

STEROID COMPOUND, AND PREPARATION METHOD THEREFOR AND USE THEREOF

[0001] The present application claims priority to Chinese Patent Application No.
5 2023109336322 filed on July 27, 2023, PCT Patent Application No.
PCT/CN2023/109660 filed on July 27, 2023, Chinese Patent Application No.
2024102813448 filed on March 12, 2024, Chinese Patent Application No.
2024108908992 filed on July 3, 2024, and Chinese Patent Application No.
2024109839491 filed on July 22, 2024. The contents of the Chinese patent
10 application are incorporated herein by reference in their entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to a steroid compound, a preparation
method therefor, and a use thereof.

15

BACKGROUND

[0003] With changes in lifestyle, including the intake of high-calorie foods and
high-sugar drinks, lack of exercise and physical activity, *etc.*, metabolic diseases
represented by hyperlipidemia, obesity, type 2 diabetes, and fatty liver have
20 become increasingly severe health issues worldwide. Among them, fatty liver
has become a major cause of chronic liver disease in Europe, America, and
affluent regions of China, with a prevalence of simple hepatic lipid accumulation
in the general adults ranging from 10% to 30%, of which 10% to 20% are
steatohepatitis. Among the latter, the incidence of cirrhosis and liver cancer
25 within 10 years reaches 25%. However, to date, the pathophysiological
mechanisms of fatty liver disease have not been fully elucidated, and clinically,
there is still a lack of effective and specific therapeutic drugs. It is known that
the accumulation of lipids such as cholesterol and triglycerides in the blood and
liver is the primary cause of hyperlipidemia, which in turn is a significant
30 pathogenic factor for atherosclerosis, stroke, and fatty liver diseases. Therefore,
the research and development of new drugs targeting lipid metabolism regulation

pathways with the guidance of lipid reduction is increasingly becoming an important direction for the research and development of new drugs for metabolic diseases.

[0004] It is known that the lipid synthesis pathway in mammalian cells is an important factor in regulating lipid metabolic balance. The key factors regulating cholesterol and fatty acid synthesis are a class of transcription factor proteins called sterol-regulatory element binding proteins (SREBPs). The precursors of this class of proteins are first synthesized on the endoplasmic reticulum (ER). The precursors are transported to the Golgi apparatus via SREBP cleavage-activating protein (SCAP), where they undergo proteolytic cleavage by two proteases (Site-1 protease (S1P) and Site-2 protease (S2P)), releasing their N-terminal active domains. These domains then enter the nucleus to function as transcription factors, binding to the SREBP response elements (SREs) in the promoter regions of target genes, thereby initiating the expression of downstream genes. The cleavage and maturation of SREBP proteins are strictly regulated by intracellular sterol levels (such as cholesterol and 25-hydroxycholesterol). When cells accumulate sufficient cholesterol in the endoplasmic reticulum, cholesterol binds to SCAP and alters the conformation of SCAP, causing the SCAP-SREBP complex to bind to the protein Insig (Insulin-induced gene), thereby blocking the transport of SREBP to the Golgi apparatus and subsequent activation of SREBP. On the contrary, the active form of SREBP in the nucleus increases, which promotes cellular lipid synthesis. In addition to cholesterol, 25-hydroxycholesterol (25-HC) is another potent endogenous inhibitor of the SREBP pathway. Unlike cholesterol-bound SCAP, 25-HC directly binds to Insig and induces the binding of SCAP and Insig.

[0005] Previous studies have found that inhibiting the SREBP pathway is an effective strategy and method for preventing and/or treating metabolic diseases such as obesity, hyperlipidemia, fatty liver, atherosclerosis, and diabetes, as well as cardiovascular and cerebrovascular diseases, skin damage, liver cancer, and other diseases.

[0006] For hyperlipidemia, its pathogenesis is mainly due to increased lipid

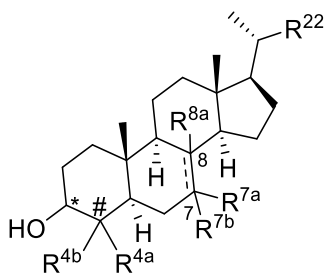
synthesis caused by factors such as diet or gene mutations, or abnormal lipid transport leading to excessive accumulation of lipids such as blood cholesterol and fatty acids. Currently, statins and fibrates are the main lipid-regulating drugs in clinical use. The mechanism of statins involves inhibiting cellular cholesterol synthesis while promoting reverse cholesterol transport in the blood. This indicates that targeting key factors in the cellular lipid synthesis pathway is an important means to effectively reduce lipid levels.

[0007] To date, there are no approved therapeutic drugs for fatty liver disease, making it important to determine treatment targets and develop new effective therapies. The pathogenesis of fatty liver disease is known to involve multiple risk factors, such as triglyceride accumulation in the form of lipid droplets, which may trigger steatosis, as well as abnormally increased cholesterol and fatty acids in cells, leading to endoplasmic reticulum stress and mitochondrial dysfunction, thereby causing cell death, inflammation, and fibrosis. Among them, free cholesterol accumulation has been reported as a key driver in the transition from simple steatosis to aggressive steatohepatitis. Secondly, in establishing a mouse model of fatty liver, a simple cholesterol-free high-fat diet can only induce steatosis even after prolonged feeding, whereas the addition of 1-2% cholesterol to the diet is necessary to achieve inflammation and fibrosis. Therefore, reducing cholesterol may become a novel therapeutic strategy for fatty liver disease. Previous studies have shown that abnormal activation of SREBP is observed in both fatty liver patients and fatty liver mouse models; the deletion or knockout of liver-specific Scap in mice can eliminate the activation of all SREBPs, thereby preventing the onset of fatty liver and hyperlipidemia. Furthermore, recent studies have shown that endoplasmic reticulum stress-induced abnormal activation of SREBP promotes lipogenesis and fatty liver. Therefore, this evidence suggests that reducing hepatic triglyceride and cholesterol levels by inhibiting the SREBP pathway is an effective strategy for preventing and/or treating metabolic disorders, including fatty liver.

CONTENT OF THE PRESENT INVENTION

[0008] The technical problem to be solved by the present disclosure is to provide novel compounds with inhibitory activity against the SREBP pathway.

[0009] The present disclosure provides a compound of Formula I or a pharmaceutically acceptable salt thereof:



I

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[0010] wherein

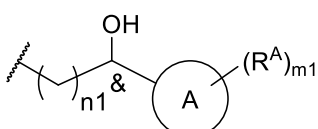
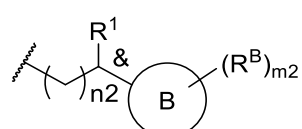
[0011] each $\equiv$ is independently a single bond or a double bond;

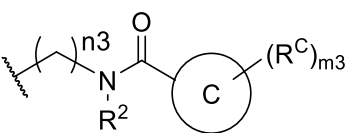
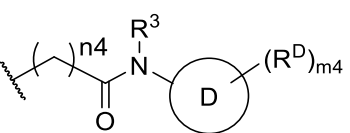
[0012] R^{4a} is H; R^{4b} is H or OH; or, R^{4a} and R^{4b} , together with the carbon atom

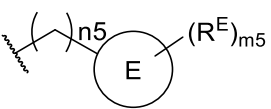
to which they are attached, form ;

10 [0013] when the bond between carbon atom 7 and carbon atom 8 is a single bond, R^{7a} and R^{7b} are independently H or halogen; R^{8a} is H;

[0014] when the bond between carbon atom 7 and carbon atom 8 is a double bond, R^{7a} is absent, R^{7b} is halogen; R^{8a} is absent;

[0015] R^{22} is , ,

15 , , or

;

[0016] n_1 , n_2 , n_3 , n_4 , and n_5 are independently 2, 3, 4, or 5;

[0017] m_1 , m_2 , m_3 , and m_4 are independently 0, 1, 2, 3, 4, or 5;

[0018] ring A, ring B, ring C, and ring D are independently C_6 - C_{10} aryl, 5- to 10-

membered heteroaryl with 1, 2, or 3 heteroatoms selected from the group consisting of 1, 2, or 3 kinds of N, O, and S, or C₃-C₆ cycloalkyl;

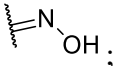
[0019] R¹ is C₁-C₆ alkoxy, , or NR^{1a}R^{1b};

[0020] R² and R³ are independently H or C₁-C₆ alkyl;

5 [0021] R^A, R^B, R^C, and R^D are independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy;

[0022] ring E is C₃-C₆ cycloalkyl;

[0023] m₅ is 0, 1, 2, or 3;

10 [0024] R^E is independently OH, NR^{e1}R^{e2}, COOH, C₁-C₆ alkyl, oxo (=O), or ;

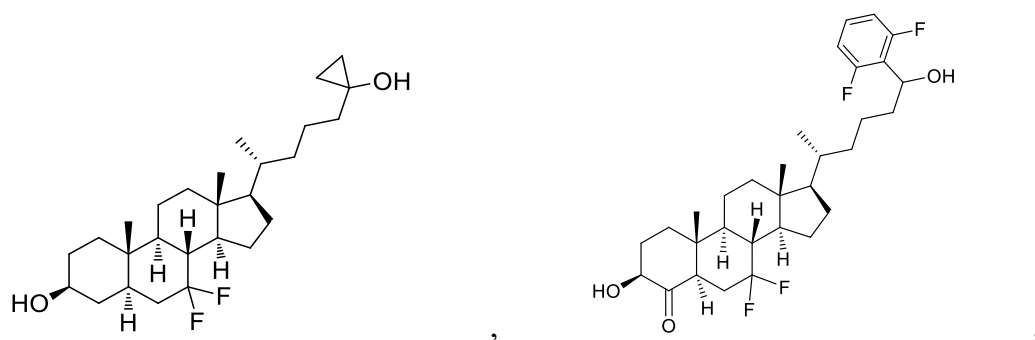
[0025] R^{1a}, R^{1b}, R^{e1}, and R^{e2} are independently H or C₁-C₆ alkyl;

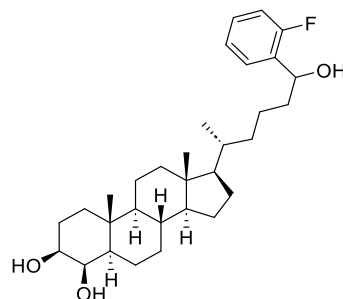
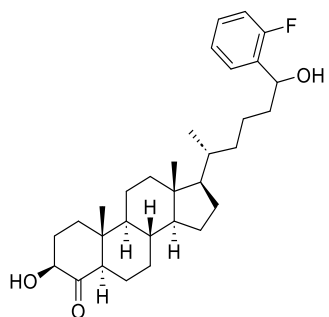
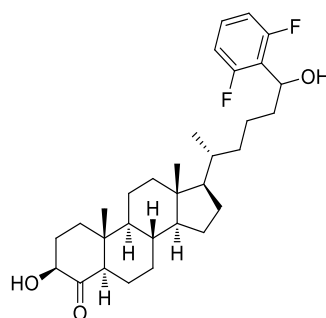
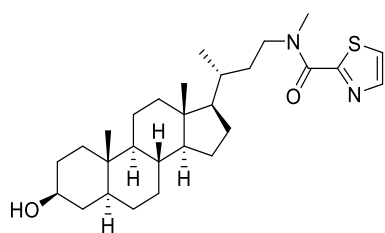
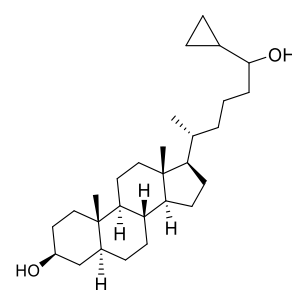
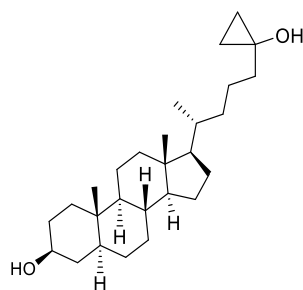
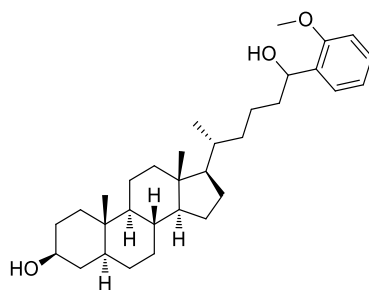
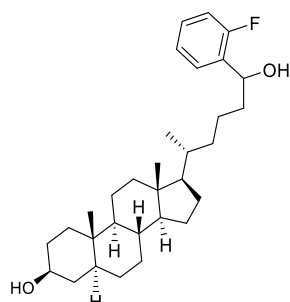
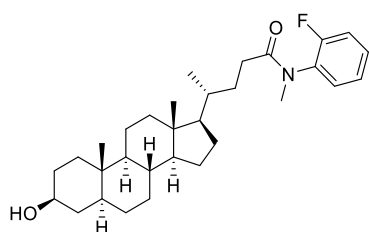
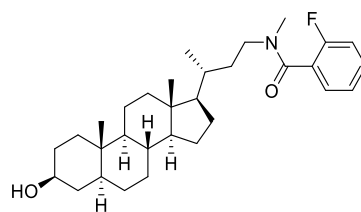
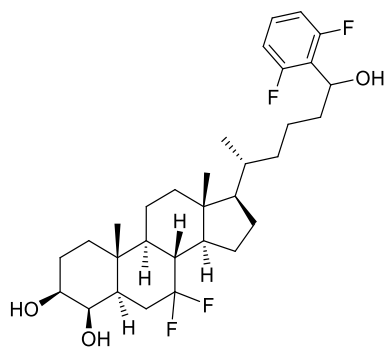
[0026] the carbon atom marked with "*" indicates that when it is a chiral carbon atom, it is in the R configuration, S configuration, or a mixture of both;

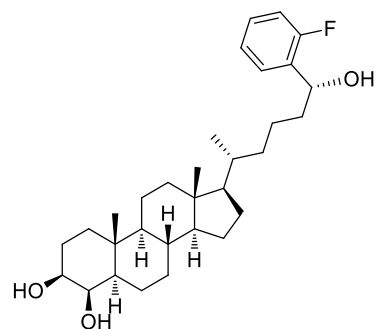
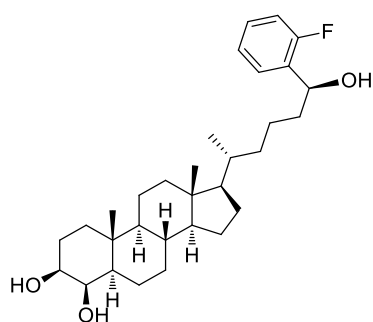
15 [0027] the carbon atom marked with "#" indicates that when it is a chiral carbon atom, it is in the R configuration, S configuration, or a mixture of both;

[0028] the carbon atom marked with "&" indicates that when it is a chiral carbon atom, it is in the R configuration, S configuration, or a mixture of both;

[0029] the compound of Formula I is not any of the following compounds:

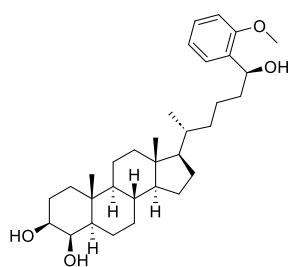
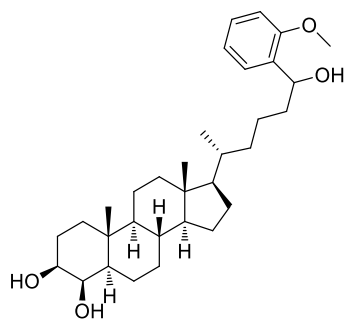






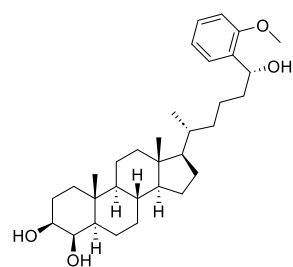
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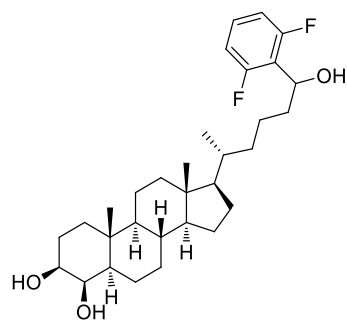
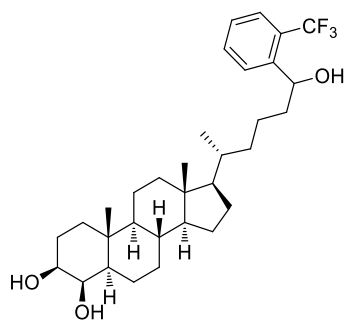


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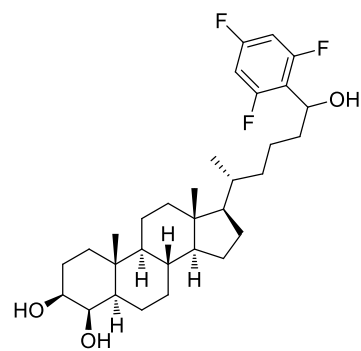
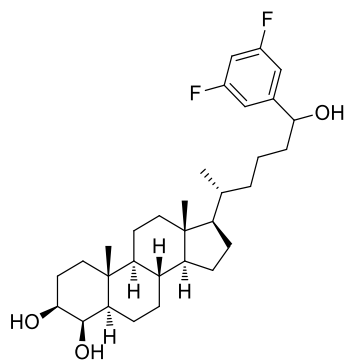


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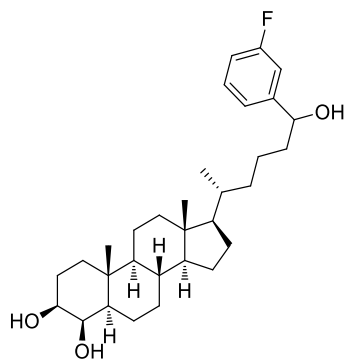
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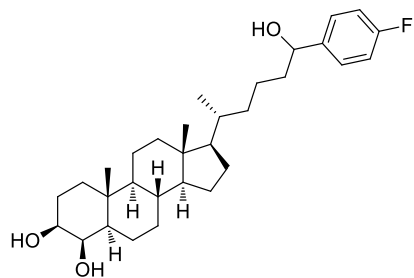


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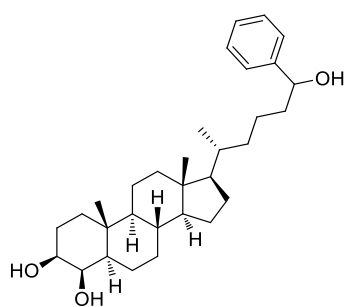
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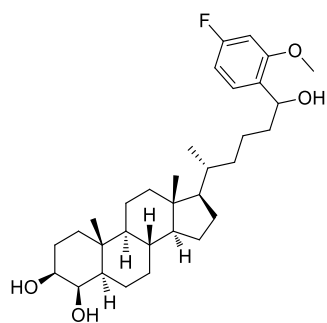
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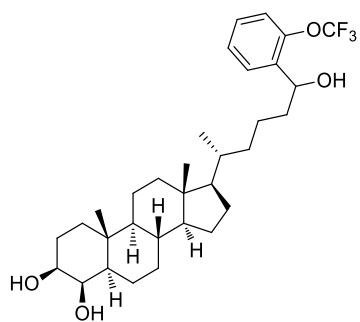
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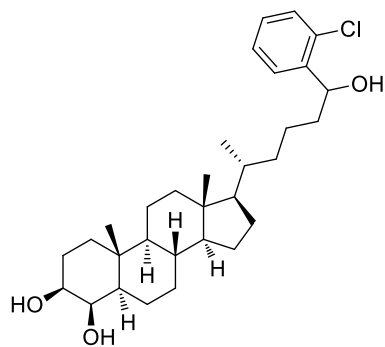
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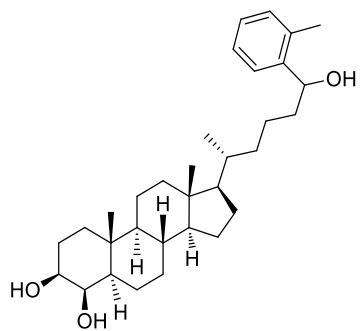
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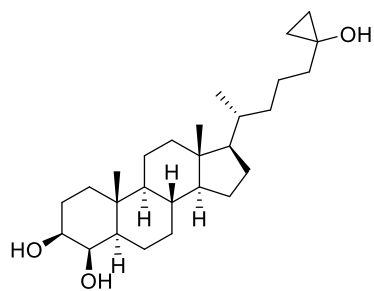
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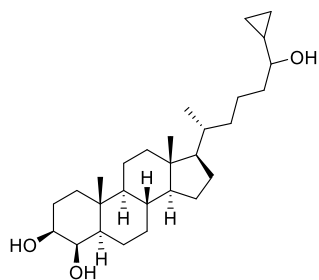
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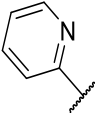
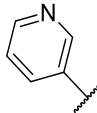
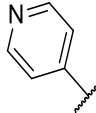


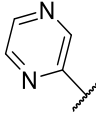
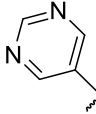
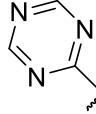
, and isomers thereof.

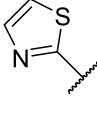
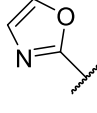
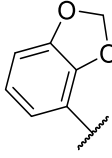
[0030] In certain preferred embodiments of the present disclosure, certain groups in the compound of Formula I or the pharmaceutically acceptable salt thereof are defined as follows, while the unmentioned groups are the same as described in any one embodiment of the present disclosure (hereinafter referred to as "in some embodiments"), in R^{7a} and R^{7b} , the halogen is independently F, Cl, Br, or I; preferably F.

[0031] In some embodiments, in ring A, ring B, ring C, and ring D, the C_6 - C_{10} aryl is independently phenyl or naphthyl, preferably phenyl.

[0032] In some embodiments, in ring A, ring B, ring C, and ring D, the 5- to 10-membered heteroaryl with 1, 2, or 3 heteroatoms selected from the group consisting of 1, 2, or 3 kinds of N, O, and S is independently 5- to 6-membered heteroaryl with 1 or 2 heteroatoms selected from the group consisting of 1, 2, or 3 kinds of N, O, and S or 9- to 10-membered heteroaryl with 1 or 2 heteroatoms

being O, preferably pyridyl (e.g., , , or ) , pyrazinyl

(e.g., ) , pyrimidinyl (e.g., ) , triazinyl (e.g., ) ,

thiazolyl (e.g., ) , oxazolyl (e.g., ) , or .

[0033] In some embodiments, in ring A, ring B, ring C, and ring D, the C_3 - C_6 cycloalkyl is independently cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or

bicyclo[1.1.1]pentyl (e.g., , preferably .

[0034] In some embodiments, in R^1 , the C_1 - C_6 alkoxy is independently methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, or *tert*-butoxy, preferably methoxy.

- 5 **[0035]** In some embodiments, in R^2 and R^3 , the C_1 - C_6 alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl; preferably methyl.

[0036] In some embodiments, in R^A , R^B , R^C , and R^D , the halogen is independently F, Cl, Br, or I; preferably F or Cl, for example, F.

- 10 **[0037]** In some embodiments, in R^A , R^B , R^C , and R^D , the C_1 - C_6 alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl.

[0038] In some embodiments, in R^A , R^B , R^C , and R^D , the C_1 - C_6 haloalkyl is independently CHF_2 , CH_2F , or CF_3 .

- 15 **[0039]** In some embodiments, in R^A , R^B , R^C , and R^D , the C_1 - C_6 alkoxy is independently methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, or *tert*-butoxy, preferably methoxy or ethoxy.

[0040] In some embodiments, in R^A , R^B , R^C , and R^D , the C_1 - C_6 haloalkoxy is independently $-OCHF_2$, $-OCH_2F$, or $-OCF_3$; preferably $-OCF_3$.

- 20 **[0041]** In some embodiments, in ring E, the C_3 - C_6 cycloalkyl is cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, or bicyclo[1.1.1]pentyl (e.g., , preferably cyclopropyl or cyclobutyl.

- [0042]** In some embodiments, in R^E , the C_1 - C_6 alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl, for example, methyl.
- 25

[0043] In some embodiments, in R^{1a} , R^{1b} , R^{e1} , and R^{e2} , the C_1 - C_6 alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl, for example, methyl.

[0044] In some embodiments, n1 is 3.

[0045] In some embodiments, n2 is 3.

[0046] In some embodiments, n3 is 2.

[0047] In some embodiments, n4 is 2.

5 [0048] In some embodiments, n5 is 2.

[0049] In some embodiments, m1 is 0, 1, 2, or 3.

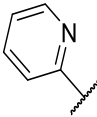
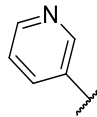
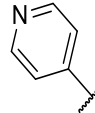
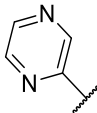
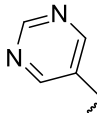
[0050] In some embodiments, m2 is 0, 1, 2, or 3, for example, 2.

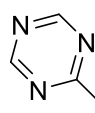
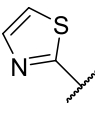
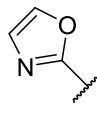
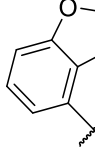
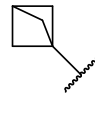
[0051] In some embodiments, m3 is 1.

[0052] In some embodiments, m4 is 1.

10 [0053] In some embodiments, m5 is 1 or 2.

[0054] In some embodiments, R^A is independently halogen, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy.

[0055] In some embodiments, ring A is phenyl, pyridyl (e.g., , ,
or , pyrazinyl (e.g., , pyrimidinyl (e.g., , triazinyl

15 (e.g., , thiazolyl (e.g., , oxazolyl (e.g., , ,
or .

[0056] In some embodiments, R^B is independently halogen, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy; for example, halogen or C₁-C₆ alkoxy.

[0057] In some embodiments, ring B is phenyl.

20 [0058] In some embodiments, R¹ is methoxy, , or NH₂.

[0059] In some embodiments, R^C and R^D are independently halogen.

[0060] In some embodiments, ring C is phenyl.

[0061] In some embodiments, ring D is phenyl.

[0062] In some embodiments, ring E is cyclopropyl or cyclobutyl.

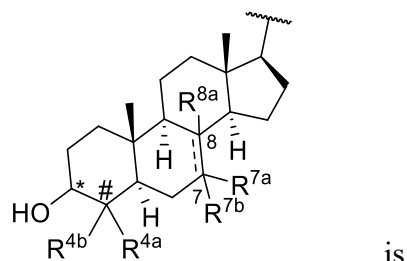
[0063] In some embodiments, R^{1a} and R^{1b} are independently H.

[0064] In some embodiments, R^{e1} and R^{e2} are independently C₁-C₆ alkyl (*e.g.*, methyl).

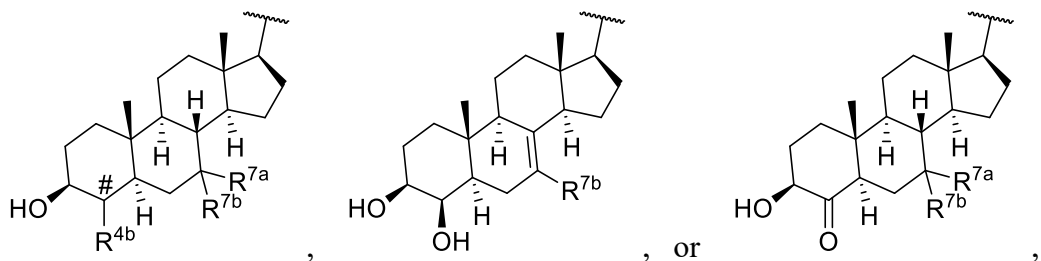
[0065] In some embodiments, the carbon atom marked with "*" indicates that when it is a chiral carbon atom, it is in the S configuration.

[0066] In some embodiments, the carbon atom marked with "#" indicates that when it is a chiral carbon atom, it is in the R configuration.

10 [0067] In some embodiments,

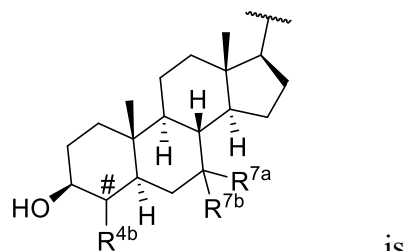


is

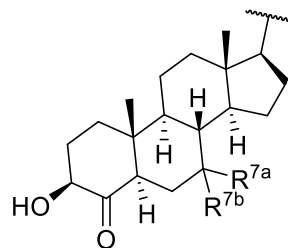
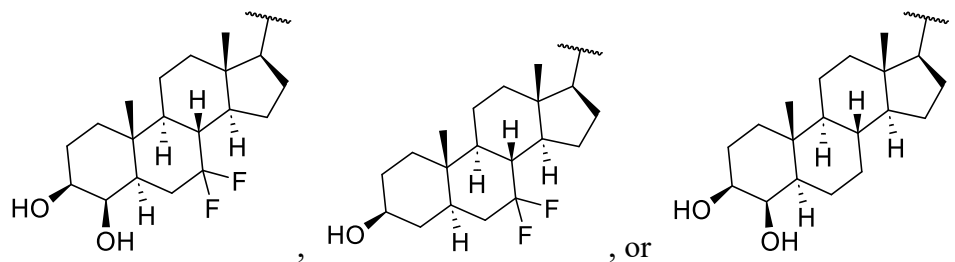


wherein R^{4b} is H or OH, and R^{7a} and R^{7b} are independently H or halogen (*e.g.*, F); preferably, R^{4b} is OH, and R^{7a} and R^{7b} are independently halogen (*e.g.*, F).

[0068] In some embodiments,

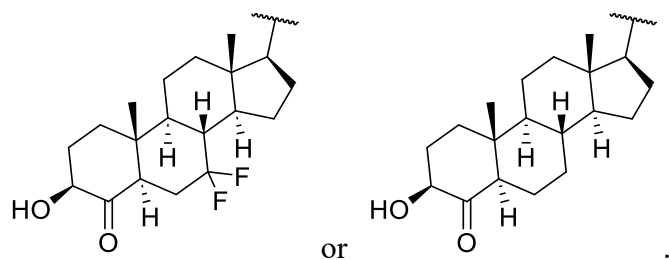


is



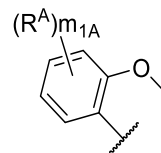
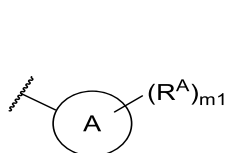
[0069] In some embodiments,

is

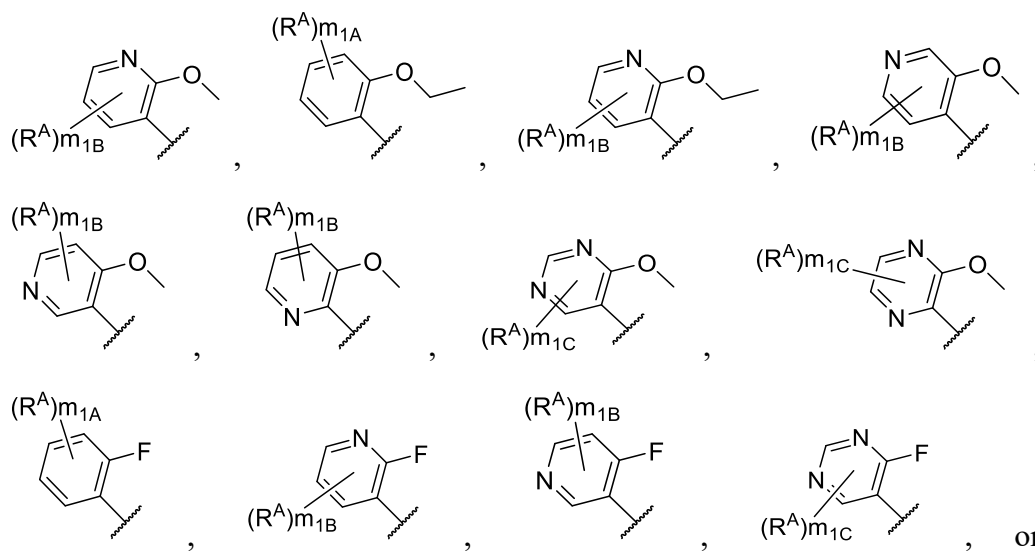


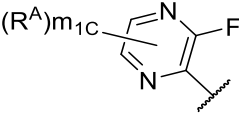
[0070] In some embodiments,

is

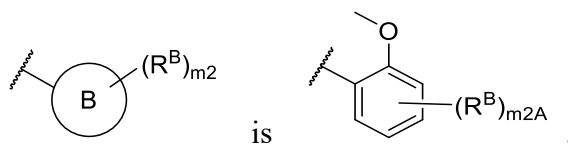


5



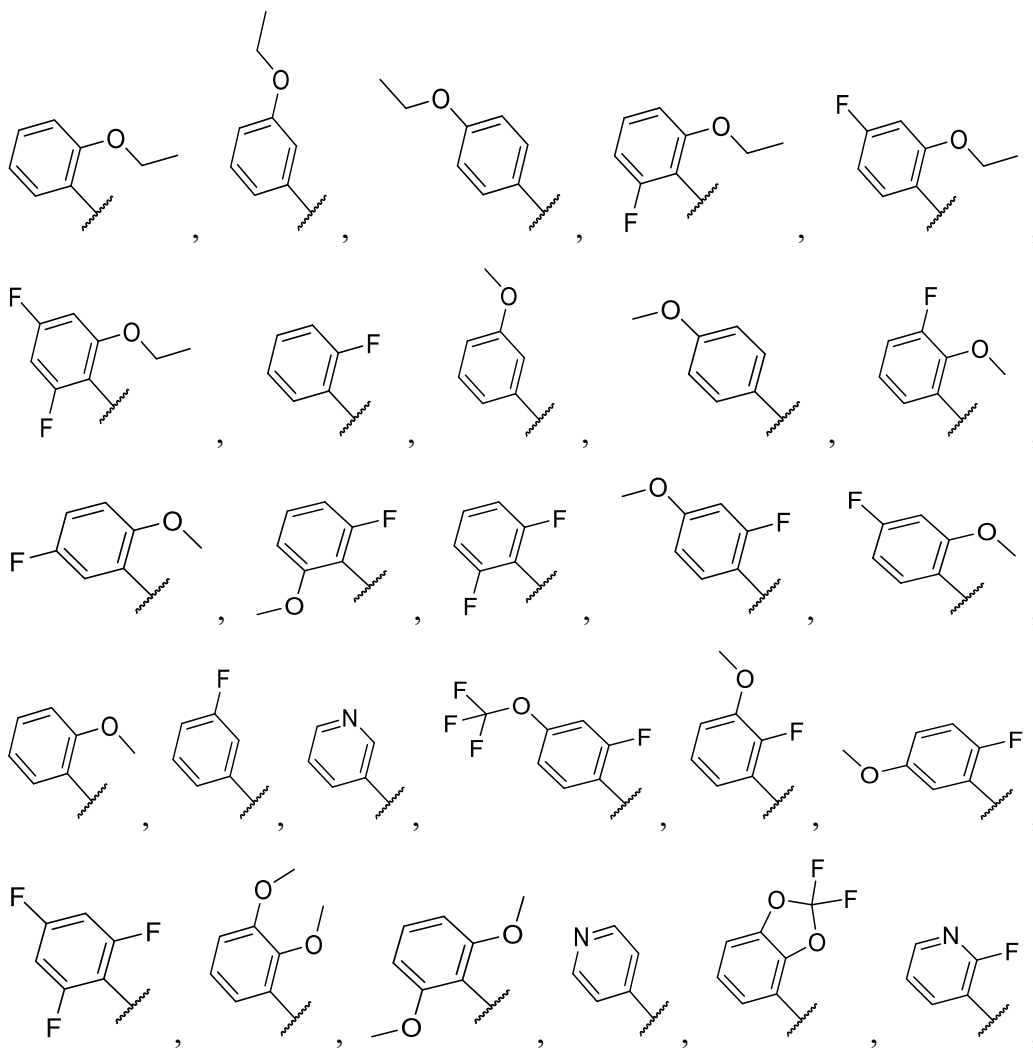
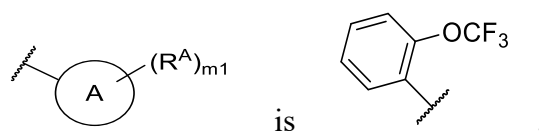

, wherein m_{1A} is 0, 1, 2, 3, or 4; m_{1B} is independently 0, 1, 2, or 3; and m_{1C} is independently 0, 1, or 2.

