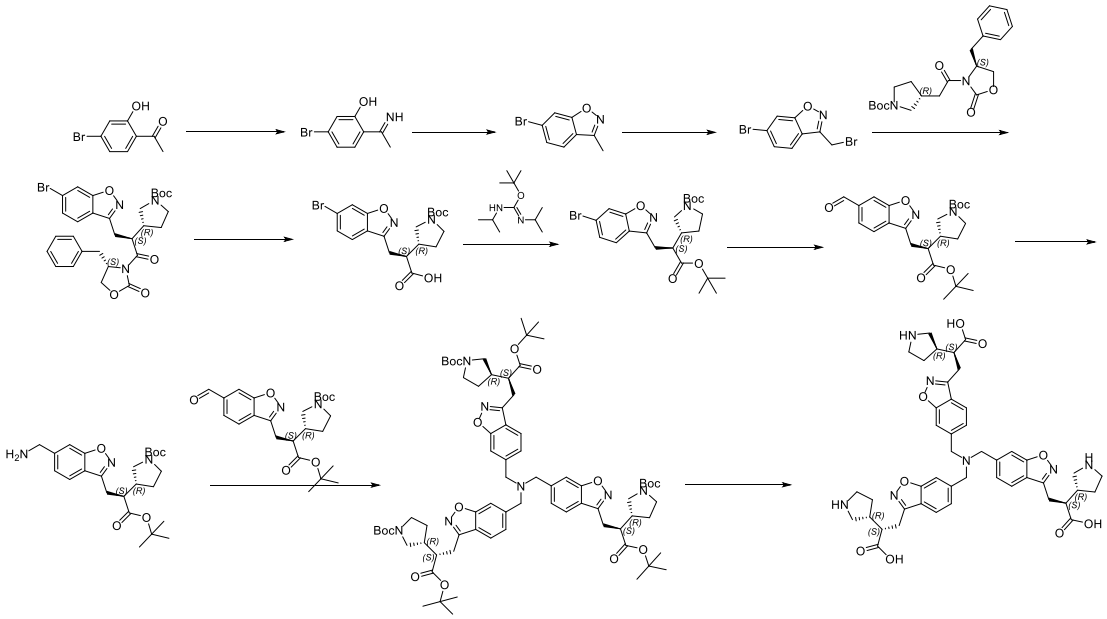
directly and separated and purified by rapid chromatography (Silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 820.2.

Step 2: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the first step (300 mg) was dissolved in ethyl acetate (10 mL), followed by adding hydrogen chloride-ethyl acetate (4.0M, 10 mL). The mixture was stirred at room temperature for 24h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to give the target compound (208.1 mg). LCMS (ESI) $[M+H]^+$ = 508.1;^{1}H NMR (400 MHz, D_2O) δ 7.23 (dt, *J* = 14.8, 7.6 Hz, 2H), 7.09 (dt, *J* = 12.7, 4.7 Hz, 4H), 7.04-6.93 (m, 2H), 4.27 (s, 2H), 3.54 (s, 2H), 3.41-3.26 (m, 4H), 3.14 (dddd, *J* = 11.7, 9.2, 7.3, 1.8 Hz, 2H), 2.87-2.63 (m, 6H), 2.44-2.30 (m, 4H), 2.04 (dq, *J* = 10.0, 3.4 Hz, 2H), 1.72-1.59 (m, 2H).

Example 58 (Compound 144)

Preparation of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzo[d]isoxazole-6,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of 5-bromo-2-(1-iminoethyl)phenol

1-(4-bromo-2-hydroxyphenyl)ethan-1-one (20 g, 93.01 mmol, 1.0 eq) was dissolved in methanol (100 mL), and a solution of ammonia in methanol (26.57 mL, 186.01 mmol, 2.0 eq, 7.0 M) was added at room temperature. The reaction was maintained at room temperature for 4h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly to give the target product (19 g). LCMS (ESI) $[M+H]^+$ = 214.0/216.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.14 (s, 1H), 10.26 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.50 (dd, J = 8.8, 2.1 Hz, 1H), 2.48 (s, 3H).

Step 2: Synthesis of 6-bromo-3-methylbenzo[d]isoxazole

5-bromo-2-(1-iminoethyl)phenol (19 g, 88.76 mmol, 1.0 eq) was dissolved in tetrahydrofuran (200 mL), potassium carbonate (24.54 g, 177.52 mmol, 2.0 eq) and N-chlorosuccinimide (17.78 g, 133.14 mmol, 1.5 eq) were added sequentially; the reaction was maintained at room temperature for 16h and LCMS showed the reaction was completed. The reaction mixture was diluted with water (300 mL), extracted with ethyl acetate (200 mL x 3), the organic phases were merged, washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give a crude product, which was separated and purified by rapid chromatography (silica, petroleum ether/ethyl acetate = 15/1) to give the target compound (16 g). LCMS (ESI) $[M+H]^+$ = 211.9/213.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 1.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 8.4, 1.5 Hz, 1H), 2.58 (s, 3H).

Step 3: Synthesis of 6-bromo-3-(bromomethyl)benzo[d]isoxazole

6-bromo-3-methylbenzo[d]isoxazole (15.6 g, 73.57 mmol, 1.0 eq) was dissolved in carbon tetrachloride (200 mL). N-bromosuccinimide (14.4 g, 80.93 mmol, 1.1 eq) and benzoyl peroxide (1.78 g, 7.36 mmol, 0.1 eq) were added at room temperature. The reaction mixture was stirred at 80°C for 16h. The mixture was diluted with water (300 mL), extracted with dichloromethane (200mL×3). The organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude product was separated and purified by rapid chromatography (silicon dioxide, petroleum ether/ethyl acetate = 15/1) to give the target product (16 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 1.2 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 8.4, 1.4 Hz, 1H), 4.71 (s, 2H).

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(6-bromobenzo[d]isoxazol-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (6 g, 15.45 mmol, 1 eq) was dissolved in tetrahydrofuran (70 mL), lithium bis(trimethylsilyl)amide (20.08 mL, 20.08 mmol, 1.3 eq, 1.0 M) was added dropwise under nitrogen protection and ice bath; the mixture was stirred for 1h under ice bath. 6-bromo-3-(bromomethyl)benzo[d]isoxazole (8 g, 19.25 mmol, 1.25 eq) was dissolved in tetrahydrofuran, and the mixture was added dropwise to the reaction system, then the reaction mixture was stirred for 16h at room temperature. LCMS showed the reaction was completed and then the reaction was quenched with aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate. The organic phases were merged and washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether/tetrahydrofuran = 3/1) to give the target product (6.0 g). LCMS (ESI) $[M+Na]^+$ = 620.1/622.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 1.2 Hz, 1H), 7.91 (dd, J = 8.3, 4.3 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.28-7.17 (m, 5H), 4.68-4.63 (m, 1H), 4.61-4.52 (m, 1H), 4.12 (d, J = 8.9 Hz, 1H), 3.54-3.44 (m, 2H), 3.38 (d, J = 9.3 Hz, 1H), 3.22-3.09 (m, 2H), 3.08-2.97 (m, 2H), 2.86-2.78 (m, 1H), 2.69-2.61 (m, 1H), 2.06-1.88 (m, 2H), 1.74-1.66 (m, 1H), 1.39 (s, 9H).

Step 5: Synthesis of (S)-3-(6-bromobenzo[d]isoxazol-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(6-bromobenzo[d]isoxazol-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (8.7 g, 14.54 mmol, 1.0 eq) was dissolved in tetrahydrofuran (100 mL), hydrogen peroxide solution (18 mL) was added under ice bath; an aqueous solution (10 mL) of lithium hydroxide (522.24 mg, 21.81 mmol, 1.5 eq) was added dropwise to the above solution under ice bath, and the mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed, and the reaction was quenched with sodium sulfate, and aqueous sodium carbonate was added to adjust the pH = 10. The mixture was extracted with ethyl acetate. The aqueous phase was retained, and its pH was adjusted to 4 with dilute hydrochloric acid (1 M). The mixture was extracted with dichloromethane, and the organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium

sulfate, filtered, and concentrated to give the target product (5.5 g). LCMS (ESI) $[M+Na]^+$ = 461.1/463.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 8.09 (d, *J* = 1.2 Hz, 1H), 7.88 (dd, *J* = 8.1, 5.9 Hz, 1H), 7.59 (dd, *J* = 8.4, 1.3 Hz, 1H), 3.63-3.48 (m, 1H), 3.44-3.38 (m, 1H), 3.29-3.23 (m, 1H), 3.17 (dd, *J* = 12.7, 7.4 Hz, 2H), 3.05 (t, *J* = 9.9 Hz, 1H), 2.94-2.83 (m, 1H), 2.46-2.30 (m, 1H), 1.97-1.89 (m, 1H), 1.67 (dq, *J* = 21.7, 10.7 Hz, 1H), 1.40 (s, 9H).

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-3-(6-bromobenzo[d]isoxazol-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(6-bromobenzo[d]isoxazol-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (5.5 g, 12.52 mmol, 1.0 eq) was dissolved in 2-methyltetrahydrofuran (60 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (7.52 g, 37.56 mmol, 3.0 eq) was added. The reaction mixture was stirred at 70°C for 16h under nitrogen protection. LCMS showed the reaction was completed. The mixture was diluted with tetrahydrofuran (50 mL), filtered, and the filter cake was washed with acetonitrile. The filtrate was concentrated and separated and purified by rapid chromatography (silicon dioxide, petroleum ether/ethyl acetate = 3/1) to give the target compound (3.5 g). LCMS (ESI) $[M+Na]^+$ = 517.1/519.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, *J* = 1.3 Hz, 1H), 7.91 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.59 (dd, *J* = 8.4, 1.5 Hz, 1H), 3.57 (dt, *J* = 14.2, 10.1 Hz, 1H), 3.42-3.35 (m, 1H), 3.25-3.12 (m, 3H), 3.08 (t, J = 10.0 Hz, 1H), 2.91-2.81 (m, 1H), 2.46-2.31 (m, 1H), 1.96-1.86 (m, 1H), 1.74-1.60 (m, 1H), 1.40 (s, 9H), 1.19 (s, 9H).

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formylbenzo[d]isoxazol-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(6-bromobenzo[d]isoxazol-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2.0 g, 4.04 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (30 mL), followed by adding sodium carbonate (855.78 mg, 8.07 mmol, 2.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (296.21 mg, 0.4 mmol, 0.1 eq), and triethylsilane (938.86 mg, 8.07 mmol, 2.0 eq); the reaction mixture was replaced with carbon monoxide gas and the reaction was maintained at 80°C for 2h under a carbon monoxide. LCMS showed the reaction was completed. The reaction was quenched with water. The mixture was extracted with ethyl acetate. The organic phases were merged and washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude

product, which was separated and purified by rapid chromatography (silica gel, petroleum ether/ethyl acetate = 5/1) to give the target compound (900 mg). LCMS (ESI) $[M+Na]^+$ = 467.1.

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-3-(6-(aminomethyl)benzo[d]isoxazol-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formylbenzo[d]isoxazol-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (400 mg, 0.9 mmol, 1.0 eq) was dissolved in ammonia methanol (10 mL, 7 M), one drop of acetic acid was added, and the mixture was stirred at room temperature for 4h; sodium cyanoborohydride (278.19 mg, 4.5 mmol, 5 eq) was added, and the reaction mixture was stirred at 70°C for 2h. LCMS showed the reaction was completed. The reaction mixture was quenched with water, concentrated, and purified by reversed-phase column chromatography (0.1% ammonia water) to give the target compound (200 mg). LCMS (ESI) $[M+H]^+$ = 446.2.

Step 9: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[d]isoxazole-6,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate)

tert-butyl (R)-3-((S)-3-(6-(aminomethyl)benzo[d]isoxazol-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg, 0.45 mmol, 1.0 eq) was dissolved in ethanol (10 mL), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(6-formylbenzo[d]isoxazol-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (399.08 mg, 0.9 mmol, 2.0 eq) was added. One drop of acetic acid was added dropwise, and the mixture was stirred at room temperature for 4h. sodium cyanoborohydride (138.77 mg, 2.24 mmol, 5 eq) was added, and the reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction of starting material was completed. The reaction mixture was quenched with water and concentrated. The residue was purified by reversed-phase column chromatography (C_{18}, 0.1% trifluoroacetic acid in water) to give the target compound (100 mg). LCMS (ESI) $[M+Na]^+$ = 1324.4.

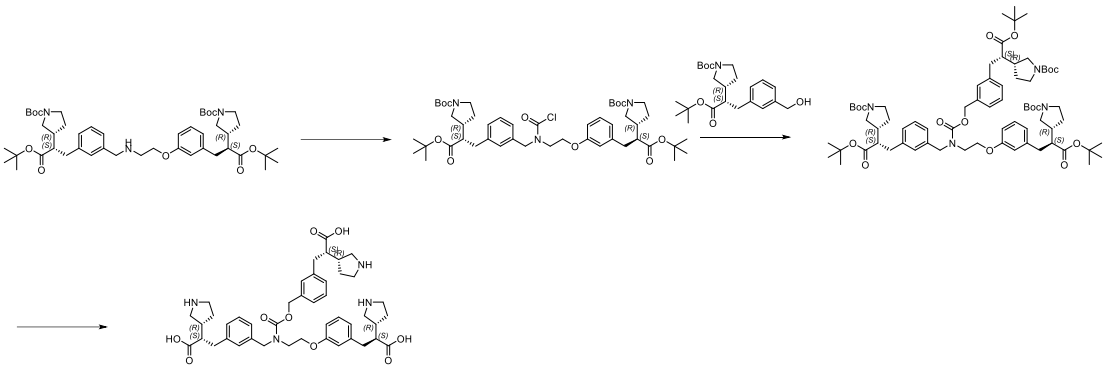
Step 10: Synthesis of (2S,2'S,2''S)-3,3',3''-((nitrilotris(methylene))tris(benzo[d]isoxazole-6,3-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid)

Tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-((nitrilotris(methylene))tris(benzo[d]isoxazole-6,3-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate) (100 mg, 0.08 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/1,4-dioxane (2

mL, 4 M) was added, and the reaction mixture was stirred at room temperature for 16h. After the reaction was completed, the mixture was concentrated to dryness, dissolved in water, adjusted to pH = 7 with sodium carbonate aqueous solution (1 M). After concentration, the mixture was purified by high pressure liquid chromatography (0.1%NH_4HCO_3) to give the target compound (17.64 g). LCMS (ESI) $[M+H]^+$ = 834.5; ^{1}H NMR (400 MHz, D_2O) δ 7.38 (d, *J* = 7.7 Hz, 3H), 7.11 (d, *J* = 24.3 Hz, 3H), 6.99 (t, *J* = 8.3 Hz, 3H), 3.31 (s, 6H), 3.25-2.98 (m, 12H), 2.84 (t, *J* = 10.6 Hz, 3H), 2.76 (d, *J* = 10.4 Hz, 3H), 2.61 (dd, *J* = 13.6, 7.9 Hz, 3H), 2.44-2.31 (m, 3H), 2.00 (s, 3H), 1.74-1.62 (m, 3H).

Example 59 (Compound 145)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (300 mg, 0.36 mmol, 1 eq) was dissolved in tetrahydrofuran (10 mL), triethylamine (364.28 mg, 3.6 mmol, 10 eq) and triphosgene (106.83 mg, 0.36 mmol, 1 eq) were added at 0°C; the mixture was stirred at 0°C for 1h. LCMS showed the reaction was completed. Water was added to the mixture, which was extracted with ethyl acetate,

and the organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to give the target compound (250 mg). LCMS (ESI) $[M+Na]^+$ = 906.3.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)oxy)carbonyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(hydroxymethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (111.93 mg, 0.28 mmol, 1.2 eq) was dissolved in tetrahydrofuran (5 mL), sodium hydride (6.35 mg, 0.28 mmol, 1.2 eq) was added at 0°C, and the mixture was stirred at 0°C for 0.5h. *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg, 0.23 mmol, 1 eq) was added, and the mixture was stirred at 0°C for 2h. LCMS showed the reaction was completed. Water was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was removed to dryness to give a crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (100 mg). LCMS (ESI) $[M+H-Boc]^+$ = 1153.6.

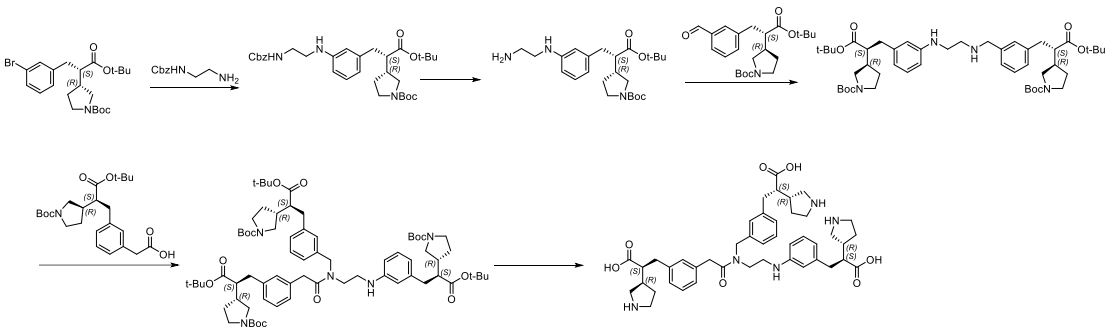
Step 3: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)oxy)carbonyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (100 mg, 0.08 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/1,4-dioxane (4 M, 2 mL) solution was added at room temperature, and the mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed, the reaction mixture was rotary-evaporated to dryness, and the crude product was purified by Pre-HPLC (30 mmol NH_4HCO_3 in H_2O / ACN) to give the target compound (33 mg). LCMS (ESI) $[M+H]^+$ = 785.6; ^1H NMR (400 MHz, D_2O) δ 7.30-7.21 (m, 1H), 7.20-7.11 (m, 4H),

7.06-6.90 (m, 4H), 6.84-6.75 (m, 1H), 6.66-6.60 (m, 1H), 6.58-6.51 (m, 1H), 5.11-5.02 (m, 2H), 4.58-4.39 (m, 2H), 4.14-3.94 (m, 2H), 3.65 (s, 2H), 3.42-3.24 (m, 6H), 3.20-3.07 (m, 3H), 2.84-2.47 (m, 9H), 2.42-2.24 (m, 6H), 2.10-1.95 (m, 3H), 1.74-1.56 (m, 3H).

Example 60 (Compound 146)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)amino)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-((2-(((benzyloxy)carbonyl)amino)ethyl)amino)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate:

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(500 mg) was dissolved in 1,4-dioxane (10 mL), benzyl (2-aminoethyl)carbamate (427.44 mg), potassium carbonate (456.24 mg) and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (99.86 mg) were added at room temperature; the mixture was stirred at 100°C for 16h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness, and the crude product was purified by column chromatography (petroleum ether:ethyl acetate = 4:1) to give the target compound (200 mg). LCMS (ESI) $[M+H]^+$ = 568.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 7.08-7.02 (m, 1H), 6.55-6.49 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 6.42-6.37 (m, 1H), 5.11 (s, 2H), 3.60-3.37 (m, 4H), 3.32-3.20 (m, 3H), 3.03-2.91 (m, 1H), 2.82-2.63 (m, 2H), 2.51-2.41 (m, 1H), 2.39-2.27 (m, 1H), 1.97-1.89 (m, 1H), 1.70-1.64 (m, 1H), 1.46 (s, 9H), 1.30 (s, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-((2-aminoethyl)amino)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate:

The product from step 1 (150 mg) was dissolved in methanol (5 mL), Pd/C (30 mg) was added at room temperature. Replaced with hydrogen gas three times, the mixture was stirred at room temperature for 16h under hydrogen. LCMS showed the reaction was completed. The reaction mixture was filtered, and the filtrate was concentrated to give the target compound (110 mg). LCMS (ESI) $[M+H]^+$ = 434.3.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)amino)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate:

The product from step 2 (110 mg) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(122.85 mg) was dissolved in ethanol (5 mL), and titanium tetraisopropanolate (144.21 mg) was added at room temperature; and the reaction mixture was stirred at room temperature for 1h. Sodium borohydride (14.4 mg) was added, and the reaction mixture was stirred the at room temperature for 2h. LCMS showed the reaction was completed. Saturated ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was rotary-evaporated to dryness to give a crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (75 mg). LCMS (ESI) $[M+H]^+$ = 822.0.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)-N-(2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)amino)ethyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate:

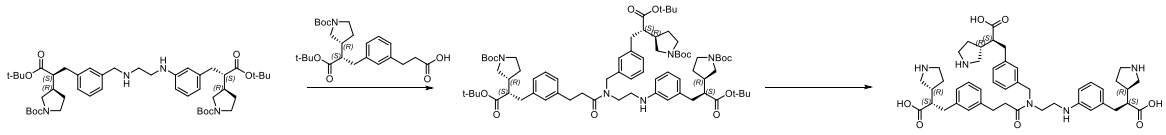
The product from step 3 (25 mg) and 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (14.52 mg) were dissolved in ethyl acetate (3 mL). 1-propanephosphonic acid anhydride (14.53 mg) and *N,N*-diisopropylethylamine (7.87 mg) were added at room temperature. The reaction mixture was

stirred at 50°C for 16h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness to give the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (20 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1136.6.

Step 5: The product from step 4 (20 mg) was dissolved in 1,4-dioxane (1 mL), hydrochloric acid/1,4-dioxane (4 M, 1 mL) was added at room temperature, and the mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed, the reaction mixture was evaporated to dryness, and the crude product was purified by Pre-HPLC (30 mmol NH_4HCO_3 in H_2O/ACN) to give the target compound (2.07 mg). LCMS (ESI) $[M+H]^+$ = 768.8; ^1H NMR (400 MHz, D_2O) δ 7.25-7.18 (m, 2H), 7.15-7.05 (m, 3H), 7.01-6.74 (m, 4H), 6.64-6.59 (m, 1H), 6.49 (dd, *J* = 20.0, 7.4 Hz, 2H), 4.62-4.51 (m, 2H), 3.70-3.58 (m, 2H), 3.53-3.41 (m, 2H), 3.37-3.19 (m, 8H), 3.18-3.05 (m, 3H), 2.83-2.65 (m, 6H), 2.64-2.52 (m, 3H), 2.45-2.25 (m, 6H), 2.09-1.94 (m, 3H), 1.73-1.55 (m, 3H).

Example 61 (Compound 147)

Preparation of (S)-3-(3-(3-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)amino)ethyl)amino)-3-oxopropyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-(N-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)-3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)propanamido)ethyl)amino)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate:

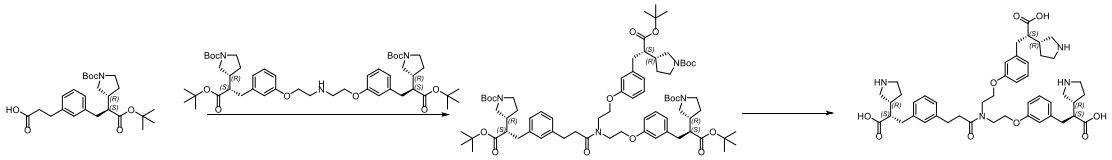
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)amino)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (50 mg, 0.06 mmol, 1 eq) and 3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)propanoic acid (29.98 mg,

0.07 mmol, 1.1 eq) were dissolved in ethyl acetate (3 mL). 1-propanephosphonic acid anhydride (29.06 mg, 0.09 mmol, 1.5 eq) and *N,N*-diisopropylethylamine (23.61 mg, 0.18 mmol, 3 eq) were added at room temperature; the reaction mixture was stirred at 50°C for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated to dryness to give the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give the target compound (50 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1150.6.

Step 2: The product from step 1 (50 mg, 0.04 mmol, 1 eq) was dissolved in 1,4-dioxane (1 mL), and hydrochloric acid/1,4-dioxane (4 M, 1 mL) solution was added at room temperature. The mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed, the reaction mixture was rotary-evaporated to dryness, and the crude product was purified by Pre-HPLC (30 mmol NH_4HCO_3 in H_2O/ACN) to give the target compound (8.8 mg). LCMS (ESI) $[M+H]^+$ = 782.6. ^1H NMR (400 MHz, D_2O) δ 7.22-6.99 (m, 5H), 6.98-6.69 (m, 4H), 6.63-6.58 (m, 1H), 6.52-6.43 (m, 2H), 4.50-4.44 (m, 1H), 4.40-4.31 (m, 1H), 3.44-3.22 (m, 8H), 3.18-3.05 (m, 5H), 2.83-2.65 (m, 8H), 2.66-2.49 (m, 5H), 2.42-2.25 (m, 6H), 2.11-1.95 (m, 3H), 1.73-1.57 (m, 3H).

Example 62 (Compound 148)

Preparation of (2S,2'S)-3,3'-(((((3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)propanoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)propanoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate

Di-*tert*-butyl 3,3'-((2S,2'S)-(((azanediylbis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)(100 mg, 0.12 mmol, 1 eq) was dissolved in ethyl acetate (4 mL), and 3-(3-((S)-3-

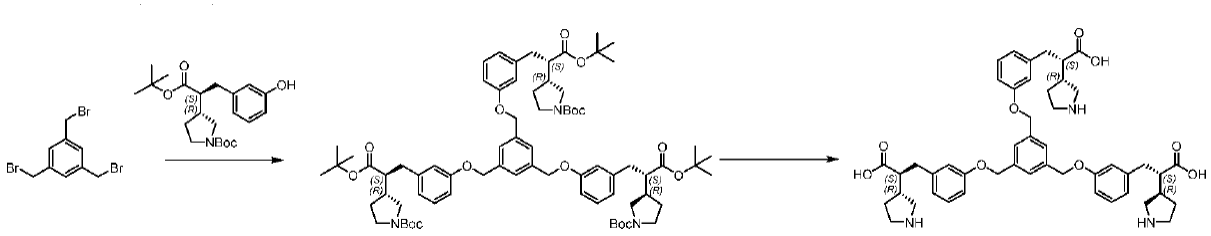
(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)propanoic acid(53.71 mg, 0.12 mmol, 1 eq), 1-propylphosphonic acid anhydride (57.27 mg, 0.18 mmol, 1.5 eq) and *N,N*-diisopropylethylamine (46.53 mg, 0.36 mmol, 3 eq) were added; the reaction was maintained at 50°C for 18h under nitrogen protection. LCMS showed the reaction was completed. The reaction mixture was concentrated to give a crude product, which was separated and purified by rapid chromatography (Silica gel, tetrahydrofuran:petroleum ether = 1:3) to give the target compound (70 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1181.6.

Step 2: Synthesis of (2S,2'S)-3,3'-(((((3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)propanoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid):

Di-*tert*-butyl 3,3'-((2S,2'S)-(((((3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)propanoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate) (70 mg, 0.05 mmol, 1 eq) was dissolved in dioxane (2 mL), hydrochloric acid/1,4-dioxane (4 M, 2 mL) was added; the reaction mixture was stirred at room temperature for 2h under nitrogen. The reaction mixture was concentrated to give a crude product, which was purified by Prep-HPLC (0.1% NH_4HCO_3 in water, MeCN) to give the target compound (12 mg). LCMS (ESI) $[M+H]^+$ = 813.5;^{1}H NMR (400 MHz, D_2O) δ 7.17 (t, *J* = 7.6 Hz, 2H), 7.04-6.98 (m, 1H), 6.97-6.91 (m, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 2H), 6.71-6.56 (m, 4H), 4.07-3.99 (m, 2H), 3.98-3.88 (m, 2H), 3.71-3.58 (m, 4H), 3.38-3.09 (m, 9H), 2.94-2.47 (m, 13H), 2.41-2.27 (m, 6H), 2.07-1.94 (m, 3H), 1.71-1.54 (m, 3H).

Example 63 (Compound 149)

Preparation of (2S,2'S,2"S)-3,3',3"-(((benzene-1,3,5-triyltris(methylene))tris(oxy))tris(benzene-3,1-diyl))tris(2-((R)-pyrrolidin-3-yl)propanoic acid):



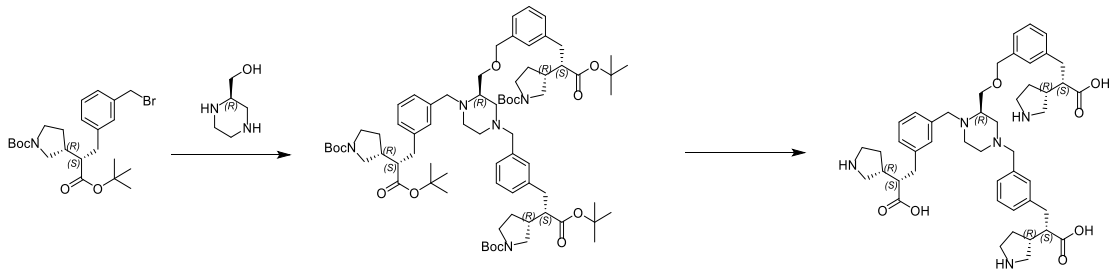
Step 1: Synthesis of tri-*tert*-butyl 3,3',3''-((2S,2'S,2''S)-(((benzene-1,3,5-triyltris(methylene))tris(oxy))tris(benzene-3,1-diyl))tris(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R,3''R)-tris(pyrrolidine-1-carboxylate):

Under nitrogen protection, 1,3,5-tris(bromomethyl)benzene (60 mg, 0.17 mmol, 1 eq) was dissolved in acetonitrile (5 mL), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(329 mg, 0.84 mmol, 5 eq) and potassium carbonate (139.42 mg, 1.01 mmol, 6 eq) were added, and the reaction mixture was stirred at 70°C for 18hours. The reaction mixture was concentrated under reduced pressure and purified by rapid chromatography (silica gel, tetrahydrofuran:petroleum ether = 1:5) to give the target compound (160 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1188.7.

Step 2: The product from step 1 (170 mg, 0.13 mmol, 1 eq) was dissolved in 1,4-dioxane (3 mL), hydrochloric acid/1,4-dioxane (3 mL, 4.0 M) was added, and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was concentrated, adjusted to pH = 7 with sodium hydroxide (1.0 M), and purified by Prep-HPLC (C_{18}, 0.1% NH_4HCO_3 in water, MeCN) to give the target compound (42.21 mg). LCMS (ESI) $[M+H]^+$ = 820.5; ^{1}H NMR (400 MHz, D_2O) δ 7.00 (t, *J* = 7.7 Hz, 3H), 6.90 (s, 3H), 6.73 (d, *J* = 7.6 Hz, 3H), 6.61 (s, 3H), 6.42 (d, *J* = 7.8 Hz, 3H), 4.39 (s, 6H), 3.27-3.17 (m, 3H), 3.06-2.95 (m, 6H), 2.69-2.58 (m, 3H), 2.52 (t, *J* = 10.3 Hz, 3H), 2.40-2.15 (m, 9H), 1.96-1.87 (m, 3H), 1.64-1.51 (m, 3H).

Example 64 (Compound 150)

Preparation of (2S,2'S)-3,3'-((((R)-2-(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)methyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((R)-2-(((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)oxy)methyl)piperazine-1,4-

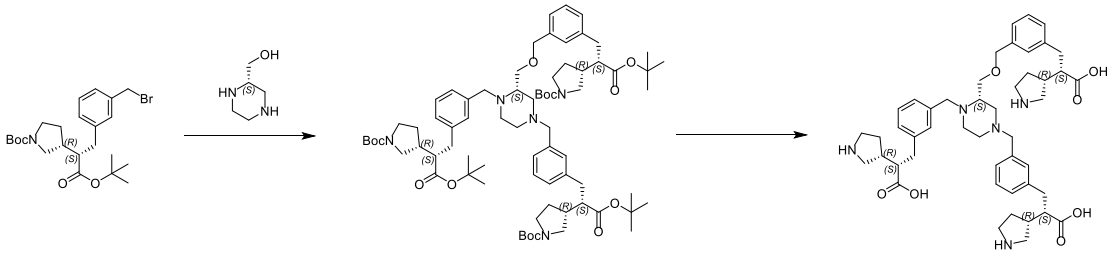
diyl)bis(methylene))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

Under nitrogen protection, (R)-piperazin-2-ylmethanol(80 mg, 0.69 mmol, 1 eq) was dissolved in acetonitrile (6 mL), *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(967.81 mg, 2.07 mmol, 3 eq) and *N,N*-diisopropylethylamine (0.36 mL, 2.07 mmol, 3 eq) were added. The mixture was stirred at 70°C for 18hours. The reaction mixture was concentrated to give a crude product, which was purified by reversed-phase column chromatography (C_{18}, 0.1% trifluoroacetic acid in acetonitrile) to give the target compound (500 mg). LCMS (ESI) $[M+H]^+$ = 1278.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50-7.34 (m, 6H), 7.31-7.23 (m, 3H), 7.18-7.07 (m, 3H), 5.10-4.79 (m, 3H), 4.44-4.31 (m, 6H), 3.88-3.61 (m, 6H), 3.52-3.30 (m, 9H), 3.23-3.00 (m, 6H), 2.98-2.88 (m, 3H), 2.81-2.65 (m, 6H), 2.34-2.21 (m, 3H), 1.88-1.78 (m, 3H), 1.62-1.53 (m, 3H), 1.38 (s, 27H), 1.19 (d, *J* = 8.0 Hz, 27H).

Step 2: The product from step 1 (300 mg, 0.23 mmol, 1 eq) was dissolved in 1,4-dioxane (5 mL), followed by adding hydrochloric acid/1,4-dioxane (5 mL, 4.0 M). The reaction mixture was stirred at room temperature for 3h. Upon completion, the reaction mixture was concentrated and the pH was adjusted to 7 with sodium hydroxide (1.0 M) aqueous solution. The mixture was separated and purified by prep-HPLC (C_{18}, 0.1%NH_4HCO_3 in H_2O/ACN) to give the target compound (57.44 mg). LCMS (ESI) $[M+H]^+$ = 810.5; ^{1}H NMR (400 MHz, D_2O) δ 7.41-7.25 (m, 7H), 7.16-7.09 (m, 5H), 4.74-4.72 (m, 2H), 4.30 (q, *J* = 13.1 Hz, 2H), 4.05 (d, *J* = 12.9 Hz, 1H), 3.89-3.79 (m, 2H), 3.53-3.41 (m, 4H), 3.38-3.29 (m, 5H), 3.24-3.07 (m, 6H), 3.00-2.89 (m, 4H), 2.83-2.67 (m, 7H), 2.44-2.31 (m, 6H), 2.08-1.97 (m, 3H), 1.74-1.58 (m, 3H).

Example 65 (Compound 151)

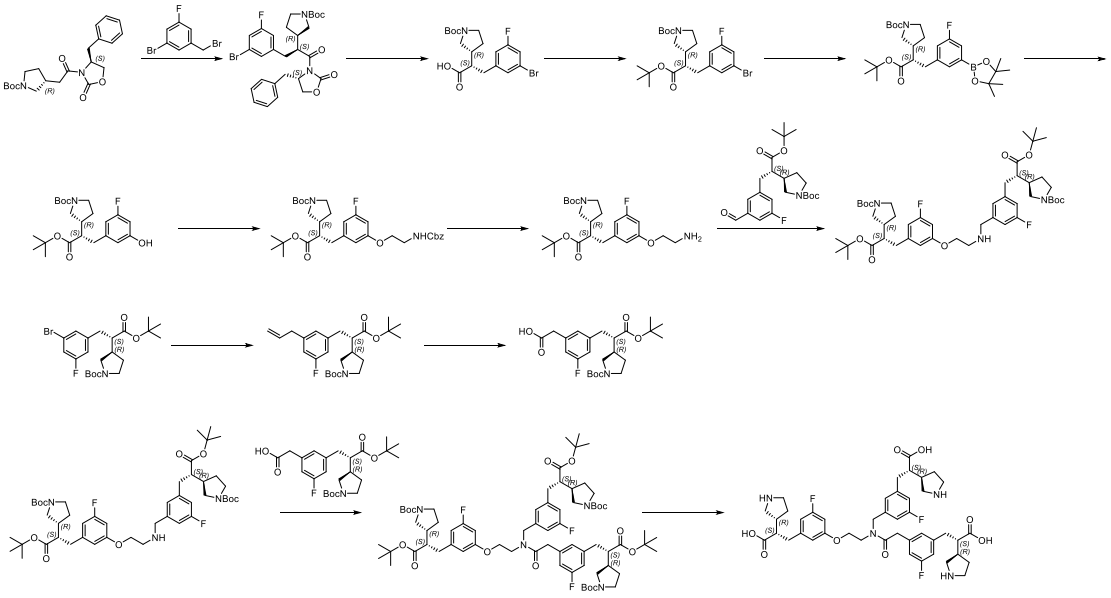
Preparation of (2S,2'S)-3,3'-((((S)-2-(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)methyl)piperazine-1,4-diyl)bis(methylene))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Compound 151 (43.77 mg) was prepared using a procedure similar to that described for Example 64, except using (S)-piperazin-2-ylmethanol(30 mg, 0.16 mmol, 1 eq) as the starting material. LCMS (ESI) $[M+H]^+$ = 810.6; ^1H NMR (400 MHz, D_2O) δ 7.42-7.22 (m, 7H), 7.19-7.09 (m, 5H), 4.78-4.72 (m, 2H), 4.37-4.24 (m, 2H), 4.08-3.99 (m, 1H), 3.86-3.74 (m, 2H), 3.55-3.40 (m, 4H), 3.39-3.28 (m, 5H), 3.28-3.08 (m, 6H), 3.02-2.69 (m, 11H), 2.48-2.31 (m, 6H), 2.12-1.96 (m, 3H), 1.75-1.56 (m, 3H).

Example 66 (Compound 152)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-5-fluorobenzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-5-fluorophenoxy)ethyl)amino)-2-oxoethyl)-5-fluorophenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromo-5-fluorophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, a solution of lithium bis(trimethylsilyl)amide (30.89 mL, 1.0 M in THF) was added dropwise to a solution of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate(10 g) in tetrahydrofuran. The reaction mixture was stirred at 0°C for 30min, then a solution of 1-bromo-3-(bromomethyl)-5-fluorobenzene (7.59 g) in tetrahydrofuran was added, and the reaction temperature was slowly raised to room temperature and stirred for 16h. LCMS showed the reaction was completed. Saturated ammonium chloride

solution was added to the mixture, which was extracted with ethyl acetate. The organic phase was washed with saturated NaCl solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the target compound (15 g). LCMS (ESI) $[M+H\text{-}Boc]^+ = 475.22$.

Step 2: Synthesis of (S)-3-(3-bromo-5-fluorophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

The crude product from Step 1 (15 g) was dissolved in tetrahydrofuran (300 mL), and lithium hydroxide (0.94 g) and hydrogen peroxide (1.33 g) were added. The reaction mixture was stirred at room temperature for 16h. LCMS showed the consumption of starting material was completed. The solvent was removed by rotary-evaporation to dryness, water and ethyl acetate were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to give the product (9 g). LCMS (ESI) $[M+H\text{-}Boc]^+ = 316.10$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromo-5-fluorophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, the product from step 2 (17.8 g) was dissolved in 2-methyltetrahydrofuran (150 mL), and *tert*-butyl N,N'-diisopropylcarbamimidate (44 g) was added. The reaction mixture was heated to 65°C and stirred for 16h. LCMS showed the reaction was completed. The insoluble materials were filtered off, and the filter cake was washed with methyl *tert*-butyl ether. The filtrate was concentrated, and separated and purified by rapid column chromatography (Silica gel, petroleum ether:ethyl acetate = 10:1) to give the product (11 g). LCMS (ESI) $[M+H\text{-}2\ tert\text{-}butyl]^+ = 360.13$.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 3 (8 g), bis(pinacolato)diboron (6.48 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (1.28 g) and potassium acetate (3.36 g) were added to 1,4-dioxane (40 mL) and H_2O (10 mL). The mixture was stirred at 90°C under nitrogen for 4h. LCMS showed the reaction was completed. After cooling to room temperature, water and ethyl acetate were added, and the mixture was extracted. The organic phase was

concentrated to give the crude product (8 g), which was used directly in the next step. LCMS (ESI) $[M+H- Boc]^+ = 420.43$.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 4 (8 g) was dissolved in tetrahydrofuran (20 mL), and hydrogen peroxide (2.62 g) was added. The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. An appropriate amount of saturated sodium thiosulfate solution was added, and the mixture was extracted with ethyl acetate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the product (6.1 g). LCMS (ESI) $[M+H-2\times tBu]^+ = 298.18$.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)-5-fluorophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 5 (6.1 g) was dissolved in N,N-dimethylformamide (50 mL), followed by adding potassium carbonate (6.1 g) and benzyl (2-bromoethyl)carbamate (7.6 g). The reaction mixture was stirred at 90°C overnight. Upon completion of the reaction as monitored by LCMS, the mixture was cooled to room temperature. Ethyl acetate and water were added, and the mixture was extracted. The organic phase was rotary-evaporated under reduced pressure, and the residue was purified by column chromatography (petroleum ether:ethyl acetate = 4:1) to give the target compound (6.8 g). LCMS (ESI) $[M+H-Boc]^+ = 487.37$.

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)-5-fluorophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 6 (6.8 g) was dissolved in tetrahydrofuran (100 mL), and Pd/C (340 mg, 10%) was added. The mixture was stirred at room temperature under a hydrogen atmosphere for 16h. LCMS showed the reaction was completed. After filtration, the filtrate was rotary-evaporated to dryness to give a crude product (4.25 g), which was used directly in the next step. LCMS (ESI) $[M+H]^+ = 453.41$.

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-

fluorophenoxy)ethyl)amino)methyl)-5-fluorophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 7 (2.2 g) was dissolved in tetrahydrofuran (25 mL), and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-fluoro-5-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2.05 g) was added. The resulting mixture was stirred at room temperature for 1h. Then, sodium cyanoborohydride (0.6 g) was added and the mixture was stirred at room temperature for 36hours. LCMS showed the reaction was completed. The reaction was quenched with saturated ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was then purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:5) to give the target compound (1.2 g). LCMS (ESI) $[M+H]^+$ = 858.78.

Step 9: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-allyl-5-fluorophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(3-bromo-5-fluorophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(3 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.47 g) and potassium phosphate (4.04 g) were dissolved in 1,4-dioxane (7 mL) and water (30 mL), and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.13 g) was added. The reaction mixture was stirred at 90°C overnight, and LCMS showed the reaction was completed. After cooling to room temperature, ethyl acetate and water were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (1.5 g). LCMS (ESI) $[M+H-2\times t\text{-butyl}]^+$ = 322.22.

Step 10: Synthesis of 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorophenyl)acetic acid

The product from step 9 (1.5 g) was dissolved in acetonitrile (15 mL) and water (15 mL), followed by adding sodium iopanoate (2.96 g) and ruthenium trichloride (60 mg); the reaction mixture was stirred at room temperature for 16h, and LCMS showed the reaction was completed. Ethyl acetate and water were added to the reaction mixture for extraction, and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which

was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the product (800 mg). LCMS (ESI) $[M+H-2\times tert\text{-butyl}]^+$ = 340.18.

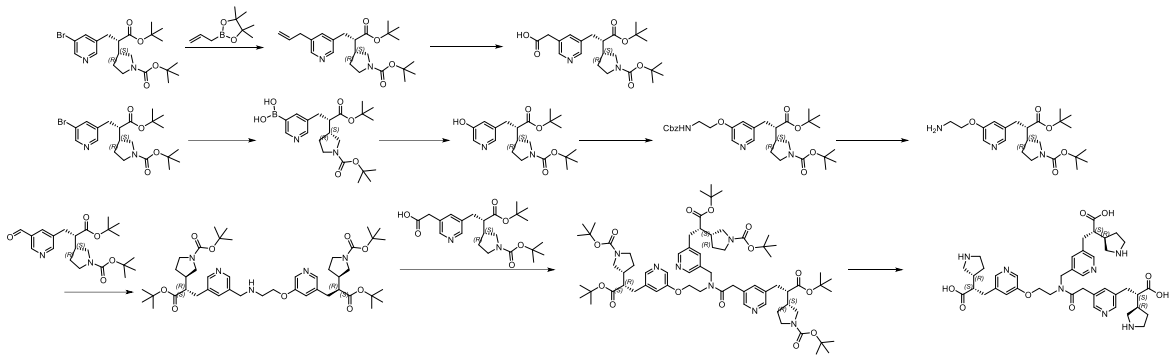
Step 11: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorophenoxy)ethyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-fluorophenyl)acetamido)methyl)-5-fluorophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 8 (700 mg) was dissolved in N,N-dimethylformamide (3 mL), followed by adding the product from step 10 (368 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (465 mg) and *N,N*-diisopropylethylamine (316 mg). The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. Ethyl acetate and water were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by rapid chromatography (petroleum ether:ethyl acetate = 1:8) to give the target compound (800 mg).

Step 12: The product from the Step 11 (1.3 g) was dissolved in 1,4-dioxane (10 mL), hydrogen chloride/1,4-dioxane (10 mL, 4.0 M) was added, and the mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation under reduced pressure, and the residue was purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the product (240 mg). LCMS (ESI) $[M+H]^+$ = 823.62; ^{1}H NMR (400 MHz, D_2O) δ 6.97-6.60 (m, 6H), 6.59-6.36 (m, 2H), 6.35-6.25 (m, 1H), 4.65-4.48 (m, 2H), 4.10-3.64 (m, 6H), 3.46-3.26 (m, 6H), 3.21-3.08 (m, 3H), 2.89-2.21 (m, 15H), 2.10-1.94 (m, 3H), 1.74-1.55 (m, 3H).

Example 67 (Compound 153)

Preparation of (S)-3-(5-(2-(2-(5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)pyridin-3-yl)-N-((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)pyridin-3-yl)methyl)acetamido)ethoxy)pyridin-3-yl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-allylpyridin-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Potassium phosphate (1006.84 mg) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (154.57 mg) were added to *tert*-butyl (R)-3-((S)-3-(5-bromopyridin-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1.08 g) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (797.05 mg) in a mixture of dioxane (15 mL) and water (3 mL) under nitrogen under nitrogen. The mixture was heated to 90°C and stirred for 2h. LCMS showed the reaction was completed. After cooled to room temperature, the mixture was dilute with water (30 mL), and extract with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was separated and purified by column chromatography (silica gel, tetrahydrofuran:petroleum ether = 1:3) to give the target compound (900 mg). LCMS (ESI) $[M+H]^+ = 417.3$.

Step 2: 2-(5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)pyridin-3-yl)acetic acid

Under ice bath, sodium periodate (2.16 g) and ruthenium(III) chloride hydrate (56.81 mg) was added to a solution of the product from step 1 (1.05 g) in acetonitrile (15 mL) and water (15 mL). The reaction mixture was stirred at 0°C for 2h. After completion of the reaction, the reaction mixture was diluted with diatomaceous earth, filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was diluted with water, extracted with ethyl acetate, and the merged organic phases were washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparative separation (C_{18}, 0.03% trifluoroacetic acid in water, acetonitrile) to give the target compound (140 mg). LCMS

(ESI) $[M+H]^+$ = 435.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 11.4 Hz, 2H), 7.51 (s, 1H), 3.59-3.52 (m, 3H), 3.18-3.10 (m, 2H), 3.02 (t, J = 9.9 Hz, 1H), 2.84-2.75 (m, 1H), 2.73-2.66 (m, 1H), 2.57-2.52 (m, 1H), 2.34-2.24 (m, 1H), 1.89-1.79 (m, 1H), 1.65-1.53 (m, 1H), 1.40 (s, 9H), 1.21 (s, 9H).

Step 3: Synthesis of (5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)pyridin-3-yl)boronic acid

Under nitrogen atmosphere, bis(pinacolato)diboron (2.34 g) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (902.27 mg) were added to a solution of *tert*-butyl (R)-3-((S)-3-(5-bromopyridin-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2.8 g) and potassium acetate (1.81 g) in 1,4-dioxane (50 mL). The reaction mixture was heated to 90°C and stirred for 16h. LCMS showed the reaction was completed. After the reaction mixture was cooled to room temperature, it was filtered through diatomaceous earth to remove the filter residue, and the filtrate was concentrated under reduced pressure to give the target compound (5 g, crude product). This intermediate was used directly in the next step without further purification. LCMS (ESI) $[M+H]^+$ = 421.2.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-hydroxypyridin-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under ice bath, hydrogen peroxide (6.74 g) was added slowly to a solution of the product from step 3 (5 g) in methanol (40 mL). The reaction mixture was warmed to room temperature and stirred for 16h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated aqueous sodium thiosulfate (8 mL), concentrated under reduced pressure, and the residue was diluted with water and extracted with ethyl acetate. The merged organic phases were washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica gel, tetrahydrofuran/petroleum ether = 1:1) to give the target compound (1.6 g). LCMS (ESI) $[M+H]^+$ = 393.2.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-(2-(((benzyloxy)carbonyl)amino)ethoxy)pyridin-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Potassium carbonate (1.48 g) was added to a solution of the product from step 4 (1.4 g) and benzyl (2-bromoethyl)carbamate (1.84 g) in *N,N*-dimethylformamide (15 mL). The reaction mixture was heated to 80°C and stirred for 4h. LCMS showed the reaction was completed. The reaction solution is cooled to room temperature, diluted with water, extracted with ethyl acetate, the organic phases are merged, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated, and the resulting residue is separated and purified by column chromatography (silica gel, tetrahydrofuran/petroleum ether = 1:3) to obtain the target compound (1.3 g). LCMS (ESI) $[M+H]^+$ = 570.4.

Step 6: Synthesis of (3*R*)-3-[(2*S*)-3-[5-(2-aminoethoxy)pyridine-3-yl]-1-(*tert*-butoxy)-1-oxopropan-2-yl]pyrrolidin-1-carboxylic acid *tert*-butyl ester:

Pd/C (650.82 mg, 10% w/t) was added to a solution of the product from step 5 (1.3 g) in tetrahydrofuran (20 mL). The reaction mixture was purged with hydrogen and stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction solution was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (C_{18}, 0.1% ammonia water in water/acetonitrile) to give the target compound (590 mg). LCMS (ESI) $[M+H]^+$ = 436.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, *J* = 2.7 Hz, 1H), 7.98 (d, *J* = 1.2 Hz, 1H), 7.25 (s, 1H), 4.00-3.92 (m, 2H), 3.56-3.47 (m, 1H), 3.40-3.37 (m, 1H), 3.17-3.09 (m, 1H), 3.02 (t, *J* = 10.0 Hz, 1H), 2.87 (t, *J* = 5.8 Hz, 2H), 2.78-2.66 (m, 2H), 2.61-2.53 (m, 1H), 2.35-2.22 (m, 1H), 1.90-1.80 (m, 1H), 1.63-1.53 (m, 1H), 1.40 (s, 9H), 1.22 (s, 9H).

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-(((2-((5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)pyridin-3-yl)oxy)ethyl)amino)methyl)pyridin-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Titanium tetraisopropanolate (421.59 mg) was added to a solution of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylpyridin-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(300 mg) and the product from step 6 (355.34 mg) in ethanol (12 mL). The reaction mixture was stirred at room temperature for 14hours, then sodium borohydride (84.17 mg) was added to the reaction system, and the reaction mixture was stirred at room temperature for another 2 hours. The reaction mixture was quenched with saturated ammonium chloride, then filtered through diatomaceous earth, and the filtrate was dried over anhydrous sodium sulfate, filtered and concentrated. The

residue was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 1:1) to give the target compound (550 mg). LCMS (ESI) $[M+H]^+$ = 824.6.

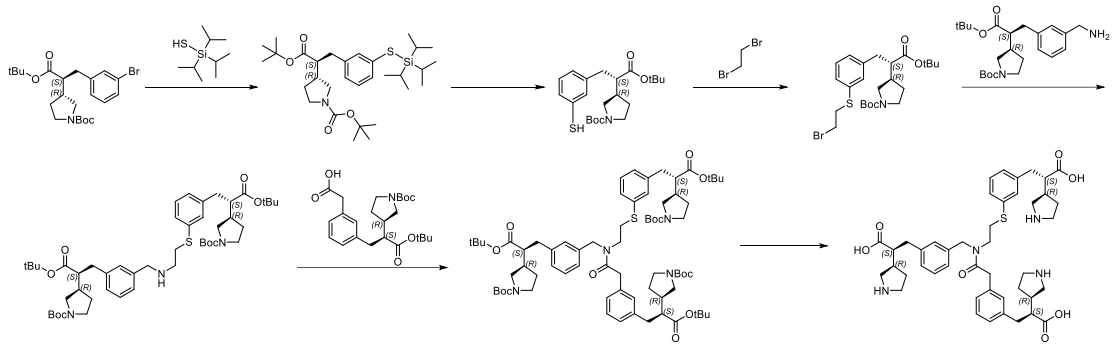
Step 8: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-((2-(5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)pyridin-3-yl)-N-(2-((5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)pyridin-3-yl)oxy)ethyl)acetamido)methyl)pyridin-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

N,N-diisopropylethylamine (13.38 mg) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (26.25 mg) were added to a solution of the product from step 7 (42.67 mg) and 2-(5-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)pyridin-3-yl)acetic acid (15 mg) in *N,N*-dimethylformamide (2 mL), respectively. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was diluted with water, extracted with ethyl acetate, and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by reversed-phase separation (C_{18}, 0.1% trifluoroacetic acid in water/acetonitrile) to give the target compound (20 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1140.3.

Step 9: The product from step 8 (20 mg) was dissolved in a solution of hydrogen chloride/1,4-dioxane (3 mL, 4.0 M), and the reaction mixture was stirred at room temperature for 6h. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure, and the pH of the resulting residue was adjusted to 7–8 with sodium hydroxide solution (1.0 M). The mixture was separated and purified by reversed-phase preparation (C_{18}, 0.03% ammonium bicarbonate in water/acetonitrile) to give the target compound (2.86 mg). LCMS (ESI) $[M+H]^+$ = 772.5; ^{1}H NMR (400 MHz, D_2O) δ 8.24 (d, *J* = 9.8 Hz, 1H), 8.16-8.06 (m, 2H), 8.01-7.80 (m, 2H), 7.70-7.26 (m, 3H), 7.09-6.86 (m, 1H), 4.63-4.52 (m, 4H), 4.22-4.15 (m, 1H), 4.05-3.98 (m, 3H), 3.84-3.80 (m, 1H), 3.53-3.39 (m, 3H), 3.37-3.30 (m, 3H), 3.22-3.12 (m, 3H), 2.96-2.81 (m, 3H), 2.75-2.66 (m, 3H), 2.63-2.49 (m, 2H), 2.42-2.29 (m, 6H), 2.09-1.98 (m, 3H), 1.74-1.60 (m, 3H).

Example 68 (Compound 158)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)thio)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-((triisopropylsilyl)thio)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(4 g, 8.8 mmol, 1 eq) was dissolved in toluene (40 mL), triisopropylsilanethiol (1.9 mL, 8.8 mmol, 1 eq), cesium carbonate (5.74 g, 17.61 mmol, 2 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.65 g, 0.88 mmol, 0.1 eq) were added; the reaction mixture was stirred at 120°C for 5hours. The reaction mixture was filtered through diatomaceous earth, the filtrate was concentrated, and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 15:1) to give the target compound (3.9 g). LCMS (ESI) $[M+H\text{-}Boc]^+ = 464.4$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.38-7.03 (m, 4H), 3.55-3.43 (m, 1H), 3.37-3.33 (m, 1H), 3.18-3.07 (m, 1H), 2.97 (t, J = 10.0 Hz, 1H), 2.80-2.64 (m, 2H), 2.49-2.45 (m, 1H), 2.31-2.19 (m, 1H), 1.87-1.79 (m, 1H), 1.61-1.52 (m, 1H), 1.39 (s, 9H), 1.24-1.18 (m, 9H), 1.01-0.96 (m, 21H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-mercaptophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, the product from step 1 (3.9 g, 6.92 mmol, 1 eq) was dissolved in dioxane (20 mL), followed by adding hydrochloric acid (40 mL, 1.0 M). The reaction mixture was stirred at 30°C for hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phases were merged and dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated. The residue was separated and purified by rapid chromatography (silica gel, ethyl acetate:petroleum ether = 1:3) to give the target compound (420 mg). LCMS (ESI) $[M+Na]^+ = 430.3$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-((2-bromoethyl)thio)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, the product from step 2 (420 mg, 1.03 mmol, 1 eq) was dissolved in acetonitrile (4 mL), 1,2-dibromoethane (967.95 mg, 5.15 mmol, 5 eq) and potassium carbonate (427.28 mg, 3.09 mmol, 3 eq) were added, and the reaction mixture was heated to 70°C and stirred for 16h. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 514.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28-7.21 (m, 3H), 7.09-7.04 (m, 1H), 3.60-3.47 (m, 3H), 3.41-3.33 (m, 4H), 3.20-3.09 (m, 1H), 2.99 (t, J = 10.0 Hz, 1H), 2.76-2.64 (m, 2H), 2.32-2.20 (m, 1H), 1.88-1.77 (m, 1H), 1.63-1.53 (m, 1H), 1.40 (s, 9H), 1.22 (s, 9H).

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)thio)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, the product from step 3 (300 mg, 0.58 mmol, 1 eq) was dissolved in acetonitrile (3 mL), and *tert*-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (235.87 mg, 0.58 mmol, 1 eq) and potassium carbonate (241.76 mg, 1.75 mmol, 3 eq) were added. The reaction mixture was heated to 90°C and stirred for 18hours. After the reaction was completed, the reaction solution was filtered through diatomaceous earth and concentrated to give the crude product, which was purified by column chromatography (silica gel: petroleum ether:ethyl acetate = 1:1) to give the target compound (80 mg). LCMS (ESI) $[M+H]^+$ = 838.8; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23-7.10 (m, 6H), 7.05-6.96 (m, 2H), 3.69-3.58 (m, 2H), 3.58-3.40 (m, 3H), 3.40-3.34 (m, 4H), 3.21-3.09 (m, 2H), 3.07-2.87 (m, 4H), 2.75-2.65 (m, 6H), 2.30-2.21 (m, 2H), 1.88-1.78 (m, 2H), 1.62-1.52 (m, 2H), 1.39 (s, 18H), 1.22 (s, 18H).

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)-N-(2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-

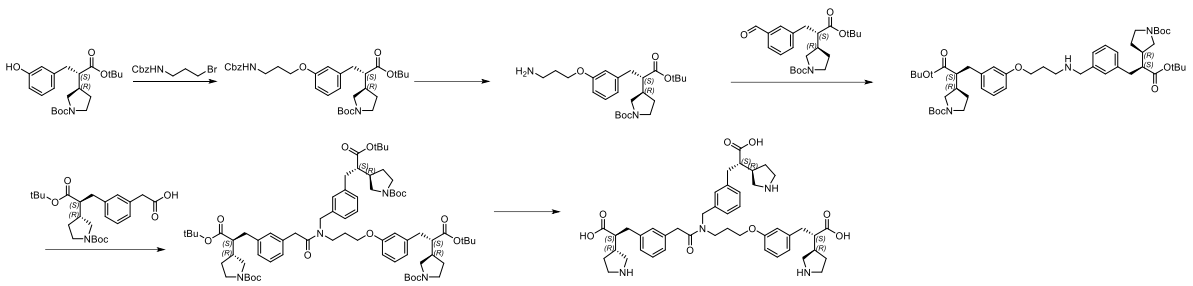
oxopropyl)phenyl)thio)ethyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 4 (140 mg, 0.17 mmol, 1 eq) was dissolved in N,N-dimethylformamide (2 mL), 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid(79.66 mg, 0.18 mmol, 1.1 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (127.02 mg, 0.33 mmol, 2 eq) and *N,N*-diisopropylethylamine (64.76 mg, 0.5 mmol, 3 eq) were added and the reaction solution was stirred at room temperature. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and concentrated, and then it was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (40 mg). LCMS (ESI) $[M+H\text{-Boc}]^+$ = 1153.7.

Step 6: The product from step 5 (35 mg, 0.03 mmol, 1 eq) was dissolved in 1,4-dioxane (1 mL), and hydrogen chloride/1,4-dioxane (1 mL, 4.0 M) was added. The reaction mixture was stirred at room temperature for 3h. After the reaction was completed, the solvent was removed by rotary-evaporation to dryness, and the pH was adjusted to 7 with sodium hydroxide (1.0 M). The residue was separated and purified by prep-HPLC (C-18, 0.1%NH_4HCO_3 in H_2O/ACN) to give the target compound (6.48 mg). LCMS (ESI) $[M+H]^+$ = 785.5; ^{1}H NMR (400 MHz, D_2O) δ 7.30-7.00 (m, 8H), 7.00-6.71 (m, 4H), 4.48-4.38 (m, 2H), 3.65-3.57 (m, 2H), 3.51-3.41 (m, 2H), 3.36-3.25 (m, 6H), 3.16-2.99 (m, 5H), 2.84-2.55 (m, 9H), 2.42-2.26 (m, 6H), 2.09-1.94 (m, 3H), 1.72-1.54 (m, 3H).

Example 69 (Compound 159)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)propyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(3-(((benzyloxy)carbonyl)amino)propoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(500 mg, 1.28 mmol, 1 eq) was dissolved in N,N-dimethylformamide (5 mL), benzyl (3-bromopropyl)carbamate (695.12 mg, 2.55 mmol, 2 eq) and potassium carbonate (529.54 mg, 3.83 mmol, 3 eq) were added, and the reaction was stirred at 80°C. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate, the organic phases were merged, washed with saturated brine, dried over sodium sulfate, filtered and concentrated. Then, it was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (690 mg).LCMS (ESI) $[M+H]^+$ = 583.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39-7.28 (m, 6H), 7.15 (t, J = 8.1 Hz, 1H), 6.77-6.71 (m, 3H), 5.01 (s, 2H), 3.94 (t, J = 6.3 Hz, 2H), 3.54-3.44 (m, 1H), 3.37-3.32 (m, 2H), 3.19-3.09 (m, 3H), 2.97 (t, J = 10.0 Hz, 1H), 2.74-2.65 (m, 2H), 2.32-2.13 (m, 1H), 1.86-1.80 (m, 3H), 1.62-1.53 (m, 1H), 1.39 (s, 9H), 1.23 (s, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(3-aminopropoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 1 (690 mg, 1.18 mmol, 1 eq) was dissolved in tetrahydrofuran (20 mL), and Pd/C (126.01 mg, 1.18 mmol, 1 eq) was added. The reaction was stirred at room temperature for 18hours under hydrogen atmosphere. After the reaction was completed, the mixture was filtered and concentrated to give the target compound (450 mg). LCMS (ESI) $[M+H]^+$ = 449.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18-7.11 (m, 1H), 6.76-6.70 (m, 3H), 4.02-3.91 (m, 2H), 3.56-3.41 (m, 2H), 3.19-3.07 (m, 2H), 2.97 (t, J = 10.0 Hz, 1H), 2.72-2.64 (m, 3H), 2.64-2.56 (m, 1H), 2.30-2.21 (m, 1H), 1.85-1.73 (m, 3H), 1.63-1.54 (m, 1H), 1.47-1.40 (m, 2H), 1.39 (s, 9H), 1.24 (s, 9H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)propyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(350 mg, 0.87 mmol, 1 eq) was dissolved in ethanol (3 mL), and titanium tetraisopropanolate (493.06 mg, 1.73 mmol, 2 eq) and the product from step 2 (428.02 mg, 0.95 mmol, 1.1 eq) were added. The reaction mixture was stirred at room temperature for 18hours. Sodium borohydride (49.22 mg, 1.3 mmol, 1.5 eq) was added to the reaction mixture, and the mixture was stirred at room temperature for 1h. Saturated ammonium chloride aqueous solution (0.2 mL) was added to the reaction mixture, and the mixture was filtered. The filtrate was concentrated and purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 1:1) to give the target compound (240 mg). LCMS (ESI) $[M+H]^+$ = 836.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20-7.12 (m, 4H), 7.03-6.99 (m, 1H), 6.75-6.69 (m, 3H), 3.98 (t, J = 6.4 Hz, 2H), 3.64 (s, 2H), 3.54-3.44 (m, 3H), 3.21-3.05 (m, 3H), 3.00-2.93 (m, 2H), 2.72-2.66 (m, 4H), 2.59 (t, J = 6.6 Hz, 2H), 2.47-2.42 (m, 1H), 2.30-2.21 (m, 2H), 1.89-1.78 (m, 5H), 1.61-1.53 (m, 2H), 1.39 (s, 18H), 1.22 (d, J = 4.8 Hz, 18H).

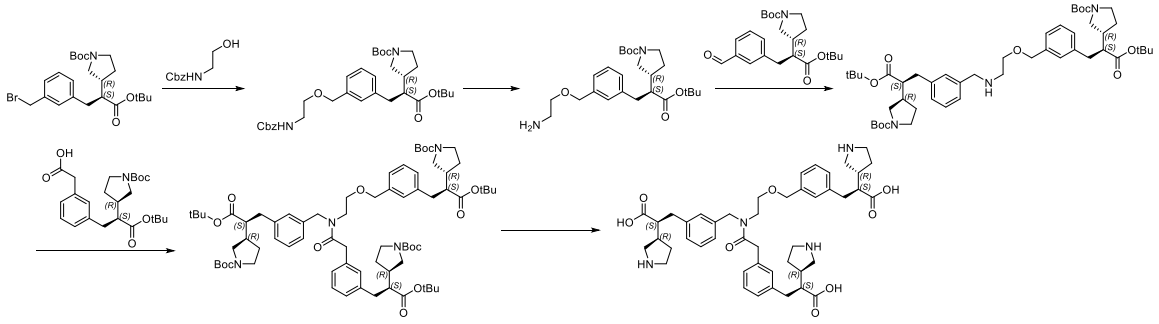
Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)propyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 3 (230 mg, 0.28 mmol, 1 eq) was dissolved in N,N-dimethylformamide (2 mL), followed by adding 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid(133.53 mg, 0.31 mmol, 1.1 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (209.19 mg, 0.55 mmol, 2 eq) and *N,N*-diisopropylethylamine (108.56 mg, 0.84 mmol, 3 eq); the reaction mixture was stirred at room temperature for 16h. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate, the organic phases were merged, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated, and purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (180 mg). LCMS (ESI) $[M+H-Boc]^+$ = 1151.7.

Step 5: The product from step 4 (170 mg, 0.14 mmol, 1 eq) was dissolved in 1,4-dioxane (3 mL), followed by adding hydrogen chloride/1,4-dioxane (3 mL, 4.0 M). The reaction mixture was stirred at room temperature for 3h. After the reaction was completed, the solvent was removed by rotary-evaporation to dryness, and the pH was adjusted to 7 with sodium hydroxide (1.0 M). The residue was separated and purified by prep-HPLC (C-18, 0.1%NH_4HCO_3 in H_2O/ACN) to give the target compound (37.59 mg). LCMS (ESI) $[M+H]^+$ = 783.5; ^{1}H NMR (400 MHz, D_2O) δ 7.24-7.14 (m, 3H), 7.10-7.03 (m, 2H), 6.99-6.79 (m, 5H), 6.74-6.63 (m, 2H), 4.57-4.48 (m, 2H), 3.95-3.85 (m, 2H), 3.76-3.65 (m, 2H), 3.52-3.39 (m, 2H), 3.37-3.22 (m, 6H), 3.18-3.07 (m, 3H), 2.83-2.54 (m, 9H), 2.42-2.25 (m, 6H), 2.06-1.82 (m, 5H), 1.71-1.51 (m, 3H).

Example 70 (Compound 160)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-((2-(((benzyloxy)carbonyl)amino)ethoxy)methyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1 g, 2.13 mmol, 1 eq) was dissolved in tetrahydrofuran (20 mL), and benzyl (2-hydroxyethyl)carbamate (833.53 mg, 4.27 mmol, 2 eq), benzyltriethylammonium chloride (48.63 mg, 0.21 mmol, 0.1 eq) and sodium hydroxide aqueous solution (10 mL, 50%) were added. The reaction solution was stirred for 18hours at room temperature. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated, and it was

purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (720 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 483.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41-7.27 (m, 6H), 7.23 (t, J = 7.7 Hz, 1H), 7.16-7.12 (m, 2H), 7.09 (d, J = 7.4 Hz, 1H), 5.01 (s, 2H), 4.42 (s, 2H), 3.53-3.46 (m, 1H), 3.45-3.36 (m, 4H), 3.21-3.12 (m, 3H), 2.97 (t, J = 9.9 Hz, 1H), 2.79-2.68 (m, 2H), 2.31-2.19 (m, 1H), 1.87-1.78 (m, 1H), 1.64-1.53 (m, 1H), 1.39 (s, 9H), 1.21 (s, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-((2-aminoethoxy)methyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 1 (720 mg, 1.24 mmol, 1 eq) was dissolved in tetrahydrofuran (2 mL), and Pd/C (131.49 mg, 1.24 mmol, 1 eq) was added. The reaction was carried out under hydrogen atmosphere at room temperature for 15 minutes. After the reaction was completed, the mixture was filtered and concentrated to give the target compound (550 mg). LCMS (ESI) $[M+H]^+$ = 449.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (t, J = 7.8 Hz, 1H), 7.18-7.13 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 4.46-4.39 (m, 2H), 3.63-3.42 (m, 3H), 3.20-3.08 (m, 2H), 2.98 (t, J = 9.8 Hz, 1H), 2.77-2.63 (m, 4H), 2.30-2.23 (m, 1H), 1.88-1.71 (m, 2H), 1.63-1.54 (m, 1H), 1.39 (s, 9H), 1.22 (s, 9H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)oxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(370 mg, 0.92 mmol, 1 eq) was dissolved in ethanol (5 mL), and titanium tetraisopropanolate (521.23 mg, 1.83 mmol, 2 eq) and the product from step 2 (452.48 mg, 1.01 mmol, 1.1 eq) were added. The reaction mixture was stirred at room temperature for 18hours. Sodium borohydride (52.03 mg, 1.38 mmol, 1.5 eq) was added to the reaction mixture, and the mixture was stirred at room temperature for 1h. After the reaction was completed, saturated ammonium chloride aqueous solution (0.2 mL) was added to the reaction mixture, and the mixture was filtered. The filtrate was concentrated and purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 1:1) to give the target compound (580 mg). LCMS (ESI) $[M+H]^+$ = 836.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27-7.06 (m, 7H), 7.02 (d, J = 7.3 Hz, 1H), 4.41 (s, 2H), 3.65 (s, 2H), 3.62-3.58 (m, 1H), 3.56-3.43 (m, 4H), 3.38-3.33 (m, 2H), 3.20-3.09 (m,

2H), 3.01-2.91 (m, 2H), 2.77-2.62 (m, 6H), 2.31-2.19 (m, 2H), 1.85-1.74 (m, 3H), 1.62-1.52 (m, 2H), 1.39 (s, 18H), 1.21 (s, 18H).