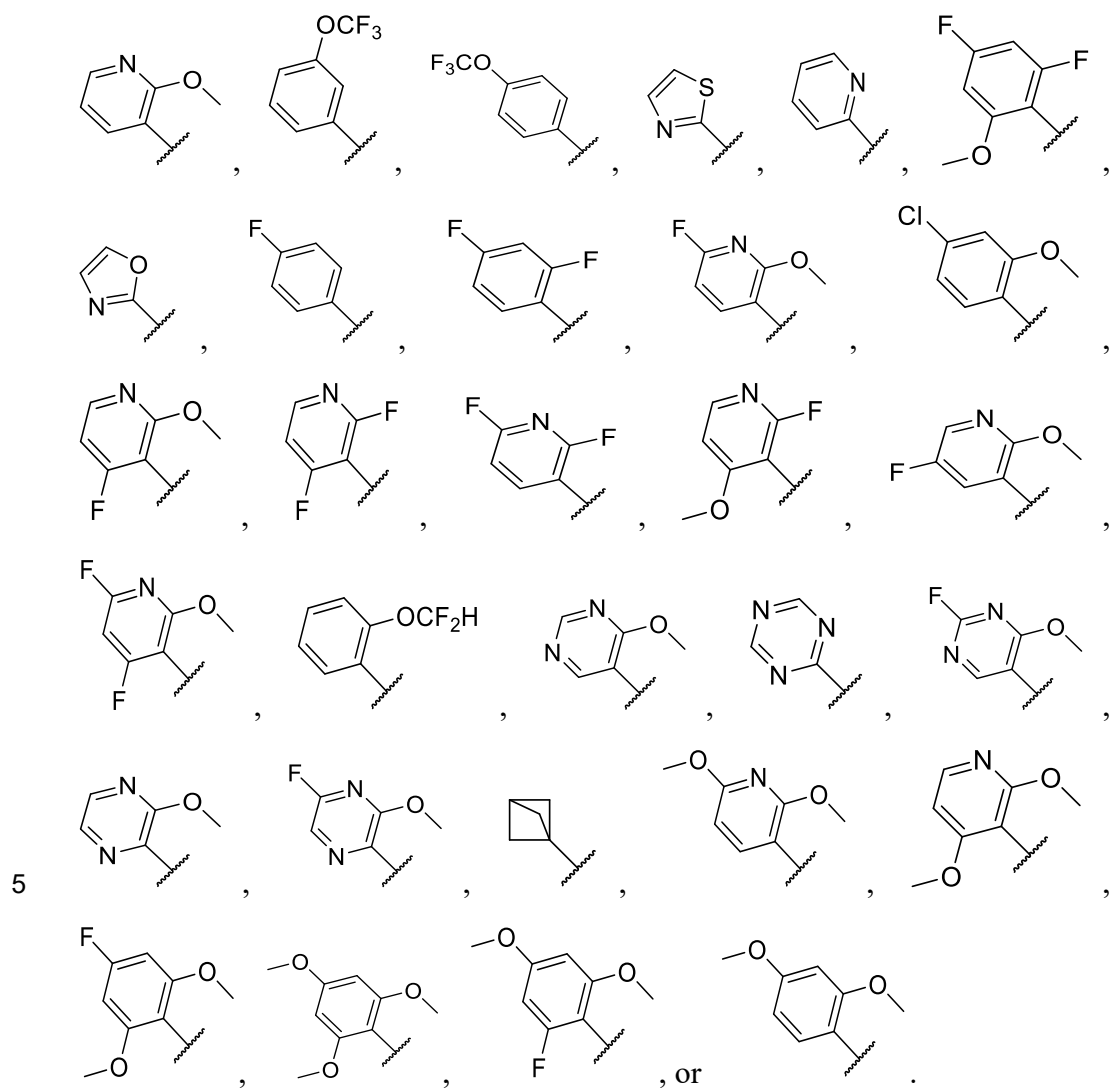
[0071] In some embodiments,



wherein m_{2A} is 0, 1, 2, 3, or 4.

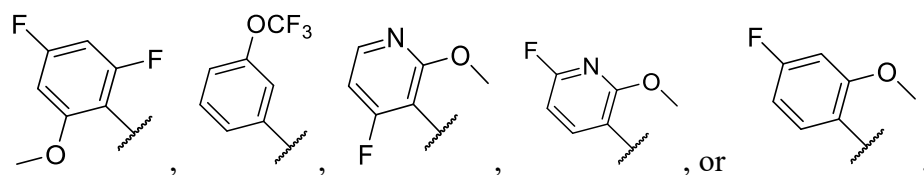
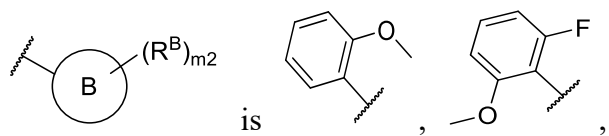
5 **[0072]** In some embodiments,



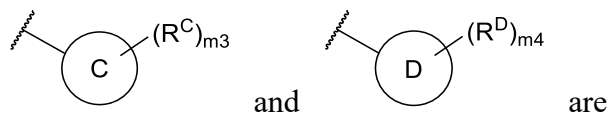


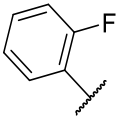
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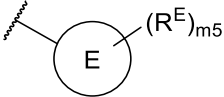
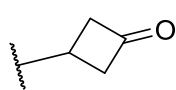
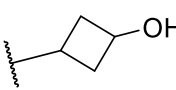
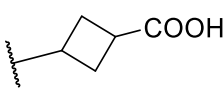
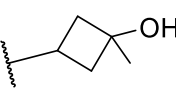
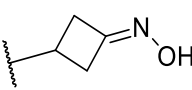
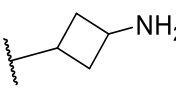
[0073] In some embodiments,

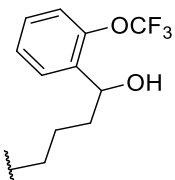
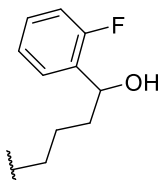


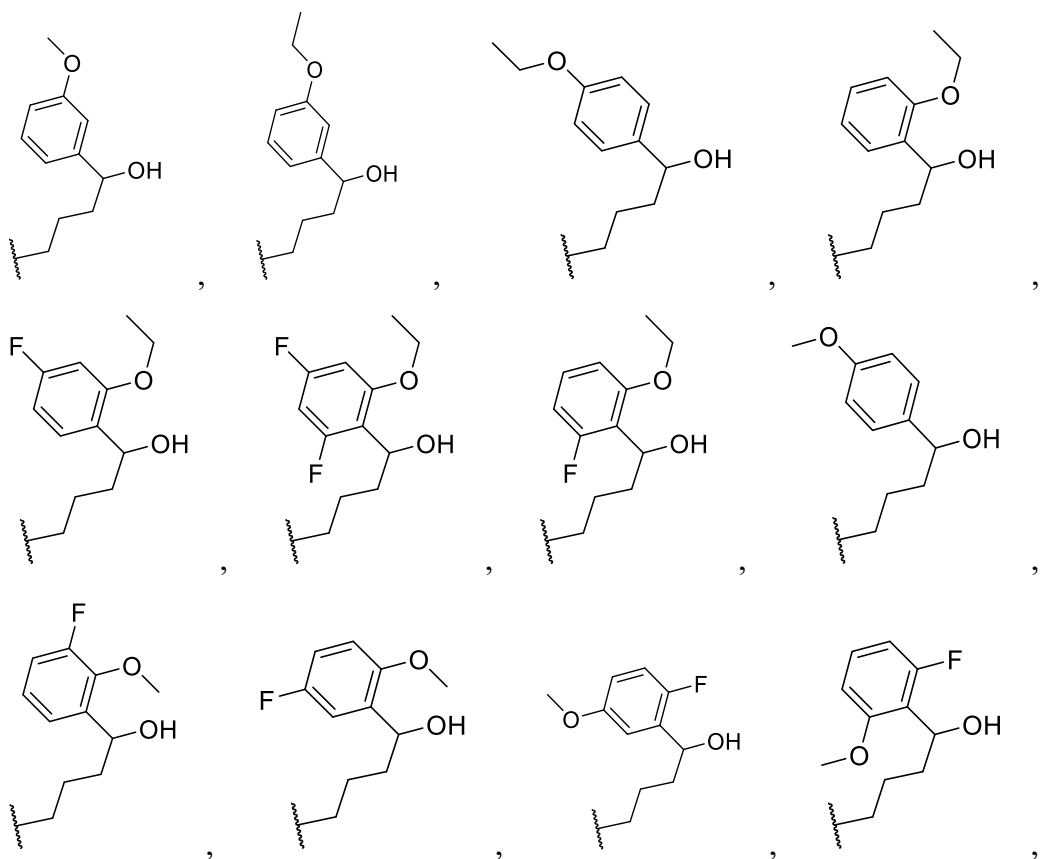
[0074] In some embodiments,

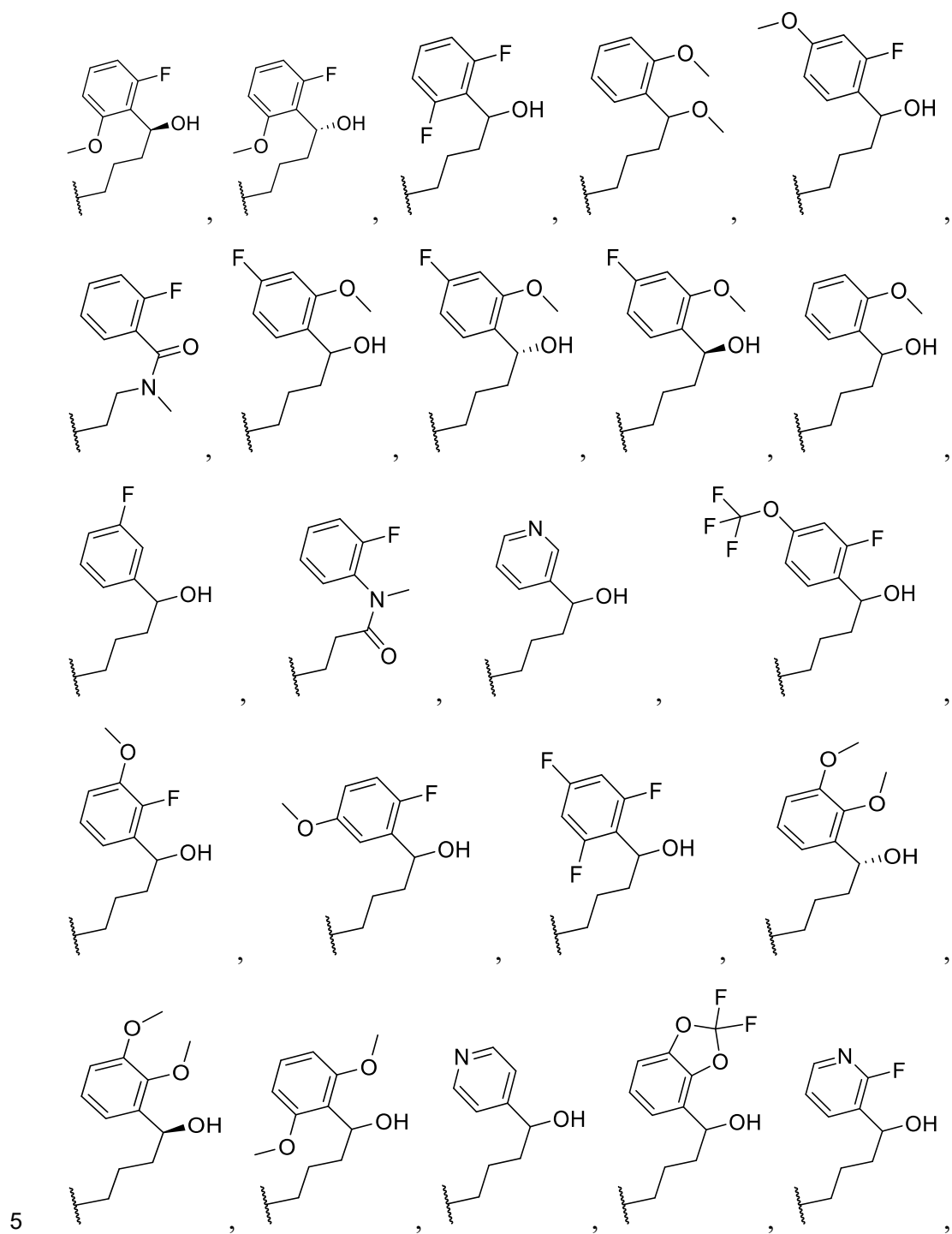


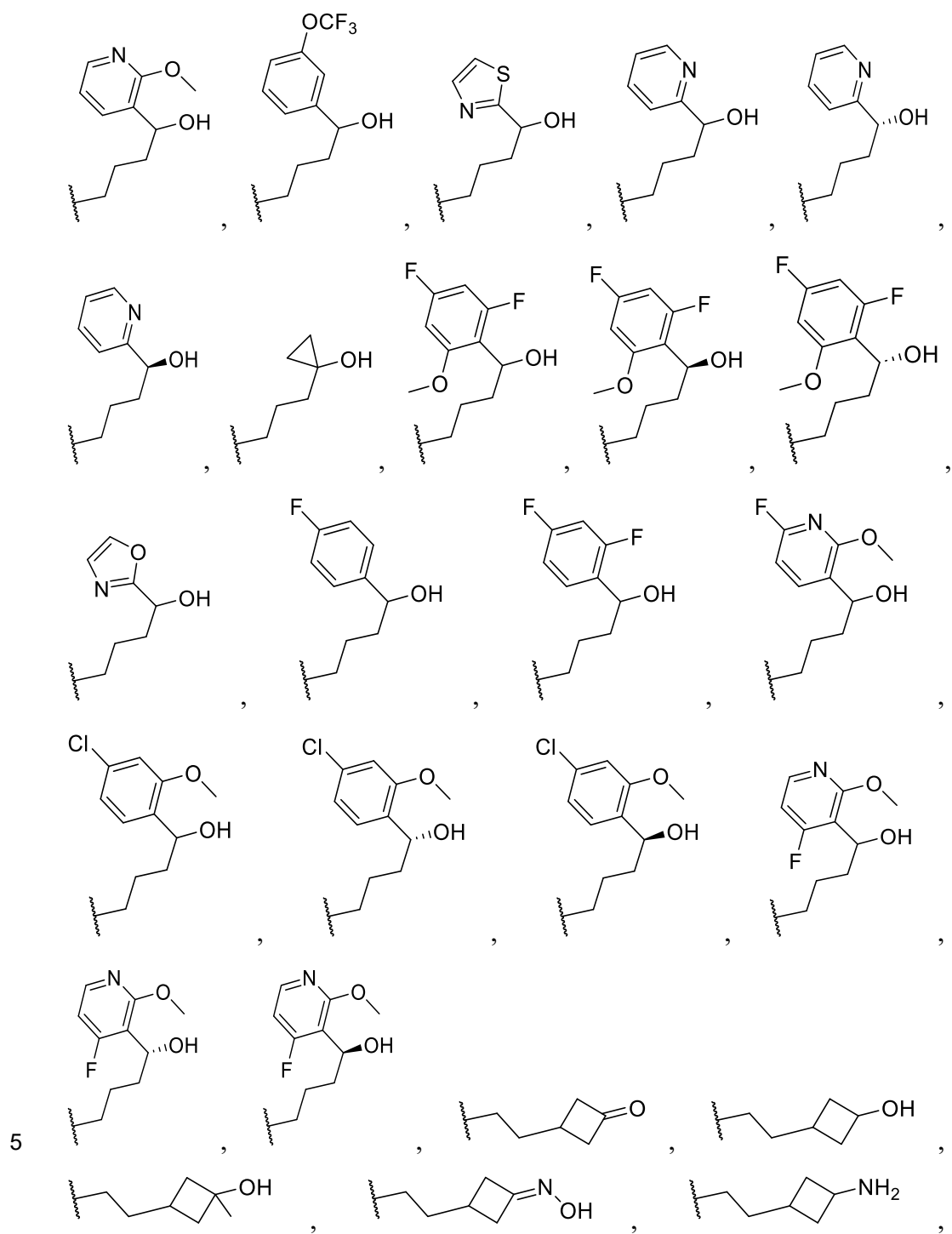
independently .

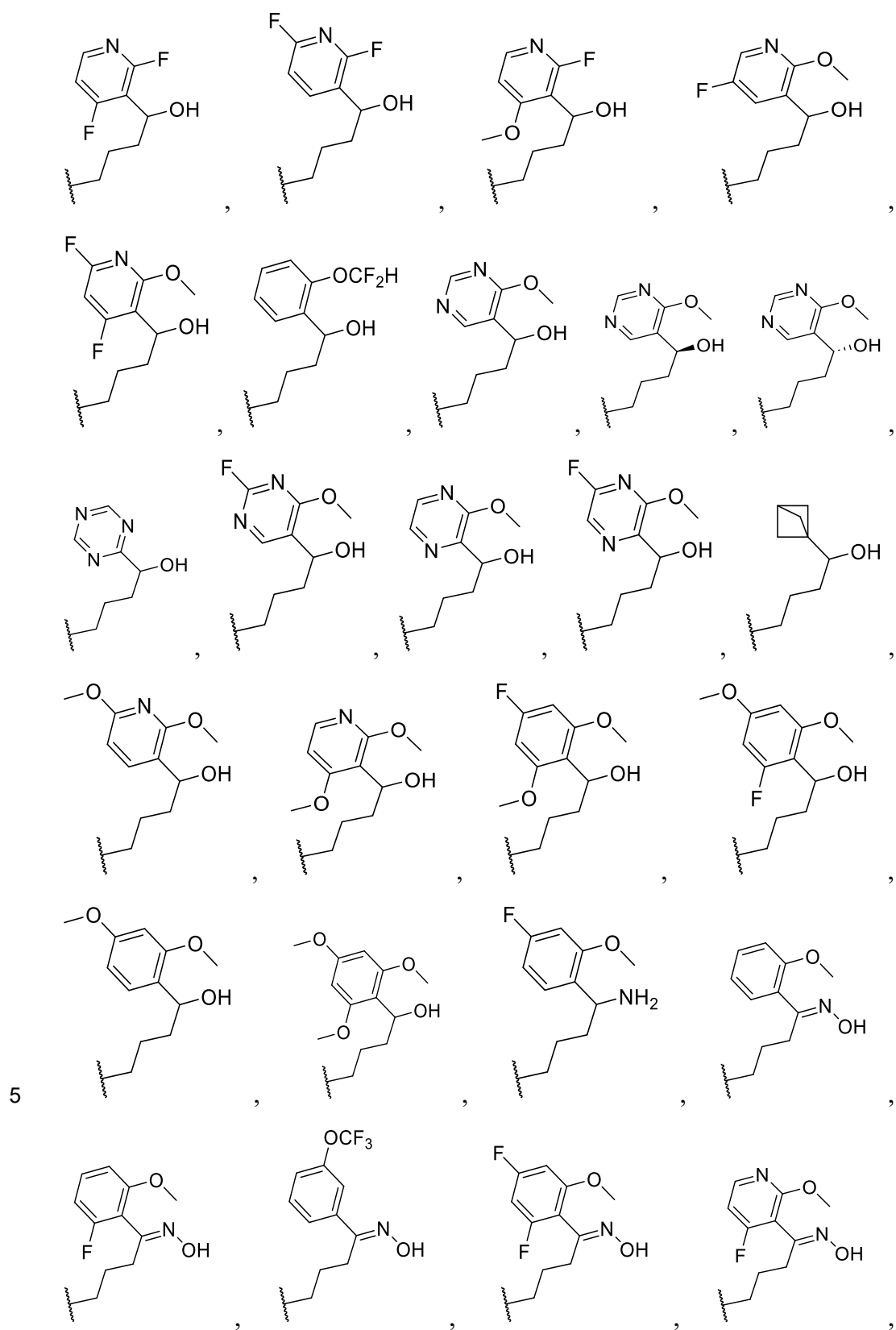
[0075] In some embodiments,  is , , , , , , or .

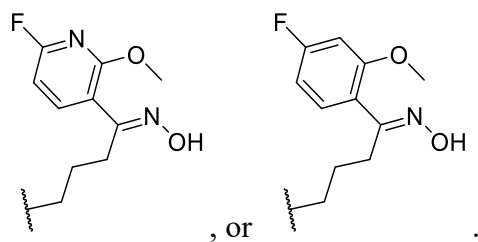
5 [0076] In some embodiments, R^{22} is , ,



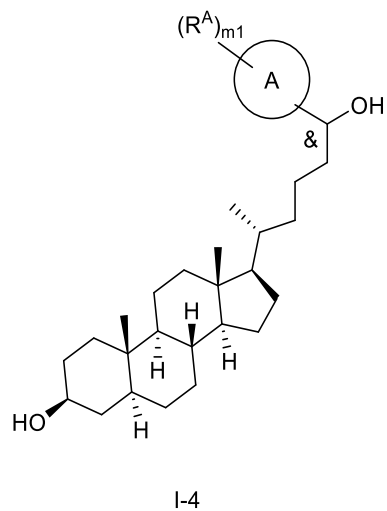
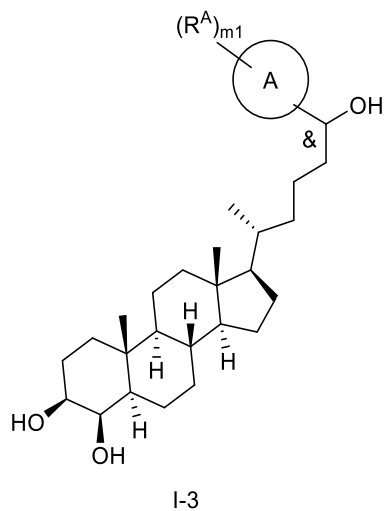
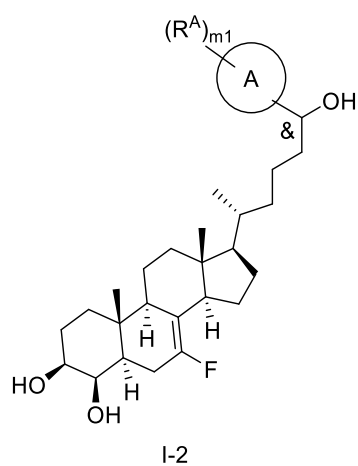
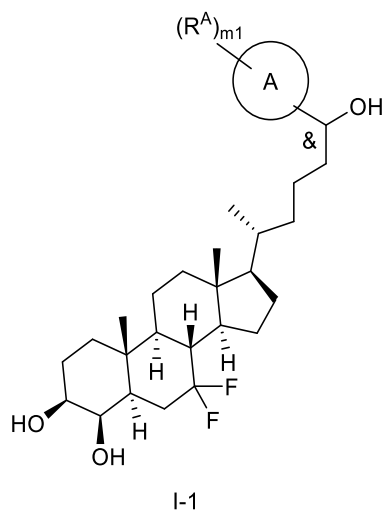


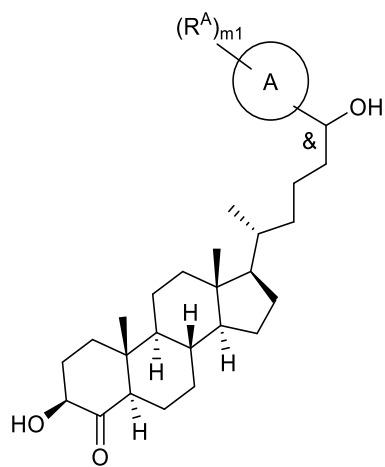




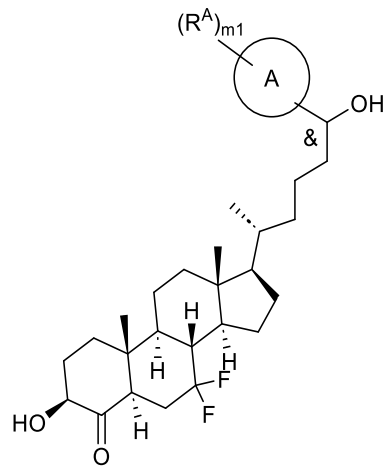


[0077] In some embodiments, the compound of Formula I is a compound of Formula I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, or I-10:

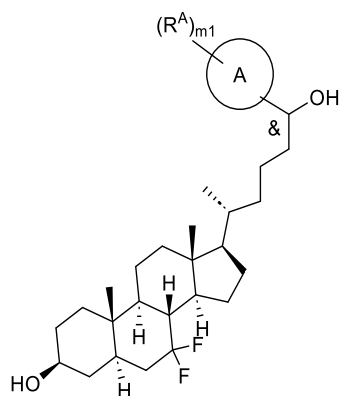




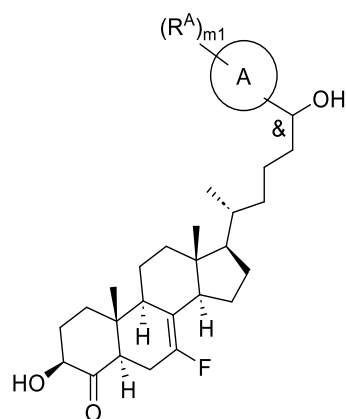
I-5



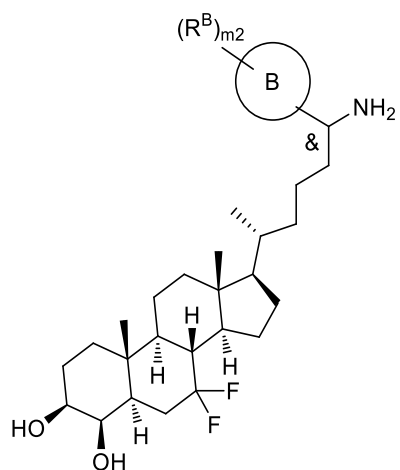
I-6



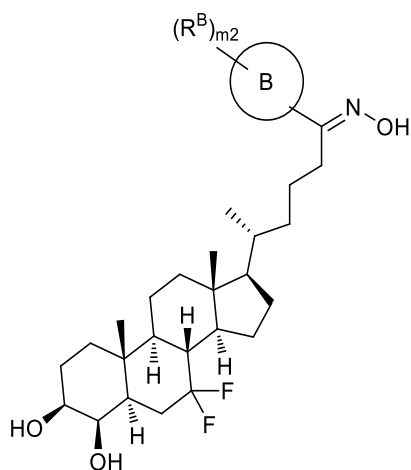
I-7



I-8



I-9



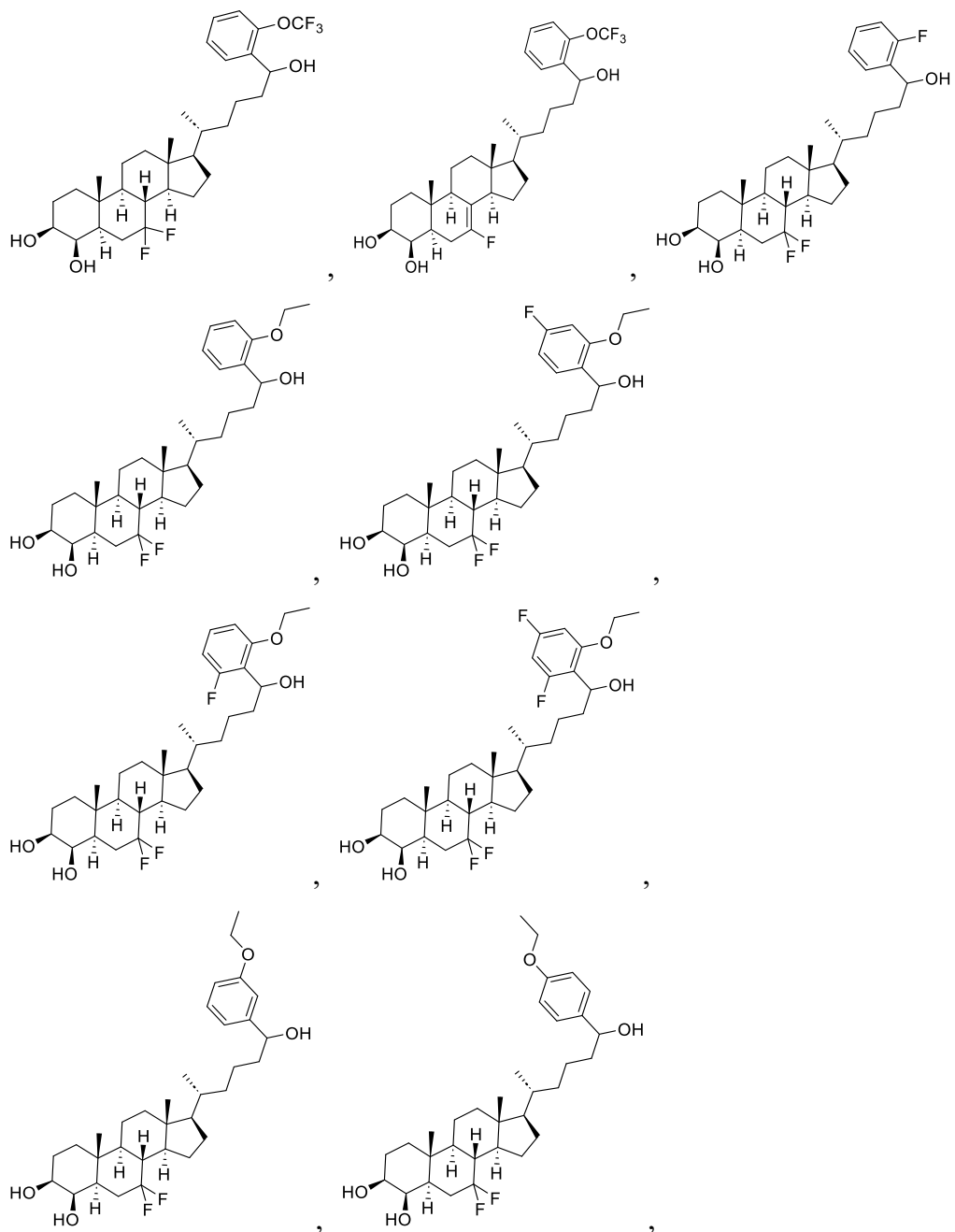
I-10

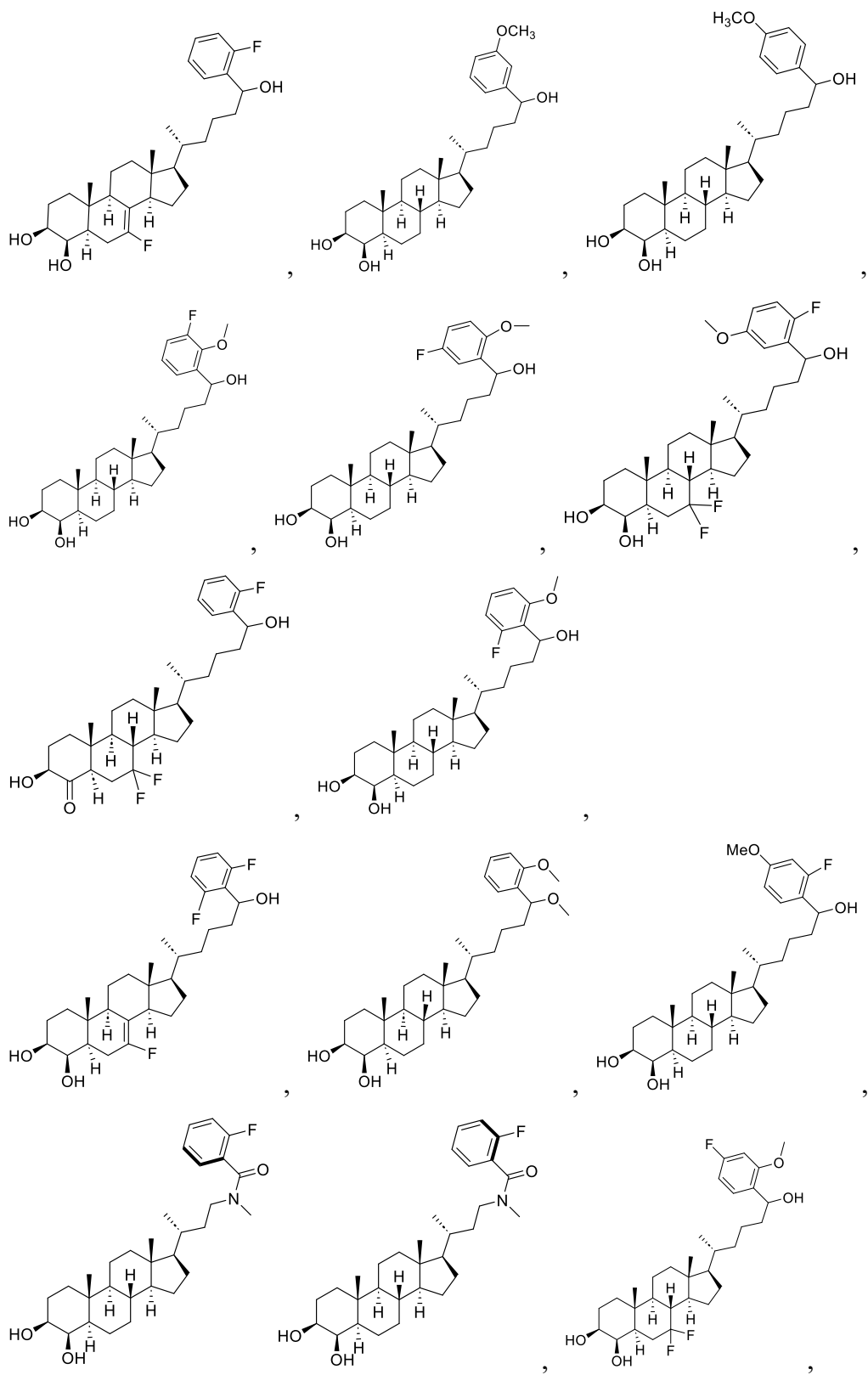
[0078] wherein the carbon atom marked with "&" indicates that when it is a
 5 chiral carbon atom, it is in the R configuration, S configuration, or a mixture of