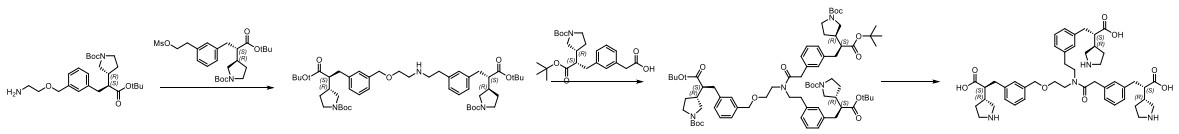
Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-(N-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)ethoxy)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from step 3 (300 mg, 0.36 mmol, 1 eq) was dissolved in N,N-dimethylformamide (3 mL), followed by adding 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid(171.11 mg, 0.39 mmol, 1.1 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (272.86 mg, 0.72 mmol, 2 eq) and *N,N*-diisopropylethylamine (139.12 mg, 1.08 mmol, 3 eq). The reaction was allowed to proceed at room temperature for 3h. Upon completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silicon gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (310 mg). LCMS (ESI) $[M+Na]^+$ = 1183.7.

Step 5: The product from step 4 (310 mg, 0.25 mmol, 1 eq) was dissolved in dioxane (3 mL), followed by adding hydrogen chloride/1,4-dioxane (3 mL, 4.0 M). The reaction mixture was stirred at room temperature for 3h. Upon completion, the reaction mixture was concentrated and adjusted to pH = 7 with sodium hydroxide (1.0 M). The resulting mixture was separated and purified by prep-HPLC (C_{18}, 0.1%NH_4HCO_3 in H_2O/ACN) to give the target compound (63.6 mg). LCMS (ESI) $[M+H]^+$ = 783.5; ^1H NMR (400 MHz, D_2O) δ 7.30-7.05 (m, 8H), 6.99-6.83 (m, 4H), 4.57-4.36 (m, 4H), 3.81 (s, 1H), 3.68 (s, 1H), 3.63-3.48 (m, 4H), 3.38-3.25 (m, 6H), 3.18-3.08 (m, 3H), 2.82-2.55 (m, 9H), 2.43-2.25 (m, 6H), 2.09-1.94 (m, 3H), 1.73-1.53 (m, 3H).

Example 71 (Compound 161)

Preparation of (S)-3-(3-(2-((2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)ethyl)(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)amino)ethoxy)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-((2-aminoethoxy)methyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(720 mg, 1.6 mmol, 1 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((methylsulfonyl)oxy)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(796.22 mg, 1.6 mmol, 1 eq) were dissolved in acetonitrile (10 mL), potassium carbonate (663.41 mg, 4.8 mmol, 3 eq) was added, and the mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 2:1) to give the target compound (680 mg). LCMS (ESI) $[M+H]^+$ = 850.9; ^{1}HNMR (400MHz, $CDCl_3$) δ 7.26-7.20 (m, 1H), 7.20-7.13 (m, 2H), 7.12-7.05 (m, 2H), 7.05-6.96 (m, 3H), 4.47 (s, 2H), 3.72-3.65 (m, 1H), 3.61-3.49 (m, 4H), 3.48-3.41 (m, 1H), 3.30-3.18 (m, 2H), 3.05-2.92 (m, 2H), 2.89-2.81 (m, 5H), 2.80-2.72 (m, 4H), 2.53-2.43 (m, 2H), 2.42-2.30 (m, 2H), 1.96-1.88 (m, 4H), 1.70-1.60 (m, 1H), 1.47 (s, 18H), 1.28 (s, 9H), 1.27 (s, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-(N-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)ethoxy)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

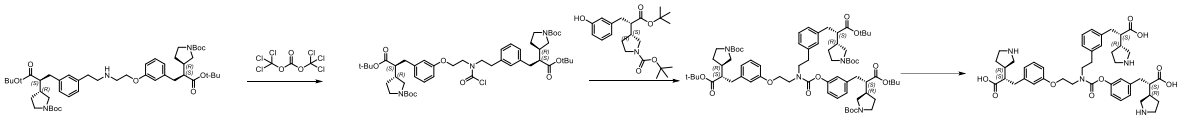
2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid(51 mg, 0.12 mmol, 1 eq) was dissolved in N,N-dimethylformamide (3 mL). Triethylamine (35.71 mg, 0.35 mmol, 3 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (67.09 mg, 0.18 mmol, 1.5 eq) and the product from step 1 (100 mg, 0.12 mmol, 1 eq) were added. The reaction mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated NaCl, dried

over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and purified by rapid chromatography (silicon gel, petroleum ether:tetrahydrofuran = 2:1) to give the target compound (130 mg). LCMS (ESI) $[M+H]^+$ = 1266.0; ^{1}HNMR (400MHz, $CDCl_3$) δ 7.26-7.15 (m, 3H), 7.14-6.97 (m, 8H), 6.95-6.86 (m, 1H), 4.44 (s, 2H), 3.79-3.72 (m, 2H), 3.71-3.64 (m, 2H), 3.62-3.36 (m, 11H), 3.31-3.21 (m, 3H), 3.04-2.91 (m, 3H), 2.90-2.80 (m, 2H), 2.79-2.69 (m, 5H), 2.52-2.42 (m, 3H), 2.41-2.30 (m, 3H), 1.98-1.89 (m, 3H), 1.64-1.57 (m, 2H), 1.47 (s, 27H), 1.26 (s, 27H).

Step 3: The product from step 2 (100 mg, 0.08 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/1,4-dioxane solution (2 mL, 4.0 M) was added, and the mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The reaction mixture was concentrated, dissolved in water, adjusted to pH = 7 with sodium hydroxide (1.0 M) aqueous solution, and purified by reversed-phase preparation (C_{18}, 0.1% ammonium bicarbonate aqueous solution, acetonitrile) to give the target product (41.91 mg). LCMS (ESI) $[M+H]^+$ = 797.5; ^{1}HNMR (400MHz, D_2O) δ 7.27-7.17 (m, 2H), 7.16-7.05 (m, 5H), 7.05-7.00 (m, 1H), 7.00-6.78 (m, 3H), 6.75-6.70 (m, 1H), 4.41 (d, *J* = 10.9 Hz, 2H), 3.64 (s, 2H), 3.59-3.41 (m, 4H), 3.39-3.21 (m, 7H), 3.21-3.19 (m, 1H), 3.17-3.04 (m, 3H), 2.83-2.65 (m, 8H), 2.64-2.52 (m, 3H), 2.42-2.25 (m, 6H), 2.08-1.95 (m, 3H), 1.71-1.55 (m, 3H).

Example 72 (Compound 162)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenethyl)((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(200

mg, 0.24 mmol, 1 eq) was dissolved in tetrahydrofuran (5 mL). At 0°C, triphosgene(70.98 mg, 0.24 mmol, 1 eq) and triethylamine (242.05 mg, 2.39 mmol, 10 eq) were added and stirred for 0.5h. LCMS showed the reaction was completed successfully. The reaction solution was directly used for the next step. LCMS (ESI) $[M+H\text{-}Boc]^+$ = 798.6.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)carbamoyl)oxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

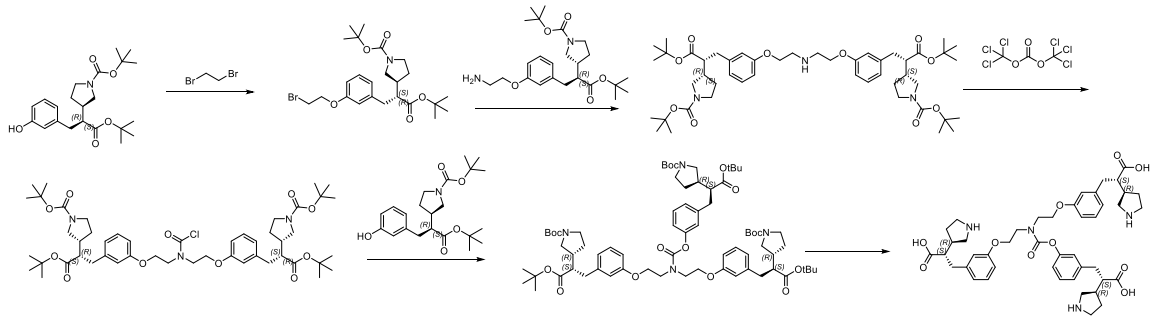
Under nitrogen protection, the product from step 1 (200 mg, 0.22 mmol, 1 eq) was dissolved in tetrahydrofuran (3 mL), and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(87.14 mg, 0.22 mmol, 1 eq) and N,N-dimethylpyridine-4-amine (2.27 mg, 0.02 mmol, 0.1 eq) were added. The mixture was stirred at 50°C for 18hours. LCMS showed the reaction was completed. The reaction mixture was concentrated and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (220 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1153.7.

Step 3: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenethyl)((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

Hydrochloric acid/1,4-dioxane (4 mL, 4.0 M) was added to a solution of the product from step 2 (300 mg, 0.24 mmol, 1 eq) in 1,4-dioxane (4 mL) and the mixture was stirred at room temperature for 2h. LCMS showed th reaction was completed. The reaction mixture was concentrated and neutralized with sodium hydroxide (1.0 M) solution. The residue was separated and purified by Prep-HPLC (C_{18}, 0.1% NH_4HCO_3 in water, ACN) to give the target compound (86 mg). LCMS (ESI) [M+H] = 785.5; ^{1}H NMR (400 MHz, D_2O) δ 7.27 (t, *J* = 7.9 Hz, 1H), 7.22-7.14 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.83-6.72 (m, 8H), 4.26 (d, *J* = 23.6 Hz, 4H), 3.79 (d, *J* = 50.9 Hz, 4H), 3.39-3.25 (m, 6H), 3.19-3.08 (m, 3H), 2.86-2.67 (m, 7H), 2.64-2.54 (m, 2H), 2.36 (d, *J* = 5.6 Hz, 6H), 2.02 (m, 3H), 1.73-1.58 (m, 3H).

Example 73 (Compound 163)

Preparation of (2S,2'S)-3,3'-((((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of *tert*-butyl (S)-3-((R)-3-(3-(2-bromoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1 g, 2.55 mmol, 1 eq) was dissolved in acetonitrile solution (10 mL), 1,2-dibromoethane (2.4 g, 12.77 mmol, 5 eq) and potassium carbonate (1.06 g, 7.66 mmol, 3 eq) were added, and the reaction was also stirred at 70°C. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried, and concentrated. Then, it was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (520 mg). LCMS (ESI) $[M+Na]^+$ = 520.2.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, the product from step 1 (520 mg, 1.04 mmol, 1 eq) was dissolved in acetonitrile (5 mL), *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(453.36 mg, 1.04 mmol, 1 eq) and potassium carbonate (432.56 mg, 3.13 mmol, 3 eq) were added. The reaction mixture was stirred at 90°C. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue was

purified by rapid chromatography (silica gel, ethyl acetate:petroleum ether = 2:1) to give the target compound (300 mg).LCMS (ESI) $[M+H]^+$ = 853.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70-11.68 (m, 2H), 7.18-7.13 (m, 2H), 6.77-6.75 (m, 2H), 6.74-6.72 (m, 2H), 5.37 (d, *J* = 3.9 Hz, 1H), 4.00 (t, *J* = 5.3 Hz, 4H), 3.82-3.76 (m, 4H), 3.49 (d, *J* = 11.1 Hz, 2H), 3.17-3.11 (m, 2H), 2.97-2.91 (m, 4H), 2.71-2.66 (m, 4H), 2.26 (s, 2H), 1.97-1.92 (m, 2H), 1.85-1.80 (m, 4H), 1.39 (s, 18H), 1.23 (s, 18H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, the product from step 2 (200 mg, 0.24 mmol, 1 eq) was dissolved in tetrahydrofuran (5 mL). Triphosgene(70.98 mg, 0.24 mmol, 1 eq) and triethylamine (242.05 mg, 2.39 mmol, 10 eq) were added at 0°C, and the mixture was stirred at 0°C for 0.5h. LCMS showed the reaction was completed, and the white turbid reaction mixture was directly used for the next step. LCMS (ESI) $[M+H]^+$ = 914.3.

Step 4: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-(((((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)carbonyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

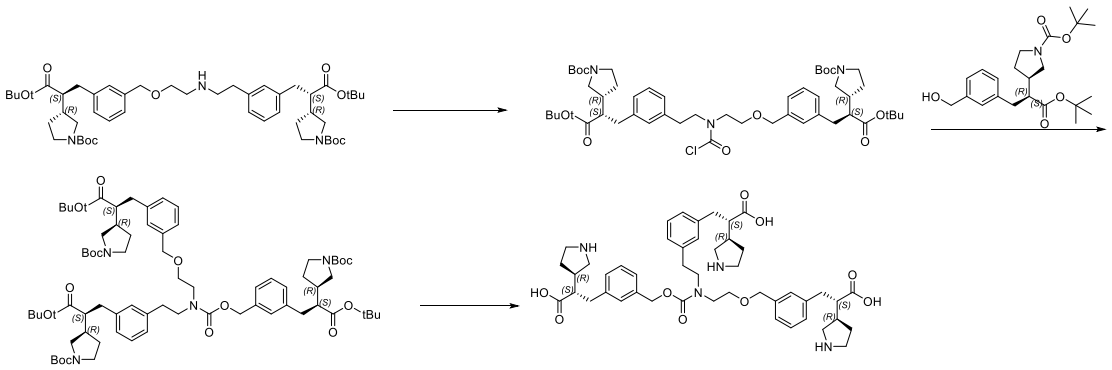
Under nitrogen protection, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(87.14 mg, 0.22 mmol, 1 eq) and N,N-dimethylpyridine-4-amine (2.27 mg, 0.02 mmol, 0.1 eq) were added to a solution of the product from step 3 (200 mg, 0.22 mmol, 1 eq) in tetrahydrofuran (4 mL). The mixture was stirred at 50°C for 18hours. LCMS showed the reaction was completed. The reaction mixture was concentrated and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 1:4) to give the target compound (100 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1169.7.

Step 5: Synthesis of (2S,2'S)-3,3'-((((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)carbonyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

Hydrochloric acid/dioxane (4 mL, 4.0 M) was added to a solution of the product from step 4 (300 mg, 0.24 mmol, 1 eq) in 1,4-dioxane (4 mL) and the mixture was stirred at room temperature for 2h. The reaction mixture was concentrated and neutralized with sodium hydroxide solution (1.0 M). Then, it was separated and purified by Prep-HPLC (C_{18}, 0.1% NH_4HCO_3 in water, ACN) to give the target compound (13 mg). LCMS (ESI) $[M+H]^+$ = 801.5; ^1H NMR (400 MHz, D_2O) δ 7.27 (t, *J* = 7.9 Hz, 1H), 7.22-7.14 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.83-6.72 (m, 8H), 4.26 (d, *J* = 23.6 Hz, 4H), 3.79 (d, *J* = 50.9 Hz, 4H), 3.39-3.25 (m, 6H), 3.19-3.08 (m, 3H), 2.86-2.67 (m, 7H), 2.64-2.54 (m, 2H), 2.36 (d, J = 5.6 Hz, 6H), 2.02 (m, 3H), 1.73-1.58 (m, 3H).

Example 74 (Compound 164)

Preparation of (S)-3-(3-(2-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)carbonyl)(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)ethyl)amino)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)(chlorocarbonyl)amino)ethoxy)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)amino)ethoxy)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(200 mg, 0.24 mmol, 1 eq) was dissolved in tetrahydrofuran (5 mL), triethylamine (242.86 mg, 2.4 mmol, 10 eq) and triphosgene (71.22 mg, 0.24 mmol, 1 eq) were added at 0°C, and the mixture was stirred at 0°C for 1h. LCMS showed the reaction was completed. Water was added to the mixture, which was extracted with ethyl acetate,

and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (200 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 812.5.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((((2-((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)benzyl)oxy)ethyl)(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)carbamoyl)oxy)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(hydroxymethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(80 mg, 0.2 mmol, 1 eq) was dissolved in tetrahydrofuran (5 mL), sodium hydride (9.07 mg, 0.39 mmol, 2 eq) was added at 0°C, and the mixture was stirred at 0°C for 0.5h. The product from step 1 (216.03 mg, 0.24 mmol, 1.2 eq) was added, and the mixture was stirred at 0°C for 2.5h. LCMS showed the reaction was completed. Water was added to the mixture, which was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and rotary-evaporated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 3:1) to give the target compound (100 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1181.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 3H), 7.17-7.06 (m, 6H), 7.03-6.96 (m, 2H), 6.95-6.87 (m, 1H), 5.30 (s, 2H), 5.08 (s, 2H), 3.75-3.35 (m, 12H), 3.30-3.18 (m, 3H), 3.09-2.92 (m, 3H), 2.88-2.63 (m, 8H), 2.52-2.30 (m, 6H), 1.99-1.87 (m, 3H), 1.69-1.62 (m, 3H), 1.47 (s, 27H), 1.25 (s, 27H).

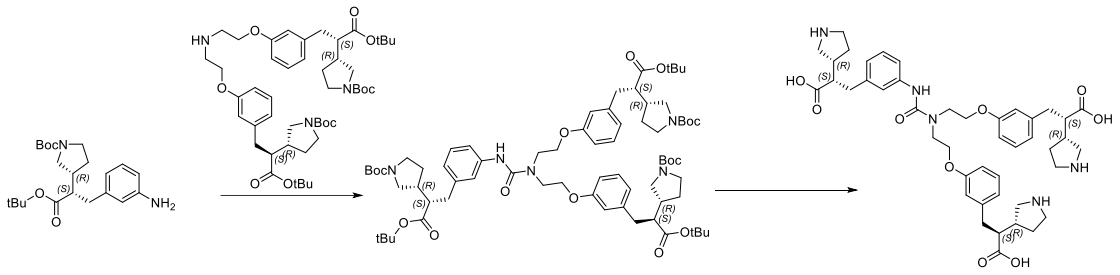
Step 3: Synthesis of (S)-3-(3-(2-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)carbonyl)(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)oxy)ethyl)amino)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from step 2 (100 mg, 0.08 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), and hydrochloric acid/1,4-dioxane (2 mL, 4.0 M) was added at room temperature. The mixture was stirred for 3h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness, and the crude product was adjusted to pH = 7–8 with sodium hydroxide solution (1.0 M). Then it was purified by pre-HPLC (C_{18}, 10 mmol NH_4HCO_3 in H_2O/ACN) to give the target compound (50.65 mg). LCMS (ESI) $[M+H]^+$ = 813.6; ^{1}H NMR (400 MHz, D_2O) δ 7.30-7.18 (m, 2H), 7.18-6.91 (m, 9H), 6.89-6.80 (m, 1H), 4.93 (s, 1H), 4.79 (s, 1H), 4.42-4.34 (m,

2H), 3.57-3.50 (m, 1H), 3.48-3.42 (m, 1H), 3.41-3.18 (m, 10H), 3.17-3.06 (m, 3H), 2.82-2.46 (m, 11H), 2.42-2.23 (m, 6H), 2.09-1.92 (m, 3H), 1.72-1.54 (m, 3H).

Example 75 (Compound 165)

Preparation of (2S,2'S)-3,3'-((((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)carbamoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: Synthesis of di-*tert*-butyl 3,3'-((2S,2'S)-((((((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)carbamoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)

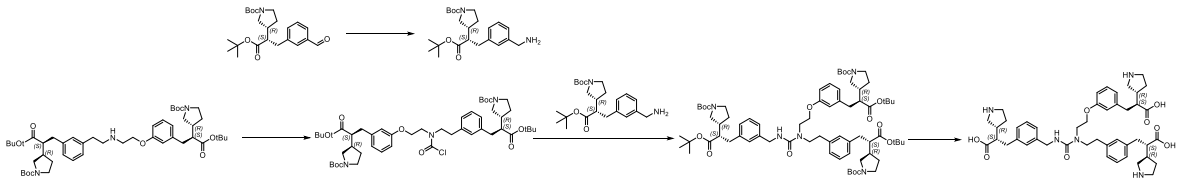
Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(3-aminophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(100 mg, 0.26 mmol, 1 eq) was dissolved in tetrahydrofuran (3 mL). Triethylamine (259.12 mg, 2.56 mmol, 10 eq) and triphosgene (37.99 mg, 0.13 mmol, 0.5 eq) were added at 0°C. The mixture was stirred at 0°C for 1h. Di-*tert*-butyl 3,3'-((2S,2'S)-(((azanediylbis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(3-(*tert*-butoxy)-3-oxopropane-1,2-diyl))(3R,3'R)-bis(pyrrolidine-1-carboxylate)(261.84 mg, 0.31 mmol, 1.2 eq) was added and the mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. Water was added to the mixture, which was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (C_{18}, 0.03% TFA in H_2O/ACN) to give the target compound (100 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1168.7.

Step 2: Synthesis of (2S,2'S)-3,3'-((((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)carbamoyl)azanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))bis(2-((R)-pyrrolidin-3-yl)propanoic acid)

The product from step 1 (100 mg, 0.08 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), and hydrochloric acid/dioxane (2 mL, 4.0 M) solution was added at room temperature. The mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The solvent was removed by rotary-evaporation to dryness to give a crude product. Water was added, and the crude product was adjusted to pH 7-8 with NaOH solution (1.0 M). The crude product was purified by Pre-HPLC (C_{18}, 10 mmol NH_4HCO_3 in H_2O/ACN) to give the target compound (20.57 mg). LCMS (ESI) $[M+H]^+$ = 800.5; ^{1}H NMR (400 MHz, D_2O) δ 7.26-7.19 (m, 1H), 7.13 (t, *J* = 7.9 Hz, 2H), 7.05-6.98 (m, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.81-6.63 (m, 6H), 4.23-4.13 (m, 4H), 3.77-3.62 (m, 4H), 3.44-3.37 (m, 1H), 3.36-3.23 (m, 5H), 3.20-3.07 (m, 3H), 2.91-2.82 (m, 1H), 2.78-2.61 (m, 6H), 2.57-2.48 (m, 2H), 2.45-2.24 (m, 6H), 2.10-1.94 (m, 3H), 1.75-1.54 (m, 3H).

Example 76 (Compound 166)

Preparation of (S)-3-(3-(2-(3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)-1-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)ureido)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1 g, 2.48 mmol, 1.0 eq) was dissolved in ammonia methanol (10 mL, 7.0 M) solution, and acetic acid (14.88 mg, 0.25 mmol, 0.1 eq) was added. The mixture was stirred at room temperature for 30min, and then sodium cyanoborohydride (1.23 g, 19.83 mmol, 8.0 eq) was added to the reaction mixture. The reaction mixture was heated to 70°C in a sealed tube and stirred for 16h. LCMS showed the reaction was completed. After the reaction mixture was cooled to room temperature and concentrated under reduced pressure to give a crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 0.1% formic acid in water/acetonitrile) to give the target compound (310 mg). LCMS (ESI) $[M+H]^+$ = 405.3; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.35 (s, 1H, HCOOH), 7.29-7.17 (m, 3H), 7.13-7.08 (m, 1H), 3.84 (s,

2H), 3.57-3.47 (m, 1H), 3.39-3.31 (m, 1H), 3.21-3.09 (m, 1H), 3.02-2.93 (m, 1H), 2.77-2.69 (m, 2H), 2.49-2.44 (m, 1H), 2.34-2.23 (m, 1H), 1.89-1.79 (m, 1H), 1.64-1.53 (m, 1H), 1.40 (s, 9H), 1.28-1.20 (m, 9H).

Step 2: *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen atmosphere, triethylamine (363.07 mg, 3.59 mmol, 10.0 eq) and triphosgene (106.48 mg, 0.36 mmol, 1.0 eq) was added to a solution of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(300 mg, 0.36 mmol, 1.0 eq) in tetrahydrofuran (12 mL) successively. The reaction mixture was stirred at 0°C for 30min, LCMS showed the reaction was completed. The crude product was used for the next step without further purification. LCMS (ESI) $[M+H\text{-}Boc]^+ = 798.6$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((3-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)-3-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)ureido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

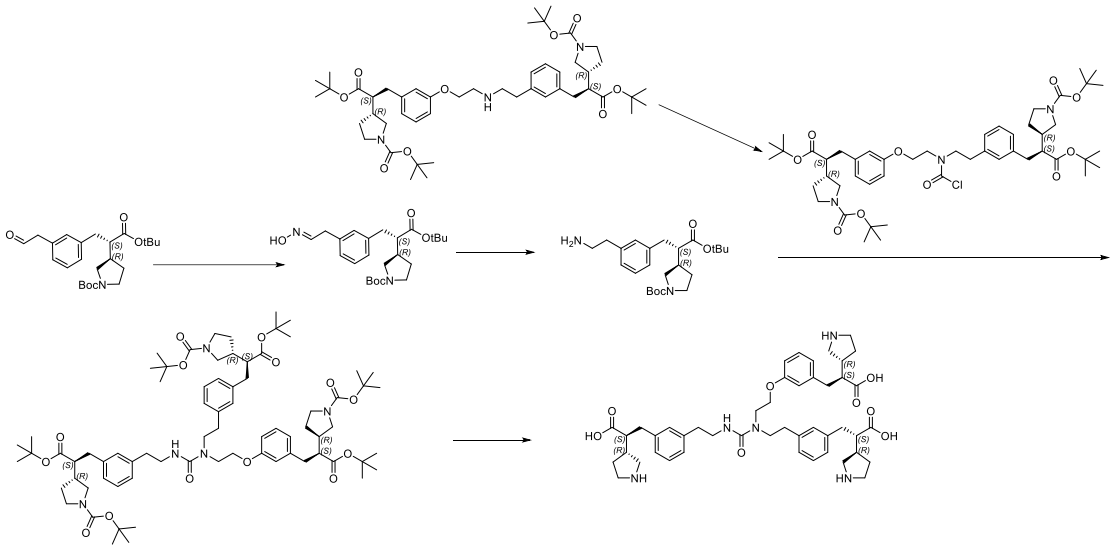
tert-butyl (R)-3-((S)-3-(3-(aminomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(160.2 mg, 0.4 mmol, 1.1 eq) and *N,N*-dimethylpyridine-4-amine (4.4 mg, 0.04 mmol, 0.1 eq) were added to the reaction solution from the previous step. The reaction mixture was heated to 50°C and stirred for 16h. After the reaction mixture was cooled to room temperature, it was concentrated under reduced pressure, and the residue was separated and purified by reversed-phase preparation (C_{18}, 0.03% aqueous trifluoroacetic acid/acetonitrile) to give the target compound (95 mg). LCMS (ESI) $[M+H\text{-}Boc]^+ = 1166.7$.

Step 4: The product from step 3 (85 mg, 0.07 mmol, 1.0 eq) was dissolved in a solution of hydrochloric acid/1,4-dioxane (4 mL, 4.0 M), and the reaction mixture was stirred at room temperature for 3h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was adjusted to pH 7-8 with sodium hydroxide solution (1.0 M). The mixture was separated and purified by preparation (C_{18}, 0.03% ammonium bicarbonate in

water/acetonitrile) to give the target compound (33.5 mg). LCMS (ESI) $[M+H]^+$ = 798.5; ^{1}H NMR (400 MHz, D_2O) δ 7.21 (t, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 13.2, 7.3 Hz, 2H), 7.08-7.02 (m, 2H), 7.00-6.91 (m, 4H), 6.79 (d, *J* = 7.3 Hz, 1H), 6.60-6.49 (m, 2H), 4.21 (s, 2H), 3.82 (s, 2H), 3.56-3.46 (m, 2H), 3.39-3.25 (m, 8H), 3.16-3.06 (m, 3H), 2.82-2.68 (m, 7H), 2.64-2.56 (m, 3H), 2.51-2.44 (m, 1H), 2.39-2.25 (m, 6H), 2.06-1.95 (m, 3H), 1.70-1.56 (m, 3H).

Example 77 (Compound 129)

Preparation of (S)-3-(3-(2-(1,3-bis(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenethyl)ureido)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((E)-2-(hydroxyimino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(2-oxoethyl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate(1.4 g, 3.35 mmol, 1.0 eq) was dissolved in ethanol (15 mL), and hydroxylamine hydrochloride (349.5 mg, 5.03 mmol, 1.5 eq) was added at room temperature. The mixture was stirred at room temperature for 4h. LCMS showed the reaction was completed. The mixture was concentrated to give a crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 6:1) to give the target compound (500 mg). LCMS (ESI) $[M+Na]^+$ = 455.3.

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

At room temperature, *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((E)-2-(hydroxyimino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(500 mg, 1.18mmol) was dissolved in ethanol (5 mL). Pd/C (20 mg, 10%) was added, and the reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated. The residue was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 1:1) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 419.4.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(200 mg, 0.24 mmol, 1.0 eq) was dissolved in tetrahydrofuran (20 mL), triethylamine (242.05 mg, 2.39 mmol, 10 eq) and triphosgene (70.98 mg, 0.24 mmol, 1 eq) were added under ice bath, and the reaction mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. The reaction solution was directly used for the next step. LCMS (ESI) $[M+Na]^+$ = 920.5.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(1,3-bis(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)ureido)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(200 mg, 0.22 mmol, 1.0 eq) in tetrahydrofuran (20 mL) at room temperature. The reaction mixture was stirred at 50°C for 16h. LCMS showed the reaction was completed. The mixture was concentrated to give a crude product, which was separated and purified by silica gel column chromatography (silica gel, petroleum ether:tetrahydrofuran = 2:1) to give the target product (200 mg). LCMS (ESI) $[M-Boc]^+$ = 1180.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21-7.13 (m, 3H), 7.08-6.97 (m, 6H), 6.73 (t, J = 8.7 Hz, 3H), 6.40 (t, J = 5.4 Hz, 1H), 3.92 (t, J = 5.6 Hz,

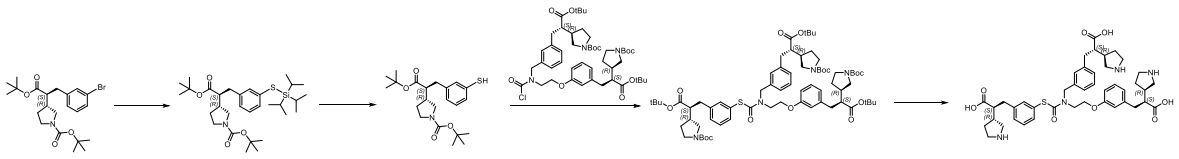
2H), 3.54-3.39 (m, 7H), 3.37-3.34 (m, 3H), 3.28-3.21 (m, 2H), 3.20-3.07 (m, 3H), 2.97 (t, *J* = 10.0 Hz, 3H), 2.77-2.63 (m, 10H), 2.49-2.42 (m, 3H), 2.26 (s, 3H), 1.89-1.76 (m, 3H), 1.63-1.51 (m, 3H), 1.39 (s, 27H), 1.22 (d, *J* = 2.9 Hz, 27H).

Step 5: Synthesis of (S)-3-(3-(2-(1,3-bis(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenethyl)ureido)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-3-(3-(2-(1,3-bis(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)ureido)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(200 mg, 0.16 mmol, 1.0 eq) was dissolved in hydrochloric acid/1,4-dioxane (5 mL, 4.0 M) and the reaction mixture was stirred at room temperature for 2h. After the reaction is completed, the mixture was concentrated to dryness, added with water to dissolve, and adjusted to pH = 7 with sodium hydroxide aqueous solution (1.0 M). Then, it was concentrated to give a crude product, which was separated and purified by preparative chromatography (C_{18}, 0.1% NH_4HCO_3 in H_2O/acetonitrile) to give the target compound (50 mg). LCMS (ESI) $[M+H]^+$ = 812.6; ^1H NMR (400 MHz, D_2O) δ 7.21-7.10 (m, 3H), 7.05-6.77 (m, 7H), 6.65-6.53 (m, 2H), 3.72 (s, 2H), 3.41-3.04 (m, 15H), 2.84-2.46 (m, 13H), 2.44-2.20 (m, 6H), 2.09-1.91 (m, 3H), 1.74-1.53 (m, 3H).

Example 78 (Compound 138)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)thio)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-((triisopropylsilyl)thio)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(200 mg, 0.44 mmol, 1 eq) was dissolved in toluene (2 mL), and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (32.29 mg, 0.04 mmol, 0.1 eq), tris(propan-2-yl)silanethiol (0.08 mL, 0.44 mmol, 1 eq) and cesium carbonate (286.81 mg,

0.88 mmol, 2 eq) were added; the reaction mixture was stirred at 120°C for 5hours. The reaction mixture was filtered through diatomaceous earth, the filtrate was concentrated, and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 15:1) to give the target compound (100 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 464.4; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.13-7.07 (m, 1H), 7.03-6.98 (m, 1H), 3.73-3.41 (m, 2H), 3.29-3.18 (m, 1H), 3.07-2.92 (m, 1H), 2.85-2.66 (m, 2H), 2.46-2.30 (m, 2H), 1.97-1.89 (m, 1H), 1.73-1.63 (m, 1H), 1.47 (s, 9H), 1.29 (d, *J* = 7.2 Hz, 9H), 1.26-1.19 (m, 3H), 1.11-1.05 (m, 18H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-mercaptophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

The product from the step 1 (800 mg, 1.42 mmol, 1 eq) was dissolved in 1,4-dioxane (6 mL), and hydrochloric acid aqueous solution (3 mL, 1.0 M) was added. The reaction mixture was stirred at room temperature for 2.5h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phases were merged, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated and separated and purified by rapid chromatography (silica gel, ethyl acetate:petroleum ether = 1:3) to give the target compound (200 mg). LCMS (ESI) $[M+Na]^+$ = 430.2.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)thio)carbonyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

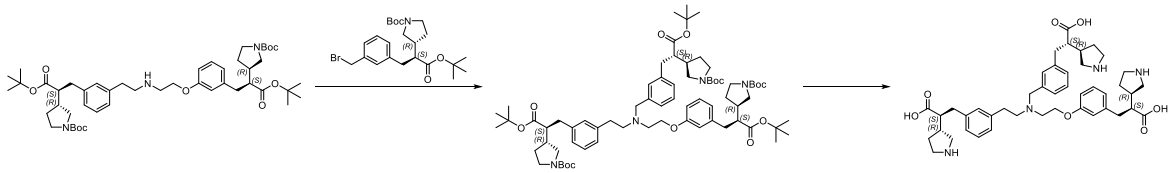
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)(chlorocarbonyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(200 mg, 0.22 mmol, 1 eq) was dissolved in tetrahydrofuran (5 mL), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-mercaptophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(88.52 mg, 0.22 mmol, 1 eq) and N,N-dimethylpyridine-4-amine (2.76 mg, 0.022 mmol, 0.1 eq) were added under nitrogen protection; the reaction mixture was stirred at room temperature for 18h. The reaction mixture was concentrated and purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 4:1) to give the target product (80 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1155.6.

Step 4: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)thio)carbonyl)amino)ethoxy)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the step 3 (70 mg, 0.06 mmol, 1 eq) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/1,4-dioxane (2 mL, 4.0 M) was added, and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was concentrated, and the pH was adjusted to 7 with sodium hydroxide (1.0 M) aqueous solution. The mixture was separated and purified by Prep-HPLC (0.1% NH_4HCO_3 in water, H_2O/MeCN) to give the target compound (8.3 mg). LCMS (ESI) $[M+H]^+$ = 787.4; ^1H NMR (400 MHz, D_2O) δ 7.33-6.98 (m, 9H), 6.84-6.67 (m, 3H), 4.16 (d, J = 39.3 Hz, 2H), 3.78 (d, J = 44.3 Hz, 2H), 3.39-3.25 (m, 6H), 3.17-3.07 (m, 3H), 2.92-2.23 (m, 17H), 2.07-1.97 (m, 3H), 1.70-1.58 (m, 3H).

Example 79 (Compound 167)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenethyl)(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)ethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(300 mg, 0.36 mmol, 1.0 eq) was dissolved in acetonitrile (6 mL). Potassium carbonate (247.95 mg, 1.79 mmol, 5 eq) and *tert*-butyl (R)-3-((S)-3-(3-(bromomethyl)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(268.91 mg, 0.57 mmol, 1.6 eq) were added at room temperature. The reaction mixture was stirred at 70°C for 16h. The mixture was concentrated to give a crude product, which was separated and purified by

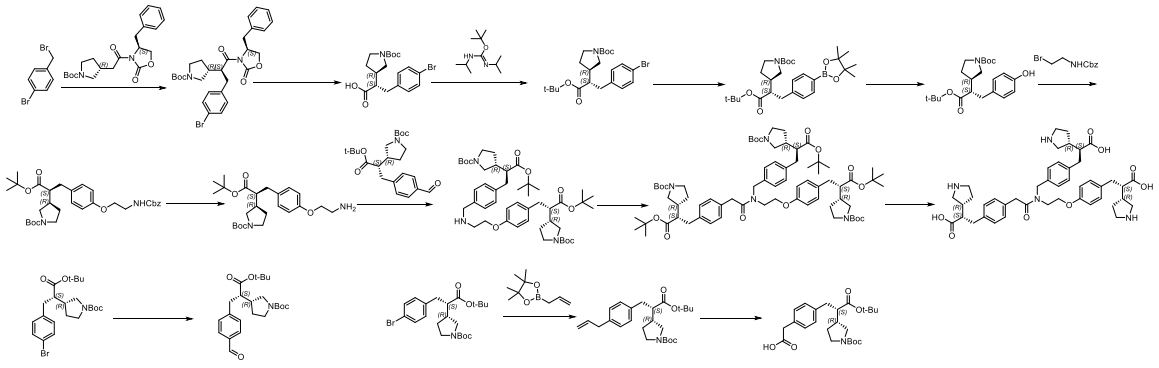
reversed-phase column chromatography (C_{18}, water:acetonitrile = 1:10) to give the target compound (260 mg). LCMS (ESI) $[M+H]^+$ = 1223.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21-7.11 (m, 5H), 7.07-6.95 (m, 4H), 6.72 (t, J = 6.0 Hz, 3H), 3.98 (t, J = 5.6 Hz, 2H), 3.69 (s, 2H), 3.56-3.42 (m, 3H), 3.38-3.33 (m, 3H), 3.19-3.06 (m, 3H), 3.02-2.91 (m, 3H), 2.85 (t, J = 5.6 Hz, 2H), 2.76-2.63 (m, 10H), 2.49-2.40 (m, 3H), 2.26 (s, 3H), 1.87-1.77 (m, 3H), 1.64-1.49 (m, 3H), 1.39 (s, 27H), 1.21 (d, J = 9.8 Hz, 27H).

Step 2: Synthesis of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)ethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid

The product from the step 1 (260 mg, 0.21 mmol, 1.0 eq) was dissolved in hydrochloric acid/1,4-dioxane (6 mL, 4.0 M) and the reaction mixture was stirred at room temperature for 4h. After the reaction was completed, the mixture was concentrated to dryness, dissolved in water, and the pH was adjusted to 7 with sodium hydroxide aqueous solution (1.0 M). The mixture was concentrated to give a crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the target compound (90 mg). LCMS (ESI) $[M+H]^+$ = 755.5; ^{1}H NMR (400 MHz, D_2O) δ 7.22-7.04 (m, 6H), 6.98 (d, J = 7.7 Hz, 1H), 6.95-6.88 (m, 2H), 6.79 (d, J = 7.6 Hz, 1H), 6.70 (s, 1H), 6.66 (d, J = 8.2 Hz, 1H), 3.98 (t, J = 5.0 Hz, 2H), 3.63 (s, 2H), 3.34-3.20 (m, 6H), 3.17-3.04 (m, 3H), 2.87-2.63 (m, 12H), 2.62-2.47 (m, 3H), 2.44-2.24 (m, 6H), 2.06-1.94 (m, 3H), 1.70-1.56 (m, 3H).

Example 80 (Compound 168)

Preparation of (S)-3-(4-(2-((4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(4-bromophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate(24.87 g) was dissolved in anhydrous tetrahydrofuran (200 mL). Cooling to 0°C in an ice-water bath, lithium bis(trimethylsilyl)amide (120.03 mL, 1.0 M) was added to the mixture, which was stirred at 0°C for 30min. Then a solution of 1-bromo-4-(bromomethyl)benzene(20 g) in tetrahydrofuran (100 mL) was added slowly at this temperature. After the addition was completed, the reaction mixture was slowly warmed to room temperature and stirred at room temperature for 15.5h. LCMS showed the reaction was completed. Saturated ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product (40 g). This crude was used directly in the next step. LCMS (ESI) $[M+H\text{-}Boc]^+ = 459.2$.

Step 2: Synthesis of (S)-3-(4-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

The product from the step 1 (40 g) was dissolved in tetrahydrofuran (300 mL). Cooling to 0°C in an ice-water bath, hydrogen peroxide (122 mL) was added; an aqueous solution (100 mL) of lithium hydroxide (2.58 g) was added dropwise to the above solution. After the addition was completed, the mixture was slowly warmed to room temperature and stirred for 3h. LCMS showed the reaction was completed. Saturated sodium bisulfite solution (100 mL) and an aqueous solution of sodium hydroxide (200 mL, 1.0 M) were added. The mixture was extracted with methyl *tert*-butyl ether; the aqueous phase was adjusted to a pH of 4-5 with hydrochloric acid (1.0 M) and extracted with ethyl acetate; the organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (18 g). LCMS (ESI) $[M+H\text{-}tert\text{-}butyl]^+ = 342.1$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(4-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(4-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid(17 g) was dissolved in anhydrous 2-methyltetrahydrofuran (200 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (25.65 g) was added at room temperature, and the reaction mixture was stirred at 70°C for 3h. LCMS showed the reaction was completed. The reaction mixture was

filtered and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (7.9 g). LCMS (ESI) $[M+H]^+$ = 456.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.09-6.98 (m, 2H), 3.62-3.40 (m, 2H), 3.32-3.20 (m, 1H), 3.07-2.91 (m, 1H), 2.86-2.68 (m, 2H), 2.47-2.40 (m, 1H), 2.39-2.30 (m, 1H), 1.99-1.89 (m, 1H), 1.72-1.64 (m, 1H), 1.47 (s, 9H), 1.29 (s, 9H).

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(4-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(3 g) was dissolved in 1,4-dioxane (50 mL), bis(pinacolato)diboron (3.35 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (484.26 mg) and potassium acetate (1.94 g) were added at room temperature; the reaction mixture was stirred at 90°C for 16h. LCMS showed the reaction was completed. Water was added to the mixture, which was extracted with ethyl acetate, and the organic phases were merged, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product (3 g). This crude was used directly in the next step. LCMS (ESI) $[M+Na]^+$ = 524.4.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate(3 g) was dissolved in methanol (30 mL), and hydrogen peroxide (3 mL) was added at room temperature. The mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. The solvent was concentrated. After the addition of water, the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (1.5 g). LCMS (ESI) $[M+H]^+$ = 392.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 20.4, 8.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 3.69-3.40 (m, 2H), 3.30-3.16 (m, 1H), 3.02-2.92 (m, 1H), 2.82-2.53 (m, 2H), 2.48-2.24 (m, 2H), 1.98-1.88 (m, 1H), 1.66-1.57 (m, 1H), 1.47 (s, 9H), 1.28 (s, 9H).

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-3-(4-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2 g) was dissolved in N,N-dimethylformamide (20 mL), potassium carbonate (2.12 g) and benzyl (2-bromoethyl)carbamate (2.64 g) were added at room temperature, and the mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. Water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated saline, dried over anhydrous sodium sulfate, filtered, and the filtrate was rotary-evaporated to dryness to give the crude product, which was purified by reversed-phase column chromatography (C_{18}, 0.03% TFA in H_2O in ACN) to give the target compound (1.6 g). LCMS (ESI) $[M+H]^+$ = 569.4.

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-3-(4-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(4-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1.6 g) was dissolved in tetrahydrofuran (20 mL), Pd/C (320 mg, 10% content) was added at room temperature. Replaced with hydrogen gas three times, the mixture was stirred for 2h under hydrogen atmosphere. LCMS showed the reaction was completed. The reaction mixture was filtered, and the filtrate was concentrated to give the target compound (1.1 g). LCMS (ESI) $[M+H]^+$ = 435.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.02 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 3.96 (t, *J* = 5.1 Hz, 2H), 3.78-3.65 (m, 2H), 3.59-3.50 (m, 1H), 3.29-3.18 (m, 1H), 3.07 (t, *J* = 5.1 Hz, 2H), 3.03-2.91 (m, 1H), 2.84-2.67 (m, 2H), 2.49-2.39 (m, 1H), 2.36-2.27 (m, 1H), 1.98-1.89 (m, 1H), 1.46 (s, 9H), 1.30 (s, 9H).

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(4-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1.2 g) was dissolved in N,N-dimethylformamide (20 mL), followed by adding triethylsilane (460.47 mg), sodium carbonate (559.63 mg) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (193.7 mg). Replaced with carbon monoxide three times, the mixture was heated to 80°C and stirred for 16h under a carbon monoxide atmosphere. LCMS showed the reaction was completed. After cooling to room temperature, water

was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate and filtered. The filtrate was rotary-evaporated to dryness to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 3:1) to give the target compound (610 mg). LCMS (ESI) $[M+H\text{-Boc-}tert\text{-butyl}]^+ = 248.5$.

Step 9: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-(((2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl *tert*-butyl (R)-3-((S)-3-(4-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(600 mg) was dissolved in ethanol (10 mL), *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(557.12 mg) and titanium tetraisopropanolate (784.83 mg) were added, and the mixture was stirred at room temperature for 5h. Sodium borohydride (78.35 mg) was added, and the mixture was stirred for another 1 h. LCMS showed the reaction was completed. Saturated ammonium chloride (0.1 mL) solution was added. The mixture was filtered, and the filtrate was rotary-evaporated to dryness. The crude product was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 3:1) to give the target compound (700 mg). LCMS (ESI) $[M+H]^+ = 822.4$.

Step 10: Synthesis of *tert*-butyl (R)-3-((S)-3-(4-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(4-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1.5 g) was dissolved in 1,4-dioxane (25 mL) and water (5 mL) under nitrogen protection, 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (831.8 mg), potassium phosphate (2.1 g) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (215.08 mg) were added. The mixture was heated to 90°C and stirred for 5h. LCMS showed the reaction was completed. After cooling to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate and filtered. The filtrate was rotary-evaporated to dryness to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (1.2 g). LCMS (ESI) $[M+H]^+ = 416.4$.

Step 11: Synthesis of 2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid

tert-butyl (R)-3-((S)-3-(4-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1.2 g) was dissolved in acetonitrile (10 mL) and water (10 mL), ruthenium trichloride (49.66 mg) and sodium periodate (2.47 g) were added, and the mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. A small amount of sodium sulfite was added, and the reaction mixture was filtered. After the addition of water, the filtrate was extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate, filtered, and the filtrate was rotary-evaporated to dryness. The crude product was purified by reversed-phase column chromatography (C_{18}, H_2O/ACN) to give the target compound (400 mg). LCMS (ESI) $[M+Na]^+ = 456.4$.

Step 12: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(4-((N-(2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

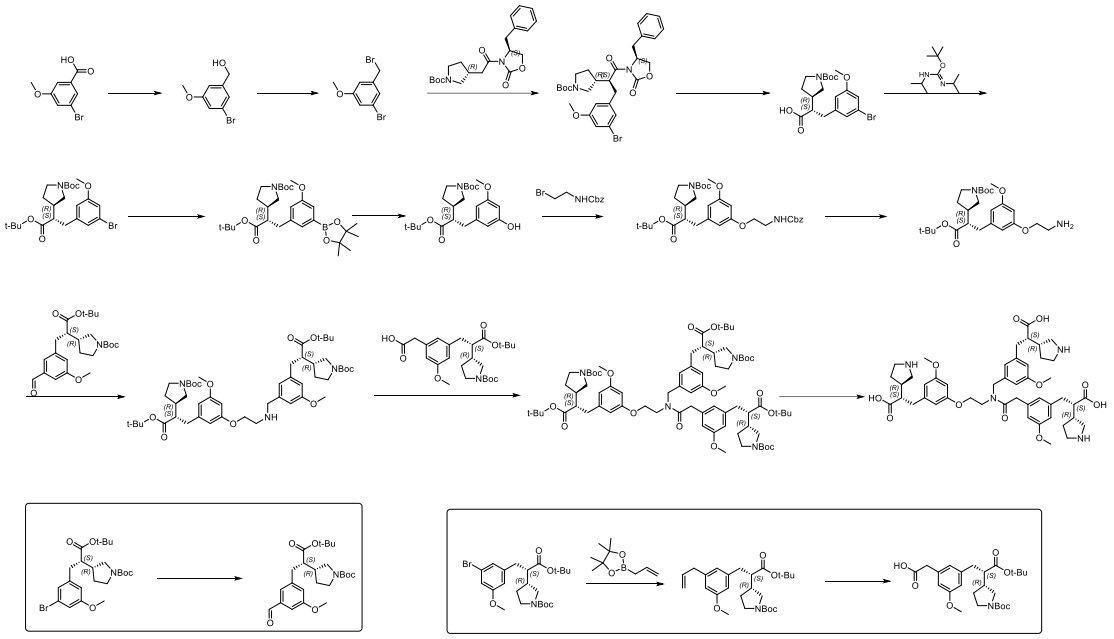
The product from step 9 (150 mg) and the product from step 11 (79.11 mg) were dissolved in N,N-dimethylformamide (5 mL), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (83.25 mg) and *N,N*-diisopropylethylamine (70.74 mg) were added, and the mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. Water was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate, and filtered. The filtrate was rotary-evaporated to dryness, and the crude product was purified by column chromatography (C_{18}, water/acetonitrile) to give the target compound (120 mg). LCMS (ESI) $[M+H-100]^+ = 1137.6$.

Step 13: The product from step 12 (120 mg) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/dioxane (2 mL, 4.0 M) solution was added at room temperature, and the mixture was stirred for 3h. LCMS showed the reaction was completed. The reaction mixture was rotary-evaporated to dryness to give a crude product, which was adjusted to a pH of 7 with sodium hydroxide solution (1.0 M). The mixture was purified by reversed-phase preparative chromatography (C_{18}, 10 mmol NH_4HCO_3 in H_2O/ACN) to give the target compound (47.25 mg). LCMS (ESI) $[M+H]^+ = 769.5$; ^{1}H NMR (400 MHz, D_2O) δ 7.17-6.96 (m, 10H), 6.79-6.71 (m,

2H), 4.60-4.51 (m, 2H), 4.11-3.94 (m, 2H), 3.82-3.74 (m, 1H), 3.70-3.56 (m, 3H), 3.42-3.27 (m, 6H), 3.22-3.08 (m, 3H), 2.87-2.59 (m, 9H), 2.45-2.28 (m, 6H), 2.11-1.98 (m, 3H), 1.74-1.56 (m, 3H).

Example 81 (Compound 176)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-5-methoxybenzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)-5-methoxyphenoxy)ethyl)amino)-2-oxoethyl)-5-methoxyphenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of (3-bromo-5-methoxyphenyl)methanol

3-bromo-5-methoxybenzoic acid (20 g, 86.57 mmol, 1 eq) was dissolved in tetrahydrofuran (200 mL), and borane/tetrahydrofuran complex (216.41 mL, 1.0M, 2.5 eq) was added under nitrogen protection and ice bath; the reaction mixture was slowly warmed to room temperature and stirred at room temperature for 18h. The reaction mixture was cooled with an ice-water bath, methanol (20 mL) was added, and the reaction mixture was directly concentrated and purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 4:1) to give the target compound (16 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.97 (t, J = 2.0 Hz, 1H), 6.84 (s, 1H), 4.64 (d, J = 3.9 Hz, 2H), 3.80 (s, 3H).

Step 2: Synthesis of 1-bromo-3-(bromomethyl)-5-methoxybenzene

(3-bromo-5-methoxyphenyl)methanol (16 g, 73.71 mmol, 1 eq) was dissolved in dichloromethane (160 mL). Phosphorus tribromide (3.46 mL, 36.86 mmol, 0.5 eq) was added under nitrogen protection and ice bath. The reaction mixture was slowly warmed to room temperature and stirred at room temperature for 2h. The reaction mixture was cooled with an ice bath, and saturated sodium bicarbonate (100 mL) was added. The mixture was extracted with dichloromethane, and the organic phase was dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 4:1) to give the target compound (13 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 1.4 Hz, 1H), 6.98 (t, J = 2.0 Hz, 1H), 6.87-6.84 (m, 1H), 4.38 (s, 2H), 3.80 (s, 3H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromo-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

A solution of lithium bis(trimethylsilyl)amide (49.43 mL, 49.43 mmol, 1.0M in THF, 1.2 eq) was added dropwise to a solution of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (16 g, 41.19 mmol, 1 eq) in tetrahydrofuran (160 mL) under ice bath and nitrogen protection. The reaction mixture was stirred at 0°C for 30 min, and a solution of 1-bromo-3-(bromomethyl)-5-methoxybenzene (13.83 g, 49.43 mmol, 1.2 eq) in tetrahydrofuran (50 mL) was added slowly. The reaction temperature was slowly raised to room temperature, and the mixture was stirred for 18h. The reaction mixture was cooled with an ice-water bath, and saturated aqueous ammonium chloride solution and water were added. The mixture was extracted with ethyl acetate, and the organic phase was washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (24 g, crude). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 487.1

Step 4: Synthesis of (S)-3-(3-bromo-5-methoxyphenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

A solution of hydrogen peroxide (69.63 mL, 61.28 mmol, 1.5 eq) was added all at once to a solution of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromo-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (24 g, 40.85 mmol, 1 eq) in tetrahydrofuran (200 mL). The reaction mixture was cooled with an ice-water bath, and a solution of lithium hydroxide monohydrate (2.57 mg, 61.28 mmol, 1.5 eq) in water (30 mL) was added.

The reaction temperature was raised to room temperature and stirred for 2.5h. LCMS showed the reaction was completed. The reaction mixture was cooled to 0°C, and an aqueous solution of sodium bisulfite was added for extraction and separation, and the organic phase was adjusted to pH>12 with an aqueous solution of sodium hydroxide (1.0 M); water was added, and the mixture was extracted with methyl *tert*-butyl ether. The aqueous phase was adjusted to pH = 3 with hydrochloric acid (1.0 M) and extracted with methyl *tert*-butyl ether. The organic phase was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (15 g). LCMS (ESI) $[M-H]^-$ = 426.1.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromo-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl N,N'-diisopropylcarbamimidate (131.91 mL, 140.08 mmol, 4 eq) was added dropwise to a solution of (S)-3-(3-bromo-5-methoxyphenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (15 g, 35.02 mmol, 1 eq) in 2-methyltetrahydrofuran (100 mL), and the mixture was stirred at 70°C for 4h. The reaction mixture was filtered, washed with methyl *tert*-butyl ether, and the filtrate was concentrated. The residue was purified by rapid chromatography (silica gel: petroleum ether:tetrahydrofuran = 5:1) to give the target compound (8.0 g). LCMS (ESI) $[M+ Na]^+$ = 506.2.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromo-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2.9 g, 6.0 mmol, 1 eq) was dissolved in 1,4-dioxane solution (30 mL), bis(pinacolato)diboron (3.04 g, 11.97 mmol, 2 eq), potassium acetate (1.76 g, 17.96 mmol, 3 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (439.24 mg, 0.6 mmol, 0.1 eq) were added; the reaction mixture was heated to 90°C under nitrogen protection and stirred at this temperature for 16h. LCMS showed the reaction was completed. Water was added, and the reaction mixture was extracted with ethyl acetate, the organic phases were merged, washed with saturated sodium chloride solution, filtered, dried over anhydrous sodium sulfate, concentrated, and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (2.9 g). LCMS (ESI) $[M+Na]^+$ = 554.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (s, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 3.73 (s, 3H), 3.58-3.48 (m, 1H), 3.38-3.32

(m, 2H), 3.18-3.11 (m, 1H), 3.00 (t, *J* = 10.0 Hz, 1H), 2.76-2.67 (m, 2H), 2.31-2.23 (m, 1H), 1.87-1.78 (m, 1H), 1.63-1.53 (m, 1H), 1.40 (s, 9H), 1.28 (d, *J* = 3.6 Hz, 12H), 1.25 (s, 9H).

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxy-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (3.5 g, 6.59 mmol, 1 eq) was dissolved in methanol (30 mL) solution, hydrogen peroxide (7.47 g, 65.85 mmol, 10 eq, 30% content) was added and the mixture was stirred at 25°C for 1h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (2.0 g). LCMS (ESI) $[M+Na]^+$ = 444.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 6.27-6.08 (m, 3H), 3.67 (d, *J* = 9.9 Hz, 3H), 3.54-3.46 (m, 2H), 3.18-3.11 (m, 1H), 3.00-2.93 (m, 1H), 2.60 (d, *J* = 8.4 Hz, 2H), 2.46-2.39 (m, 1H), 2.29-2.20 (m, 1H), 1.87-1.80 (m, 1H), 1.61-1.53 (m, 1H), 1.40 (s, 9H), 1.28 (s, 9H).

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxy-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1 g, 2.37 mmol, 1 eq) was dissolved in N,N-dimethylformamide (10 mL) solution, benzyl (2-bromoethyl)carbamate (1.22 g, 4.74 mmol, 2 eq) and potassium carbonate (983.63 mg, 7.12 mmol, 3 eq) were added. The reaction mixture was stirred at 80°C for 18h under nitrogen protection. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 0.1% formyl, acetonitrile:water = 3:1) to give the target compound (380 mg). LCMS (ESI) $[M+Na]^+$ = 621.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (d, *J* = 2.9 Hz, 5H), 6.38-6.31 (m, 3H), 5.03 (s, 2H), 3.94 (t, *J* = 5.7 Hz, 2H), 3.70 (s, 3H), 3.51-3.42 (m, 3H), 3.16 (d,

J = 6.3 Hz, 1H), 2.98 (t, *J* = 10.0 Hz, 1H), 2.66 (d, *J* = 8.1 Hz, 2H), 2.30-2.21 (m, 1H), 1.87-1.80 (m, 1H), 1.61-1.54 (m, 1H), 1.40 (s, 9H), 1.26 (s, 9H).

Step 9: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (760 mg, 1.27 mmol, 1 eq) in tetrahydrofuran (10 mL) was added with Pd/C (13.52 mg, 0.127 mmol, 0.1 eq, 10%) and the mixture was stirred at room temperature for 18h under a hydrogen atmosphere. LCMS showed the reaction was completed. The mixture was filtered and the filtrate was concentrated to give the target compound (560 mg). LCMS (ESI) $[M+H]^+$ = 465.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.40-6.30 (m, 3H), 3.92 (t, *J* = 5.4 Hz, 2H), 3.70 (s, 3H), 3.59 (d, *J* = 6.3 Hz, 1H), 3.52-3.45 (m, 2H), 3.16 (d, *J* = 6.8 Hz, 1H), 3.00-2.89 (m, 3H), 2.66 (d, *J* = 8.0 Hz, 2H), 2.28-2.19 (m, 1H), 1.87-1.79 (m, 1H), 1.78-1.74 (m, 1H), 1.40 (s, 9H), 1.27 (s, 9H).

Step 10: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formyl-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromo-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1000 mg, 2.1 mmol, 1 eq) was dissolved in N,N-dimethylformamide (50 mL), sodium carbonate (437.6 mg, 4.1 mmol, 2 eq), triethylsilane (0.49 mL, 3.1 mmol, 1.5 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (151.5 mg, 0.2 mmol, 0.1 eq) were added; the reaction mixture was stirred at 80°C for 18h under a carbon monoxide atmosphere. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (700 mg). LCMS (ESI) $[M+H-Boc]^+$ = 334.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.31-7.27 (m, 1H), 7.26-7.22 (m, 1H), 6.99 (s, 1H), 3.85 (s, 3H), 3.75-3.44 (m, 2H), 3.30-3.21 (m, 1H), 3.10-2.79 (m, 3H), 2.54-2.35 (m, 2H), 1.99-1.91 (m, 1H), 1.75-1.65 (m, 1H), 1.47 (s, 9H), 1.29 (s, 9H).

Step 11: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-

methoxyphenoxy)ethyl)amino)methyl)-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formyl-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (420 mg, 0.97 mmol, 1 eq) was dissolved in ethanol (5 mL) solution, *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(495.09 mg, 1.07 mmol, 1.1 eq) and titanium tetraisopropanolate (0.55 mL, 1.94 mmol, 2 eq) were added. The reaction mixture was stirred at room temperature for 17h. The reaction mixture was cooled in an ice bath, and sodium borohydride (54.85 mg, 1.45 mmol, 1.5 eq) was added. The mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. Ammonium chloride was added to quench the reaction. The mixture was filtered through celite, concentrated, and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 3:2) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 882.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, J = 14.8 Hz, 2H), 6.61 (s, 1H), 6.37-6.29 (m, 3H), 4.02-3.92 (m, 2H), 3.75-3.66 (m, 8H), 3.62-3.58 (m, 6H), 3.52-3.44 (m, 2H), 3.17-3.08 (m, 2H), 2.96 (t, J = 10.0 Hz, 2H), 2.80 (t, J = 5.7 Hz, 2H), 2.68-2.65 (m, 2H), 2.30-2.22 (m, 2H), 1.86-1.79 (m, 2H), 1.61-1.52 (m, 2H), 1.39 (s, 18H), 1.25 (d, J = 5.2 Hz, 18H).

Step 12: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-allyl-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(3-bromo-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.5 g, 3.1 mmol, 1 eq) was dissolved in tetrahydrofuran (20 mL) and water (5 mL), followed by adding 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1040.67 mg, 6.19 mmol, 2 eq), potassium phosphate (1971.87 mg, 9.3 mmol, 3 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (227.2 mg, 0.31 mmol, 0.1 eq); the reaction mixture was stirred at 80°C for 2h. The mixture was diluted with water, extracted with ethyl acetate, and the organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (1.2 g). LCMS (ESI) $[M+Na]^+$ = 468.4.

Step 13: Synthesis of 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-methoxyphenyl)acetic acid

tert-butyl (R)-3-((S)-3-(3-allyl-5-methoxyphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1 g) was dissolved in acetonitrile (10 mL) and water (10 mL), sodium periodate (3.36 g) and ruthenium trichloride(46.55 mg) were added at room temperature; and the mixture was stirred for 3h at room temperature. The mixture was diluted with acetonitrile, filtered, and the filter cake was washed with acetonitrile. The filtrate was concentrated, diluted with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated and purified by reversed-phase rapid chromatography (C_{18}, 0.1% TFA, acetonitrile:water = 1:1) to give the target compound (350 mg). LCMS (ESI) $[M+H]^+$ = 464.3.

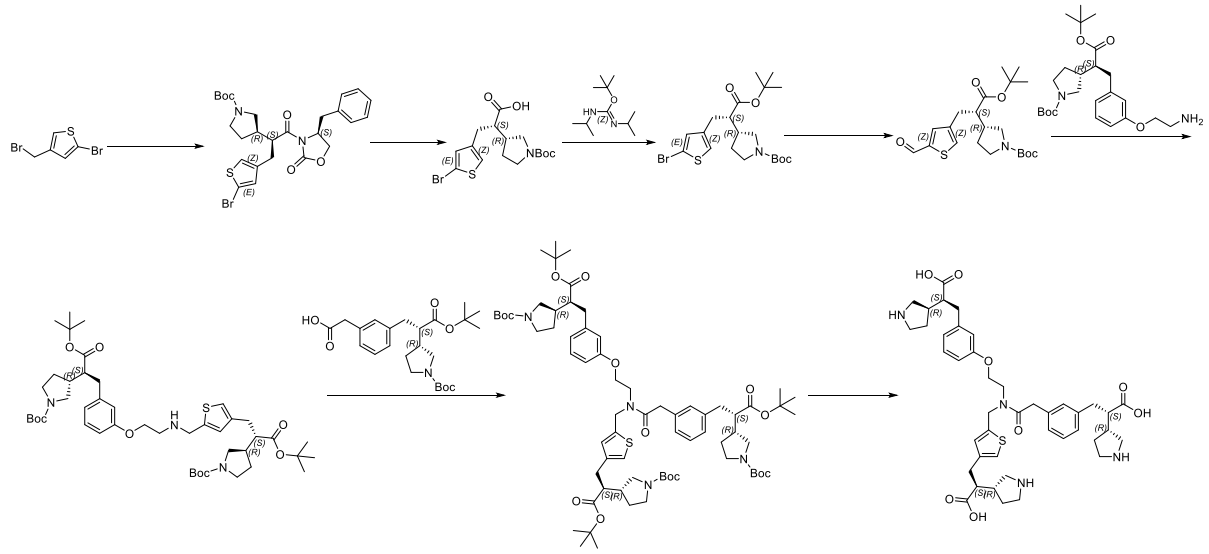
Step 14: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-methoxyphenoxy)ethyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-methoxyphenyl)acetamido)methyl)-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-methoxyphenyl)acetic acid (173.42 mg, 0.37 mmol, 1.1 eq) was dissolved in N,N-dimethylformamide (5 mL), and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (193.97 mg, 0.51 mmol, 1.5 eq), triethylamine (103.24 mg, 1.02 mmol, 3 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)-5-methoxyphenoxy)ethyl)amino)methyl)-5-methoxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (300 mg, 0.34 mmol, 1 eq) were added; the reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The residue was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 2:1) to give the target compound (230 mg). ^{1}HNMR (400MHz, $CDCl_3$) δ 6.71-6.45 (m, 6H), 6.37-6.22 (m, 3H), 4.67-4.56 (m, 2H), 3.97-3.85 (m, 2H), 3.80-3.71 (m, 9H), 3.69-3.64 (m, 4H), 3.62-3.43 (m, 6H), 3.31-3.20 (m, 3H), 3.06-2.89 (m, 3H), 2.87-2.67 (m, 6H), 2.52-2.41 (m, 3H), 2.39-2.28 (m, 3H), 1.97-1.89 (m, 3H), 1.71-1.63 (m, 3H), 1.46 (s, 27H), 1.31-1.26 (m, 27H).

Step 15: The product from step 14 (200 mg, 0.15 mmol, 1 eq) was dissolved in dioxane (2 mL), hydrochloric acid/dioxane (2 mL, 4.0 M) was added, and the reaction mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The reaction mixture was concentrated, dissolved in water, neutralized with sodium hydroxide (1.0 M) aqueous solution, and purified by reversed-phase preparative chromatography (C_{18}, 0.1% ammonium bicarbonate aqueous solution, acetonitrile) to give the target compound (61.33 mg). LCMS (ESI) $[M+H]^+$ = 858.8; ^1H NMR (400 MHz, D_2O) δ 6.72-6.67 (m, 1H), 6.65-6.53 (m, 3H), 6.52-6.39 (m, 2H), 6.39-5.93 (m, 3H), 4.64-4.48 (m, 2H), 4.13-3.94 (m, 1H), 3.87-3.81 (m, 2H), 3.77 (s, 1H), 3.72-3.59 (m, 8H), 3.57-3.50 (m, 3H), 3.39-3.20 (m, 6H), 3.19-3.04 (m, 3H), 2.87-2.44 (m, 9H), 2.41-2.23 (m, 6H), 2.09-1.93 (m, 3H), 1.72-1.57 (m, 3H).

Example 82 (Compound 177)

Preparation of (S)-3-(3-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)thiophen-2-yl)methyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (10 g, 25.74 mmol, 1.0 eq) was dissolved in tetrahydrofuran (150 mL), lithium bis(trimethylsilyl)amide (33.47 mL, 33.47 mmol, 1.3 eq) was added dropwise

under ice bath, and the mixture was stirred for 1h; 2-bromo-4-(bromomethyl)thiophene (9.88 g, 38.61 mmol, 1.5 eq) was dissolved in tetrahydrofuran and added dropwise to the above reaction mixture, which was warmed to room temperature and stirred for another 15h. The reaction mixture was quenched with saturated ammonium chloride aqueous solution, diluted with water, extracted with ethyl acetate, and the organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the target compound (20.3 g, crude). The crude product was used directly in the next step without further purification. LCMS (ESI) $[M+Na]^+$ = 585.1.

Step 2: Synthesis of (S)-3-(5-bromothiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

Under ice bath, *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (19.8 g, 35.14 mmol, 1.0 eq) was dissolved in tetrahydrofuran (150 mL), followed by adding hydrogen peroxide (39.83 g, 351.38 mmol, 10 eq, 30% content) and a solution of lithium hydroxide monohydrate (2.21 g, 52.71 mmol, 1.5 eq) in water (15 mL); the above reaction mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated sodium sulfite solution, diluted with water, washed with methyl *tert*-butyl ether, and the aqueous phase was adjusted to a pH of about 4 with hydrochloric acid (1.0 M), extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (7.2 g). LCMS (ESI) $[M+Na]^+$ = 426.0.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-bromothiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromothiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (7.4 g, 18.3 mmol, 1.0 eq) in 2-methyltetrahydrofuran (100 mL) solution was added with *tert*-butyl N,N'-diisopropylcarbamimidate (18.33 g, 91.51 mmol, 5.0 eq); the reaction mixture was heated to 65°C under nitrogen protection and stirred for 16h. The reaction mixture was cooled to room temperature, filtered, and the filter cake was washed with methyl *tert*-butyl ether. The filtrate was concentrated under reduced pressure to give a crude product, which was separated and purified by column chromatography (tetrahydrofuran/petroleum ether = 1:5) to give the target compound

(4.3 g). LCMS (ESI) $[M+H]^+$ = 460.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (s, 1H), 7.08 (d, *J* = 3.5 Hz, 1H), 3.52-3.41 (m, 1H), 3.38-3.32 (m, 1H), 3.18-3.09 (m, 1H), 2.94 (t, *J* = 10.0 Hz, 1H), 2.76-2.62 (m, 2H), 2.49-2.45 (m, 1H), 2.28-2.17 (m, 1H), 1.88-1.77 (m, 1H), 1.61-1.51 (m, 1H), 1.40-1.38 (m, 9H), 1.28 (s, 9H).

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(5-bromothiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1 g, 2.17 mmol, 1.0 eq) was dissolved in *N,N*-dimethylformamide (12 mL), followed by adding sodium carbonate (460.4 mg, 4.34 mmol, 2.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (159.36 mg, 0.22 mmol, 0.1 eq) and triethylsilane (505.09 mg, 4.34 mmol, 2.0 eq); after replacing with carbon monoxide, the reaction mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. The reaction mixture was added with aqueous solution, extracted with ethyl acetate. The organic phases were merged, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was separated and purified by column chromatography (tetrahydrofuran/petroleum ether = 1:5) to give the target compound (800 mg). LCMS (ESI) $[M+Na]^+$ = 432.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (d, *J* = 1.2 Hz, 1H), 7.89 (s, 1H), 7.80 (s, 1H), 3.55-3.44 (m, 1H), 3.39-3.33 (m, 1H), 3.21-3.09 (m, 1H), 2.98 (t, *J* = 9.9 Hz, 1H), 2.84-2.74 (m, 2H), 2.62-2.54 (m, 1H), 2.35-2.21 (m, 1H), 1.90-1.80 (m, 1H), 1.65-1.52 (m, 1H), 1.40 (s, 9H), 1.26 (s, 9H).

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-(((4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)methyl)amino)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(5-formylthiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (400 mg, 0.98 mmol, 1.0 eq) and *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(466.89 mg, 1.07 mmol, 1.1 eq) in ethanol (20 mL) solution was added with titanium tetraisopropanolate (555.2 mg, 1.95 mmol, 2.0 eq); the reaction mixture was stirred at room temperature for 14h, sodium borohydride (110.85 mg, 2.93 mmol, 3.0 eq) was added to the reaction system, and the reaction mixture was stirred at room temperature for another 2h. The reaction mixture was added with

saturated ammonium chloride (0.5 mL), filtered through celite, and the filtrate was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by column chromatography (petroleum ether:tetrahydrofuran = 1:3) to give the target compound (800 mg). LCMS (ESI) $[M+H]^+$ = 828.6.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)((4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)methyl)amino)-2-oxoethyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

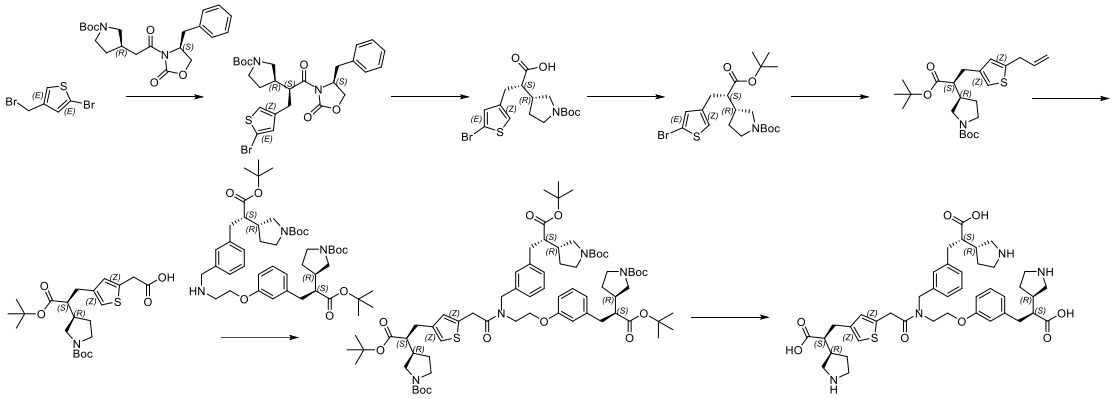
2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid(190 mg, 0.44 mmol, 1.0 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-(((4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)methyl)amino)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (399.21 mg, 0.48 mmol, 1.1 eq) in *N,N*-dimethylformamide (15 mL) solution was added with *N,N*-diisopropylethylamine (169.92 mg, 1.31 mmol, 3.0 eq) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (249.96 mg, 0.66 mmol, 1.5 eq) at room temperature; the reaction mixture was stirred at room temperature for 16h. The reaction mixture was added with water, extracted with ethyl acetate, and the organic phases were merged, washed with water and saturated saline respectively, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 0.1% trifluoroacetic acid, water/acetonitrile = 3:1) to give the target compound (400 mg). LCMS (ESI) $[M+H\text{-Boc}]^+$ = 1243.7.

Step 7: The product from step 6 (400 mg, 0.32 mmol, 1.0 eq) was dissolved in hydrochloric acid/1,4-dioxane (15 mL, 4.0 M) solution, and the reaction mixture was stirred at room temperature for 4h. LCMS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to give the crude product which was adjusted to a pH of 7-8 with sodium hydroxide (1.0 M) solution; and the mixture was separated and purified by reversed-phase preparative chromatography (C_{18}, 0.03% ammonium bicarbonate, water/acetonitrile = 8:1) to give the target compound (151.43 mg). LCMS (ESI) $[M+H]^+$ = 775.4; ^{1}H NMR (400 MHz, D_2O) δ 7.24-7.14 (m, 2H), 7.09-7.04 (m, 1H), 7.01-6.86 (m, 3H), 6.81 (d, J = 7.4 Hz, 1H), 6.76-6.62 (m,

3H), 4.12-4.02 (m, 2H), 3.82-3.69 (m, 4H), 3.41-3.07 (m, 10H), 2.88-2.45 (m, 10H), 2.42-2.26 (m, 6H), 2.07-1.97 (m, 3H), 1.71-1.57 (m, 3H).

Example 83 (Compound 178)

Preparation of ((S)-3-(5-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)thiophen-3-yl)-2-((R)-pyrrolidin-3-yl)propanoic acid)



Step 1: *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection and ice bath, a solution of lithium bis(trimethylsilyl)amide (11.72 mL, 1.0 M in THF) was added dropwise to a solution of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate (4.56 g) in tetrahydrofuran. The reaction mixture was stirred at 0°C for 30 min, and a solution of 2-bromo-4-(bromomethyl)thiophene (3 g) in tetrahydrofuran was added. The reaction mixture was slowly warmed to room temperature and stirred for 16h. LCMS showed the reaction was completed. A saturated solution of ammonium chloride was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (5.0 g). LCMS (ESI) $[M+H\text{-}tert\text{-butyl}]^+ = 507.17$.

Step 2: Synthesis of (S)-3-(5-bromothiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(5-bromothiophen-3-yl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (5 g) was dissolved in tetrahydrofuran (50 mL), lithium hydroxide (0.318 g) and hydrogen peroxide (0.452 g) were added. The mixture was stirred at room temperature for 16h. LCMS showed the consumption of starting material was completed. The solvent was removed by rotary-evaporation to dryness and added with water. The mixture was extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to give the target compound (3.5 g). LCMS (ESI) $[M+H-Boc]^+ = 304.04$.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-bromothiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

(S)-3-(5-bromothiophen-3-yl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic acid (3.5 g) was dissolved in tetrahydrofuran (25 mL), and *tert*-butyl N,N'-diisopropylcarbamimidate (8.66 g) was added. The mixture was heated to 65°C under nitrogen protection and stirred for 16h. LCMS showed the reaction was completed. The insoluble mateirals were filtered off, and the filter cake was washed with methyl *tert*-butyl ether. The filtrate was concentrated to give a crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (2.50 g). LCMS (ESI) $[M+H-2\times$*tert*-butyl$]^+ = 348.03$.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-allylthiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(5-bromothiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2 g), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (310 mg) and potassium phosphate (2690 mg) were dissolved in water (2 mL) and dioxane (10 mL), and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1420 mg) was added. The mixture was stirred at 90°C for 16h under nitrogen protection, and LCMS showed the reaction was completed. The reaction mixture was cooled to room temperature, and ethyl acetate and water were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate and concentrated to give a crude product,

which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (750 mg). LCMS (ESI) $[M+H-2\times tert\text{-butyl}]^+ = 310.19$.

Step 5: Synthesis of 2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)acetic acid

tert-butyl (R)-3-((S)-3-(5-allylthiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(500 mg) was dissolved in acetonitrile (2 mL) and water (2 mL), sodium periodate (1016 mg) and ruthenium trichloride (16 mg) were added, and the mixture was stirred at room temperature overnight; LCMS showed the reaction was completed. Ethyl acetate and water were added, and the mixture was extracted, and the organic phase was dried over anhydrous sodium sulfate, concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (250 mg). LCMS (ESI) $[M+H\text{-Boc}]^+ = 340.25$.

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

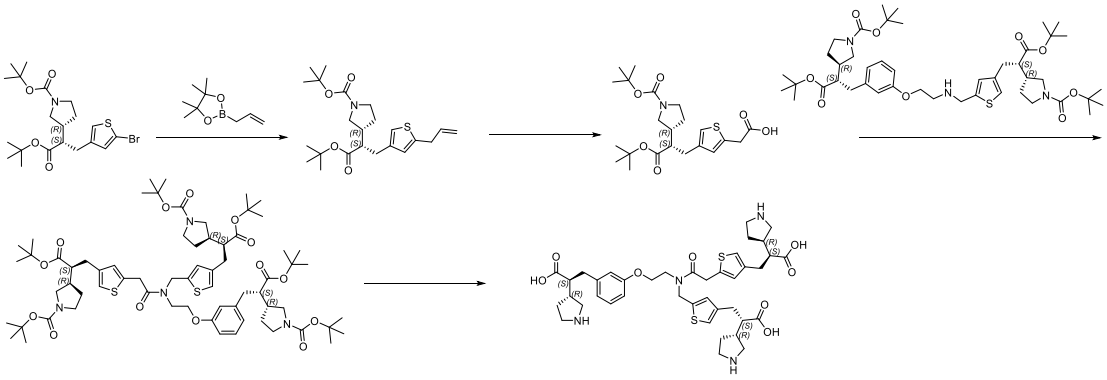
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (460 mg) was dissolved in N,N-dimethylformamide (5 mL), followed by adding 2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)acetic acid (250 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (320 mg) and *N,N*-diisopropylethylamine (215 mg). The mixture was stirred at room temperature for 16h, and LCMS showed the reaction was completed. Ethyl acetate and water were added, and the mixture was extracted. The organic phase was dried over anhydrous sodium sulfate and concentrated to give a crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (150 mg). LCMS (ESI) $[M+H\text{-Boc}]^+ = 1143.91$.

Step 7: The product from step 6 (150 mg) was dissolved in 1,4-dioxane (2 mL), hydrochloric acid/1,4-dioxane (1 mL, 4.0 M) was added, and the mixture was stirred at room temperature overnight. LCMS showed the reaction was completed. The solvent was removed by

rotary-evaporation to dryness, and the residue was separated and purified by Prep-HPLC (C_{18}, 10mmol/L NH_4HCO_3 in water, MeCN) to give the target compound (23 mg). LCMS (ESI) $[M+H]^+$ = 775.56; ^1H NMR (400 MHz, D_2O) δ 7.32-6.51 (m, 10H), 4.12-3.99 (m, 3H), 3.87-3.66 (m, 3H), 3.52-3.03 (m, 10H), 2.92-2.22 (m, 16H), 2.10-1.94 (m, 3H), 1.72-1.56 (m, 3H).

Example 84 (Compound 180)

Preparation of (S)-3-(5-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)thiophen-2-yl)methyl)amino)-2-oxoethyl)thiophen-3-yl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-3-(5-allylthiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(5-bromothiophen-3-yl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2.0 g, 4.34 mmol, 1.0 eq) was dissolved in 1,4-dioxane (30 mL) and water (6 mL), followed by adding potassium phosphate (2.77 g, 13.03 mmol, 3.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (318.71 mg, 0.43 mmol, 0.1 eq) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(1.46 g, 8.69 mmol, 2.0 eq), and the reaction mixture was stirred at 90°C for 16h. Water was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 9:1) to give the target compound (1.6 g). LCMS (ESI) $[M+Na]^+$ = 444.4; ^1H NMR (400 MHz, DMSO-d_6) δ 6.93 (s, 1H), 6.69 (s, 1H), 6.01-5.85 (m, 1H), 5.09 (dd, J = 23.0, 13.5 Hz, 2H), 3.55-3.42 (m, 3H), 3.39-3.34 (m, 1H), 3.19-3.07 (m, 1H), 2.94 (t, J = 10.0 Hz, 1H),

2.76-2.58 (m, 2H), 2.48-2.40 (m, 1H), 2.27-2.15 (m, 1H), 1.88-1.77 (m, 1H), 1.64-1.52 (m, 1H), 1.39 (t, J = 2.8 Hz, 9H), 1.28 (s, 9H).

Step 2: Synthesis of 2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)acetic acid

At room temperature, the product from step 1 (1.6 g, 3.8 mmol, 1.0 eq) was dissolved in acetonitrile (20 mL) and water (20 mL), ruthenium trichloride (39.36 mg, 0.19 mmol, 0.05 eq) and sodium periodate (4.06 g, 18.98 mmol, 5.0 eq) were added; the mixture was stirred at room temperature for 2h. LCMS showed there was no remaining starting materials. Water was added, and the mixture was extracted with ethyl acetate. The organic phases were merged and washed with sodium thiosulfate solution and saturated sodium chloride aqueous solution in sequence. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 10 mmol NH_4HCO_3, water/acetonitrile = 1:3) to give the target compound (100 mg). LCMS (ESI) $[M+Na]^+$ = 462.3.

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-(2-(4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)-N-((4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)methyl)acetamido)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

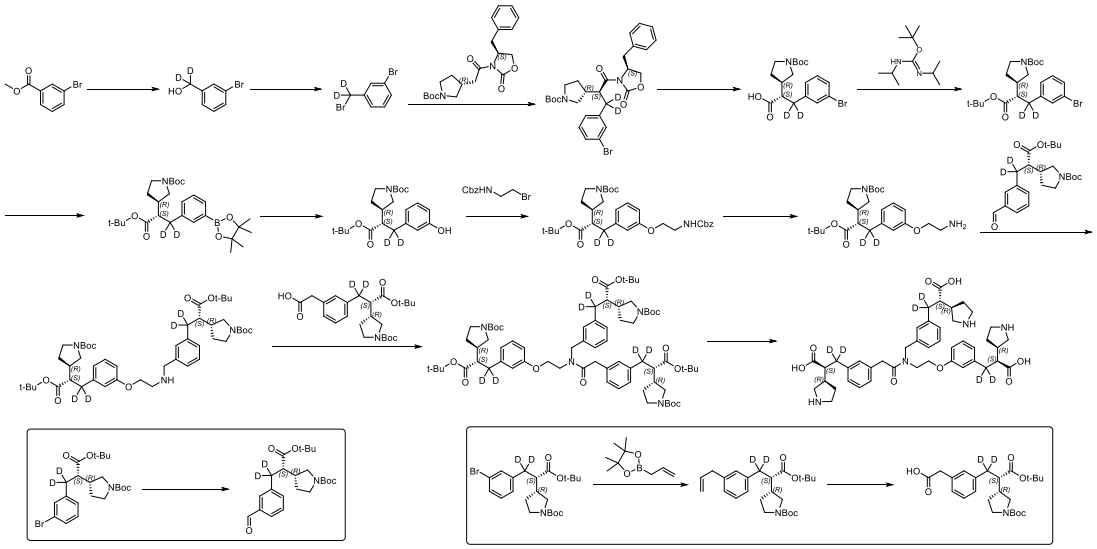
The product from step 2 (80 mg, 0.18 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (5 mL), followed by adding triethylamine (92.08 mg, 0.91 mmol, 5 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (138.4 mg, 0.36 mmol, 2 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(2-(((4-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)thiophen-2-yl)methyl)amino)ethoxy)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(150.71 mg, 0.18 mmol, 1.0 eq) at room temperature; the reaction mixture was stirred at room temperature for 16h. Water was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 10 mM NH_4HCO_3, water/acetonitrile = 1:8) to give the target compound (80 mg). LCMS (ESI) $[M+H]^+$ = 1249.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (dt, J = 11.5, 8.2 Hz, 1H), 7.09-

6.95 (m, 2H), 6.84 (s, 1H), 6.79-6.69 (m, 4H), 4.75 (d, *J* = 57.4 Hz, 2H), 4.14-3.90 (m, 4H), 3.71-3.58 (m, 2H), 3.56-3.42 (m, 3H), 3.36 (s, 3H), 3.20-3.08 (m, 3H), 3.03-2.82 (m, 3H), 2.74-2.55 (m, 6H), 2.48-2.37 (m, 3H), 2.24 (s, 3H), 1.83 (s, 3H), 1.64-1.51 (m, 3H), 1.39 (s, 27H), 1.29-1.22 (m, 27H).

Step 4: The product from step 3 (80 mg, 0.06 mmol, 1.0 eq) was dissolved in hydrochloric acid/1,4-dioxane (3 mL, 4.0 M). The reaction mixture was stirred at room temperature for 16h. The reaction mixture was concentrated to dryness, dissolved in water, adjusted to pH = 7 with sodium hydroxide aqueous solution (1.0 M). The crude product was separated and purified by preparative column chromatography (C_{18}, 0.1% NH_4HCO_3, water/acetonitrile = 10:1) to give the target compound (25 mg). LCMS (ESI) $[M+H]^+$ = 781.3; ^{1}H NMR (400 MHz, D_2O) δ 7.21-7.13 (m, 1H), 6.92 (d, *J* = 5.4 Hz, 1H), 6.87 (d, *J* = 11.8 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.75-6.63 (m, 4H), 4.64 (s, 2H), 4.06 (dt, *J* = 16.4, 4.9 Hz, 2H), 3.92 (d, *J* = 24.2 Hz, 2H), 3.77-3.66 (m, 2H), 3.39-3.23 (m, 6H), 3.20-3.07 (m, 3H), 2.87-2.48 (m, 9H), 2.43-2.22 (m, 6H), 2.08-1.96 (m, 3H), 1.71-1.57 (m, 3H).

Example 85 (Compound 190)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl-1,1-*d*$_2$)benzyl)(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl-1,1-*d*$_2$)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic-3,3-d2 acid



Step 1: Synthesis of (3-bromophenyl)methan-d2-ol

At 0°C, a solution of methyl 3-bromobenzoate (20 g, 93.01 mmol, 1 eq) in tetrahydrofuran (100 mL) was added dropwise to the solution of lithium aluminium deuteride (2.34 g, 55.80 mmol, 0.6 eq) in tetrahydrofuran (100 mL). After stirring at 0°C for 1.5 h, the reaction was quenched with sodium sulfate decahydrate, filtered through celite, concentrated and purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (14.7 g). LCMS (ESI) $[M+H-H_2O]^+$ = 171.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53-7.48 (m, 1H), 7.44-7.40 (m, 1H), 7.32-7.28 (m, 2H), 5.27 (s, 1H).

Step 2: Synthesis of 1-bromo-3-(bromomethyl-d_2)benzene

(3-bromophenyl)methan-d2-ol (14.7 g, 77.76 mmol, 1 eq) was dissolved in diethyl ether (150 mL), phosphorus tribromide (5.12 mL, 54.43 mmol, 0.7 eq) was added at 0°C; the reaction mixture was stirred at 40°C for 2h. Upon completion of the reaction, the reaction mixture was slowly poured into water and extracted with ethyl acetate. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 10:1) to give the target compound (17 g). LCMS (ESI) $[M+Na]^+$ = 273; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (t, J = 1.8 Hz, 1H), 7.53-7.50 (m, 1H), 7.47-7.44 (m, 1H), 7.33 (t, J = 7.8 Hz, 1H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

Under nitrogen protection and ice bath, a solution of lithium bis(trimethylsilyl)amide (58.69 mL, 58.69 mmol, 1.0 M in THF, 1.2 eq) was added dropwise to the solution of *tert*-butyl (R)-3-(2-((S)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)pyrrolidine-1-carboxylate(19 g, 48.91 mmol, 1 eq) in tetrahydrofuran (150 mL). The mixture was stirred at 0°C for 30 min, then a solution of 1-bromo-3-(bromomethyl-d_2)benzene (12.32 g, 48.97 mmol, 1 eq) in tetrahydrofuran (50 mL) was added slowly. The reaction temperature was slowly raised to room temperature and the mixture was stirred for 18h. The reaction mixture was cooled with an ice-water bath, and the saturated ammonium chloride aqueous solution was added; then, water was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (25 g, crude). LCMS (ESI) [M+H-*tert*-butyl]$^+$ = 503.

Step 4: Synthesis of (S)-3-(3-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic-3,3-d2 acid

tert-butyl (R)-3-((S)-1-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3-(3-bromophenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (25 g, 44.68 mmol, 1 eq) was dissolved in tetrahydrofuran (300 mL), and hydrogen peroxide (60 mL) and an aqueous solution of lithium hydroxide (1.61 g, 67.03 mmol, 1.5 eq) were added at 0°C; the reaction mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction was quenched with sodium sulfite, and the mixture was diluted with water, adjusted to pH = 13 with sodium hydroxide (1.0 M), and extracted with ethyl acetate; the aqueous phase was adjusted to pH = 5 with hydrochloric acid (1.0 M), extracted with dichloromethane. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give the target compound (8 g). LCMS (ESI) $[M+H\text{-}Boc]^+ = 300$.

Step 5: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

(S)-3-(3-bromophenyl)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)propanoic-3,3-d2 acid (8 g, 19.99 mmol, 1 eq) was dissolved in methyltetrahydrofuran (100 mL), *tert*-butyl N,N'-diisopropylcarbamimidate (12.01 mL, 59.96 mmol, 3 eq) was added; under nitrogen protection, the reaction mixture was heated to 65°C and stirred for 16h. The LCMS showed the reaction was completed. The reaction mixture was filtered, concentrated and purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 4:1) to give the target compound (3 g). LCMS (ESI) $[M+H]^+ = 456.3$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43-7.36 (m, 2H), 7.26-7.19 (m, 2H), 3.55-3.45 (m, 1H), 3.35-3.34 (m, 1H), 3.18-3.13 (m, 1H), 2.99 (t, J = 10.1 Hz, 1H), 2.34-2.24 (m, 2H), 1.86-1.80 (m, 1H), 1.61-1.53 (m, 1H), 1.40 (s, 9H), 1.23 (s, 9H).

Step 6: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (3 g, 6.57 mmol, 1 eq) was dissolved in 1,4-dioxane (40 mL), potassium acetate (1.94 g, 19.72 mmol, 3 eq), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.48 g, 0.66 mmol, 0.1 eq) and bis(pinacolato)diboron (3.34 g, 13.15 mmol, 2 eq) was added, under nitrogen protection, the

reaction mixture was heated to 90°C, and stirred for 18h. LCMS showed the reaction was completed. Water was added to the reaction mixture, which was extracted with ethyl acetate, and the organic phases were merged, dried over anhydrous sodium sulfate, filtered and concentrated to give the target compound (3 g, crude), which was used directly in the next step. LCMS (ESI) $[M+H\text{-}Boc]^+ = 404.3$.

Step 7: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (3 g, 5.96 mmol, 1 eq) was dissolved in methanol (40 mL). Hydrogen peroxide (2.03 mL, 59.59 mmol, 10 eq) was added at 0°C, and the mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. The reaction mixture was concentrated, added with water, extracted with ethyl acetate. The organic phases were merged, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (2.2 g). LCMS (ESI) $[M+H]^+ = 394.3$.

Step 8: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (2 g, 5.08 mmol, 1 eq) was dissolved in N,N-dimethylformamide (20 mL), benzyl (2-bromoethyl)carbamate (2.62 g, 10.16 mmol, 2 eq) and potassium carbonate (2.11 g, 15.25 mmol, 3 eq) were added, under nitrogen protection, the reaction mixture was heated to 80°C and stirred for 18h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (1.3 g). LCMS (ESI) $[M+H]^+ = 571.5$.

Step 9: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (1.3 g, 2.28 mmol, 1 eq) was dissolved in tetrahydrofuran (20 mL), Pd/C (242.41 mg, 2.28 mmol, 1 eq) was added, and the reaction was maintained at room temperature for 18h under hydrogen atmosphere (balloon pressure). LCMS showed the reaction was completed. The mixture was filtered and concentrated to give the target compound (0.9 g). LCMS (ESI) $[M+H]^+$ = 437.4.

Step 10: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (1 g, 2.19 mmol, 1 eq) was dissolved in N,N-dimethylformamide (10 mL), sodium carbonate (464.24 mg, 4.38 mmol, 2 eq), triethylsilane (0.53 mL, 3.29 mmol, 1.5 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (160.68 mg, 0.22 mmol, 0.1 eq) were added, and the reaction mixture was heated to 80°C under carbon monoxide atmosphere (balloon pressure) and stirred for 18h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (400 mg). LCMS (ESI) $[M+H]^+$ = 406.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.78-7.71 (m, 2H), 7.57-7.49 (m, 2H), 3.59-3.47 (m, 1H), 3.39-3.34 (m, 1H), 3.20-3.10 (m, 1H), 3.01 (t, J = 10.0 Hz, 1H), 2.58-2.52 (m, 1H), 2.35-2.25 (m, 1H), 1.89-1.79 (m, 1H), 1.65-1.53 (m, 1H), 1.40 (s, 9H), 1.19 (s, 9H).

Step 11: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (400 mg, 0.99 mmol, 1 eq) was dissolved in ethanol (7 mL), followed by adding titanium tetraisopropanolate (560.7 mg, 1.97 mmol, 2 eq) and *tert*-butyl (R)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (473.7 mg, 1.09 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 18h. Sodium borohydride (55.97 mg, 1.48 mmol, 1.5 eq) was added. The mixture was stirred for another

1 h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.4 mL), filtered, and the filtrate was concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 1:1) to give the target compound (650 mg). LCMS (ESI) $[M+H]^+$ = 826.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51-7.08 (m, 6H), 6.79-6.76 (m, 2H), 4.37-4.20 (m, 2H), 4.14-4.06 (m, 2H), 3.98-3.92 (m, 1H), 3.60-3.42 (m, 5H), 3.39-3.36 (m, 1H), 3.19-2.94 (m, 6H), 2.33-2.23 (m, 2H), 1.88-1.79 (m, 2H), 1.63-1.52 (m, 2H), 1.39 (s, 18H), 1.23 (d, J = 1.4 Hz, 18H).

Step 12: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate(1.5 g, 3.29 mmol, 1 eq) was dissolved in tetrahydrofuran (20 mL) and water (5 mL), potassium phosphate (2.09 g, 9.86 mmol, 3 eq), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.38 mg, 8.22 mmol, 2.5 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (241.14 mg, 0.33 mmol, 0.1 eq) were added, and the reaction mixture was stirred at 90°C for 18h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (1.3 g). LCMS (ESI) $[M+H]^+$ = 418.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (t, J = 7.5 Hz, 1H), 7.06-6.94 (m, 3H), 6.01-5.83 (m, 1H), 5.16-4.93 (m, 2H), 3.56-3.45 (m, 1H), 3.31-3.27 (m, 2H), 3.18-3.11 (m, 1H), 2.97 (t, J = 10.0 Hz, 1H), 2.47-2.41 (m, 1H), 2.37-2.21 (m, 2H), 1.86-1.78 (m, 1H), 1.68-1.54 (m, 1H), 1.40 (s, 9H), 1.22 (s, 9H).

Step 13: Synthesis of 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)phenyl)acetic acid

tert-butyl (R)-3-((S)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate (1.3 g, 3.11 mmol, 1 eq) was dissolved in acetonitrile (10 mL) and water (10 mL), ruthenium trichloride hydrate (70.18 mg, 0.31 mmol, 0.1 eq) and sodium periodate (3.33 g, 15.57 mmol, 5 eq) were added, and the reaction mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. The reaction mixture was added with

acetonitrile, filtered, and the filtrate was concentrated. After concentration, water was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product, which was purified by reversed-phase column chromatography (C_{18}, water/acetonitrile = 1:1) to give the target compound (800 mg). LCMS (ESI) $[M+H]^+$ = 436.3.

Step 14: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)phenoxy)ethyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate

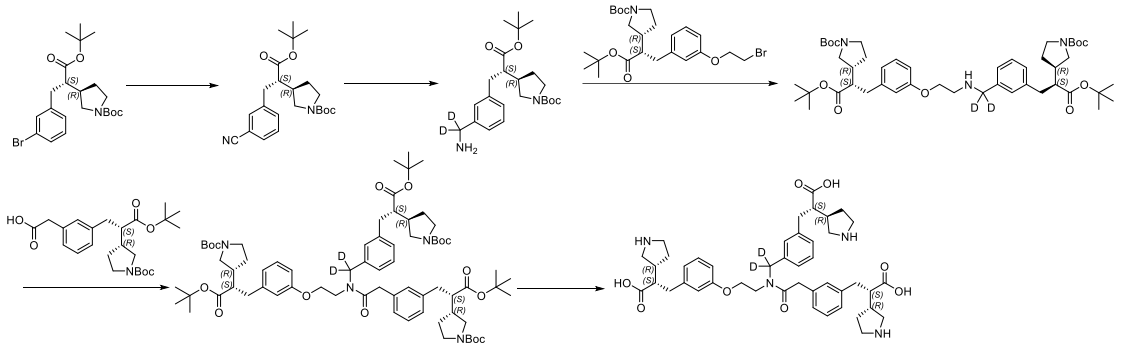
tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl-3,3-d_2)pyrrolidine-1-carboxylate(550 mg, 0.67 mmol, 1 eq) was dissolved in N,N-dimethylformamide (5 mL), and 2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl-1,1-d_2)phenyl)acetic acid (318 mg, 0.73 mmol, 1.1 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (506.29 mg, 1.33 mmol, 2 eq) and *N,N*-diisopropylethylamine (0.33 mL, 2 mmol, 3 eq) were added. The reaction was maintained at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was purified by column chromatography (C_{18}, water:acetonitrile = 1:10) to give the target compound (460 mg). LCMS (ESI) $[M+H\text{-Boc}]^+$ = 1143.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32-6.89 (m, 9H), 6.79-6.70 (m, 3H), 4.79-4.39 (m, 2H), 4.11-3.94 (m, 2H), 3.84 (s, 1H), 3.74-3.42 (m, 6H), 3.39-3.33 (m, 3H), 3.21-3.08 (m, 3H), 3.01-2.86 (m, 3H), 2.48-2.34 (m, 3H), 2.33-2.19 (m, 3H), 1.91-1.75 (m, 3H), 1.62-1.50 (m, 3H), 1.39 (s, 27H), 1.26-1.16 (m, 27H).

Step 15: The product from step 14 (450 mg, 0.36 mmol, 1 eq) was dissolved in dioxane (5 mL), hydrochloric acid/dioxane (5 mL, 4.0 M) was added, and the reaction mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was concentrated, added with water (20 mL), and adjusted to pH = 7 with aqueous sodium hydroxide solution (1.0 M). The mixture was separated and purified by prep-HPLC (C_{18}, 0.1% NH_4HCO_3 in

H_2O/ACN) to give the target compound (118.9 mg). LCMS (ESI) $[M+H]^+$ = 775.4; ^1H NMR (400 MHz, D_2O) δ 7.25-6.79 (m, 10H), 6.68-6.57 (m, 2H), 4.62-4.48 (m, 2H), 4.15-3.99 (m, 1H), 3.97-3.89 (m, 1H), 3.86-3.77 (m, 1H), 3.76-3.52 (m, 3H), 3.37-3.19 (m, 6H), 3.18-3.05 (m, 3H), 2.83-2.62 (m, 3H), 2.42-2.23 (m, 6H), 2.10-1.93 (m, 3H), 1.72-1.52 (m, 3H).

Example 86 (Compound 193)

Preparation of (S)-3-(3-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenyl)methyl-*d*$_2$)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-cyanophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (500 mg, 1.1 mmol, 1.0 eq) in N,N-dimethylformamide (7.0 mL) solution was added with zinc cyanide (193.79 mg, 1.65 mmol, 1.5 eq) and tetrakis(triphenylphosphine)palladium (127.15 mg, 0.11 mmol, 0.1 eq). After replacing with nitrogen, the reaction mixture was heated to 130°C and stirred for 2h. After the reaction mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic phases were merged, washed with water and saturated saline solution in sequence, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by silica gel column chromatography (silica gel, petroleum ether:ethyl acetate = 3:1) to give the target compound (320 mg). LCMS (ESI) $[M+Na+acetonitrile]^+$ = 464.3; ^1H NMR (400 MHz, DMSO-d_6) δ 7.70-7.66 (m, 2H), 7.58-7.54 (m, 1H), 7.49 (t, J = 7.9 Hz, 1H), 3.56-3.45 (m, 1H), 3.40-3.35 (m, 1H), 3.20-3.09 (m, 1H), 3.05-2.96 (m, 1H), 2.89-2.80 (m, 1H), 2.80-2.71 (m, 1H), 2.62-2.53 (m, 1H), 2.35-2.22 (m, 1H), 1.89-1.79 (m, 1H), 1.64-1.51 (m, 1H), 1.42-1.39 (m, 9H), 1.23-1.19 (m, 9H).

Step 2: Synthesis of *tert*-butyl (R)-3-((S)-3-(3-(aminomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-cyanophenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg, 0.5 mmol, 1.0 eq) was placed in a three-necked flask. The reaction apparatus was replaced with nitrogen and added with samarium(II) iodide (29.96 mL, 3 mmol, 6.0 eq), triethylamine (1819.1 mg, 17.98 mmol, 36 eq) and deuterium oxide (1.3 mL), sequentially; the reaction mixture was stirred at room temperature for 1.5h. LCMS showed the reaction was completed. The reaction mixture was added with sodium hydroxide solution (10.0 mL, 1.0 M), diluted with water, extracted with dichloromethane, and the organic phases were merged, washed with saturated saline solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 0.1% trifluoroacetic acid, water:acetonitrile = 1:1) to give the target compound (180 mg). LCMS (ESI) $[M+H]^+$ = 407.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21-7.11 (m, 3H), 7.00 (d, J = 7.1 Hz, 1H), 3.54-3.46 (m, 1H), 3.20-3.11 (m, 1H), 2.97 (t, J = 9.6 Hz, 1H), 2.75-2.68 (m, 2H), 2.47-2.41 (m, 1H), 2.33-2.22 (m, 1H), 1.86-1.76 (m, 2H), 1.62-1.54 (m, 1H), 1.40 (s, 9H), 1.24 (s, 9H).

Step 3: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl-d_2)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((S)-3-(3-(aminomethyl-d_2)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (260 mg, 0.64 mmol, 1.0 eq) in acetonitrile (20 mL) solution was added with *tert*-butyl (R)-3-((S)-3-(3-(2-bromoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (382.52 mg, 0.77 mmol, 1.2 eq) and potassium carbonate (176.77 mg, 1.28 mmol, 2.0 eq). The reaction mixture was heated to 80°C and stirred for 72h. The reaction mixture was cooled to room temperature, filtered, and the filter cake was washed thoroughly with tetrahydrofuran. The filtrate was concentrated to give a crude product, which was separated and purified by column chromatography (silica gel, tetrahydrofuran:petroleum ether = 1:2) to give the target compound (260 mg). LCMS (ESI) $[M+H]^+$ = 825.1.

Step 4: Synthesis of *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-2-(3-((S)-3-

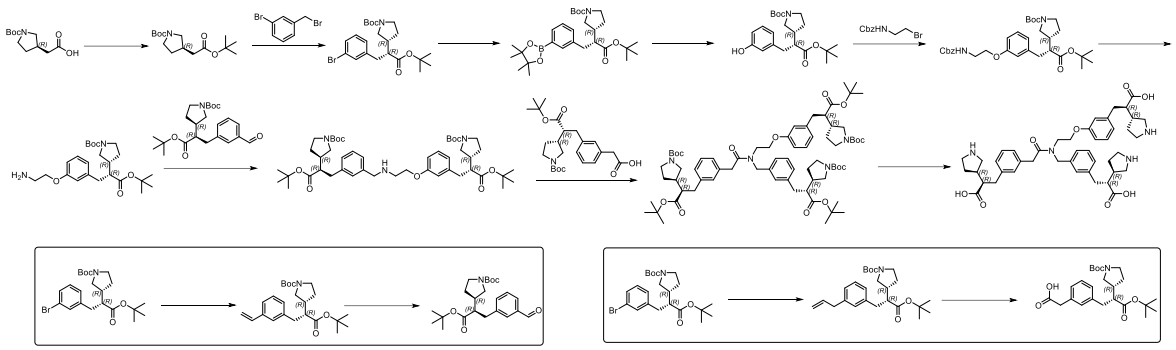
(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl-d_2)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid(164.14 mg, 0.38 mmol, 1.2 eq) in N,N-dimethylformamide (10 mL) solution was added with *N,N*-diisopropylethylamine (122.33 mg, 0.95 mmol, 3.0 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (215.93 mg, 0.57 mmol, 1.8 eq) and *tert*-butyl (R)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl-d_2)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(260 mg, 0.32 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged and washed with water and saturated saline solution, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was separated and purified by reversed-phase column chromatography (C_{18}, 0.1% trifluoroacetic acid, water:acetonitrile = 1:10) to give the target compound (300 mg). LCMS (ESI) $[M+H-100]^+$ = 1039.

Step 5: The product from step 4 (250 mg, 0.2 mmol, 1.0 eq) was dissolved in a solution of hydrochloric acid/1,4-dioxane (8 mL, 4.0 M), and the reaction mixture was stirred at room temperature for 3h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure, and the residue was adjusted to a pH of 7-8 with sodium hydroxide solution (1.0 M); the mixture was separated and purified by reversed-phase preparative chromatography (C_{18}, 0.03% ammonium bicarbonate, water:acetonitrile = 8:1) to give the target compound (105.61 mg). LCMS (ESI) $[M+H]^+$ = 771.4; ^{1}H NMR (400 MHz, D_2O) δ 7.28-7.13 (m, 3H), 7.12-6.80 (m, 7H), 6.70-6.60 (m, 2H), 4.66-4.53 (m, 1H), 4.09 (t, *J* = 5.1 Hz, 1H), 3.98 (t, *J* = 4.8 Hz, 1H), 3.86 (s, 1H), 3.77-3.72 (m, 1H), 3.71-3.63 (m, 2H), 3.40-3.22 (m, 6H), 3.19-3.07 (m, 3H), 2.87-2.48 (m, 9H), 2.42-2.25 (m, 6H), 2.09-1.96 (m, 3H), 1.72-1.57 (m, 3H).

Example 87 (Compound 209)

Preparation of (R)-3-(3-(2-((3-((R)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((R)-2-carboxy-2-((R)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((R)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (R)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate

Under nitrogen protection, (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (51 g, 222.45 mmol, 1.0 eq) was dissolved in 2-methyltetrahydrofuran (500 mL), followed by adding *tert*-butyl N,N'-diisopropylcarbamimidate (133.68 g, 667.34 mmol, 3.0 eq), and the reaction mixture was stirred at 65°C for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (41.0 g). LCMS (ESI) $[M+H]^+$ = 286.0.

Step 2: Synthesis of *tert*-butyl (R)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection and ice bath, a solution of lithium bis(trimethylsilyl)amide (158.03 mL, 1.0 M in THF, 1.1 eq) was added dropwise to a solution of *tert*-butyl (R)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate (41 g, 143.67 mmol, 1.0 eq) in tetrahydrofuran (450 mL). The reaction mixture was stirred at 0°C for 30min; then a solution of 1-bromo-3-(bromomethyl)benzene (37.702 g, 150.85 mmol, 1.05 eq) in tetrahydrofuran (50 mL) was slowly added. The reaction temperature was slowly raised to room temperature and the mixture was stirred for 24h. The reaction mixture was cooled with an ice-water bath, and a saturated aqueous solution of ammonium chloride and water were added. The mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated to give a racemate (17.0 g). LCMS (ESI) $[M+H-2\times$*tert*-butyl$]^+$ = 341.8.

10 g of the racemate was separated by chiral column to give 6.2 g of the target compound.

Step 3: Synthesis of *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2.0 g, 4.4 mmol, 1.0 eq) was dissolved in 1,4-dioxane (20 mL), followed by adding bis(pinacolato)diboron (2236 mg, 8.8 mmol, 2.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (323 mg, 0.44 mmol, 0.1 eq) and potassium acetate (1296 mg, 13.2 mmol, 3 eq), and the reaction mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (1.5 g). LCMS (ESI) $[M+H]^+$ = 416.

Step 4: Synthesis of *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((R)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (1.5 g, 2.99 mmol, 1.0 eq) was dissolved in tetrahydrofuran (20 mL), followed by adding hydrogen peroxide (3 mL). The mixture was stirred at room temperature for 16h. LCMS showed the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (800 mg). LCMS (ESI) $[M+H-2\times tert\text{-butyl}]^+$ = 392.0.

Step 5: Synthesis of *tert*-butyl (R)-3-((R)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(800 mg, 2.04 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (10 mL) under nitrogen protection, followed by adding benzyl (2-bromoethyl)carbamate (1055 mg, 4.09 mmol, 2.0 eq) and potassium carbonate (847 mg, 6.13 mmol, 3.0 eq), and the reaction mixture was stirred at 80°C for 16h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phase was washed with saturated saline, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated and purified by rapid chromatography

(silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (700 mg). LCMS (ESI) $[M+H]^+$ = 569.1.

Step 6: Synthesis of *tert*-butyl (R)-3-((R)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((R)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (700 mg, 1.23 mmol, 1.0 eq) was dissolved in methanol (10 mL), and Pd/C (150 mg) was added. The mixture was stirred at room temperature for 16h under a hydrogen atmosphere. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (500 mg). LCMS (ESI) $[M+H]^+$ = 435.1.

Step 7: Synthesis of *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-1-oxo-3-(3-vinylphenyl)propan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (2000 mg, 4.4 mmol, 1.0 eq) was dissolved in 1,4-dioxane (25 mL) and water (5 mL), followed by adding potassium vinyltrifluoroborate (1179 mg, 8.8 mmol, 2.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (323 mg, 0.44 mmol, 0.1 eq) and cesium carbonate (4302 mg, 13.2 mmol, 3.0 eq); the mixture was stirred at 90°C for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (1500 mg). LCMS $[M+H]^+$ = 402.1.

Step 8: Synthesis of *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((R)-1-(*tert*-butoxy)-1-oxo-3-(3-vinylphenyl)propan-2-yl)pyrrolidine-1-carboxylate (1500 mg, 3.74 mmol, 1.0 eq) was dissolved in 1,4-dioxane/water (3:1, 20 mL), followed by adding sodium periodate (3196 g, 14.94 mmol, 4 eq) and potassium osmate dihydrate (131 mg, 0.37 mmol, 0.1 eq), and the mixture was stirred at room temperature for 24h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated

and purified by rapid chromatography (silica gel column, petroleum ether:ethyl acetate = 1:1) to give the target compound (800 mg). LCMS (ESI) $[M+Na]^+$ = 426.0.

Step 9: Synthesis of *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-3-(3-(((2-(3-((R)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (R)-3-((R)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (320 mg, 0.74 mmol, 1.0 eq) was dissolved in methanol (10 mL), followed by adding *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (297 mg, 0.74 mmol, 1.0 eq) and sodium cyanoborohydride (46 mg, 0.74 mmol, 1.0 eq). The mixture was stirred at room temperature for 24h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:5) to give the target compound (260 mg). LCMS (ESI) $[M+H]^+$ = 822.2.

Step 10: Synthesis of *tert*-butyl (R)-3-((R)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(2000 mg, 4.4 mmol, 1.0 eq) was dissolved in 1,4-dioxane (25 mL) and water (5 mL), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.109 g, 6.6 mmol, 1.5 eq), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (359 mg, 0.44 mmol, 0.1 eq) and potassium phosphate (2.803 g, 13.2 mmol, 3 eq) were added, and the mixture was stirred at 80°C for 16h. LCMS showed that the reaction was completed. The reaction mixture was directly concentrated, separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give the target compound (1500 mg). LCMS $[M+H]^+$ = 416.1.

Step 11: Synthesis of 2-(3-((R)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid

tert-butyl (R)-3-((R)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(1500 mg, 3.61 mmol, 1.0 eq) was dissolved in acetonitrile/water (1:1, 40 mL), followed by adding sodium periodate (3.860 g, 18.05 mmol, 5 eq) and ruthenium trichloride (75

mg, 0.36 mmol, 0.1 eq), and the mixture was stirred at room temperature for 24h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:1) to give the target compound (750 mg). LCMS (ESI) $[M+H]^+$ = 434.1.

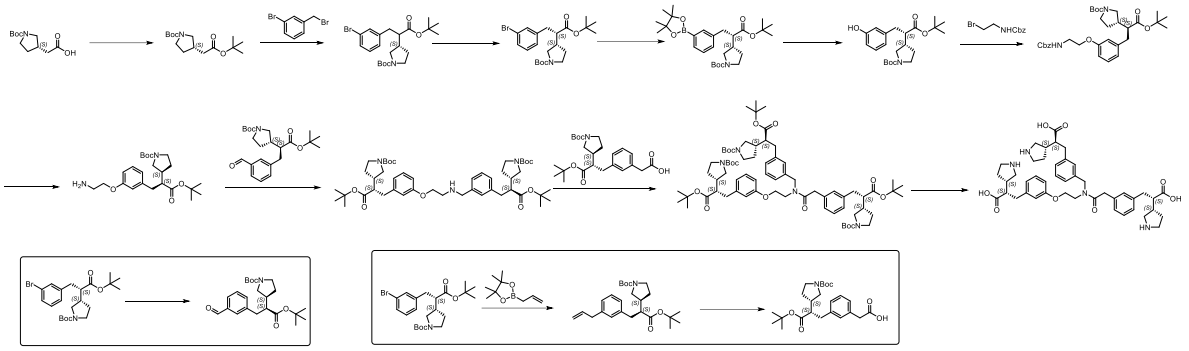
Step 12: Synthesis of *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((R)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-2-(3-((R)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (R)-3-((R)-1-(*tert*-butoxy)-3-(3-(((2-(3-((R)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (240 mg, 0.29 mmol, 1.0 eq) was dissolved in DMF (10 mL), followed by adding 2-(3-((R)-3-(*tert*-butoxy)-2-((R)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (139 mg, 0.32 mmol, 1.1 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (222 mg, 0.58 mmol, 2.0 eq) and *N,N*-diisopropylethylamine (113 mg, 0.88 mmol, 3.0 eq). The mixture was stirred at room temperature for 20h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly and separated and purified by rapid chromatography (silica gel, petroleum ether:ethyl acetate = 1:8) to give the target compound (300 mg). LCMS (ESI) $[M+H]^+$ = 1237.3.

Step 13: The product from step 12 (300 mg, 0.24 mmol, 1.0 eq) was dissolved in 1,4-dioxane (8 mL), hydrogen chloride/dioxane (8 mL, 4.0 M) was added and the mixture was stirred at room temperature for 20h. LCMS showed the reaction was completed. The reaction mixture was concentrated directly, separated and purified by preparative chromatography to give the target compound (152.67 mg). LCMS (ESI) $[M+H]^+$ = 769.1; ^{1}H NMR (400 MHz, D_2O) δ 7.27-6.78 (m, 10H), 6.71-6.55 (m, 2H), 4.65-4.58 (m, 2H), 4.09 (t, *J* = 5.2 Hz, 1H), 3.98 (t, *J* = 5.1 Hz, 1H), 3.87 (s, 1H), 3.77 (d, *J* = 5.1 Hz, 1H), 3.69 (d, *J* = 6.9 Hz, 2H), 3.27 (dt, *J* = 17.5, 11.4 Hz, 6H), 3.12 (dt, *J* = 17.4, 7.2 Hz, 3H), 2.93-2.79 (m, 3H), 2.78-2.52 (m, 6H), 2.45-2.23 (m, 6H), 2.20-2.00 (m, 3H), 1.54 (ddt, *J* = 41.8, 19.7, 9.5 Hz, 3H).

Example 88 (Compound 210)

Preparation of (S)-3-(3-(2-((3-((S)-2-carboxy-2-((S)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((S)-2-carboxy-2-((S)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((S)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (S)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate

Under nitrogen protection, a solution of (S)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (10 g) in 2-methyltetrahydrofuran (100 mL) was added with *tert*-butyl N,N'-diisopropylcarbamimidate (43.69 g), and the reaction mixture was heated to 70°C and stirred for 16h. After cooled to room temperature, the reaction mixture was filtered to remove the filter residue. The filter cake was fully washed with methyl *tert*-butyl ether. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (silica gel, tetrahydrofuran:petroleum ether = 1:5) to give the target compound (11 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.54-3.45 (m, 1H), 3.38-3.33 (m, 1H), 3.27-3.16 (m, 1H), 2.94-2.84 (m, 1H), 2.49-2.39 (m, 1H), 2.38-2.32 (m, 2H), 2.07-1.96 (m, 1H), 1.63-1.51 (m, 1H), 1.50-1.40 (m, 18H).

Step 2: Synthesis of *tert*-butyl (3S)-3-(3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (S)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate (20 g) was dissolved in anhydrous tetrahydrofuran (280 mL), and after the mixture was cooled to -5°C in an ice-salt bath, lithium bis(trimethylsilyl)amide (84.1 mL) was slowly added to the reaction system, the mixture was stirred at -5°C for 1h. Then a solution of 1-bromo-3-(bromomethyl)benzene (19.27 g) in tetrahydrofuran (20 mL) was slowly added dropwise to the reaction mixture which was heated to room temperature and stirred for 15h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated ammonium chloride solution, diluted with water, and extracted with ethyl acetate. The organic phase was washed with

saturated saline, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was separated and purified by reversed-phase column (C_{18}, 0.1% trifluoroacetic acid, water:acetonitrile = 1:4) to give the target compound (10 g). LCMS (ESI) $[M+Na]^+$ = 476; ^1H NMR (400 MHz, DMSO-d6) δ 7.44-7.38 (m, 2H), 7.28-7.19 (m, 2H), 3.66-3.56 (m, 1H), 3.42-3.29 (m, 2H), 3.23-3.11 (m, 1H), 3.05-2.86 (m, 2H), 2.72-2.63 (m, 1H), 2.35-2.21 (m, 1H), 2.14-2.01 (m, 1H), 1.76-1.60 (m, 1H), 1.43-1.36 (m, 9H), 1.24 (s, 9H).

Step 3: Synthesis of *tert*-butyl (S)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (3S)-3-(3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(10 g) was separated by chiral column to give the target compound (3.2 g).

Step 4: Synthesis of *tert*-butyl (S)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (S)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.3 g) was dissolved in 1,4-dioxane solution (15 mL), bis(pinacolato)diboron (1.45 g), potassium acetate (842.04 mg) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (212.78 mg) were added, and the reaction mixture was stirred at 90°C for 18h. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give the crude product, which was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (1.3 g). LCMS (ESI) $[M+Na]^+$ = 524.8; ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 10.8 Hz, 2H), 7.34-7.25 (m, 2H), 3.60-3.48 (m, 1H), 3.39-3.35 (m, 1H), 3.16 (d, J = 9.1 Hz, 1H), 3.04-2.97 (m, 1H), 2.74 (d, J = 10.2 Hz, 2H), 2.49-2.43 (m, 1H), 2.31 (d, J = 19.7 Hz, 1H), 1.84 (d, J = 5.3 Hz, 1H), 1.59 (d, J = 11.2 Hz, 1H), 1.41 (s, 9H), 1.29 (d, J = 3.5 Hz, 12H), 1.23 (s, 9H).

Step 5: Synthesis of *tert*-butyl (S)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((S)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (1.3 g) was dissolved in methanol (10 mL), hydrogen peroxide (0.88 mL) was added, and the mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was added with water and

extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, concentrated, and separated and purified by rapid chromatography (petroleum ether:tetrahydrofuran = 5:1) to give the target compound (950 mg). LCMS (ESI) $[M+Na+acetonitrile]^+$ = 455.3; ^1H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 7.15-6.85 (m, 1H), 6.65-6.49 (m, 3H), 3.56-3.42 (m, 1H), 3.37 (s, 1H), 3.22-3.08 (m, 1H), 3.01-2.90 (m, 1H), 2.64 (d, *J* = 9.4 Hz, 2H), 2.44 (d, *J* = 7.3 Hz, 1H), 2.27 (s, 1H), 1.83 (d, *J* = 5.6 Hz, 1H), 1.66-1.51 (m, 1H), 1.40 (s, 9H), 1.24 (s, 9H).

Step 6: Synthesis of *tert*-butyl (S)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((S)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (950 mg) was dissolved in N,N-dimethylformamide (10 mL), benzyl (2-bromoethyl)carbamate (1.25 g) and potassium carbonate (1.01 g) were added, and the mixture was stirred at 80°C for 18h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated and purified by reversed-phase chromatography (C_{18}, 0.1% trifluoroacetic acid, acetonitrile:water = 4:1) to give the target compound (690 mg). LCMS (ESI) $[M+Na]^+$ = 591.9; ^1H NMR (400 MHz, DMSO-d_6) δ 7.54-7.41 (m, 1H), 7.39-7.26 (m, 5H), 7.16 (s, 1H), 6.84-6.71 (m, 3H), 3.95 (t, *J* = 5.8 Hz, 2H), 3.56-3.42 (m, 3H), 3.36 (d, *J* = 6.0 Hz, 4H), 3.17-3.11 (m, 1H), 2.98 (t, *J* = 10.0 Hz, 1H), 2.69 (d, *J* = 9.1 Hz, 2H), 2.35-2.20 (m, 1H), 1.84 (d, *J* = 5.5 Hz, 1H), 1.63-1.51 (m, 1H), 1.40 (s, 9H), 1.23 (s, 9H).

Step 7: Synthesis of *tert*-butyl (S)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

A solution of *tert*-butyl (S)-3-((S)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (680 mg) in methanol (10 mL) was added with Pd/C (12.72 mg, 10%). The mixture was stirred at room temperature for 18h under a hydrogen atmosphere. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated to give the target compound (360 mg). LCMS (ESI) $[M+H]^+$ = 435.6; ^1H NMR (400 MHz, DMSO-d_6) δ 7.22-7.10 (m, 1H), 6.82-6.69 (m, 3H), 3.92 (t, *J* = 5.7 Hz, 2H),

3.54-3.42 (m, 1H), 3.38 (s, 3H), 3.19-3.08 (m, 1H), 2.98 (t, *J* = 10.0 Hz, 1H), 2.91 (s, 1H), 2.70 (d, *J* = 9.1 Hz, 2H), 2.32-2.20 (m, 1H), 1.84 (d, *J* = 8.9 Hz, 1H), 1.65-1.51 (m, 1H), 1.40 (s, 9H), 1.25 (s, 9H).

Step 8: Synthesis of *tert*-butyl (S)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (400 mg) was dissolved in N,N-dimethylformamide (5 mL), sodium carbonate (186.54 mg), triethylsilane (0.15 mL) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (64.57 mg), and the reaction mixture was stirred at 80°C for 18h under a carbon monoxide atmosphere. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate, the organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (277 mg). LCMS (ESI) $[M+Na+acetonitrile]^+ = 467.3$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 7.79-7.73 (m, 2H), 7.58-7.50 (m, 2H), 3.57-3.50 (m, 1H), 3.39-3.37 (m, 1H), 3.20-3.11 (m, 1H), 3.02 (t, *J* = 10.0 Hz, 1H), 2.92-2.77 (m, 2H), 2.60-2.55 (m, 1H), 2.34-2.24 (m, 1H), 1.90-1.80 (m, 1H), 1.65-1.54 (m, 1H), 1.41 (s, 9H), 1.20 (s, 9H).

Step 9: Synthesis of *tert*-butyl (S)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((S)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (200 mg) was dissolved in ethanol (5 mL), *tert*-butyl (S)-3-((S)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (236.93 mg) and titanium tetraisopropanolate (0.29 mL) were added, and the reaction mixture was stirred at room temperature for 17h. Sodium borohydride (28.13 mg) was added under ice bath, and the mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. The reaction was quenched with saturated ammonium chloride solution, and the mixture was filtered through celite, concentrated and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 3:2) to give the target compound (120 mg). LCMS (ESI) $[M+H]^+ = 822.6$.

Step 10: Synthesis of *tert*-butyl (S)-3-((S)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (S)-3-((S)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (600 mg) was dissolved in 1,4-dioxane (10 mL) and water (1 mL), potassium phosphate (840.86 mg), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (96.88 mg) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (443.77 mg) were added; the reaction was maintained at 90°C for 16h. LCMS showed the reaction of starting material was completed. The mixture was diluted with water, extracted with ethyl acetate, and the organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude product was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (300 mg). LCMS (ESI) $[M+Na]^+ = 438.3$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.84-13.76 (m, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.8 Hz, 3H), 5.98-5.86 (m,1H), 5.11-4.98 (m, 2H), 3.57-3.45 (m, 1H), 3.38-3.33 (m, 2H), 3.30 (s, 1H), 3.22-3.08 (m, 1H), 2.97 (t, J = 10.0 Hz, 1H), 2.77-2.64 (m, 2H), 2.48-2.42 (m, 1H), 2.34-2.21 (m, 1H), 1.89-1.77 (m, 1H), 1.65-1.50 (m, 1H), 1.40 (s, 9H), 1.22 (s, 9H).

Step 11: Synthesis of 2-(3-((S)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid

At room temperature, *tert*-butyl (S)-3-((S)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (300 mg) was dissolved in acetonitrile (5 mL) and water (5 mL), sodium periodate (772.04 mg) and ruthenium trichloride hydrate (14.97 mg) were added. The mixture was stirred at room temperature for 1h. The mixture was diluted with acetonitrile, filtered, and the filter cake was washed with acetonitrile. The filtrate was concentrated, diluted with water, and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (120 mg). LCMS (ESI) $[M+Na]^+ = 456.3$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.08 (dd, J = 12.2, 7.4 Hz, 3H), 3.56-3.48 (m, 4H), 3.21-3.09 (m, 1H), 2.99 (t, J = 10.0 Hz, 1H), 2.79-2.66 (m, 2H), 2.50-2.42 (m, 1H), 2.35-2.24 (m, 1H), 1.90-1.80 (m, 1H), 1.65-1.53 (m, 1H), 1.40 (s, 9H), 1.23 (s, 9H).

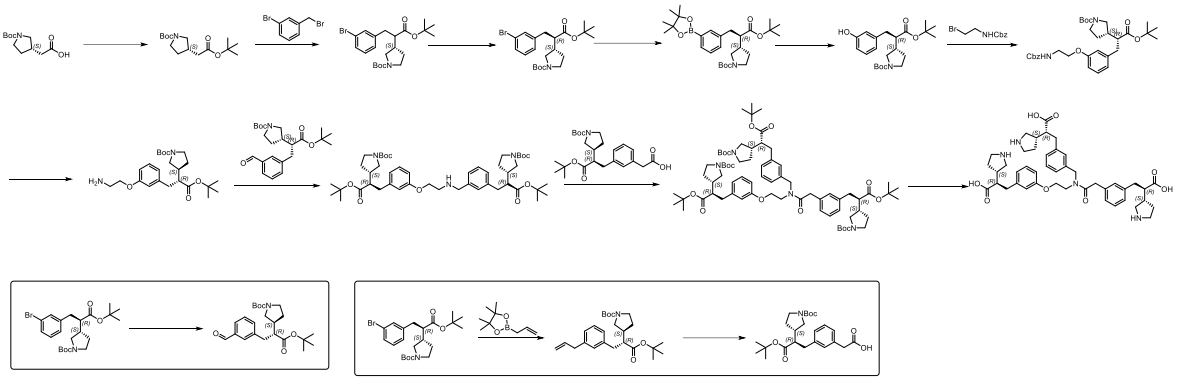
Step 12: Synthesis of *tert*-butyl (S)-3-((S)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((S)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-2-(3-((S)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((S)-1-(*tert*-butoxy)-3-(3-(((2-(3-((S)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate(120 mg) was dissolved in N,N-dimethylformamide (3 mL) solution, 2-(3-((S)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (71.53 mg), *N,N*-diisopropylethylamine (58.16 mg) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (114.07 mg) were added, and the mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, concentrated and separated and purified by rapid chromatography (C_{18}, water:acetonitrile = 1:10) to give the target compound (130 mg). LCMS (ESI) $[M+H\text{-Boc}]^+$ = 1137.7; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.27-6.95 (m, 9H), 6.74 (d, *J* = 7.3 Hz, 3H), 4.78-4.45 (m, 2H), 4.03 (s, 2H), 3.84 (s, 1H), 3.62 (d, *J* = 28.9 Hz, 3H), 3.48 (d, *J* = 8.7 Hz, 6H), 3.27-3.04 (m, 4H), 3.00-2.87 (m, 3H), 2.69 (d, *J* = 10.1 Hz, 7H), 2.33-2.20 (m, 3H), 2.04-1.97 (m, 1H), 1.90-1.75 (m, 3H), 1.58 (d, *J* = 8.9 Hz, 3H), 1.39 (s, 27H), 1.25-1.19 (m, 27H).

Step 13: A solution of the product from step 12 (120 mg) in 1,4-dioxane (2 mL, 4.0 M) was added with hydrochloric acid/dioxane solution (2 mL, 4.0 M), and the mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The reaction mixture was concentrated, neutralized with sodium hydroxide solution (1.0 M) and separated and purified by Prep-HPLC (C_{18}, 0.1% NH_4HCO_3 in water, acetonitrile) to give the target compound (32.6 mg). LCMS (ESI) $[M+H]^+$ = 769.6; ^{1}H NMR (400 MHz, D_2O) δ 7.28-7.15 (m, 3H), 7.10-6.81 (m, 7H), 6.70-6.60 (m, 2H), 4.61 (s, 2H), 4.12 (s, 1H), 4.02 (s, 1H), 3.90 (s, 1H), 3.80 (s, 1H), 3.71 (s, 2H), 3.38-3.24 (m, 6H), 3.18-3.08 (m, 3H), 2.89-2.81 (m, 1H), 2.78-2.49 (m, 8H), 2.41-2.27 (m, 6H), 2.08-1.98 (m, 3H), 1.70-1.57 (m, 3H).

Example 89 (Compound 211)

Preparation of (R)-3-(3-(2-((3-((R)-2-carboxy-2-((S)-pyrrolidin-3-yl)ethyl)benzyl)(2-(3-((R)-2-carboxy-2-((S)-pyrrolidin-3-yl)ethyl)phenoxy)ethyl)amino)-2-oxoethyl)phenyl)-2-((S)-pyrrolidin-3-yl)propanoic acid



Step 1: Synthesis of *tert*-butyl (S)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate

Under nitrogen protection, a solution of (S)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (10 g, 43.62 mmol, 1 eq) in 2-methyltetrahydrofuran (100 mL) was added with *tert*-butyl N,N'-diisopropylcarbamimidate (43.69 g, 218.08 mmol, 5 eq), and the reaction mixture was heated to 70°C and stirred for 16h. After cooled to room temperature, the reaction mixture was filtered to remove the filter residue. The filter cake was fully washed with methyl *tert*-butyl ether. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (silica gel, tetrahydrofuran:petroleum ether = 1:5) to give the target compound (11 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.54-3.45 (m, 1H), 3.38-3.33 (m, 1H), 3.27-3.16 (m, 1H), 2.94-2.84 (m, 1H), 2.49-2.39 (m, 1H), 2.38-2.32 (m, 2H), 2.07-1.96 (m, 1H), 1.63-1.51 (m, 1H), 1.50-1.40 (m, 18H).

Step 2: Synthesis of *tert*-butyl (3S)-3-(3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (S)-3-(2-(*tert*-butoxy)-2-oxoethyl)pyrrolidine-1-carboxylate (20 g, 70.08 mmol, 1 eq) was dissolved in ultra-dry tetrahydrofuran (280 mL), and after the mixture was cooled to -5°C in an ice-salt bath, lithium bis(trimethylsilyl)amide (84.1 mmol, 1.2 eq) was slowly added to the reaction system, the mixture was stirred at -5°C for 1h. Then a solution of 1-bromo-3-(bromomethyl)benzene (19.27 g, 77.09 mmol, 1.1 eq) in tetrahydrofuran (20 mL) was slowly added dropwise to the reaction mixture which was heated to

room temperature and stirred for 15h. LCMS showed the reaction was completed. The reaction mixture was quenched with saturated ammonium chloride solution, diluted with water, and extracted with ethyl acetate. The organic phase was washed with saturated saline, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was separated and purified by reversed-phase column chromatography (C_{18}, 0.1% trifluoroacetic acid, water:acetonitrile = 1:4) to give the target compound (10 g). LCMS (ESI) $[M+Na]^+$ = 476; ^1H NMR (400 MHz, DMSO-d6) δ 7.44-7.38 (m, 2H), 7.28-7.19 (m, 2H), 3.66-3.56 (m, 1H), 3.42-3.29 (m, 2H), 3.23-3.11 (m, 1H), 3.05-2.86 (m, 2H), 2.72-2.63 (m, 1H), 2.35-2.21 (m, 1H), 2.14-2.01 (m, 1H), 1.76-1.60 (m, 1H), 1.43-1.36 (m, 9H), 1.24 (s, 9H).

Step 3: Synthesis of *tert*-butyl (S)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (3S)-3-(3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (10 g) was separated by chiral column to give the target compound (4.0 g).

Step 4: Synthesis of *tert*-butyl (S)-3-((R)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (S)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1.5 g, 3.3 mmol, 1 eq) was dissolved in 1,4-dioxane (15 mL), and bis(pinacolato)diboron (1.68 g, 6.6 mmol, 2 eq), potassium acetate (971.59 mg, 9.9 mmol, 3 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (242.13 mg, 0.33 mmol, 0.1 eq) were added; the reaction mixture was stirred at 90°C for 18h. LCMS showed the reaction was completed. The mixture was filtered, concentrated, and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (1.4 g). LCMS (ESI) $[M+Na]^+$ = 524.3; ^1H NMR (400 MHz, DMSO-d_6) δ 7.61-7.45 (m, 2H), 7.39-7.24 (m, 2H), 3.39 (d, J = 8.3 Hz, 1H), 3.33-3.30 (m, 1H), 3.24-3.11 (m, 1H), 3.05-2.85 (m, 2H), 2.76-2.64 (m, 1H), 2.49-2.41 (m, 1H), 2.36-2.22 (m, 1H), 2.15-2.02 (m, 1H), 1.68 (d, J = 6.0 Hz, 1H), 1.39 (s, 9H), 1.29 (s, 12H), 1.24 (s, 9H).

Step 5: Synthesis of *tert*-butyl (S)-3-((R)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((R)-1-(*tert*-butoxy)-1-oxo-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)pyrrolidine-1-carboxylate (1.4 g, 2.79 mmol, 1 eq) was dissolved in methanol (10 mL), hydrogen peroxide (0.95 mL, 27.92 mmol, 10 eq) was added, and the mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, concentrated and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (1 g). LCMS (ESI) $[M+Na]^+$ = 414.1; ^1H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 7.20-6.90 (m, 1H), 6.66-6.50 (m, 3H), 3.40-3.34 (m, 1H), 3.32-3.29 (m, 1H), 3.22-3.09 (m, 1H), 3.03-2.88 (m, 1H), 2.83-2.71 (m, 1H), 2.65-2.55 (m, 1H), 2.46-2.36 (m, 1H), 2.30-2.18 (m, 1H), 2.06 (d, J = 10.3 Hz, 1H), 1.70-1.54 (m, 1H), 1.38 (s, 9H), 1.25 (s, 9H).

Step 6: Synthesis of *tert*-butyl (S)-3-((R)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((R)-1-(*tert*-butoxy)-3-(3-hydroxyphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1 g, 2.55 mmol, 1 eq) was dissolved in N,N-dimethylformamide (10 mL), benzyl (2-bromoethyl)carbamate (1.32 g, 5.11 mmol, 2 eq) and potassium carbonate (1.06 g, 7.66 mmol, 3 eq) were added, and the reaction mixture was stirred at 80°C for 18h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated, and the crude product was separated and purified by reversed-phase chromatography (C_{18}, 0.1% trifluoroacetic acid, acetonitrile:water = 4:1) to give the target compound (700 mg). LCMS (ESI) $[M+H]^+$ = 569.4; ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 (s, 1H), 7.40-7.31 (m, 5H), 7.19-7.14 (m, 1H), 6.77-6.73 (m, 3H), 5.03 (s, 2H), 4.28 (s, 2H), 3.95 (t, J = 5.8 Hz, 2H), 3.41-3.37 (m, 1H), 3.33-3.28 (m, 1H), 3.21-3.12 (m, 1H), 3.01-2.91 (m, 1H), 2.85-2.78 (m, 1H), 2.69-2.61 (m, 1H), 2.29-2.19 (m, 1H), 2.11-1.97 (m, 2H), 1.70-1.60 (m, 1H), 1.38 (s, 9H), 1.23 (s, 9H).

Step 7: Synthesis of *tert*-butyl (S)-3-((R)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

A solution of *tert*-butyl (S)-3-((R)-3-(3-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (700 mg, 1.23 mmol, 1 eq) in methanol (10 mL) was added with Pd/C (13.1 mg, 0.12 mmol, 0.1 eq, 10%). The mixture was stirred at room temperature for 18h under a hydrogen atmosphere. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated to give the target compound (470 mg). LCMS (ESI) $[M+H]^+$ = 435.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24-7.14 (m, 1H), 6.88-6.66 (m, 3H), 4.09-3.99 (m, 3H), 3.40-3.32 (m, 2H), 3.17 (t, *J* = 8.9 Hz, 1H), 3.11-3.01 (m, 2H), 3.00-2.92 (m, 1H), 2.88-2.80 (m, 1H), 2.71-2.62 (m, 1H), 2.31-2.19 (m, 1H), 2.06 (d, *J* = 7.8 Hz, 1H), 1.74-1.58 (m, 1H), 1.38 (s, 9H), 1.25 (s, 9H).

Step 8: Synthesis of *tert*-butyl (S)-3-((R)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (500 mg, 1.1 mmol, 1 eq) was dissolved in N,N-dimethylformamide (6 mL), sodium carbonate (233.25 mg, 2.2 mmol, 2 eq), triethylsilane (0.27 mL, 1.65 mmol, 1.5 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (80.74 mg, 0.11 mmol, 0.1 eq) were added; and the reaction mixture was stirred at 80°C for 18h under a carbon monoxide atmosphere. After the reaction was completed, the reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated saline, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 5:1) to give the target compound (380 mg). LCMS (ESI) $[M+Na]^+$ = 426.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.79-7.72 (m, 2H), 7.58-7.49 (m, 2H), 3.43-3.34 (m, 2H), 3.23-3.13 (m, 1H), 3.03-2.91 (m, 2H), 2.82-2.74 (m, 1H), 2.58-2.52 (m, 1H), 2.34-2.25 (m, 1H), 2.15-2.04 (m, 1H), 1.74-1.63 (m, 1H), 1.39 (d, *J* = 3.2 Hz, 9H), 1.20 (s, 9H).