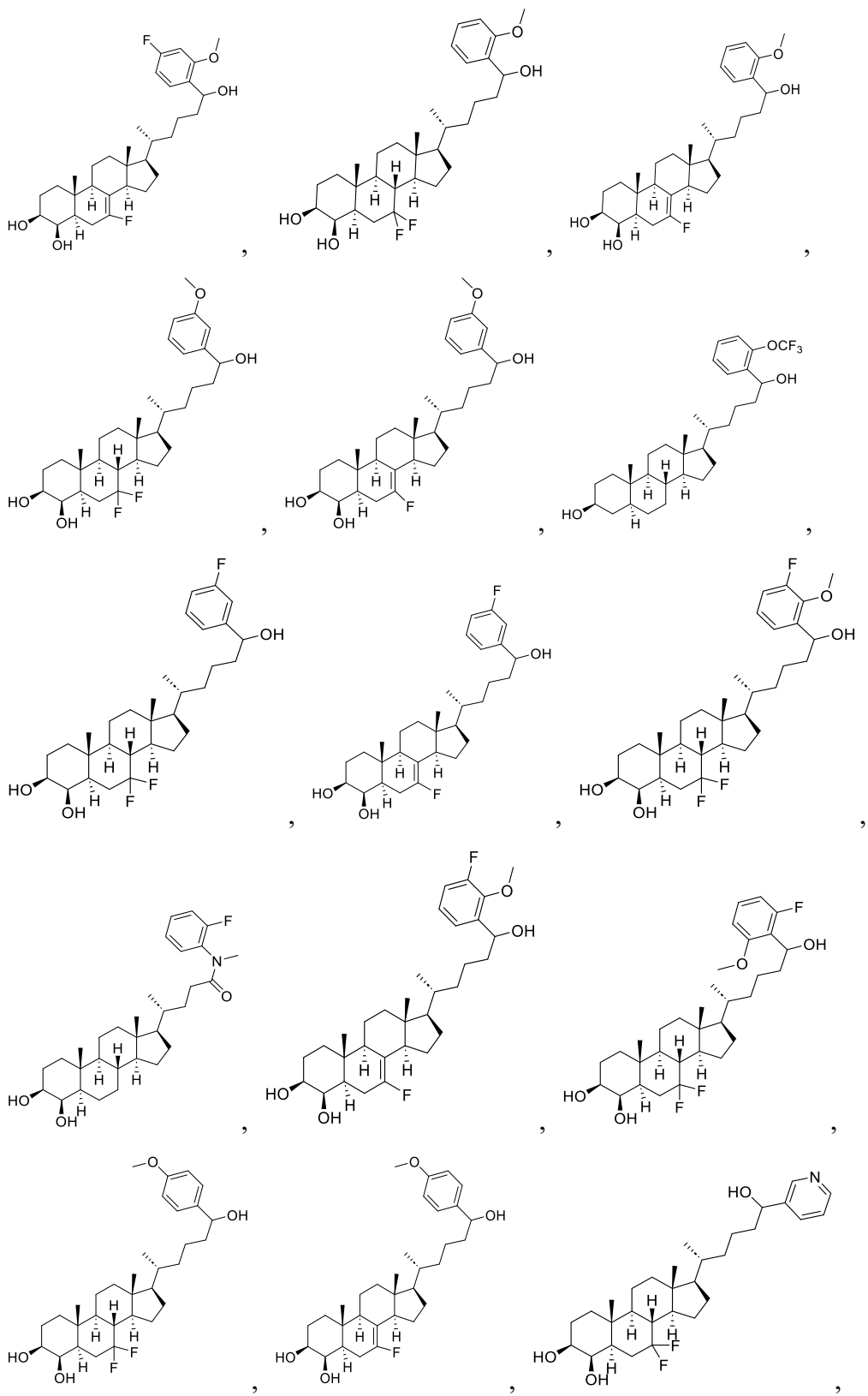
both;

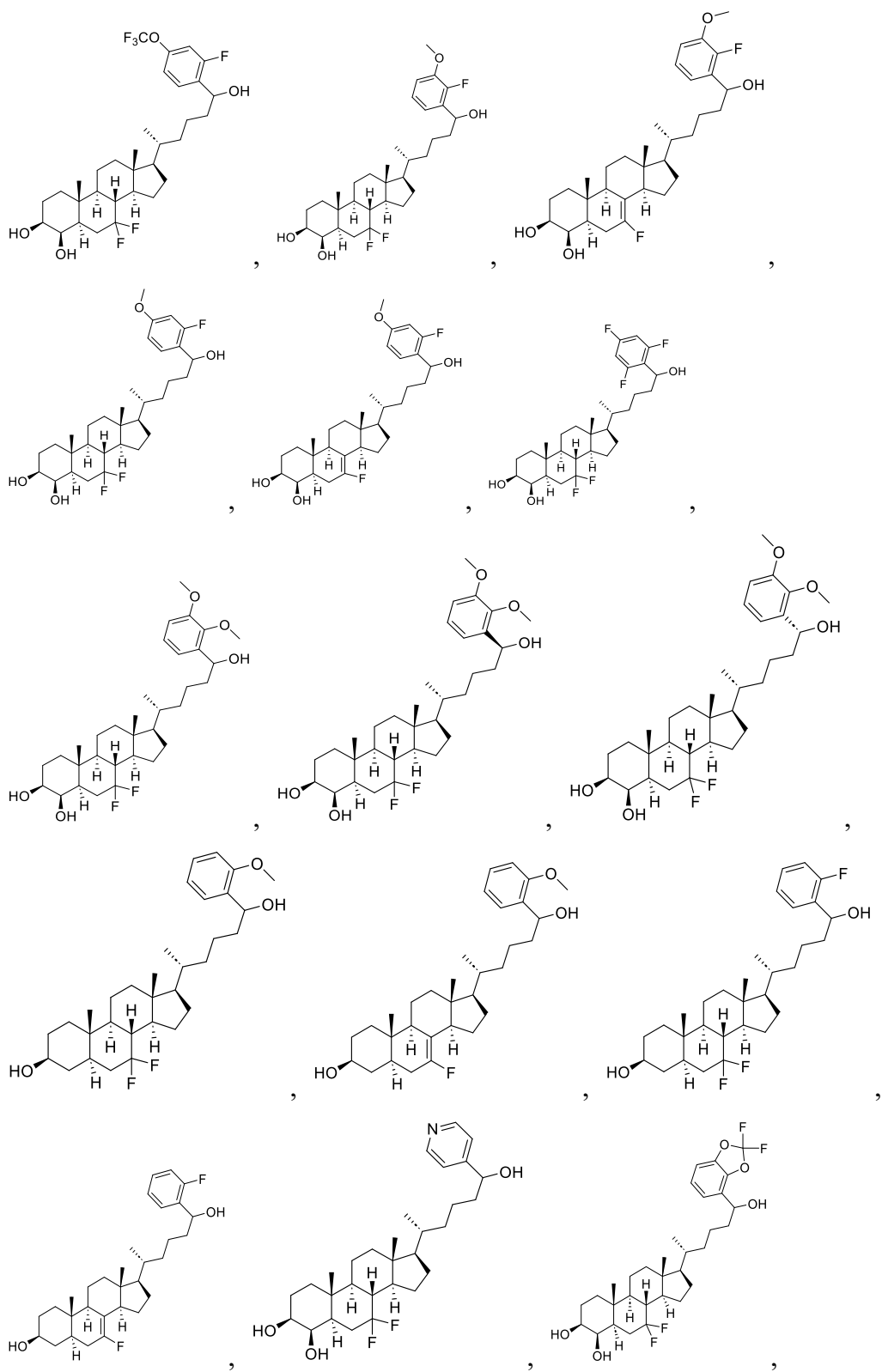
[0079] ring A, ring B, R^A, R^B, m1, and m2 are as defined in any one embodiment of the present disclosure.

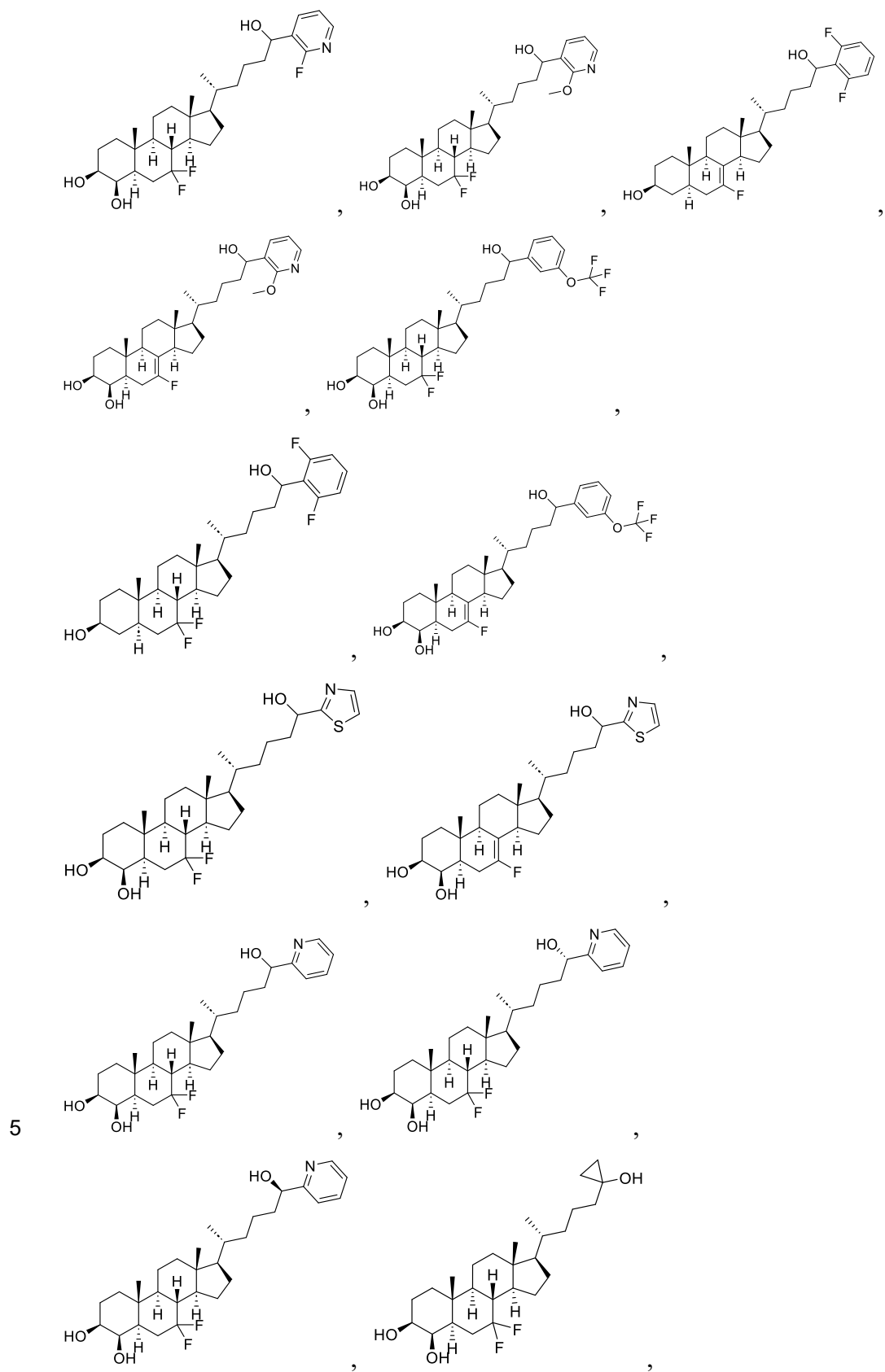
[0080] In some embodiments, the compound of Formula I is any one of the
5 following compounds:

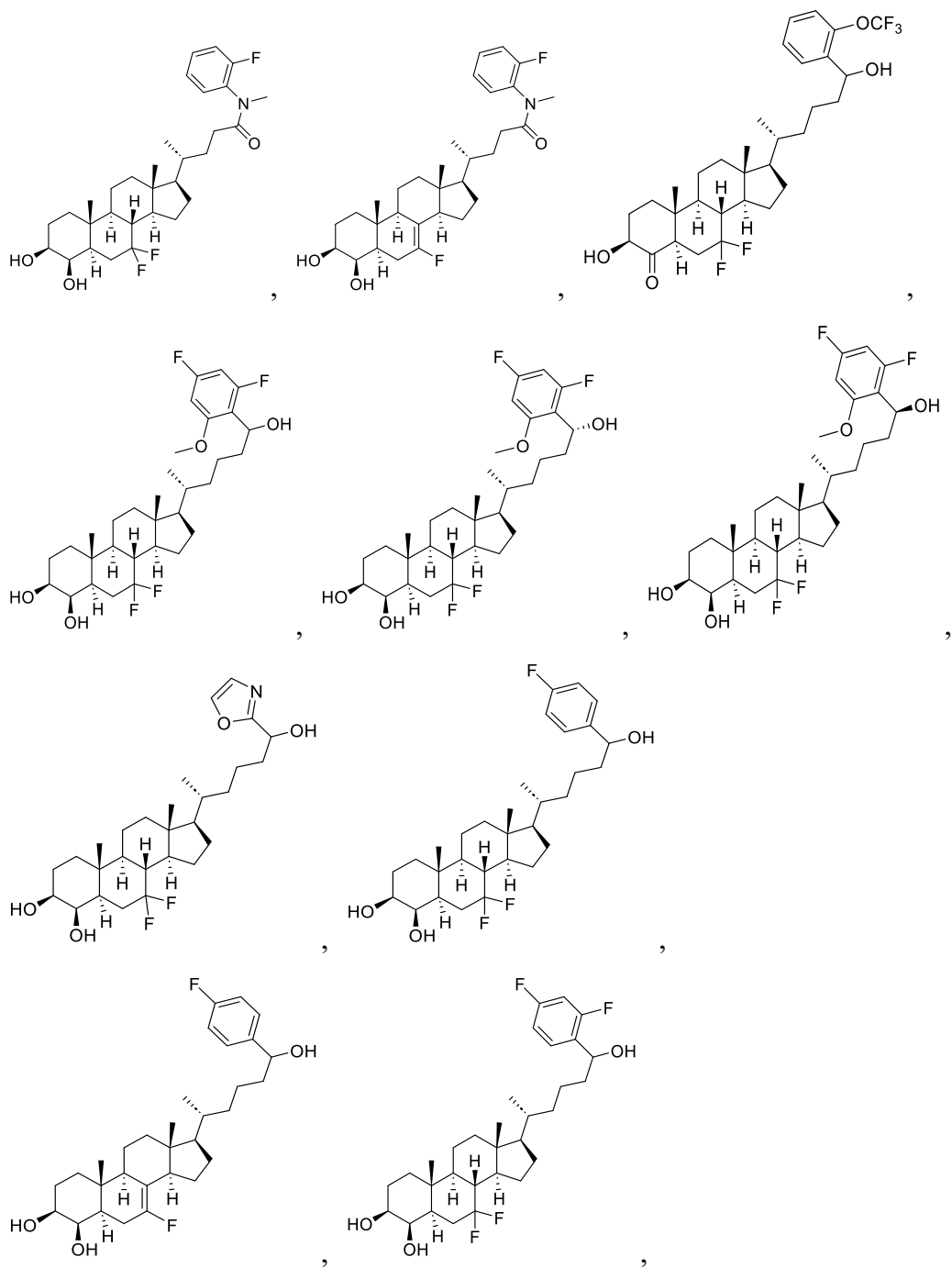


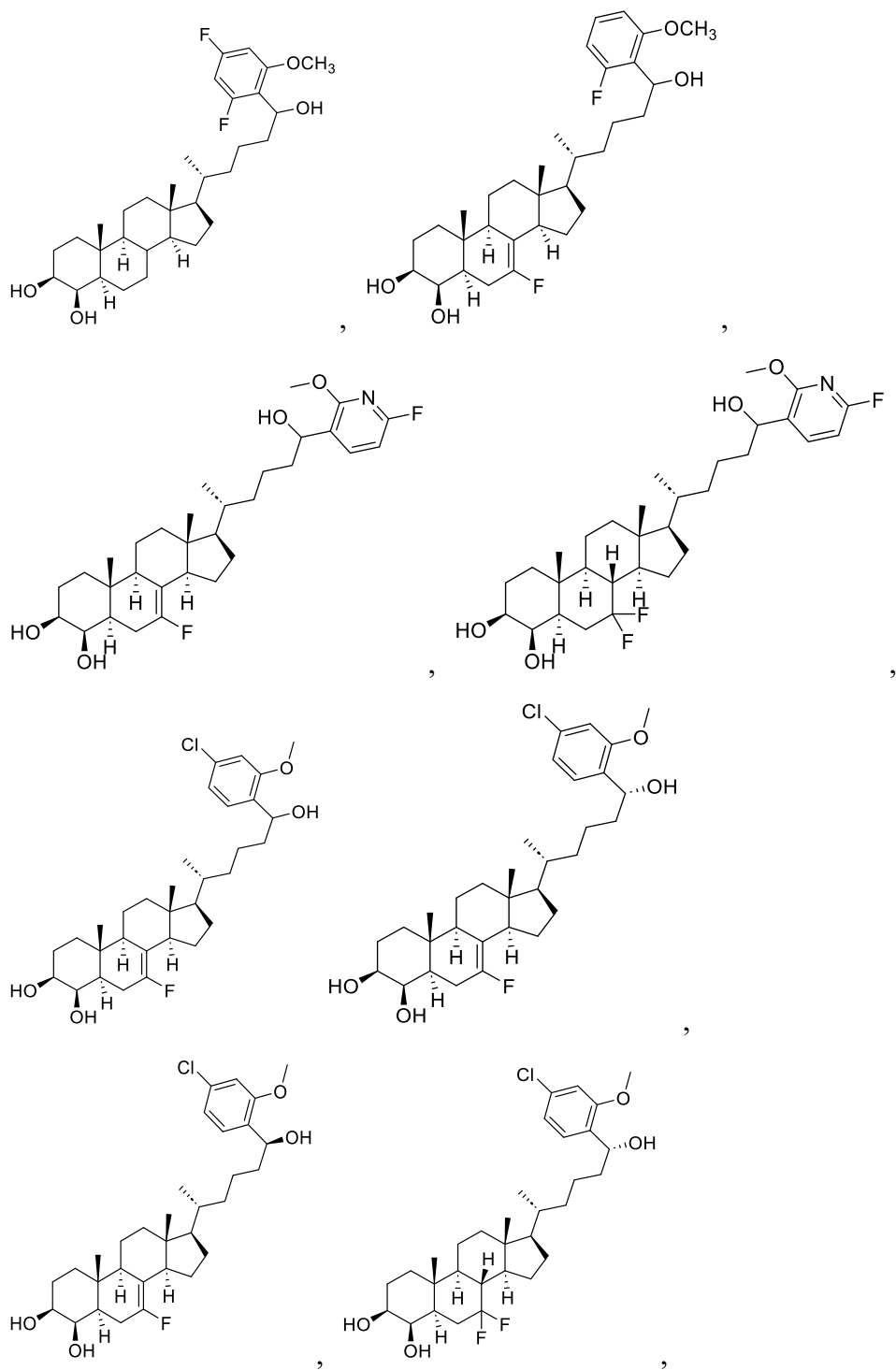


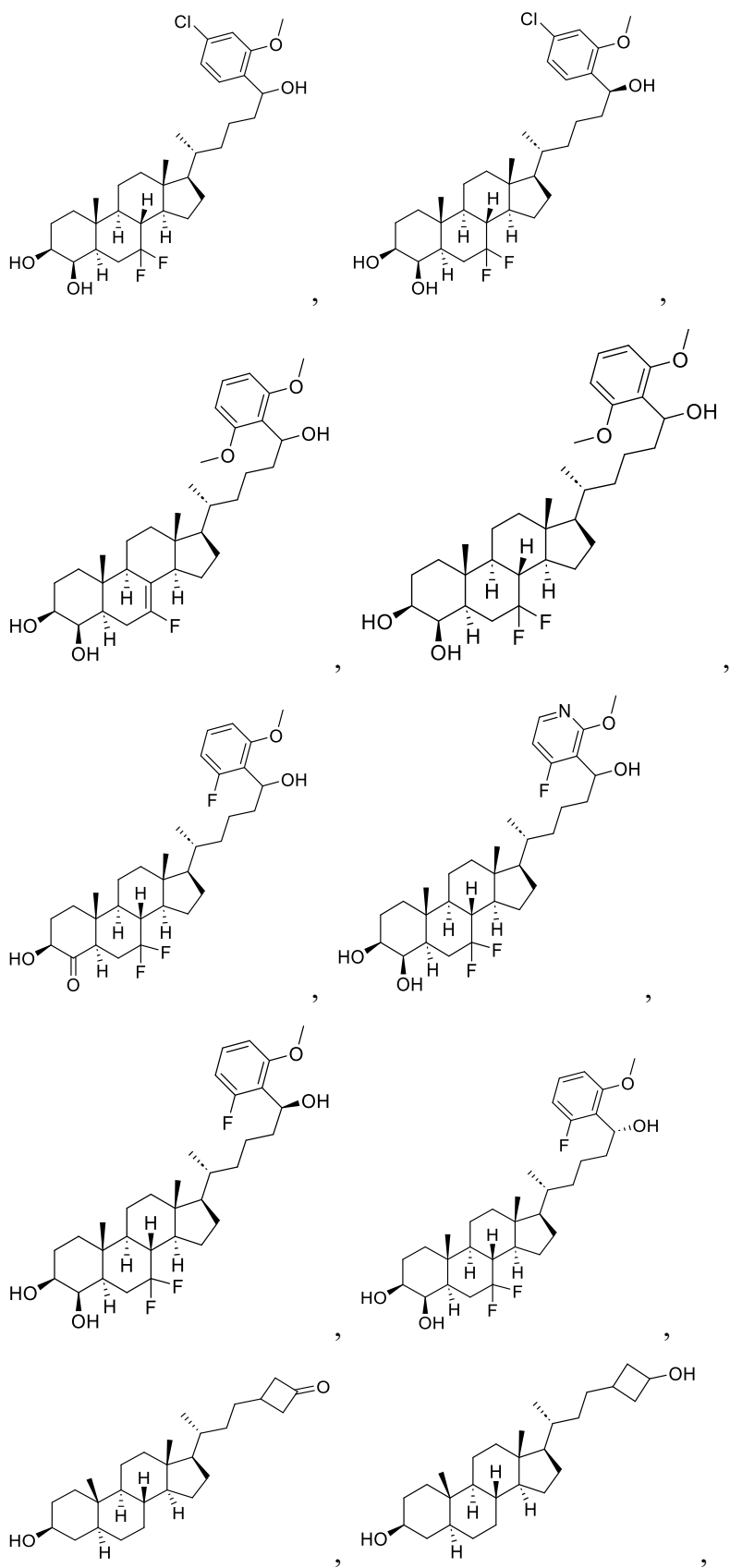


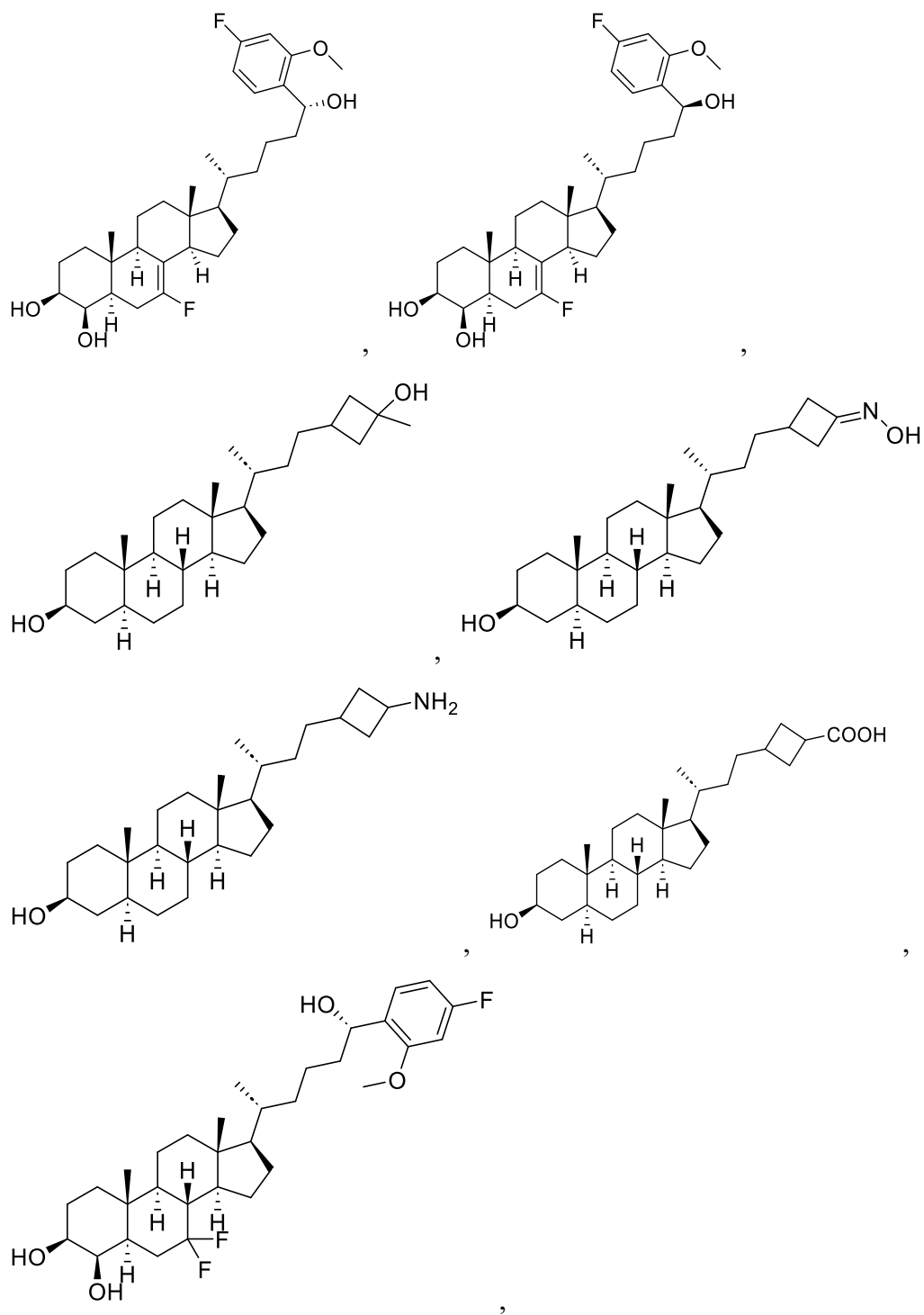


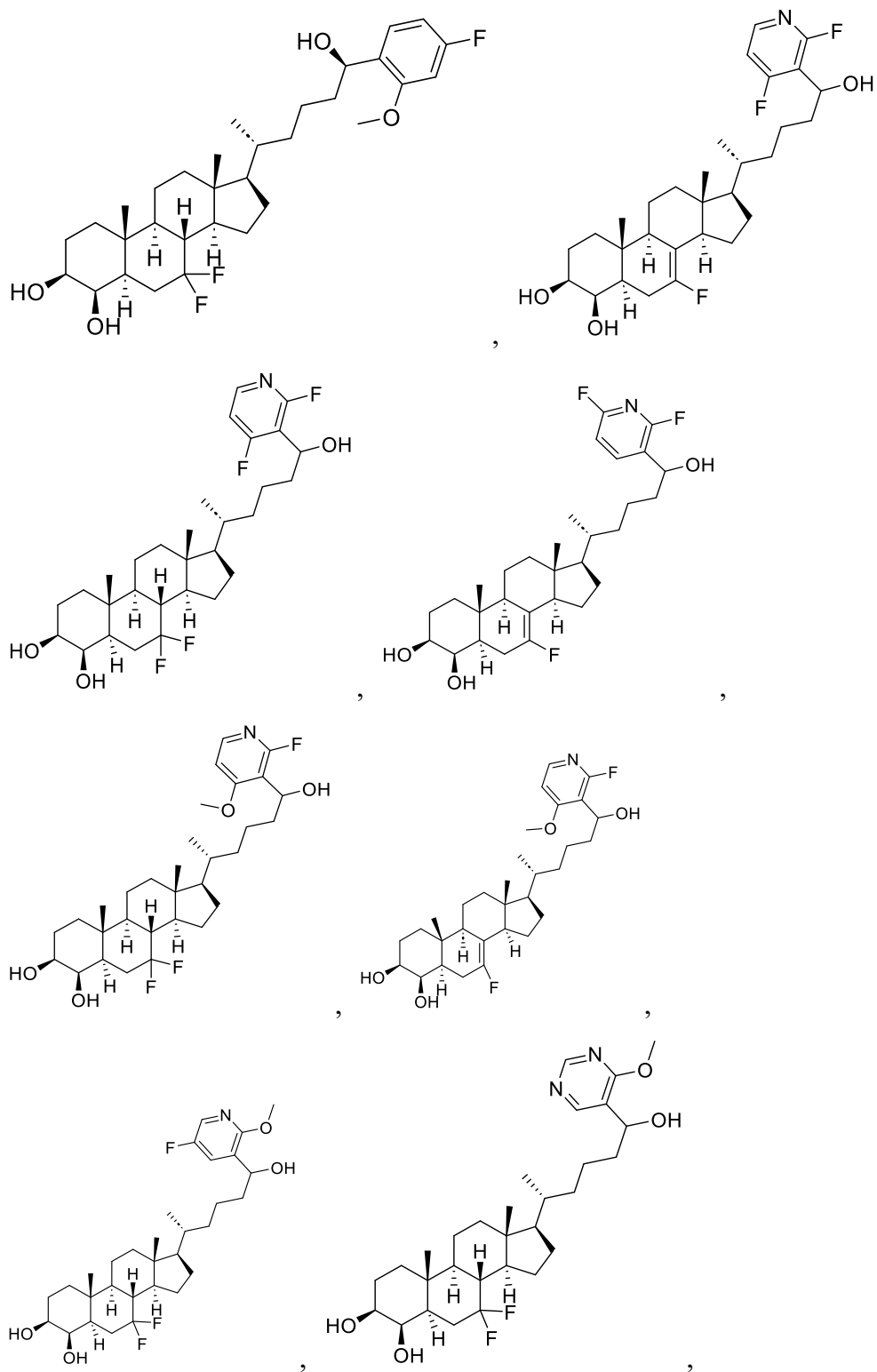


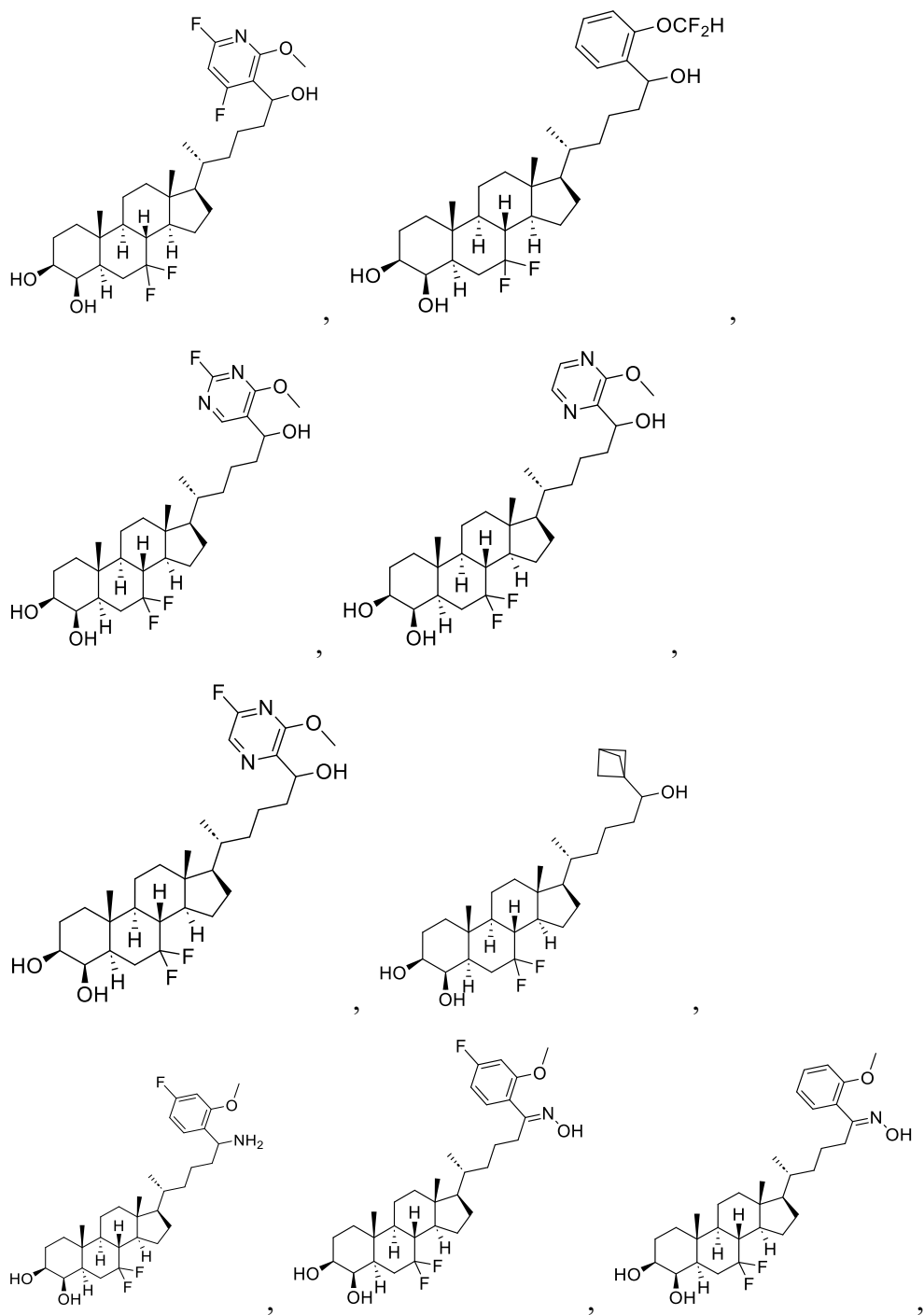


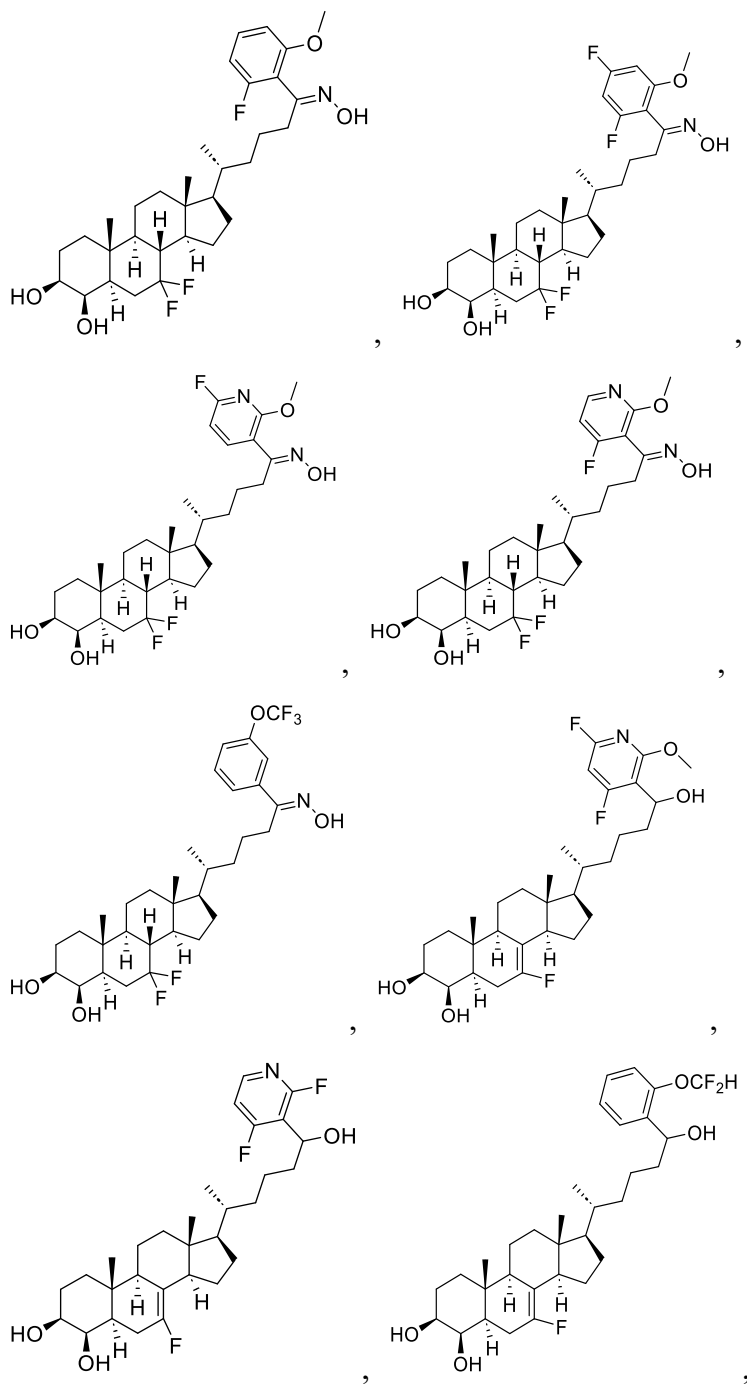


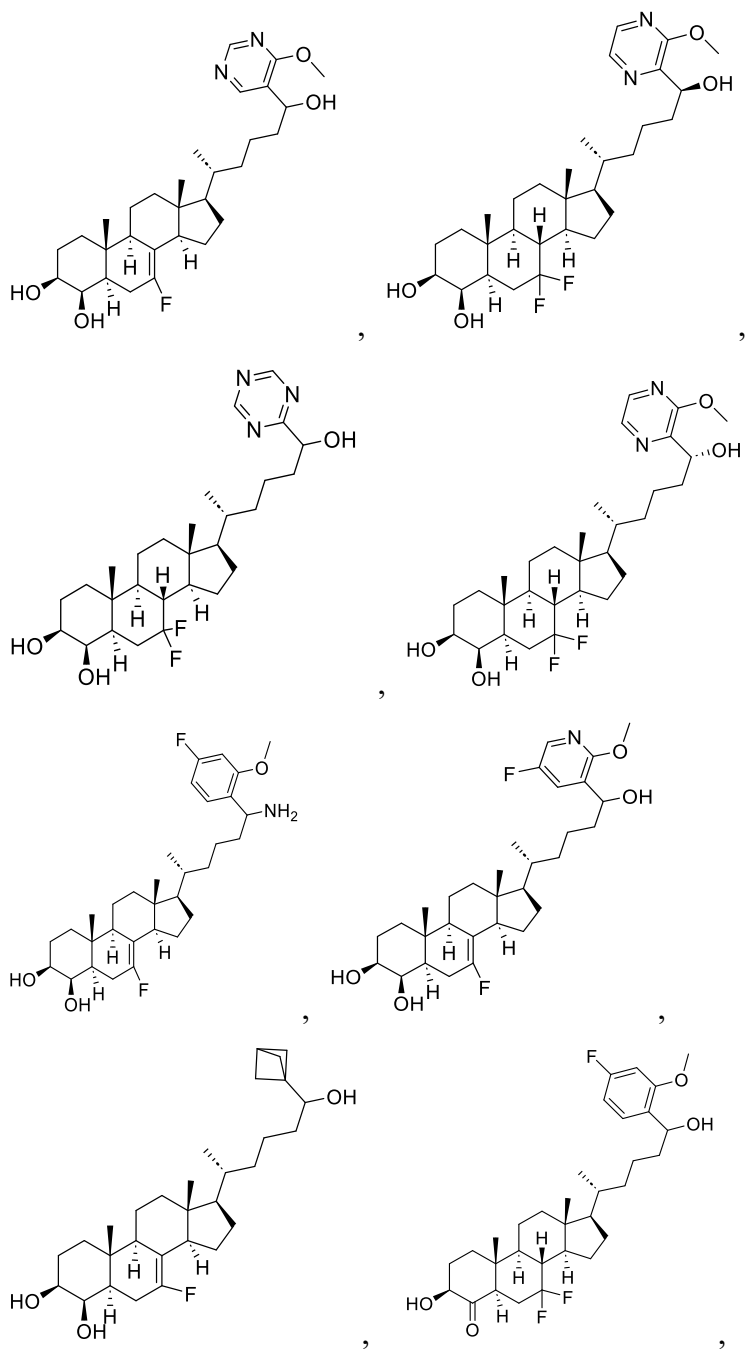


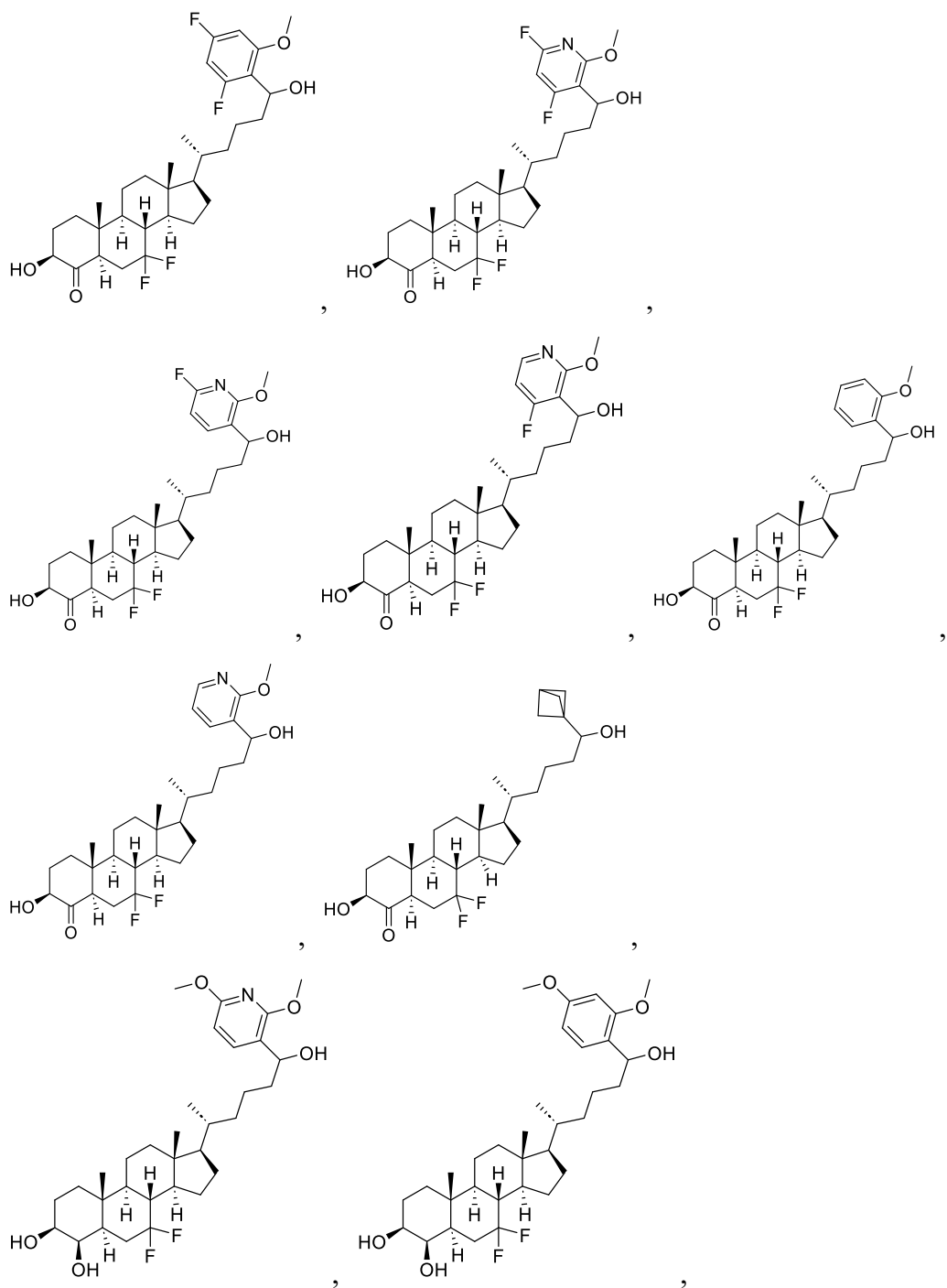


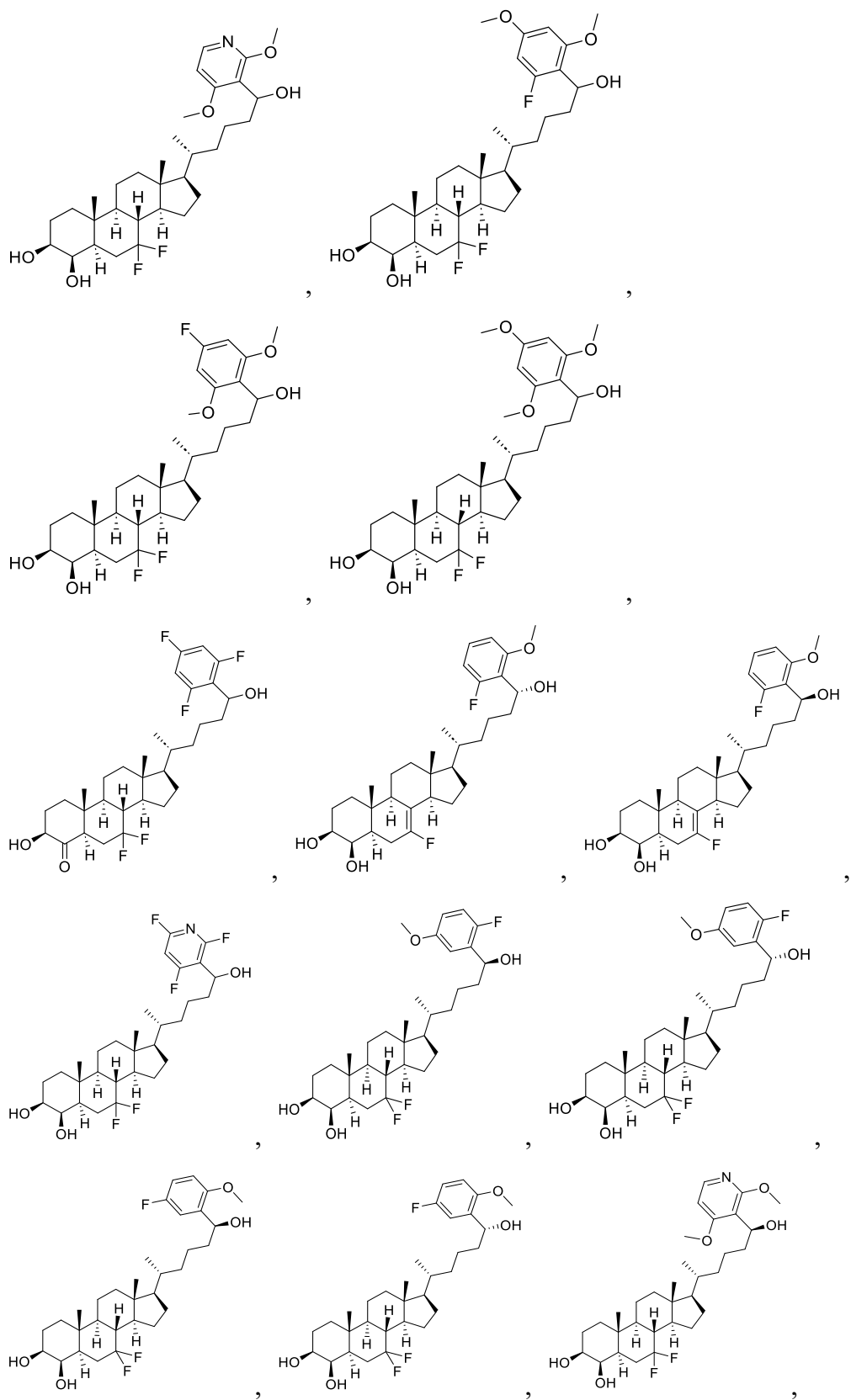


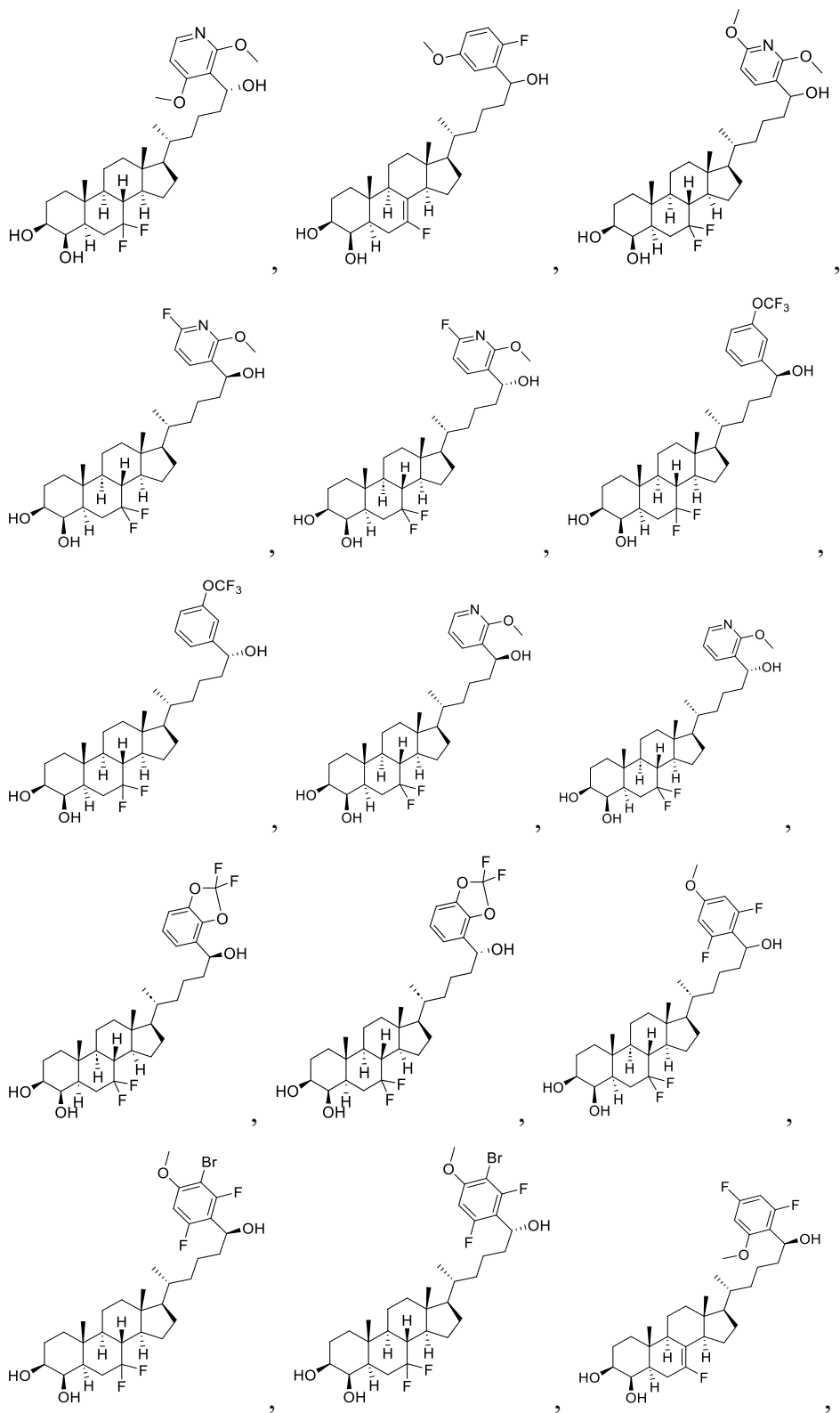


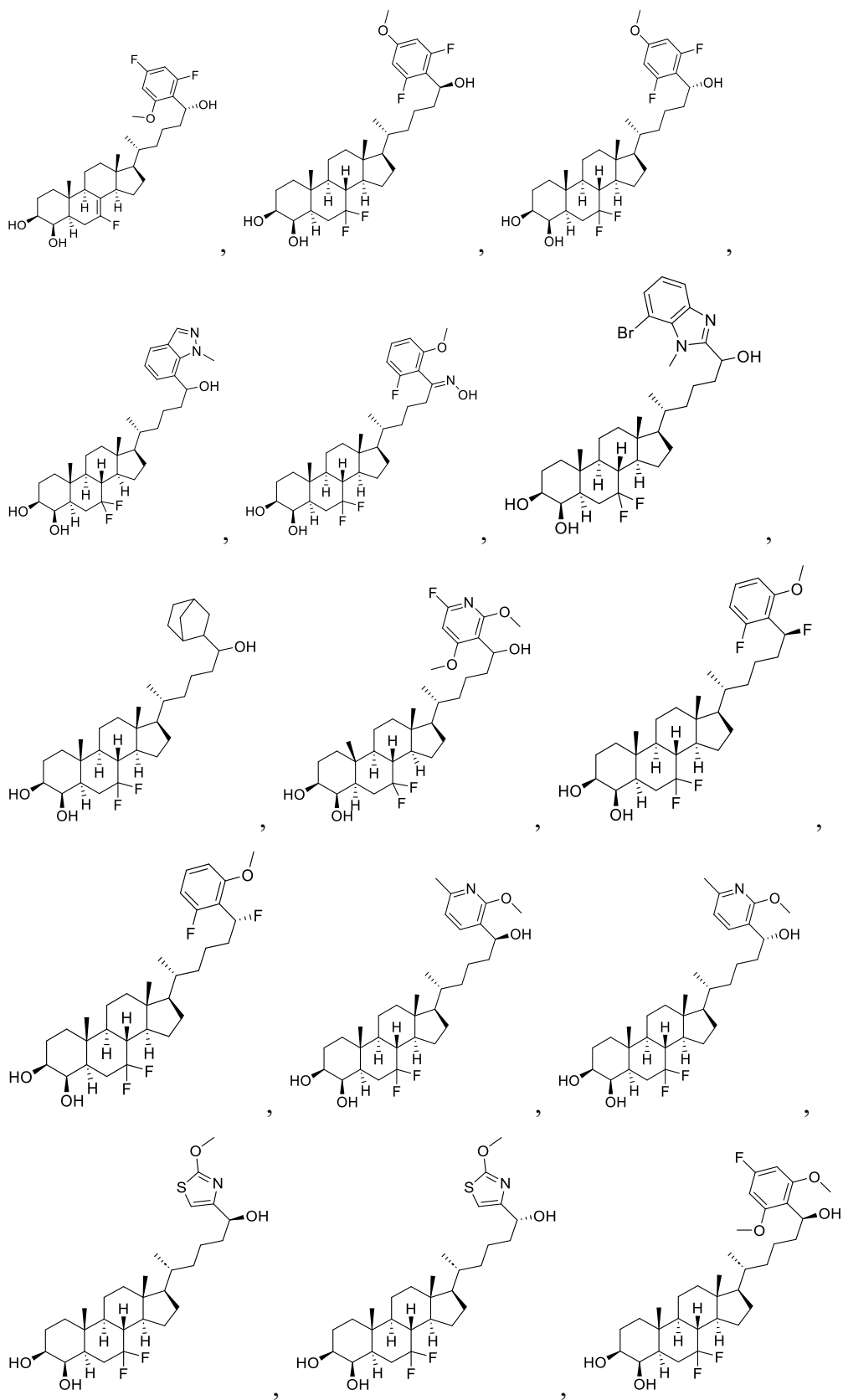


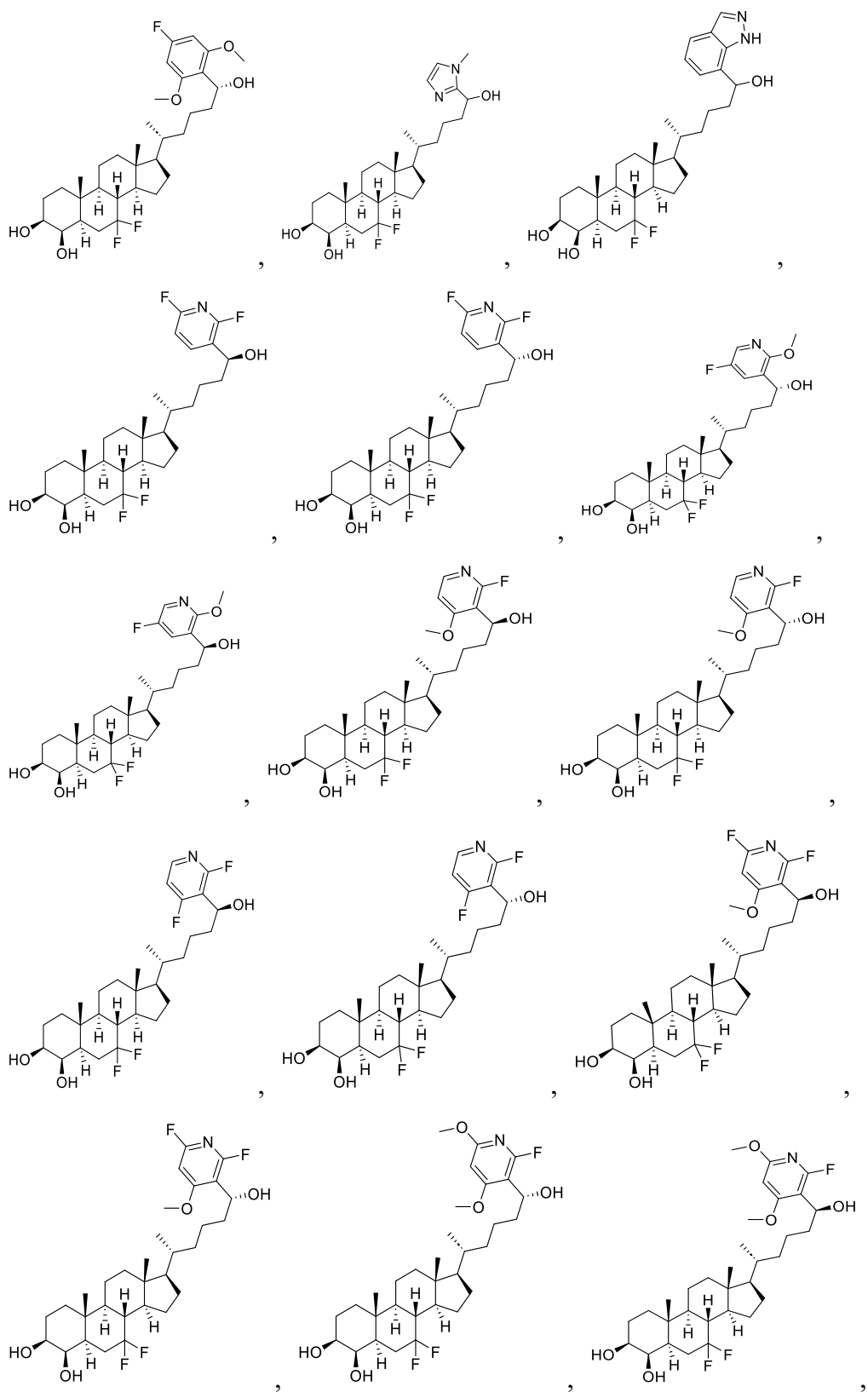


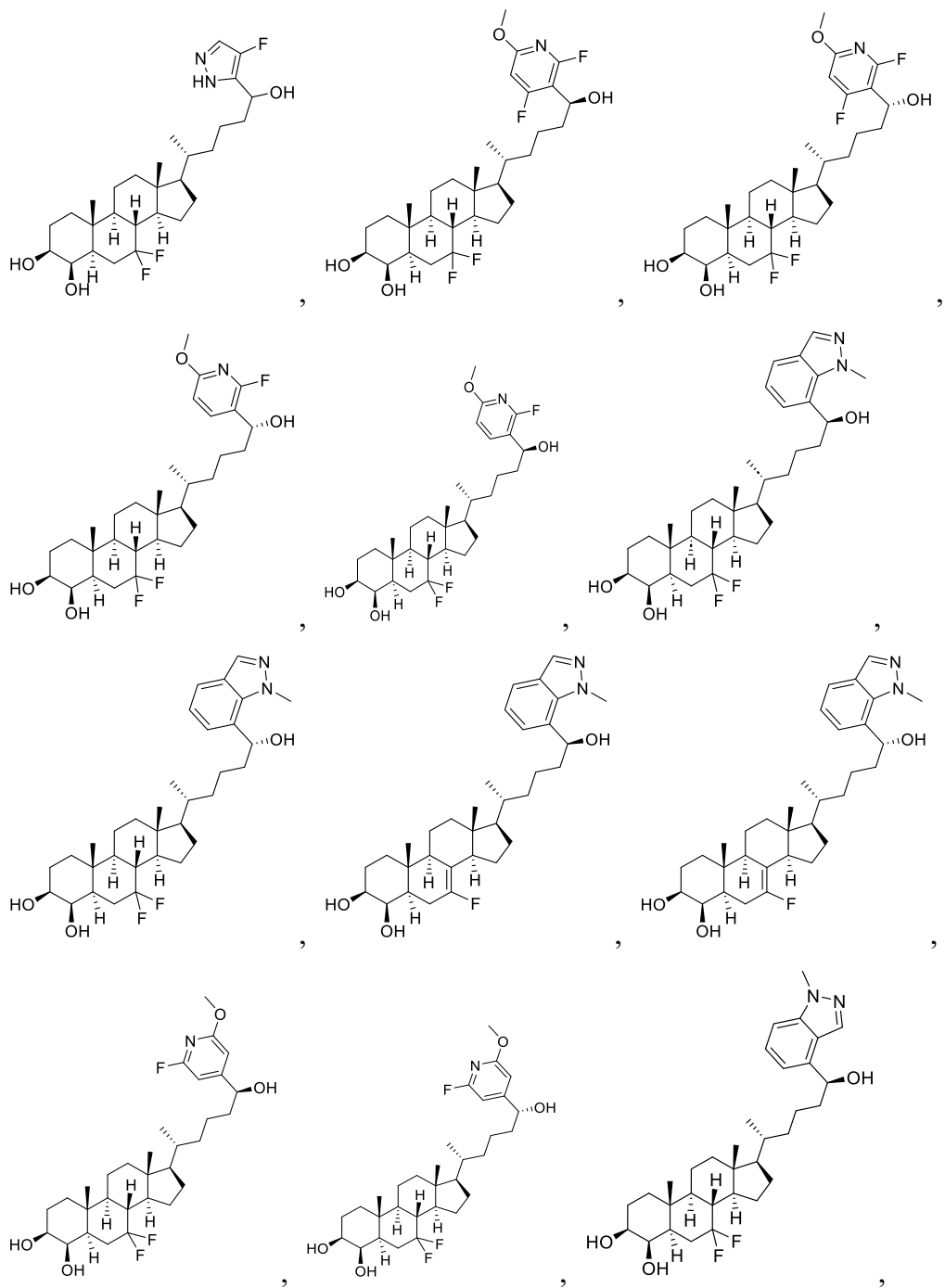


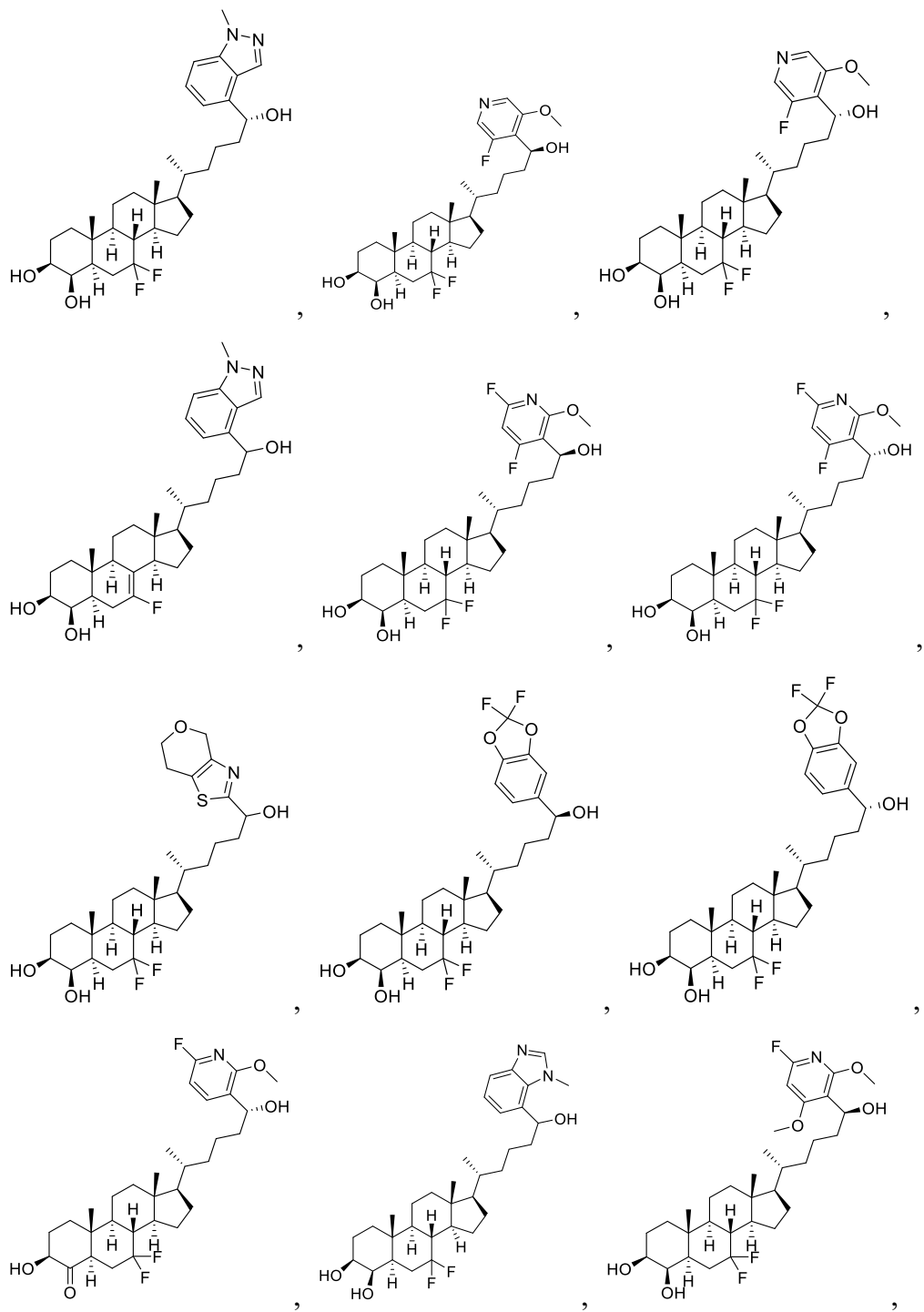


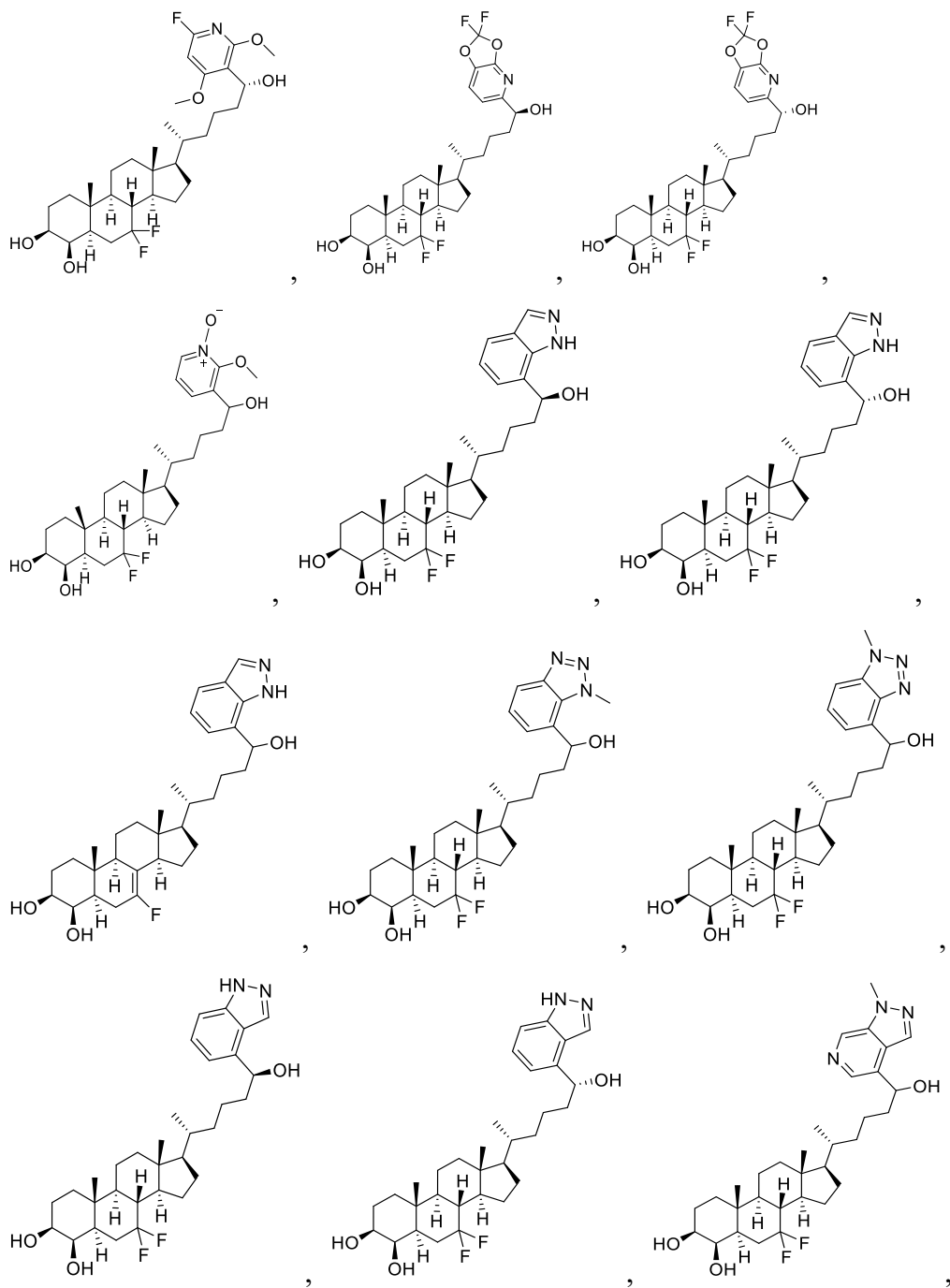


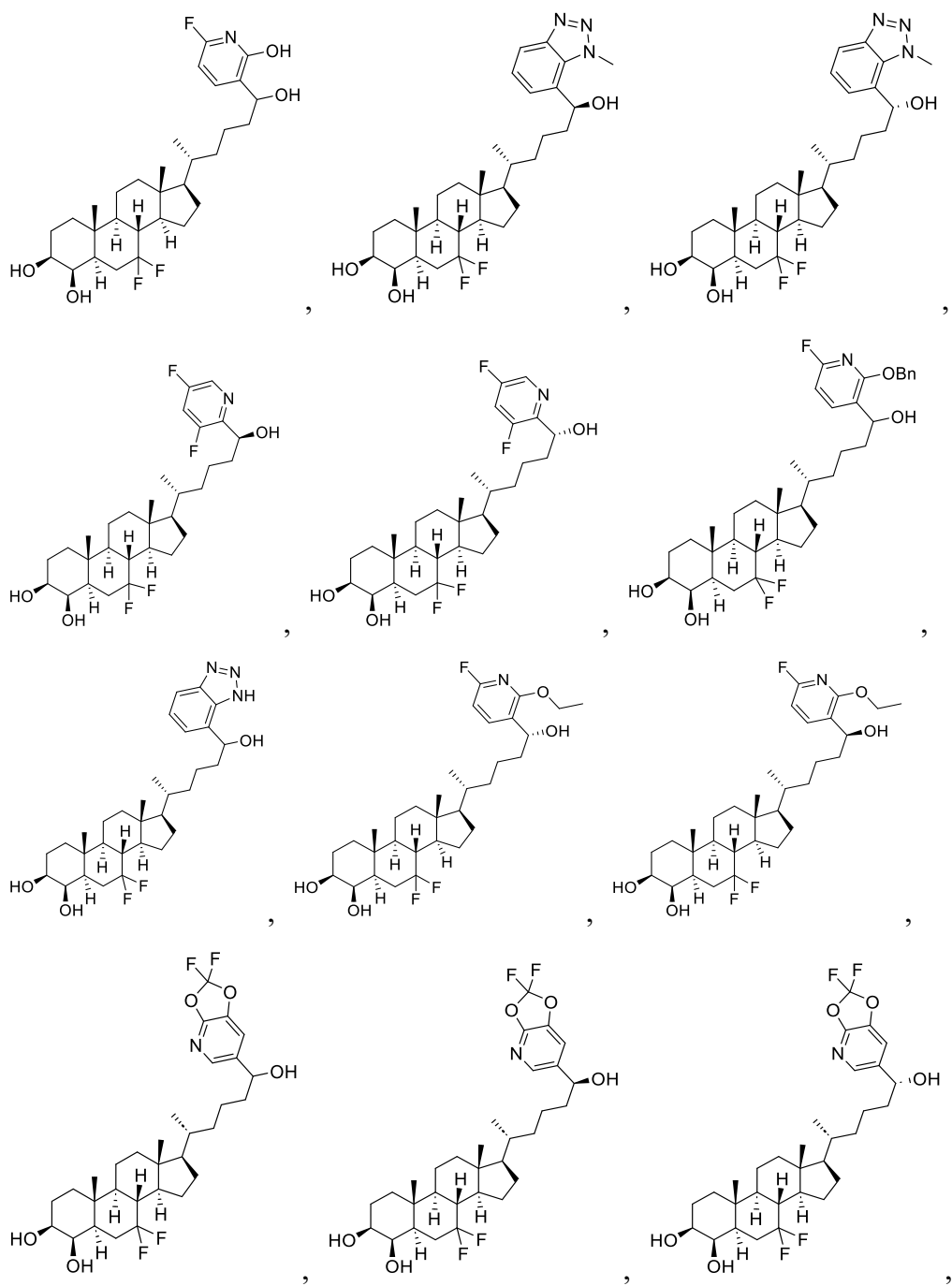


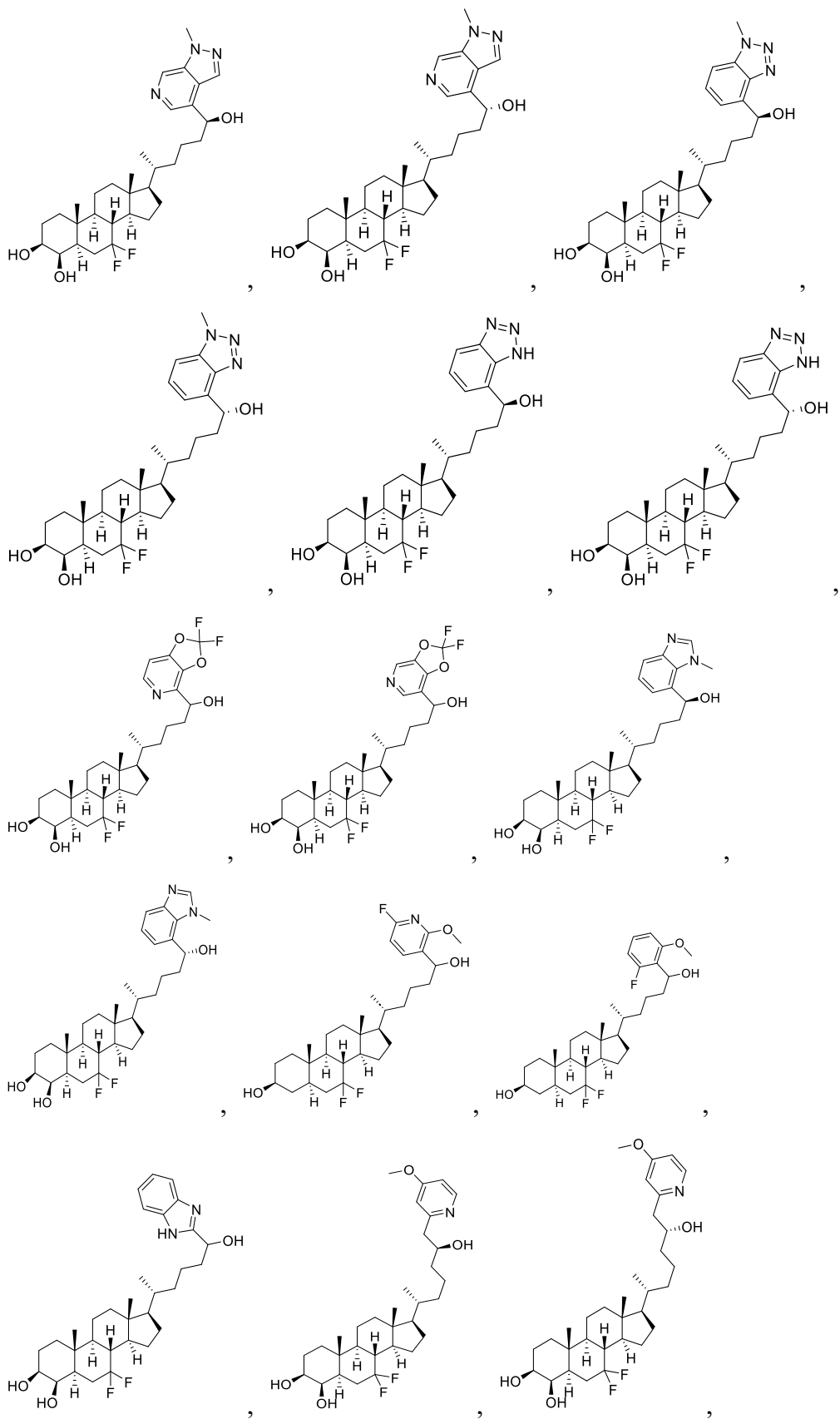


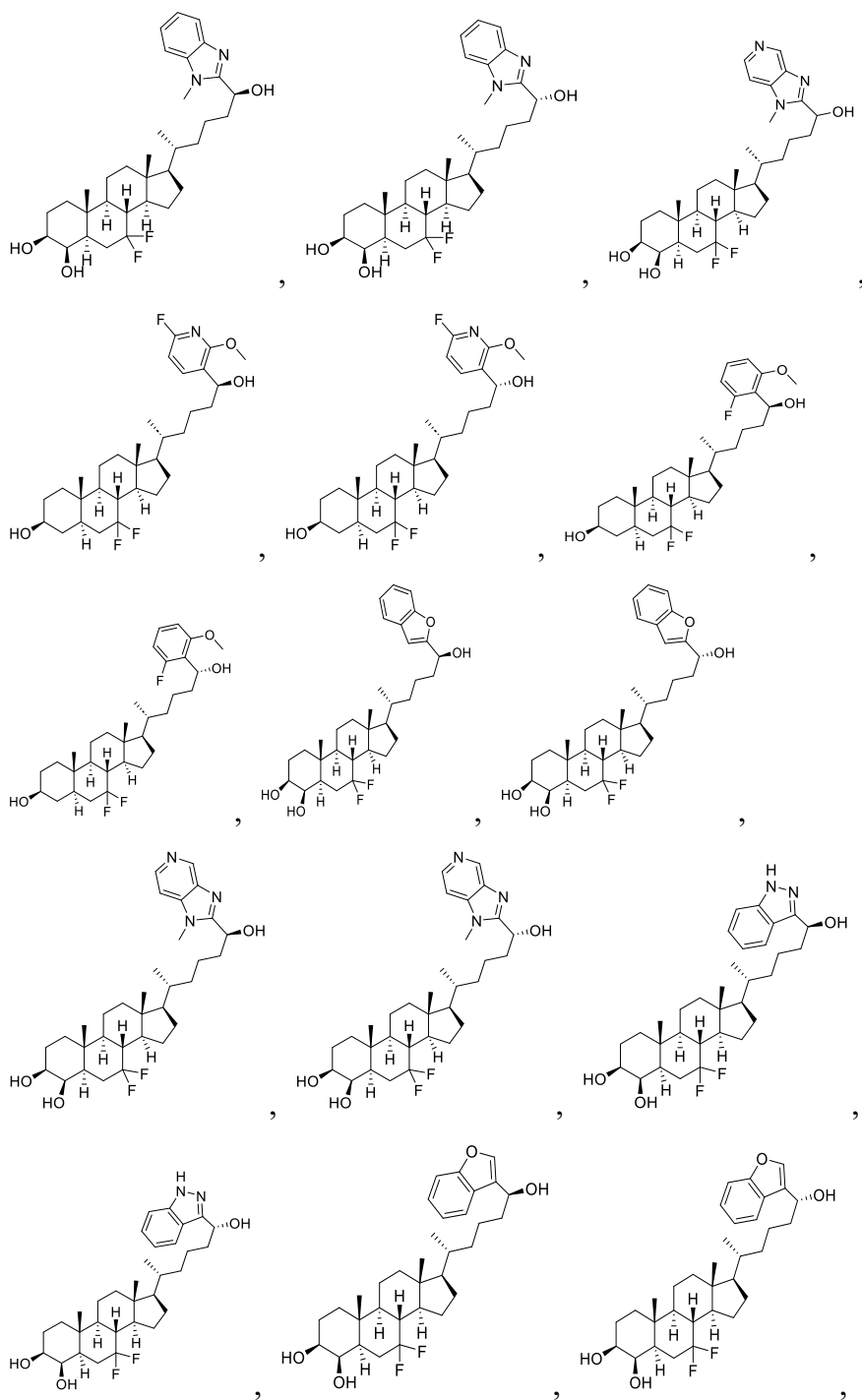


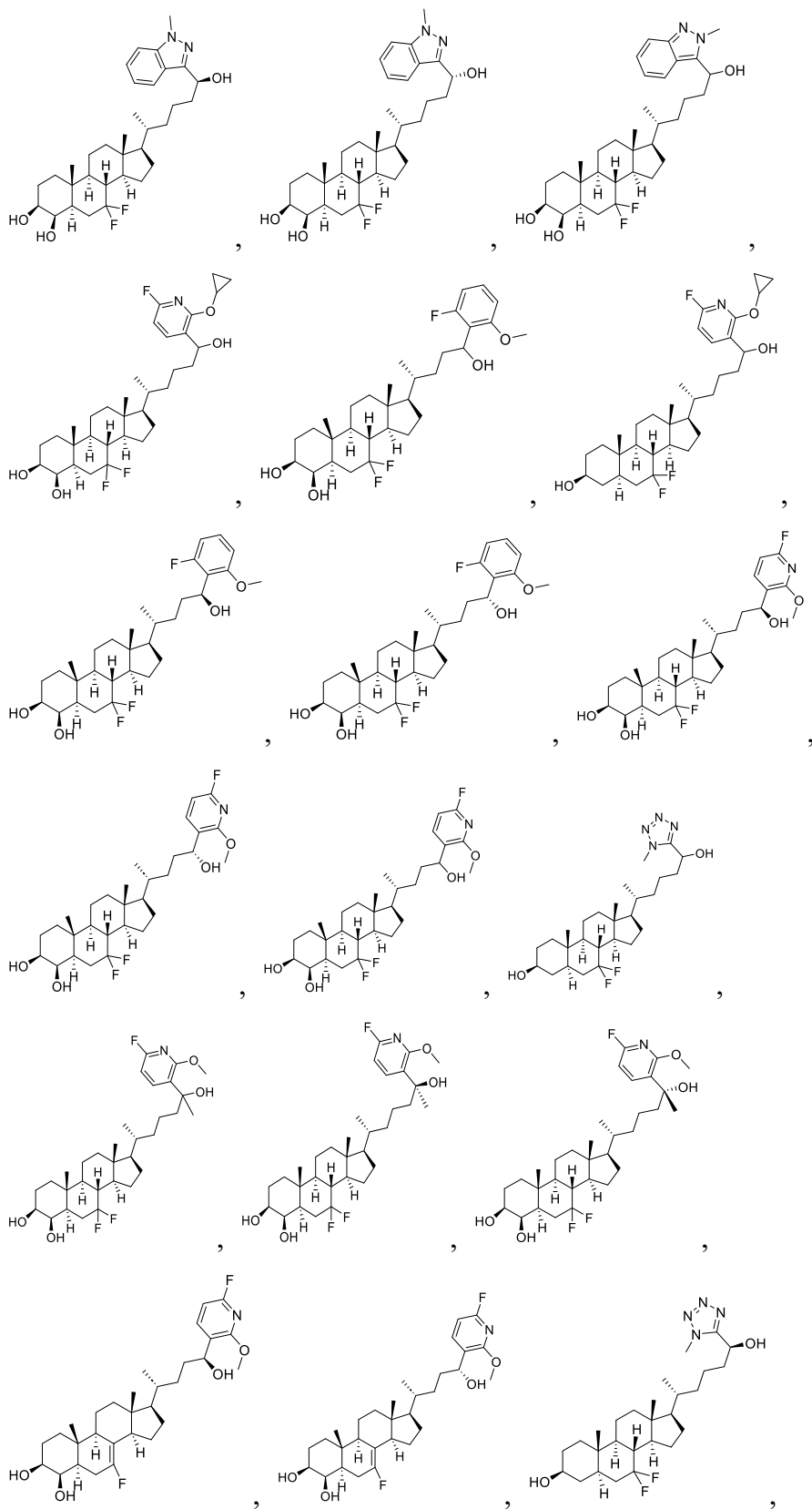


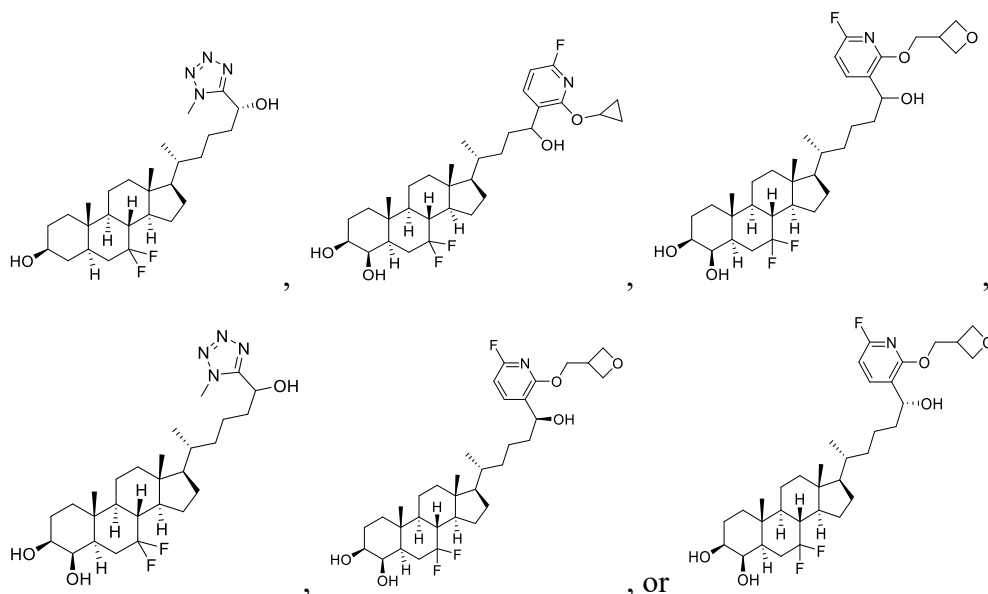












[0081] The present disclosure also provides a pharmaceutical composition comprising the compound according to any one embodiment of the present disclosure or a pharmaceutically acceptable salt thereof, and at least one pharmaceutical excipient.

[0082] The present disclosure also provides a use of the compound according to any one embodiment of the present disclosure or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to any one embodiment of the present disclosure in the manufacture of a medicament for preventing and/or treating a disease, wherein the disease is obesity, hyperlipidemia, fatty liver, diabetes, atherosclerosis, cardiovascular and cerebrovascular diseases, liver cancer, or skin injury.

[0083] The present disclosure also provides a use of the compound according to any one embodiment of the present disclosure or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described above in the manufacture of a medicament for inhibiting the SREBP pathway.

[0084] The present disclosure also provides a method of inhibiting the SREBP pathway, comprising administering to a subject an effective amount of the compound as described above or a pharmaceutically acceptable salt thereof.

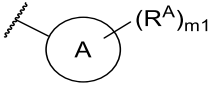
[0085] The present disclosure also provides a method of preventing and/or treating a disease, comprising administering to a subject an effective amount of

the compound according to any one embodiment of the present disclosure or a pharmaceutically acceptable salt thereof, wherein the disease is obesity, hyperlipidemia, fatty liver, diabetes, atherosclerosis, cardiovascular and cerebrovascular diseases, liver cancer, or skin injury.

5 **[0086]** Definitions and Explanations

[0087] Unless otherwise specified, the following terms and phrases used herein are intended to have the following meanings. A specific term or phrase not specifically defined should not be considered indefinite or unclear but should be understood in its ordinary meaning. When a trade name appears herein, it is
10 intended to refer to the corresponding product or its active ingredient.

[0088] In this text, the term "substituted" or "substituent" refers to the replacement of a hydrogen atom in a group with the specified group. When the substitution position is not specified, substitution may occur at any position, but only the formation of a stable or chemically feasible compound is permitted. For

15 example, the structure  indicates that the hydrogen atoms on ring A are substituted by m1 R^A groups, where each R^A is the same or different when multiple R^A groups are present.

[0089] When any variable (*e.g.*, R^A) appears more than once in the composition or structure of a compound, its definition is independent in each case.

20 **[0090]** In this text, the term "alkyl" refers to a saturated linear or branched monovalent hydrocarbon group. C₁-C₆ alkyl represents an alkyl group having 1 to 6 carbon atoms. In some embodiments, C₁-C₆ alkyl may be C₁-C₄ alkyl. C₁-C₄ alkyl includes methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

25 **[0091]** In this text, the term "haloalkyl" refers to a group formed by replacing one or more hydrogen atoms in an alkyl group with halogen, wherein the alkyl group is defined as above. Examples of the haloalkyl include, but are not limited to, monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, *etc.*

[0092] In this text, the term "alkoxy" refers to -O-alkyl, wherein the alkyl is
30 defined as above. C₁-C₄ alkoxy refers to -O-(C₁-C₄ alkyl), wherein the C₁-C₄

alkyl is defined as above. That is, C₁-C₄ alkoxy may specifically be methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, or *tert*-butoxy.

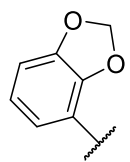
[0093] In this text, the term "cycloalkyl" refers to a saturated monocyclic or polycyclic (*e.g.*, fused, spiro, or bridged) cyclic hydrocarbon group. Examples
5 of the cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl,



cyclopentyl, cyclohexyl, *etc.* C₃₋₆ cycloalkyl may specifically be C₃, C₄, C₅, or C₆ cycloalkyl. In some embodiments, the cycloalkyl is monocyclic. In some embodiments, the cycloalkyl is polycyclic (*e.g.*, fused, spiro, or bridged).

[0094] In this text, the term "C₆₋₁₀ aryl" refers to phenyl or naphthyl.

10 [0095] In this text, the term "heteroaryl" refers to an aromatic monocyclic or fused ring group formed by carbon atoms and at least one heteroatom, wherein the heteroatom is independently selected from the group consisting of 1, 2, or 3 kinds of N, O, and S. The 5- to 10-membered heteroaryl may specifically be 5-, 6-, 7-, 8-, 9-, or 10-membered heteroaryl, such as 5- to 6-membered heteroaryl or
15 8- to 10-membered fused heteroaryl. The 5- to 6-membered heteroaryl is monocyclic, and specific examples include, but are not limited to, pyrrole, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrazole, imidazole, pyridine, pyrimidine, and pyrazine. Examples of the 8- to 10-membered fused heteroaryl include, but are not limited to, benzopyrrole, benzofuran, benzothiophene,
20 benzoxazole, benzoisoxazole, benzothiazole, benzoisothiazole, benzopyrazole, benzimidazole, benzopyridine, benzopyrimidine, benzopyrazine, thiazolothiazole,



pyridopyridine, pyridopyrazine, pyridopyrimidine, and

[0096] In this text,  in chemical structural formulas denotes the connection position. When  is included in a cyclic group and the ring atom to which
25  is connected is not specified,  may connect to any ring atom, provided that only a stable or chemically feasible compound is formed.

[0097] In this text, the term "pharmaceutically acceptable salt" refers to a salt formed by a suitable non-toxic organic acid, inorganic acid, organic base, or inorganic base with the compound, which retains the biological activity of the compound. The organic acid may be any conventional organic acid capable of forming salts in the field. The inorganic acids may be any conventional inorganic acids capable of forming salts in the field. The organic base may be any conventional organic base capable of forming salts in the field. The inorganic base may be any conventional inorganic base capable of forming salts in the field.