Step 9: Synthesis of *tert*-butyl (S)-3-((R)-1-(*tert*-butoxy)-3-(3-(((2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((R)-1-(*tert*-butoxy)-3-(3-formylphenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (274 mg, 0.68 mmol, 1 eq) was dissolved in ethanol (6 mL), followed by adding *tert*-butyl (S)-3-((R)-3-(3-(2-aminoethoxy)phenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-

carboxylate (324.6 mg, 0.75 mmol, 1.1 eq) and titanium tetraisopropanolate (0.4 mL, 1.36 mmol, 2 eq). The reaction mixture was stirred at room temperature for 17h. Sodium borohydride (38.53 mg, 1.02 mmol, 1.5 eq) was added under ice bath, and the mixture was stirred at room temperature for 1h. LCMS showed the reaction was completed. The reaction was quenched with saturated ammonium chloride solution, and the mixture was filtered through celite, concentrated and separated and purified by rapid chromatography (silica gel, petroleum ether:tetrahydrofuran = 3:2) to give the target compound (290 mg). LCMS (ESI) $[M+H]^+$ = 822.6.

Step 10: Synthesis of *tert*-butyl (S)-3-((R)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

Under nitrogen protection, *tert*-butyl (S)-3-((R)-3-(3-bromophenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (1 g, 2.2 mmol, 1 eq) was dissolved in tetrahydrofuran (16 mL) and water (4 mL), potassium phosphate (1.4 g, 6.6 mmol, 3 eq), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.92 g, 5.5 mmol, 2.5 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (161.42 mg, 0.22 mmol, 0.1 eq) were added, and the reaction mixture was stirred at 90°C for 3h. After the reaction was completed, the reaction mixture was added with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 10:1) to give the target compound (700 mg). LCMS (ESI) $[M+H]^+$ = 416; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (t, J = 7.5 Hz, 1H), 7.07-6.94 (m, 3H), 6.00-5.85 (m, 1H), 5.11-4.96 (m, 2H), 3.42-3.33 (m, 2H), 3.32-3.29 (m, 2H), 3.22-3.10 (m, 1H), 3.01-2.89 (m, 1H), 2.88-2.81 (m, 1H), 2.70-2.62 (m, 1H), 2.48-2.41 (m, 1H), 2.31-2.19 (m, 1H), 2.13-2.00 (m, 1H), 1.72-1.58 (m, 1H), 1.38 (d, J = 2.4 Hz, 9H), 1.23 (s, 9H).

Step 11: Synthesis of 2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid

tert-butyl (S)-3-((R)-3-(3-allylphenyl)-1-(*tert*-butoxy)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (700 mg, 1.68 mmol, 1 eq) was dissolved in acetonitrile (15 mL) and water (15 mL), ruthenium trichloride hydrate (37.97 mg, 0.17 mmol, 0.1 eq) and sodium periodate (2161.7 mg, 10.11 mmol, 6 eq) were added, and the reaction was maintained at room temperature for 1h. After the reaction was completed, the reaction mixture was added with acetonitrile, filtered, and the filtrate was concentrated, added with water, extracted with ethyl acetate, dried over anhydrous

sodium sulfate, filtered and concentrated to give a crude product, which was purified by column chromatography (silica gel, petroleum ether:tetrahydrofuran = 5:1) to give the target compound (354 mg). LCMS (ESI) $[M+Na]^+$ = 456.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 7.24-7.17 (m, 1H), 7.12-7.03 (m, 3H), 3.49 (s, 2H), 3.42-3.36 (m, 2H), 3.20-3.13 (m, 1H), 3.01-2.92 (m, 1H), 2.88-2.81 (m, 1H), 2.71-2.64 (m, 1H), 2.46-2.41 (m, 1H), 2.30-2.21 (m, 1H), 2.12-2.03 (m, 1H), 1.70-1.59 (m, 1H), 1.38 (s, 9H), 1.23 (s, 9H).

Step 12: Synthesis of *tert*-butyl (S)-3-((R)-1-(*tert*-butoxy)-3-(3-((N-(2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)-2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetamido)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate

tert-butyl (S)-3-((R)-1-(*tert*-butoxy)-3-(3-(((2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenoxy)ethyl)amino)methyl)phenyl)-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (235 mg, 0.29 mmol, 1 eq) was dissolved in N,N-dimethylformamide (4 mL), followed by adding 2-(3-((R)-3-(*tert*-butoxy)-2-((S)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-3-oxopropyl)phenyl)acetic acid (136.33 mg, 0.31 mmol, 1.1 eq), *N,N*-diisopropylethylamine (110.83 mg, 0.86 mmol, 3 eq) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (217.39 mg, 0.57 mmol, 2 eq). The mixture was stirred at room temperature for 3h. LCMS showed the reaction was completed. The reaction mixture was added with water and extracted with ethyl acetate. The organic phases were merged, washed with saturated sodium chloride solution, dried, concentrated and separated and purified by reversed-phase chromatography (C_{18}, water:acetonitrile = 1:10) to give the target compound (300 mg). LCMS (ESI) $[M+H\text{-}Boc]^+$ = 1137.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25-6.97 (m, 9H), 6.79-6.71 (m, 3H), 4.66-4.50 (m, 2H), 4.04 (s, 2H), 3.84 (s, 1H), 3.67-3.53 (m, 3H), 3.15 (s, 4H), 3.01-2.89 (m, 3H), 2.86-2.76 (m, 3H), 2.74-2.55 (m, 4H), 2.50-2.37 (m, 6H), 2.31-2.20 (m, 3H), 2.10-1.94 (m, 4H), 1.66-1.54 (m, 3H), 1.38 (s, 27H), 1.25-1.19 (m, 27H).

Step 13: A solution of the product from step 12 (250 mg, 0.2 mmol, 1 eq) in 1,4-dioxane (3 mL) was added with hydrochloric acid/dioxane solution (3 mL, 4.0 M) and the mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The reaction mixture was concentrated, neutralized with sodium hydroxide (1.0 M) solution and separated and purified by Prep-HPLC (C_{18}, 0.1% NH_4HCO_3 in water, acetonitrile) to give the target compound

(83.41 mg). LCMS (ESI) $[M+H]^+$ = 769.5; ^{1}H NMR (400 MHz, D_2O) δ 7.26-7.14 (m, 3H), 7.10-6.81 (m, 7H), 6.70-6.58 (m, 2H), 4.63 (s, 2H), 4.10 (d, *J* = 5.3 Hz, 1H), 4.00 (s, 1H), 3.89 (s, 1H), 3.79 (s, 1H), 3.70 (d, *J* = 7.2 Hz, 2H), 3.35-3.25 (m, 6H), 3.17-3.07 (m, 3H), 2.93-2.83 (m, 3H), 2.74 (t, *J* = 8.4 Hz, 3H), 2.66-2.55 (m, 3H), 2.39-2.26 (m, 6H), 2.11 (d, *J* = 21.7 Hz, 3H), 1.64-1.46 (m, 3H).

Synthesis of Compounds 1-4, 7, 9, 10, 13-46, 48, 50-61, 63, 64, 66, 68-70, 72, 73-79, 82-88, 92, 114-116, 118-120, 124, 125, 154-157, 169-175, 179, 181-189, 191-192, 194-208, and 212-228

Compounds 29-31 were prepared according to the preparation method of Example 1.

Compounds 1-4, 7, 9, 10, 13-46, 48, 50-61, 63, 64, 66, 68-70, 72, 73-79, 82-88, 92, 114-116, 118-120, 124, 125, and 172 were prepared according to the preparation method of Examples 1-8. Specifically, for example

Compounds 1, 7, 9, 10, 14-26, 32-46, 48, 50-61, 118-120, and 124 were prepared according to the preparation method of Examples 2 and 4;

Compounds 13, 79, 83-84, and 114-116 were prepared according to the preparation method of Example 3;

Compounds 2-4 were prepared according to the preparation method of Example 5;

Compounds 27, 28, 63, 64, 66, 68-70, 72, and 73 were prepared according to the preparation method of Example 6;

Compounds 170, 171, 174, 175, 204-208 were prepared according to the preparation method of Compounds 152 and 176.

Compounds 154 and 155 were prepared according to the preparation method of Compound 150.

Compounds 156 and 157 were prepared according to the preparation method of Compound 129.

Compounds 169, 191, 192, and 194-196 were prepared according to the preparation method of Compound 190 and 193.

Compounds 179 and 181-189 were prepared according to the preparation method of Compound 177, 178, and 180.

Compounds 197-203 were prepared according to the preparation method of Compounds 74, 96, and 138.

Compounds 173 and 212-221 were prepared according to the preparation method of Compound 96.

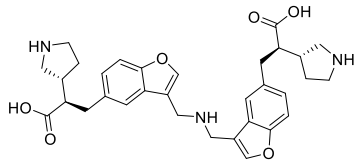
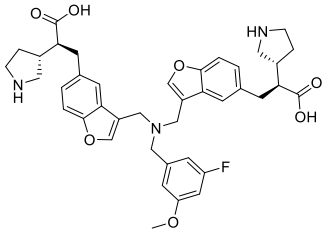
Compound 222 was prepared according to the preparation method of Compound 160.

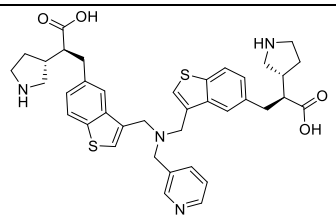
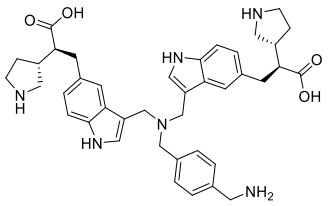
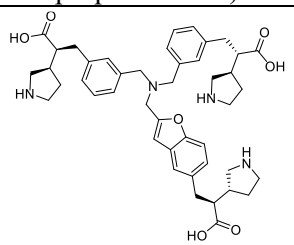
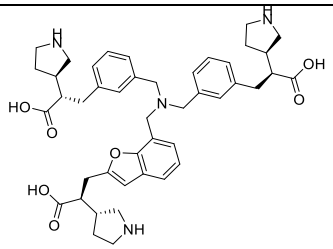
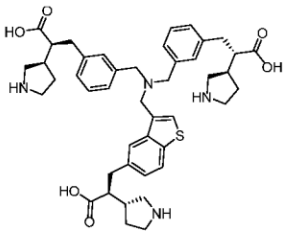
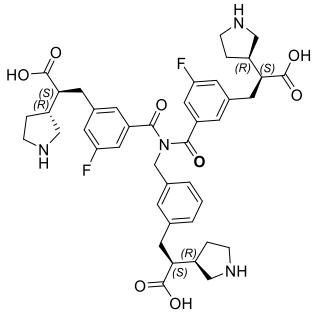
Compounds 224 and 225 were prepared according to the preparation method of Compounds 96 and 146.

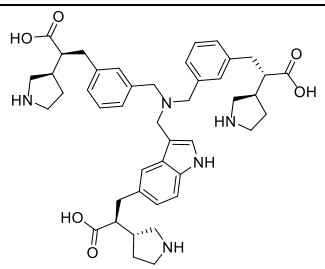
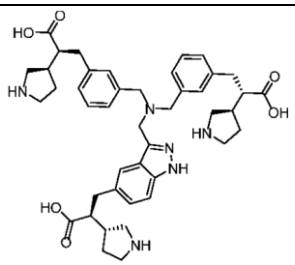
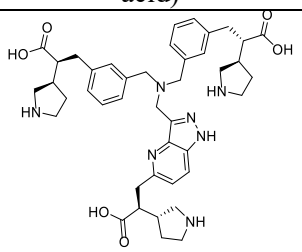
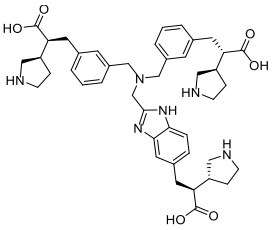
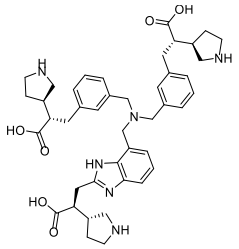
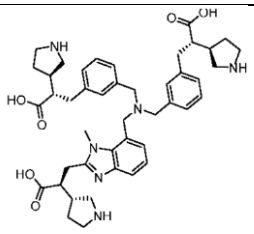
Compound 226 was prepared according to the preparation method of Compounds 146 and 147;

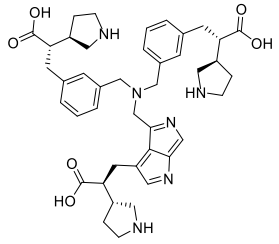
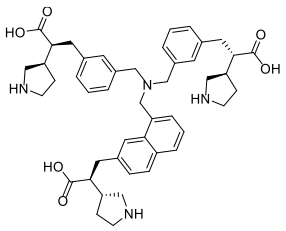
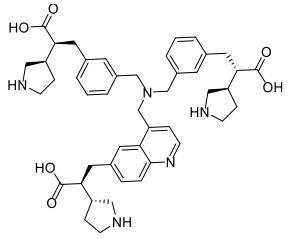
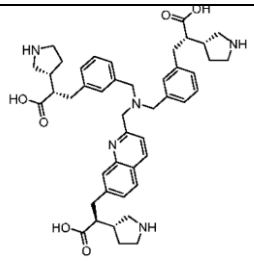
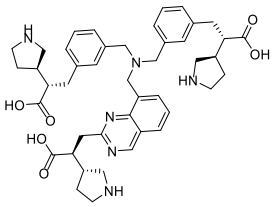
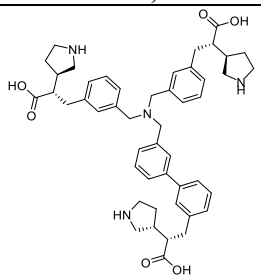
Compounds 223 and 227 were prepared according to the preparation method of Compound 158;

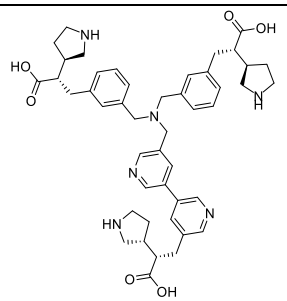
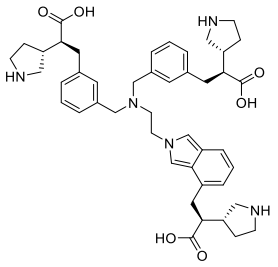
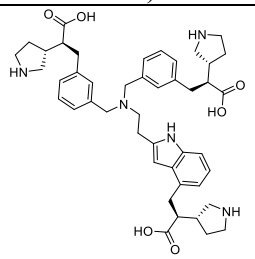
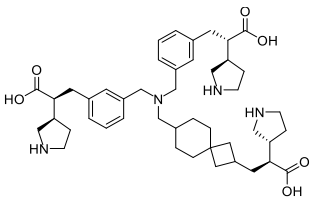
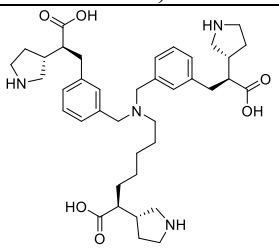
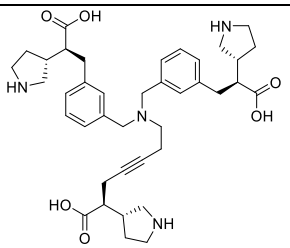
Compound 228 was prepared according to the preparation method of Compound 159.

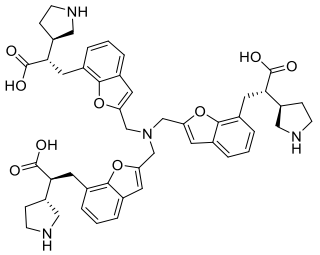
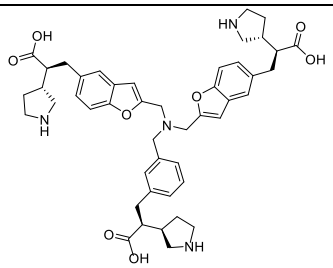
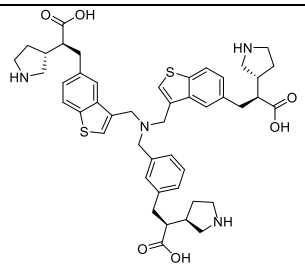
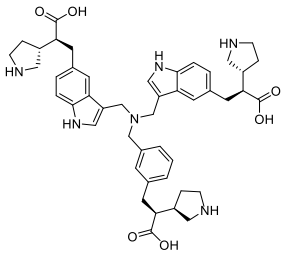
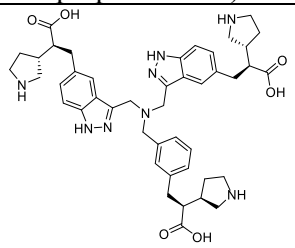
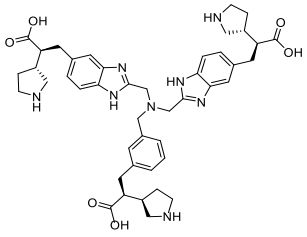
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
1	 (2S, 2'S)-3, 3‘-((azobis-bis (methylene)) bis (benzofuran-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	560.27	2	 (2S, 2'S)-3, 3'-((((3-fluoro-5-methoxybenzyl) azodiyl) bis (methylene)) bis (benzofuran-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	698.32

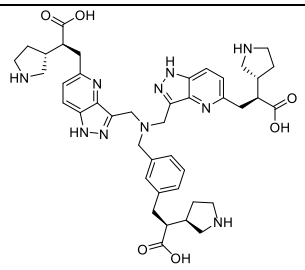
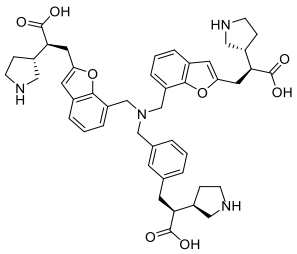
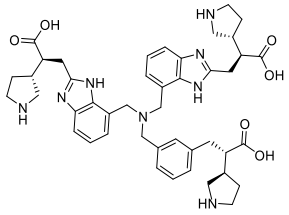
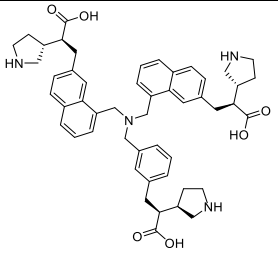
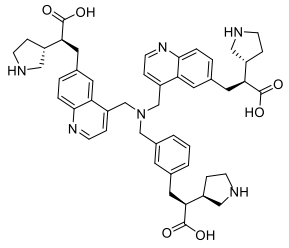
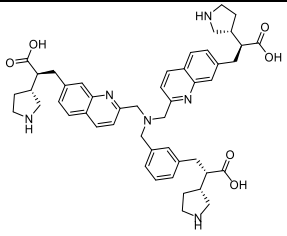
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
3	 (2S, 2'S)-3, 3'-((((pyridin-3-yl-methyl) azodiyl) bis (methylene)) bis (benzo [b] thiophene-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	683.26	4	 (2S, 2'S)-3, 3'-((((4-(aminomethyl) benzyl) azodiyl) bis (methylene)) bis (1H-indole-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	677.37
7	 (2S, 2'S)-3, 3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzofuran-2-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	751.40	9	 (2S, 2'S)-3, 3'-(((((2-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzofuran-7-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	751.40
10	 (2S, 2'S)-3, 3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzo [b] thiophen-3-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	767.38	13	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (carbonyl)) bis (5-fluoro-3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	775.34

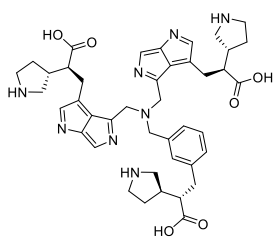
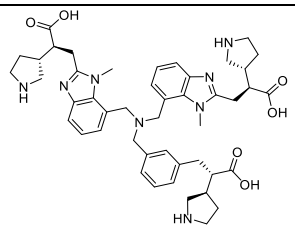
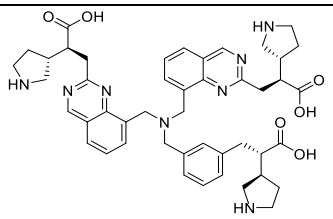
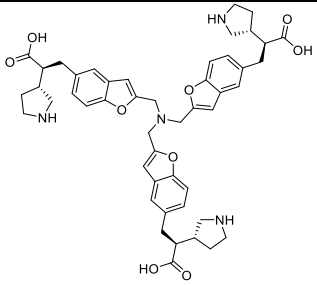
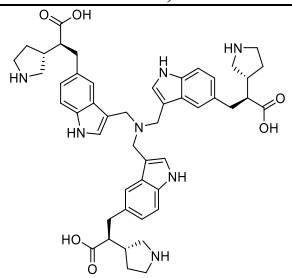
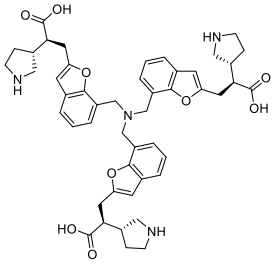
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
14	 (2S, 2'S)-3, 3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1H-indol-3-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	750.42	15	 (2S, 2'S)-3, 3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1H-indazol-3-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	751.41
16	 (2S, 2'S)-3, 3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1H-pyrazolo [4, 3-b] pyridin-3-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	752.41	17	 (2S, 2'S)-3, 3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1H-benzo [d] imidazol-2-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	751.41
18	 (2S, 2'S)-3, 3'-(((((2-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1H-benzo [d] imidazol-7-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	751.41	19	 (2S, 2'S)-3, 3'-(((((2-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1-methyl-1H-benzo [d] imidazol-7-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	765.43

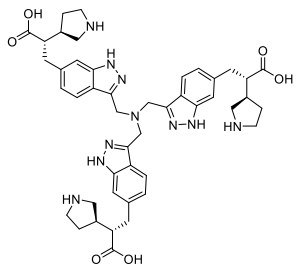
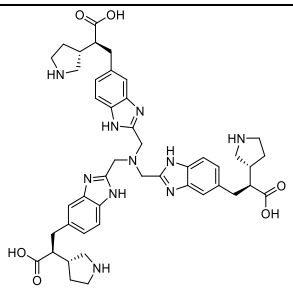
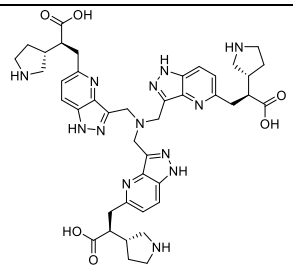
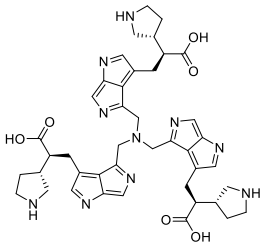
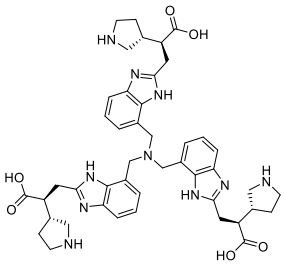
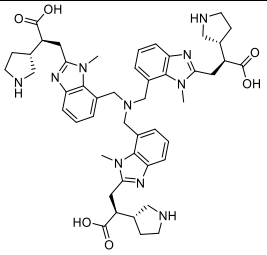
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
20	 (2S, 2'S)-3, 3'-(((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) pyrrolo [3, 4-b] pyrrol-4-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	737.39	21	 (2S, 2'S)-3, 3'-(((((7-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) naphthalen-1-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	761.42
22	 (2S, 2'S)-3, 3'-(((((6-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) quinolin-4-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	762.42	23	 (2S, 2'S)-3, 3'-(((((7-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) quinolin-2-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	762.42
24	 (2S, 2'S)-3, 3'-(((((2-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) quinazolin-8-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	763.42	25	 (2S, 2'S)-3, 3'-(((((3'-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-[1, 1'-biphenyl]-3-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	787.44

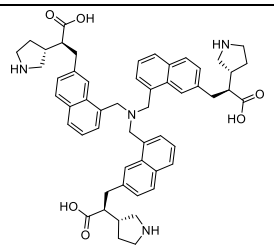
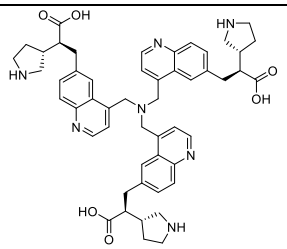
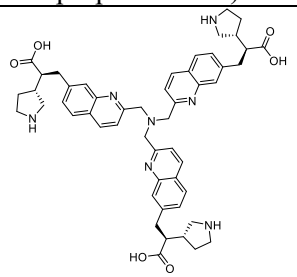
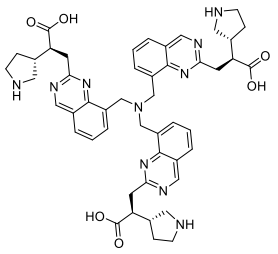
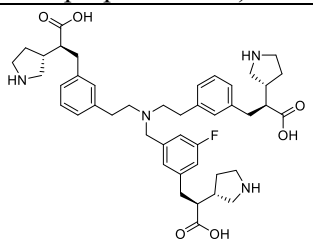
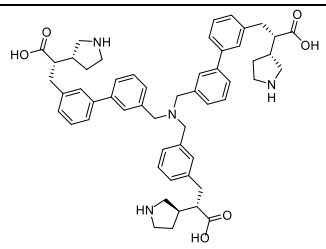
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
26	 (2S, 2'S)-3, 3'-(((((5'-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-[3, 3'-bipyridin]-5-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	789.73	27	 (2S, 2'S)-3, 3'-((((2-(4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-2H-isoindol-2-yl) ethyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	764.43
28	 (2S, 2'S)-3, 3'-((((2-(4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1H-indol-2-yl) ethyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	764.43	29	 (2S, 2'S)-3, 3'-(((((2-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) spiro [3.5] nonan-7-yl) methyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	757.48
30	 (2S, 2'S)-3, 3'-(((((S)-6-carboxy-6-((R)-pyrrolidin-3-yl) hexyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	677.42	31	 (2S, 2'S)-3, 3'-(((((S)-6-carboxy-6-((R)-pyrrolidin-3-yl) hex-3-yn-1-yl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	673.39

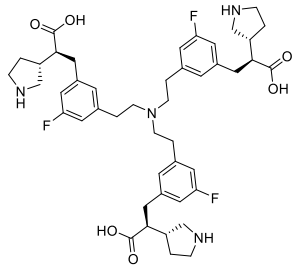
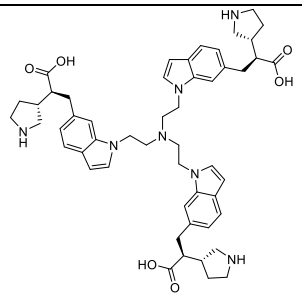
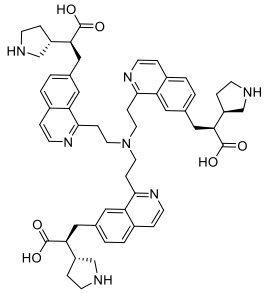
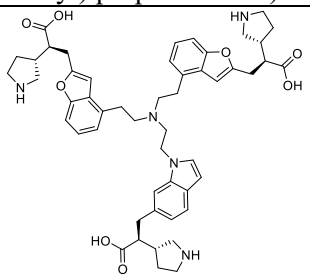
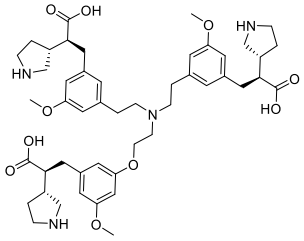
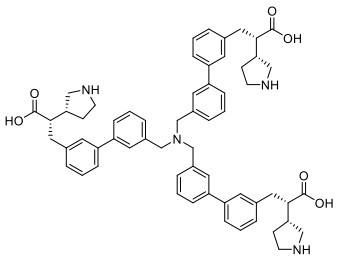
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
32	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (benzofuran-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.39	33	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (benzofuran-2, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	791.39
34	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (benzo [b] thiophene-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	823.35	35	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (1H-indole-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	789.43
36	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (1H-indazole-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	791.42	37	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (1H-benzo [d] imidazole-2, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	791.42

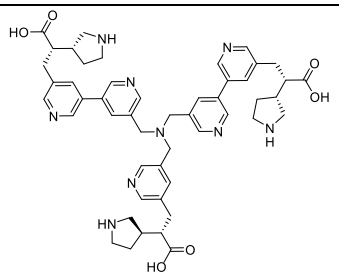
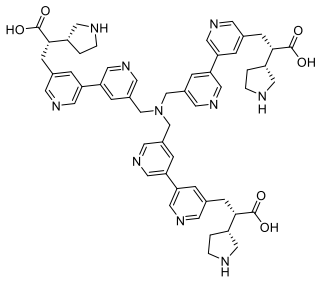
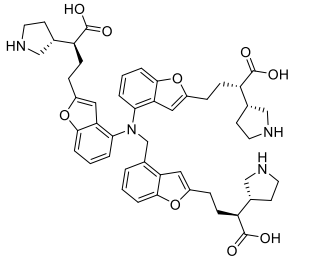
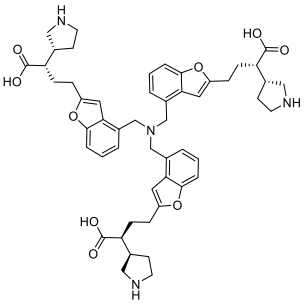
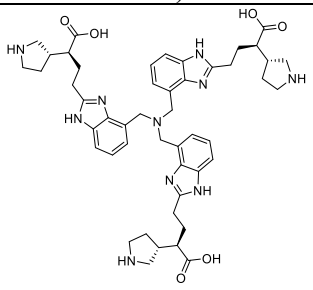
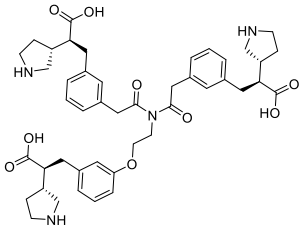
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
38	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (1H-pyrazolo [4, 3-b] pyridine-3, 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	793.41	39	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (benzofuran-7, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	791.39
40	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (1H-benzo [d] imidazole-7, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	791.42	41	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (naphthalene-8, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	811.44
42	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (quinoline-4, 6-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	813.43	43	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (quinoline-2, 7-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	813.43

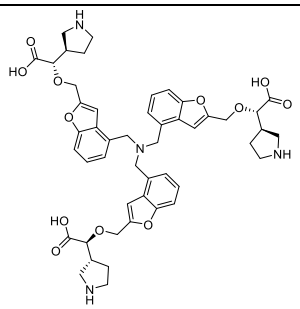
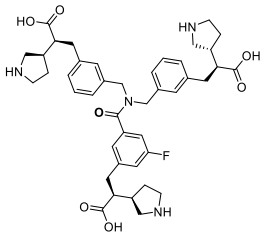
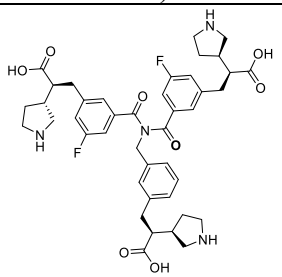
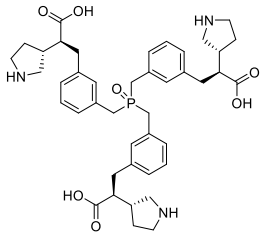
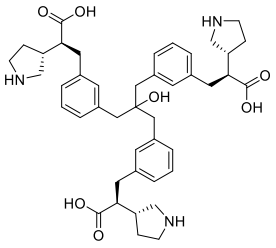
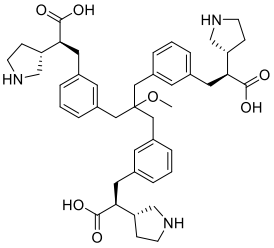
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
44	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (pyrrolo [3, 4-b] pyrrole-4, 3-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	763.39	45	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (1-methyl-1H-benzo [d] imidazole-7, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	819.45
46	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis (quinazoline-8, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	815.42	48	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (benzofuran-2, 5-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.39
50	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (1H-indole-3, 5-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	828.44	51	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (benzofuran-7, 2-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.39

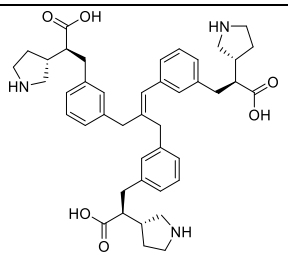
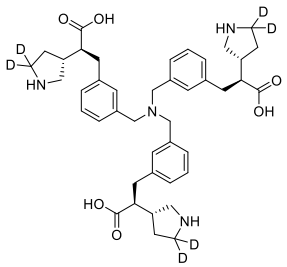
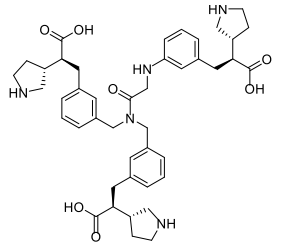
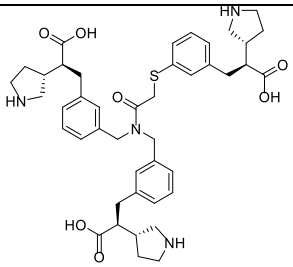
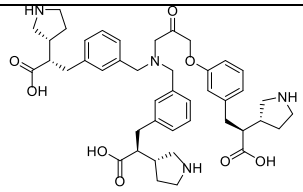
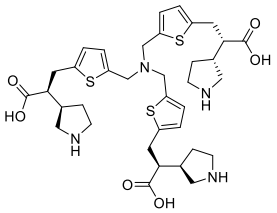
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
136	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (1H-indazole-3, 6-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.42	53	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (1H-benzo [d] imidazole-2, 5-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.42
54	 (2S, 2'S, 2" S)-3, 3', 3" ((nitrilotris (methylene)) tris (1H-pyrazolo [4, 3-b] pyridine-3, 5-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	834.41	55	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (pyrrolo [3, 4-b] pyrrole-4, 3-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	789.38
56	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (1H-benzo [d] imidazole-7, 2-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.42	57	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (1-methyl-1H-benzo [d] imidazole-7, 2-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	873.47

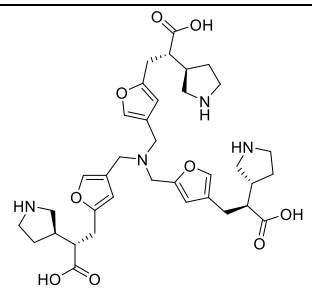
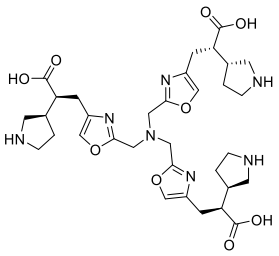
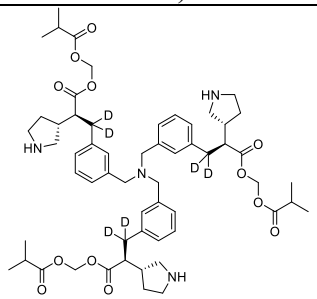
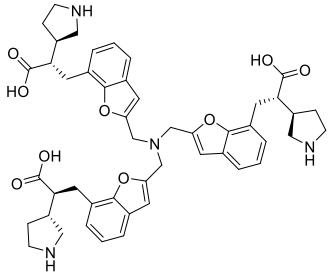
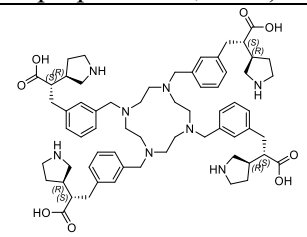
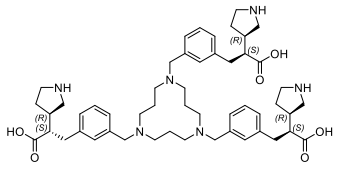
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
58	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (naphthalene-8, 2-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	861.45	59	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (quinoline-4, 6-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	864.44
60	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (quinoline-2, 7-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	864.44	61	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (quinazoline-8, 2-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	867.44
63	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((S)-pyrrolidin-3-yl) ethyl)-5-fluorobenzyl) azodiyl) bis (ethane-2, 1-diyl)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	757.43	64	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (methylene)) bis ([1, 1'-biphenyl]-3', 3-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	862.47

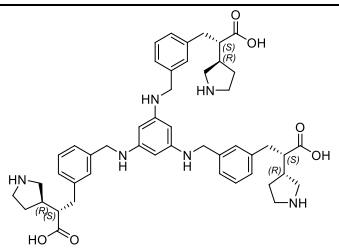
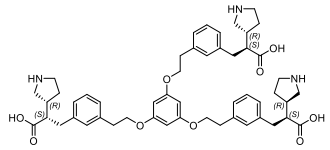
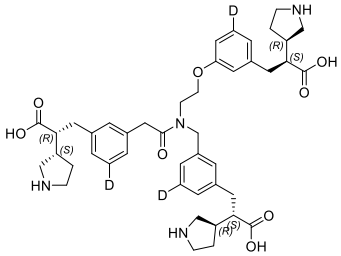
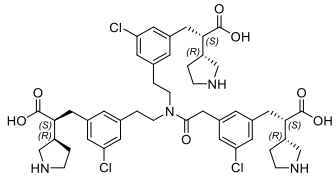
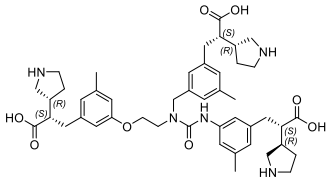
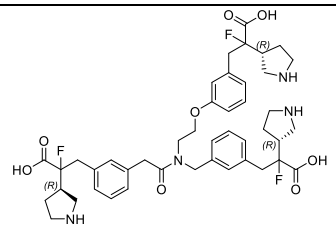
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
66	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (ethane-2, 1-diyl)) tris (5-fluorobenzene-3, 1-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	807.42	68	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (ethane-2, 1-diyl)) tris (1H-indole-1, 6-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	870.48
69	 (2S, 2'S, 2" S)-3, 3', 3" ((nitrilotris (ethane-2, 1-diyl)) tris (isoquinoline-1, 7-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	906.48	70	 (2S, 2'S)-3, 3'-((((2-(6-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-1H-indol-1-yl) ethyl) azodiyl) bis (ethane-2, 1-diyl)) bis (benzofuran-4, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	872.45
72	 (2S, 2'S)-3, 3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-methoxyphenoxy) ethyl) azodiyl) bis (ethane-2, 1-diyl)) bis (5-methoxy-3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	859.48	73	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris ([1, 1′-biphenyl]-3′, 3-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	939.50

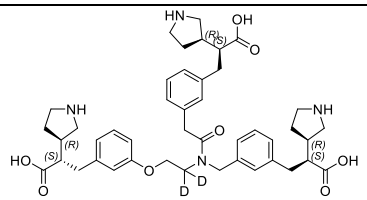
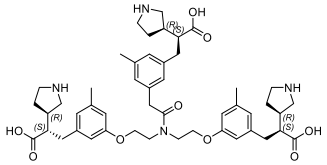
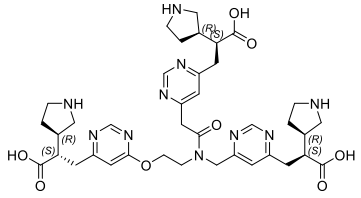
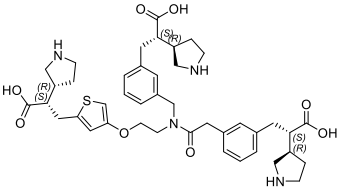
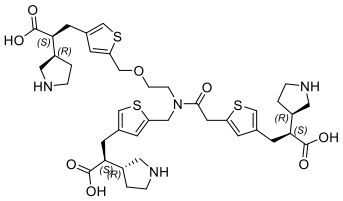
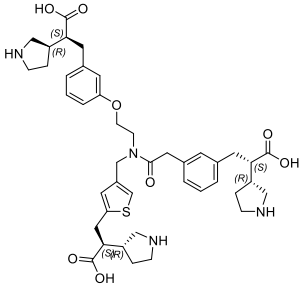
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
74	 (2S, 2'S)-3, 3'-(((((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) pyridin-3-yl) methyl) azodiyl) bis (methylene)) bis ([3, 3'-bipyridine]-5', 5-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	867.45	75	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris ([3, 3′-bipyridine]-5′, 5-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	944.47
76	 (2S, 2'S)-4, 4'-((((2-((S)-3-carboxy-3-((R)-pyrrolidin-3-yl) propyl) benzofuran-4-yl) methyl) azodiyl) bis (benzofuran-4, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) butanoic acid)	845.40	77	 (2S, 2′S, 2″S)-4, 4′, 4″ ((nitrilotris (methylene)) tris (benzofuran-4, 2-diyl)) tris (2-((R)-pyrrolidin-3-yl) butanoic acid)	873.44
78	 (2R, 2' R)-4, 4'-(((((2-((S)-3-carboxy-3-((S)-pyrrolidin-3-yl) propyl)-1H-benzo [d] imidazol-4-yl) methyl) azodiyl) bis (methylene)) bis (1H-benzo [d] imidazole-4, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) butanoic acid)	873.47	79	 (2S, 2'S)-3, 3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) azodiyl) bis (2-oxoethane-2, 1-diyl)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	797.40

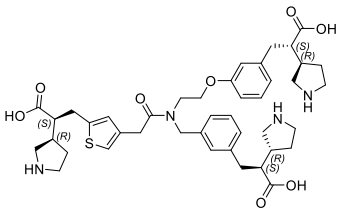
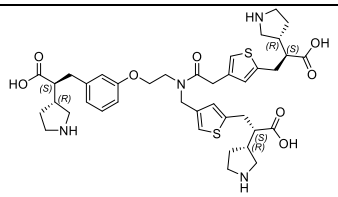
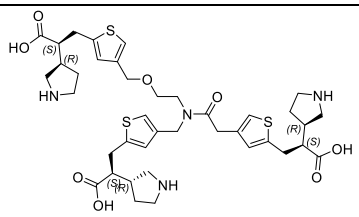
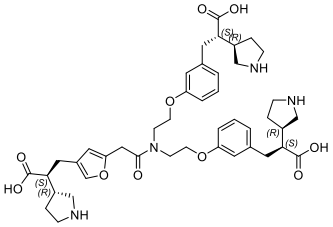
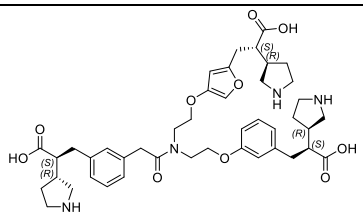
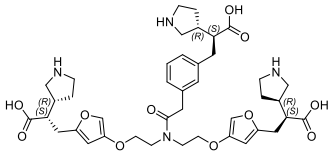
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
82	 (2S, 2′S, 2″S)-2, 2′, 2″ (((methylene)) tris (benzofuran-4, 2-diyl)) tris (methylene)) tris (oxy)) tris (2-(R)-pyrrolidin-3-yl) acetic acid)	879.37	83	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-fluorobenzoyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	743.37
84	 (2S, 2'S)-3, 3'-((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) azodiyl) bis (carbonyl)) bis (5-fluoro-3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	775.34	85	 (2S, 2′S, 2″S)-3, 3′, 3″ (((oxo-15-phosphetidintriyl) tris (methylene)) tris (benzene-3, 1-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	744.37
86	 (2*S*)-3-[3-(2-Hydroxy-3-{3-[(2*S*)-2-carboxy-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] ethyl] phenyl}-2-({3-[(2*S*)-2-carboxy-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] ethyl] phenyl} methyl) propyl) phenyl]-2-[(3*R*-tetrahydro-1*H*-pyrrol-3-yl] propanoic acid	726.40	87	 (2*S*)-3-[3-(3-{3-[(2*S*)-2-carboxy-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] ethyl] phenyl}-2-({3-[(2*S*)-2-carboxy-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] ethyl] phenyl} methyl)-2-methoxypropyl) phenyl]-2-[(3*R*-tetrahydro-1*H*-pyrrol-3-yl] propanoic acid	740.42

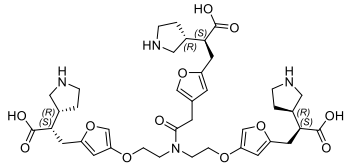
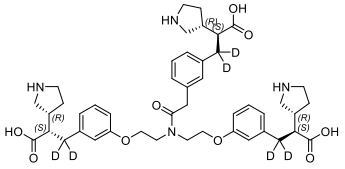
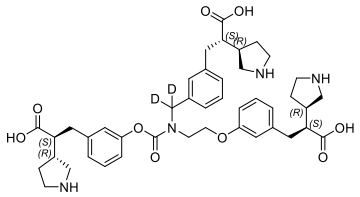
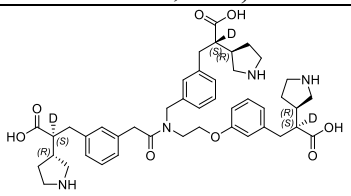
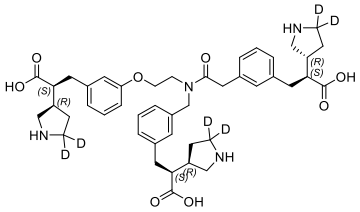
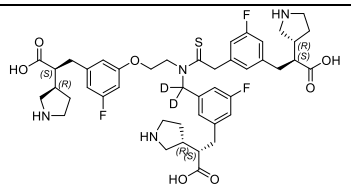
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
88	 (2*S*)-3-[3-(3-{3-[(2*S*)-2-carboxy-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] ethyl] phenyl}-2-({3-[(2*S*)-2-carboxy-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] ethyl] phenyl} methyl) prop-2-enyl) phenyl]-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] propanoic acid	708.39	92	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (benzene-3, 1-diyl)) tris (2-((R)-pyrrolidin-3-yl-5, 5-d2) propanoic acid)	717.44
114	 (2S, 2'S)-3, 3'-(((((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) glycyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	754.40	115	 (2S, 2'S)-3, 3'-((((2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) thio) acetyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	771.37
116	 (2S, 2'S)-3, 3'-((((3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy)-2-oxopropyl) azodiyl) bis (methylene)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	769.40	118	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (thiophene-5, 2-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	729.40

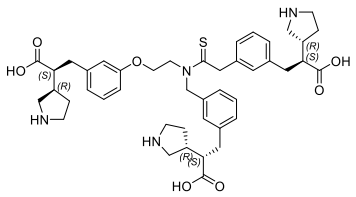
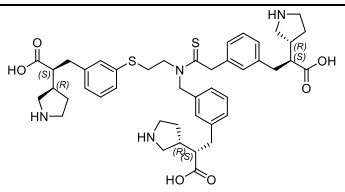
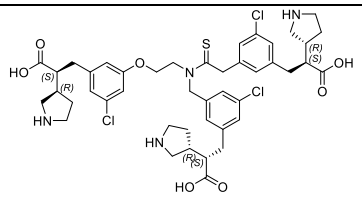
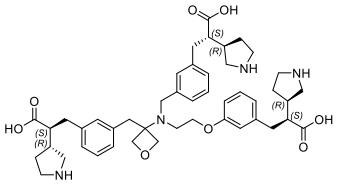
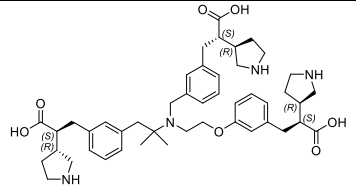
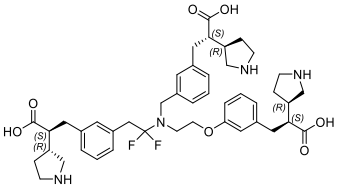
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
119	 (2S, 2'S)-3, 3'-(((((4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) furan-2-yl) methyl) azodiyl) bis (methylene)) bis (furan-4, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	681.40	120	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (oxazole-2, 4-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	684.33
124	 tris ((isobutyryloxy) methyl) 3, 3′, 3″ ((nitrilotris (methylene)) tris (benzene-3, 1-diyl)) (2S, 2′S, 2″S)-tris (2-((R)-pyrrolidin-3-yl) propionate-3′, 3′-d2)	1017.50	125	 (2S, 2′S, 2″S)-3, 3′, 3″ ((nitrilotris (methylene)) tris (benzofuran-2, 7-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.39
154	 (2S, 2′S, 2″S, 2‴S)-3, 3′, 3″, 3‴ ((1, 4, 7, 10-tetraazacyclododecane-3, 1, 3-tetrayl) tetrakis (methylene)) tetrakis (benzene-3, 1-diyl)) tetrakis (2-((R)-pyrrolidin-3-yl) propanoic acid) 1, 4, 7, 10	1097.80	155	 (2S, 2'S, 2" S)-3, 3', 3"-((1, 5, 9-triazacyclododecane-3, 1, 3-triyl) tris (methylene)) tris (benzene-3, 1-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid) 1, 5, 9	865.47

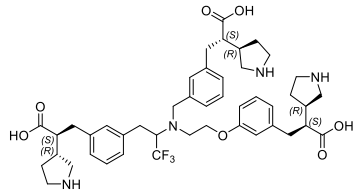
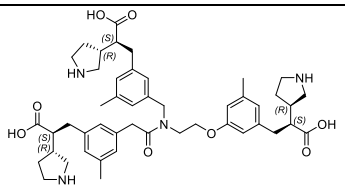
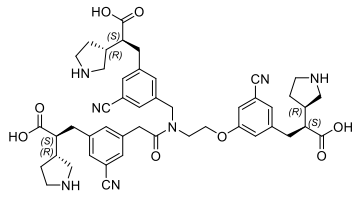
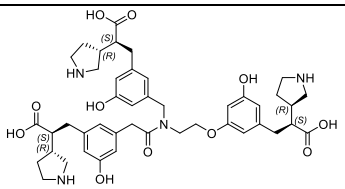
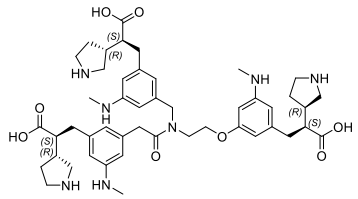
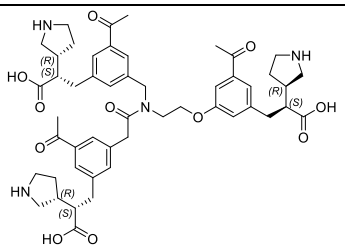
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
156	 (2S, 2′S, 2″S)-3, 3′, 3″ (((benzene-1, 3, 5-tris (azodiyl)) tris (methylene)) tris (benzene-3, 1-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	817.58	157	 (2S, 2′S, 2″S)-3, 3′, 3″ (((benzene-3, 1, 3, 5-tris (oxy)) tris (ethane-2, 1-diyl)) tris (benzene-3, 1-diyl)) tris (2-((R)-pyrrolidin-3-yl) propanoic acid)	862.64
169	 (2*R*-3-(3-{2-[(2-{[5-(carboxymethyl)-3-deuterophenyl] oxy} ethyl) ({2-[(2 *S*)-2-carboxy-2-[(3*R*)-tetrahydro-1*H*-pyrrol-3-yl] ethyl]-4-deuterocyclopenta-2, 4-dienyl} methyl) amino]-2-oxoethyl}-5-deuterophenyl)-2-[(3*S*)-tetrahydro-1*H*-pyrrol-3-yl] propanoic acid	772.64	170	 (2S, 2'S)-3, 3'-((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-chlorophenyl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (5-chloro-3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	869.51
171	 (S)-3-(3-(3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-methylbenzyl)-3-(2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-methylphenoxy) ethyl) ureido)-2-((R)-pyrrolidin-3-yl) propanoic acid	812.67	172	 3-(3-(2-((3-(2-carboxy-2-fluoro-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-(3-(2-carboxy-2-fluoro-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl)-2-fluoro-2-((R)-pyrrolidin-3-yl) propanoic acid	823.56

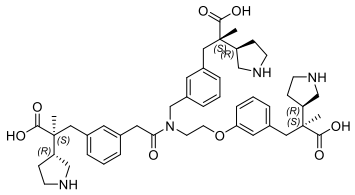
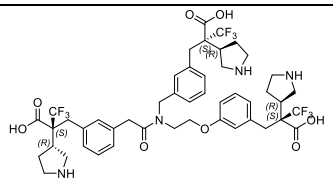
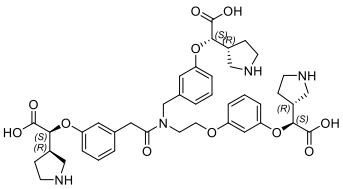
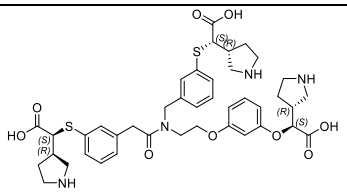
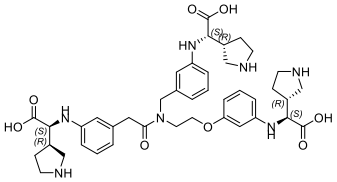
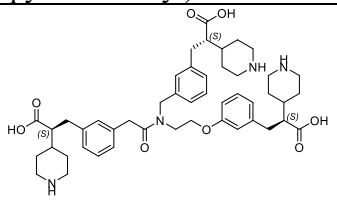
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
173	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl-1, 1-d2) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	771.64	174	 (2S, 2'S)-3, 3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-methylphenyl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (oxy)) bis (5-methyl-3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	841.60
175	 (S)-3-(6-(2-(6-(S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) pyrimidin-4-yl)-N-((6-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) pyrimidin-4-yl) methyl) acetamido) ethoxy) pyrimidin-4-yl)-2-((R)-pyrrolidin-3-yl) propanoic acid	775.52	179	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) thiophen-3-yl) oxy) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	775.56
181	 (S)-3-(5-((2-(2-(4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) thiophen-2-yl)-N-((4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) thiophen-2-yl) methyl) acetamido) ethoxy) methyl) thiophen-3-yl)-2-((R)-pyrrolidin-3-yl) propanoic acid	801.43	182	 (S)-3-(3-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) ((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) thiophen-3-yl) methyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	775.64

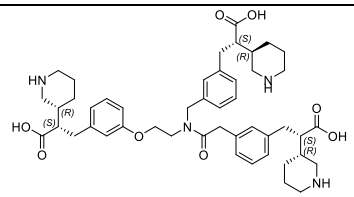
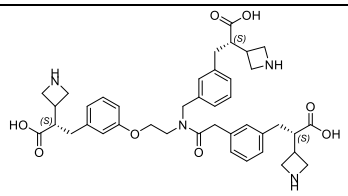
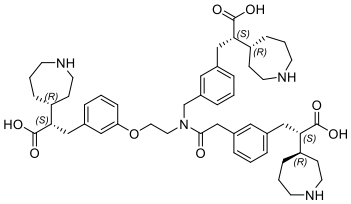
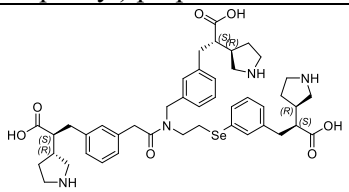
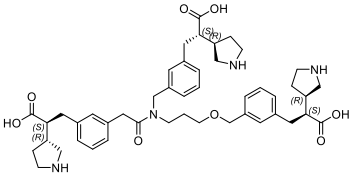
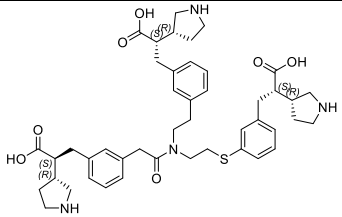
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
183	 (S)-3-(4-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) amino)-2-oxoethyl) thiophen-2-yl)-2-((R)-pyrrolidin-3-yl) propanoic acid	775.37	184	 (S)-3-(4-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) ((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) thiophen-3-yl) methyl) amino)-2-oxoethyl) thiophen-2-yl)-2-((R)-pyrrolidin-3-yl) propanoic acid	781.50
185	 (S)-3-(4-((2-(2-(5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) thiophen-3-yl)-N-((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) thiophen-3-yl) methyl) acetamido) ethoxy) methyl) thiophen-2-yl)-2-((R)-pyrrolidin-3-yl) propanoic acid	801.41	186	 (2S, 2'S)-3, 3'-(((((2-(4-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) furan-2-yl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (oxy)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	789.57
187	 (S)-3-(3-(2-((2-((5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) furan-3-yl) oxy) ethyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	789.63	188	 (2S, 2'S)-3, 3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (oxy)) bis (furan-4, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	779.53

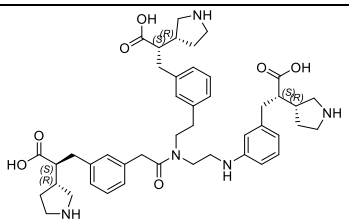
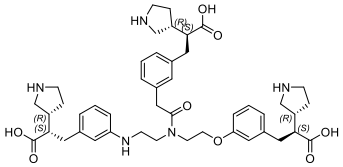
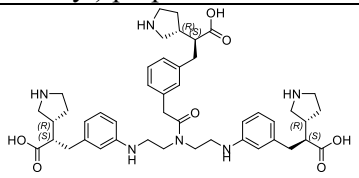
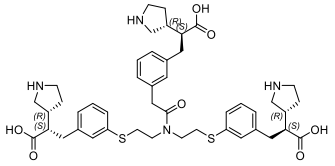
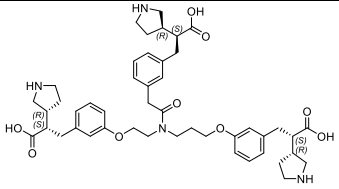
Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
189	 (2S, 2'S)-3, 3'-(((((2-(5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) furan-3-yl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (oxy)) bis (furan-4, 2-diyl)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	769.51	191	 (2S, 2'S)-3, 3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl-1, 1-d2) phenyl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (oxy)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid-3, 3-d2)	805.68
192	 (S)-3-(3-(2-(((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) carbonyl) ((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) methyl-d2) amino) ethoxy) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	773.52	194	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl-2-d) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl-2-d) phenoxy) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid-2-d	772.61
195	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl-5, 5-d2) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl-5, 5-d2) ethyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl-5, 5-d2) propanoic acid	775.56	196	 (S)-3-(3-(2-((2-(3-(S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-fluorophenoxy) ethyl) ((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-fluorophenyl) methyl-d2) amino)-2-thioxoethyl)-5-fluorophenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	841.60

Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
197	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) amino)-2-((R)-pyrrolidin-3-yl) propanoic acid	785.40	198	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) thio) ethyl) amino)-2-((R)-pyrrolidin-3-yl) propanoic acid	801.51
199	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-chlorobenzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-chlorophenoxy) ethyl) amino)-2-thioxoethyl)-5-chlorophenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	887.42	200	 (S)-3-(3-((3-(((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) amino) oxetan-3-yl) methyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	797.40
201	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (1-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl)-2-methylpropan-2-yl) amino) ethoxy) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	783.60	202	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) amino)-2, 2-difluoroethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	791.60

Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
203	 (2S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) amino)-3, 3, 3-trifluoropropyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	823.40	204	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-methylbenzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-methylphenoxy) ethyl) amino)-2-oxoethyl)-5-methylphenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	811.60
205	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-cyanobenzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-cyanophenoxy) ethyl) amino)-2-oxoethyl)-5-cyanophenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	844.50	206	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-hydroxybenzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-hydroxyphenoxy) ethyl) amino)-2-oxoethyl)-5-hydroxyphenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	817.50
207	 (S)-3-(3-(2-((3-(S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-(methylamino) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl)-5-(methylamino) phenoxy) ethyl)-2-oxoethyl)-5-(methylamino) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	856.70	208	 (S)-3-(3-acetyl-5-((N-(2-(3-acetyl-5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl)-2-(3-acetyl-5-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) acetamido) methyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	895.50

Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
212	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) propyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) propyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl)-2-methyl-2-((R)-pyrrolidin-3-yl) propanoic acid	811.52	213	 (S)-2-(3-(2-((3-(S)-2-carboxy-2, 3, 3, 3,-trifluoro-2-((R)-pyrrolidin-3-yl) propyl) benzyl) (2-(3-((S)-2-carboxy-2, 3, 3, 3,-trifluoro-2-((R)-pyrrolidin-3-yl) propyl) phenoxy) ethyl) amino)-2-oxoethyl) benzyl)-3, 3, 3,-trifluoro-2-((R)-pyrrolidin-3-yl) propanoic acid	973.60
214	 (S)-2-(3-(2-((3-((S)-carboxy ((R)-pyrrolidin-3-yl) methoxy) benzyl) (2-(3-((S)-carboxy ((R)-pyrrolidin-3-yl) methoxy) phenoxy) ethyl) amino)-2-oxoethyl) phenoxy)-2-((R)-pyrrolidin-3-yl) acetic acid	775.48	215	 (S)-2-((3-(2-((3-(((S)-carboxy ((R)-pyrrolidin-3-yl) methoxy) phenoxy) ethyl) (3-(((S)-carboxy ((R)-pyrrolidin-3-yl) methyl) thio) benzyl) amino)-2-oxoethyl) phenyl) thio)-2-((R)-pyrrolidin-3-yl) acetic acid	807.38
216	 (S)-2-((3-(2-((3-(((S)-carboxy ((R)-pyrrolidin-3-yl) methyl) amino) benzyl) (2-(3-(((S)-carboxy ((R)-pyrrolidin-3-yl) methyl) amino) phenoxy) ethyl) amino)-2-((R)-pyrrolidin-3-yl) acetic acid	772.80	217	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-(piperidin-4-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-(piperidin-4-yl) ethyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl)-2-(piperidin-4-yl) propanoic acid	811.46

Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
218	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-piperidin-3-yl) ethyl) benzyl) (2-(3-((S)-2-carboxy-2-((R)-piperidin-3-yl) ethyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-piperidin-3-yl) propanoic acid	811.46	219	 (S)-2-(azetidin-3-yl)-3-(3-(2-((3-((S)-2-(azetidin-3-yl)-2-carboxyethyl) benzyl) (2-(3-((S)-2-(azetidin-3-yl)-2-carboxyethyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl) propanoic acid	727.52
220	 (S)-2-((R)-Azepin-4-yl)-3-(3-(2-((3-((S)-2-((R)-azepin-4-yl)-2-carboxyethyl) benzyl) (2-(3-((S)-2-((R)-azepin-4-yl)-2-carboxyethyl) phenoxy) ethyl) amino)-2-oxoethyl) phenyl) propanoic acid	853.47	221	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) selenyl) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	833.28
222	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) (3-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) benzyl) oxy) propyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	797.50	223	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) (2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) thio) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	799.62

Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$	Compound No.	Chemical structure	LCMS (ESI) $[M+H]^+$
224	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) (2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) amino) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	782.68	225	 (S)-3-(3-(2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) (2-((3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) amino) ethyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	798.67
226	 (2S, 2'S)-3, 3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (azodiyl)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	797.60	227	 (2S, 2'S)-3, 3'-(((((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenyl) acetyl) azodiyl) bis (ethane-2, 1-diyl)) bis (sulfinyl)) bis (3, 1-phenylene)) bis (2-((R)-pyrrolidin-3-yl) propanoic acid)	831.50
228	 (S)-3-(3-(2-((2-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) ethyl) (3-(3-((S)-2-carboxy-2-((R)-pyrrolidin-3-yl) ethyl) phenoxy) propyl) amino)-2-oxoethyl) phenyl)-2-((R)-pyrrolidin-3-yl) propanoic acid	813.54			

The following are the effect tests and data of the compounds of the invention.

Biological Test Evaluation

Test Example 1 and Methods of ELISA Assay on Screening Lp(a) Assembly Inhibition

1. Reagents, Consumables, Instruments

Reagent	**Manufacturer**	**Catalog No.**
HepG2 cells overexpressing ApoA protein	\	\
DMEM medium	Gibco	11995-065
DPBS buffer	Invitrogen	14190-250
Trypan Blue	Invitrogen	T10282
FBS	Gibco	10091148
DMSO	Solarbio	D8371
Penicillin-streptomycin	Solarbio	P1400
Puromycin	Gibco	A1113802
DuoSet ELISA kit	R&D	DY008
EACA	Sigma	A2504
Tween-20	Solarbio	T8220
PBS buffer	Solarbio	P1020
Consumable	**Manufacturer**	**Catalog No.**
Culture flask (T75)	Corning	430641
96-well plate	Corning	3599
Centrifuge tubes (15 mL, 50 mL)	BD	352096, 352070
Reagent reservoir	JET BIOFIL	LTT001050
Instrument	**Manufacturer**	**Catalog No.**
Biosafety cabinet	Thermo Scientific	1300 Series A2
Centrifuge	Eppendorf	5804R
Carbon dioxide incubator	Thermo Scientific	371
Cell counter	Invitrogen	C10281
Dispenser	BIOHIT	Easypet
Microscope	Olympus	CKX41
Microplate reader	Perkin Elmer	Envision 2104

2. Cell Culture Media Preparation

2.1. Complete Cell Culture Media

DMEM medium	90%
FBS	10%
Penicillin-streptomycin	1%
Puromycin	2 μg/ml

2.2. Test Culture Media

DMEM medium	90%
FBS	10%
Penicillin-streptomycin	1%
HEPES buffer	20 mM

3. Test Procedure

3.1 Cell Culture and Passage

1) Preheated the culture media, DPBS, and pancreatin in a 37°C water bath in advance.

2) Digested cells with pancreatin, transferred the cell suspension to a 15 mL centrifuge tube, and centrifuged at 1000 rpm for 5 min.

3) Resuspended the cells with culture media and transferred the cell suspension to a new T75 cell culture flask.

4) Cultured at 37°C in a 5% CO_2 incubator.

3.2. Cell Seeding and Drug Administration

1) Seeded HepG2 cells overexpressing of ApoA protein into a 96-well plate at 100 μl per well and incubated overnight for attachment.

2) Replaced with fresh culture media the next day, then added diluted compounds, and cultured the cell plate in a 5% CO_2, 37°C incubator for 24h.

3.3. Preparation of Cell Culture Supernatant

1) Added 10 μl of 1.5 M EACA to each well.

2) Centrifuged at 1000 rpm for 1 min, and transferred 100 μl of cell culture supernatant to a pre-coated ELISA plate.

3.4. ELISA Test

1) Added 100 μl of capture antibody to each well of a pre-coated ELISA plate and incubated overnight at 25°C.

2) Added 300 μl of washing solution to each well and washed 5 times for 1min each time.

3) Added 100 μl of blocking solution to each well and incubated at 25°C for 2h.

4) Added 300 μl of washing solution to each well and washed 5 times for 1min each time.

5) Added 100 μl of sample to each well and incubated at 25°C for 1h.

6) Added 300 μl of washing solution to each well and washed 5 times for 1min each time.

7) Added 100 μl of detection antibody to each well and incubated at 25°C for 1h.

8) Added 300 μl of washing solution to each well and washed 5 times for 1min each time.

9) Added 100 μl substrate solution (Color Reagent A: Color Reagent B, 1:1) to each well and incubated for 20min at 25°C in the dark.

10) Added 50 ml of stop solution to each well, gently blowed and sucked several times with the pipette tip, and read within 5 min.

4. IC50 Data Analysis

H = Ave (DMSO or H_2O)

L = Ave (1 μM Reference)

SD (H) = STDEV (DMSO or H_2O)

SD (L) = STDEV (1 μM Reference)

CV% (DMSO) = 100* (SD_H/Ave_H)

CV% (1uM Reference) = 100*SD_L/Ave_L

Z' = 1-3*(SD_H+SD_L)/(Ave_H-Ave_L)

Inhibition% = (Ave_H-Sample)/(Ave_H-Ave_L)

Nonlinear Fitting Regression Equation for the Compound IC50:

Y = Bottom+(Top-Bottom)/(1+10^((LogIC50-X)*HillSlope))

X: cpd concentration

Y: inhibition%

Top and Bottom: Plateaus in same units as Y

logIC50: same log units as X

HillSlope: Slope factor or Hill slope

5. Test Results

The results showed that the compounds of the invention had strong inhibitory effects on Lp(a) assembly, and exemplary compounds were shown in Table 1.

Table 1

Compound No.	**Lp(a)/IC_{50} (nM)**	**Compound No.**	**Lp(a)/IC_{50} (nM)**
LY3473329	1.05	121	1.53
5	4.12	122	1.87
6	1.13	126	1.26
11	0.89	127	0.90
12	1.17	128	1.34
47	1.03	130	1.45
49	3.22	131	1.19
65	0.87	132	0.88
67	8.55	133	0.94
71	0.54	134	0.85
80	2.31	135	0.71
81	0.85	136	2.16

Compound No.	Lp(a)/IC_{50} (nM)	Compound No.	Lp(a)/IC_{50} (nM)
90	0.83	137	1.08
91	1.03	138	2.00
93	0.81	139	0.66
94	0.65	140	0.79
95	0.68	141	1.02
96	0.58	142	3.19
97	1.46	143	3.81
98	0.85	144	1.18
99	0.96	145	1.72
100	1.12	146	0.93
101	2.71	147	0.86
102	0.74	148	1.50
103	2.11	149	2.53
104	1.04	152	1.26
105	0.84	153	2.91
106	1.84	158	1.65
107	1.66	159	1.68
108	1.16	160	1.37
111	1.02	161	1.89
112	3.40	176	1.81
113	1.17	177	1.26
117	2.58	210	1.52

Test Example 2 and Pharmacokinetic Test in C57BL/6J Female Mice

C57BL/6J female mice were used as test animals, and the drug concentrations in the plasma of the C57BL/6J female mice at different time points after intravenous and gavage administration was determined to study the pharmacokinetic characteristics of the compound in the C57BL/6J female mice.

Test animals: C57BL/6J female mice

Drug formulation: a specific amount of the compound was weighed and normal saline was added to prepare clear, colorless solutions of 0.4 mg/mL (IV) and 1 mg/mL (PO).

Test procedure: The C57BL/6J female mice were fasted overnight before gavage administration, followed by non-fasted intravenous administration. The intravenous dose was 2 mg/kg, and the gavage dose was 10 mg/kg. Approximately 0.03 mL of blood was collected from the orbital venous plexus at 0.083 (IV), 0.25, 0.5, 1, 2, 4, 8, and 24 h after administration, respectively, placed in a centrifuge tube containing EDTA-K2, centrifuged at 3000 rpm/min at 2-8°C for 10min to obtain plasma, and stored at −80°C.

Determination of the content of the compound to be tested in plasma of the C57BL/6J female mice at different blood collection time points: 10 μL of plasma of the C57BL/6J female mice collected at each time point after administration of LY3473329 and the compound of this application was added with 200 μL of 500 mM trichloroacetic acid aqueous solution to precipitate protein, which contained 100 ng/mL internal standard, vortexed for 1 min, centrifuged at 14000 rpm for 7min for samples treated with test tubes, and centrifuged at 4000 rpm for 10min for samples treated with 96-well plates, and 190 μL of the supernatant was transferred to a 96-well plate, and 8 μL of the supernatant was injected for LC-MS/MS analysis. WO2023078333A1 Example 6:12 μL of plasma of C57BL/6J female mice collected at each time point after administration was added with 240 μL of methanol to precipitate protein, which contained 10 ng/mL internal standard, vortexed for 1 min, centrifuged at 14000 rpm for 7min for samples treated with test tubes, and centrifuged at 4000 rpm for 10min for samples treated with 96-well plates. 220 μL of the supernatant was transferred to a 96-well plate, and 10 μL of the supernatant was taken for LC-MS/MS analysis.