[0098] In the chemical structure, a solid wedge bond () and a dashed wedge bond () are used to indicate the absolute configuration of a stereocenter, while a solid straight bond () and a dashed straight bond () are used to indicate the relative configuration of a stereocenter. The bond "  " does not specify a configuration, meaning that if configurational isomers exist in the chemical structure, the bond "  " can be "  " or "  ", or it may simultaneously include both configurations "  " and "  " (for example, the ratio of "  " to "  " is 1:1). When the carbon-carbon double bond is not specified for its particular configuration, it can be either E or Z configuration. Stereoisomers can be synthesized using chiral starting materials, prepared by chiral resolution, or resolved using conventional techniques such as, but not limited to, high-performance liquid chromatography (HPLC) with a chiral column.

[0099] In this text, the term "subject" includes any animal, preferably a mammal, and more preferably a human.

[0100] In this text, the term "effective amount" refers to a sufficient amount of a medicament or agent that is non-toxic but achieves the desired effect. The determination of an effective amount varies from person to person, depending on the age and general condition of the recipient, as well as the specific active substance. The appropriate effective amount in individual cases can be determined by those skilled in the art through routine experimentation.

[0101] Without departing from the common knowledge in the field, the above

preferred conditions can be combined arbitrarily to obtain various preferred embodiments of the present disclosure.

[0102] The reagents and raw materials used in the present disclosure are all commercially available.

5 [0103] The positive and progressive effects of the present disclosure are as follows: The present disclosure provides a novel class of compounds, which exhibit inhibitory activity against the SREBP pathway and can be used for preventing and/or treating diseases such as obesity, hyperlipidemia, fatty liver, diabetes, atherosclerosis, cardiovascular and cerebrovascular diseases, liver
10 cancer, skin damage, *etc.*

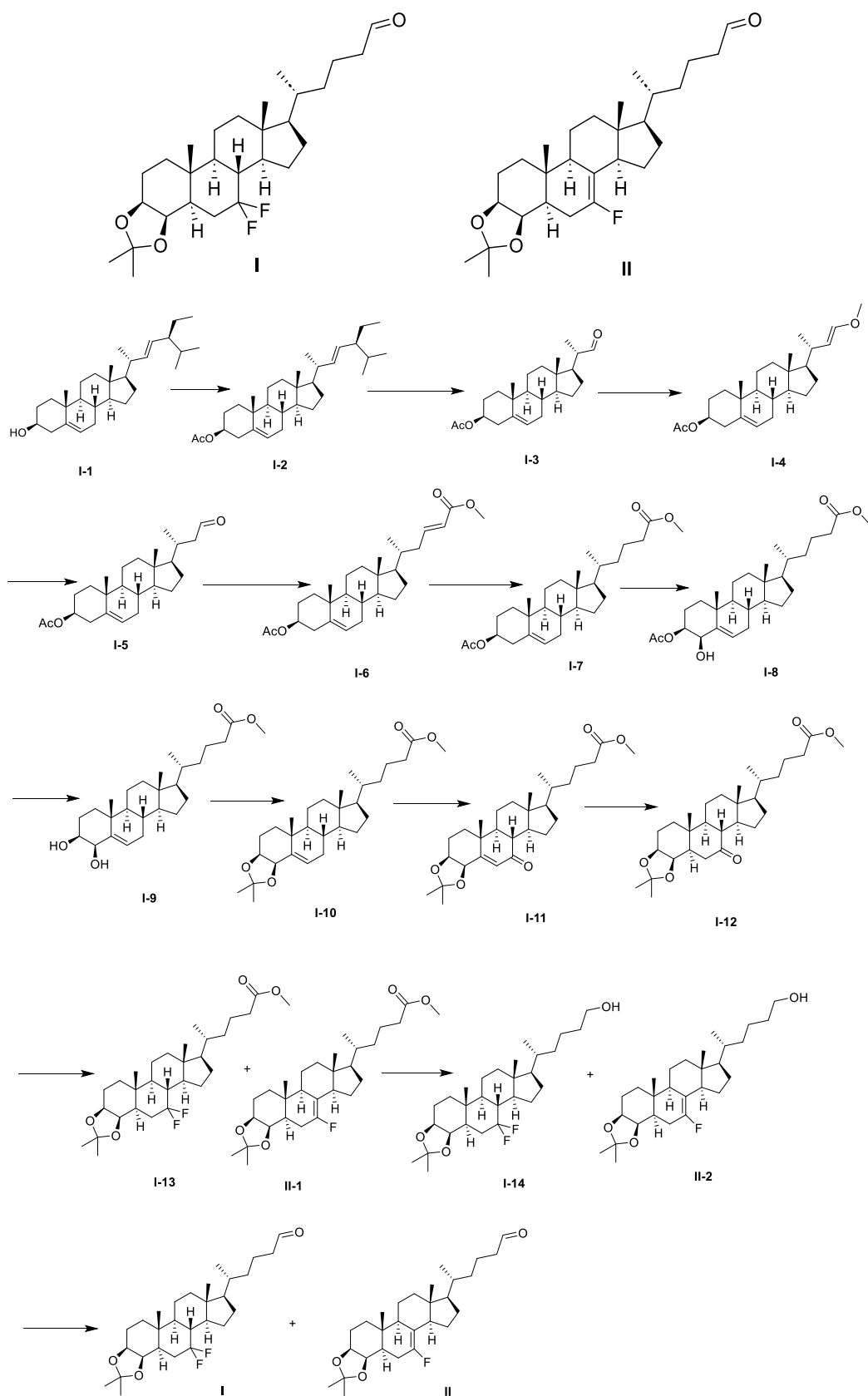
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0104] The present disclosure is further illustrated below through examples, but it is not thereby limited to the scope of the described examples. The
15 experimental methods for which specific conditions are not specified in the following examples are selected according to the conventional methods and conditions, or according to the commercial instructions.

[0105] Preparation of key intermediates

[0106] Examples I & II

20 [0107] Preparation of intermediate I (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal I and
[0108] intermediate II (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-
25 fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal II



[0109] Step 1: (22E,24S)-Stigmasta-6(5),22(23)-dien-3 β -ol **I-1** (5.00 g, 12.11 mmol, 1.0 eq) was dissolved in dichloromethane (50 mL), and the reaction system was placed in an ice-water bath and cooled to approximately 5°C. Acetic anhydride (3.4 mL, 36.35 mmol, 3.0 eq), 4-dimethylaminopyridine (300 mg, 2.42 mmol, 0.2 eq), and triethylamine (8 mL, 60.57 mmol, 5.0 eq) were sequentially added to the reaction system. The reaction system was stirred at room temperature for 2 hours. After the completion of the reaction was confirmed by TLC (petroleum ether: ethyl acetate = 10:1), the reaction was quenched with methanol (20 mL). The reaction mixture was washed once with saturated sodium bicarbonate (about 50 mL) and once with water (about 50 mL), dried over anhydrous sodium sulfate, and concentrated. When the reaction mixture was almost concentrated to dryness, methanol (about 20 mL) was added, and the mixture was stirred in an ice bath for 30 minutes. The mixture was then filtered under suction, and the filter cake was rinsed with a small amount of methanol. The filter cake was dried to obtain (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R,3E,5S)-5-ethyl-6-methylhept-3-en-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-2** (5.30 g, purity: 90.0%, yield: 86.58%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.37 (d, J = 4.8 Hz, 1H), 5.09 (ddd, J = 56.1, 15.2, 8.6 Hz, 2H), 4.61 (ddd, J = 15.9, 9.0, 4.2 Hz, 1H), 2.32 (d, J = 7.3 Hz, 2H), 2.03 (s, 3H), 2.01 – 1.92 (m, 2H), 1.87 (dd, J = 8.9, 6.6 Hz, 2H), 1.73 – 1.40 (m, 12H), 1.30 – 1.07 (m, 6H), 1.02 (t, J = 3.3 Hz, 6H), 0.87 – 0.79 (m, 9H), 0.70 (s, 3H).

[0110] Step 2: (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R,3E,5S)-5-Ethyl-6-methylhept-3-en-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-2** (10.0 g, 22 mmol, 1 eq) was weighed and dissolved in tetrahydrofuran (200 mL) and water (20.0 mL). Pyridine (4.5 mL, 55 mmol, 2.5 eq), 4-methylmorpholine N-oxide (10.30 g, 88 mmol, 4 eq), and potassium osmate (0.81 g, 2.2 mmol, 0.1 eq) were added at room temperature, and the reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl

acetate = 3:1), which showed partial remaining starting material and the formation of an intermediate (vicinal diol formation). Subsequently, sodium periodate (18.80 g, 88 mmol, 4 eq) was added to the reaction mixture at 0°C, and the reaction mixture was stirred for 1 hour at room temperature. The reaction was

5 monitored by TLC (petroleum ether: ethyl acetate = 3:1), which showed partial remaining starting material and the conversion of the intermediate to the product. Water (50 mL) was then added, and the mixture was extracted with ethyl acetate (50 mL × 3). After drying and concentration, the crude product was purified by column chromatography (petroleum ether: ethyl acetate = 60:1) to obtain

10 (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R,3E,5S)-5-ethyl-6-methylhept-3-en-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-3** (3.3 g, purity: 60%, yield: 19.8%) as a white solid and (1R,3aS,3bS,7S,9aR,9bS,11aS)-1-[(1S)-1-formylethyl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-

15 cyclopenta[1,2-i]phenanthren-7-yl acetate (1.9 g, purity: 90.0%, yield: 21.20%). ¹H NMR (400 MHz, CDCl₃) δ 9.50 (d, J = 3.3 Hz, 1H), 5.31 (d, J = 5.1 Hz, 1H), 4.54 (dd, J = 6.4, 4.2 Hz, 1H), 2.34 – 2.23 (m, 3H), 1.96 (s, 3H), 1.89 (dt, J = 6.6, 3.6 Hz, 2H), 1.83 – 1.72 (m, 3H), 1.66 – 1.09 (m, 14H), 1.06 (d, J = 6.8 Hz, 3H), 0.96 (s, 3H), 0.66 (s, 3H).

20 **[0111]** Step 3: (Methoxymethyl)triphenylphosphonium chloride (55.21 g, 161.052 mmol, 5.0 eq) was dissolved in anhydrous tetrahydrofuran (100 mL). The system was cooled to -10°C in a dry ice-ethyl acetate bath, and sodium bis(trimethylsilyl)amide (80.526 mL, 1 mol/L, 2.5 eq) was added. After stirring for 30 minutes while maintaining the dry ice-ethyl acetate bath,

25 (1R,3aS,3bS,7S,9aR,9bS,11aS)-1-[(1S)-1-formylethyl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-3** (12.0 g, 13.4 mmol, 1.0 eq) dissolved in anhydrous tetrahydrofuran (50 mL) was added to the reaction mixture. The system was allowed to warm to room temperature and stirred for 30 minutes. The reaction

30 was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. 100 mL of saturated sodium bicarbonate solution was slowly added to the reaction

system, followed by extraction with ethyl acetate (100 mL $\times$ 3). The organic phases were collected, washed with water (100 mL $\times$ 2) and saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2S,3E)-4-methoxybut-3-en-2-yl]-9a,11a-

5 dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-4** (8 g, purity: 90.0%, yield: 65.0%) as a yellow solid. The crude product was directly used in the next step without further purification.