Pharmacokinetic Parameter Results

After plasma concentrations were determined by LC/MS/MS analysis method, pharmacokinetic parameters (e.g. C_{max}, AUC, $T_{1/2}$, etc.) were calculated using WinNonlin software and noncompartmental analysis.

The results showed that some compounds of the present invention exhibited favorable pharmacokinetic properties, with better plasma exposure after intravenous and gavage administration and a long half-life, indicating excellent oral administration performance; the pharmacokinetic properties of the preferred compounds, such as plasma exposure and half-life,

were superior to those of the control compound LY3473329 and the compound of Example 6 in WO2023078333A1. The pharmacokinetic parameters for intravenous and gavage administration of an exemplary compound to the C57BL/6J female mice are shown in Tables 2 and 3.

Table 2: Pharmacokinetic parameters for gavage administration to C57BL/6J female mice

Compound No.	mg/kg	C_{max} (ng/ mL)	AUC (ng/mL*h)	$T_{1/2}$ (h)	F%
LY3473329	10	629	4462	7.4	10.1
96	10	919	12377	11.4	13.9
131	10	893	14278	16.0	13.2
159	10	874	21050	28.9	13.5
160	10	816	23547	28.8	15.9
Example 6 of WO2023078333A1	10	511	5840	9.9	13.2

Table 3: Pharmacokinetic parameters for intravenous administration to C57BL/6J female mice

Compound No.	mg/kg	AUC (ng/mL*h)	$T_{1/2}$ (h)
LY3473329	2	8820	9.8
96	2	22925	23.3
131	2	31337	33.7
159	2	33427	35.5
160	2	19182	12.1
Example 6 of WO2023078333A1	2	7673	7.7

Test Example 3 and Humanized Mouse Lp(a) Inhibition Test

The *in vivo* pharmacodynamics of the compounds in reducing Lp(a) was evaluated in a humanized Lp(a) transgenic mouse model. Lp(a) mice were obtained by crossing mice expressing humanized apoB-100 with mice expressing humanized apo(a) containing 16 Kringle repeats. Female mice aged 8-9 weeks were selected for the test. Housing conditions: standard light cycle (12 h light/12 h dark), temperature 20-25°C, humidity 40-70%, free access to water and normal diet.

One day before the test, mice were divided into vehicle control group and test article group (n = 5/group) according to body weight and baseline plasma Lp(a) concentration. Mice were orally

administered with vehicle (normal saline, 10 mL/kg) or test compound (prepared with normal saline to 3 or 0.5 mg/mL, each mouse received 10 mL/kg), once daily (9:00 am) for 3 consecutive days, and blood was collected to determine the change of serum Lp(a). Eight hours after the last dose, 10 μL of blood was collected from the tail vein and transferred to a 1.5 mL centrifuge tube containing 90 μL of normal saline, mixed well, and left to stand on ice for 30min. The above samples were centrifuged at 4°C, 3000 rpm for 10 min, and the supernatant was collected and placed on ice. The Lp(a) concentration in the supernatant was measured by double-antibody sandwich ELISA using an anti-apo(a) capture antibody and an HRP-conjugated anti-ApoB detection antibody, with TMB for color development. The reaction was stopped with 1 N sulfuric acid, and the OD value was read at 450 nm on a Tecan microplate reader. Inhibition rate was calculated for each dosing group. Inhibition rate (%) = (vehicle control group Lp(a) concentration or self pre-dose Lp(a) concentration post-dose Lp(a) concentration)/vehicle control group Lp(a) concentration or self pre-dose Lp(a) concentration * 100.

The results showed that the compounds of the present invention significantly reduced serum Lp(a) levels in mice.

Some compounds of the present invention were significantly more effective in reducing serum Lp(a) levels in mice than the control compound LY3473329 and/or the compound of Example 6 in WO2023078333A1.

The inhibition rates of exemplary compounds against Lp(a) *in vivo* were shown in Table 4.

Table 4 Single-dose *in Vivo* Pharmacodynamic Study in Mice

Compound No.	Dose (mg/kg)	Lp(a) Inhibition Rate
95	30	95%
96	30	96%
96	5	91%
100	5	86%
111	5	92%
113	5	79%
131	5	81%
138	5	88%

152	5	90%
159	5	84%
160	5	83%
161	5	83%
162	5	79%
163	5	81%
176	5	78%
177	5	90%
178	5	84%
180	5	80%
190	5	83%
193	5	88%
Example 6 of WO2023078333A1	5	75%
LY3473329	5	56%

LY3473329 is the compound of Example 1 in CN114008021A, the preparation method of which is shown in Example 1 of patent CN114008021A, and the preparation method of Example 6 compound in WO2023078333A1 is shown in Example 6 of patent WO2023078333A1.

Test Example 4 and Safety Assessment Test for Selective Effects on 44 Targets

The activity of 44 early safety targets closely related to the heart, central nervous system, gastrointestinal tract, and immune system was tested. The off-target effects of the test compound on 44 targets (including 24 G protein-coupled receptors (GPCRs), 8 ion channel targets, 3 transporters, 2 nuclear receptors, and 7 enzymes) were examined *in vitro* at the cellular or molecular level using radioisotope binding methods, calcium flow assays, and enzymatic fluorescence or chemiluminescence techniques.

The results showed that at a single concentration of 10 μM (the test concentration of Eta agonism was 12 μM), some compounds of the present invention had no significant binding, inhibition or agonistic effect on 44 targets (inhibition rate/agonism rate< 50%).

Test Example 5 and Safety Assessment Test in Rats

The safety of the compounds of the present invention was evaluated by oral gavage administration to SD rats as the test animals.

Test method: 50 SD rats (half males and half females) were randomly divided into vehicle control group and test article group according to their body weight. The vehicle saline or the compound of the present invention or LY3473329 (300 mg/kg, 1000 mg/k g) was administered orally once daily for 14 consecutive days.

Results: no changes related to the compound(s) of the invention or LY3473329 were observed in clinical observation, body weight and weight gain, food consumption, hematology, blood biochemistry, urine, organ weight and coefficients, and histopathology in all dose groups. The no observed adverse effect level (NOAEL) of the compound(s) of the present invention was 1000 mg/kg, suggesting that the compound(s) of the present invention has excellent safety.

Test example 6 and The affinity between compound and human plasminogen (PLG) detected by SPR test

1.Reagent

Reagent	Manufacturer
HBS-EP buffer	Cytiva
DMSO solution	Sigma
Amine Coupling Kit	Cytiva
Plasminogen	MCE
CM5 CHIP	Cytiva

2.Test Procedure

2.1 The Running buffer preparation

The Running buffer was prepared from Storage buffer to a final concentration of 10mM Hepes, 150mM NaCl, 3mM EDTA, 0.05% Surfactant P20, pH 7.4 (HBS-EP), 3% DMSO, and filtered by 0.22μm filtration membrane.

2.2. Sample Preparation

2.2.1. Stock solution: Dilute compounds into 10mM with DMSO.

2.2.2. Testing solution: The stock solution was gradiently diluted to 8 concentrations with DMSO-free running buffer.

2.3. Human Plasminogen Protein Immobilization

2.3.1. Balance Series S Chip C5 chip to room temperature.

2.3.2. Immobilize the human PLG protein on Fc2 via amine-coupling method.

2.3.3. EDC+NHS solution flowed through Fcl and Fc2 at a flow rate of 10 μL/min, with 1 injections of 420 seconds each, to activate the chip surface.

2.3.4. Dilute PLG protein to 40μg/mL, in running buffer, following injected PLG over Fc2 at a flow rate of 5uL/min, injection time was 720 s, and the final protein capture level was 15000RU/channel.

2.3.5. Injected Ethanolamine-HCL solution over Fcl and Fc2 for 420s at a flow rate of 10uL/min to block sensor chip.

2.4. Setting of Sample Injection Procedure

2.4.1. The 8 concentrations of compounds testing solution were injected from low to high concentration, flowing through Fcl to Fc2. The association phase lasted for 90 seconds, followed by a dissociation phase of 150 seconds, with a flow rate of 30 μL/min.

3. Data Analysis

3.1. Subtracted experimental channel signal value (Fc2) from the reference channel (Fc1) and buffer blank control to obtain the final association and dissociation sensorgram. The affinity data was derived from fitting the data using a Bivalent Fit model.

3.2. QC verification criteria for experiment results: at least 5 concentration points meets concentration-dependence, The Chi^2 value is less than or equal to 1/10 Rmax value.

3.3. Exported the real-time response value (RU) of association and dissociation from the Biacore-S200 instrument.

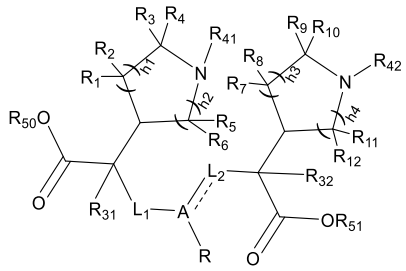
3.4. Exported the constants Ka. Kd and KD from the Biacore-S200 instrument. KD = Kd/Ka.

4. Results

Preferred compound(s) of this invention exhibited a low affinity for PLG, suggesting good specificity.

CLAIMS

1. A compound represented by formula (I) or a pharmaceutically acceptable salt thereof, having the following structure:



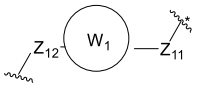
(I)

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

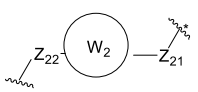
A is CR_X, P, P(O), N, C_{6-12} aryl, 5-14-membered heteroaryl, C_{3-8} carbocyclyl, or 5-18-membered heterocyclyl; the aryl, heteroaryl, carbocyclyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

when --- is a single bond, R_X is H, -OH, or C_{1-3} alkoxy;

when --- is a double bond, R_X is absent;

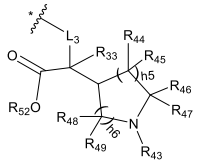
L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

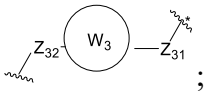
L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally

substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl;

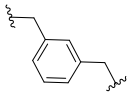
each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -O-, -S-, -NH-, -Se-, -C_{1-4} alkylene-, -C_{1-8} oxaalkylene-, -C_{1-4} thiaalkylene-, -C_{1-4} azaalkylene-, and -C_{1-4} selenaalkylene-; the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents independently selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen, oxo, thio, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom linked thereto form C_{3-6} cycloalkyl, 3-6-membered heterocyclyl, phenyl, and 5-6-membered heteroaryl;

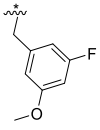
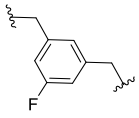
each of R_{31}, R_{32}, and R_{33} is independently selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} deuteroalkoxy;

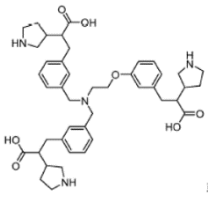
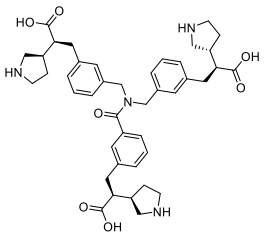
each of h1, h2, h3, h4, h5, and h6 is independently 0, 1, or 2;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, and R_{49} is independently selected from H, deuterium, -CN, -OH, -NH_2, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -N(C_{1-3} alkyl)$_2$, and -NH(C_{1-3} alkyl);

each of R_{50}, R_{51}, and R_{52} is independently selected from H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, -C_{1-3} alkylene-O-C_{1-6} alkyl, and -C_{1-3} alkylene-O-C(O)-C_{1-6} alkyl; the alkyl, alkenyl, alkoxy, and alkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, -OH, -NH_2, -CN, oxo, C_{1-3} alkyl, and C_{1-3} alkoxy;

provided that when A is N, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, and R_{49} are all H, L_1, L_2, and L_3 are not  at the same time;

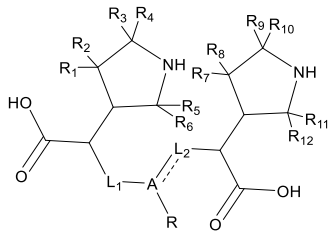
provided that when A is N, R is  , and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{41}, and R_{42} are all H, L_1 and L_2 are not  at the same time, wherein * is the linking end of R to A;

provided that the compound is not  or  ;

a heteroatom in the heterocyclyl and heteroaryl is independently selected from O, N, and S, and the number of heteroatoms is 1, 2, 3, or 4;

for example, R is a group comprising L_3, L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2$O-, and -S-C(O)-.

2. A compound represented by formula (I-1-P1), formula (I-1-P2), formula (I-1-P3), or formula (I-1-P4), or a pharmaceutically acceptable salt thereof,



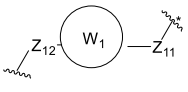
(I-1-P1)

wherein ⎓ is a single bond or a double bond;

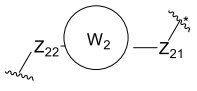
A is CR_X, P, P(O), or N;

when ⎓ is a single bond, R_X is H, -OH, or C_{1-3} alkoxy;

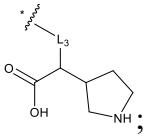
when ⎓ is a double bond, R_X is absent;

L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

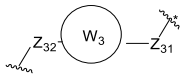
L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-

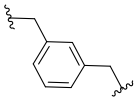
membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

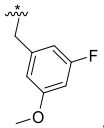
; the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

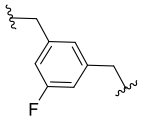
each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-4} alkylene-, and -C_{1-4} oxaalkylene-; the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

provided that when A is N, L_1, L_2, and L_3 are not  at the same time;

provided that when A is N, R is 

, L_1 and L_2 are not 

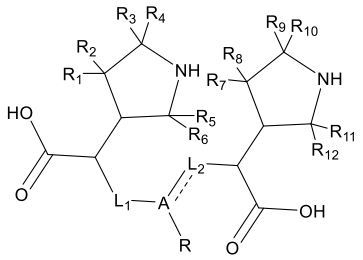
at the same time, wherein * is the linking end of R to A;

a heteroatom in the heterocyclyl and heteroaryl is independently selected from O, N, and S, and the number of heteroatoms is 1, 2, or 3;

for example, in the compound represented by formula (I-1-P1), R is a group comprising L_3, L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11},

Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

or



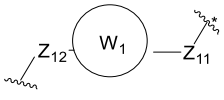
(I-1-P2)

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

A is CR_X, P, P(O), or N;

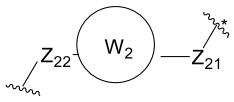
when ⁼⁼⁼ is a single bond, R_X is H, -OH, or C_{1-3} alkoxy;

when ⁼⁼⁼ is a double bond, R_X is absent;

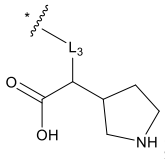
L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

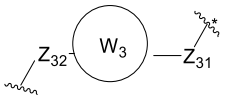
L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-

membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

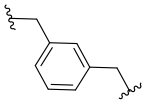
L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

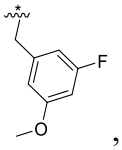
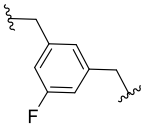
; the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-4} alkylene-, -C_{1-4} oxaalkylene-, -C_{1-4} thiaalkylene-, and -C_{1-4} azaalkylene-; the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

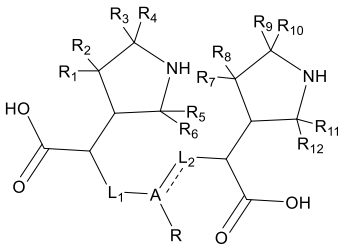
provided that when A is N, L_1, L_2, and L_3 are not  at the same time;

provided that when A is N, R is  , L_1 and L_2 are not  at the same time, wherein * is the linking end of R to A;

a heteroatom in the heterocyclyl and heteroaryl is independently selected from O, N, and S, and the number of heteroatoms is 1, 2, or 3;

for example, in the compound represented by formula (I-1-P2), R is a group comprising L_3, L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

or



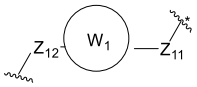
(I-1-P3)

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

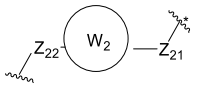
A is CR_X, P, P(O), N, C_{6-12} aryl, 5-14-membered heteroaryl, and 5-18-membered heterocyclyl; the aryl, heteroaryl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

when ⁼⁼⁼ is a single bond, R_X is H, -OH, or C_{1-3} alkoxy;

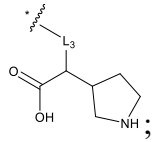
when ⁼⁼⁼ is a double bond, R_X is absent;

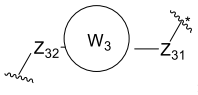
L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

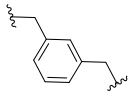
R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and  ; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

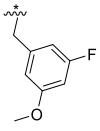
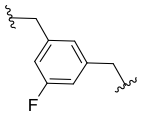
L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and  ; the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

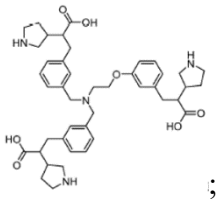
each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-4} alkylene-, -C_{1-4} oxaalkylene-, -C_{1-4} thiaalkylene-, and -C_{1-4} azaalkylene-; the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

provided that when A is N, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1, L_2, and L_3 are not  at the same time;

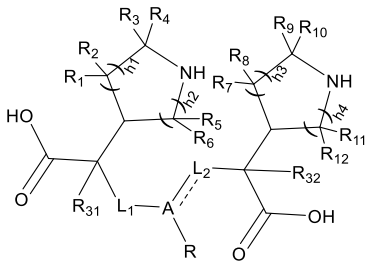
provided that when A is N, R is  , and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1 and L_2 are not  at the same time, wherein * is the linking end of R to A;

provided that the compound is not  ;

a heteroatom in the heterocyclyl and heteroaryl is independently selected from O, N, and S, and the number of heteroatoms is 1, 2, 3, or 4;

for example, in the compound represented by formula (I-1-P3), R is a group comprising L_3, L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-;

or



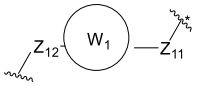
(I-1-P4)

wherein ⎓ is a single bond or a double bond;

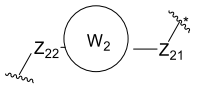
A is CR_X, P, P(O), N, C_{6-12} aryl, 5-14-membered heteroaryl, or 5-18-membered heterocyclyl; the aryl, heteroaryl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

when ⎓ is a single bond, R_X is H, -OH, or C_{1-3} alkoxy;

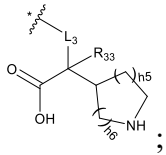
when ⎓ is a double bond, R_X is absent;

L_1 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

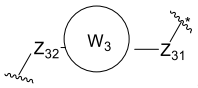
; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A;

L_2 is selected from -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A;

R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, C_{1-6} alkyl, and 

; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkenylene-, -C_{2-6} alkynylene-, -C_{1-3} alkylene-C_{6-10} aryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-C_{6-10} aryl-5-12-membered heteroaryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-C_{6-10} aryl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-12-membered heteroaryl-5-12-membered heteroaryl-C_{1-3} alkylene-, and 

; the alkylene, alkenylene, and alkynylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of L_3 to A;

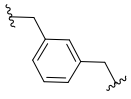
each of the rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, C_{6-14} cycloalkyl, and 5-12-membered heterocyclyl; the aryl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl;

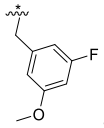
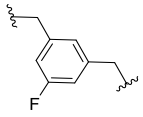
each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -O-, -S-, -NH-, -Se-, -C_{1-4} alkylene-, -C_{1-8} oxaalkylene-, -C_{1-4} thiaalkylene-, -C_{1-4} azaalkylene-, and -C_{1-4} selenaalkylene-; the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents independently selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen, oxo, thio, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom linked thereto form C_{3-6} cycloalkyl, 3-6-membered heterocyclyl, phenyl, or 5-6-membered heteroaryl;

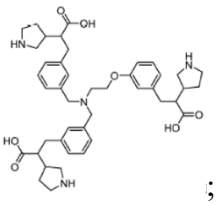
each of R_{31}, R_{32}, and R_{33} is independently selected from hydrogen, deuterium, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} deuteroalkoxy;

each of h1, h2, h3, h4, h5, and h6 is independently 0, 1, or 2;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from H and deuterium;

provided that when A is N, and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1, L_2, and L_3 are not  at the same time;

provided that when A is N, R is  , and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are all H, L_1 and L_2 are not  at the same time; * is the linking end of R to A;

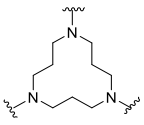
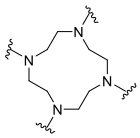
provided that the compound is not  ;

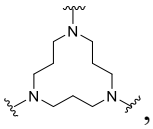
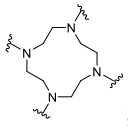
a heteroatom in the heterocyclyl and heteroaryl is independently selected from O, N, and S, and the number of heteroatoms is 1, 2, 3, or 4;

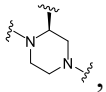
for example, in the compound represented by formula (I-1-P4), R is a group comprising L_3, L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected

from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-.

3. The compound according to any one of claims 1 and 2, or a pharmaceutically acceptable salt thereof, wherein A is CR_X, P, P(O), N, phenyl, 5-6-membered heterocyclyl, or 12-membered heterocyclyl; a heteroatom in the heterocyclyl is N, and the number of heteroatoms is 1, 2, 3, or 4;

preferably, A is CR_X, P, P(O), N, phenyl, piperazinyl,  , or  ; or

A is CR_X, P, P(O), N, , , , , ,  , or  ; preferably,

A is N, , ,  , or ; or

A is N; or

A is P(O); or

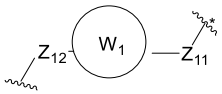
A is CR_X; R_X is H, -OH, or methoxy; or

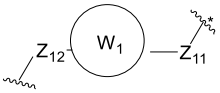
A is selected from C-OH and C-OCH_3; or

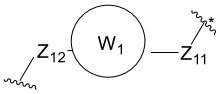
A is 6-membered heterocyclyl; preferably, A is piperazinyl, preferably , , , or ; or

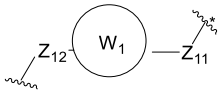
A is phenyl, preferably .

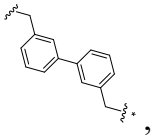
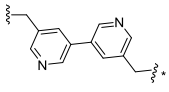
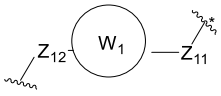
4. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein L_1 is selected from -C_{1-3} alkylene-phenyl-phenyl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-

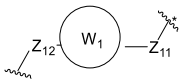
6-membered heteroaryl-5-6-membered heteroaryl-C_{1-3} alkylene-, and  ; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to N;

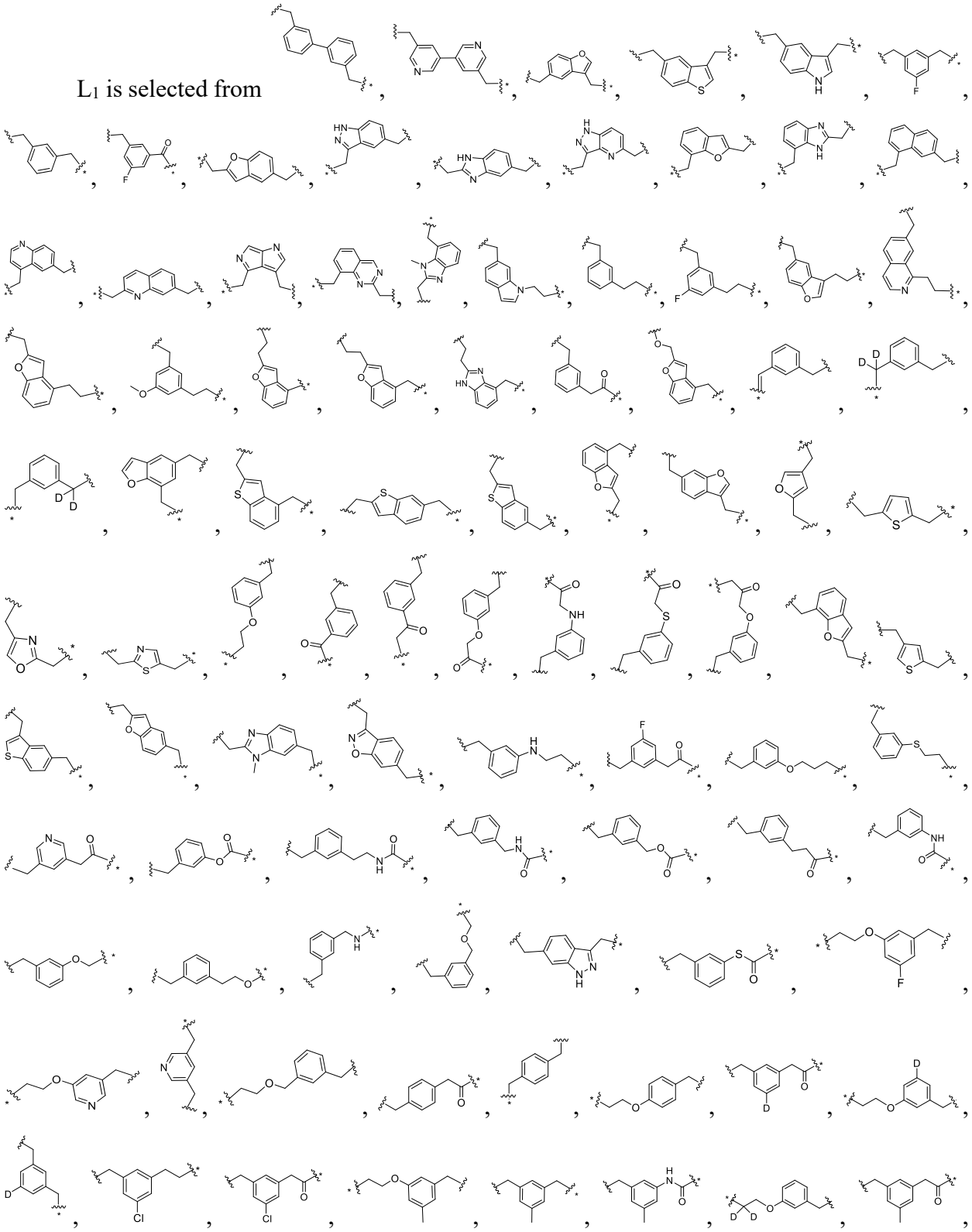
preferably, L_1 is selected from -methylene-phenyl-phenyl-methylene-, -ethylene-phenyl-phenyl-ethylene-, -methylene-5-6-membered heteroaryl-5-6-membered heteroaryl-methylene-, -ethylene-5-6-membered heteroaryl-5-6-membered heteroaryl-ethylene-, and  ; the methylene and ethylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A; or

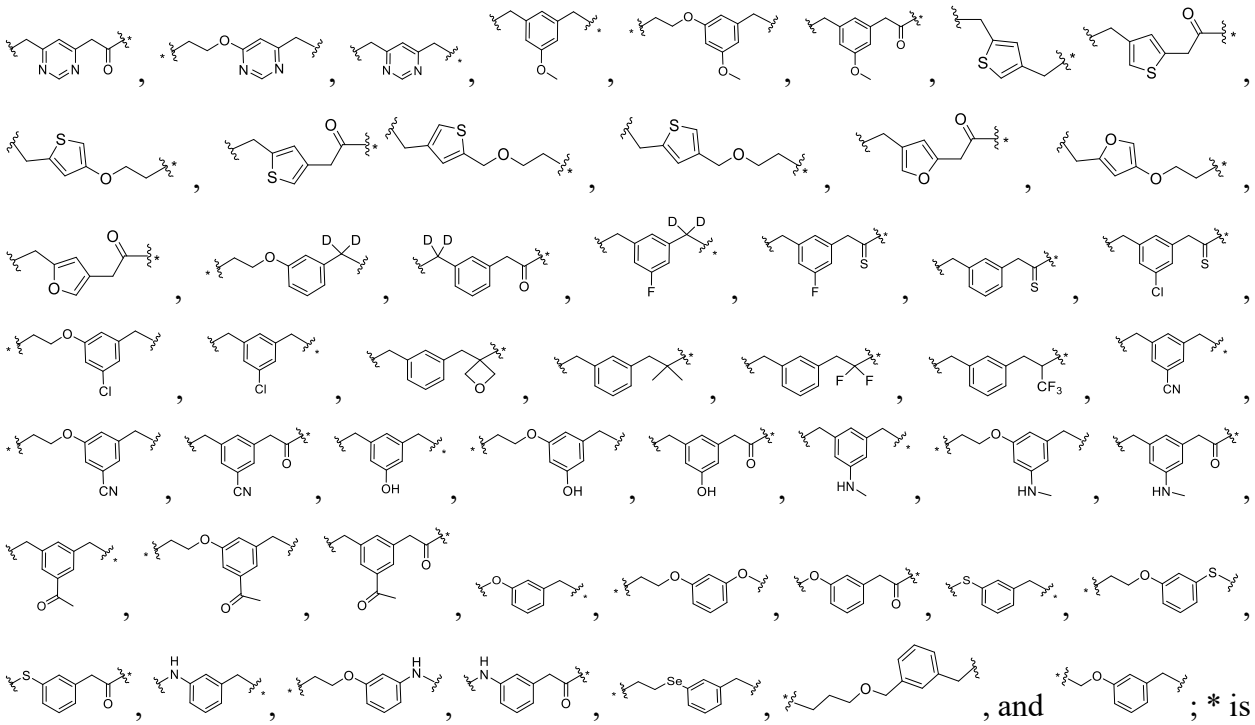
L_1 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-6-membered heteroaryl-6-membered heteroaryl-methylene-, and  ; the methylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_1 to A; or

L_1 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-pyridinyl-pyridinyl-methylene-, and  ; * is the linking end of L_1 to A; or

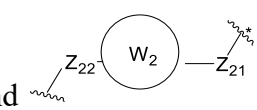
L_1 is selected from  ,  , and  ; * is the linking end of L_1 to A; or

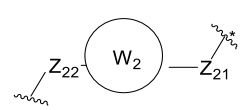
L_1 is  ; * is the linking end of L_1 to A; or

L_1 is selected from 

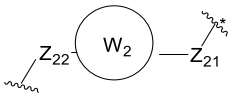


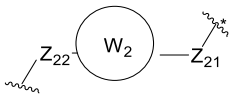
, and ; * is the linking end to A.

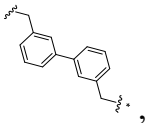
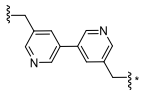
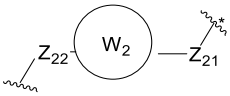
5. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L_2 is selected from -C_{1-3} alkylene-phenyl-phenyl-C_{1-3} alkylene-, -C_{1-3} alkylene-5-6-membered heteroaryl-5-6-membered heteroaryl-C_{1-3} alkylene-, and  ; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to N;

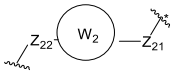
preferably, L_2 is selected from -methylene-phenyl-phenyl-methylene-, -ethylene-phenyl-phenyl-ethylene-, -methylene-5-6-membered heteroaryl-5-6-membered heteroaryl-methylene-, -ethylene-5-6-membered heteroaryl-5-6-membered heteroaryl-ethylene-, and  ; the methylene and ethylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the phenyl and heteroaryl

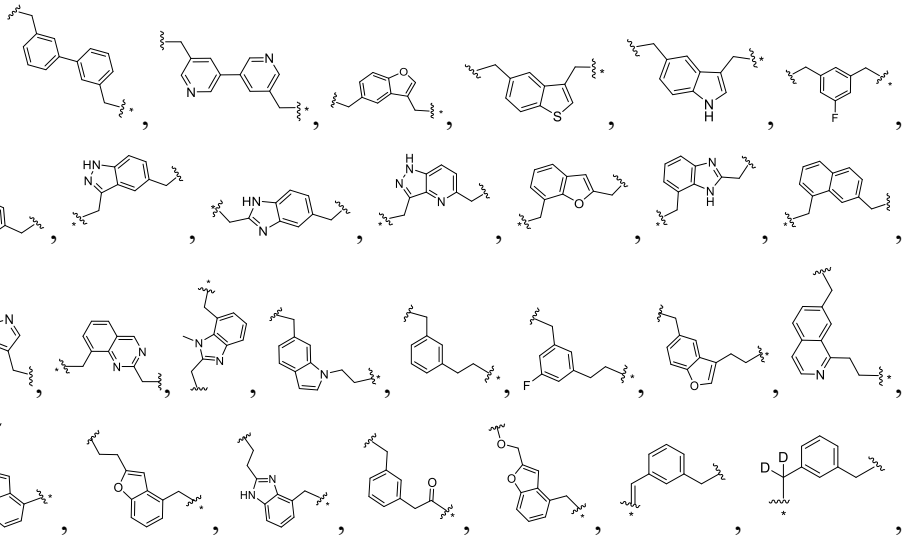
are optionally substituted by one or more substituents independently selected from halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A; or

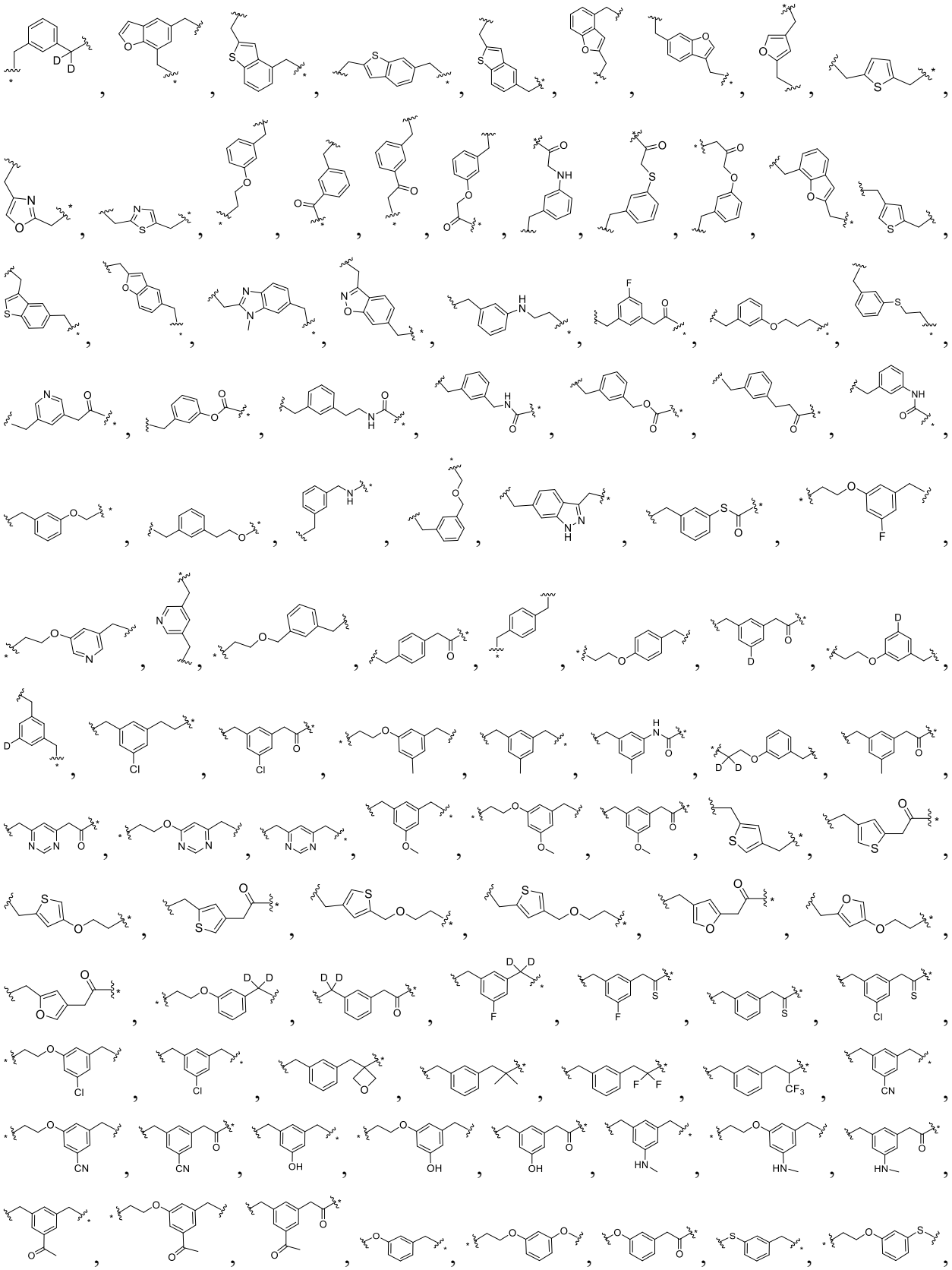
L_2 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-6-membered heteroaryl-6-membered heteroaryl-methylene-, and  ; the methylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, and C_{1-3} alkoxy; * is the linking end of L_2 to A; or

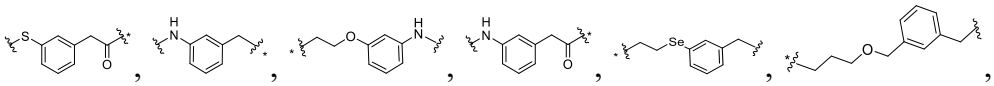
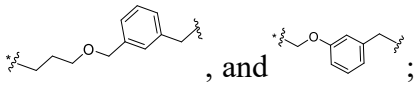
L_2 is selected from -methylene-phenyl-phenyl-methylene-, -methylene-pyridinyl-pyridinyl-methylene-, and  ; * is the linking end of L_2 to A; or

L_2 is selected from  ,  , and  ; * is the linking end of L_2 to A; or

L_2 is  ; * is the linking end of L_2 to A; or

L_2 is selected from  .



 , and  ; * is the linking end to A.

6. The compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein each of rings W_1, W_2, and W_3 is independently selected from C_{6-12} aryl, 5-12-membered heteroaryl, and C_{6-14} cycloalkyl; the aryl, heteroaryl, and cycloalkyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy;

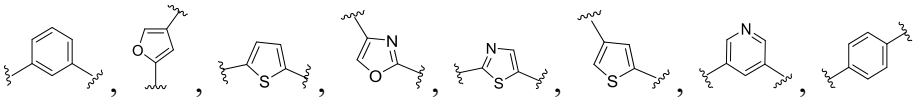
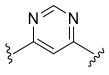
preferably, each of rings W_1, W_2, and W_3 is independently selected from C_{6-10} aryl, 5-10-membered heteroaryl, and C_{6-10} cycloalkyl; the aryl, heteroaryl, and cycloalkyl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, -CN, methyl, ethyl, methoxy, and ethoxy; or

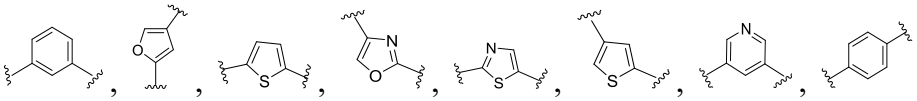
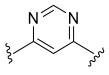
each of rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, 8-10-membered bicyclic heteroaryl, C_{8-10} bicyclic cycloalkyl, and 5-6-membered monocyclic heteroaryl; the phenyl, naphthyl, heteroaryl, and cycloalkyl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkyl, and C_{1-3} alkoxy; or

each of the rings W_1, W_2, and W_3 is independently selected from phenyl, naphthyl, 5-membered/5-membered fused heteroaryl, 5-membered/6-membered fused heteroaryl, 6-membered/5-membered fused heteroaryl, 6-membered/6-membered fused heteroaryl, 4-membered/6-membered spirocycloalkyl, 6-membered/4-membered spirocycloalkyl, 5-membered/5-membered spirocycloalkyl, 5-membered/6-membered spirocycloalkyl, 6-membered/5-membered spirocycloalkyl, 6-membered/6-membered spirocycloalkyl, and 5-6-membered monocyclic heteroaryl; the phenyl, naphthyl, fused heteroaryl, spirocycloalkyl, and monocyclic heteroaryl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, -CN, methyl, ethyl, methoxy, and ethoxy; or

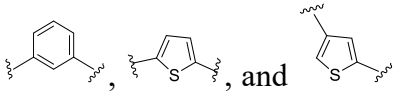
each of the rings W_1, W_2, and W_3 is independently selected from phenyl and 5-6-membered monocyclic heteroaryl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl,

C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl; a heteroatom in the heteroaryl is O, N, or S, the number of heteroatoms is 1 or 2; or

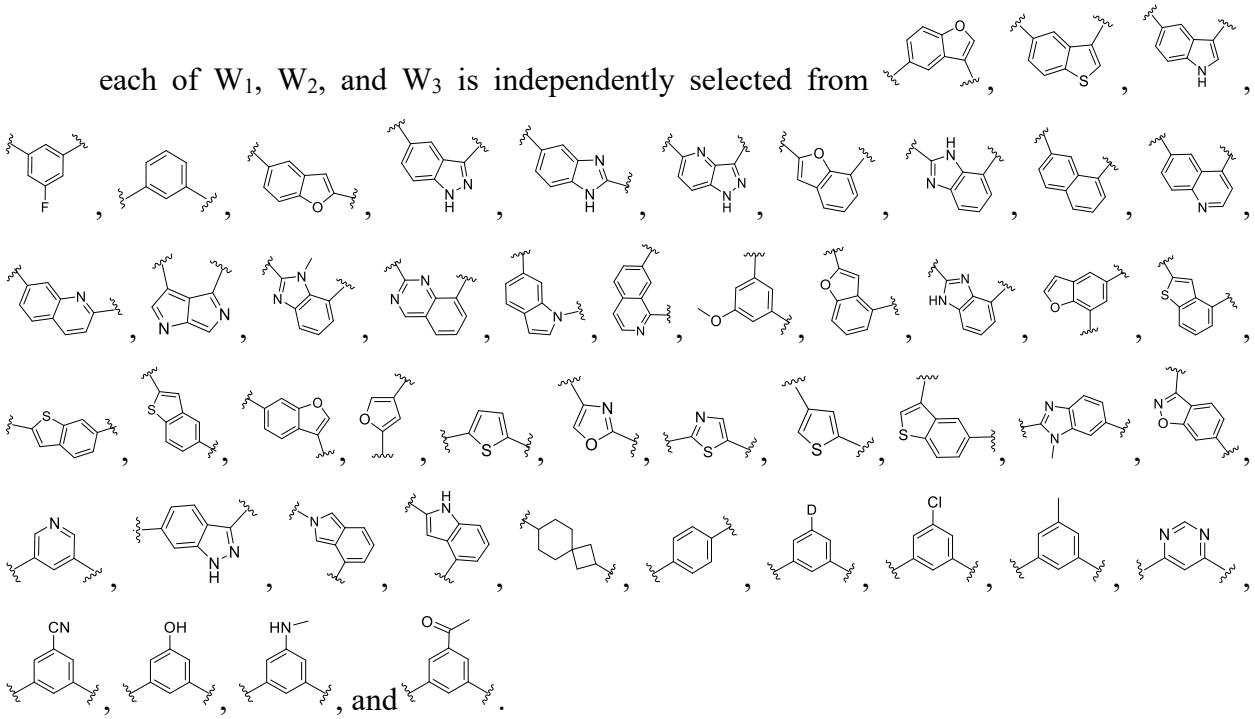
each of the rings W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  , and  ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl; or

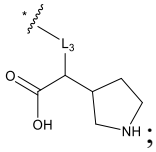
each of the rings W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  , and  ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -CN, -OH, -NH_2, -CHO, methyl, ethyl, methoxy, ethoxy, -N(CH_3)$_2$, -NH(CH_3), and -C(O)CH_3; or

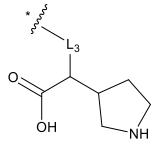
each of the rings W_1, W_2, and W_3 is independently selected from phenyl and thienyl; the phenyl and thienyl are optionally substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -CN, -OH, -NH_2, -CHO, methyl, ethyl, methoxy, ethoxy, -N(CH_3)$_2$, -NH(CH_3), and -C(O)CH_3; or

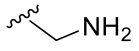
each of the rings W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -CN, -OH, -NH_2, -CHO, methyl, ethyl, methoxy, ethoxy, -N(CH_3)$_2$, -NH(CH_3), and -C(O)CH_3; or

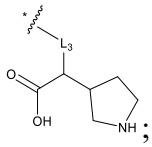
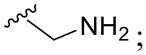
each of the rings W_1, W_2, and W_3 is independently selected from phenyl; the phenyl is optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy; or

each of W_1, W_2, and W_3 is independently selected from  , and .

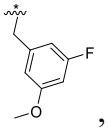
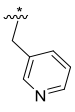
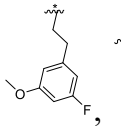
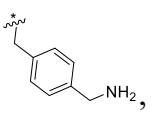
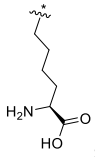
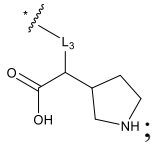
7. The compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-10-membered heteroaryl, C_{1-6} alkyl, and  ; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, and -NH_2; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, methoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy; * is the linking end of R to A;

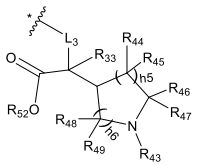
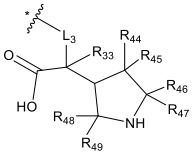
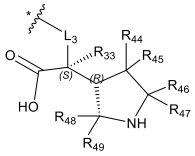
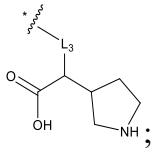
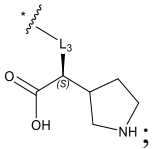
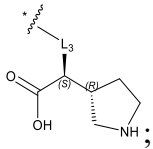
preferably, R is selected from H, -methylene-phenyl, -ethylene-phenyl, -methylene-5-6-membered heteroaryl, -ethylene-5-6-membered heteroaryl, C_{1-6} alkyl, and  ; the methylene and ethylene are optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, and -NH_2; the phenyl and heteroaryl are optionally

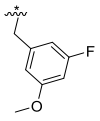
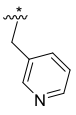
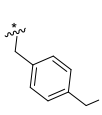
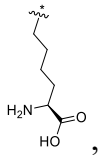
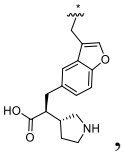
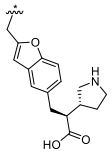
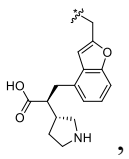
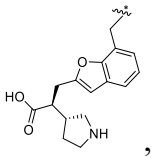
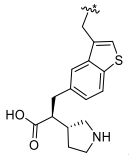
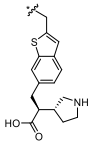
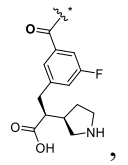
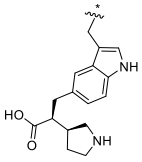
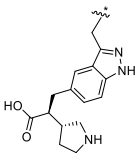
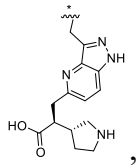
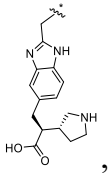
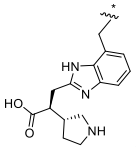
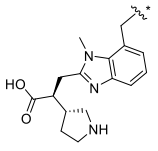
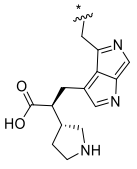
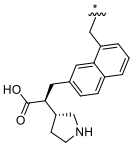
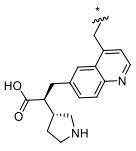
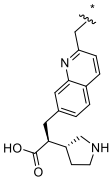
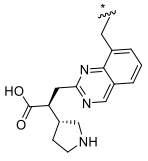
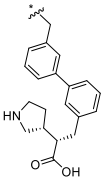
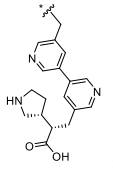
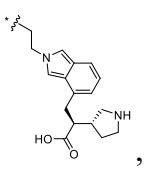
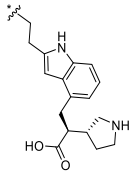
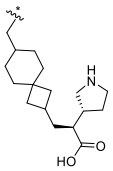
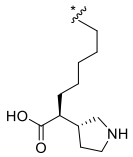
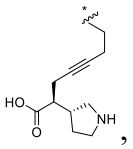
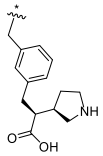
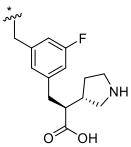
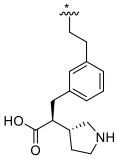
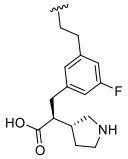
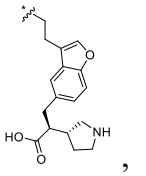
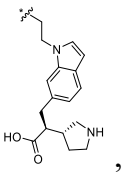
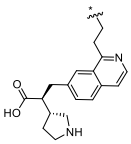
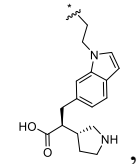
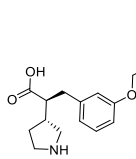
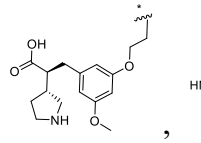
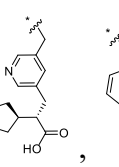
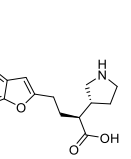
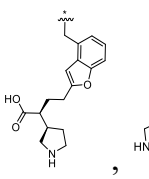
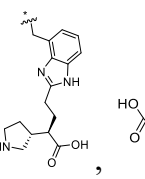
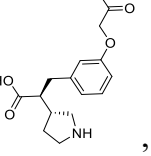
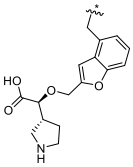
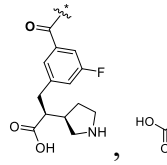
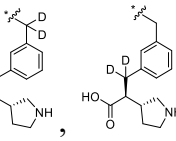
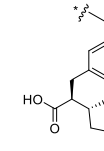
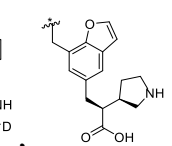
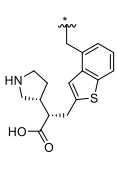
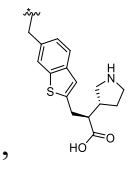
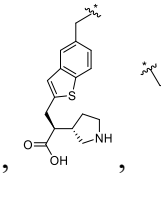
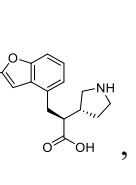
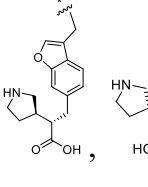
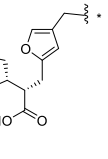
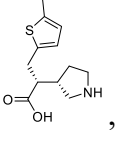
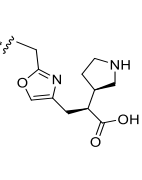
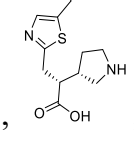
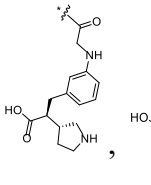
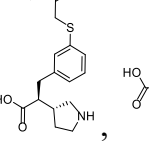
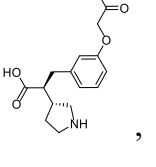
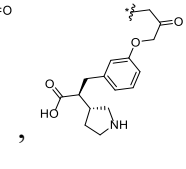
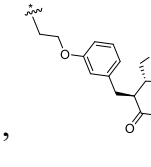
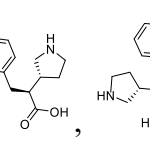
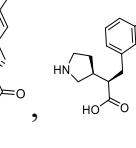
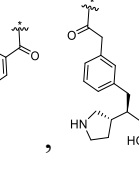
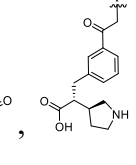
substituted by one or more substituents independently selected from halogen, -CN, methoxy, and  ; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, oxo, carboxyl, -CN, -OH, and $-NH_2$; * is the linking end of R to A; or

R is selected from H, -methylene-phenyl, -ethylene-phenyl, -methylene-pyridinyl, -ethylene-pyridinyl, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *n*-pentyl, *n*-hexyl, and  ; the phenyl and pyridinyl are optionally substituted by one or more substituents independently selected from halogen, methoxy, and  ; the methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *n*-pentyl, and *n*-hexyl are optionally substituted by one or more substituents independently selected from carboxyl, and $-NH_2$; * is the linking end of R to A; or

R is selected from H, $-C_{1-3}$ alkylene-phenyl, $-C_{1-3}$ alkylene-5-6-membered heteroaryl, and C_{1-6} alkyl; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, $-NH_2$, and C_{1-3} alkyl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, carboxyl, $-NH_2$, methyl, and methoxy; or

R is selected from H,  ,  ,  ,  ,  , and  ; * is the linking end of R to A; or

R is selected from H and  ; preferably  ; preferably  ; preferably  ; preferably  ; preferably  ; wherein * is the linking end to A; or

R is selected from H,  ,  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  ,  ,  ,
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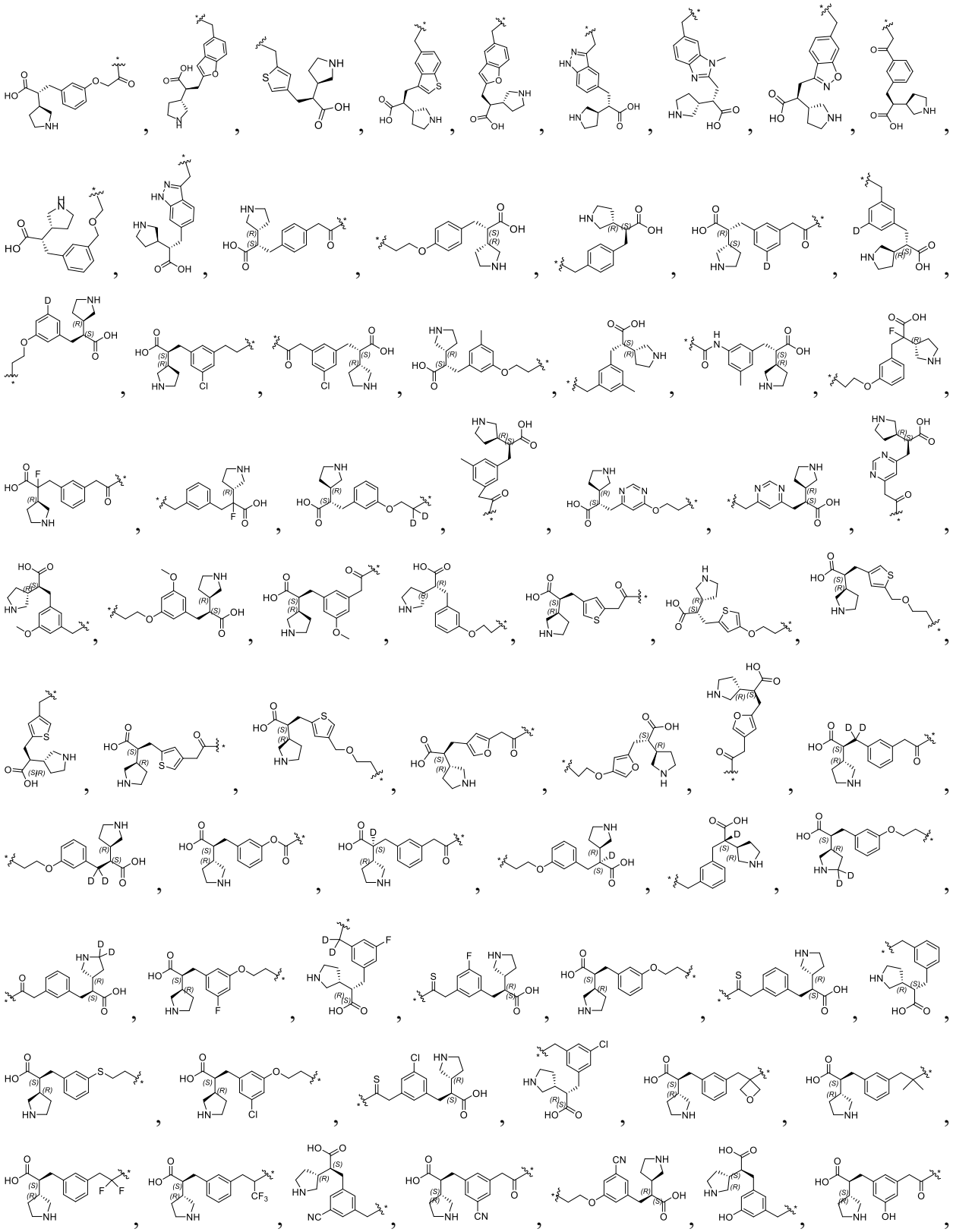
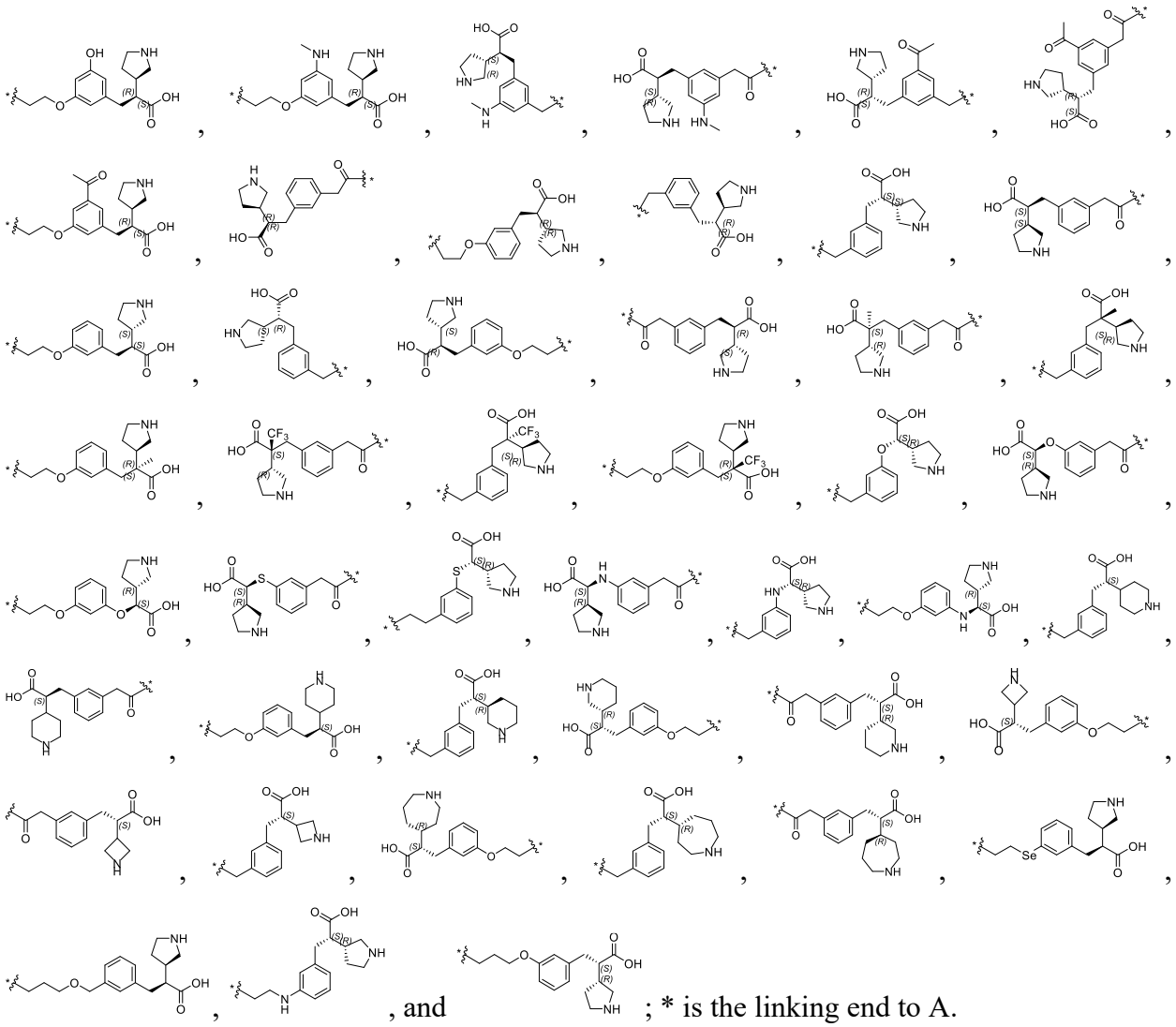
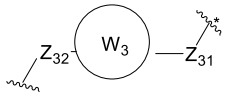
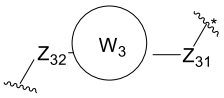




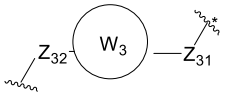
; * is the linking end to A.

8. The compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkynylene-, -methylene-phenyl-phenyl-methylene-, -ethylene-phenyl-phenyl-ethylene-, -methylene-5-6-membered heteroaryl-5-6-membered heteroaryl-methylene-, -ethylene-5-6-membered heteroaryl-5-6-membered heteroaryl-ethylene-, and,  ; the alkylene, methylene, ethylene, and alkynylene are optionally substituted by one or more substituents independently selected from halogen, oxo, -CN, -OH, -NH_2, methyl, and ethyl; the phenyl and heteroaryl are optionally substituted by one or more

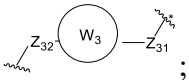
substituents independently selected from halogen, -CN, methyl, ethyl, methoxy, and ethoxy; * is the linking end of L_3 to A;

preferably, L_3 is selected from -C_{1-6} alkylene-, -C_{2-6} alkynylene-, -methylene-phenyl-phenyl-methylene-, -methylene-6-membered heteroaryl-6-membered heteroaryl-methylene-, and 

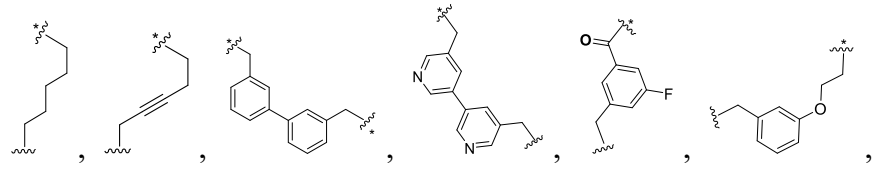
; the alkylene and methylene are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, oxo, -CN, -OH, and -NH_2; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from fluorine, chlorine, bromine, -CN, methyl, ethyl, methoxy, and ethoxy; * is the linking end of L_3 to A; or

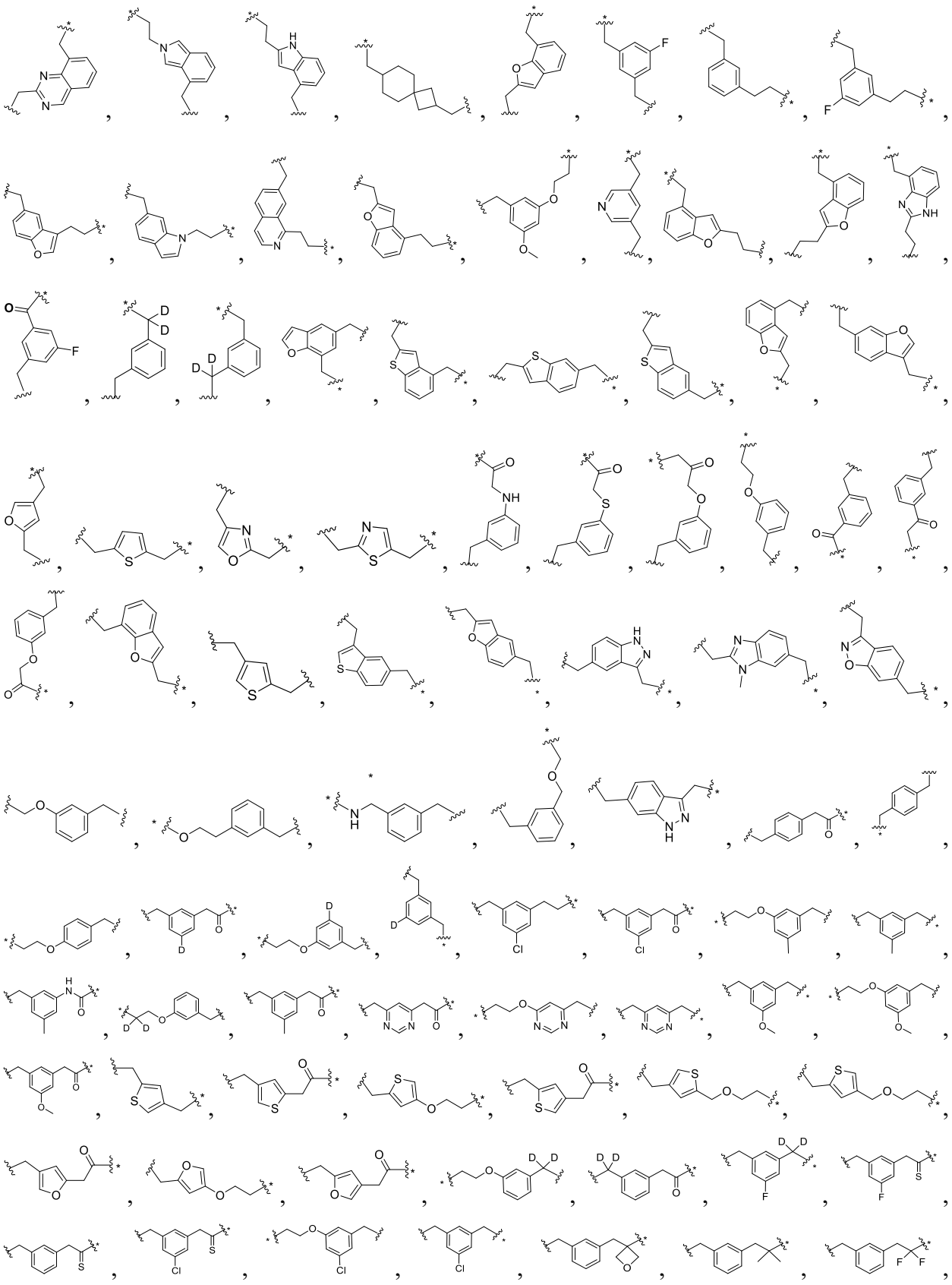
L_3 is selected from methylene, ethylene, *n*-propylene, isopropylene, *n*-butylene, *n*-pentylene, *n*-hexylene, *n*-propynylene, *n*-butynylene, *n*-pentynylene, *n*-hexynylene, -methylene-phenyl-phenyl-methylene-, -methylene-pyridinyl-pyridinyl-methylene-, and 

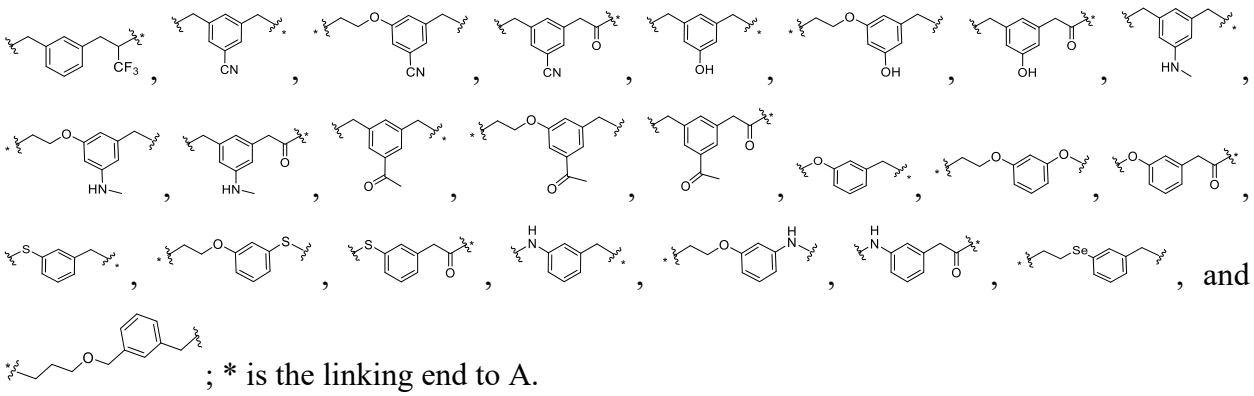
; * is the linking end of L_3 to A; or

L_3 is selected from 

; * is the linking end of L_3 to A; or

L_3 is selected from 




; * is the linking end to A.

9. The compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -O-, -S-, -NH-, -Se-, -C_{1-4} alkylene-, -C_{1-6} oxaalkylene-, -C_{1-4} thiaalkylene-, -C_{1-4} azaalkylene-, and -C_{1-4} selenaalkylene-; the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents independently selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen (e.g., fluorine or chlorine), oxo, thio, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom linked thereto form C_{3-6} cycloalkyl, or 3-6-membered heterocyclyl (e.g., oxetanyl); a heteroatom in the heterocyclyl is O, N, or S, the number of heteroatoms is 1 or 2;

preferably, each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-3} alkylene-, -C_{1-3} oxaalkylene-, -C_{1-3} thiaalkylene-, and -C_{1-3} azaalkylene-; the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy; preferably, the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -C_{1-2} alkylene-, -C_{1-2} oxaalkylene-, -C_{1-2} thiaalkylene-, and -C_{1-2} azaalkylene-; the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo; or

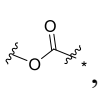
each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -C_{1-3} alkylene-, and -C_{1-3} oxaalkylene-; the alkylene and oxaalkylene are optionally substituted by one

or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy; preferably, the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium and oxo; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -C_{1-2} alkylene-, -C_{1-3} oxaalkylene-, and -C_{1-3} azaalkylene-; the alkylene, oxaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from and oxo; or

when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one heteroatom or heteroatom group is comprised, and the heteroatom or heteroatom group is selected from -O-, -S-, -Se-, -NH-, -CO-, and -C(S)-; or

when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one heteroatom or heteroatom group is comprised, and the heteroatom or heteroatom group is selected from -CO- or -C(S)-; or

when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one group selected from , , ,  , , and , preferably , is present; * is the linking end to A; or

when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, at least one heteroatom or heteroatom group is present, and the heteroatom or heteroatom group is selected from -O-, -NH-, and -CO-; or

when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, 1-4 heteroatoms or heteroatom groups are comprised, the heteroatom or heteroatom group is selected from -O-, -S-, -Se-, -NH-, -CO-, and -C(S)-, and the number of heteroatoms or heteroatom groups is specifically 1, 2, 3, or 4; preferably 1-3 heteroatoms or heteroatom groups are comprised, specifically 1, 2, or 3; or preferably 2-4 heteroatoms or heteroatom groups are comprised, specifically 2, 3, or 4; further preferably 2 or 3 heteroatoms or heteroatom groups are comprised; the heteroatom or heteroatom group is preferably -O-, -S-, -NH-, or -CO-; the heteroatom or heteroatom group is more preferably -O- or -CO-; preferably, the heteroatom or heteroatom group at least contains -CO- or -C(S)-; or

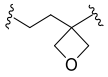
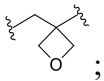
Z_{21} contains a heteroatom or heteroatom group selected from -O-, -S-, -Se-, and -NH-; and Z_{31} contains a heteroatom or heteroatom group selected from -CO-, and -C(S)-; and in a combination of Z_{21} and Z_{31}, the total number of heteroatoms or heteroatom groups is 1-4; or

when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, 1-4, preferably 1-3, more preferably 2-3 heteroatoms or heteroatom groups are comprised, and the heteroatom or heteroatom group is selected from -O-, -NH-, and -CO-; preferably, the heteroatom or heteroatom group at least contains -CO-; or

Z_{11}, Z_{21}, and Z_{31} all together contain 1-4 heteroatoms or heteroatom groups, and the heteroatom or heteroatom group is selected from -O-, -NH-, and -CO-, specifically the number of heteroatoms or heteroatom groups is 1, 2, 3, or 4; or

Z_{11}, Z_{21}, and Z_{31} all together contain 1-3 heteroatoms or heteroatom groups, and the heteroatom or heteroatom group is selected from -O-, -NH-, and -CO-, specifically the number of heteroatoms or heteroatom groups is 1, 2, or 3; or

Z_{11}, Z_{21}, and Z_{31} all together contain 2-3 heteroatoms or heteroatom groups, and the heteroatom or heteroatom group is selected from -O-, -NH-, and -CO-, specifically the number of heteroatoms or heteroatom groups is 2 or 3; preferably, the heteroatom or heteroatom group at least contains -CO-; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -CD_2-, -C_{1-4} alkylene-, -OC_{1-3} alkylene-, -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-2} alkyl-O-C_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, -C_{1-3} alkylene-C(S)-, -Se-C_{1-3} alkylene-,  , and  ; the alkylene, methylene, and ethylene are optionally substituted by one or more substituents independently selected from deuterium, fluorine, and chlorine; or

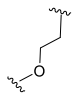
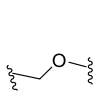
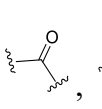
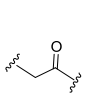
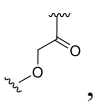
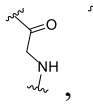
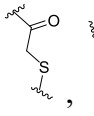
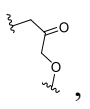
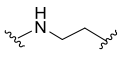
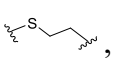
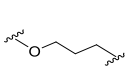
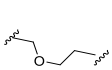
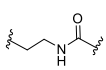
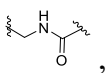
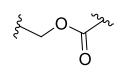
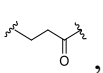
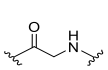
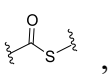
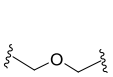
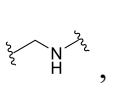
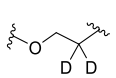
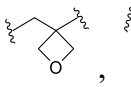
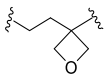
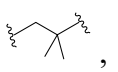
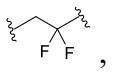
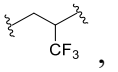
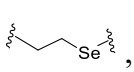
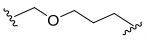
each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -CD_2-, -C_{1-3} alkylene-, -OC_{1-3} alkylene-, -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-3} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-O-C_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-; or

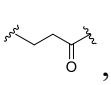
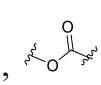
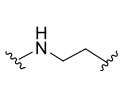
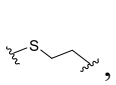
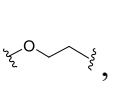
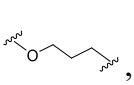
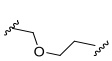
each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -CD_2-, -C_{1-3} alkylene-, -OC_{1-3} alkylene-, -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, and -O-C_{1-3} alkylene-C(O)-C_{1-3} alkylene-; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -C_{1-3} alkylene-, -OC_{1-3} alkylene-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C(O)-, and -O-C(O)-; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from -CD_2-, -C_{1-2} alkylene-, -OC_{1-3} alkylene-, -C(O)-, -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C_{1-2} alkylene-C(O)-, -S-C_{1-2} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-2} alkylene-, -C_{1-2} alkylene-O-C_{1-2} alkylene-, -NH-C_{1-2} alkylene-, -S-C_{1-2} alkylene-, -C_{1-2} alkylene-NH-C(O)-, -C_{1-2} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, -CD_2-, -C_{1-2} alkylene-, -OC_{1-2} alkylene-, -C(O)-, -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C_{1-2} alkylene-C(O)-, -S-C_{1-2} alkylene-C(O)-, and -O-C_{1-2} alkylene-C(O)-C_{1-2} alkylene-; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from a bond, methylene, ethylene, -CD_2-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  , ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  , and ; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from methylene, ethylene, , ,  , ,  , , ,  ,  ,  ,  , and  ; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from methylene, ethylene, -CD_2, , , , , , , , , , , , and ; * is the linking end to A; or

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2, and Z_{11} is selected from methylene, ethylene, -CD_2, , , , , and ; and Z_{21} is selected from methylene, ethylene, -CD_2, , , , , and ; and Z_{31} is selected from , , , , , , and ; for example, Z_{31} is selected from , , , , , and ; * is the linking end to A; or

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2, and Z_{11} is selected from methylene, ethylene, -CD_2, and ; and Z_{21} is selected from methylene, ethylene, -CD_2, , , and ; and Z_{31} is selected from , , , and ; * is the linking end to A; or

each of Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} is independently selected from methylene, ethylene, , , , , , and ; or

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from -CD_2 and methylene; or methylene; or

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from -CD_2, methylene, and ethylene; or

Z_{12}, Z_{22}, and Z_{32} are all -CD_2 or methylene; or

Z_{11} is selected from -CD_2, -C_{1-3} alkylene-, and -OC_{1-3} alkylene-; or -C_{1-3} alkylene-; or -CD_2, methylene, ethylene, methyleneoxy, and ethyleneoxy; or methylene; or

Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; or -OC_{1-3} alkylene-, -NH-C_{1-2} alkylene-, -S-C_{1-2} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; or

Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-; or -C(O)-, -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-; or -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-; or -CH_2C(O)-; or

Z_{11} is independently selected from -OC_{1-3} alkyl-, -NH-C_{1-3} alkyl-, -S-C_{1-3} alkyl-, -Se-C_{1-3} alkyl-, and -C_{1-3} alkyl-O-C_{1-3} alkyl-; and Z_{21} is independently selected from -OC_{1-3} alkyl-, -NH-C_{1-3} alkyl-, -S-C_{1-3} alkyl-, -Se-C_{1-3} alkyl-, and -C_{1-3} alkyl-O-C_{1-3} alkyl-; or

Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkyl-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-; or

Z_{11} is selected from -CD_2, -C_{1-3} alkylene-, and -OC_{1-3} alkylene-; and Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-; or

Z_{11} is -C_{1-3} alkylene-, -OC_{1-3} alkylene-; and Z_{21} is selected from -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, -C_{1-2} alkylene-O-C_{1-3} alkylene-; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-; or

Z_{11} is selected from -CD_2, -C_{1-3} alkylene-, and -OC_{1-3} alkylene-*; and Z_{21} is selected from -OC_{1-3} alkylene-*, -NH-C_{1-3} alkylene-*, -S-C_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -C_{1-2} alkylene-O-C_{1-3} alkylene-*; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-3}

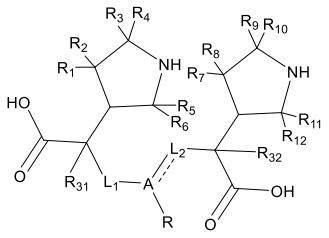
alkylene-C(O)-*, -NH-C_{1-3} alkylene-C(O)-*, -S-C_{1-3} alkylene-C(O)-*, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-*, -C_{1-3} alkylene-NH-C(O)-*, -C_{1-3} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-3} alkylene-C(S)-*; * is the linking end to A; or

Z_{11} is selected from -C_{1-3} alkylene- and -OC_{1-3} alkylene-*; and Z_{21} is selected from -OC_{1-3} alkylene-*, -NH-C_{1-3} alkylene-*, -S-C_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -C_{1-2} alkylene-O-C_{1-3} alkylene-*; and Z_{31} is selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-3} alkylene-C(O)-*, -NH-C_{1-3} alkylene-C(O)-*, -S-C_{1-3} alkylene-C(O)-*, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-*, -C_{1-3} alkylene-NH-C(O)-*, -C_{1-3} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-3} alkylene-C(S)-*; * is the linking end to A; or

Z_{11} is selected from -CD_2, -C_{1-2} alkylene-, and -OC_{1-2} alkylene-*; and Z_{21} is selected from -OC_{1-2} alkylene-*, -NH-C_{1-2} alkylene-*, -S-C_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*; and Z_{31} is selected from -C(O)-, -C_{1-2} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -NH-C_{1-2} alkylene-C(O)-*, -S-C_{1-2} alkylene-C(O)-*, -C_{1-2} alkylene-NH-C(O)-*, -C_{1-2} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*; for example, Z_{31} is selected from -C_{1-2} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -NH-C_{1-2} alkylene-C(O)-*, -S-C_{1-2} alkylene-C(O)-*, -C_{1-2} alkylene-NH-C(O)-*, -C_{1-2} alkylene-O-C(O)-*, -CH_2NH-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*; for example, Z_{31} is selected from -C_{1-2} alkylene-C(O)-*, -OCH_2-C(O)-*, -CH_2-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, and -S-C(O)-*; for example, Z_{31} is selected from -CH_2C(O)-*; * is the linking end to A.

10. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein

the compound has a structure as represented by formula (I-2):



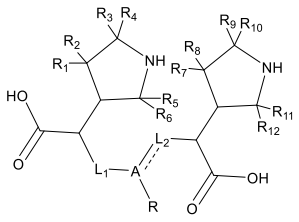
(I-2),

wherein A, ---, L_1, L_2, R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{31}, and R_{32} are as defined in any one of claims 1 to 9;

for example, in the compound represented by formula (I-2), R is a group comprising L_3, L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from $-CH_2-$, $-CD_2-$, $-CH_2CH_2-$, $-CD_2CH_2-$, -C(O)-, $-CH_2C(O)-$, -NHC(O)-, -OC(O)-, $-CH_2CH_2O-$, $-OCH_2C(O)-$, $-CH_2OC(O)-$, $-CH_2CH_2CH_2O-$, and -S-C(O)-;

or

the compound has a structure as represented by formula (I-3):



(I-3),

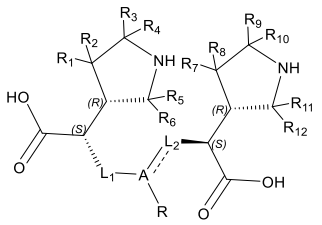
wherein A, ---, L_1, L_2, R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are as defined in any one of claims 1 to 9;

for example, in the compound represented by formula (I-3), R is a group comprising L_3, L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about

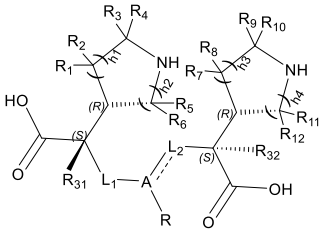
44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

or

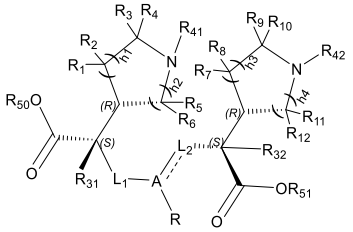
the compound has a structure as represented by formula (I'-1), formula (I'-2), or formula (I'-3):



(I'-1),



(I'-2),



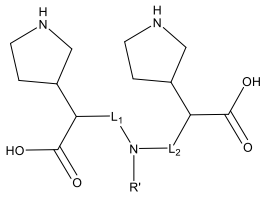
(I'-3),

wherein A, L_1, L_2, R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{31}, R_{32}, R_{41}, R_{42}, R_{50}, R_{51}, h1, h2, h3, and h4 are as defined in any one of claims 1 to 9;

for example, in the compound represented by formula (I'-1), (I'-2), or (I'-3), R is a group comprising L_3, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

or

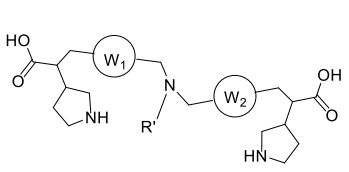
the compound has a structure as represented by formula (II):

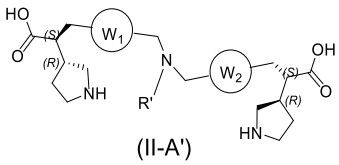

(II),

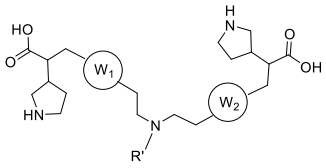
wherein L_1 and L_2 are as defined in any one of claims 1 to 9, R' is selected from H, -C_{1-3} alkylene-C_{6-10} aryl, -C_{1-3} alkylene-5-12-membered heteroaryl, and C_{1-6} alkyl; the C_{1-3} alkylene is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, and C_{1-3} alkyl; the aryl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, C_{1-3} alkoxy, and C_{1-3} aminoalkyl; the C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, carboxyl, -CN, -OH, -NH_2, C_{1-3} alkyl, and C_{1-3} alkoxy;

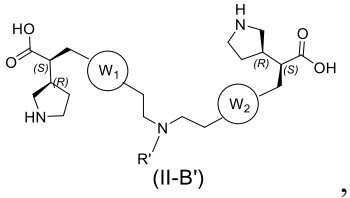
or

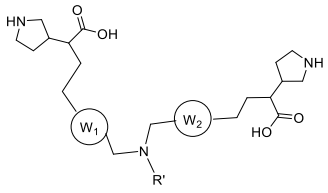
the compound has a structure as represented by formula (II-A), formula (II-B), formula (II-C), formula (II-A'), formula (II-B'), or formula (II-C'):

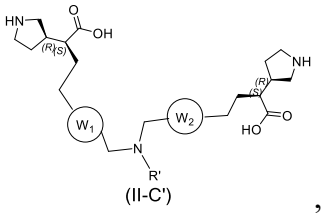

(II-A),


(II-A'),


(II-B),


(II-B'),

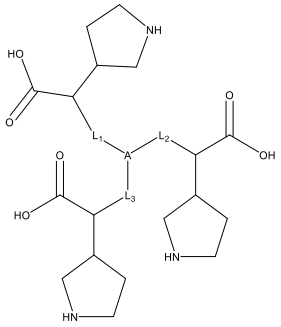

(II-C),


(II-C'),

wherein W_1, W_2, and R' are as defined in any one of claims 1 to 9;

or

the compound has a structure as represented by formula (III):



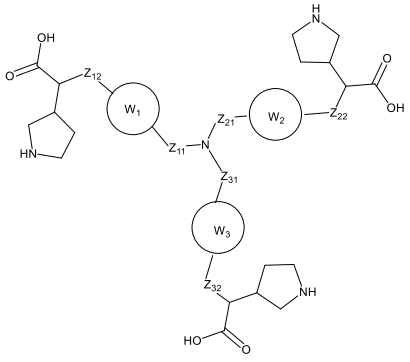
(III),

wherein A, L_1, L_2, and L_3 are as defined in any one of claims 1 to 9;

for example, in the compound represented by formula (III), L_1, L_2, and L_3 are groups comprising Z_{11}, Z_{21}, and Z_{31} respectively, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

or

the compound has a structure as represented by formula (III-1):



(III-1),

wherein W_1, W_2, W_3, Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, and Z_{32} are as defined in any one of claims 1 to 9;

preferably, each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, and ethylene;

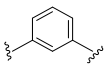
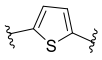
each of Z_{11}, Z_{21}, Z_{31} is independently selected from a bond, -C_{1-4} alkylene-, -C_{1-6} oxaalkylene- (e.g., -C_{1-4} oxaalkylene-), -C_{1-4} thiaalkylene-, -C_{1-4} azaalkylene-, and -C_{1-4} selenaalkylene-; the alkylene, oxaalkylene, thiaalkylene, azaalkylene, and selenaalkylene are optionally substituted by one or more substituents independently selected from Z_{41}; Z_{41} is independently selected from deuterium, halogen (e.g., fluorine and chlorine), oxo, thio, -CN, -OH, -NH_2, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; or any two Z_{41} together with an atom linked thereto form C_{3-6} cycloalkyl, or 3-6-membered heterocyclyl (e.g., oxetanyl); a heteroatom in the heterocyclyl is O, N, or S, and the number of heteroatoms is 1;

each of the rings W_1, W_2, and W_3 is independently selected from phenyl and 5-6-membered monocyclic heteroaryl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl; a heteroatom in the heteroaryl is O, N, or S, and the number of heteroatoms is 1 or 2; or

Z_{12}, Z_{22}, and Z_{32} are all methylene; or

when Z_{11}, Z_{21}, and Z_{31} are present in the compound at the same time, in a combination of the definitions of Z_{11}, Z_{21}, and Z_{31}, 2 or 3 heteroatoms or heteroatom groups are comprised, and the heteroatom or heteroatom group is selected from -O-, -S-, -NH-, and -CO-; or

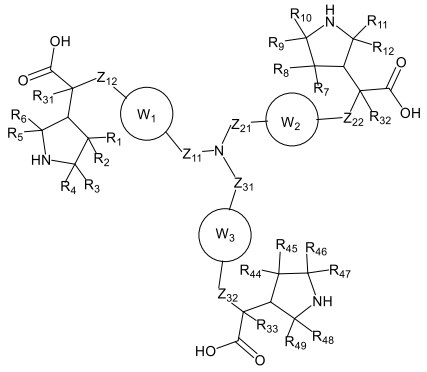
each of the rings W_1, W_2, and W_3 is independently selected from phenyl and thienyl; the phenyl and thienyl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), and -C(O)C_{1-3} alkyl; or

each of the rings W_1, W_2, and W_3 is independently selected from  ,  , and , which are optionally substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy;

for example, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2$O-, and -S-C(O)-;

or

the compound has a structure as represented by formula (III-2):



(III-2),

wherein W_1, W_2, W_3, Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, Z_{32}, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{31}, R_{32}, and R_{33} are as defined in any one of claims 1 to 9;

preferably, the heteroatom or heteroatom group in Z_{31} comprises -CO- or -C(S)-; or

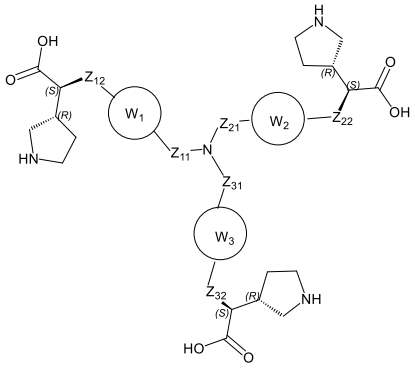
R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{31}, R_{32}, and R_{33} are selected from hydrogen or deuterium;

for example, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently

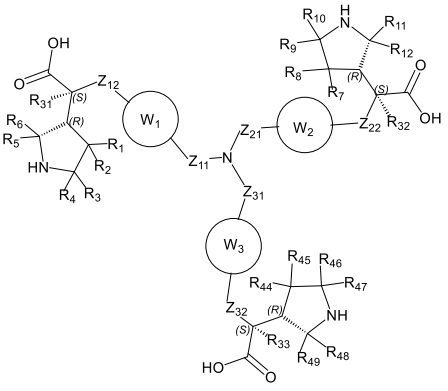
have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2$O-, and -S-C(O)-;

or

the compound has a structure as represented by formula (III-1-1) or formula (III-2-1):



(III-1-1),



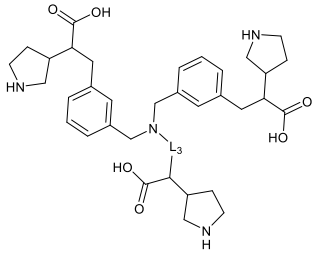
(III-2-1),

wherein W_1, W_2, W_3, Z_{11}, Z_{12}, Z_{21}, Z_{22}, Z_{31}, Z_{32}, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{31}, R_{32}, and R_{33} are as defined in any one of claims 1 to 9;

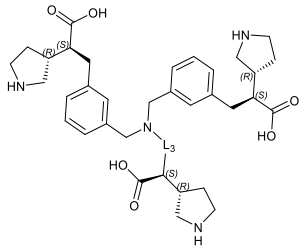
for example, one and only one of Z_{11}, Z_{21}, and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11}, Z_{21}, and Z_{31} are different from each other, or two groups not containing the double bond in Z_{11}, Z_{21}, and Z_{31} are the same, and the two same groups contain -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11}, Z_{21}, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2$O-, and -S-C(O)-;

or

the compound has a structure as represented by formula (III-A) or formula (III-A'):



(III-A),

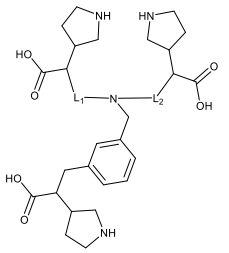


(III-A'),

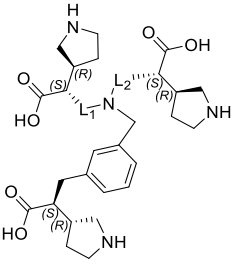
wherein L_3 are as defined in any one of claims 1 to 9;

or

the compound has a structure as represented by formula (III-B) or formula (III-B'-1):

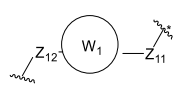


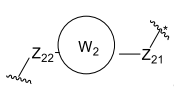
(III-B),



(III-B'-1),

wherein L_1 and L_2 are as defined in any one of claims 1 to 9;

preferably, L_1 is  , wherein *represents the linking end to A; or

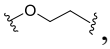
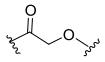
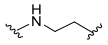
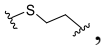
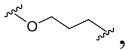
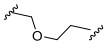
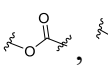
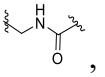
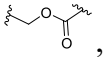
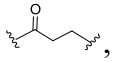
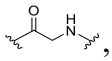
L_2 is  , wherein * is the linking end to A; or

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from $-C_{1-3}$ alkylene-, $-C_{1-3}$ oxaalkylene-, $-C_{1-3}$ thiaalkylene-, and $-C_{1-3}$ azaalkylene-; the alkylene, oxaalkylene, thiaalkylene, and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, methyl, and methoxy; or

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from $-C_{1-3}$ alkylene-, and $-C_{1-3}$ oxaalkylene-; the alkylene and oxaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, $-NH_2$, methyl, and methoxy; or

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from $-C_{1-2}$ alkylene-, $-C_{1-2}$ oxaalkylene-, $-C_{1-2}$ thiaalkylene-, and $-C_{1-2}$ azaalkylene-; the alkylene, oxaalkylene, thiaalkylene,

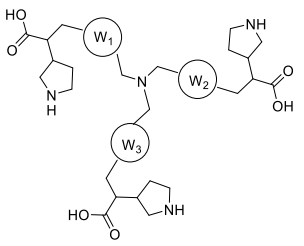
and azaalkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, oxo, -CN, -OH, -NH_2, methyl, and methoxy; or

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from methylene, ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  ,  , and ;

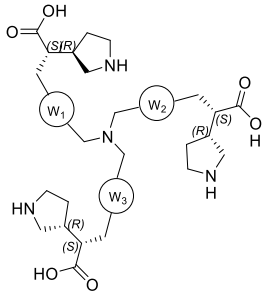
for example, L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, and one and only one of Z_{11} and Z_{21} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; preferably, the double bond is for example a double bond between C and O in -C(O)-; further preferably, neither Z_{11} nor Z_{21} is methylene, or a group not containing the double bond in Z_{11} and Z_{21} contains -O-, -NH-, -S-, or -Se-, preferably, -O-; still further preferably, Z_{11} and Z_{21} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

or

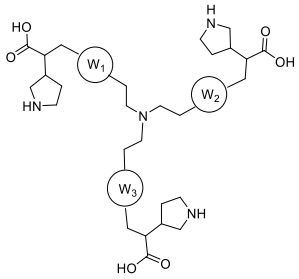
the compound has a structure as represented by formula (III-C), formula (III-C'), formula (III-D), formula (III-D'), formula (III-E), or formula (III-E'):



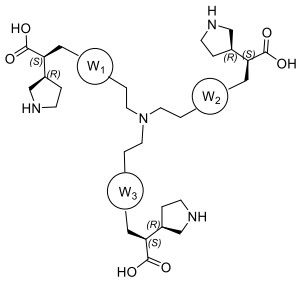
(III-C),



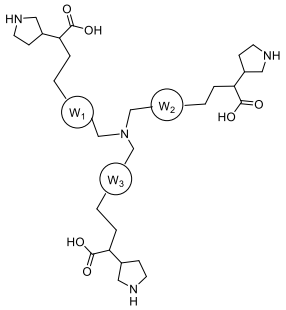
(III-C'),



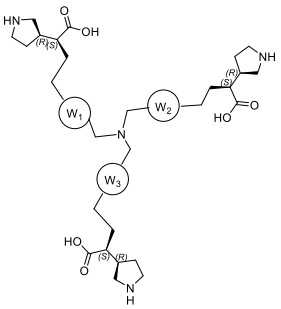
(III-D),



(III-D'),



(III-E),

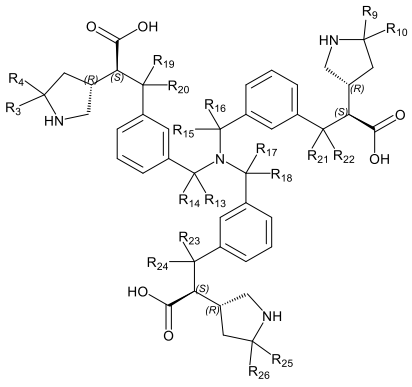


(III-E'),

wherein W_1, W_2, and W_3 are as defined in any one of claims 1 to 9;

or

the compound has a structure as represented by formula (IV):

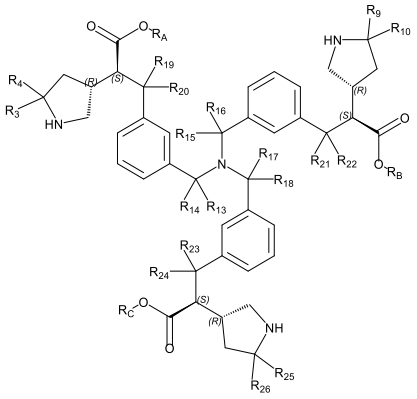


(IV),

wherein R_3, R_4, R_9, R_{10}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} are each independently selected from H and deuterium, and at least one of R_3, R_4, R_9, R_{10}, and R_{13}-R_{26} is deuterium;

or

the compound has a structure as represented by formula (A):



(A),

wherein R_3, R_4, R_9, R_{10}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} are each independently selected from H and deuterium, and at least one of R_3, R_4, R_9, R_{10}, and R_{13}-R_{26} is deuterium; R_A, R_B, and R_C are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, -C_{1-3} alkylene-O-C_{1-6} alkyl, and -C_{1-3} alkylene-O-C(O)-C_{1-6} alkyl; the alkyl, alkenyl, alkoxy, and alkylene are optionally substituted by one or more substituents independently selected from deuterium, halogen, -OH, -NH_2, -CN, oxo, C_{1-3} alkyl, and C_{1-3} alkoxy;

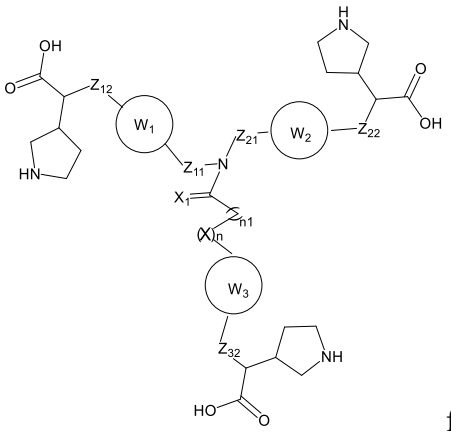
preferably, R_A, R_B, and R_C are each independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, -C_{1-2} alkylene-O-C_{1-4} alkyl, and -C_{1-2} alkylene-O-C(O)-C_{1-4} alkyl; the alkyl, C_{1-6} alkoxy, and alkylene are optionally substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, -OH, -NH_2, -CN, oxo, methyl, ethyl, *n*-propyl, isopropyl, methoxy, ethoxy, *n*-propyloxy, and isopropyloxy; or

R_A, R_B, and R_C are each independently selected from C_{1-3} alkyl, -methylene-O-C_{1-4} alkyl, and -methylene-O-C(O)-C_{1-3} alkyl; the methylene and alkyl are optionally substituted by one or more substituents independently selected from methyl, ethyl, *n*-propyl, and isopropyl; or

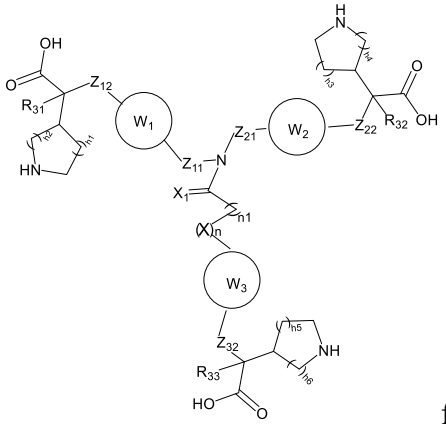
R_A, R_B, and R_C are each independently selected from methyl, ethyl, and -CH_2-OC(O)-$CH(CH_3)_2$;

or

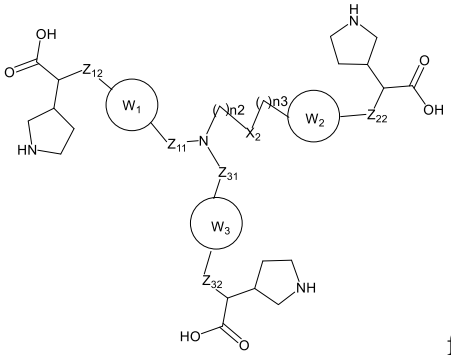
the compound has a structure as represented by formula (B), formula (B-1), formula (C), formula (C-1), formula (D), formula (D-1), formula (B-2), formula (B-3), formula (C-2), formula (C-3), formula (D-2), or formula (D-3):



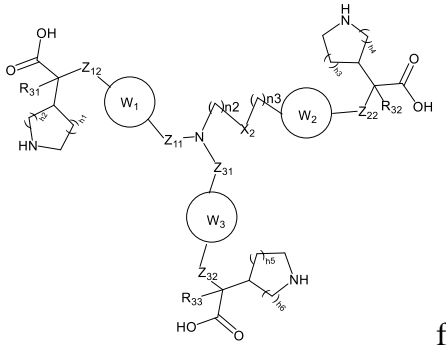
formula (B),



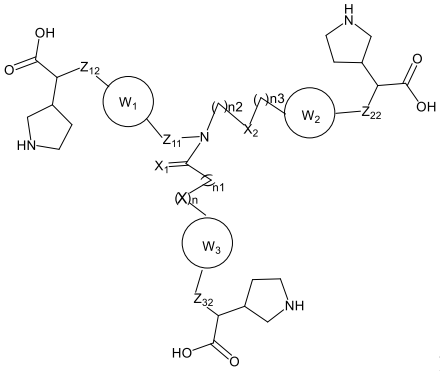
formula (B-1),



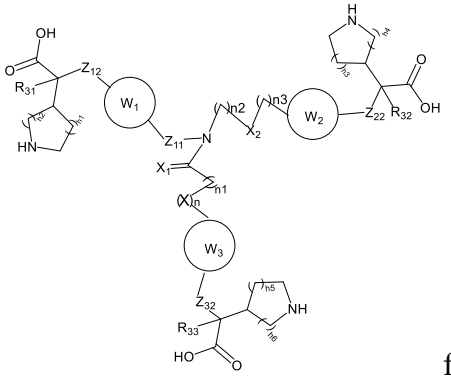
formula (C),



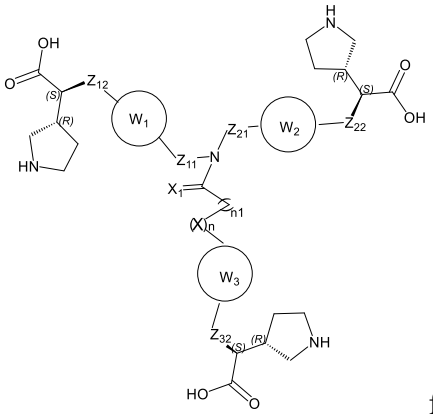
formula (C-1),



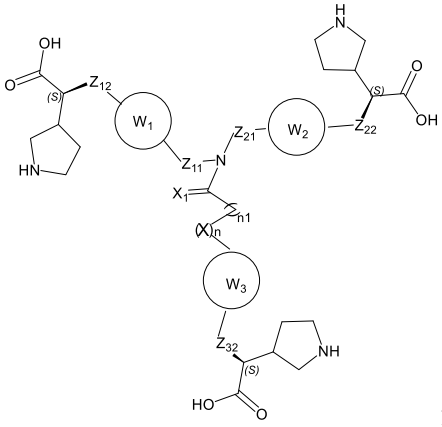
formula (D),



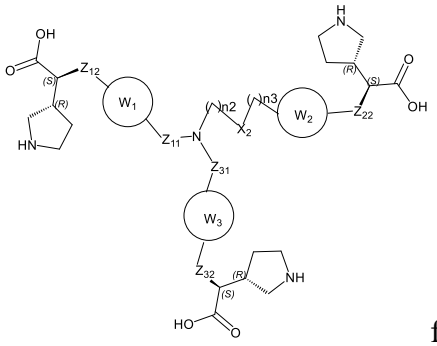
formula (D-1),



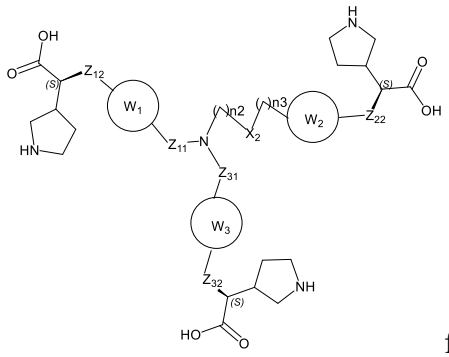
formula (B-2),



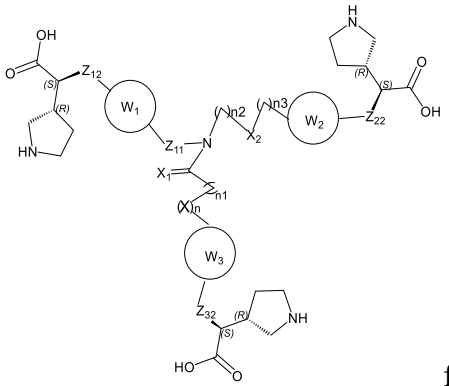
formula (B-3),



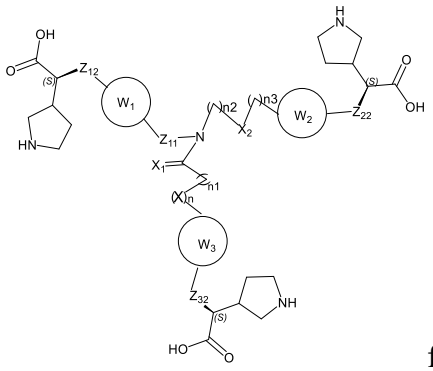
formula (C-2),



formula (C-3)



formula (D-2),



formula (D-3)

wherein

Z_{11}, Z_{21}, Z_{31}, R_{31}, R_{32}, R_{33}, h1, h2, h3, h4, h5, and h6 are as defined in any one of claims 1 to 9,

X is selected from O, CH_2, NH, S, and Se, or X is selected from O, CH_2, NH, and S; or X is CH_2;

X_2 is selected from O, CH_2, NH, S, and Se, or X_2 is selected from O, NH, and S; or X_2 is O;

X_1 is independently selected from O and S, or X_1 is O;

n, n1, and n3 are each independently 0 or 1,

n2 is independently 0, 1, 2, or 3;

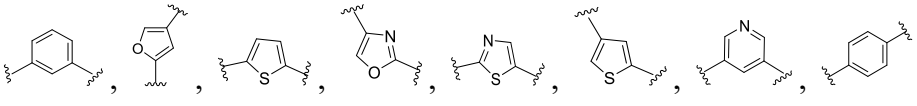
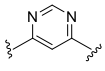
each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, ethylene, and -CD_2-;

or each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

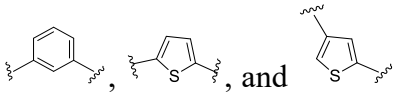
or Z_{12}, Z_{22}, and Z_{32} are all methylene;

each of the rings W_1, W_2, and W_3 is independently selected from phenyl, and 5-6-membered monocyclic heteroaryl; the phenyl and heteroaryl are optionally substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}$ alkyl$)_2$, $-NH(C_{1-3}$ alkyl), and $-C(O)C_{1-3}$ alkyl; a heteroatom in the heteroaryl is O, N, or S, and the number of heteroatoms is 1 or 2;

or

each of the rings W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  , and  ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}$ alkyl$)_2$, $-NH(C_{1-3}$ alkyl), and $-C(O)C_{1-3}$ alkyl;

or

each of the rings W_1, W_2, and W_3 is independently selected from the following optionally substituted groups:  ; wherein the "optionally substituted" refers to unsubstituted or substituted by one or more substituents independently selected from deuterium, fluorine, chlorine, bromine, methyl, ethyl, methoxy, and ethoxy;

preferably,

the sum of n2 and n3 is not greater than 3 (specifically 0, 1, 2, or 3); for example the sum of n2 and n3 is not greater than 2 (specifically 0, 1, or 2); for example the sum of n2 and n3 is 1 or 2 (specifically n2 is 2 and n3 is 0; or n2 is 1 and n3 is 1; or n2 is 0 and n3 is 2); or

the sum of n and n1 is 0, 1, or 2; for example the sum of n and n1 is 1 or 2 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1; or n is 1 and n1 is 1; or n is 0 and n1 is 2; or n is 2 and n1 is 0); or

the sum of n and n1 is 1 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1);

for example:

n2 is 0 or 1, n3 is 0, and X_2 is CH_2; or

n2 is 2 or 3, n3 is 0, and X_2 is O, NH, or S; or

n2 is 1 or 2, n3 is 1, and X_2 is O, NH, or S; or

n2 is 2 or 3, n3 is 0, and X_2 is O; or

n2 is 2, n3 is 1, and X_2 is O; or

n2 is 2, n3 is 0, and X_2 is O, NH, or S; or

n2 is 2, n3 is 0, and X_2 is O;

and/or for example:

X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or

X is O or CH_2, n is 1, and n1 is 1; or

X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or

X_1 is O, X is O or CH_2, n is 1, and n1 is 1; or

X_1 is O, X is selected from O or CH_2, n is 1, and n1 is 0; or

X_1 is O, X is O or CH_2, n is 1, and n1 is 1; or

X_1 is O, X is selected from CH_2, n is 1, and n1 is 0;

and/or, preferably:

Z_{11} is -CD_2-; or

Z_{11} is independently selected from -C_{1-3} alkylene-, -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; or, Z_{11} is independently selected from -C_{1-3} alkylene- and -OC_{1-3} alkylene-; or, Z_{11} is independently selected from methylene, ethylene, methyleneoxy, and ethyleneoxy; or, Z_{11} is independently selected from methylene and -CD_2-; preferably, Z_{11} is independently selected from methylene; and/or

Z_{21} is -CD_2-; or

Z_{21} is independently selected from -C_{1-3} alkylene-, -OC_{1-3} alkylene-, -NH-C_{1-3} alkylene-, -S-C_{1-3} alkylene-, -Se-C_{1-3} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-; or, Z_{21} is -OC_{1-3} alkylene-, -NH-C_{1-2} alkylene-, -S-C_{1-2} alkylene-, and -C_{1-2} alkylene-O-C_{1-3} alkylene-;

and/or, preferably:

Z_{31} is independently selected from -C(O)-, -C_{1-3} alkylene-C(O)-, -OC_{1-3} alkylene-C(O)-, -NH-C_{1-3} alkylene-C(O)-, -S-C_{1-3} alkylene-C(O)-, -O-C_{1-2} alkylene-C(O)-C_{1-3} alkylene-, -C_{1-3} alkylene-NH-C(O)-, -C_{1-3} alkylene-O-C(O)-, -NH-C(O)-, -O-C(O)-, -S-C(O)-, and -C_{1-3} alkylene-C(S)-; or, Z_{31} is -C(O)-, -C_{1-2} alkylene-C(O)-, -OC_{1-2} alkylene-C(O)-, -NH-C(O)-, -O-C(O)-, and -S-C(O)-;

for example, in the above-mentioned formula (B) and formula (B-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

each of Z_{11} and Z_{21} is independently selected from -CD_2-, -C_{1-3} alkylene- (for example -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (for example -OC_{1-2} alkylene-*), -SC_{1-3} alkylene-*, -NHC_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, wherein * is the linking end to N;

X_1 is O or S, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X_1 is O or S, X is O or CH_2, n is 1, and n1 is 1; or X_1 is O or S, n is 0, and n1 is 0; or

for another example, in the above-mentioned formula (B) and formula (B-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, -OCH_2-*, and -OCH_2CH_2-*, wherein * is the linking end to N;

Z_{21} is independently selected from -OCH_2CH_2-*, -CH_2OCH_2CH_2-*, and -O$CH_2CH_2CH_2$-*, wherein * is the linking end to N;

X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or X_1 is O, X is O or CH_2, n is 1, and n1 is 1; or

for another example, in the above-mentioned formula (B) and formula (B-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

each of Z_{11} and Z_{21} is independently selected from -CD_2-, -C_{1-3} alkylene- (for example -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (for example -OC_{1-2} alkylene-*), -SC_{1-3} alkylene-*, -NHC_{1-3} alkylene-*, -Se-C_{1-3} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, wherein * is the linking end to N,

X_1 is O or S,

X is selected from O, CH_2, NH, and S,

the sum of n and n1 is 0, 1, or 2;

further for example,

Z_{21} is independently selected from -OCH_2CH_2-*, -$CH_2OCH_2CH_2$-*, and -$OCH_2CH_2CH_2$-*, wherein * is the linking end to N;

X_1 is O, X is selected from O, CH_2, NH, and S,

the sum of n and n1 is 1 or 2;

further for example, in any of the above-mentioned formula (B), formula (B-1), formula (B-2), and formula (B-3), each of Z_{11} and Z_{21} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} and Z_{21} are identical or different, and at least one of Z_{11} and Z_{21} is a group containing -O-, -NH-, -S-, or -Se-, preferably, a group containing -O-, e.g., *-CH_2O- or *-CH_2CH_2O-, wherein * is the linking end to N; still further preferably, Z_{11}, Z_{21}, and *-$C(X_1)$-$(CH_2)_{n1}$-$(X)_n$- each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -$CH_2C(O)$-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -$OCH_2C(O)$-, -$CH_2OC(O)$-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

for example, in the above-mentioned formula (C) and formula (C-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-; and/or

Z_{11} is independently selected from -CD_2-, -C_{1-3} alkylene- (for example -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (for example -OC_{1-2} alkylene-*), -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, wherein * is the linking end to N; and/or

Z_{31} is independently selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -$NHCH_2$-C(O)-*, -SCH_2-C(O)-*, -CH_2-NHC(O)-*, -C_{1-2} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*, wherein * is the linking end to N; and/or

n2 is 2 or 3, n3 is 0, and X_2 is O, NH, and S; or

n2 is 1 or 2, n3 is 1, and X_2 is O, NH, and S; or

n2 is 0 or 1, n3 is 0, and X_2 is CH_2;

for another example, in the above-mentioned formula (C) and formula (C-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-; and/or

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, -OCH_2-*, and -OCH_2CH_2-*, wherein * is the linking end to N; and/or

Z_{31} is independently selected from -C(O)-, -CH_2CH_2C(O)-*, -CH_2C(O)-*, -OCH_2C(O)-*, -NHC(O)-*, -OC(O)-*, and -SC(O)-*, wherein * is the linking end to N; and/or

n2 is 2 or 3, n3 is 0, and X_2 is O; or

n2 is 1 or 2, n3 is 1, and X_2 is O; or

n2 is 0 or 1, n3 is 0, and X_2 is CH_2;

for another example, in the above-mentioned formula (C) and formula (C-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-; Z_{11} is independently selected from -CD_2-, -C_{1-3} alkylene- (for example -C_{1-2} alkylene-), -OC_{1-3} alkylene-* (for example -OC_{1-2} alkylene-*), -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, and/or

Z_{31} is independently selected from -C(O)-, -C_{1-3} alkylene-C(O)-*, -OC_{1-2} alkylene-C(O)-*, -$NHCH_2$-C(O)-*, -SCH_2-C(O)-*, -CH_2-NHC(O)-*, -C_{1-2} alkylene-O-C(O)-*, -NH-C(O)-*, -O-C(O)-*, -S-C(O)-*, and -C_{1-2} alkylene-C(S)-*, wherein * is the linking end to N; further for example, Z_{31} is independently selected from -CH_2CH_2C(O)-*, -CH_2C(O)-*, -OCH_2C(O)-*, -NHC(O)-*, -OC(O)-*, and -SC(O)-*, wherein * is the linking end to N; and/or

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, and -OCH_2CH_2-*, wherein * is the linking end to N; and/or

X_2 is O, NH, S, or Se, and the sum of n2 and n3 is 1, 2, or 3; further for example, X_2 is O, and the sum of n2 and n3 is 2, or 3;

further for example, in any of the above-mentioned formula (C), formula (C-1), formula (C-2), and formula (C-3), one and only one of Z_{11} and Z_{31} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, the group not containing the double bond in Z_{11} and Z_{31} is identical to or different from *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- (* is the linking end to N); still further

preferably, Z_{11}, -$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$-, and Z_{31} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

for example, in the above-mentioned formula (D) and formula (D-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene, and -CD_2-; and/or

Z_{11} is independently selected from -CD_2-, -C_{1-2} alkylene-, -OC_{1-2} alkylene-*, -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, wherein * is the linking end to N; and/or

n2 is 2 or 3, n3 is 0, and X_2 is O, NH, or S; or

n2 is 1 or 2, n3 is 1, and X_2 is O, NH, or S; or

n2 is 0 or 1, n3 is 0, and X_2 is CH_2; and/or

X_1 is O or S, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or

X_1 is O or S, X is O or CH_2, n is 1, and n1 is 1;

alternatively for example, in the above-mentioned formula (D) and formula (D-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-; and/or

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, -OCH_2-*, and -OCH_2CH_2-*, wherein * is the linking end to N; and/or

n2 is 2 or 3, n3 is 0, and X_2 is O; or

n2 is 1 or 2, n3 is 1, and X_2 is O; or

n2 is 0 or 1, n3 is 0, and X_2 is CH_2; and/or

X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or

X_1 is O, X is O or CH_2, n is 1, and n1 is 1;

alternatively for example, in the above-mentioned formula (D) and formula (D-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-; and/or

Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, and -OCH_2CH_2-*, wherein * is the linking end to N; and/or

n2 is 2 or 3, n3 is 0, and X_2 is O; or

n2 is 2, n3 is 1, and X_2 is O; and/or

X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0;

alternatively for example, in the above-mentioned formula (D) and formula (D-1),

each of Z_{12}, Z_{22}, and Z_{32} is independently selected from methylene and -CD_2-;

Z_{11} is independently selected from -CD_2-, -C_{1-2} alkylene-, -OC_{1-2} alkylene-*, -SC_{1-2} alkylene-*, -NHC_{1-2} alkylene-*, -Se-C_{1-2} alkylene-*, and -CH_2-O-C_{1-2} alkylene-*, wherein * is the linking end to N; or, Z_{11} is independently selected from -CD_2-, -CH_2-, -CH_2CH_2-, and -OCH_2CH_2-*, wherein * is the linking end to N; and/or

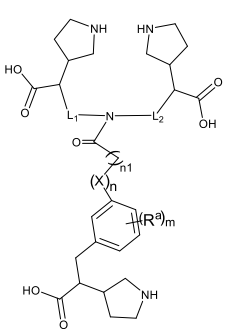
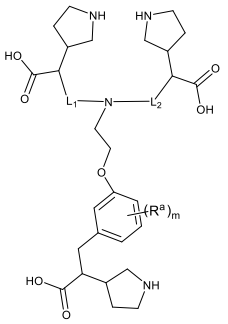
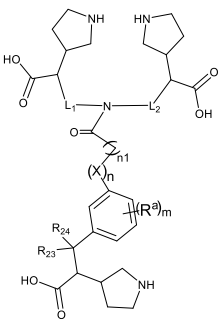
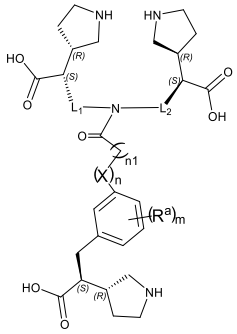
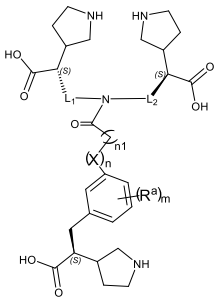
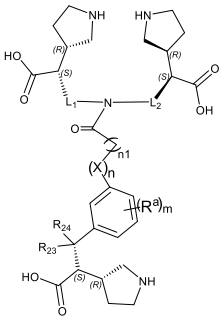
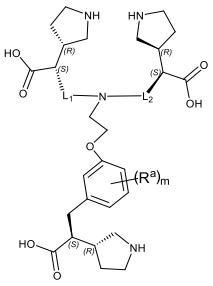
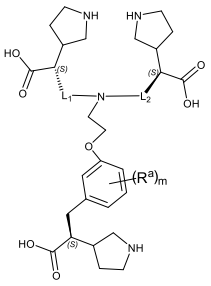
X_2 is O, NH, S, or Se, the sum of n2 and n3 is 1, 2, or 3; or, X_2 is O, and the sum of n2 and n3 is 2, or 3; and/or

X_1 is O or S, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 0, 1, or 2; or, X_1 is O, X is selected from O, CH_2, NH, and S, and the sum of n and n1 is 1 or 2; and/or

further for example, in any of the above-mentioned formula (D), formula (D-1), formula (D-2), and formula (D-3), Z_{11} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} is identical to or different from *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- (* is the linking end to N); still further preferably, Z_{11}, -$C(X_1)$-$(CH_2)_{n1}$-$(X)_n$-, and -$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$- each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

or

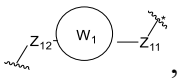
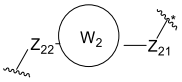
the compound has a structure as represented by formula (E), formula (F), formula (E-1), formula (E-2), formula (E-3), formula (E-4), formula (F-1), or formula (F-2):


(E),

(F),

(E-1),

(E-2),

(E-3),

(E-4),

(F-1),

(F-2),

wherein

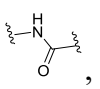
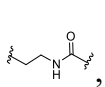
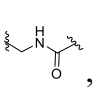
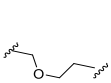
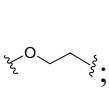
L_1 and L_2 are as defined in any one of claims 1 to 9, X is O, CH_2, or NH, R^a is deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}$ alkyl$)_2$, $-NH(C_{1-3}$ alkyl), or $-C(O)C_{1-3}$ alkyl, n1 is 0 or 1, m is 0 or 1, n is 0 or 1; R_{23} and R_{24} are each independently selected from H and deuterium;

for example,

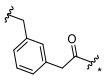
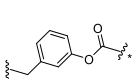
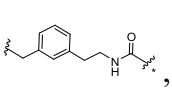
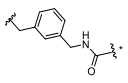
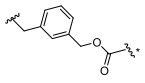
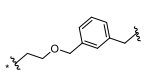
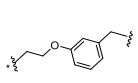
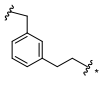
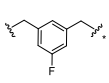
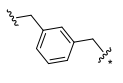
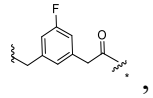
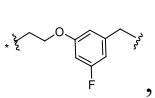
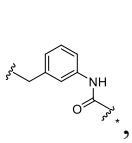
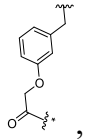
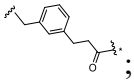
L_1 is  , and L_2 is  , wherein * is the linking end to N; wherein

each of the rings W_1 and W_2 is independently selected from ; the phenyl is optionally substituted by one or more substituents independently selected from halogen, and C_{1-3} alkoxy (preferably fluorine or methoxy);

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from $-C_{1-2}$ alkylene-, $-OC_{1-3}$ alkylene-, $-NH-C_{1-2}$ alkylene-, $-S-C_{1-2}$ alkylene-, $-C_{1-2}$ alkylene-O-C_{1-2} alkylene-, $-C_{1-2}$ alkylene-C(O)-, $-OC_{1-2}$ alkylene-C(O)-, $-C_{1-2}$ alkylene-NH-C(O)-, $-C_{1-2}$ alkylene-O-C(O)-, -NH-C(O)-, $-NH-C_{1-2}$ alkylene-C(O)-, -O-C(O)-, and -S-C(O)-; or

each of Z_{11}, Z_{12}, Z_{21}, and Z_{22} is independently selected from methylene, ethylene, ,  , , , ,  ,  , ,  , and  ;

or, for example

each of L_1 and L_2 is independently selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; * is the linking end to N;

X is selected from O, CH_2, NH, and S, for example X is O, CH_2, or NH, e.g., X is CH_2; and/or

R^a is deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}\ alkyl)_2$, $-NH(C_{1-3}\ alkyl)$, or $-C(O)C_{1-3}$ alkyl, for example, R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy; for example, R^a is fluorine; and/or

n1 is 0 or 1, and/or

m is 0 or 1, for example m is 1, and/or

n is 0 or 1; for example, the sum of n and n1 is 0, 1, or 2; for example, the sum of n and n1 is 1 or 2 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1; or n is 1 and n1 is 1; or n is 0 and n1 is 2; or n is 2 and n1 is 0); for example, the sum of n and n1 is 1 (i.e., n is 1 and n1 is 0; or n is 0 and n1 is 1);

preferably,

X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or

X is O or CH_2, n is 1, n1 is 1;

alternatively preferably,

R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy,

m is 1,

X is selected from O, CH_2, NH, and S,

the sum of n and n1 is 0, 1, or 2;

alternatively preferably,

R^a is fluorine or methoxy,

m is 1,

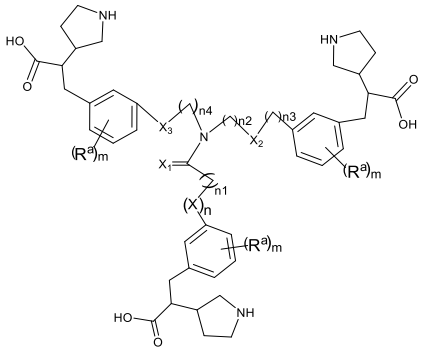
X is selected from O, CH_2, NH, and S,

the sum of n and n1 is 1 or 2;

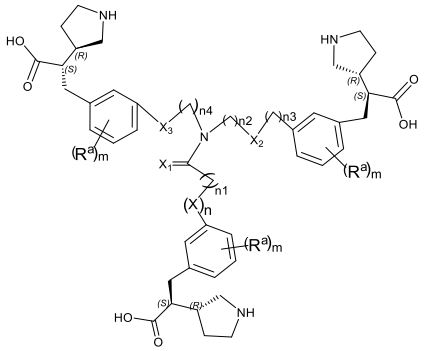
for example, in any of the above-mentioned formula (E), formula (E-1), formula (E-2), formula (E-3), and formula (E-4), L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, and each of Z_{11} and Z_{21} is a group not containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, Z_{11} and Z_{21} are identical or different, and at least one of Z_{11} and Z_{21} is identical to or different from *-C(O)-$(CH_2)_{n1}$-X_n- (* is the linking end to N); still further preferably, Z_{11}, Z_{21}, and -C(O)-$(CH_2)_{n1}$-$(X)_n$- each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-; or

in any of the above-mentioned formula (F), formula (F-1), and formula (F-2), L_1 and L_2 are groups comprising Z_{11} and Z_{21} respectively, and one and only one of Z_{11} and Z_{21} is a group containing a double bond; the double bond is, for example, a double bond between C and O in -C(O)-, or a double bond between C and S in -C(S)-; further preferably, the group not containing the double bond in Z_{11} and Z_{21} is identical to or different from *-$(CH_2)_2$-O- (*represents the linking end to N); still further preferably, Z_{11} and Z_{21} each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about 30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

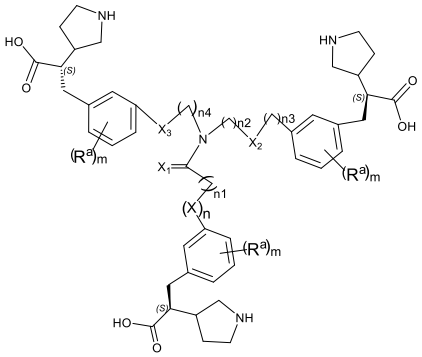
or, the compound has a structure as represented by formula (G), formula (G-1), formula (G-2), formula (G-3), or formula (G-4):



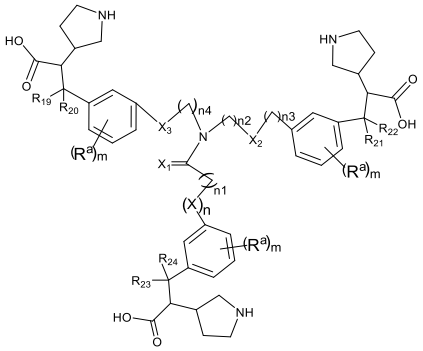
(G),



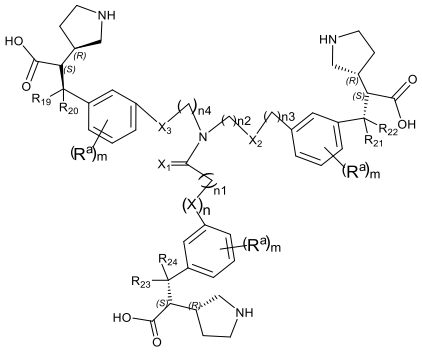
(G-1),



(G-2),



(G-3),



(G-4),

wherein

X, X_1, X_2, n, n1, n2, and n3 are as defined in any of formula (B), formula (C), and formula (D),

m is independently 0 or 1, for example m is 1;

n4 is 0, 1, 2, or 3, or, n4 is 0, 1, or 2, or n4 is 0 or 1, or n4 is 0;

X_3 is O, S, CH_2, or NH; or X_3 is O, S, CH_2, NH, or CD_2; or X_3 is O or CH_2; or X_3 is O, CH_2, or CD_2;

R^a is deuterium, halogen, -CN, -OH, $-NH_2$, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(C_{1-3}\ alkyl)_2$, $-NH(C_{1-3}\ alkyl)$, or $-C(O)C_{1-3}$ alkyl; for example, R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy; for example, R^a is fluorine or methoxy;

R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each independently selected from H and deuterium;

preferably,

X_3 is O, and n4 is 2; or

X_3 is CH_2, and n4 is 0 or 1; or

X_3 is CH_2 or CD_2, and n4 is 0 or 1; or

X_3 is CH_2 or CD_2, and n4 is 0; or

alternatively preferably

R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy;

m is 1;

X_2 is O, NH, S, or Se,

the sum of n2 and n3 is 1, 2, or 3;

X_1 is O or S,

X is selected from O, CH_2, NH, and S,

the sum of n and n1 is 0, 1, or 2; and

X_3 is O, and n4 is 2; or

X_3 is CH_2 or CD_2, and n4 is 0 or 1; or

alternatively preferably

R^a is fluorine, chlorine, or methoxy; m is 1;

X_2 is O, and the sum of n2 and n3 is 2 or 3;

X_1 is O, and X is selected from O, CH_2, NH, and S,

the sum of n and n1 is 1, or 2;

X_3 is O, and n4 is 2; or

X_3 is CH_2 or CD_2, and n4 is 0 or 1; or

alternatively preferably

R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy;

m is 1;

X_3 is O, and n4 is 2; or

X_3 is CH_2 or CD_2, and n4 is 0 or 1;

n2 is 2 or 3, n3 is 0, and X_2 is O, NH, or S; or

n2 is 1 or 2, n3 is 1, and X_2 is O, NH, or S; or

n2 is 0 or 1, n3 is 0, and X_2 is CH_2;

X_1 is O or S, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or

X_1 is O or S, X is O or CH_2, n is 1, and n1 is 1; or

alternatively preferably

R^a is fluorine, chlorine, or methoxy;

m is 1;

X_3 is O, and n4 is 2; or

X_3 is CH_2 or CD_2, and n4 is 0 or 1;

n2 is 2 or 3, n3 is 0, and X_2 is O; or

n2 is 1 or 2, n3 is 1, and X_2 is O; or

n2 is 0 or 1, n3 is 0, and X_2 is CH_2; and

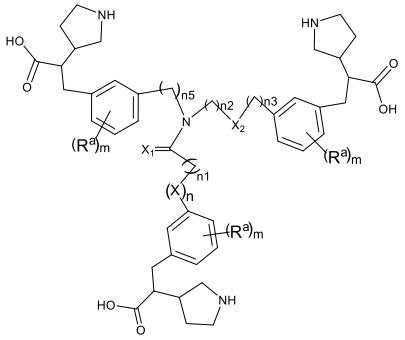
X_1 is O, X is selected from O, CH_2, NH, and S, n is 1, and n1 is 0; or

X_1 is O, X is O or CH_2, n is 1, and n1 is 1;

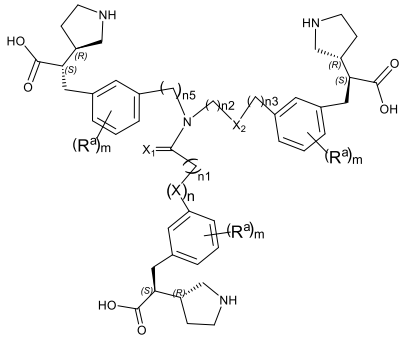
in any of the above-mentioned formula (G), formula (G-1), formula (G-2), formula (G-3), and formula (G-4), *-$(CH_2)_{n4}$-X_3-, *-$(CH_2)_{n2}$-X_2-$(CH_2)_{n3}$-, and *-$C(X_1)$-$(CH_2)_{n1}$-$(X)_n$- (* is the linking end to N) are identical to or different from each other, and they each independently have a molecular weight of 14.0-107.1, preferably 14.0-60; preferably about 14, about 16, about 28, about

30, about 42, about 43, about 44, about 46, about 58, or about 60; still more further preferably, Z_{11}, Z_{21}, and Z_{31} are selected from -CH_2-, -CD_2-, -CH_2CH_2-, -CD_2CH_2-, -C(O)-, -CH_2C(O)-, -NHC(O)-, -OC(O)-, -CH_2CH_2O-, -OCH_2C(O)-, -CH_2OC(O)-, -$CH_2CH_2CH_2O$-, and -S-C(O)-;

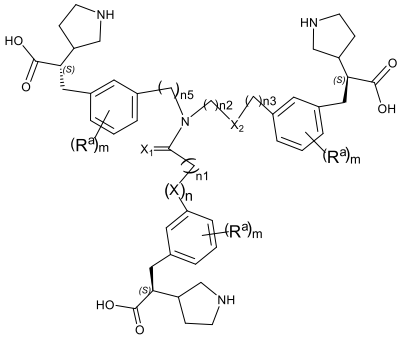
or, the compound has a structure as represented by formula (H), formula (H-1), formula (H-2), formula (H-3), or formula (H-4):



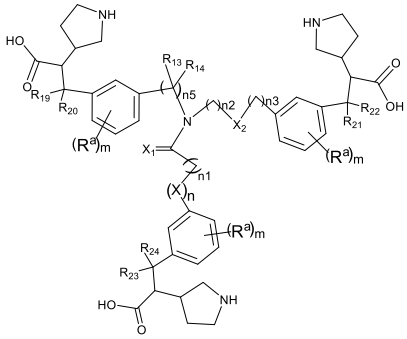
(H),



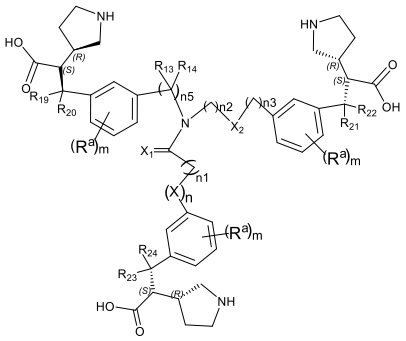
(H-1),



(H-2),



(H-3),



(H-4),

wherein

X, X_1, X_2, n, n1, n2, and n3 are as defined in formula (B), formula (C), formula (D), or formula (G),

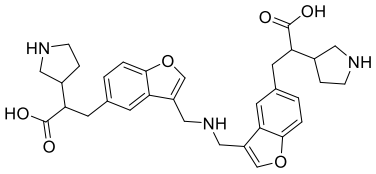
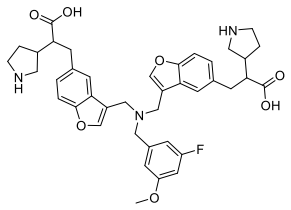
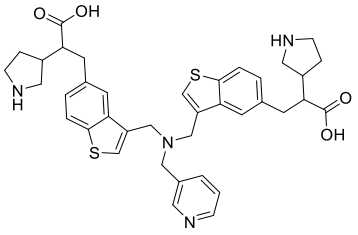
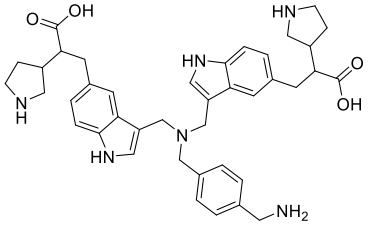
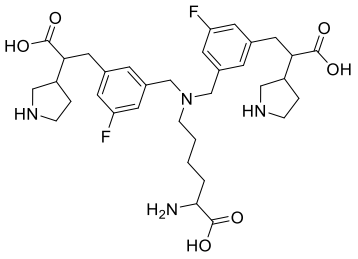
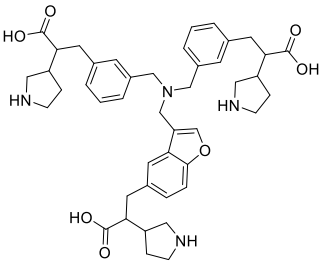
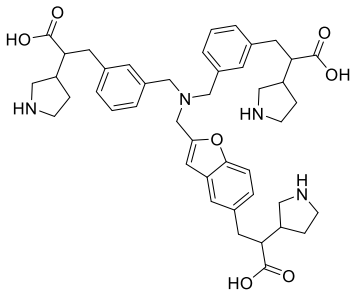
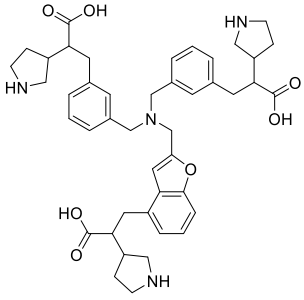
m is independently 0 or 1, or m is 1;

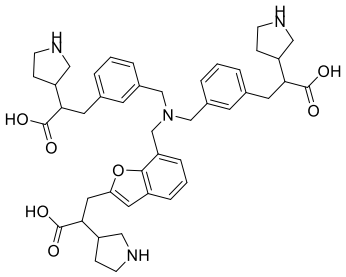
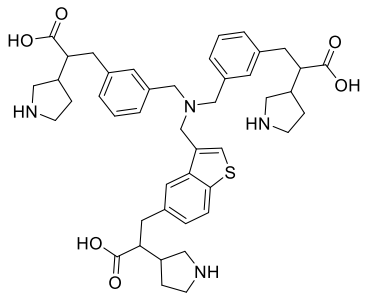
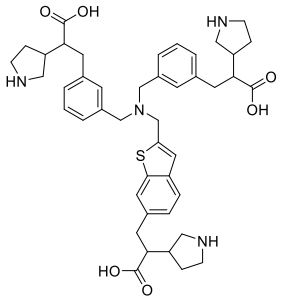
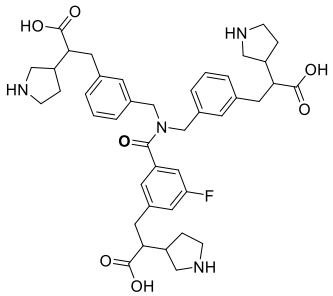
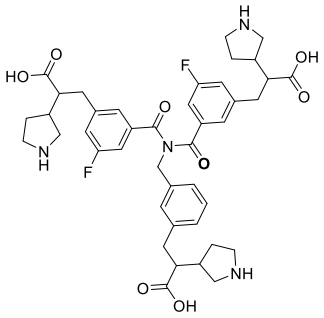
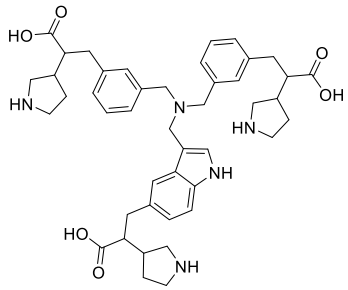
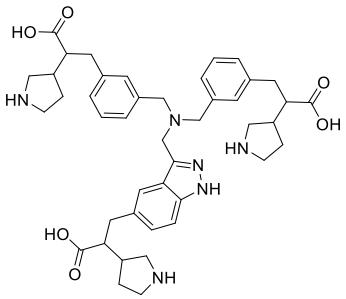
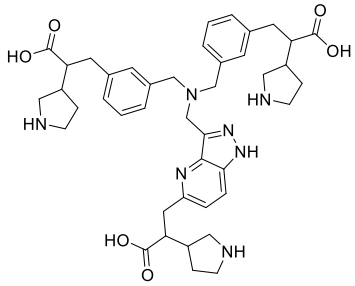
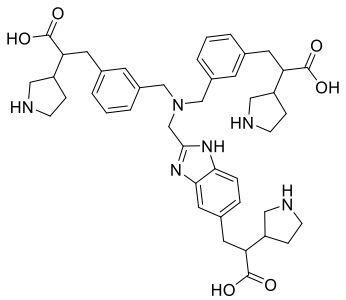
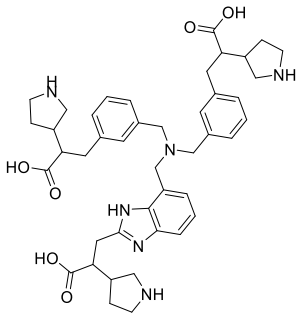
n5 is 1, 2, 3, or 4, or n5 is 1, 2, or 3, or n5 is 1 or 2, or n5 is 1;

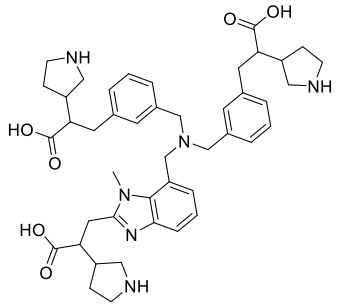
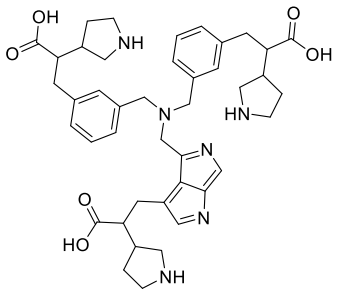
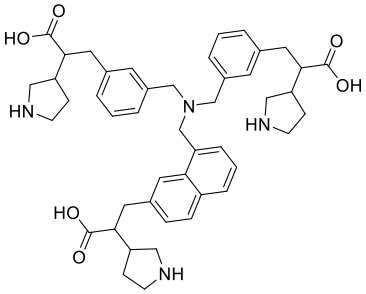
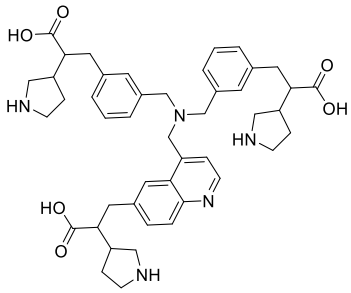
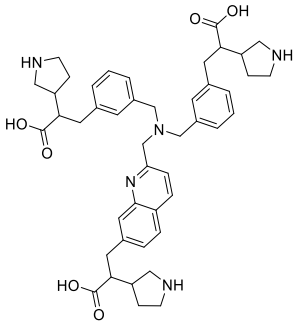
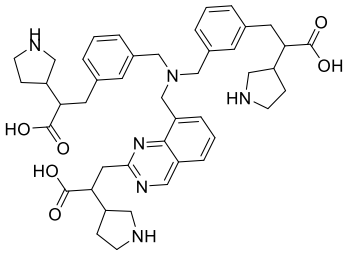
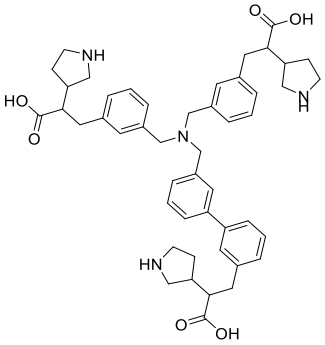
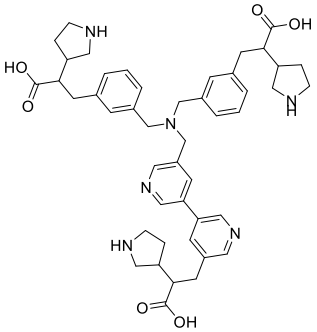
R^a is deuterium, halogen, -CN, -OH, -NH_2, -CHO, C_{1-3} alkyl, C_{1-3} alkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), or -C(O)C_{1-3} alkyl; or R^a is fluorine, chlorine, methyl, ethyl, methoxy, or ethoxy; or R^a is F or methoxy;

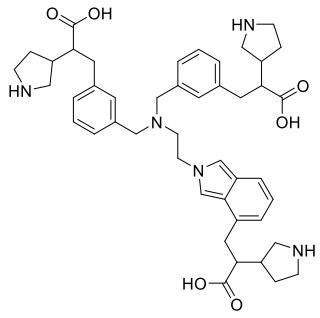
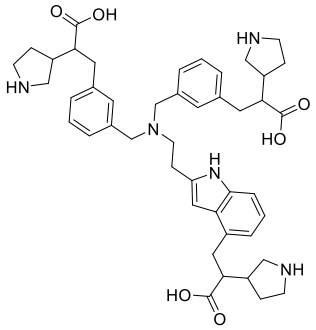
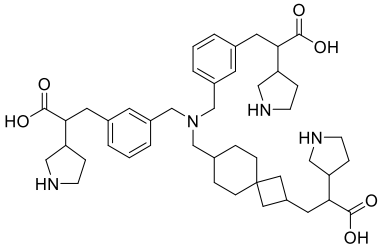
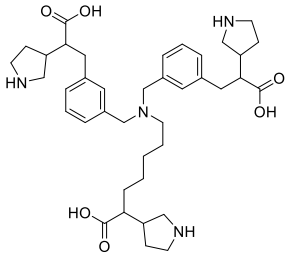
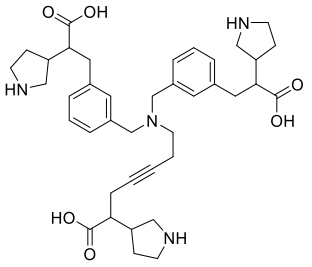
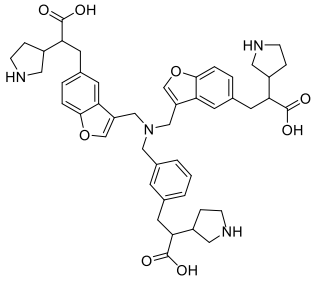
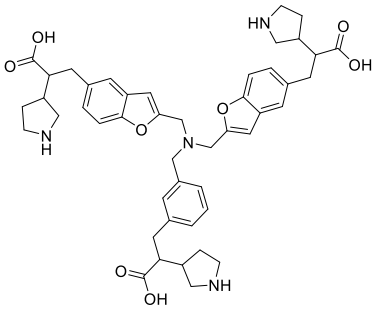
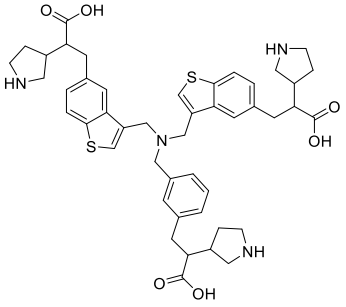
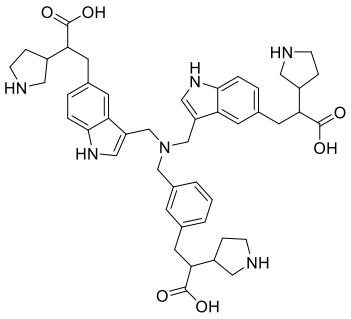
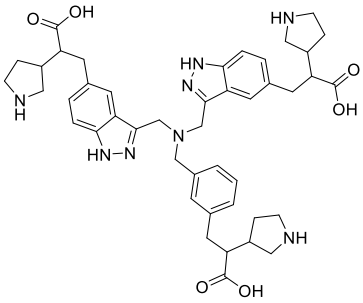
each of R_{13}, R_{14}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} is independently selected from H and deuterium.