[0112] Step 4: (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2S,3E)-4-Methoxybut-3-en-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-

10 cyclopenta[1,2-i]phenanthren-7-yl acetate **I-4** (8 g, 1.0 eq) was dissolved in tetrahydrofuran (100 mL), and dilute hydrochloric acid (5 mol/L, 50 mL) was slowly added. The reaction mixture was stirred at room temperature for 30 minutes. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the reaction was completed, 80 mL of water was added to the

15 reaction. The reaction mixture was extracted with ethyl acetate (50 mL $\times$ 3), washed with saturated brine (20 mL $\times$ 3), and dried over anhydrous sodium sulfate. The organic phases were collected and concentrated to obtain a crude product. The crude product was subjected to silica gel column chromatography (petroleum ether: ethyl acetate = 50:1 to 30:1 to 4:1) and concentrated to obtain

20 (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R)-1-formylpropan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-5** (6.3 g, purity: 90%, yield: 48.63%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.76 (dd, *J* = 3.3, 1.3 Hz, 1H), 5.37 (d, *J* = 4.9 Hz, 1H), 4.65 – 4.55 (m, 1H), 2.46 (dd, *J* = 15.6, 2.8 Hz, 1H), 2.32 (d, *J* = 7.0 Hz, 2H),

25 2.22 – 2.14 (m, 1H), 2.03 (s, 3H), 2.03 – 1.93 (m, 2H), 1.89 – 1.78 (m, 3H), 1.66 – 1.40 (m, 9H), 1.17 (dddd, *J* = 16.5, 14.2, 10.9, 7.1 Hz, 6H), 1.03 (dd, *J* = 7.5, 3.5 Hz, 6H), 0.73 (d, *J* = 5.3 Hz, 3H).

[0113] Step 5: Reactant (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R)-1-formylpropan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-

30 tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-5** (10.00 g, 25.87 mmol, 1.0 eq) was dissolved in anhydrous tetrahydrofuran (150 mL). Methyl

(triphenylphosphoranylidene)acetate (51.89 g, 155.21 mmol, 6.0 eq) was added, and the reaction system was stirred at 90°C for 18 hours. The consumption of the starting material was monitored by ¹H NMR. 100 mL of water was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were collected, washed with water (100 mL × 2) and saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 60:1 to 30:1) to obtain methyl (2E,5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hex-2-enoate **I-6** (9.0 g, purity: 90%, yield: 71.1%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 6.95 (ddd, J = 15.4, 8.7, 6.4 Hz, 1H), 6.26 (d, J = 11.6 Hz, 0H), 5.82 (d, J = 15.5 Hz, 1H), 5.37 (d, J = 4.9 Hz, 1H), 4.60 (tdd, J = 10.9, 6.6, 4.2 Hz, 1H), 3.72 (d, J = 10.2 Hz, 3H), 2.35 – 2.24 (m, 3H), 2.03 (s, 3H), 2.01 – 1.91 (m, 3H), 1.90 – 1.78 (m, 3H), 1.68 – 1.40 (m, 8H), 1.31 – 1.07 (m, 5H), 1.02 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.72 – 0.68 (m, 3H).

[0114] Step 6: Reactant methyl (2E,5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hex-2-enoate **I-6** (10 g, 22.59 mmol, 1.0 eq) was dissolved in a mixed solvent of tetrahydrofuran (100 mL) and methanol (50 mL). Nickle chloride (2.93 g, 22.59 mmol, 1.0 eq) was added, followed by slow addition of sodium borohydride (1.28 g, 33.89 mmol). The reaction system was stirred at room temperature for 1 hour. The consumption of the starting material was monitored by ¹H NMR. 100 mL of water was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were collected, washed with water (100 mL × 2) and saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 60:1 to 30:1) to obtain methyl (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-

a]phenanthren-1-yl]hexanoate **I-7** (9 g, purity: 90%, yield: 80.6%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.37 (d, J = 4.9 Hz, 1H), 4.66 – 4.54 (m, 1H), 3.67 (s, 3H), 2.29 (ddd, J = 15.9, 11.9, 6.6 Hz, 4H), 2.03 (s, 3H), 2.02 – 1.93 (m, 2H), 1.82 (ddd, J = 13.0, 10.8, 8.3 Hz, 3H), 1.62 – 1.38 (m, 11H), 1.19 (dddd, J = 32.6, 25.0, 13.7, 6.9 Hz, 9H), 1.01 (d, J = 5.8 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (tdd, J = 10.2, 4.8, 2.0 Hz, 4H), 0.67 (s, 3H).

[0115] Step 7: In a 250 mL round-bottom flask at room temperature, methyl (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-7** (2.5 g, 5.62 mmol) was dissolved in chloroform (80 mL). N-Methylmorpholine (1.71 g, 16.87 mmol) and selenium dioxide (1.56 g, 14.06 mmol) were added at room temperature, and the reaction mixture was then stirred at 70°C for 18 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the reaction was completed, the reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (80 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 10:1) to obtain methyl (5R)-5-[(1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-7-acetoxy-6-hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-8** (1.4 g, purity: 90%, yield: 48.65%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 5.75 – 5.65 (m, 1H), 4.80 – 4.65 (m, 1H), 4.25 (d, J=2.6, 1H), 3.67 (s, 3H), 2.33 – 2.22 (m, 2H), 2.10 (s, 3H), 2.07 – 1.98 (m, 2H), 1.92 – 1.36 (m, 17H), 1.22 (s, 3H), 1.19 – 1.06 (m, 5H), 0.93 (d, J=6.6, 3H), 0.68 (s, 3H).

[0116] Step 8: Reactant methyl (5R)-5-[(1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-7-acetoxy-6-hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-8** (5 g, 11.5 mmol, 1.0 eq) was dissolved in methanol (150 mL). Potassium carbonate (6.37 g, 46 mmol, 4.0 eq) was added, and the reaction system was stirred at room temperature for 30 min. The reaction was monitored by TLC (petroleum ether:

ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (100 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×50 mL). The ethyl acetate layers were combined and washed with saturated brine (3×50 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product methyl (5R)-5-[(1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-9**, which was directly used in the next step without further purification.

[0117] Step 9: Reactant methyl (5R)-5-[(1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-9** (5 g, 1 eq) was dissolved in acetone (150 mL). *p*-Toluenesulfonic acid (1.59 g, 8.4 mmol, 0.7 eq) and 4A molecular sieves were added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the starting material was completely consumed, the reaction was quenched with saturated sodium sulfite. 100 mL of water was added to the reaction system, and the mixture was extracted with ethyl acetate (50 mL $\times 3$). The organic phases were collected, dried over anhydrous sodium sulfate, and rotary evaporated to dryness under vacuum to obtain a crude product. The crude product was dissolved in ethyl acetate and purified by column chromatography (petroleum ether: ethyl acetate = 95:5) to obtain methyl (5R)-5-[(3aR,3R,5aS,9aS,9bS)-7-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-3a,6,6-trimethyl-2,3,3a,4,5,5a,6,9,9a,9b-decahydro-1H-cyclopenta[1,2-a]naphthalen-3-yl]hexanoate **I-10** (3.8 g, purity: 90%, yield: 62%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 5.80 (d, $J = 2.9$ Hz, 1H), 4.41 (d, $J = 5.8$ Hz, 1H), 4.10 (dd, $J = 13.5, 6.5$ Hz, 1H), 3.67 (s, 3H), 2.35 – 2.20 (m, 2H), 2.14 – 1.98 (m, 2H), 1.87 – 1.56 (m, 10H), 1.53 (s, 3H), 1.45 – 1.37 (m, 3H), 1.35 (s, 3H), 1.28 – 1.21 (m, 1H), 1.16 (s, 3H), 1.14 – 0.97 (m, 6H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.69 (s, 3H).

[0118] Step 10: Compound methyl (5R)-5-[(3aR,3R,5aS,9aS,9bS)-7-[(4R)-2,2-

dimethyl-1,3-dioxolan-4-yl]-3a,6,6-trimethyl-2,3,3a,4,5,5a,6,9,9a,9b-decahydro-1H-cyclopenta[1,2-a]naphthalen-3-yl]hexanoate **I-10** (3.8 g, 8.2 mmol, 1.0 eq) was dissolved in acetone (50 mL). N-Hydroxyphthalimide (0.54 g, 3.3 mmol, 0.8 eq), *tert*-butyl hydroperoxide (12 mL, 66 mmol, 8.0 eq), and anhydrous cobalt(II) acetate (0.29 g, 1.6 mmol, 0.2 eq) were added. The resulting mixture was stirred under N₂ at 25°C for 18 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). When the starting material was basically consumed, the reaction was quenched with saturated sodium sulfite. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, washed with saturated brine (15 mL), 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 = 87:13) to obtain methyl (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanoate **I-11** (2.5 g, purity: 95%, yield: 60%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.85 (s, 1H), 4.45 (d, J = 6.4 Hz, 1H), 4.26 (dd, J = 11.3, 5.5 Hz, 1H), 3.60 (s, 3H), 2.34 – 2.25 (m, 2H), 1.86 – 1.70 (m, 2H), 1.58 (dddd, J = 16.6, 11.8, 6.3, 2.3 Hz, 5H), 1.50 (s, 3H), 1.40 (ddd, J = 16.5, 9.3, 3.9 Hz, 4H), 1.30 (s, 3H), 1.26 (s, 4H), 1.12 – 0.97 (m, 4H), 0.87 (d, J = 6.6 Hz, 3H), 0.66 – 0.59 (m, 3H).

[0119] Step 11: Compound methyl (5R)-5-[(1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-7-acetoxy-6-hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-11** (2.4 g, 5.1 mmol, 1.0 eq) was dissolved in methanol (100 mL) and ethyl acetate (50 mL). Palladium on carbon (1.2 g, 11 mmol, 2.2 eq) was then added, and the reaction system was purged with hydrogen. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. The reaction system was filtered, and the organic phase was collected and concentrated to obtain a crude product. The crude product was subjected to

silica gel column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain methyl (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-

5 yl]hexanoate **I-12** (1.7 g, purity: 95%, yield: 67%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.00 – 3.87 (m, 2H), 3.60 (s, 3H), 2.75 – 2.66 (m, 1H), 2.36 (t, J = 11.3 Hz, 1H), 2.25 – 2.09 (m, 4H), 1.85 (dddd, J = 28.9, 13.2, 6.5, 3.1 Hz, 3H), 1.62 (dddd, J = 20.4, 14.3, 6.7, 3.3 Hz, 4H), 1.46 (s, 3H), 1.43 – 1.26 (m, 5H), 1.23 (s, 6H), 0.98 (ddt, J = 14.4, 11.7, 7.4 Hz, 5H), 0.86 (d, J = 6.6 Hz, 3H),
10 0.59 (s, 3H).

[0120] Step 12: Compound methyl (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanoate **I-12** (1.7 g, 3.6
15 mmol) was dissolved in diethylaminosulfur trifluoride (10 mL). The resulting mixture was stirred at 80°C for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 10:1) until completion. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (50 mL) and carefully quenched by dropwise addition of ice water. The organic phase
20 was separated and collected, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic phases were combined, washed with saturated brine (40 mL), filtered, and concentrated to obtain a crude product. The crude product was added with silica gel and purified by column chromatography (petroleum ether: ethyl acetate = 93:7) to obtain a mixture of
25 methyl (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanoate **I-13** and methyl (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanoate **II-1** (1.4 g, **I-13** purity: 95%, yield based on **I-13**: 74%) as a
30

colorless transparent solid.

[0121] Compound I-3: ¹H NMR (400 MHz, CDCl₃) δ 4.02 (d, J = 15.0 Hz, 2H), 3.67 (s, 2H), 2.33 – 2.23 (m, 2H), 2.18 – 1.58 (m, 6H), 1.51 (s, 2H), 1.46 – 1.34 (m, 2H), 1.30 (s, 2H), 1.13 (dd, J = 17.2, 7.0 Hz, 1H), 1.07 (s, 1H), 0.93 (d, J = 6.3 Hz, 2H), 0.68 (s, 3H).

[0122] Step 13: A mixture of compounds methyl (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanoate **I-13** and methyl (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanoate **II-1** (1.3 g, 2.6 mmol, 1.0 eq) was dissolved in tetrahydrofuran (50 mL). Lithium aluminum hydride (0.3 g, 7.8 mmol, 3 eq) was added, and the resulting mixture was stirred at 25°C for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. The reaction was quenched with sodium sulfate decahydrate, filtered, and concentrated to obtain the crude product (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **I-14** and methyl (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanoate **II-2** (0.9 g, purity: 96%, yield based on **I-14**: 92%) as a white solid, which was directly used in the next step.

[0123] Step 14: A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **I-14** and methyl (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-

cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanoate **II-2** (1.3 g, 1.0 eq) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (2.3 g, 5.5 mmol, 2 eq) was added, and the resulting mixture was stirred under N₂ at 25°C for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. Saturated sodium bicarbonate (10 mL) was added to the reaction system. The organic phase was extracted with saturated sodium sulfite (3 × 30 mL), collected, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 92:8) to obtain a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (0.95 g, purity: 90%, yield based on compound **I**: 66%) as a white solid.

[0124] Compound **I**: ¹H NMR (400MHz, CDCl₃) δ 9.70 (t, J = 1.7Hz, 1H), 3.98 – 3.91 (m, 2H), 2.39 – 2.25 (m, 2H), 1.96 – 1.86 (m, 1H), 1.81 – 1.71 (m, 2H), 1.64(ddd, J = 10.7, 10.3, 4.7Hz, 1H), 1.57 – 1.52 (m, 1H), 1.44 (s, 2H), 1.38 – 1.28 (m, 2H), 1.23 (s, 1H), 1.18 (d, J = 9.1Hz, 1H), 1.08 – 1.02 (m, 1H), 1.00 (s, 1H), 0.87 (d, J = 6.5Hz, 2H), 0.83 – 0.77 (m, 1H), 0.60 (d, J = 12.0Hz, 2H).

[0125] Example **III**

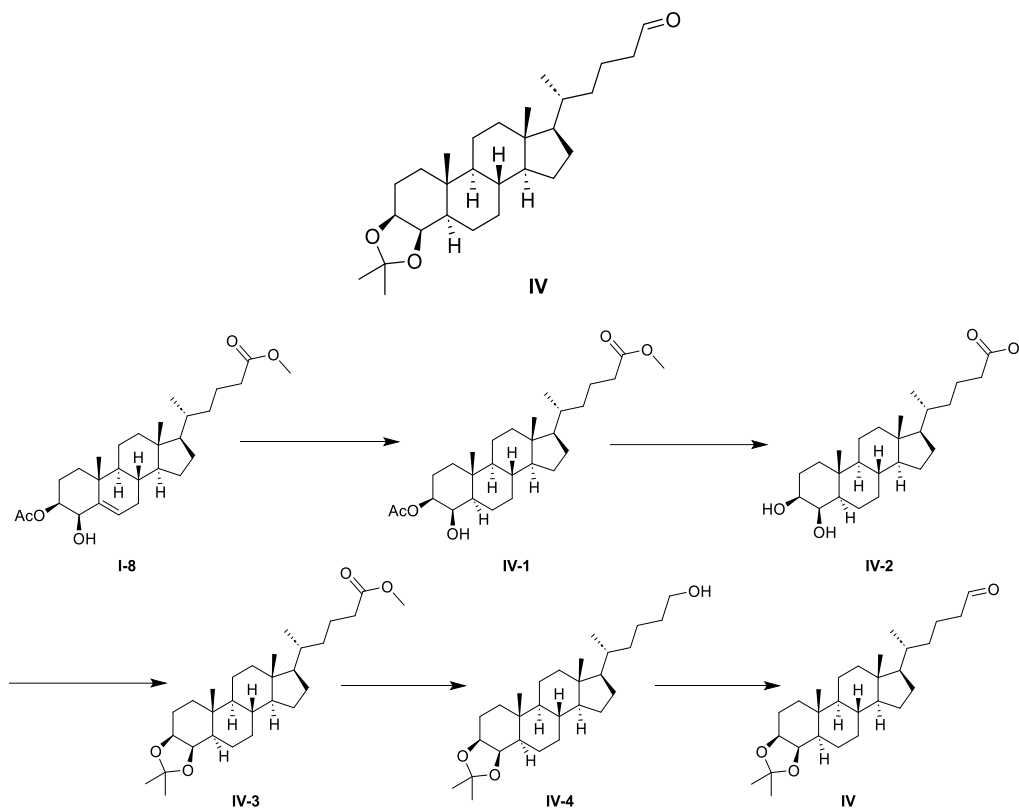
[0126] Preparation of intermediate **III** **(5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal (III)**

[0127] Step 1: Compound methyl (5R)-5-
[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-
4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-
cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanoate **I-10** (1 g, 2.18
mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (50 mL). After nitrogen
purging, lithium aluminum hydride (0.12 g, 3.270 mmol, 1.5 *eq*) was added, and
the reaction mixture was stirred at 25°C for 1 hour. The reaction progress was
monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting
material was completely consumed. The reaction mixture was quenched with
sodium sulfate decahydrate, filtered, and the filtrate was concentrated to obtain a
crude product. The crude product was purified by silica gel column
chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-
[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-
4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-
cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **III-1** (1000
mg, 2.09 mmol, purity: 90%, yield: 96%) as a white solid. ¹H NMR (400 MHz,
CDCl₃) δ 5.80 (d, J = 2.6 Hz, 1H), 4.41 (d, J = 5.8 Hz, 1H), 4.09 (m, 1H), 3.64 (t,
J = 6.5 Hz, 2H), 2.08 (m, 2H), 1.84 (tt, J = 18.5, 7.8 Hz, 2H), 1.67 (m, 8H), 1.41
(td, J = 12.7, 6.2 Hz, 4H), 1.35 (s, 3H), 1.24 (m, 2H), 1.17 (s, 4H), 1.08 (m, 5H),
0.93 (d, J = 6.5 Hz, 4H), 0.69 (d, J = 4.6 Hz, 3H).

[0128] Step 2: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **III-1** (1 g, 1.0 eq) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (1.18 g, 2.79 mmol, 1.2 eq) was added, and the reaction mixture was stirred at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. The reaction was quenched with saturated sodium sulfite, and water (10 mL) was added to the reaction system. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic phases were combined, washed with saturated brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **III** (750 mg, 1.58 mmol, purity: 90%, yield: 68%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H), 5.80 (d, J = 2.7 Hz, 1H), 4.41 (d, J = 5.8 Hz, 1H), 4.10 (dd, J = 13.6, 6.3 Hz, 1H), 2.39 (m, 2H), 2.12 (m, 1H), 2.01 (m, 1H), 1.83 (m, 1H), 1.66 (m, 10H), 1.53 (s, 4H), 1.42 (dd, J = 12.5, 4.2 Hz, 3H), 1.35 (s, 3H), 1.17 (s, 3H), 1.10 (m, 4H), 0.92 (dd, J = 18.2, 5.8 Hz, 4H), 0.71 (d, J = 12.1 Hz, 3H).

[0129] Example IV

[0130] Preparation of intermediate **IV** (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal (**IV**)



- [0131]** Step 1: Compound methyl (5R)-5-[(1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-7-acetoxy-6-hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-8** (150 mg, 0.326 mmol, 1.0 eq) was dissolved in ethyl acetate (5 mL). Platinum dioxide (36.97 mg, 0.163 mmol, 0.5 eq) was added, and the resulting mixture was stirred under H₂ at 25°C for 3 hours. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 3:1), and the starting material was completely consumed. The mixture was filtered, and the filtrate was concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain methyl (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-7-acetoxy-6-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **IV-1** (100 mg, 59.74%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.72 (m, 1H), 3.83 (s, 1H), 3.66 (s, 3H), 2.27 (dd, J = 16.4, 8.7 Hz, 2H), 2.10 (d, J = 8.1 Hz, 3H), 1.79 (dddd, J = 37.0, 16.1, 10.1, 3.7 Hz, 8H), 1.29 (m, 8H), 0.99 (m, 14H), 0.62 (d, J = 14.3 Hz, 4H).

[0132] Step 2: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6-Hydroxy-1-[(2R)-6-methoxy-6-oxohexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **IV-1** (300 mg, 0.65 mmol, 1.0 eq.) was weighed and dissolved in anhydrous methanol (5 mL), and potassium carbonate (897 mg, 6.5 mmol) was added. The reaction mixture was then warmed to 25°C and stirred for 16 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 2:1), and the reaction was completed. The reaction mixture was filtered and concentrated. The resulting crude product was purified by column chromatography (petroleum ether: ethyl acetate = 0 to 50%) to obtain methyl (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **IV-2** (210 mg, 0.5 mmol, 76.9%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 3.71 (d, J = 3.1 Hz, 1H), 3.65 (s, 3H), 3.53 (dt, J = 11.3, 4.4 Hz, 1H), 2.33 – 2.18 (m, 2H), 1.97 – 1.84 (m, 2H), 1.83 – 1.60 (m, 8H), 1.42 – 1.28 (m, 5H), 1.28 – 1.15 (m, 3H), 1.11 – 1.01 (m, 4H), 1.00 (s, 3H), 0.90 (d, J = 6.5 Hz, 4H), 0.62 (s, 3H), 0.57 (td, J = 11.4, 4.2 Hz, 1H).

[0133] Step 3: Methyl (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **IV-2** (250 mg, 0.59 mmol) was weighed and dissolved in acetone (20 mL). 4A molecular sieves (250 mg) and *p*-toluenesulfonic acid (203 mg, 1.18 mmol) were added, and the reaction mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 2:1). After the reaction was completed, the insoluble material was removed by filtration. The filtrate was concentrated and purified by column chromatography (petroleum ether: ethyl acetate = 0 to 30%) to obtain methyl (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanoate **IV-3** (220 mg, 0.48 mmol, 81.3%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 3.97 (dt, J = 8.8, 5.7 Hz, 2H), 3.65 (s, 3H), 2.25 (ddd, J = 10.5, 8.5, 6.7 Hz, 2H), 1.97 – 1.90 (m, 1H), 1.76 (td, J = 11.5, 6.6 Hz, 3H), 1.71 – 1.63 (m, 3H), 1.58 – 1.52

(m, 1H), 1.49 (s, 4H), 1.47 – 1.32 (m, 6H), 1.28 (s, 3H), 1.23 (ddd, J = 14.1, 8.9, 5.6 Hz, 3H), 1.08 (td, J = 10.7, 9.2, 3.7 Hz, 3H), 1.02 (s, 3H), 0.98 – 0.93 (m, 1H), 0.90 (d, J = 6.4 Hz, 3H), 0.86 – 0.80 (m, 2H), 0.64 (s, 3H), 0.61 – 0.54 (m, 1H).

[0134] Step 4: Methyl (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-
 5 2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-
 hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-
 yl]hexanoate **IV-3** (180 mg, 0.39 mmol) was weighed and dissolved in diethyl
 ether (20 mL). The reaction mixture was cooled to -78°C in a dry ice-acetone
 bath, followed by dropwise addition of diisobutylaluminum hydride (1 M, 1.17
 10 mL). After the dropwise addition was completed, the reaction mixture was
 warmed to room temperature with stirring. The reaction was monitored by TLC
 (petroleum ether: ethyl acetate = 3:1). After the reaction was completed, the
 reaction mixture was quenched with saturated ammonium chloride aqueous
 solution and extracted with ethyl acetate. The organic phase was separated,
 15 dried, and concentrated. The residue was purified by column chromatography
 (petroleum ether: ethyl acetate = 0 to 30%) to obtain (5R)-5-
 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-
 4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-
 cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **IV-4** (120 mg,
 20 0.28 mmol, 71.8%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 3.98
 (d, J = 7.6 Hz, 2H), 3.62 (t, J = 6.6 Hz, 2H), 1.94 (d, J = 12.3 Hz, 1H), 1.76 (d, J
 = 10.5 Hz, 3H), 1.65 (t, J = 13.8 Hz, 3H), 1.54 (d, J = 9.8 Hz, 4H), 1.49 (s, 4H),
 1.48 – 1.34 (m, 7H), 1.29 (s, 3H), 1.25 (d, J = 11.2 Hz, 6H), 1.13 – 1.05 (m, 3H),
 1.02 (s, 3H), 1.00 (d, J = 6.1 Hz, 1H), 0.89 (d, J = 6.2 Hz, 4H), 0.84 (s, 1H), 0.64
 25 (s, 3H), 0.63 – 0.54 (m, 1H).

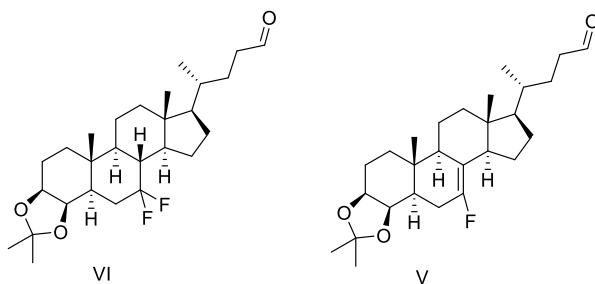
[0135] Step 5: (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-
 2,2,5a,7a-Tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-
 hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-
 yl]hexan-1-ol **IV-4** (100 mg, 0.23 mmol) was weighed and dissolved in
 30 dichloromethane (10 mL). Dess-Martin periodinane (195 mg, 0.46 mmol) was
 added at room temperature, and then the reaction mixture was stirred at room

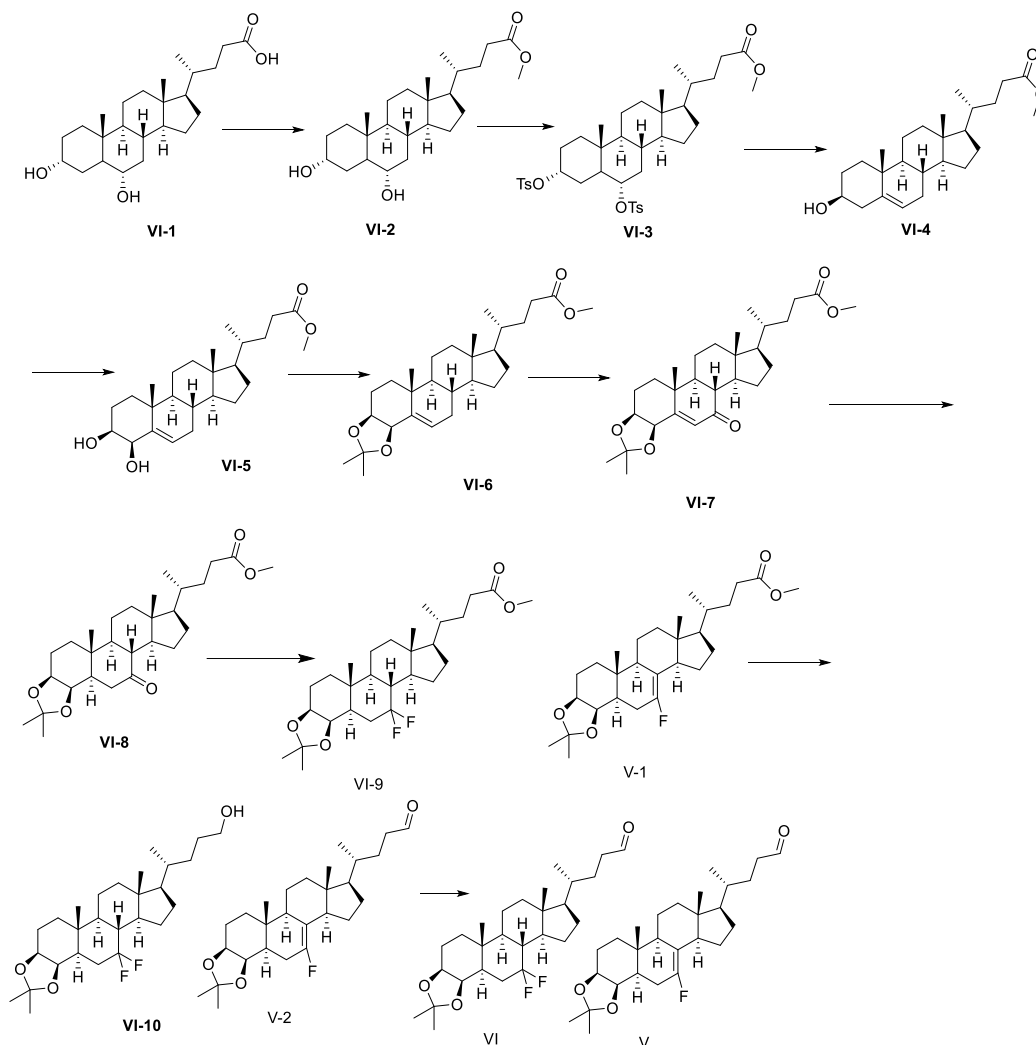
temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After the reaction was completed, the reaction mixture was quenched with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic phase was separated, dried, and concentrated. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 0 to 30%) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **IV** (53 mg, 0.12 mmol, 52.2%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 9.74 (t, J = 1.8 Hz, 1H), 3.97 (dt, J = 8.9, 5.7 Hz, 2H), 2.37 (tdd, J = 8.1, 6.8, 1.9 Hz, 2H), 1.94 (d, J = 12.5 Hz, 1H), 1.76 (td, J = 10.3, 5.3 Hz, 3H), 1.71 – 1.62 (m, 3H), 1.56 (s, 3H), 1.49 (s, 3H), 1.48 – 1.36 (m, 5H), 1.29 (s, 3H), 1.24 (dq, J = 12.6, 4.6, 3.8 Hz, 5H), 1.08 (dd, J = 11.8, 7.5 Hz, 3H), 1.02 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.89 – 0.83 (m, 2H), 0.64 (s, 3H), 0.58 (d, J = 2.5 Hz, 1H).

[0136] Examples VI and V

[0137] Preparation of intermediate VI (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]pentanal and

[0138] intermediate V (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]pentanal





- [0139]** Step 1: 6 α -Hydroxy-3 α -hydroxy-5 β -cholan-24-oic acid **VI-1** (15 g, 38.2 mmol, 1.0 eq) was dissolved in MeOH (200 mL). Sulfuric acid (5 mL, 93.8 mmol, 2.5 eq) was slowly added to the reaction system, which was then stirred at 75°C for 2 hours. After the reaction was monitored by TLC (dichloromethane: methanol = 10:1) until completion, the reaction mixture was cooled to room temperature and slowly added to saturated sodium bicarbonate (about 200 mL). The reaction system was washed once with saturated sodium bicarbonate solution (about 100 mL) and once with water (about 100 mL), dried over anhydrous sodium sulfate, and concentrated to dryness to obtain the crude product methyl 6 α -hydroxy-3 α -hydroxy-5 β -cholan-24-oate **VI-2** (15 g, yield: 86.90%), which was directly used in the next step.

[0140] Step 2: Methyl 6 α -hydroxy-3 α -hydroxy-5 β -cholan-24-oate **VI-2** (15.0 g, 36.9 mmol, 1.0 eq) was dissolved in pyridine (50 mL), and *p*-toluenesulfonyl chloride (42.2 g, 221.3 mmol, 6 eq) was added at room temperature. The reaction mixture was stirred at room temperature overnight, and the completion of the reaction was confirmed by TLC (petroleum ether: ethyl acetate = 5:1). The reaction mixture was poured into 5% hydrochloric acid solution (100 mL) containing crushed ice. After the solid was precipitated, the mixture was filtered under suction, washed with water, and dried to obtain the crude product (1R,3aS,3bS,5aR,5S,7R,9aR,9bS,11aR)-1-[(2R)-5-methoxy-5-oxopentan-2-yl]-9a,11a-dimethyl-7-{[(4-methylphenyl)dioxo- λ 6-sulfanyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-5-yl 4-methylbenzenesulfonate **VI-3** (20 g, yield: 70.20%).

[0141] Step 3: (1R,3aS,3bS,5aR,5S,7R,9aR,9bS,11aR)-1-[(2R)-5-Methoxy-5-oxopentan-2-yl]-9a,11a-dimethyl-7-{[(4-methylphenyl)dioxo- λ 6-sulfanyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-5-yl 4-methylbenzenesulfonate **VI-3** (10 g, 69.9 mmol, 1.0 eq) was dissolved in water (20 mL) and N,N-dimethylformamide (200 mL). The system was heated to 110°C and refluxed for 4 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the reaction mixture was cooled to room temperature, and a white solid precipitated. The reaction mixture was poured into 5% hydrochloric acid solution (500 mL) containing crushed ice, washed with water (50 mL $\times$ 2), and dried to obtain an intermediate. This intermediate was then dissolved in 4% KOH methanol solution (250 mL), and the reaction mixture was stirred at room temperature for 3 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the pH was adjusted to neutral with 5% hydrochloric acid. The reaction mixture was extracted with ethyl acetate (100 mL $\times$ 3), washed with saturated brine (100 mL $\times$ 3), and dried over anhydrous sodium sulfate. The organic phases were collected and concentrated to obtain a crude product. The crude product was subjected to silica gel column chromatography (petroleum ether: ethyl acetate = 30:1 to 10:1 to 5:1) to obtain

methyl 3 β -hydroxychol-5(6)-en-24-oate **VI-4** (30 g, yield 75.6%) as a white solid.

[0142] Compound **VI-4**: ^1H NMR (400 MHz, CDCl_3) δ 5.37 – 5.33 (m, 1H), 3.66 (s, 3H), 2.34 (dt, J = 13.0, 4.0 Hz, 1H), 2.30 – 2.23 (m, 2H), 2.24 – 2.18 (m, 2H), 2.05 – 1.93 (m, 3H), 1.82 (tdd, J = 10.1, 8.1, 4.9 Hz, 5H), 1.53 – 1.40 (m, 7H), 1.36 – 1.25 (m, 3H), 1.01 (s, 3H), 0.92 (t, J = 5.1 Hz, 5H), 0.68 (s, 4H).

[0143] Step 4: Reactant methyl 3 β -hydroxychol-5(6)-en-24-oate **VI-4** (15 g, 38.5 mmol, 1.0 eq) was dissolved in chloroform (90 mL). Selenium dioxide (10.5 g, 89.7 mmol, 2.5 eq) and NMM (12.7 mL, 115.8 mmol, 3.0 eq) were added, and the reaction system was stirred at 75°C for 18 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). When most of the starting material was consumed and the product spot became more concentrated than the starting material spot, the reaction was stopped. 100 mL of water was added to the reaction system, and the mixture was extracted with ethyl acetate (50 mL $\times$ 3). The organic phases were combined, washed with water (50 mL $\times$ 2) and saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 10:1 to 6:1 to 3:1) to obtain methyl 4 β -hydroxy-3 β -hydroxychol-5(6)-en-24-oate **VI-5** (10 g, purity: 70%, yield: 50.3%) as a white solid.

[0144] Compound **VI-5**: ^1H NMR (400 MHz, CDCl_3) δ 5.71 – 5.63 (m, 1H), 4.14 (d, J = 3.2 Hz, 1H), 3.66 (s, 3H), 3.56 (d, J = 11.5 Hz, 1H), 2.34 (dd, J = 10.2, 5.2 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.07 (s, 1H), 2.00 (d, J = 12.5 Hz, 1H), 1.89 (s, 1H), 1.88 – 1.78 (m, 3H), 1.65 – 1.51 (m, 4H), 1.46 – 1.39 (m, 3H), 1.36 – 1.25 (m, 2H), 1.18 (s, 3H), 1.15 – 1.05 (m, 4H), 1.03 – 0.96 (m, 1H), 0.92 (d, J = 6.5 Hz, 4H), 0.68 (s, 3H).

[0145] Referring to Examples **I & II**, by replacing **I-9** with **VI-5**, (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]pentanal **VI** and (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-

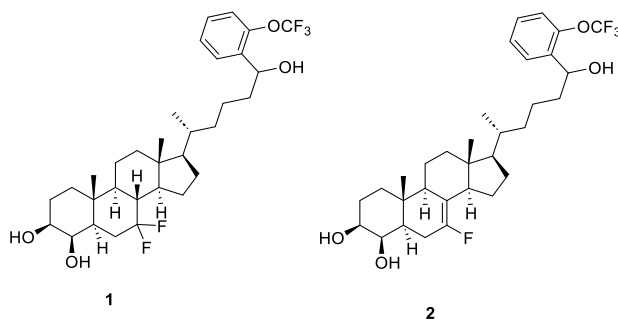
cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]pentanal **V** (2.5 g, purity: 90%, yield based on compound **VI**: 56%) were obtained.

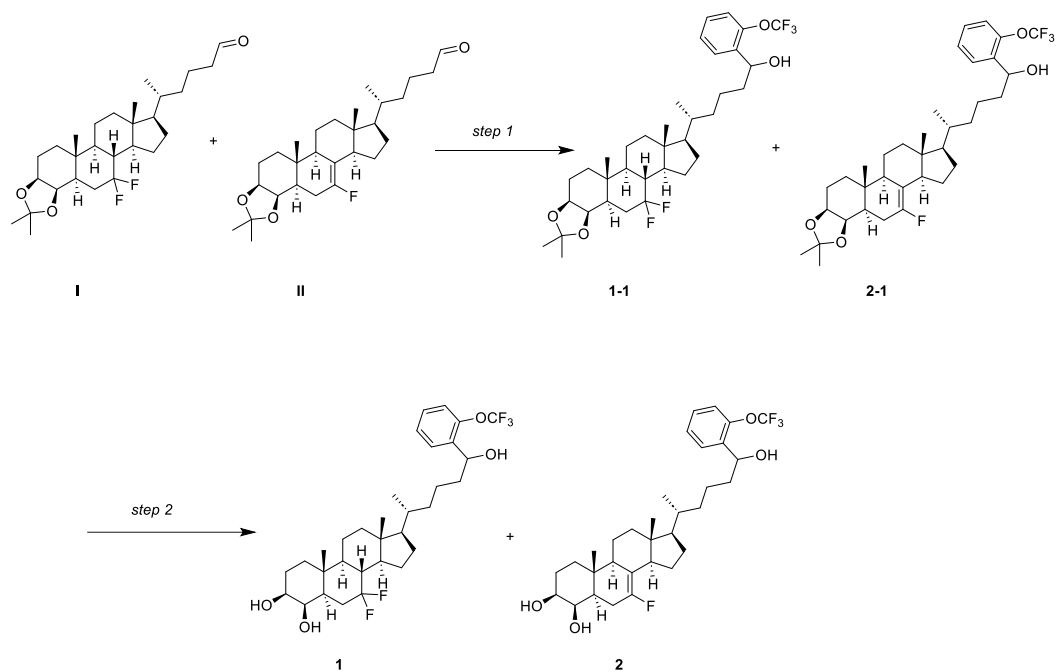
[0146] Compound **VI**: ^1H NMR (400 MHz, CDCl_3) δ 9.77 (t, $J = 1.9$ Hz, 1H), 4.01 (dt, $J = 8.4, 6.2$ Hz, 2H), 2.50 – 2.30 (m, 2H), 2.18 – 2.02 (m, 1H), 1.96 (ddd, $J = 8.1, 7.3, 3.0$ Hz, 2H), 1.88 – 1.76 (m, 4H), 1.72 – 1.66 (m, 1H), 1.65 – 1.58 (m, 2H), 1.56 (d, $J = 9.3$ Hz, 2H), 1.51 (s, 3H), 1.48 – 1.41 (m, 2H), 1.39 – 1.25 (m, 7H), 1.18 – 1.05 (m, 5H), 0.99 (dd, $J = 11.9, 3.8$ Hz, 1H), 0.95 – 0.89 (m, 4H), 0.67 (d, $J = 12.1$ Hz, 3H).

[0147] Examples **1** & **2**

[0148] Preparation of compound **1** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-{2-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0149] compound **2** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-{2-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





[0150] Step 1: 1-Bromo-2-[(trifluoromethyl)oxy]benzene (126 mg, 0.5 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 *eq*) was added dropwise. The reaction system was stirred at -78°C for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. 10 mL of water was added to the reaction system, followed by extraction with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried over sodium sulfate, and concentrated to obtain a crude product. The crude product was subjected to silica gel column chromatography (petroleum ether: ethyl acetate = 90:10) to

obtain a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **1-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **2-1** (70 mg, purity: 95%, yield based on compound **1-1**: 70%) as a white solid.

[0151] Compound **1-1**: ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.49 (m, 1H), 7.24 (dt, J = 6.2, 4.0 Hz, 2H), 7.15 (dd, J = 4.7, 2.9 Hz, 1H), 5.03 – 4.96 (m, 1H), 3.94 (dt, J = 8.3, 6.2 Hz, 2H), 2.09 – 1.85 (m, 3H), 1.78 – 1.51 (m, 12H), 1.44 (s, 3H), 1.38 – 1.26 (m, 5H), 1.23 (s, 3H), 1.20 – 1.10 (m, 2H), 1.05 (dd, J = 10.9, 6.5 Hz, 1H), 1.00 (s, 3H), 0.97 – 0.86 (m, 2H), 0.83 (dd, J = 6.4, 3.9 Hz, 3H), 0.59 (t, J = 5.9 Hz, 3H).

[0152] Step 2: A mixture of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **1-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **2-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The ethyl acetate layers were combined, washed with saturated brine (3×10 mL), 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 = 70:30) to obtain a white solid, and then separated by chiral resolution using SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-{2-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **1** (33.65 mg, purity: 99%, yield: 51%, retention time t_R = 0.793 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-{2-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **2** (3.29 mg, purity: 96%, yield: 5%, retention time t_R = 1.109 min).

[0153] Compound **1**: ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.49 (m, 1H), 7.28 – 7.20 (m, 2H), 7.17 – 7.12 (m, 1H), 5.02 – 4.96 (m, 1H), 3.67 (s, 1H), 3.56 – 3.49 (m, 1H), 2.22 – 2.04 (m, 1H), 1.90 (d, J = 12.7 Hz, 1H), 1.83 – 1.56 (m, 13H), 1.43 – 1.15 (m, 10H), 0.99 (s, 3H), 0.95 – 0.87 (m, 2H), 0.83 (dd, J = 6.5, 3.9 Hz, 3H), 0.59 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -56.80, -56.81, -88.64, -89.27, -110.64, -111.27.

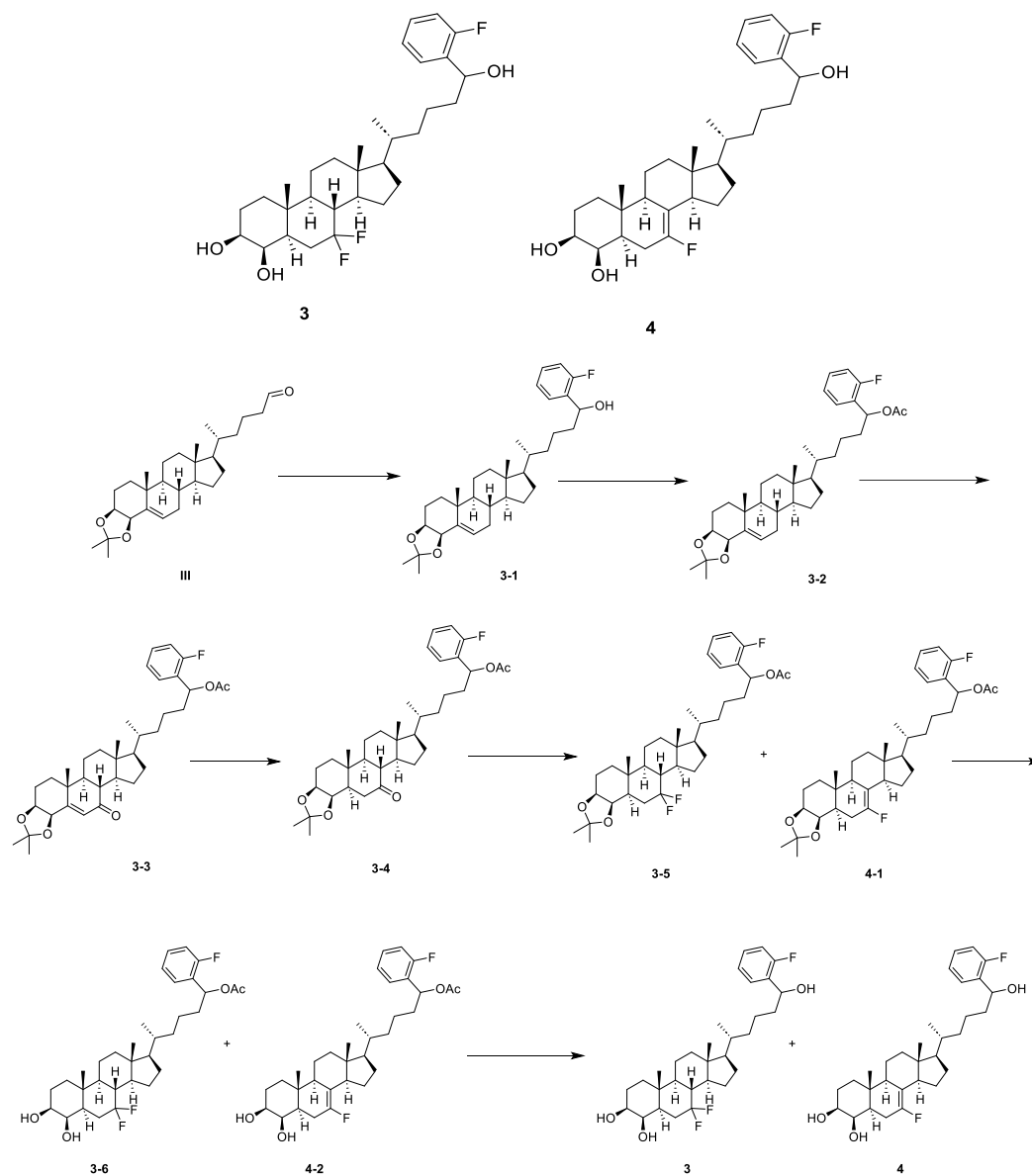
[0154] Compound **2**: ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 7.4 Hz, 1H), 7.28 – 7.21 (m, 2H), 7.15 (d, J = 7.4 Hz, 1H), 4.99 (dd, J = 11.4, 5.4 Hz, 1H), 3.78 (s, 1H), 3.52 (d, J = 12.0 Hz, 1H), 2.57 (d, J = 12.0 Hz, 1H), 1.95 (d, J = 12.6 Hz, 1H), 1.83 – 1.50 (m, 16H), 1.41 – 1.17 (m, 11H), 1.06 – 0.99 (m, 3H), 0.97 (s, 3H), 0.84 (dd, J = 6.4, 4.1 Hz, 3H), 0.56 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -56.79, -56.81, -109.80. LC-MS: [M-H₂O]⁺ = 551.80.

[0155] Examples **3 & 4**

[0156] Preparation of compound **3** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0157] compound **4** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol

5



[0158] Step 1: Compound 1-bromo-2-fluorobenzene (195.96 mg, 1.12 mmol, 1.2 eq) was dissolved in tetrahydrofuran (30 mL). Under a nitrogen atmosphere, the solution was cooled to -78°C in a dry ice bath, and *n*-butyllithium (2.5 M in *n*-hexane, 89.67 mg, 1.400 mmol, 1.5 eq) was added. The mixture was stirred for 30 minutes at this temperature, followed by addition of (5R)-5-

[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **III** (400 mg, 0.933 mmol, 1.0 *eq*). The reaction was then allowed to warm to room temperature naturally. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the reaction was quenched with saturated ammonium chloride, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with saturated brine (15 mL). The ethyl acetate layer was dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexan-1-ol **3-1** (400 mg, purity: 80%, yield: 65%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.46 (t, J = 7.4 Hz, 1H), 7.23 (s, 1H), 7.15 (s, 1H), 7.02 (m, 1H), 5.80 (s, 1H), 5.00 (dd, J = 12.0, 7.0 Hz, 1H), 4.41 (d, J = 5.8 Hz, 1H), 4.10 (dd, J = 13.9, 6.1 Hz, 1H), 2.06 (dd, J = 44.2, 10.2 Hz, 3H), 1.65 (dd, J = 30.7, 25.0 Hz, 9H), 1.41 (d, J = 9.7 Hz, 4H), 1.35 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H), 1.10 (m, 6H), 0.90 (dd, J = 6.4, 4.0 Hz, 3H), 0.68 (m, 3H).

[0159] Step 2: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexan-1-ol **3-1** (400 mg, 0.76 mmol, 1.0 *eq*) was dissolved in dichloromethane (20 mL). Acetic anhydride (0.215 mL, 2.29 mmol, 3.0 *eq*), triethylamine (0.530 mL, 3.81 mmol, 5.0 *eq*), and 4-dimethylaminopyridine (93.09 mg, 0.76 mmol, 1.0 *eq*) were added. The resulting mixture was stirred at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was quenched with methanol. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with dichloromethane (3 × 20 mL).

The organic phases were combined and washed with saturated brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 95:5) to obtain (5R)-5-
 5 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **3-2** (400 mg, purity: 90%, yield: 83%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.12 (t, J = 7.5
 10 Hz, 1H), 7.03 (m, 1H), 6.01 (m, 1H), 5.80 (d, J = 2.8 Hz, 1H), 4.41 (d, J = 5.8 Hz, 1H), 4.10 (dd, J = 13.6, 6.3 Hz, 1H), 2.08 (d, J = 2.4 Hz, 3H), 1.61 (m, 8H), 1.43 (s, 4H), 1.34 (d, J = 6.2 Hz, 5H), 1.26 (s, 3H), 1.16 (s, 5H), 1.02 (m, 9H), 0.86 (m, 7H), 0.67 (m, 4H).

[0160] Step 3: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-
 15 2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **3-2** (120 mg, 0.21 mmol, 1.0 *eq*) was dissolved in acetone (5 mL). N-Hydroxyphthalimide (6.92 mg, 0.042 mmol, 0.2 *eq*), *tert*-butyl hydroperoxide (0.170 mL, 0.848 mmol, 4.0 *eq*), and anhydrous cobalt(II)
 20 acetate (1.88 mg, 0.011 mmol, 0.05 *eq*) were added. The resulting mixture was stirred at 25°C for 18 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). The reaction was quenched with saturated sodium sulfite. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The ethyl acetate layers were
 25 combined, washed with saturated brine (15 mL), dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl
 30 acetate **3-3** (60 mg, purity: 90%, yield: 44%). ¹H NMR (400 MHz, CDCl₃) δ

7.34 (t, $J = 7.3$ Hz, 1H), 7.23 (m, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.03 (m, 1H), 6.02 (d, $J = 5.0$ Hz, 1H), 5.92 (s, 1H), 4.52 (d, $J = 6.4$ Hz, 1H), 4.32 (d, $J = 5.6$ Hz, 1H), 2.34 (d, $J = 10.6$ Hz, 2H), 2.08 (s, 3H), 2.02 (m, 1H), 1.82 (dd, $J = 20.1, 10.2$ Hz, 4H), 1.57 (t, $J = 12.4$ Hz, 13H), 1.34 (m, 17H), 1.07 (m, 5H), 0.87 (dd, $J = 11.7, 6.8$ Hz, 4H), 0.80 (d, $J = 5.9$ Hz, 1H), 0.69 (d, $J = 3.5$ Hz, 3H)

[0161] Step 4: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **3-3** (60 mg, 0.10 mmol) was dissolved in methanol (5 mL). Palladium on carbon (11 mg, 0.103 mmol) was added, and the mixture was purged with hydrogen three times. The resulting mixture was stirred under hydrogen at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 3:1), and the starting material was completely consumed. The mixture was filtered and concentrated to obtain a crude product.

The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **3-4** (40 mg, purity: 90%, yield: 60%) as a white solid. ¹HNMR (400 MHz, CDCl₃) δ 7.34 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 7.03 (s, 1H), 6.01 (dd, $J = 10.9, 6.4$ Hz, 1H), 3.98 (d, $J = 3.4$ Hz, 2H), 2.77 (s, 1H), 2.42 (s, 1H), 2.19 (dd, $J = 12.7, 2.7$ Hz, 2H), 2.08 (s, 3H), 1.74 (m, 9H), 1.53 (s, 3H), 1.38 (dd, $J = 11.7, 7.8$ Hz, 4H), 1.28 (d, $J = 17.1$ Hz, 10H), 0.95 (ddd, $J = 10.8, 9.5, 6.5$ Hz, 10H), 0.64 (d, $J = 3.2$ Hz, 3H).

[0162] Step 5: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **3-4** (250 mg, 0.43 mmol) was dissolved in diethylaminosulfur trifluoride (5 mL). The resulting mixture was stirred at 80°C for 1 hour. The reaction

progress was monitored by TLC (petroleum ether: ethyl acetate = 10:1), and the starting material was completely consumed. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL) and carefully quenched by dropwise addition of ice water. The organic phase was separated and collected, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic phases were combined, washed with saturated brine (15 mL), filtered, and concentrated to obtain a crude product. The crude product was added with silica gel and purified by column chromatography (petroleum ether: ethyl acetate = 93:7) to obtain a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **3-5** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **4-1** (210 mg, purity: 90%, yield based on **3-5**: 72.85%) as a colorless transparent solid.

[0163] Compound 3-5 ¹H NMR: (400 MHz, CDCl₃) δ 7.34 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 6.6 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.05 – 5.98 (m, 1H), 4.07 – 3.98 (m, 2H), 2.08 (d, J = 1.3 Hz, 3H), 1.98 – 1.68 (m, 9H), 1.63 – 1.57 (m, 2H), 1.50 (s, 3H), 1.39 (dd, J = 10.5, 5.0 Hz, 4H), 1.30 (s, 3H), 1.07 (s, 3H), 1.05 – 0.90 (m, 4H), 0.87 (dd, J = 6.3, 4.7 Hz, 4H), 0.64 (dd, J = 11.7, 3.6 Hz, 3H).

[0164] Step 6: A mixture of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **3-5** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **4-1** (210 mg, 0.34 mmol, 1.0 eq) was dissolved in

tetrahydrofuran (10 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the aqueous layer was

5 extracted with ethyl acetate (3 × 25 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 70:30) to obtain a mixture of (5R)-5-

10 [(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl acetate **3-6** and (5R)-5-[(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-6,7-dihydroxy-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl

15 acetate **4-2** (200 mg, purity: 95%, yield based on **3-6**: 96.9%) as a white solid.

[0165] **3-6**: ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, J = 7.4 Hz, 1H), 7.23 (s, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.07 – 6.98 (m, 1H), 6.01 (dd, J = 11.2, 6.4 Hz, 1H), 3.85 (s, 0H), 3.74 (s, 1H), 3.64 – 3.55 (m, 1H), 2.09 (s, 3H), 1.96 (d, J = 12.7 Hz, 1H), 1.88 – 1.67 (m, 9H), 1.49 – 1.29 (m, 8H), 1.09 (d, J = 4.6 Hz, 1H), 1.05 (s, 3H),

20 1.03 – 0.94 (m, 2H), 0.89 – 0.84 (m, 3H), 0.63 (dd, J = 12.0, 3.6 Hz, 3H).

[0166] Step 7: A mixture of compounds (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-

25 fluorophenyl)hexyl acetate **3-6** and (5R)-5-[(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-6,7-dihydroxy-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl acetate **4-2** (50 mg, 0.09 mmol, 1 eq) was dissolved in a mixed solvent of tetrahydrofuran (2 mL) and methanol (2 mL). Potassium carbonate (122 mg, 0.89 mmol, 10 eq) was added, and the resulting mixture was stirred at 25°C for 1

30 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 1:1). The reaction mixture was diluted with ethyl acetate (20 mL) and washed with

saturated brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 71:29) to obtain a white mixture, which was then separated by chiral resolution (instrument: Waters Acquity; UPCC column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain white solids:

5 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **3** (25.6 mg, purity: 95.02%, yield: 52.56%, retention time *t_R* = 1.205 min) and 7(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **4** (3.74 mg, purity: 82.29%, yield: 6.89%, retention time

10 *t_R* = 1.666 min).

[0167] Compound **3**: ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.02 (m, 1H), 5.00 (d, *J* = 7.1 Hz, 1H), 3.74 (s, 1H), 3.61 (s, 1H), 2.07 (dd, *J* = 11.2, 9.0 Hz, 2H), 1.95 (s, 1H), 1.79 (m, 6H), 1.67 (m, 4H), 1.37 (m, 10H), 1.10 (d, *J* = 5.4 Hz, 2H), 1.06 (s, 3H), 1.00 (d, *J* = 3.4 Hz, 2H), 0.89 (dd, *J* = 6.5, 4.1 Hz, 3H), 0.65 (d, *J* = 2.0 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 161.90, 127.19, 124.26, 115.44, 115.19, 112.45, 73.44, 71.86, 68.51, 55.22, 50.95, 48.56, 44.03, 43.15, 39.34, 39.17, 38.55, 38.42, 36.22, 35.63, 35.52, 34.93, 28.46, 25.58, 25.39, 22.36, 22.22, 20.57, 18.66, 15.87, 15.53, 13.78, 11.84, -0.01. ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.63, -111.25, -

15 119.75, -119.78.

[0168] Compound **4**: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 6.0 Hz, 1H), 7.15 (s, 1H), 7.02 (m, 1H), 5.00 (d, *J* = 7.0 Hz, 1H), 3.85 (s, 1H), 3.59 (d, *J* = 11.8 Hz, 1H), 2.65 (s, 1H), 2.06 (d, *J* = 16.1 Hz, 4H), 1.78 (dd, *J* = 27.9, 5.7 Hz, 6H), 1.60 (s, 3H), 1.44 (s, 3H), 1.26 (s, 7H), 1.09 (d, *J* = 17.5 Hz, 3H), 1.04 (s, 3H), 0.91 (dd, *J* = 6.3, 3.8 Hz, 3H), 0.62 (d, *J* = 1.8 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -109.79, -119.75, -119.78.

20

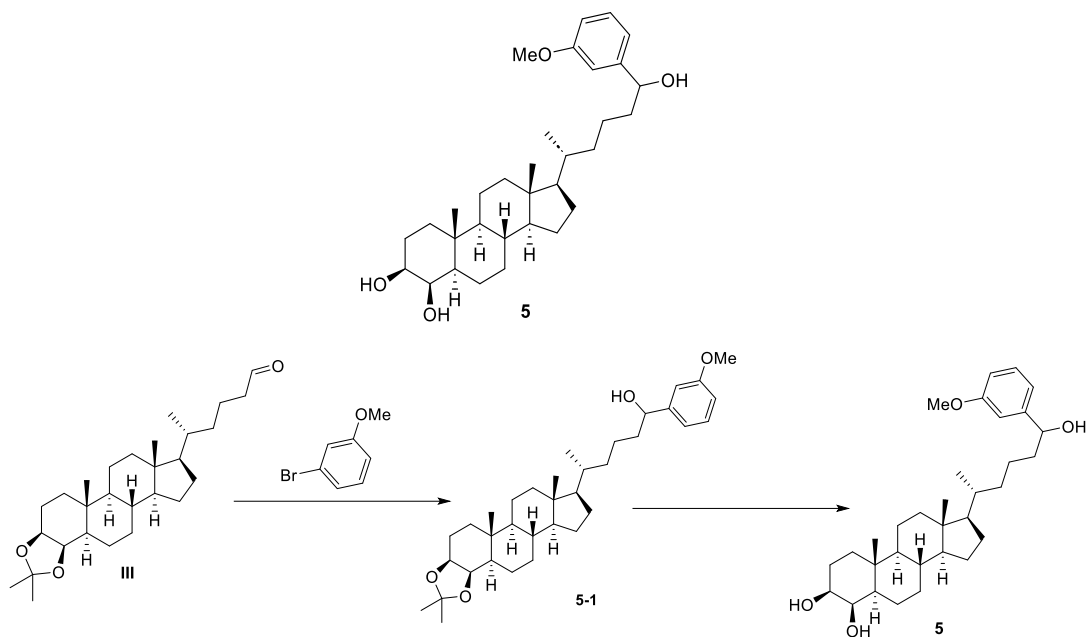
25

30

[0169] Example 5

[0170] Preparation of compound 5: 24-[hydroxy(3-methoxyphenyl)methyl]-5 α -cholane-3 β ,4 β -diol

5



[0171] **Step 1:** *m*-Bromoanisole (109 mg, 0.6 mol, 5.0 eq.) was weighed and dissolved in ultra-dry tetrahydrofuran (5 mL), cooled to -78°C with a dry ice-acetone bath, and *n*-butyllithium (1.6 M, 0.45 mL) was added dropwise. The mixture was stirred at this temperature for 30 minutes. In another flask, (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **III** (50 mg, 0.12 mmol) was dissolved in ultra-dry tetrahydrofuran (5 mL) and then added dropwise to the above solution at -78°C. After the dropwise addition was completed, the temperature was gradually raised to room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After the reaction was completed, the reaction was quenched with saturated ammonium chloride aqueous solution. The organic phase was separated, dried, and concentrated. The resulting crude product was purified by column chromatography (petroleum ether: ethyl acetate = 0 to 30%) to obtain 5R-1-(3-methoxyphenyl)-5-

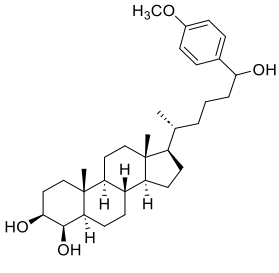
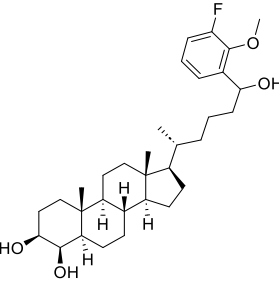
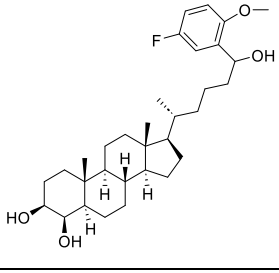
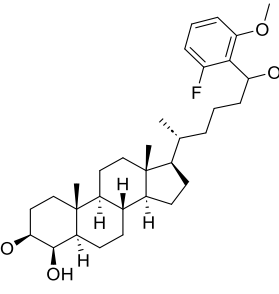
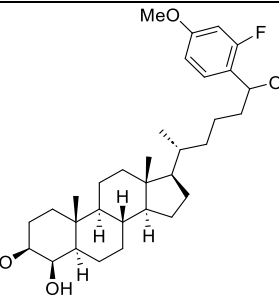
((3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethylhexadecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)hexan-1-ol **5-1** (30 mg, 0.056 mmol, 48.0%) as a white solid.

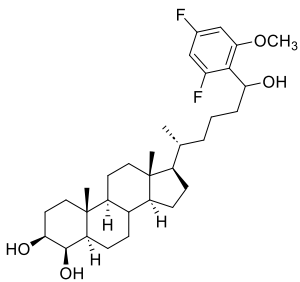
[0172] Step 2: (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-Tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **5-1** (30 mg, 0.056 mmol) was weighed and dissolved in anhydrous methanol (10 mL), and 2 M hydrochloric acid (3 mL) was added at room temperature. After the addition was completed, the mixture was stirred at room temperature, and the reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1) until completion. Water and ethyl acetate were added for extraction. The organic phase was separated, dried, and concentrated. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 0 to 50%) to obtain 24-[hydroxy(3-methoxyphenyl)methyl]-5 α -cholane-3 β ,4 β -diol **5** (15 mg, 0.030 mmol, 54.1%) as a white solid.

[0173] Compound 5: ¹H NMR (399 MHz, Chloroform-d) δ 6.91 (d, J = 7.1 Hz, 2H), 4.63 (q, J = 6.3 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 1H), 3.55 (dd, J = 11.5, 5.0 Hz, 1H), 1.93 (d, J = 12.5 Hz, 1H), 1.75 (s, 2H), 1.73 – 1.67 (m, 4H), 1.64 (s, 4H), 1.36 (s, 2H), 1.35 – 1.30 (m, 3H), 1.24 (s, 2H), 1.08 (d, J = 8.6 Hz, 1H), 1.06 – 1.02 (m, 3H), 1.00 (s, 3H), 0.97 – 0.91 (m, 2H), 0.86 (dd, J = 6.5, 4.7 Hz, 3H), 0.62 (d, J = 2.7 Hz, 3H). ¹³C NMR (100 MHz, Chloroform-d) δ 159.69, 129.43, 118.22, 118.14, 112.91, 112.86, 111.31, 111.24, 74.82, 74.58, 72.26, 56.51, 56.13, 56.11, 55.22, 55.18, 48.77, 42.57, 39.85, 39.52, 39.48, 36.82, 35.67, 35.44, 35.36, 32.36, 28.24, 25.96, 25.83, 24.18, 22.46, 22.37, 20.55, 18.58, 18.56, 14.66, 12.05. LC-MS: [M+H]⁺ = 498.37.

[0174] The synthesis of Examples 6, 7, 8, 20, 28, and 104 was completed using the synthesis method described in Example 5.

Example	Structural formula	Compound name
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6		24-[Hydroxy(4-methoxyphenyl)methyl]-5 α -cholane-3 β ,4 β -diol
7		24-[(3-Fluoro-2-methoxyphenyl)(hydroxy)methyl]-5 α -cholane-3 β ,4 β -diol
8		24-[(5-Fluoro-2-methoxyphenyl)(hydroxy)methyl]-5 α -cholane-3 β ,4 β -diol
20		24-[(2-Fluoro-6-methoxyphenyl)(hydroxy)methyl]-5 α -cholane-3 β ,4 β -diol
28		24-[(2-Fluoro-4-methoxyphenyl)(hydroxy)methyl]-5 α -cholane-3 β ,4 β -diol

104		(1R,3aS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,4-Difluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol
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[0175] Structural spectral analysis of compounds 6, 7, 8, 20, 28, and 104

Example	Structural spectral analysis of compounds
6	¹ H NMR (399 MHz, Chloroform-d) δ 7.26 (s, 1H), 7.23 (s, 1H), 6.86 (d, J = 8.6 Hz, 2H), 4.59 (q, J = 6.3 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 1H), 3.53 (dd, J = 10.7, 5.4 Hz, 1H), 1.92 (d, J = 11.2 Hz, 2H), 1.69 (dd, J = 14.4, 6.5 Hz, 3H), 1.61 (d, J = 16.1 Hz, 3H), 1.41 – 1.34 (m, 3H), 1.31 (t, J = 6.4 Hz, 3H), 1.24 (d, J = 11.4 Hz, 2H), 1.21 – 1.15 (m, 1H), 1.08 (d, J = 4.3 Hz, 1H), 1.07 – 1.00 (m, 4H), 0.99 (s, 3H), 0.94 (t, J = 4.2 Hz, 1H), 0.90 (d, J = 7.7 Hz, 1H), 0.84 (t, J = 6.1 Hz, 3H), 0.60 (d, J = 3.0 Hz, 3H). ¹³ C NMR (101 MHz, Chloroform-d) δ 127.13, 127.06, 113.75, 74.79, 74.25, 72.25, 56.50, 56.10, 55.25, 55.18, 48.77, 42.55, 39.84, 39.40, 36.82, 35.66, 35.43, 35.35, 32.35, 28.22, 25.94, 25.82, 24.17, 20.54, 18.56, 14.63, 12.04, 1.00. LC-MS: [M-H ₂ O-OH] ⁺ = 463.3.
7	¹ H NMR (399 MHz, Chloroform-d) δ 7.09 (dt, J = 7.4, 3.4 Hz, 1H), 7.01 – 6.95 (m, 2H), 4.88 (q, J = 7.0 Hz, 1H), 3.95 (dd, J = 2.2, 1.0 Hz, 3H), 3.71 (d, J = 3.2 Hz, 1H), 3.54 (dd, J = 11.3, 4.8 Hz, 1H), 1.93 (d, J = 12.7 Hz, 1H), 1.75 (t, J = 5.6 Hz, 3H), 1.71 (d, J = 4.9 Hz, 3H), 1.67 (s, 2H), 1.41 – 1.34 (m, 4H), 1.33 (d, J = 4.2 Hz, 2H), 1.28 – 1.21 (m, 3H), 1.17 (d, J = 11.9 Hz, 1H), 1.08 (dd, J = 8.8, 3.8 Hz, 1H), 1.04 (d, J = 9.6 Hz, 3H), 0.99 (s, 3H), 0.95 (q, J = 3.6 Hz, 1H), 0.90 (d, J = 8.9 Hz, 1H), 0.88 – 0.85 (m, 3H), 0.83 (s, 1H), 0.61

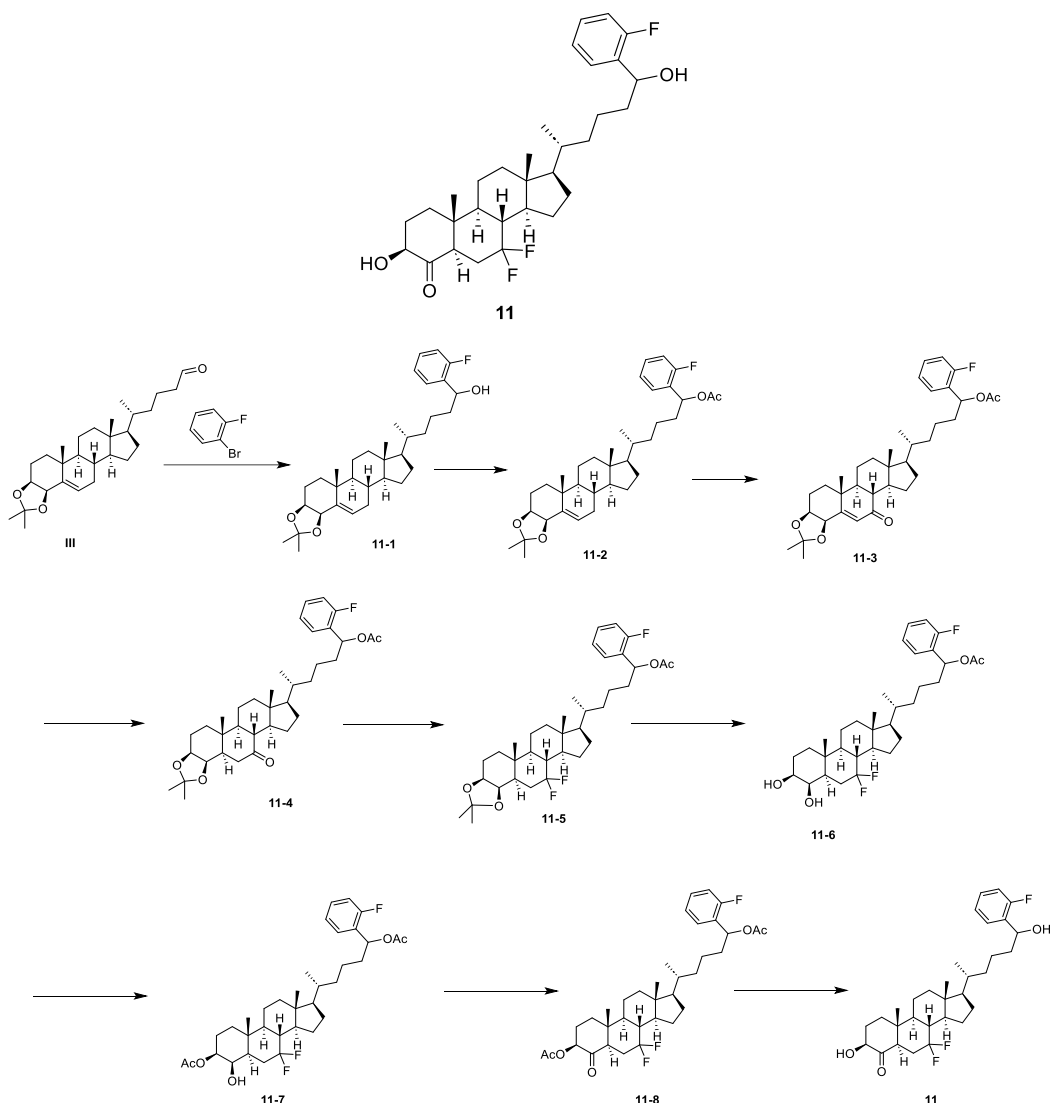
	(d, J = 2.6 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 123.58 , 123.50 , 121.92 , 115.79 , 115.60 , 72.26 , 56.51 , 55.18 , 48.77 , 42.56 , 39.86 , 36.82 , 35.44 , 35.35 , 32.35 , 28.23 , 25.95 , 25.82 , 24.18 , 20.54 , 18.55 , 14.64 , 12.05. ^{19}F NMR (376 MHz, cdCl_3) δ -130.53, -130.57.
8	^1H NMR (400 MHz, Chloroform-d) δ 7.07 – 7.01 (m, 1H), 6.92 – 6.85 (m, 1H), 6.77 (dd, J = 9.0, 4.3 Hz, 1H), 4.83 (q, J = 7.8 Hz, 1H), 3.80 (t, J = 1.4 Hz, 3H), 3.71 (s, 1H), 3.53 (dd, J = 10.9, 5.4 Hz, 1H), 1.93 (d, J = 12.6 Hz, 1H), 1.73 (s, 3H), 1.69 (d, J = 12.8 Hz, 4H), 1.63 (s, 3H), 1.52 (s, 2H), 1.36 (s, 3H), 1.33 (s, 2H), 1.23 (s, 4H), 1.11 – 1.03 (m, 3H), 0.99 (s, 3H), 0.93 (d, J = 11.1 Hz, 2H), 0.88 – 0.84 (m, 3H), 0.61 (t, J = 2.0 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 152.48 , 113.87 , 113.63 , 72.26 , 70.41 , 70.00 , 56.52 , 56.17 , 56.12 , 55.79 , 55.18 , 48.77 , 42.56 , 39.86 , 37.68 , 37.46 , 36.82 , 35.71 , 35.62 , 35.57 , 35.44 , 35.35 , 32.36 , 28.23 , 25.94 , 25.82 , 24.18 , 22.37 , 20.55 , 18.55 , 14.64 , 12.05 . ^{19}F NMR (376 MHz, Chloroform-d) δ -123.52 (dt, J = 8.8, 4.4 Hz). LC-MS: $[\text{M}-\text{H}_2\text{O}-\text{OH}]^+ = 481.4$.
20	^1H NMR (399 MHz, Chloroform-d) δ 7.15 (q, J = 8.0 Hz, 1H), 6.66 (dt, J = 9.1, 4.8 Hz, 2H), 4.98 (s, 1H), 3.86 (s, 3H), 3.71 (s, 1H), 3.53 (s, 1H), 1.92 (d, J = 13.1 Hz, 2H), 1.74 (s, 4H), 1.67 (s, 1H), 1.63 (s, 3H), δ 1.42 (s, 1H), 1.36 (d, J = 4.3 Hz, 3H), 1.33 (s, 2H), 1.25 (d, J = 9.9 Hz, 2H), 1.07 – 1.00 (m, 4H), 0.99 (s, 3H), 0.98 – 0.88 (m, 3H), 0.85 (t, J = 6.1 Hz, 3H), 0.61 (d, J = 4.7 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 128.39, 119.59, 106.71, 72.25 , 56.51 , 56.15 , 56.13 , 55.84 , 55.17 , 48.76 , 42.55 , 39.85 , 38.00 , 37.81 , 36.82 , 35.71 , 35.65 , 35.49 , 35.44 , 35.35 , 32.36 , 30.95 , 28.20 , 25.94 , 25.83 , 24.18 , 22.64 , 22.52 , 20.54 , 18.52 , 18.49 , 14.64 , 12.04.