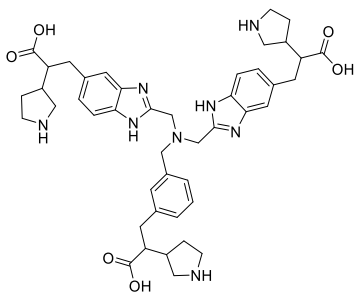
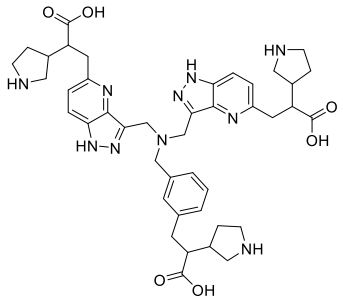
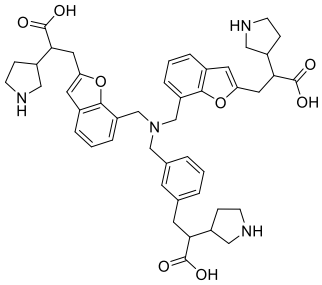
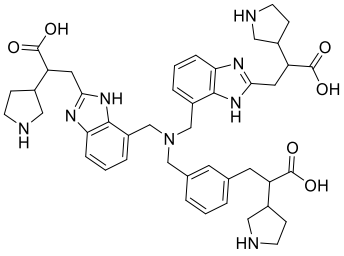
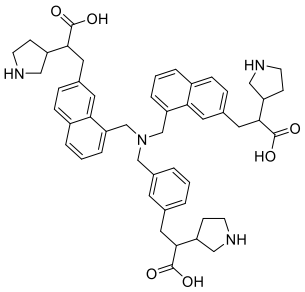
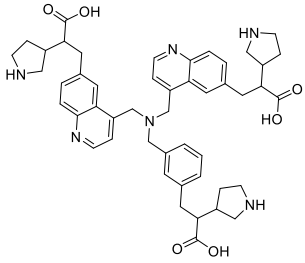
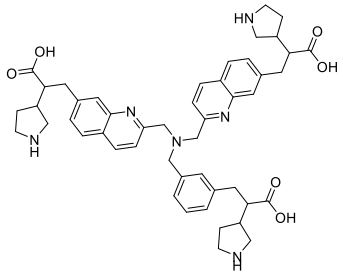
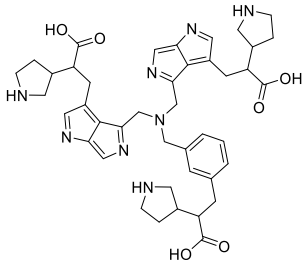
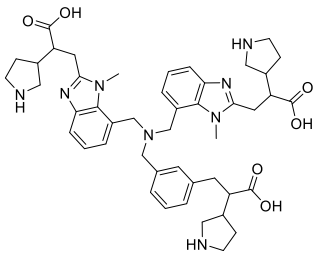
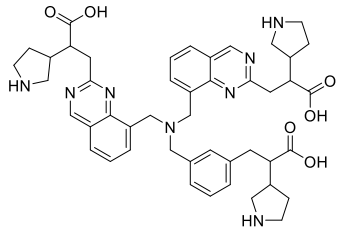
11. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

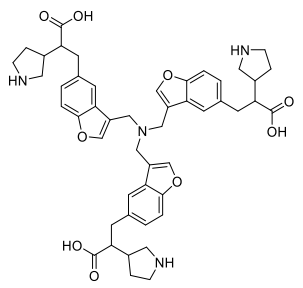
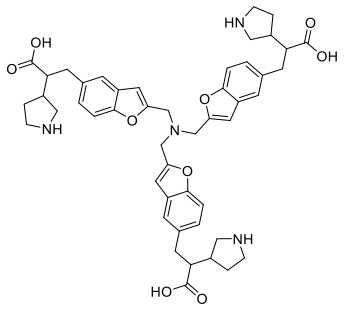
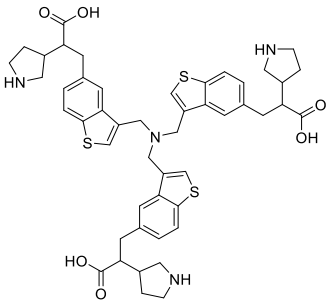
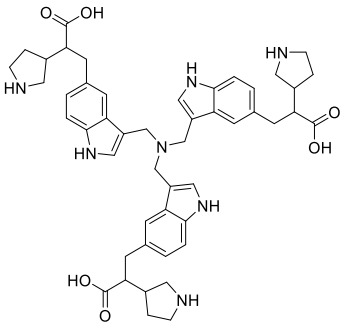
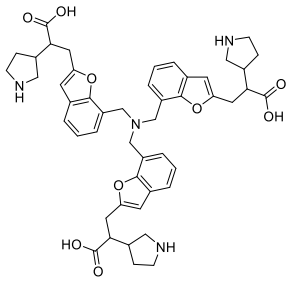
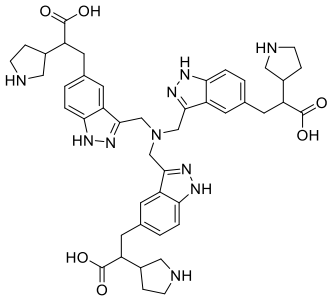
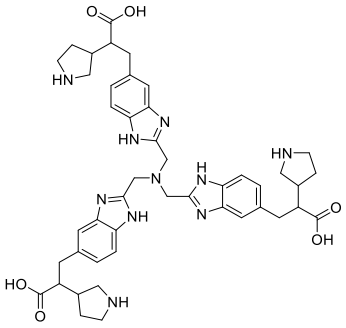
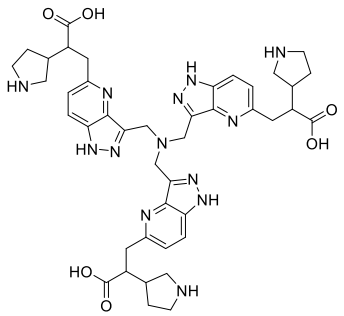
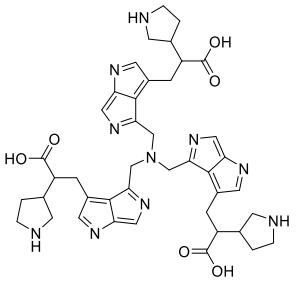
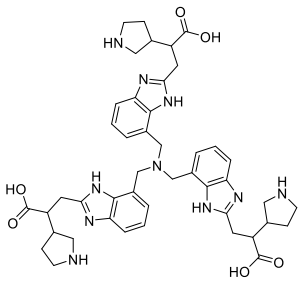
Compound No.	Compound structure	Compound No.	Compound structure
1-a		2-a	
3-a		4-a	
5-a		6-a	
7-a		8-a	

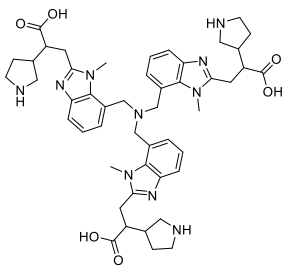
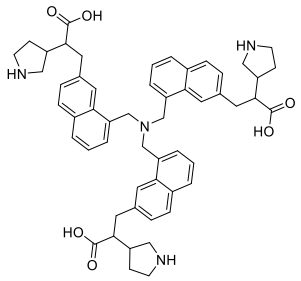
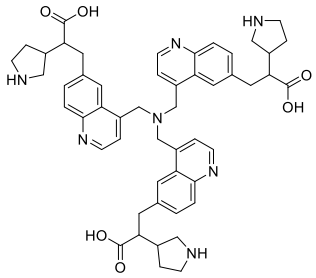
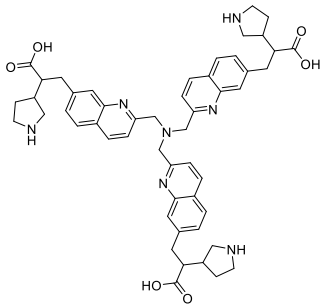
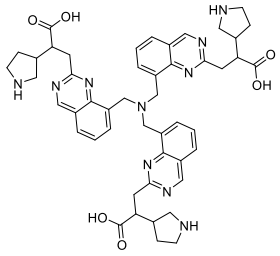
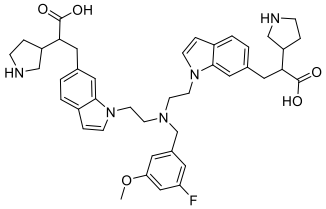
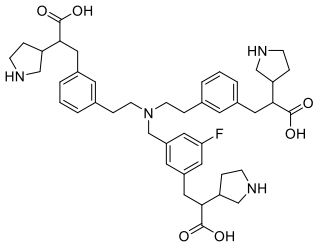
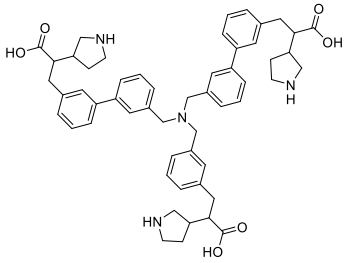
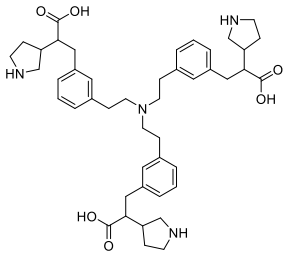
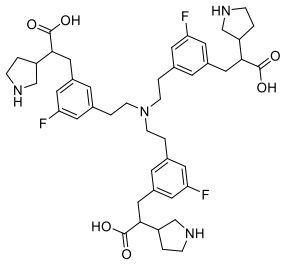
Compound No.	Compound structure	Compound No.	Compound structure
9-a		10-a	
11-a		12-a	
13-a		14-a	
15-a		16-a	
17-a		18-a	

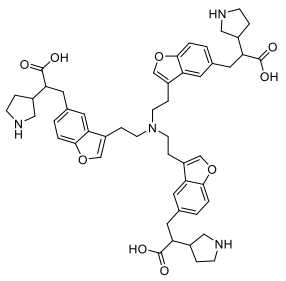
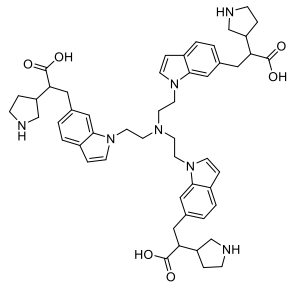
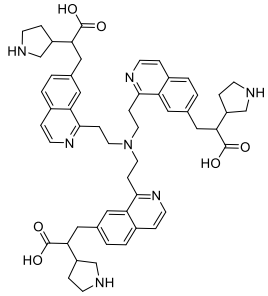
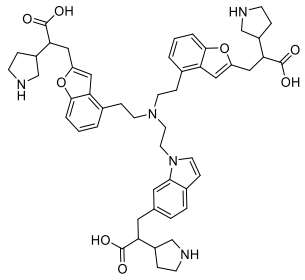
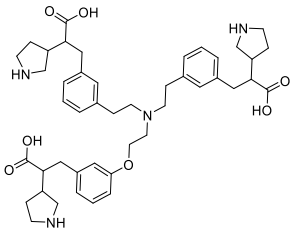
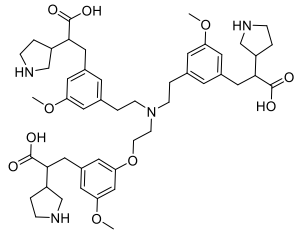
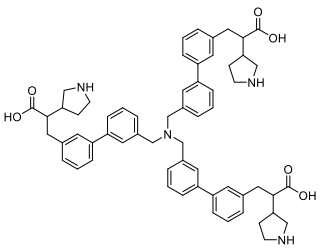
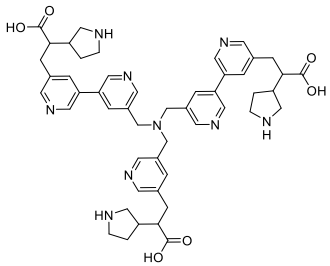
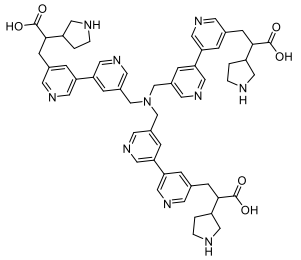
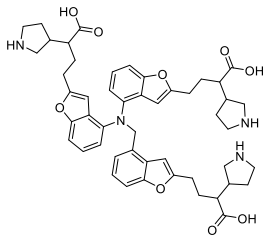
Compound No.	Compound structure	Compound No.	Compound structure
19-a		20-a	
21-a		22-a	
23-a		24-a	
25-a		26-a	

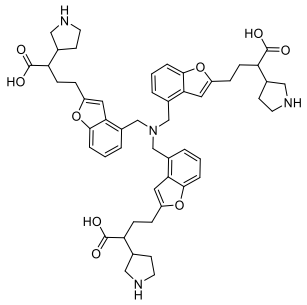
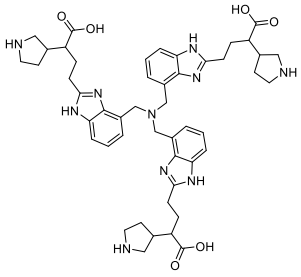
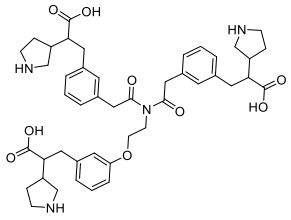
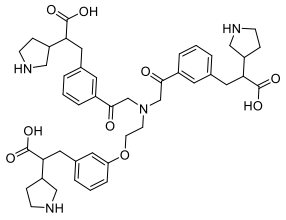
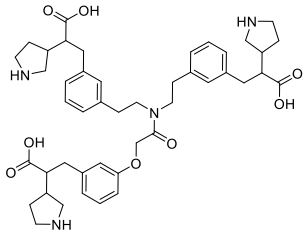
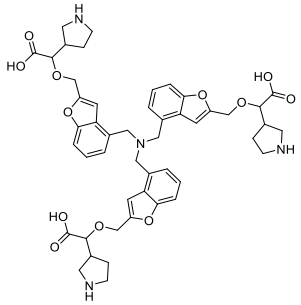
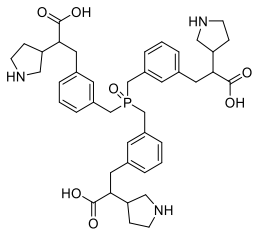
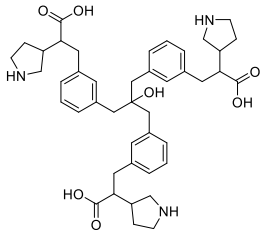
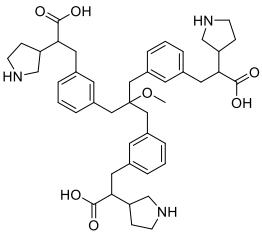
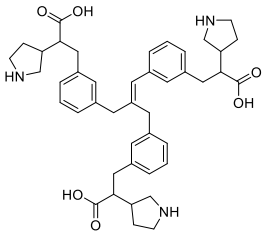
Compound No.	Compound structure	Compound No.	Compound structure
27-a		28-a	
29-a		30-a	
31-a		32-a	
33-a		34-a	
35-a		36-a	

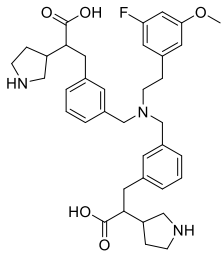
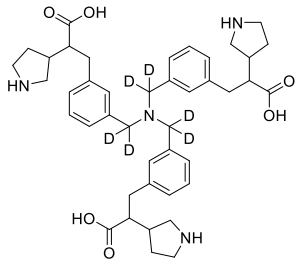
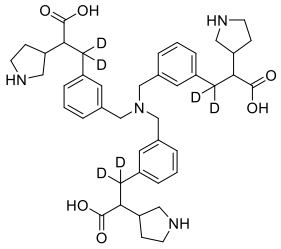
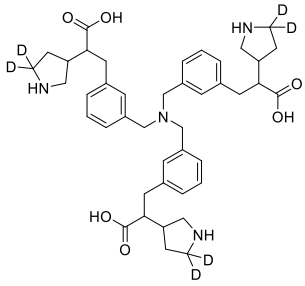
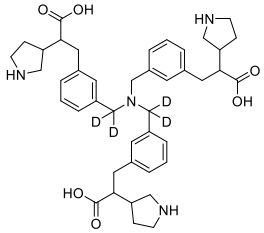
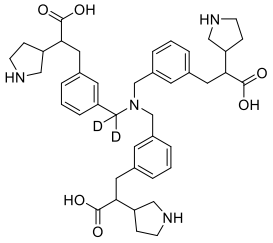
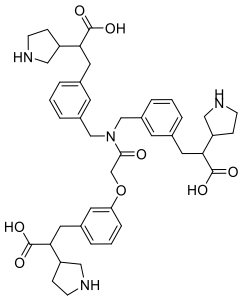
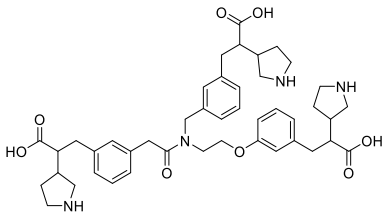
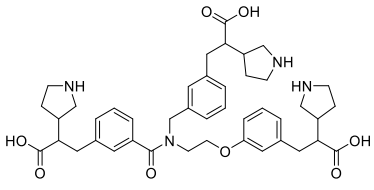
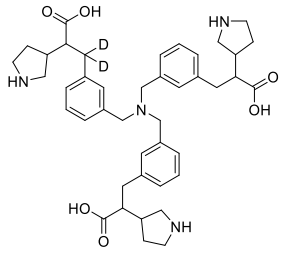
Compound No.	Compound structure	Compound No.	Compound structure
37-a		38-a	
39-a		40-a	
41-a		42-a	
43-a		44-a	
45-a		46-a	

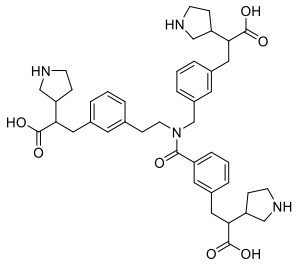
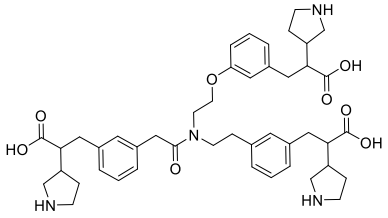
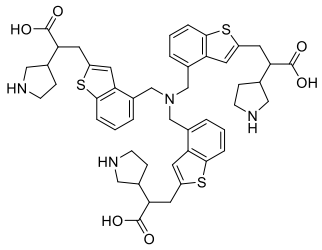
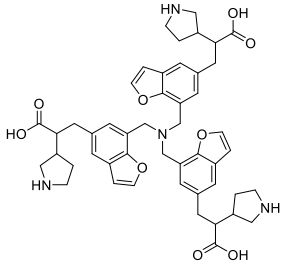
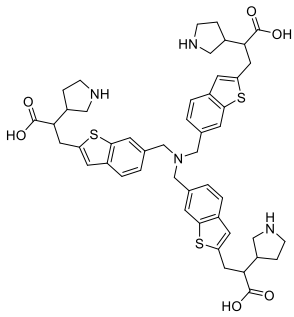
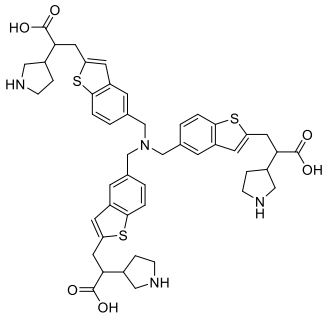
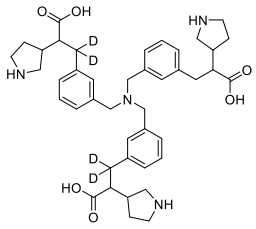
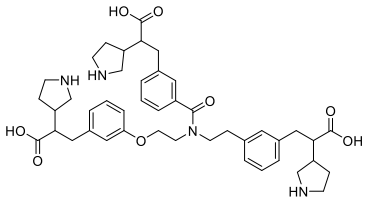
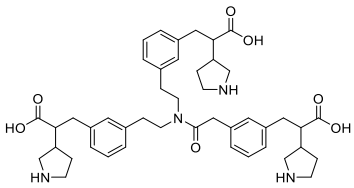
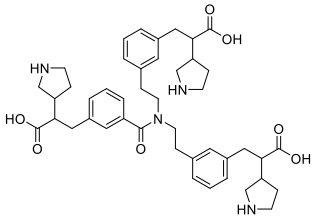
Compound No.	Compound structure	Compound No.	Compound structure
47-a		48-a	
49-a		50-a	
51-a		52-a	
53-a		54-a	
55-a		56-a	

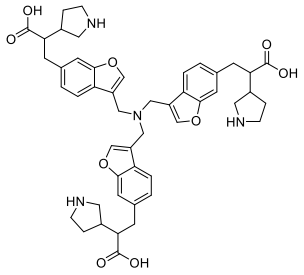
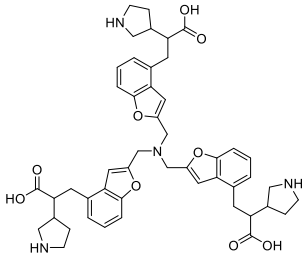
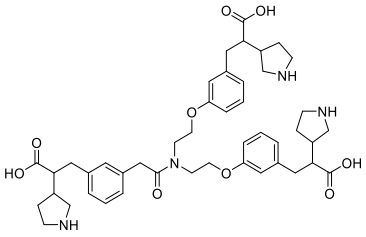
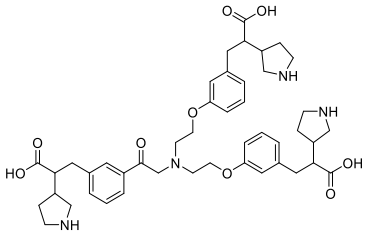
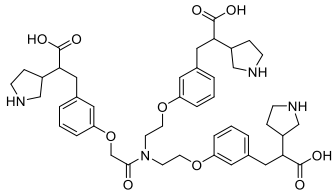
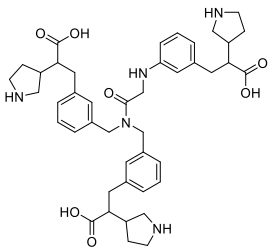
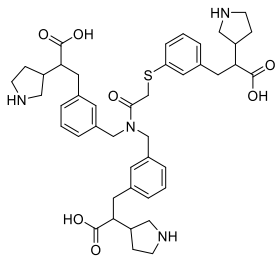
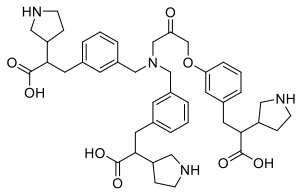
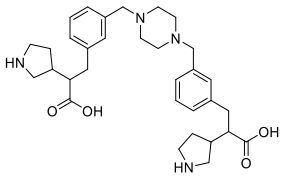
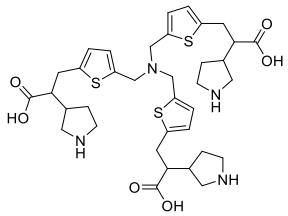
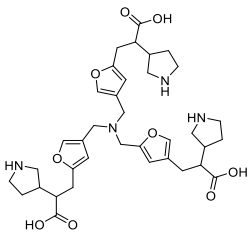
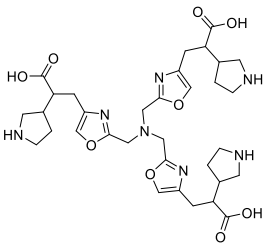
Compound No.	Compound structure	Compound No.	Compound structure
57-a		58-a	
59-a		60-a	
61-a		62-a	
63-a		64-a	
65-a		66-a	

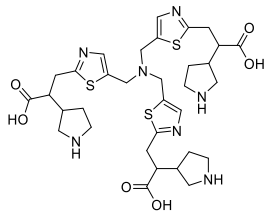
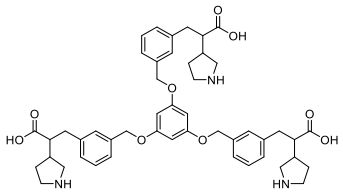
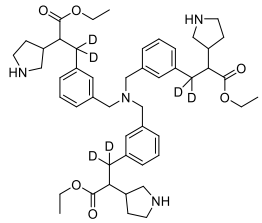
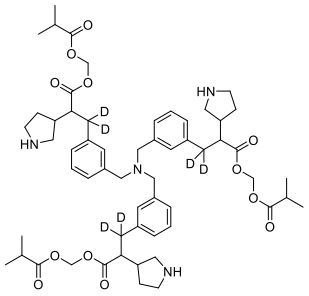
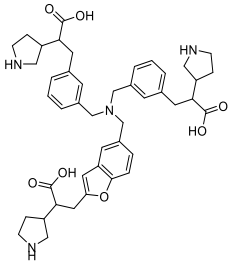
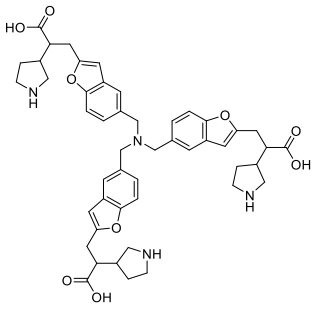
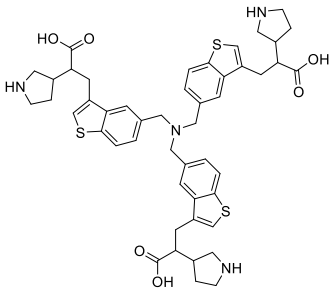
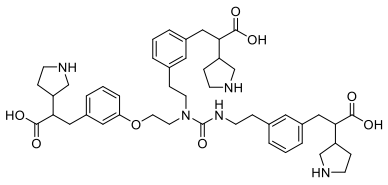
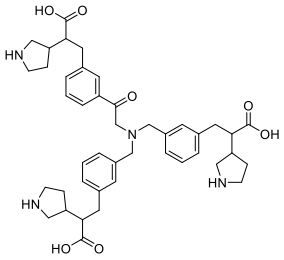
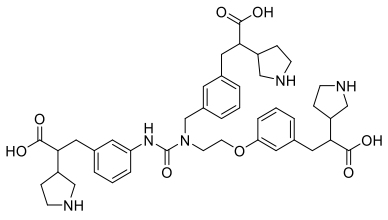
Compound No.	Compound structure	Compound No.	Compound structure
67-a		68-a	
69-a		70-a	
71-a		72-a	
73-a		74-a	
75-a		76-a	

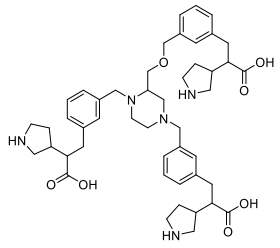
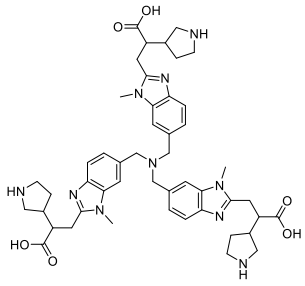
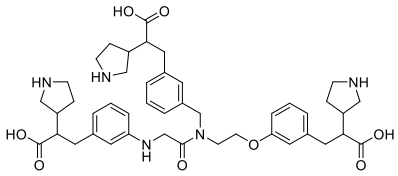
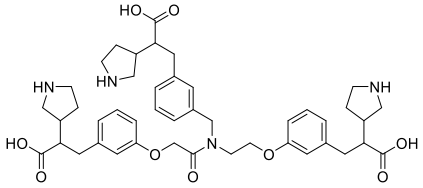
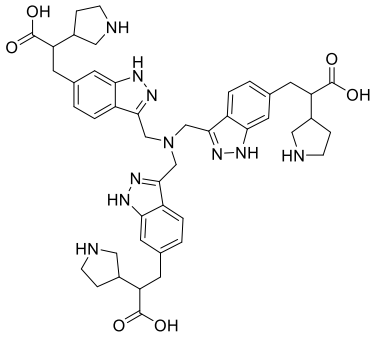
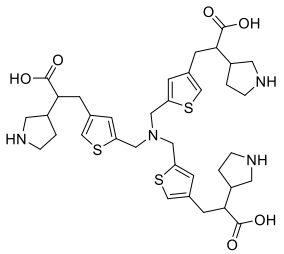
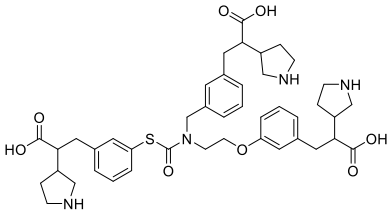
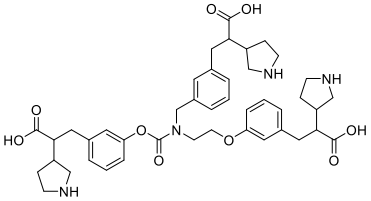
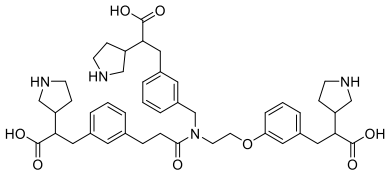
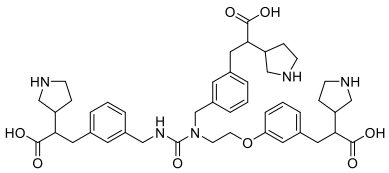
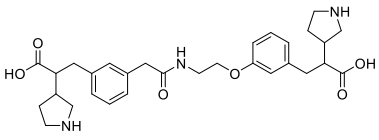
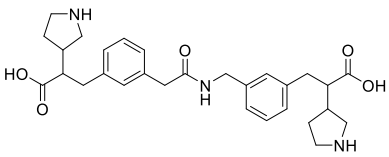
Compound No.	Compound structure	Compound No.	Compound structure
77-a		78-a	
79-a		80-a	
81-a		82-a	
85-a		86-a	
87-a		88-a	

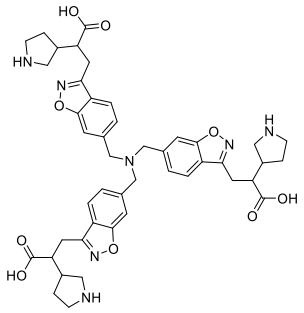
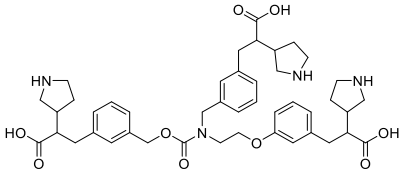
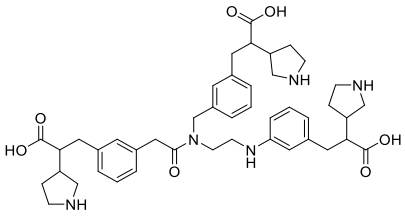
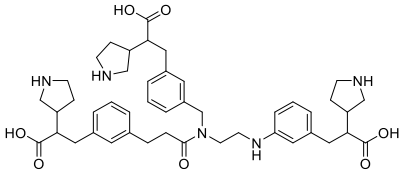
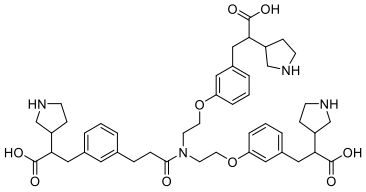
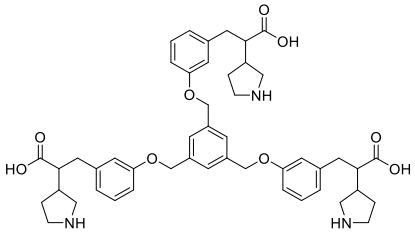
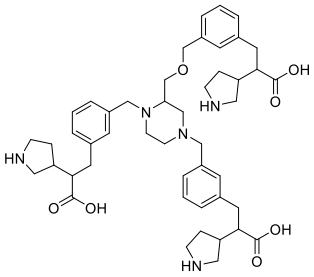
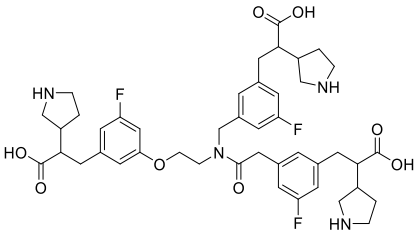
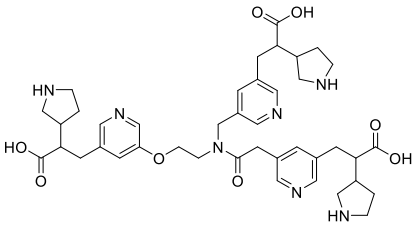
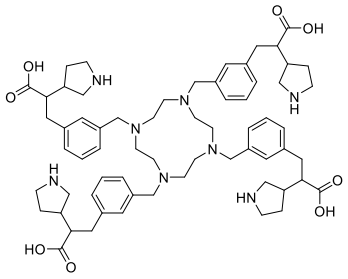
Compound No.	Compound structure	Compound No.	Compound structure
89-a		90-a	
91-a		92-a	
93-a		94-a	
95-a		96-a	
97-a		98-a	

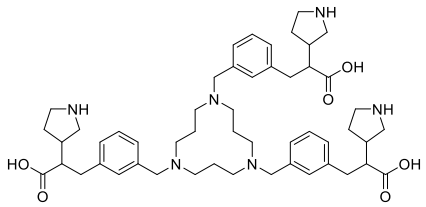
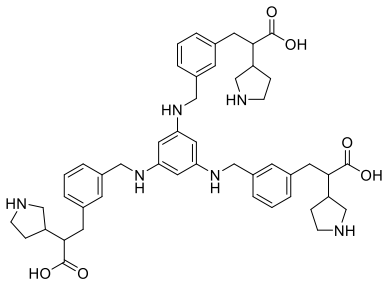
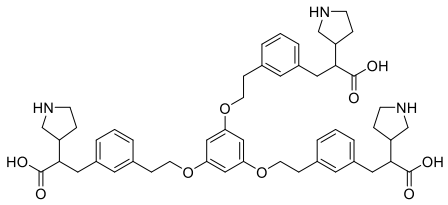
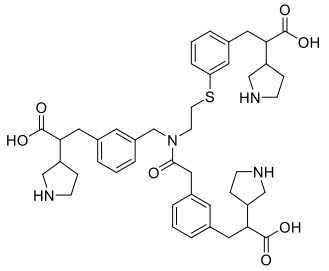
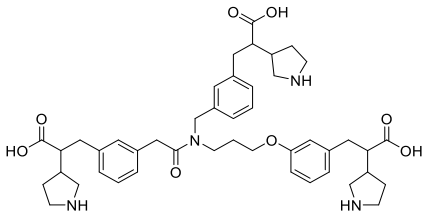
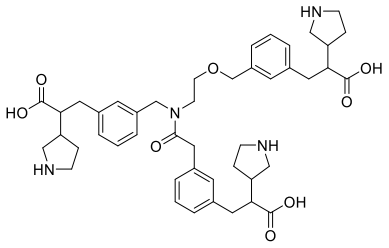
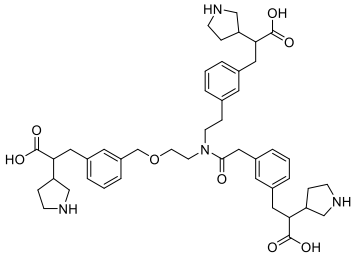
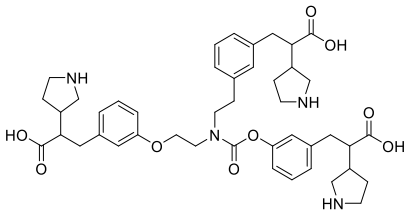
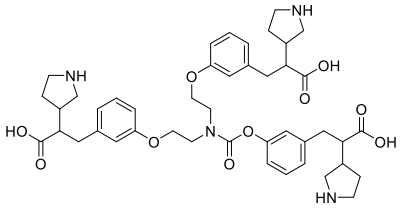
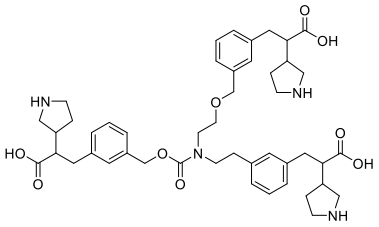
Compound No.	Compound structure	Compound No.	Compound structure
99-a		100-a	
101-a		102-a	
103-a		104-a	
105-a		106-a	
107-a		108-a	

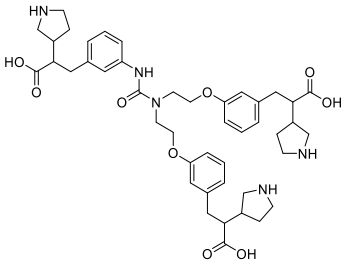
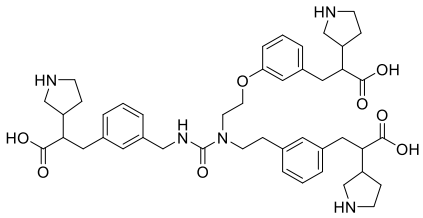
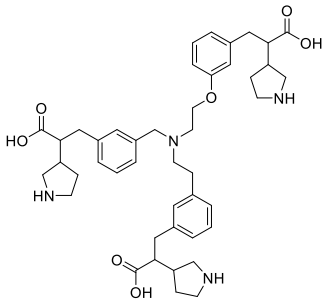
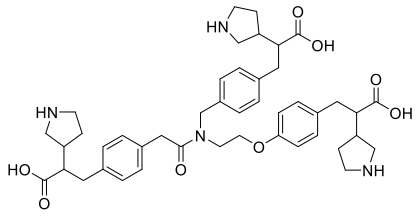
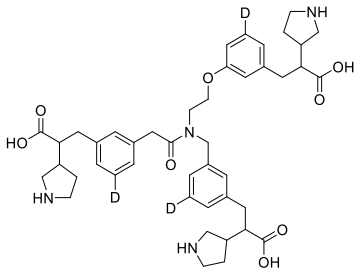
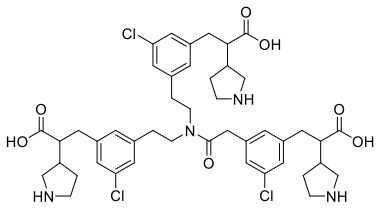
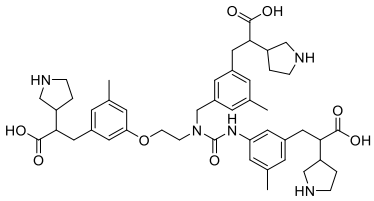
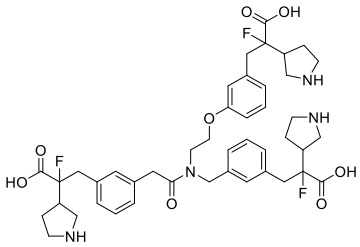
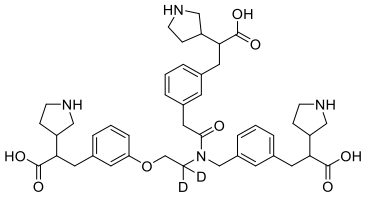
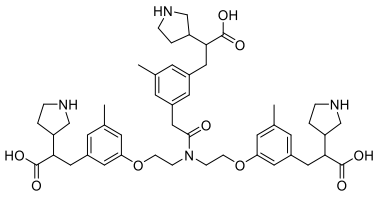
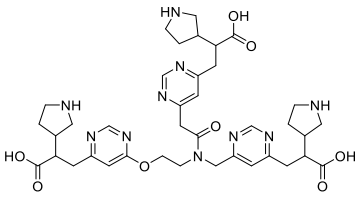
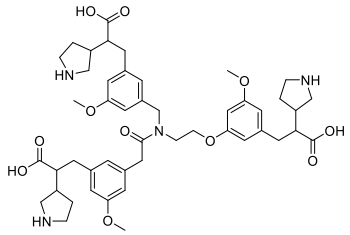
Compound No.	Compound structure	Compound No.	Compound structure
109-a		110-a	
111-a		112-a	
113-a		114-a	
115-a		116-a	
117-a		118-a	
119-a		120-a	

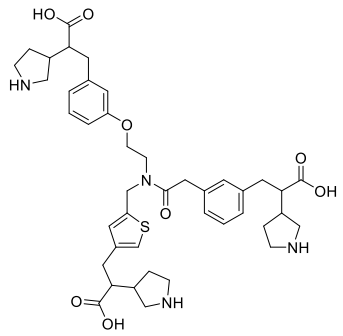
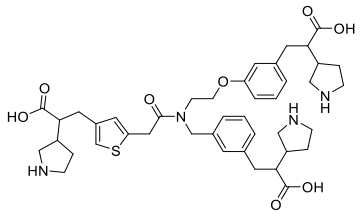
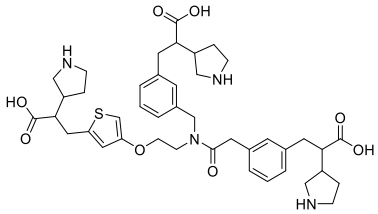
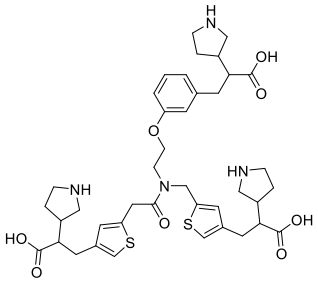
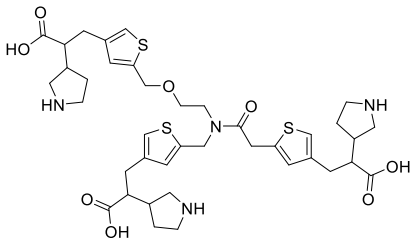
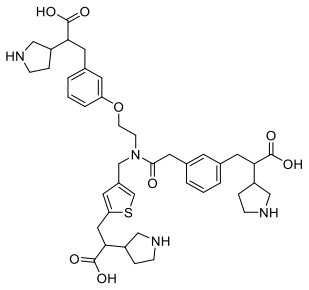
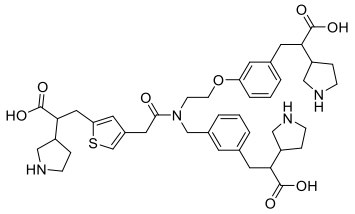
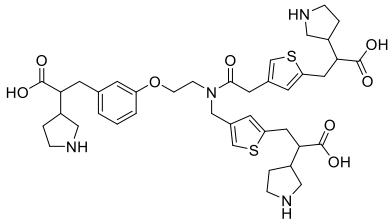
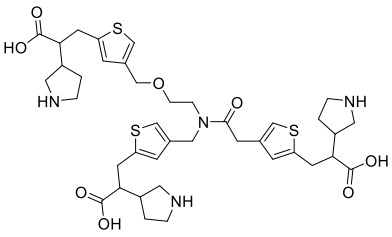
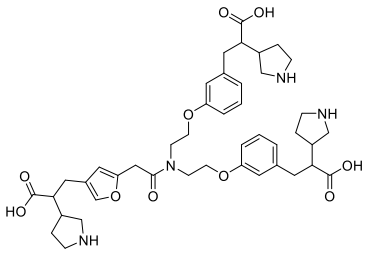
Compound No.	Compound structure	Compound No.	Compound structure
121-a		122-a	
123-a		124-a	
126-a		127-a	
128-a		129-a	
130-a		131-a	

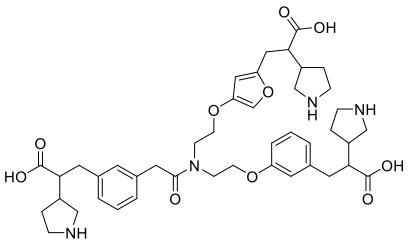
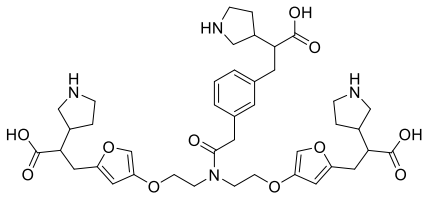
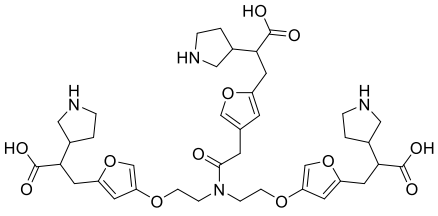
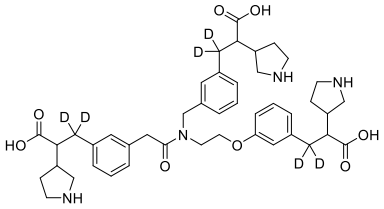
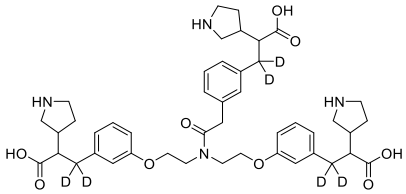
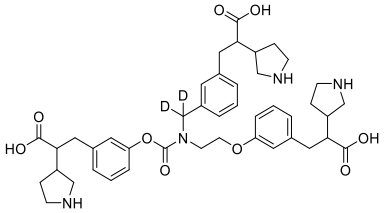
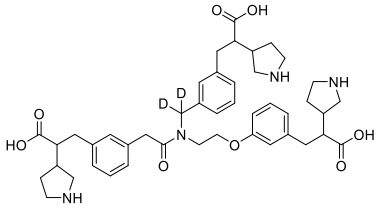
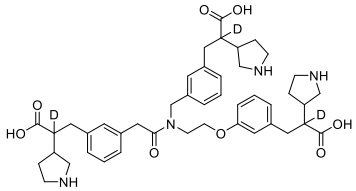
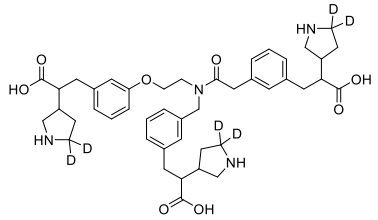
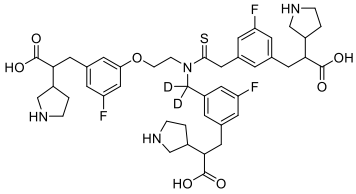
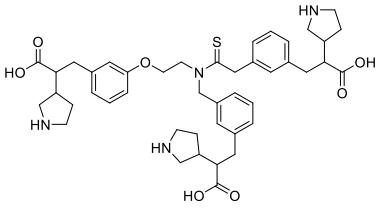
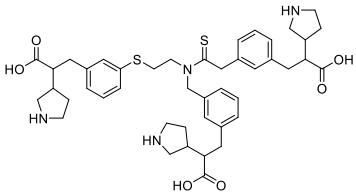
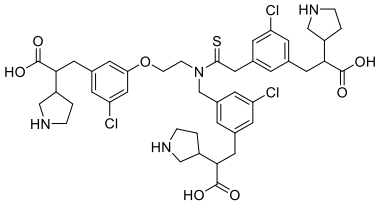
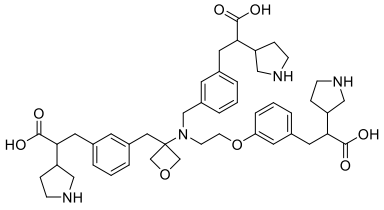
Compound No.	Compound structure	Compound No.	Compound structure
132-a		133-a	
134-a		135-a	
136-a		137-a	
138-a		139-a	
140-a		141-a	
142-a		143-a	

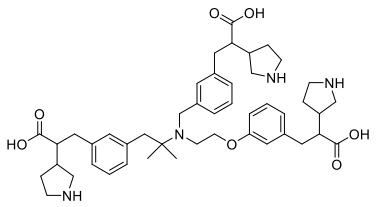
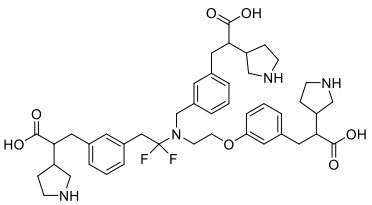
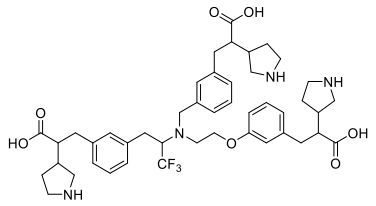
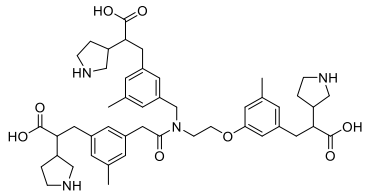
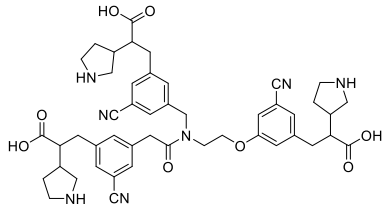
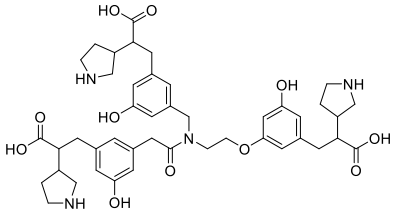
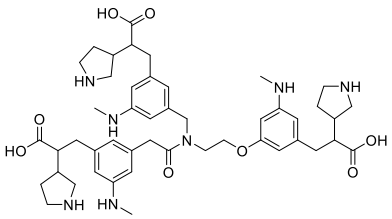
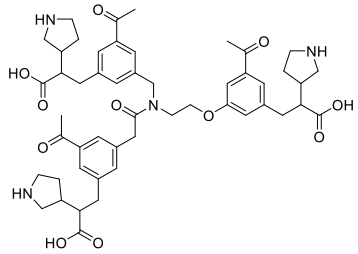
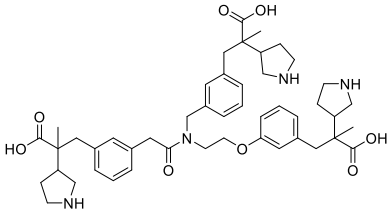
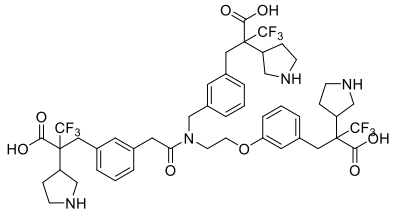
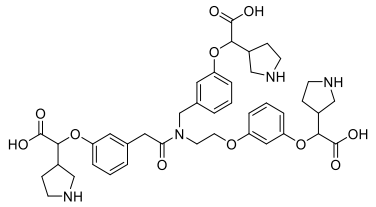
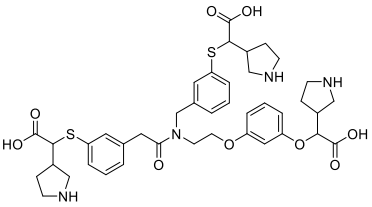
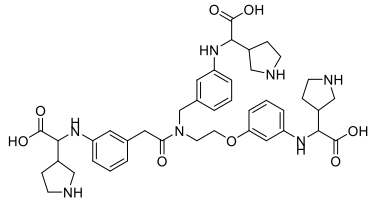
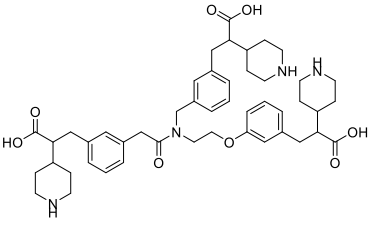
Compound No.	Compound structure	Compound No.	Compound structure
144-a		145	
146-a		147-a	
148-a		149-a	
150-a		152-a	
153-a		154-a	

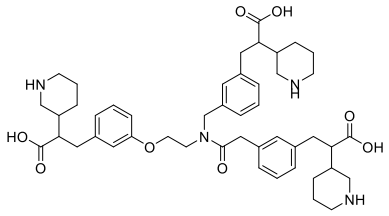
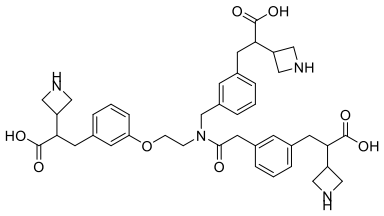
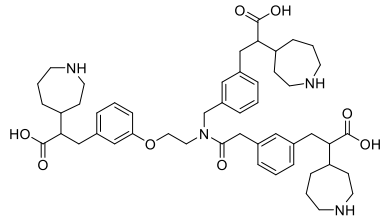
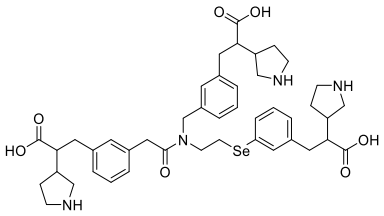
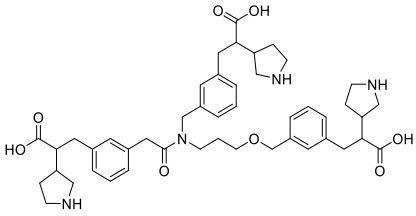
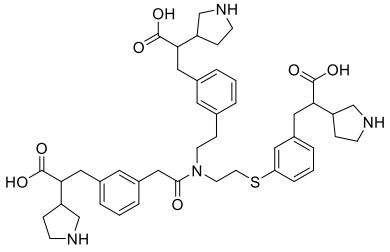
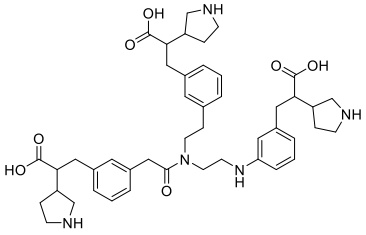
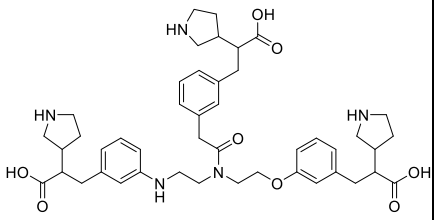
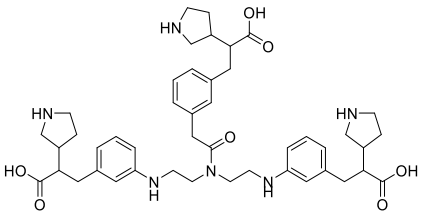
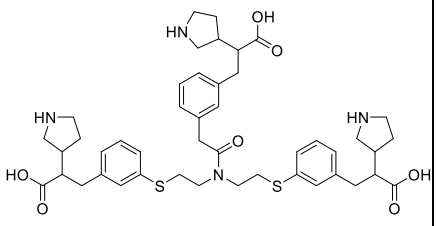
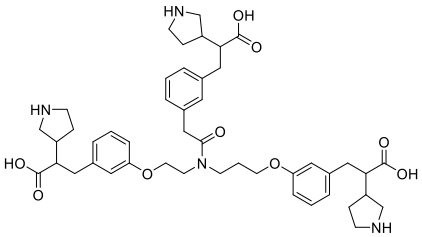
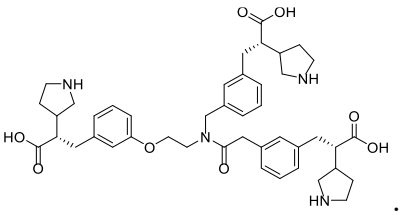
Compound No.	Compound structure	Compound No.	Compound structure
155-a		156-a	
157-a		158-a	
159-a		160-a	
161-a		162-a	
163-a		164-a	

Compound No.	Compound structure	Compound No.	Compound structure
165-a		166-a	
167-a		168-a	
169-a		170-a	
171-a		172-a	
173-a		174-a	
175-a		176-a	

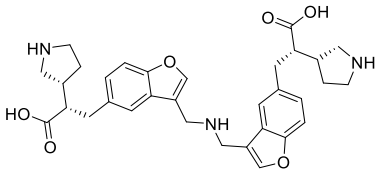
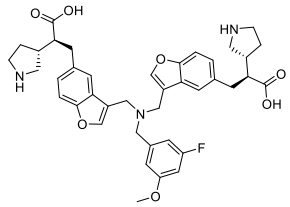
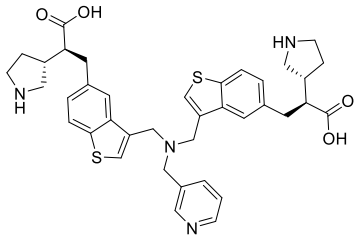
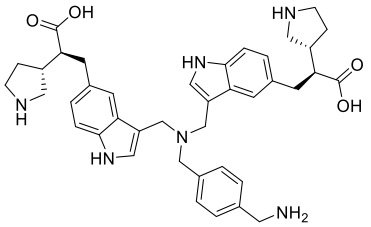
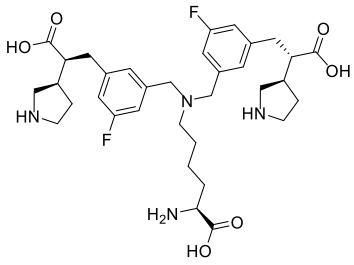
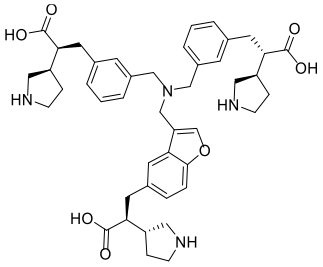
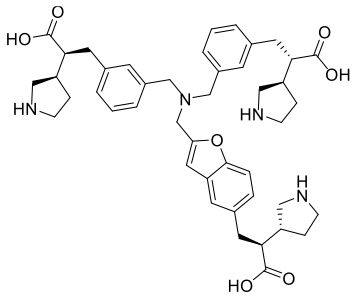
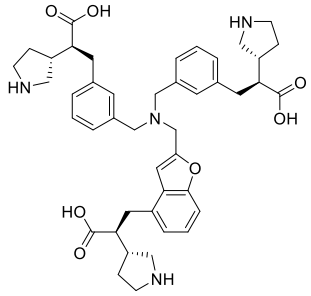
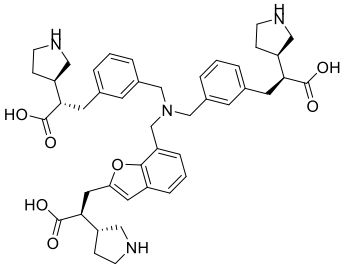
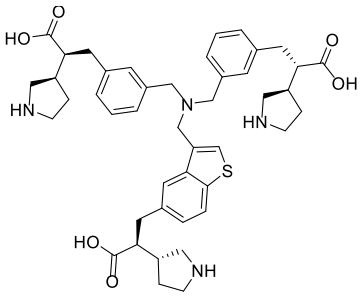
Compound No.	Compound structure	Compound No.	Compound structure
177-a		178-a	
179-a		180-a	
181-a		182-a	
183-a		184-a	
185-a		186-a	

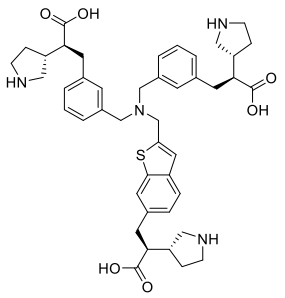
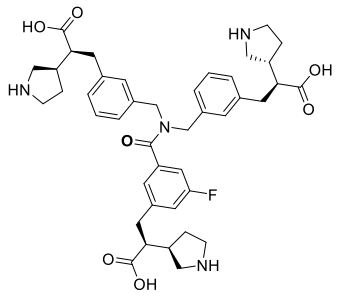
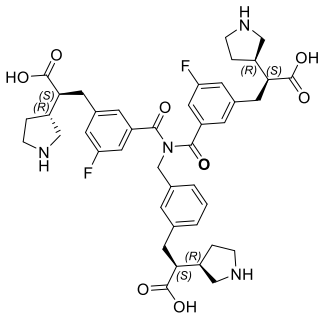
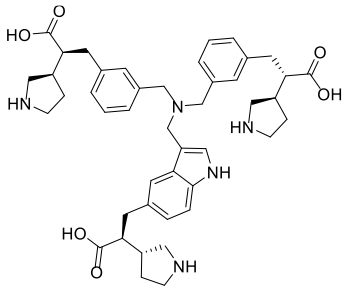
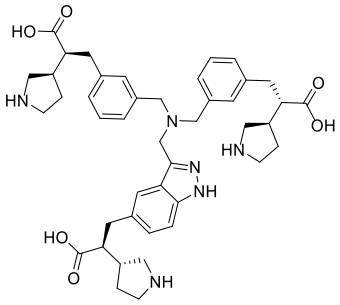
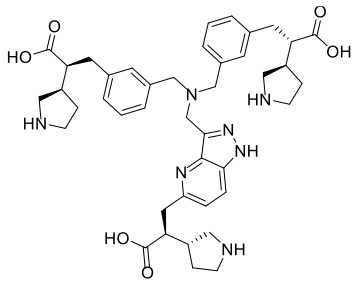
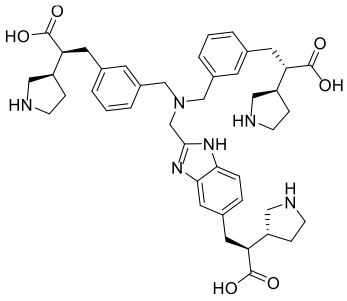
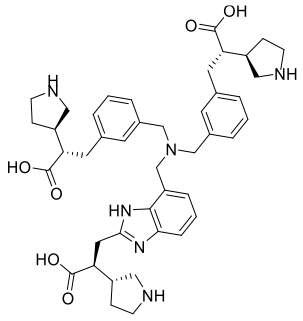
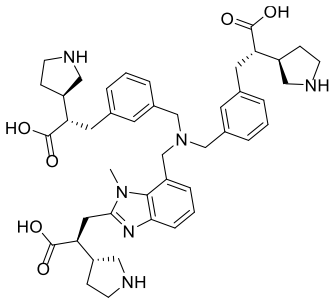
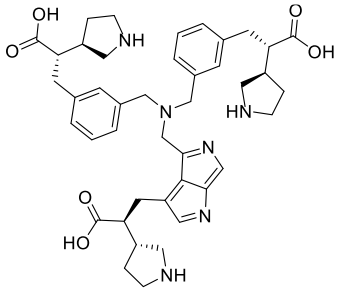
Compound No.	Compound structure	Compound No.	Compound structure
187-a		188-a	
189-a		190-a	
191-a		192-a	
193-a		194-a	
195-a		196-a	
197-a		198-a	
199-a		200-a	

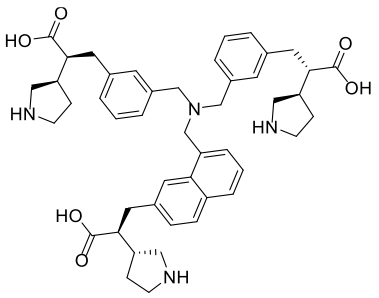
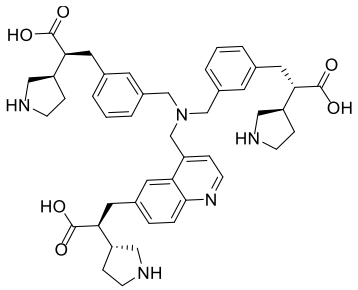
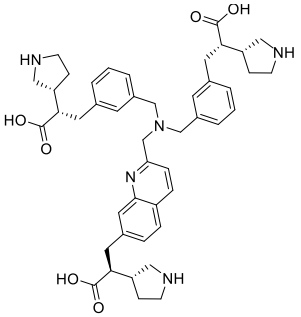
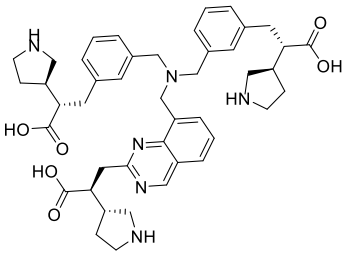
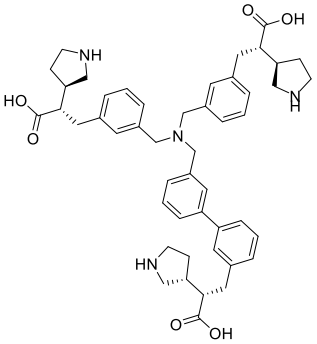
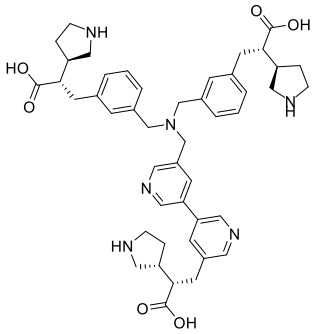
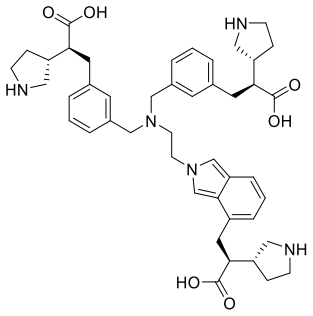
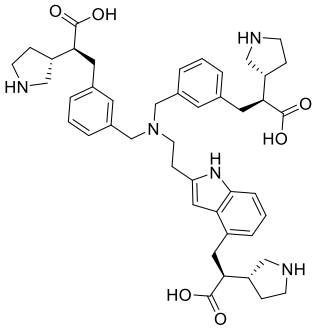
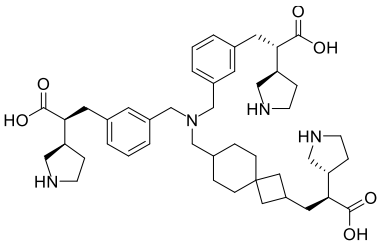
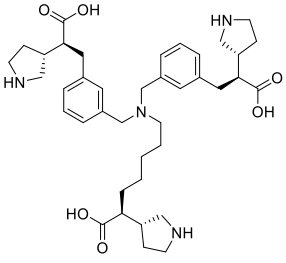
Compound No.	Compound structure	Compound No.	Compound structure
201-a		202-a	
203-a		204-a	
205-a		206-a	
207-a		208-a	
212-a		213-a	
214-a		215-a	
216-a		217-a	

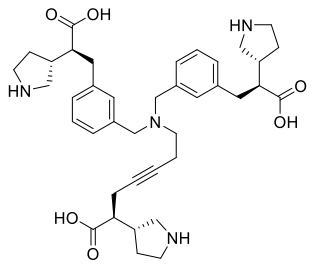
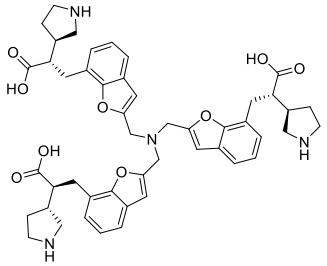
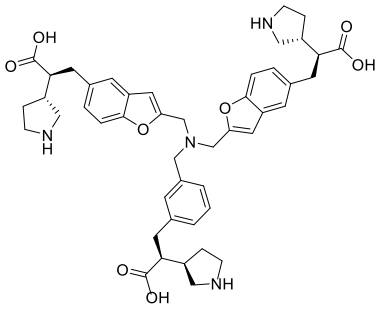
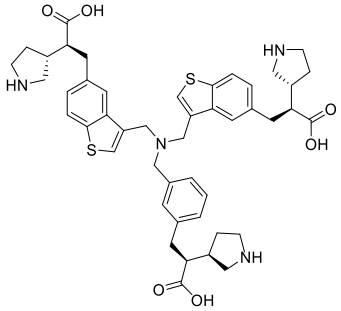
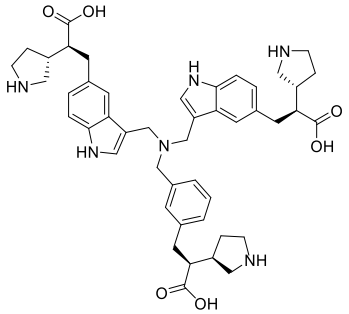
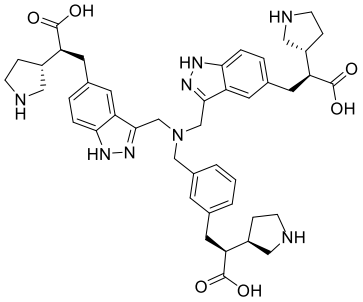
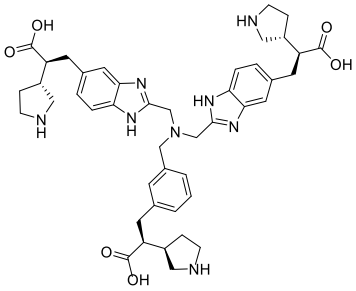
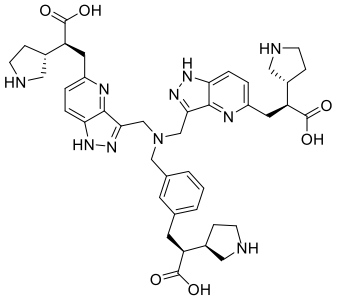
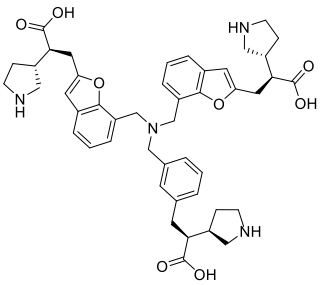
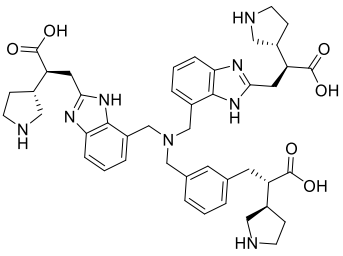
Compound No.	Compound structure	Compound No.	Compound structure
218-a		219-a	
220-a		221-a	
222-a		223-a	
224-a		225-a	
226-a		227-a	
228-a		96-b	

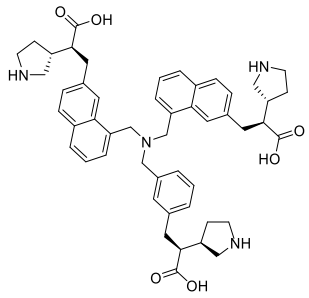
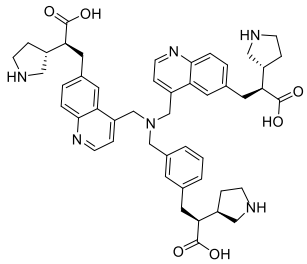
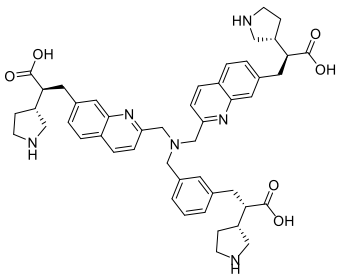
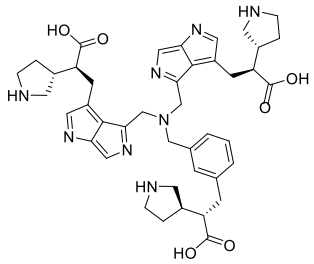
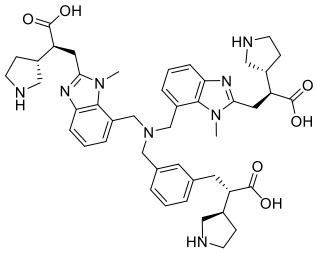
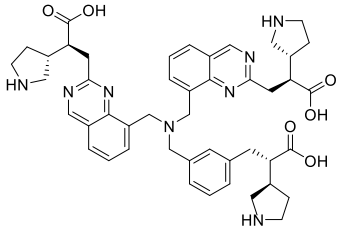
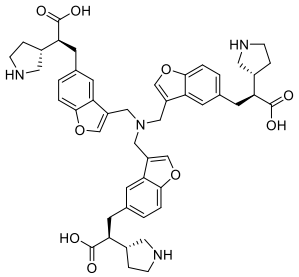
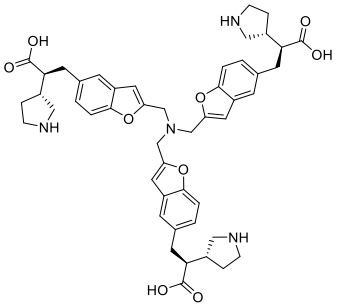
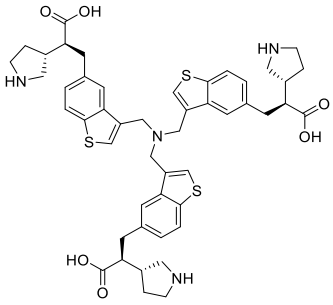
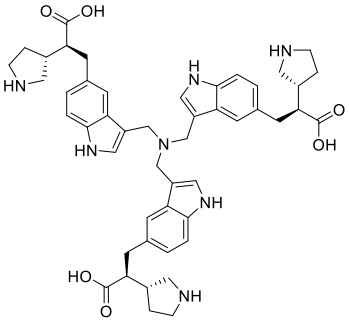
12. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

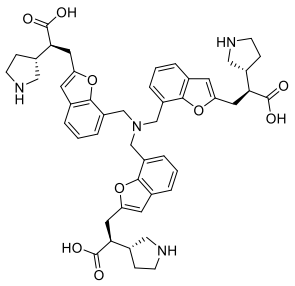
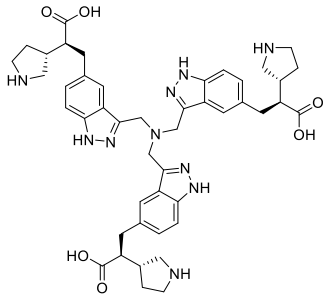
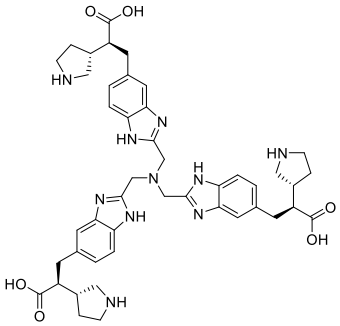
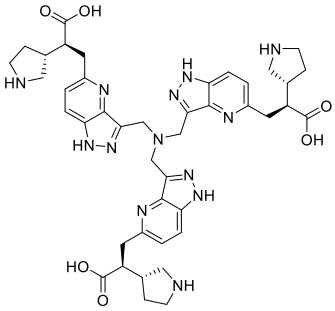
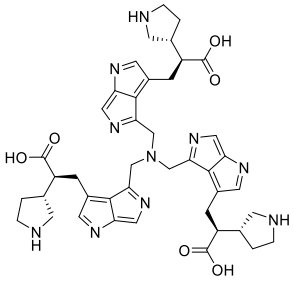
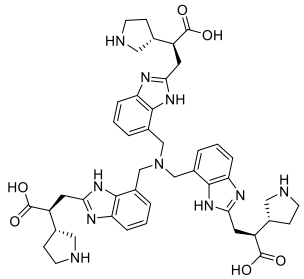
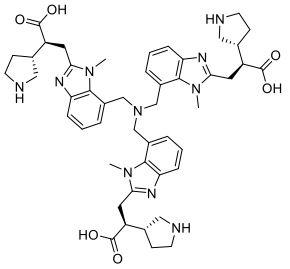
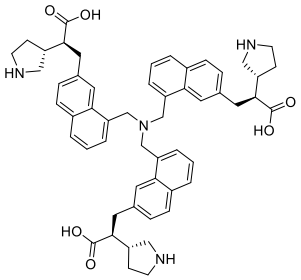
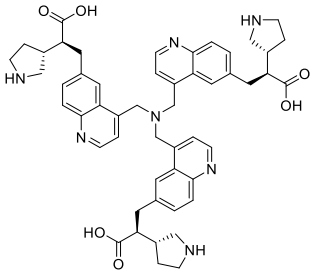
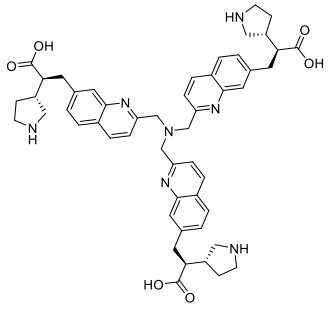
Compound No.	Structure	Compound No.	Structure
1		2	
3		4	
5		6	
7		8	
9		10	

Compound No.	Structure	Compound No.	Structure
11		12	
13		14	
15		16	
17		18	
19		20	

Compound No.	Structure	Compound No.	Structure
21		22	
23		24	
25		26	
27		28	
29		30	

Compound No.	Structure	Compound No.	Structure
31		32	
33		34	
35		36	
37		38	
39		40	

Compound No.	Structure	Compound No.	Structure
41		42	
43		44	
45		46	
47		48	
49		50	

Compound No.	Structure	Compound No.	Structure
51		52	
53		54	
55		56	
57		58	
59		60	

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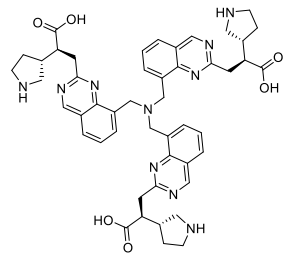
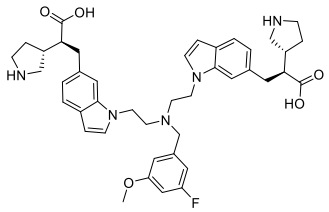
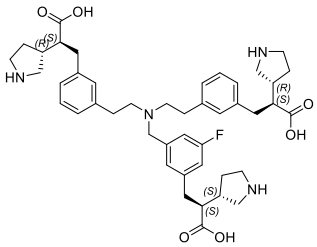
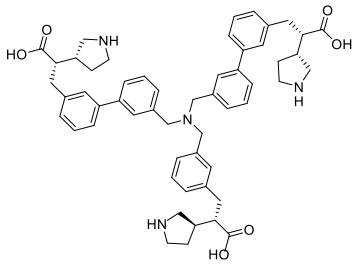
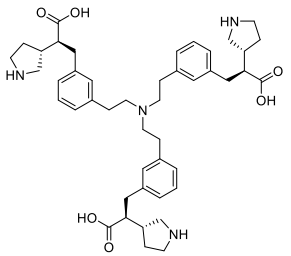
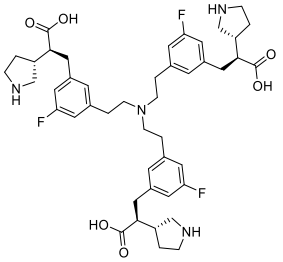
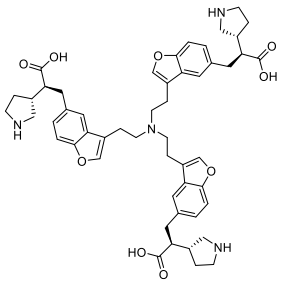
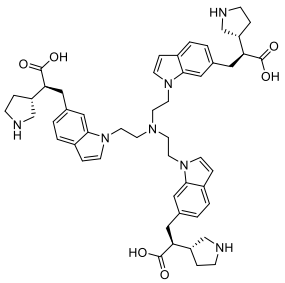
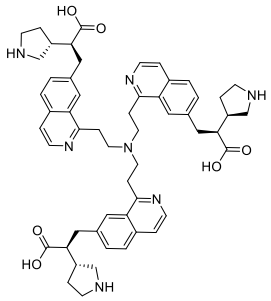
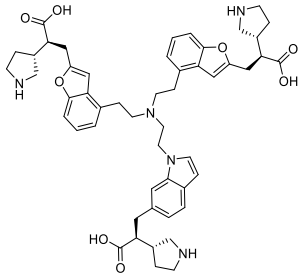
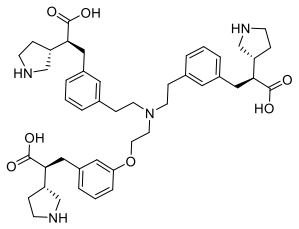
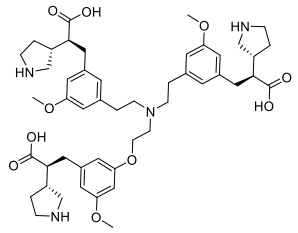
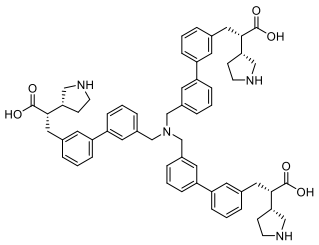
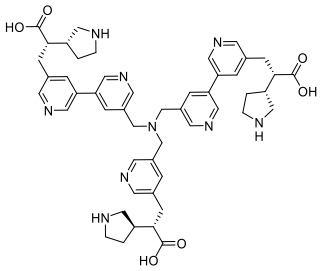
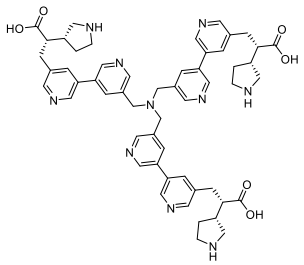
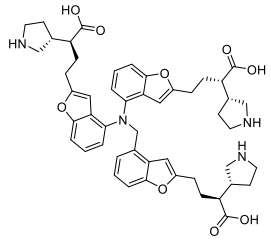
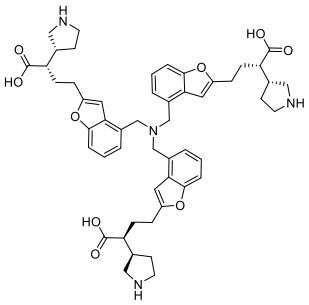
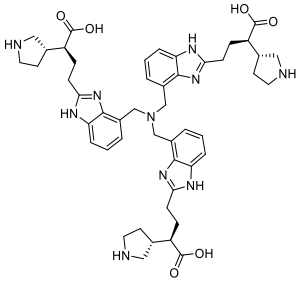
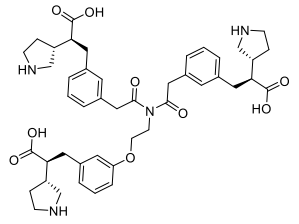
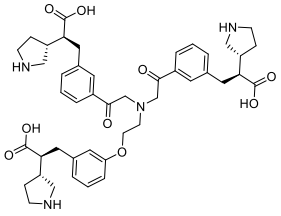
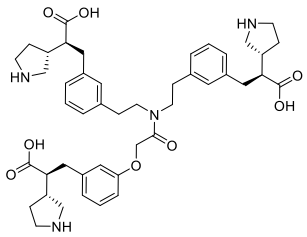
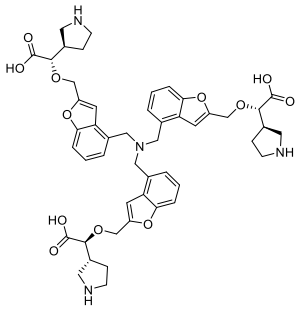
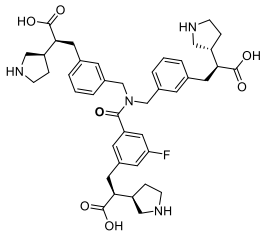
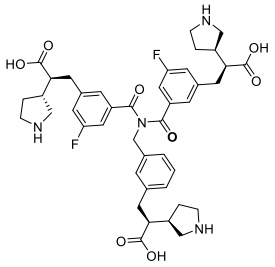
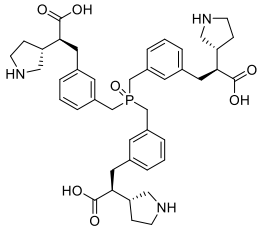
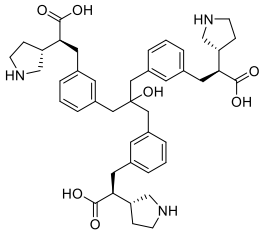
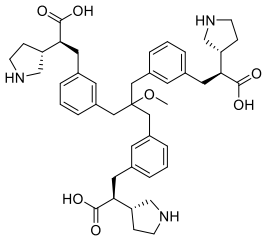
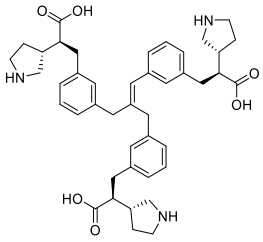
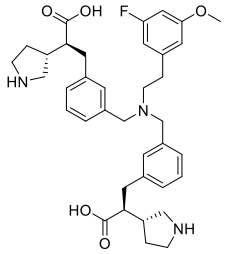
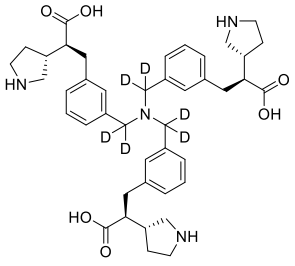
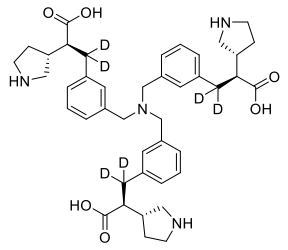
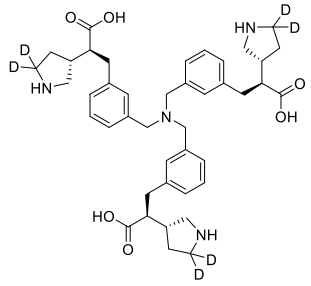
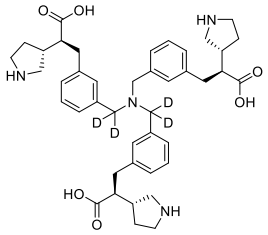
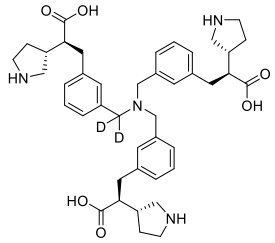
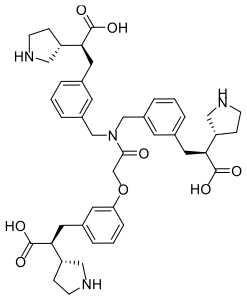
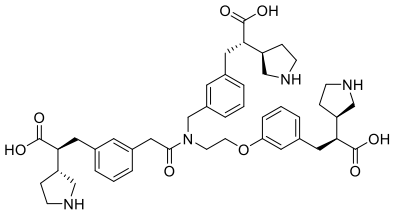
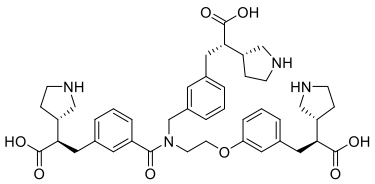
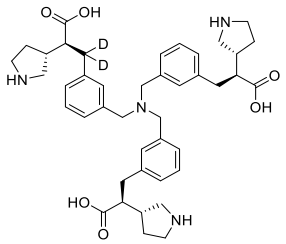
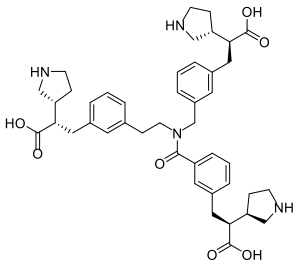
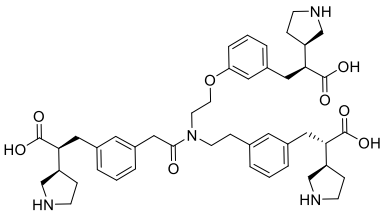
61		62	
63		64	
65		66	
67		68	
69		70	

Compound No.	Structure	Compound No.	Structure
71		72	
73		74	
75		76	
77		78	
79		80	

Compound No.	Structure	Compound No.	Structure
81		82	
83		84	
85		86	
87		88	
89		90	

Compound No.	Structure	Compound No.	Structure
91		92	
93		94	
95		96	
97		98	
99		100	

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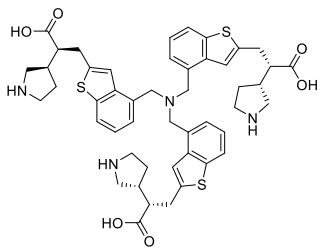
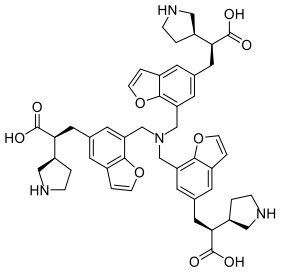
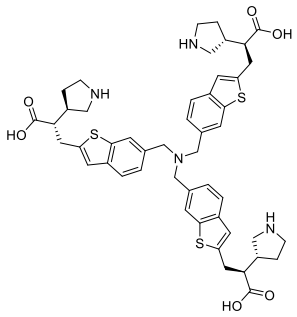
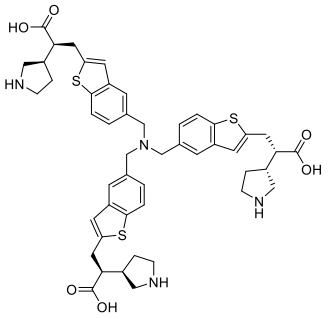
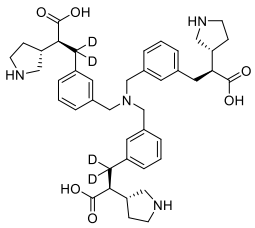
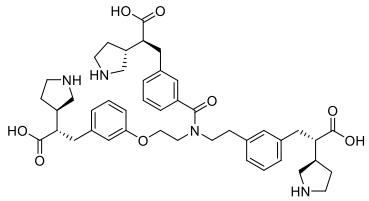
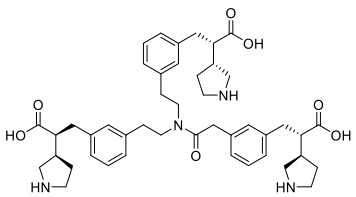
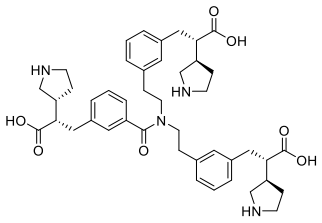
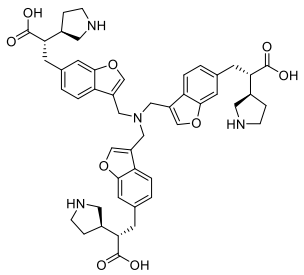
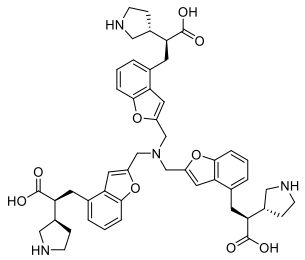
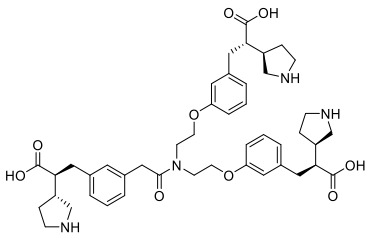
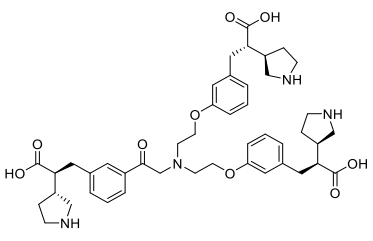
101		102	
103		104	
105		106	
107		108	
109		110	
111		112	

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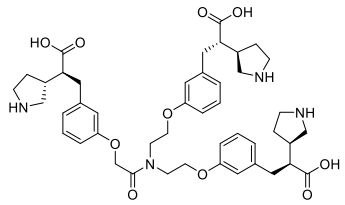
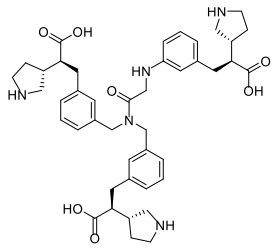
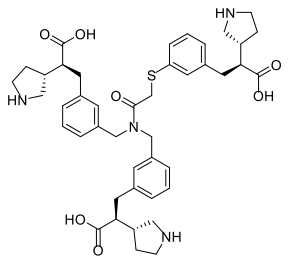
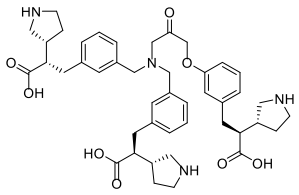
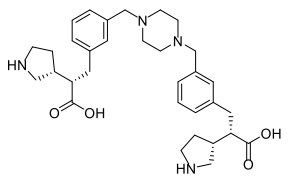
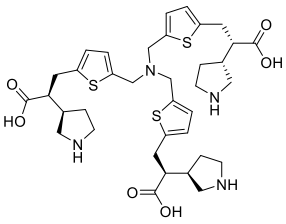
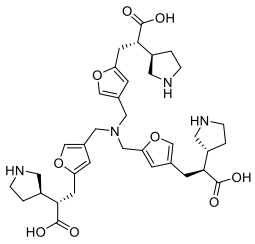
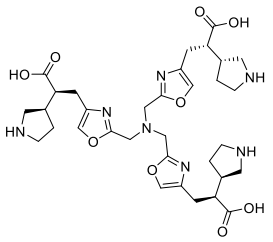
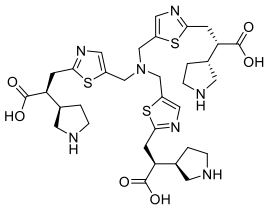
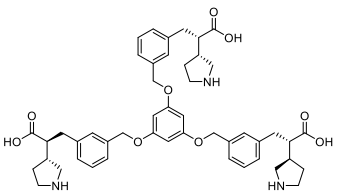
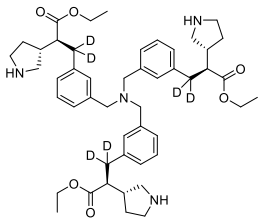
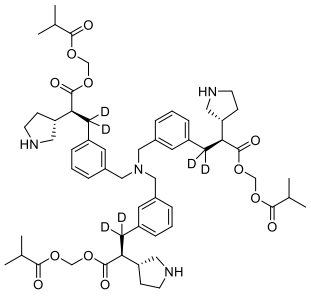
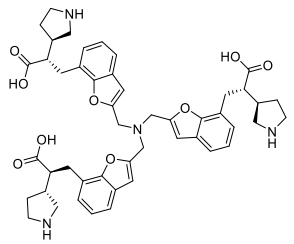
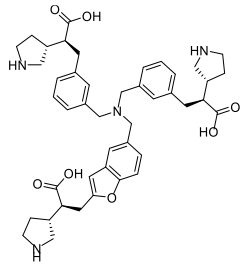
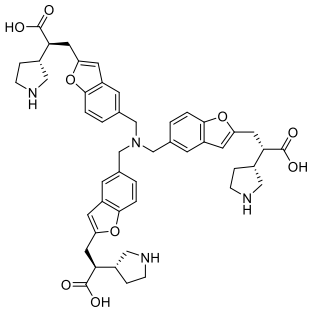
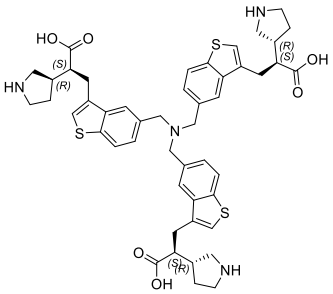
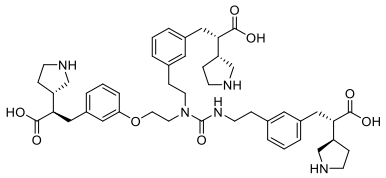
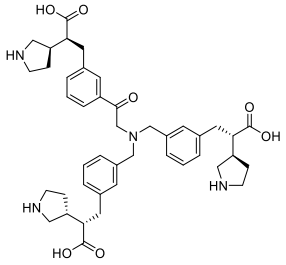
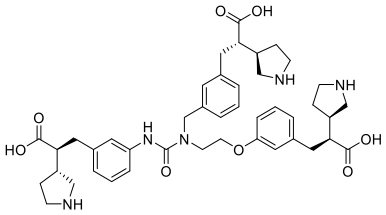
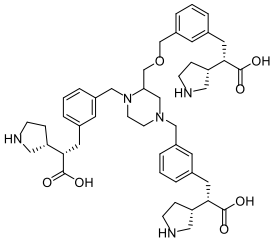
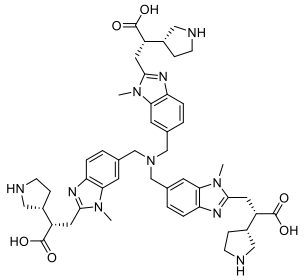
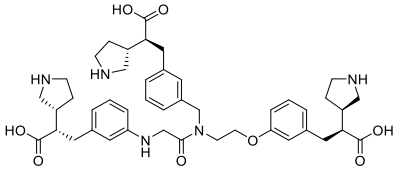
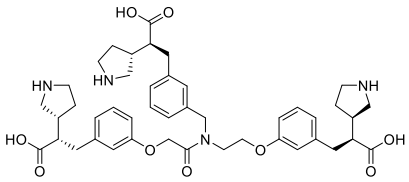
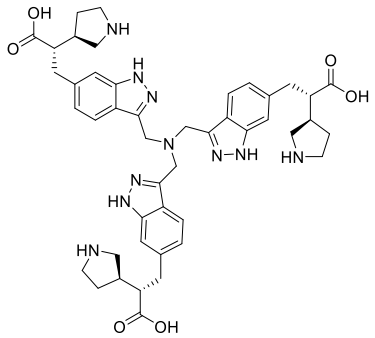
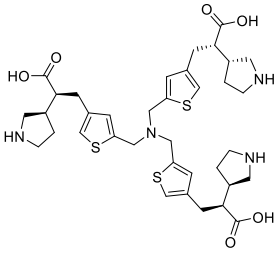
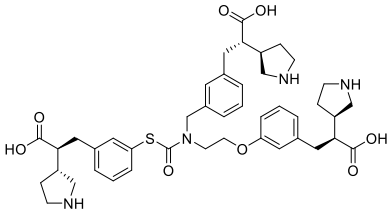
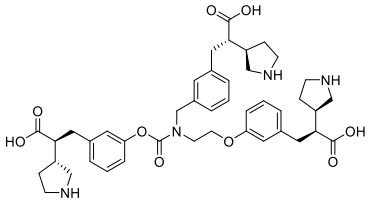
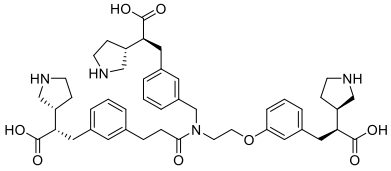
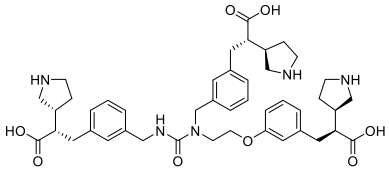
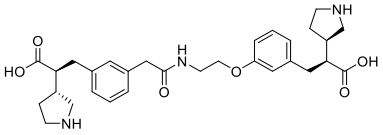
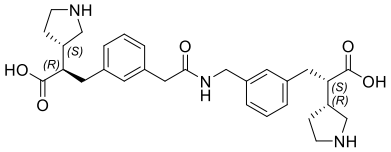
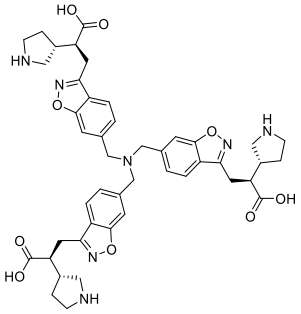
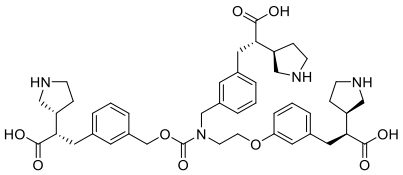
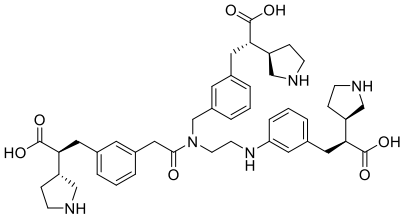
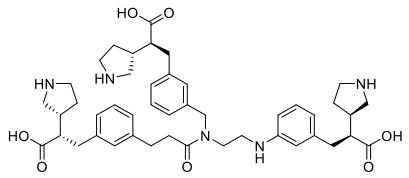
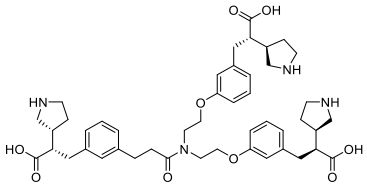
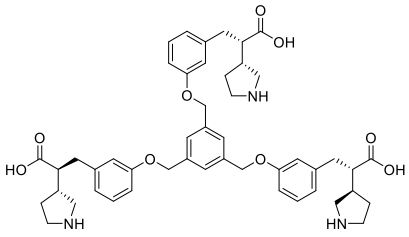
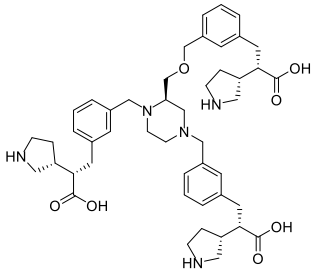
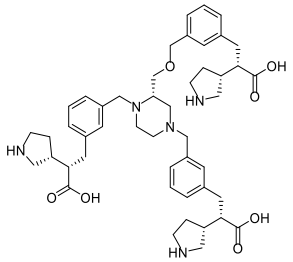
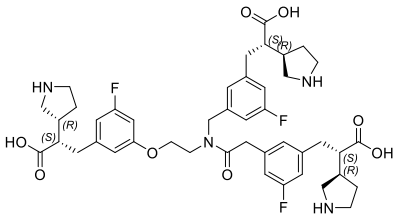
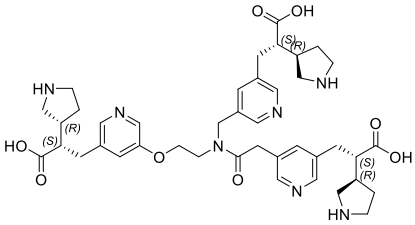
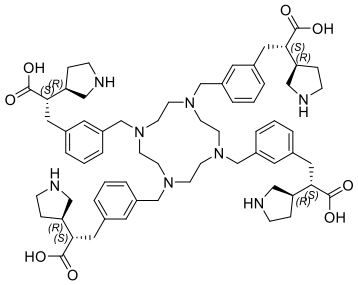
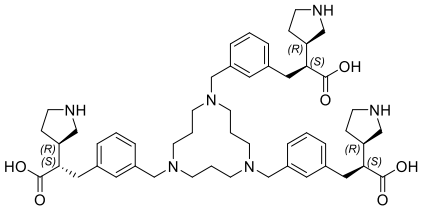
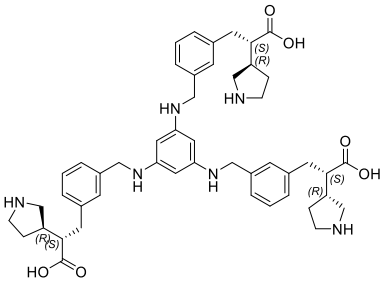
113		114	
115		116	
117		118	
119		120	
121		122	
123		124	

Compound No.	Structure	Compound No.	Structure
125		126	
127		128	
129		130	
131		132	
133		134	

Compound No.	Structure	Compound No.	Structure
135		136	
137		138	
139		140	
141		142	
143		144	
145		146	

Compound No.	Structure	Compound No.	Structure
147		148	
149		150	
151		152	
153		154	
155		156	

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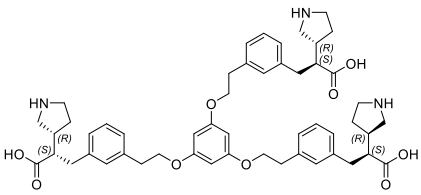
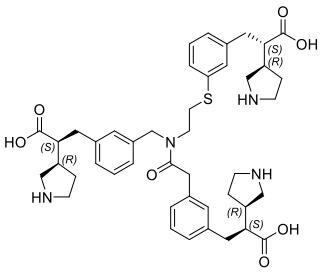
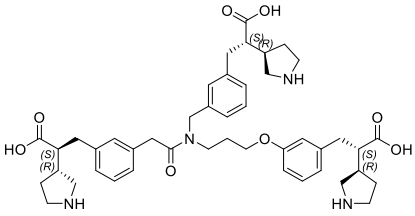
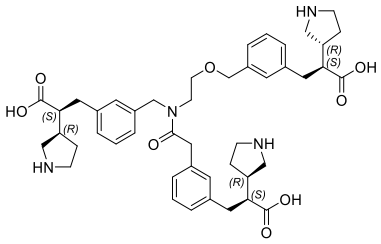
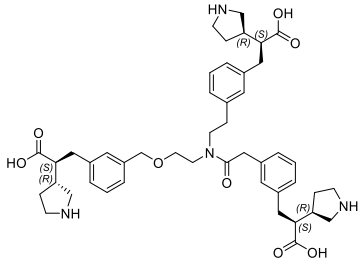
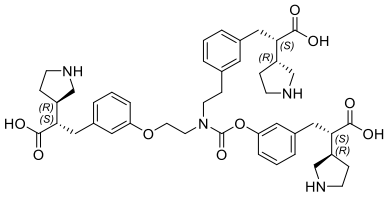
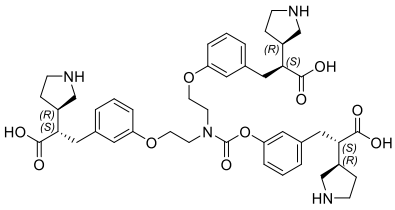
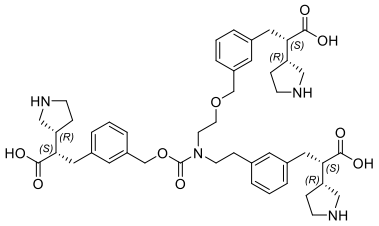
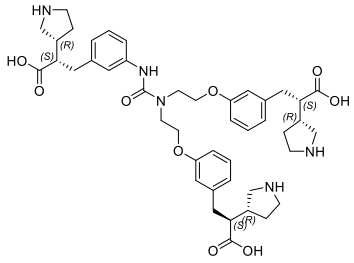
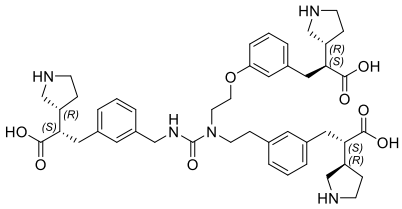
157		158	
159		160	
161		162	
163		164	
165		166	

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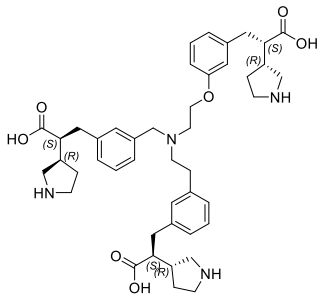
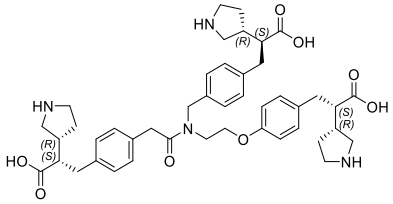
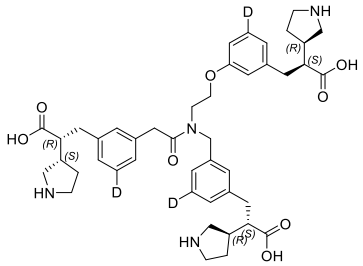
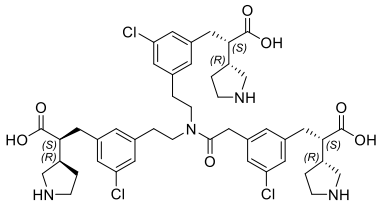
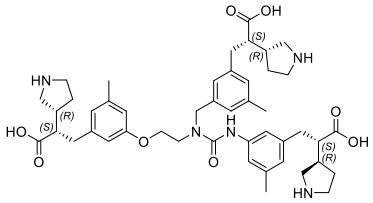
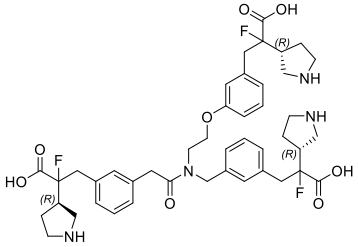
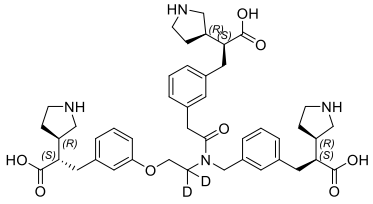
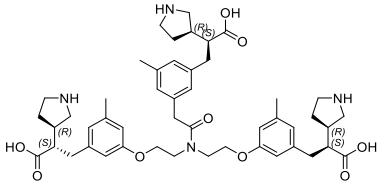
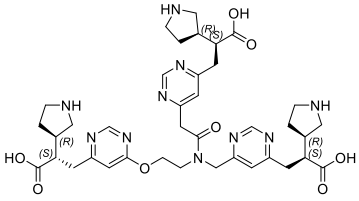
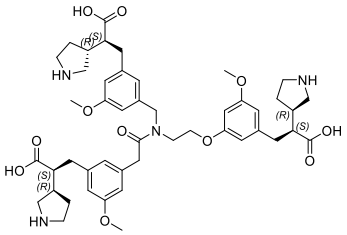
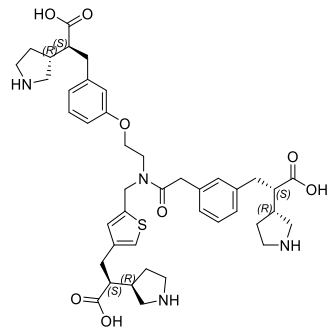
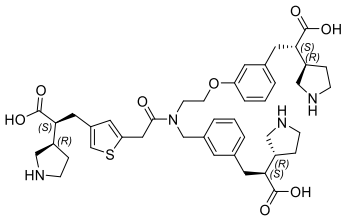
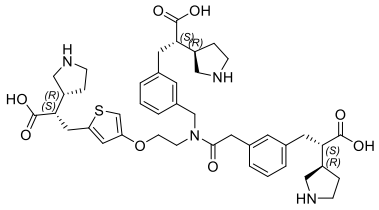
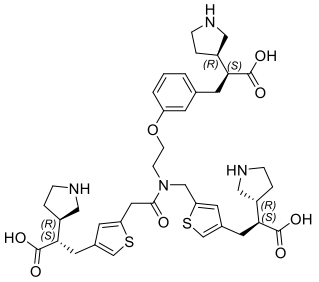
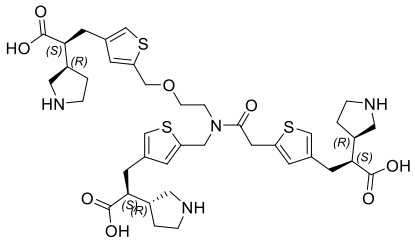
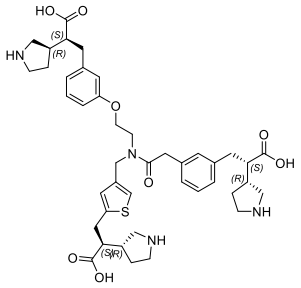
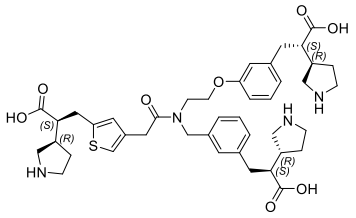
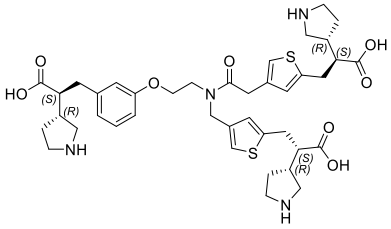
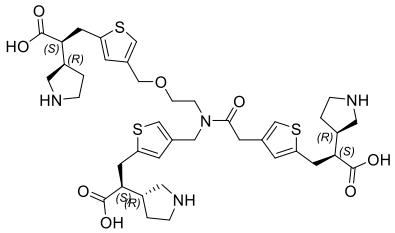
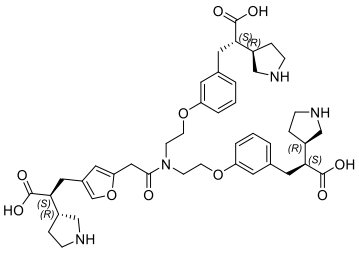
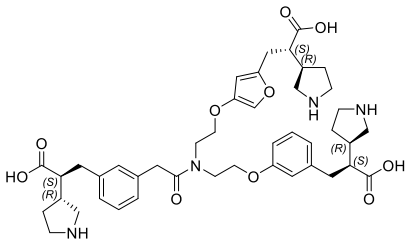
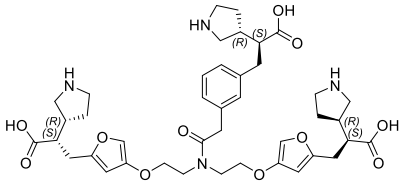
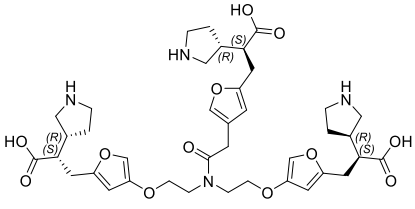
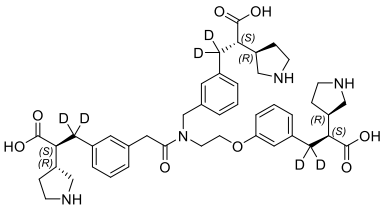
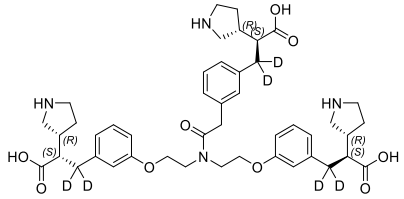
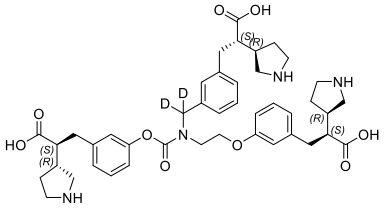
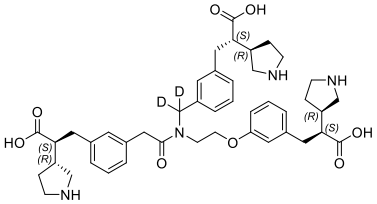
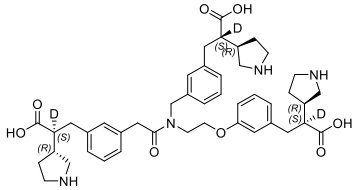
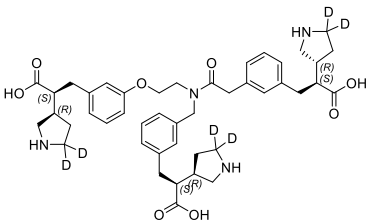
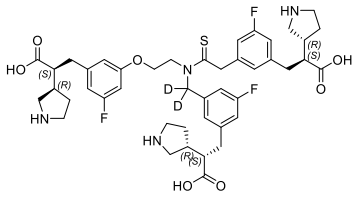
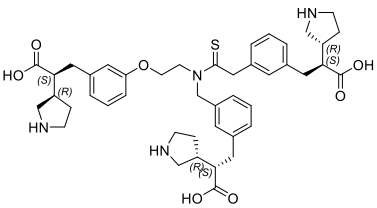
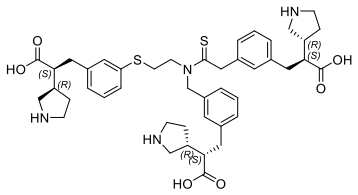
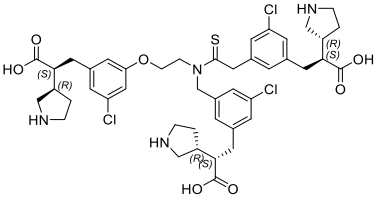
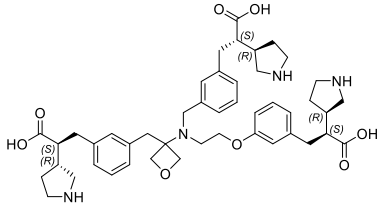
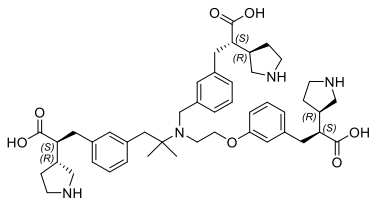
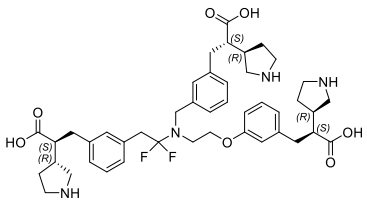
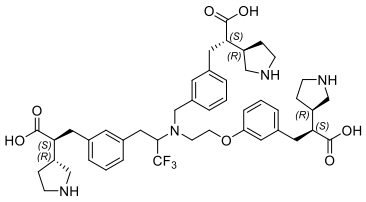
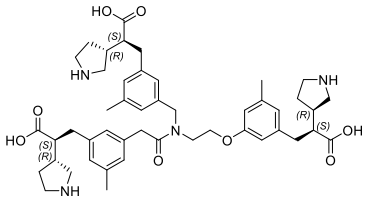
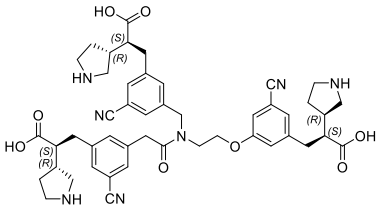
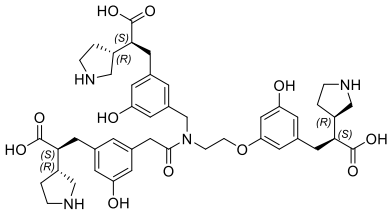
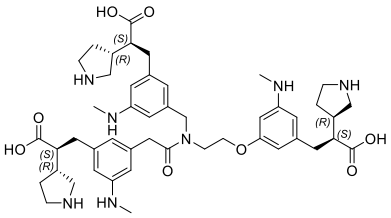
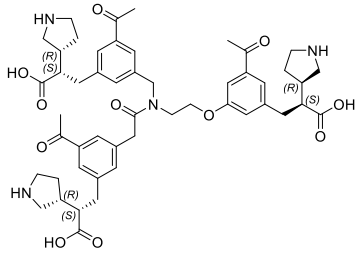
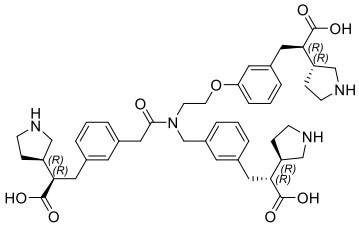
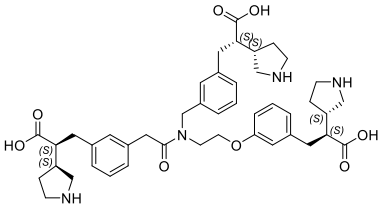
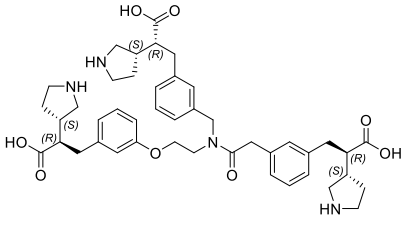
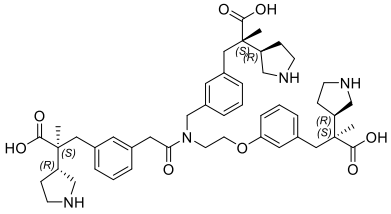
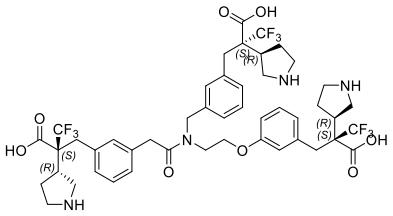
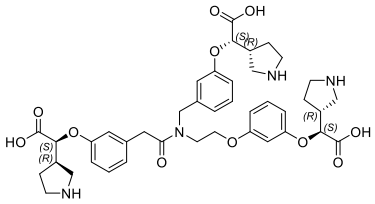
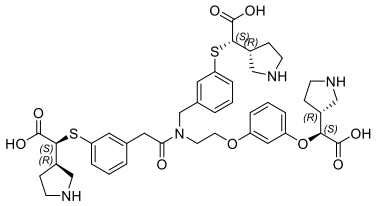
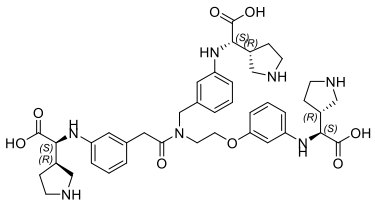
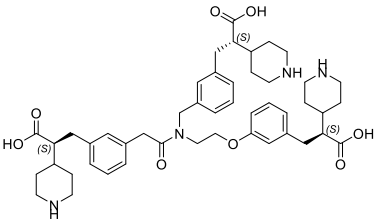
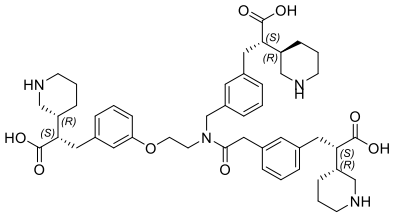
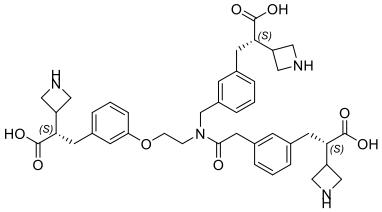
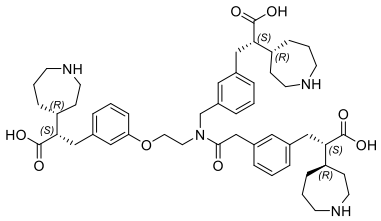
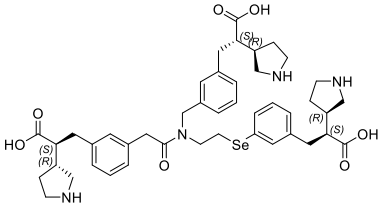
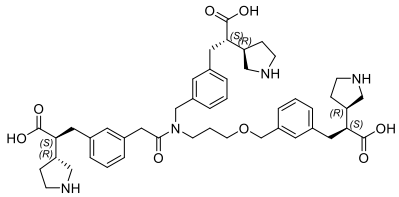
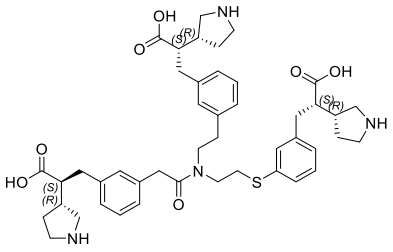
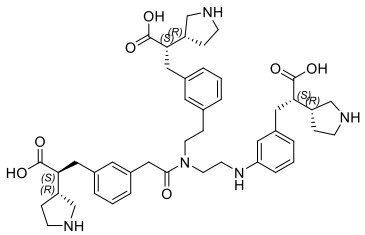
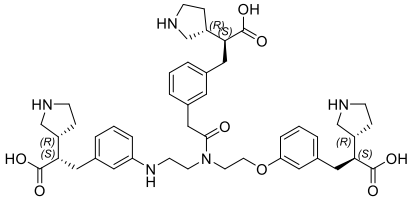
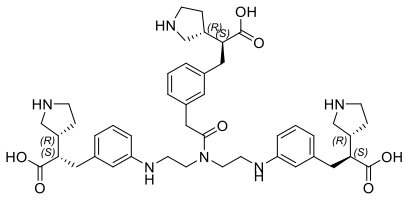
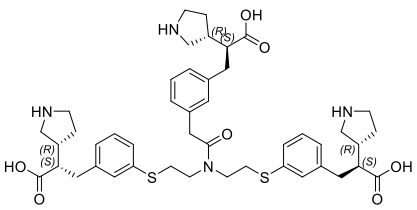
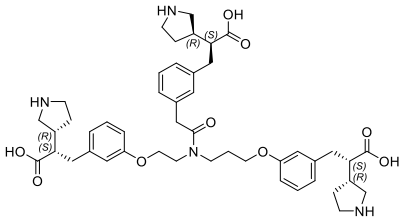
167		168	
169		170	
171		172	
173		174	
175		176	

Compound No.	Structure	Compound No.	Structure
177		178	
179		180	
181		182	
183		184	
185		186	

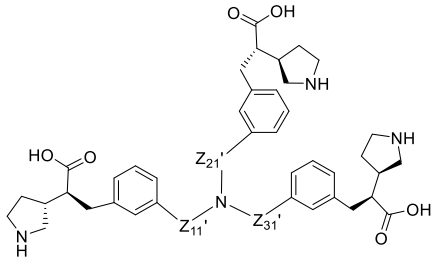
Compound No.	Structure	Compound No.	Structure
187		188	
189		190	
191		192	
193		194	
195		196	
197		198	
199		200	

Compound No.	Structure	Compound No.	Structure
201		202	
203		204	
205		206	
207		208	
209		210	
211		212	

Compound No.	Structure	Compound No.	Structure
213		214	
215		216	
217		218	
219		220	
221		222	
223		224	
225		226	

Compound No.	Structure	Compound No.	Structure
227		228	

alternatively the compound is selected from:

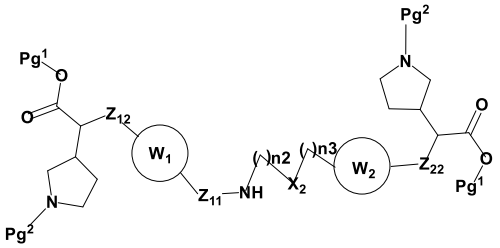
 , wherein * is the linking end to N,

Compound No.	Z_{31}'	Z_{11}'	Z_{21}'
229	C(O)	CH_2	$CH_2CH_2CH_2$
230	C(O)	CH_2	*CH_2CH_2S
231	C(O)	CH_2	*CH_2CH_2NH
232	C(O)	CH_2	*$CH_2CH_2CH_2O$
233	C(O)	CH_2	*$CH_2CH_2C(O)$
234	C(O)	CH_2	*$CH_2CH_2C(S)$
235	C(O)	CH_2	*$CH_2CH_2C(O)O$
236	C(O)	CH_2	*$CH_2CH_2C(O)NH$
237	C(O)	CH_2	*$CH_2CH_2C(O)NCH_2$
238	C(O)	CH_2	*$CH_2CH_2NHC(O)$
239	C(O)	CH_2CH_2	$CH_2CH_2CH_2$
240	C(O)	CH_2CH_2	*CH_2CH_2S
241	C(O)	CH_2CH_2	*$CH_2CH_2CH_2O$
242	C(O)	*CH_2CH_2O	*CH_2CH_2O
243	C(O)	*CH_2CH_2O	*CH_2CH_2S
244	C(O)	*CH_2CH_2O	*CH_2CH_2NH
245	C(O)	*CH_2CH_2O	*$CH_2CH_2C(O)$

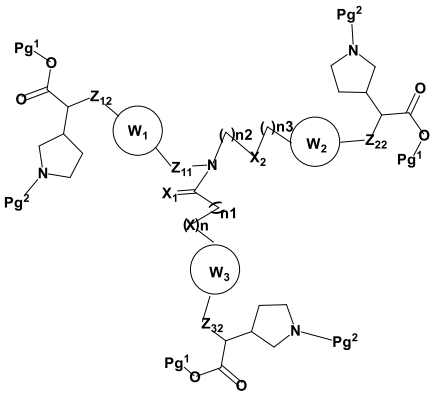
Compound No.	Z_{31}'	Z_{11}'	Z_{21}'
246	C(O)	*CH_2CH_2O	*$CH_2CH_2C(O)NH$
247	*$C(O)CH_2$	CH_2	CH_2
248	*$C(O)CH_2$	CH_2	CH_2CH_2
249	*$C(O)CH_2$	CH_2CH_2	$CH_2CH_2CH_2$
250	*$C(O)CH_2$	*CH_2CH_2O	$CH_2CH_2CH_2$
251	*$C(O)CH_2$	*CH_2CH_2O	*CH_2CH_2S
252	*$C(O)CH_2CH_2$	*CH_2CH_2O	*$CH_2CH_2CH_2S$
253	*$C(O)CH_2CH_2$	*CH_2CH_2O	*$CH_2CH_2C(O)$
254	*$C(O)CH_2CH_2$	*CH_2CH_2O	CH_2CH_2
255	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2CH_2O$
256	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2C(O)$
257	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2C(O)O$
258	*$C(O)CH_2CH_2$	CH_2	*$CH_2CH_2C(O)NH$
259	*$CH_2C(O)$	CH_2	CH_2CH_2
260	*$CH_2C(O)$	CH_2	*CH_2CH_2O
261	*$CH_2C(O)$	CH_2	*CH_2CH_2NH
262	*$CH_2CH_2C(O)$	CH_2	CH_2
263	*$CH_2CH_2C(O)$	CH_2	CH_2CH_2
264	*$CH_2CH_2C(O)$	CH_2	*CH_2CH_2O
265	*$CH_2CH_2C(O)$	CH_2	*CH_2CH_2S
266	*CH_2CH_2O	*CH_2CH_2O	*CH_2CH_2O
267	*CH_2CH_2O	*CH_2CH_2O	*$CH_2CH_2C(O)$
268	*CH_2CH_2O	*CH_2CH_2O	*$CH_2CH_2C(O)NH$
269	*CH_2CH_2NH	CH_2	*$CH_2CH_2C(O)NCH_2$
270	*CH_2CH_2NH	CH_2	*$CH_2CH_2NHC(O)$
271	*CH_2CH_2NH	*CH_2CH_2NH	*CH_2CH_2O
272	*CH_2CH_2NH	*$CH_2CH_2NCH_2$	*$CH_2CH_2C(O)$
273	*CH_2CH_2NH	*CH_2CH_2O	*$CH_2CH_2C(O)NH$
274	*$C(O)OCH_2$	CH_2	*CH_2CH_2NH
275	*$C(O)OCH_2$	CH_2	*CH_2CH_2S

Compound No.	Z_{31}'	Z_{11}'	Z_{21}'
276	*C(O)OCH$_2$	CH$_2$CH$_2$	*CH$_2$CH$_2$O
277	*C(O)OCH$_2$	CH$_2$CH$_2$	*CH$_2$CH$_2$S
278	*C(O)OCH$_2$	*CH$_2$CH$_2$NH	*CH$_2$CH$_2$O
279	*C(O)OCH$_2$	*CH$_2$CH$_2$NH	*CH$_2$CH$_2$CH$_2$O
280	*C(O)OCH$_2$	CH$_2$	CH$_2$
281	*C(O)OCH$_2$	CH$_2$CH$_2$	CH$_2$
282	*C(O)NHCH$_2$	CH$_2$	*CH$_2$CH$_2$NH
283	*C(O)NHCH$_2$	CH$_2$CH$_2$	*CH$_2$CH$_2$NH
284	*C(O)NHCH$_2$	*CH$_2$CH$_2$NH	*CH$_2$CH$_2$O
285	*C(O)NH	CH$_2$	*CH$_2$CH$_2$S
286	*C(O)NH	CH$_2$CH$_2$	*CH$_2$CH$_2$NH
287	*C(O)NH	CH$_2$CH$_2$	*CH$_2$CH$_2$O
288	*C(O)NH	CH$_2$CH$_2$	*CH$_2$CH$_2$S
289	*C(O)NH	*CH$_2$CH$_2$NH	*CH$_2$CH$_2$O
290	*C(O)O	CH$_2$	*CH$_2$CH$_2$S
291	*C(O)O	CH$_2$CH$_2$	*CH$_2$CH$_2$S
292	*C(O)CH$_2$O	CH$_2$	*CH$_2$CH$_2$NH
293	*C(O)CH$_2$O	CH$_2$CH$_2$	*CH$_2$CH$_2$C(O)NH
294	*C(O)CH$_2$O	CH$_2$CH$_2$	*CH$_2$CH$_2$O
295	*C(O)CH$_2$O	CH$_2$CH$_2$	*CH$_2$CH$_2$NH
296	*C(O)CH$_2$NH	*CH$_2$CH$_2$O	*CH$_2$CH$_2$S
297	*C(O)CH$_2$NH	*CH$_2$CH$_2$O	*CH$_2$CH$_2$O
298	*C(O)CH$_2$NH	CH$_2$CH$_2$	*CH$_2$CH$_2$NH
299	CH$_2$	*CH$_2$CH$_2$O	*CH$_2$CH$_2$O.

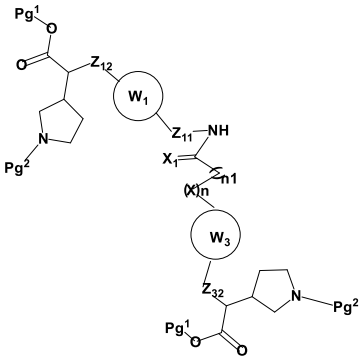
13. A compound having a structure as represented by formula (D-c), formula (D-f), formula (D-g), or formula (D-h), or a pharmaceutically acceptable salt thereof:



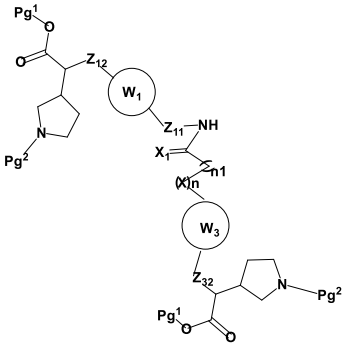
(D-c),



(D-f),



(D-g),



(D-h),

wherein Pg^1 and Pg^2 are protecting groups respectively; Z_{11}, Z_{12}, Z_{22}, Z_{32}, X, X_1, X_2, n, n1, n2, n3, and the rings W_1, W_2, and W_3 are as defined in any one of claims 1 to 12;

for example, Pg^1 is independently selected from tert-butyl, methyl, and benzyl, Pg^2 is independently selected from tert-butyloxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (FMOC), and benzyloxycarbonyl (Cbz); or

Pg^2 is Boc.

14. A pharmaceutical composition comprising the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof; optionally, the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

15. A use of the compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 14 in the preparation

of a medicament for preventing and/or treating a disease or condition associated with an elevated blood plasma Lp(a) level; preferably, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD); preferably, the cardiovascular disease (CVD) comprises, but is not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, aortic valve stenosis, heart failure, and atrial fibrillation; the ASCVD comprises peripheral vascular disease, coronary heart disease, and ischemic stroke.

16. A method of preventing and/or treating a disease or condition associated with an elevated blood plasma Lp(a) level, comprising administrating to a patient a therapeutically effective dose of the compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 14;

preferably, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD); preferably, the cardiovascular disease (CVD) comprises, but is not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, aortic valve stenosis, heart failure, and atrial fibrillation; the ASCVD comprises peripheral vascular disease, coronary heart disease, and ischemic stroke.

17. A use of the compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 14 as a medicament.

18. A use of the compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 14 in the prevention and/or treatment of a disease or condition associated with an elevated blood plasma Lp(a) level;

preferably, the disease or condition associated with an elevated blood plasma Lp(a) level is a cardiovascular disease (CVD); preferably, the cardiovascular disease (CVD) comprises, but is not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, aortic valve stenosis, heart failure, and atrial fibrillation; the ASCVD comprises peripheral vascular disease, coronary heart disease, and ischemic stroke.

19. A use of the compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 14 in combination with another compound in the prevention and/or treatment of a cardiovascular disease;

preferably, the other compound is used for preventing and/or treating a cardiovascular disease;

preferably, the cardiovascular disease is a disease or condition associated with an elevated blood plasma Lp(a) level;

preferably, the disease or condition associated with an elevated blood plasma Lp(a) level comprises, but is not limited to, atherosclerotic cardiovascular disease (ASCVD), coronary artery stenosis, aortic valve stenosis, heart failure, and atrial fibrillation; the ASCVD comprises peripheral vascular disease, coronary heart disease, and ischemic stroke.