28	¹ H NMR (399 MHz, Chloroform-d) δ 7.31 (td, <i>J</i> = 8.7, 2.5 Hz, 1H), 6.68 (dd, <i>J</i> = 8.6, 2.5 Hz, 1H), 6.57 (dd, <i>J</i> = 12.1, 2.4 Hz, 1H), 4.94 – 4.86 (m, 1H), 3.78 (s, 3H), 3.72 (s, 1H), 3.54 (dd, <i>J</i> = 11.0, 5.3 Hz, 1H), 1.93 (d, <i>J</i> = 12.4 Hz, 1H), 1.73 (d, <i>J</i> = 14.9 Hz, 6H), 1.65 (d, <i>J</i> = 19.1 Hz, 10H), 1.52 (s, 2H), 1.32 (d, <i>J</i> = 6.3 Hz, 3H), 1.25 (d, <i>J</i> = 12.1 Hz, 5H), 1.17 (d, <i>J</i> = 13.6 Hz, 1H), 1.05 (dd, <i>J</i> = 11.2, 7.6 Hz, 4H), 0.99 (s, 3H), 0.93 (d, <i>J</i> = 10.9 Hz, 2H), 0.87 (s, 1H), 0.87–0.84 (m, 3H), 0.62 (d, <i>J</i> = 2.2 Hz, 3H), 0.55 (dd, <i>J</i> = 11.3, 3.7 Hz, 1H). ¹³ C NMR (100 MHz, cdcl ₃) δ 140.04, 127.79, 126.83, 109.99, 77.31, 77.19, 76.99, 76.67, 74.82, 72.27, 56.51, 56.11, 55.18, 48.77, 42.56, 39.85, 36.82, 35.63, 35.44, 35.35, 32.36, 28.21, 25.96, 25.83, 24.17, 20.54, 18.54, 14.65, 12.04, 1.01. ¹⁹ F NMR (376 MHz, cdcl ₃) δ -117.81, -117.91. LC-MS: [M-H ₂ O-OH] ⁺ = 481.5.
104	¹ H NMR (400 MHz, CDCl ₃) δ 6.44 (dd, <i>J</i> = 9.7, 7.9 Hz, 2H), 4.99 – 4.88 (m, 1H), 3.82 (d, <i>J</i> = 33.1 Hz, 3H), 3.73 (s, 1H), 3.58 – 3.50 (m, 1H), 1.97 – 1.89 (m, 2H), 1.75 (dd, <i>J</i> = 16.0, 6.6 Hz, 6H), 1.70 – 1.61 (m, 4H), 1.58 – 1.49 (m, 2H), 1.36 (dd, <i>J</i> = 21.3, 9.9 Hz, 6H), 1.27 (d, <i>J</i> = 12.4 Hz, 4H), 1.07 (dd, <i>J</i> = 18.2, 10.2 Hz, 5H), 1.01 (s, 3H), 0.94 (dd, <i>J</i> = 13.1, 6.2 Hz, 2H), 0.87 (t, <i>J</i> = 5.9 Hz, 3H), 0.63 (d, <i>J</i> = 3.6 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -125.5, -122.3, -123.4.

[0176] Example 11

[0177] Preparation of compound 11 (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-7-hydroxy-

5 9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one.



[0178] Step 1: Compound 1-bromo-2-fluorobenzene (195.96 mg, 1.12 mmol, 1.2 *eq*) was dissolved in tetrahydrofuran (30 mL). Under a nitrogen atmosphere, the solution was cooled to -78°C in a dry ice bath, and *n*-butyllithium (2.5 M in *n*-hexane, 89.67 mg, 1.400 mmol, 1.5 *eq*) was added. The mixture was stirred for 30 minutes at this temperature, followed by addition of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **III** (400 mg, 0.933 mmol, 1.0 *eq*). The reaction was then allowed to warm to room temperature naturally. The reaction progress was monitored by TLC (petroleum

ether: ethyl acetate = 5:1). After the reaction was completed, the reaction was quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with saturated brine (15 mL). The ethyl acetate layer was dried over Na₂SO₄,
 5 filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexan-1-ol **11-1** (400 mg, purity: 80%, yield: 65%) as a white solid.
 10 ¹H NMR (400 MHz, CDCl₃) δ 7.46 (t, J = 7.4 Hz, 1H), 7.23 (s, 1H), 7.15 (s, 1H), 7.02 (m, 1H), 5.80 (s, 1H), 5.00 (dd, J = 12.0, 7.0 Hz, 1H), 4.41 (d, J = 5.8 Hz, 1H), 4.10 (dd, J = 13.9, 6.1 Hz, 1H), 2.06 (dd, J = 44.2, 10.2 Hz, 3H), 1.65 (dd, J = 30.7, 25.0 Hz, 9H), 1.41 (d, J = 9.7 Hz, 4H), 1.35 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H), 1.10 (m, 6H), 0.90 (dd, J = 6.4, 4.0 Hz, 3H), 0.68 (m, 3H).
 15 **[0179] Step 2:** Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexan-1-ol **11-1** (400 mg, 0.76 mmol, 1.0 eq) was dissolved in
 20 dichloromethane (20 mL). Acetic anhydride (0.215 mL, 2.29 mmol, 3.0 eq), triethylamine (0.530 mL, 3.81 mmol, 5.0 eq), and 4-dimethylaminopyridine (93.09 mg, 0.76 mmol, 1.0 eq) were added. The resulting mixture was stirred at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the
 25 reaction was quenched with methanol. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic phases were combined, washed with saturated brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl
 30 acetate = 95:5) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-

3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **11-2** (400 mg, purity: 90%, yield: 83%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.03 (m, 1H), 6.01 (m, 1H), 5.80 (d, *J* = 2.8 Hz, 1H), 4.41 (d, *J* = 5.8 Hz, 1H), 4.10 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.08 (d, *J* = 2.4 Hz, 3H), 1.61 (m, 8H), 1.43 (s, 4H), 1.34 (d, *J* = 6.2 Hz, 5H), 1.26 (s, 3H), 1.16 (s, 5H), 1.02 (m, 9H), 0.86 (m, 7H), 0.67 (m, 4H).

[0180] Step 3: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **11-2** (120 mg, 0.21 mmol, 1.0 *eq*) was dissolved in acetone (5 mL). N-Hydroxyphthalimide (6.92 mg, 0.042 mmol, 0.2 *eq*), *tert*-butyl hydroperoxide (0.170 mL, 0.848 mmol, 4.0 *eq*), and anhydrous cobalt(II) acetate (1.88 mg, 0.011 mmol, 0.05 *eq*) were added. The resulting mixture was stirred at 25°C for 18 hours. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 10:1), and the starting material was completely consumed. The reaction was quenched with saturated sodium sulfite. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The ethyl acetate layers were combined, washed with saturated brine (15 mL), dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **11-3** (60 mg, purity: 90%, yield: 44%). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, *J* = 7.3 Hz, 1H), 7.23 (m, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.03 (m, 1H), 6.02 (d, *J* = 5.0 Hz, 1H), 5.92 (s, 1H), 4.52 (d, *J* = 6.4 Hz, 1H), 4.32 (d, *J* = 5.6 Hz, 1H), 2.34 (d, *J* = 10.6 Hz, 2H), 2.08 (s, 3H), 2.02 (m, 1H), 1.82 (dd, *J* = 20.1, 10.2 Hz, 4H), 1.57 (t, *J* = 12.4 Hz, 13H), 1.34 (m, 17H), 1.07 (m, 5H), 0.87 (dd, *J* = 11.7, 6.8 Hz, 4H), 0.80 (d, *J* = 5.9 Hz, 1H), 0.69 (d, *J* = 3.5 Hz, 3H).

[0181] Step 4: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **11-3** (60 mg, 0.10 mmol) was dissolved in methanol (5 mL). Palladium on carbon (11 mg, 0.103 mmol) was added, and the mixture was purged with hydrogen three times. The resulting mixture was stirred under hydrogen at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After the starting material was completely consumed, the mixture was filtered and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **11-4** (40 mg, 0.062 mmol, purity: 90%, yield: 60%) as a white solid. ¹HNMR (400 MHz, CDCl₃) δ 7.34 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 7.03 (s, 1H), 6.01 (dd, J = 10.9, 6.4 Hz, 1H), 3.98 (d, J = 3.4 Hz, 2H), 2.77 (s, 1H), 2.42 (s, 1H), 2.19 (dd, J = 12.7, 2.7 Hz, 2H), 2.08 (s, 3H), 1.74 (m, 9H), 1.53 (s, 3H), 1.38 (dd, J = 11.7, 7.8 Hz, 4H), 1.28 (d, J = 17.1 Hz, 10H), 0.95 (ddd, J = 10.8, 9.5, 6.5 Hz, 10H), 0.64 (d, J = 3.2 Hz, 3H).

[0182] Step 5: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **11-4** (250 mg, 0.43 mmol) was dissolved in diethylaminosulfur trifluoride (5 mL). The resulting mixture was stirred at 80°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 10:1), and the starting material was completely consumed. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL) and carefully quenched by dropwise addition of ice water. The organic phase was separated and collected, and the aqueous layer was extracted with dichloromethane (3 $\times$ 10

mL). The organic phases were combined, washed with saturated brine (15 mL), filtered, and concentrated to obtain a crude product. The crude product was added with silica gel and purified by column chromatography (petroleum ether: ethyl acetate = 93:7) to obtain (5R)-5-
 5 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **11-5** (210 mg, purity: 90%, yield: 72.85%) as a colorless transparent solid. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 6.6 Hz, 1H),
 10 7.12 (t, J = 7.5 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.05 – 5.98 (m, 1H), 4.07 – 3.98 (m, 2H), 2.08 (d, J = 1.3 Hz, 3H), 1.98 – 1.68 (m, 9H), 1.63 – 1.57 (m, 2H), 1.50 (s, 3H), 1.39 (dd, J = 10.5, 5.0 Hz, 4H), 1.30 (s, 3H), 1.07 (s, 3H), 1.05 – 0.90 (m, 4H), 0.87 (dd, J = 6.3, 4.7 Hz, 4H), 0.64 (dd, J = 11.7, 3.6 Hz, 3H).
[0183] Step 6: (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-
 15 6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl acetate **11-5** (130 mg, 0.23 mmol, 1.0 eq) was dissolved in dichloromethane (8 mL). The reaction system was placed in an ice-water bath and cooled to approximately 5°C. Acetic anhydride (0.022 mL, 0.23 mmol, 1.0 eq), 4-dimethylaminopyridine (5.62 mg, 0.046 mmol,
 20 0.2 eq), and triethylamine (0.064 mL, 0.46 mmol, 2.0 eq) were sequentially added to the reaction system. The reaction system was then stirred at room temperature for 1 hour. After the reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion, the reaction was quenched with methanol (20 mL). The reaction mixture was washed with water (40 mL × 2) and saturated
 25 sodium bicarbonate (40 mL × 2). The aqueous phase was extracted with dichloromethane (40 mL × 2), and the organic phases were collected and concentrated under vacuum to obtain a crude product. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-
 30 6-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl acetate **11-6** (90 mg, purity: 95%, yield: 61%) as a

white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.34 (t, $J = 7.4$ Hz, 1H), 7.24 (d, $J = 5.8$ Hz, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.02 (dd, $J = 15.2, 6.7$ Hz, 1H), 6.05 – 5.97 (m, 1H), 4.73 (dd, $J = 9.2, 6.0$ Hz, 1H), 3.88 (d, $J = 39.4$ Hz, 1H), 2.30 – 2.12 (m, 1H), 2.09 (s, 6H), 1.98 – 1.69 (m, 10H), 1.48 – 1.29 (m, 8H), 1.16 – 1.09 (m, 2H),
 5 1.08 (s, 3H), 1.03 (d, $J = 8.7$ Hz, 3H), 0.87 (dd, $J = 6.4, 4.1$ Hz, 3H), 0.63 (dd, $J = 12.2, 3.5$ Hz, 3H).

[0184] Step 7: Compound (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-6-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl acetate **11-6** (80 mg,
 10 0.132 mmol) was dissolved in dichloromethane (10 mL). Dess-Martin periodinane (67 mg, 0.158 mmol) was added, and the mixture was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×25 mL). The ethyl acetate
 15 layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer was dried over Na_2SO_4 , filtered, and concentrated to obtain a crude product. After the reaction was completed, the reaction mixture was filtered. The filtrate was washed with water, and the organic phase was dried and concentrated. The crude product was purified by flash column chromatography
 20 (petroleum ether: ethyl acetate = 84:16) to obtain (5R)-5-[(1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-9a,11a-dimethyl-6-oxohexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl acetate **11-7** (85 mg, purity: 95%, yield: 90%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.34 (t, $J = 7.4$ Hz, 1H), 7.25 (s, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.07 – 7.00 (m, 1H), 6.05 – 5.99 (m, 1H), 5.18 (dd, $J = 12.2, 7.4$ Hz, 1H), 2.53 (t, $J = 10.2$ Hz, 1H), 2.09 (s, 3H), 2.05 (s, 4H), 1.99 – 1.56 (m, 11H), 1.38 (ddd, $J = 26.0, 14.1, 6.7$ Hz, 6H), 1.22 – 0.99 (m, 4H), 0.89 – 0.85 (m, 3H), 0.77 (d, $J = 10.9$ Hz, 3H), 0.63 (dd, $J = 15.2, 3.6$ Hz, 3H).

[0185] Step 8: Compound (5R)-5-[(1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-9a,11a-dimethyl-6-oxohexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluorophenyl)hexyl acetate **11-7** (87 mg, 0.144 mmol, 1
 30

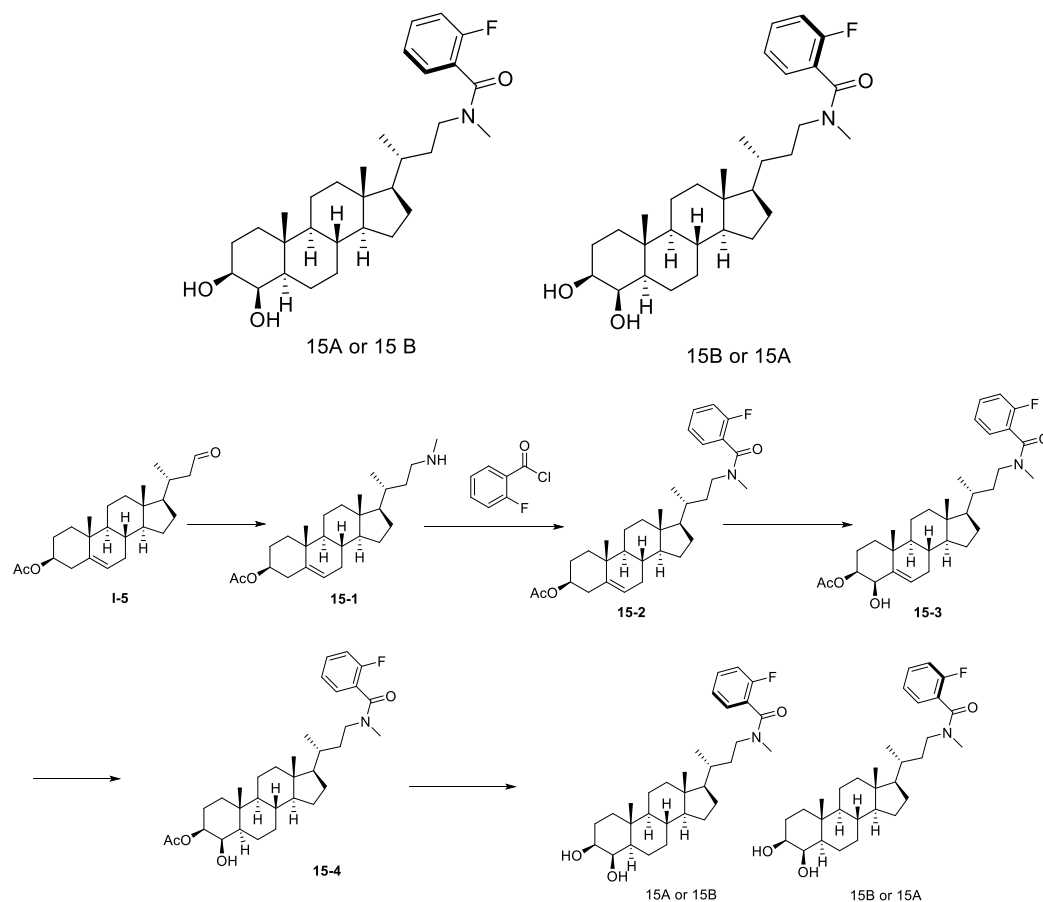
eq) was dissolved in a mixed solvent of tetrahydrofuran (2.5 mL) and methanol (2.5 mL). Lithium hydroxide aqueous solution (0.5 mL, 3 mol/L) was added, and the resulting mixture was stirred at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 1:1). After the starting material was completely consumed, the reaction mixture was diluted with ethyl acetate (20 mL), washed with saturated brine, and the organic phase was dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to obtain a crude product, which was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 76:24). Subsequently, further SFC separation was performed (instrument: Waters Acquity UPCC; column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C; retention time t_R = 2.417 min) to obtain (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one **11** (6.04 mg, purity: 95.12%, yield: 8.34%) as a white solid.

[0186] Compound **11**: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 5.9 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.05 – 6.98 (m, 1H), 5.04 – 4.96 (m, 1H), 4.14 (dd, *J* = 11.2, 8.1 Hz, 1H), 2.46 (ddd, *J* = 16.8, 12.7, 8.3 Hz, 2H), 2.18 – 2.07 (m, 1H), 1.77 – 1.50 (m, 11H), 1.27 (dddd, *J* = 55.4, 28.2, 14.6, 6.8 Hz, 12H), 0.90 (dd, *J* = 6.4, 4.0 Hz, 3H), 0.76 (s, 3H), 0.66 (d, *J* = 2.0 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -90.21, -90.85, -111.50, -112.14, -119.77, -119.80.

[0187] Examples **15A** & **15B**

[0188] Preparation of compounds **15A** & **15B**: 2-fluoro-N-[(3R)-3-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-5a,9a,11a-trimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]butyl]-N-methylbenzamide and 2-fluoro-N-[(3R)-3-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-5a,9a,11a-trimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]butyl]-N-

methylbenzamide



- [0189] Step 1:** (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R)-1-Formylpropan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-5** (300 mg, 0.776 mmol) was weighed and dissolved in tetrahydrofuran (5 mL). Zinc chloride (105.76 mg, 0.776 mmol) and a solution of methylamine in tetrahydrofuran (1.552 mL) were added sequentially at room temperature, followed by stirring for 30 minutes at room temperature. Sodium cyanoborohydride (48.77 mg, 0.776 mmol) was then added. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was separated, dried, and concentrated. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 5:1) to obtain (1R,3aS,3bS,7S,9aR,9bS,11aR)-9a,11a-dimethyl-1-[(2R)-4-(methylamino)butan-2-yl]-

2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **15-1** (220 mg, 0.438 mmol, 56.47%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 5.35 (d, *J* = 5.0 Hz, 1H), 4.59 (d, *J* = 13.0 Hz, 1H), 2.95 (d, *J* = 36.8 Hz, 2H), 2.69 (s, 2H), 2.30 (d, *J* = 7.3 Hz, 2H), 2.01 (s, 3H), 1.96 (d, *J* = 13.5 Hz, 2H), 1.88 – 1.81 (m, 3H), 1.56 (d, *J* = 10.6 Hz, 3H), 1.50 (d, *J* = 16.6 Hz, 3H), 1.45 – 1.36 (m, 2H), 1.33 – 1.24 (m, 2H), 1.20 – 1.01 (m, 5H), 0.99 (s, 3H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.94 – 0.84 (m, 1H), 0.68 (s, 3H).

[0190] Step 2: (1R,3aS,3bS,7S,9aR,9bS,11aR)-9a,11a-Dimethyl-1-[(2R)-4-(methylamino)butan-2-yl]-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-

1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **15-1** (60 mg, 0.149 mmol) was weighed and dissolved in DCM (5 mL). Diisopropylethylamine (0.074 mL, 0.448 mmol) was added, followed by addition of 2-fluorobenzoyl chloride (47.37 mg, 0.299 mmol) under stirring. The mixture was then stirred at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the reaction was completed, water (20 mL) and ethyl acetate (15 mL) were added for extraction. The organic phase was separated, dried, and concentrated. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 30:1 to 5:1) to obtain (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R)-4-[(2-

fluorophenyl)carbonyl](methylamino}butan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **15-2** (40 mg, 0.061 mmol, 40.90%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 7.32 (dt, *J* = 15.8, 6.9 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.07 (q, *J* = 8.8 Hz, 1H), 5.36 (d, *J* = 5.7 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 3.20 – 3.09 (m, 1H), 3.07 (s, 2H), 2.86 (d, *J* = 1.5 Hz, 1H), 2.30 (t, *J* = 5.8 Hz, 2H), 2.01 (d, *J* = 1.9 Hz, 4H), 1.97 – 1.87 (m, 2H), 1.83 (t, *J* = 9.9 Hz, 2H), 1.51 – 1.36 (m, 5H), 1.34 – 1.25 (m, 2H), 1.14 (ddd, *J* = 33.9, 16.5, 6.5 Hz, 5H), 1.01 (dd, *J* = 14.9, 8.0 Hz, 6H), 0.96 – 0.83 (m, 2H), 0.69 (s, 1H), 0.63 (d, *J* = 5.9 Hz, 2H), 0.59 (s, 2H).

[0191] Step 3: (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R)-4-[(2-Fluorophenyl)carbonyl](methylamino}butan-2-yl]-9a,11a-dimethyl-

2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-
 i]phenanthren-7-yl acetate **15-2** (232 mg, 0.443 mmol) was weighed and
 dissolved in chloroform (10 mL). Selenium dioxide (245.76 mg, 2.215 mmol)
 and NMM (268.84 mg, 2.658 mmol) were added sequentially under stirring at
 5 room temperature. The reaction mixture was then heated to 75°C with stirring.
 The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After
 the reaction was completed, the reaction mixture was cooled to room temperature
 and filtered. The filtrate was added with water and dichloromethane for
 extraction. The organic phase was separated, dried, and concentrated. The
 10 residue was purified by column chromatography (petroleum ether: ethyl acetate
 = 20:1 to 5:1) to obtain (1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-1-[(2R)-4-[(2-
 fluorophenyl)carbonyl](methyl)amino}butan-2-yl]-6-hydroxy-9a,11a-dimethyl-
 2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-
 i]phenanthren-7-yl acetate **15-3** (136 mg, 0.202 mmol, 45.51%) as a white solid.
 15 ¹H NMR (399 MHz, Chloroform-d) δ 7.32 (dt, J = 15.9, 7.0 Hz, 2H), 7.17 (t, J =
 7.5 Hz, 1H), 7.07 (q, J = 8.7 Hz, 1H), 5.69 (d, J = 5.6 Hz, 1H), 4.69 (d, J = 11.4
 Hz, 1H), 4.22 (d, J = 4.2 Hz, 1H), 3.67 (s, 1H), 3.43 (s, 1H), 3.15 (s, 1H), 3.07 (s,
 1H), 2.86 (s, 1H), 2.08 (s, 4H), 2.00 (s, 1H), 1.85 (q, J = 12.1 Hz, 3H), 1.65 (d, J
 = 9.2 Hz, 3H), 1.49 – 1.38 (m, 3H), 1.30 (s, 3H), 1.19 (d, J = 9.7 Hz, 3H), 1.11
 20 (dd, J = 23.4, 9.3 Hz, 3H), 1.03 (d, J = 6.6 Hz, 2H), 0.98 – 0.80 (m, 3H), 0.69 (s,
 1H), 0.64 (d, J = 5.9 Hz, 1H), 0.59 (s, 1H).

[0192] Step 4: (1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-1-[(2R)-4-[(2-
 Fluorophenyl)carbonyl](methyl)amino}butan-2-yl]-6-hydroxy-9a,11a-dimethyl-
 2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-
 25 i]phenanthren-7-yl acetate **15-3** (136 mg, 0.252 mmol) was weighed and
 dissolved in acetic acid (3 mL). Platinum dioxide (85.83 mg, 0.378 mmol) was
 added, and the system was purged with hydrogen. The reaction mixture was
 then heated to 60°C with stirring. The reaction was monitored by TLC
 (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the
 30 platinum dioxide was removed by filtration. Most of the acetic acid was
 removed by concentration. The residue was then added with saturated sodium

bicarbonate aqueous solution and extracted with ethyl acetate. The organic phase was separated, dried, and concentrated to obtain the crude product (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-4-[(2-fluorophenyl)carbonyl](methylamino)butan-2-yl]-6-hydroxy-5a,9a,11a-trimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **15-4** (130 mg), which was directly used in the next step.

[0193] Step 5: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-4-[(2-Fluorophenyl)carbonyl](methylamino)butan-2-yl]-6-hydroxy-5a,9a,11a-trimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **15-4** (130 mg, 0.234 mmol) was weighed and dissolved in a mixed solution of methanol (1 mL) and tetrahydrofuran (2 mL). Lithium hydroxide aqueous solution (2.339 mL) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 2:1). After the reaction was completed, water and ethyl acetate were added for extraction. The organic phase was separated, dried, and concentrated. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 20:1 to 1:1) to obtain 2-fluoro-N-[(3R)-3-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-5a,9a,11a-trimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]butyl]-N-methylbenzamide **15A** (14 mg, 0.026 mmol, 10.95%) and 2-fluoro-N-[(3R)-3-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-dihydroxy-5a,9a,11a-trimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]butyl]-N-methylbenzamide **15B** (18 mg, 0.035 mmol, 14.82%).

[0194] 15A: ^1H NMR (399 MHz, Chloroform-d) δ 7.33 (d, J = 22.2 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.08 (q, J = 8.3 Hz, 1H), 4.01 (s, 1H), 3.88 (t, J = 11.1 Hz, 1H), 3.67 (s, 1H), 3.44 (s, 1H), 3.17 (d, J = 14.2 Hz, 1H), 3.08 (s, 2H), 2.87 (s, 1H), 1.99 (s, 6H), 1.81 (d, J = 39.6 Hz, 2H), 1.64 (s, 3H), 1.47 (s, 2H), 1.41 (d, J = 9.7 Hz, 2H), 1.29 (d, J = 9.4 Hz, 2H), 1.18 (d, J = 15.9 Hz, 3H), 1.05 (s, 2H), 1.01 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 9.2 Hz, 3H), 0.66 (s, 1H), 0.62 (d, J = 5.9 Hz, 1H), 0.56 (s, 2H). ^{19}F NMR (376 MHz, Chloroform-d) δ -115.20. LC-MS: $[\text{M}+\text{H}]^+ = 500.35$.

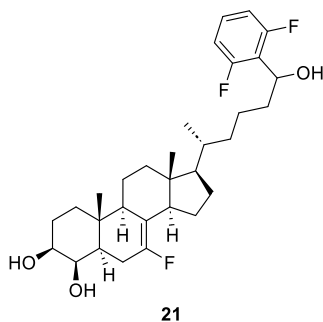
[0195] 15B: ^1H NMR (399 MHz, Chloroform- d) δ 7.39 – 7.28 (m, 2H), 7.18 (d, J = 7.7 Hz, 1H), 7.07 (q, J = 8.4 Hz, 1H), 3.74 (s, 1H), 3.56 (s, 1H), 3.44 (s, 1H), 3.16 (d, J = 13.0 Hz, 1H), 3.07 (s, 2H), 2.86 (s, 1H), 2.46 (s, 4H), 1.95 (d, J = 13.2 Hz, 1H), 1.73 (d, J = 12.6 Hz, 5H), 1.48 (s, 1H), 1.33 (s, 3H), 1.10 (dd, J = 22.5, 10.9 Hz, 5H), 0.98 (d, J = 9.3 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H), 0.65 (s, 1H), 0.61 (d, J = 5.6 Hz, 2H), 0.55 (s, 2H). ^{19}F NMR (376 MHz, Chloroform- d) δ -115.13 (d, J = 49.4 Hz). ^{13}C NMR (100 MHz, Chloroform- d) δ 110.00, 77.21, 77.01, 56.37, 55.94, 55.59, 55.06, 48.60, 44.95, 42.65, 42.54, 35.31, 33.76, 33.40, 32.78, 32.25, 30.96, 20.45, 18.72, 18.43, 14.58, 11.96. LC-MS: $[\text{M}+\text{H}]^+ = 500.40$.

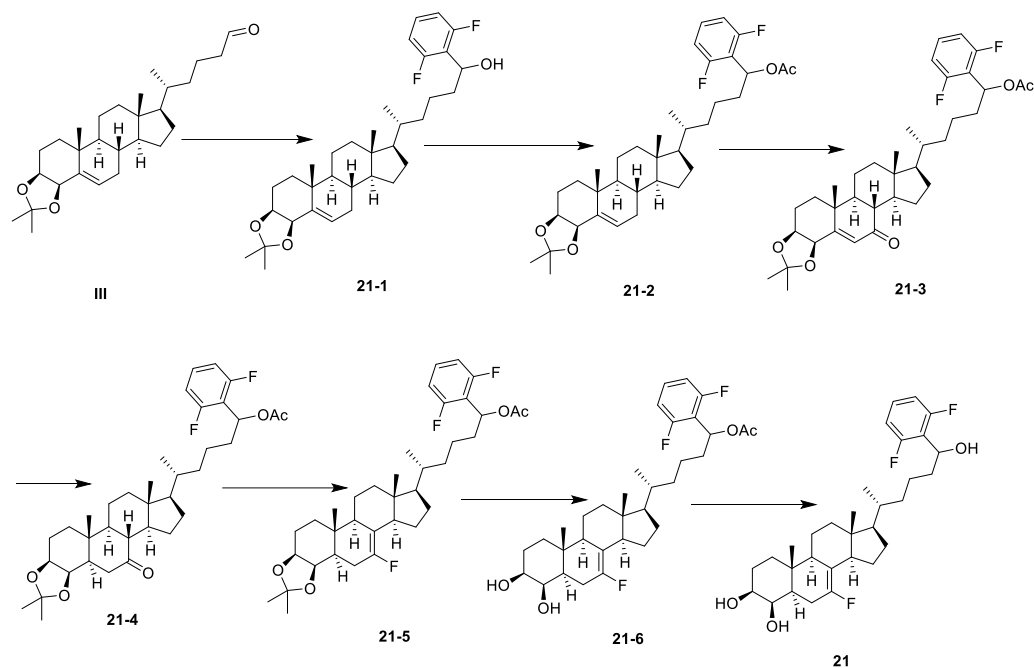
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[0196] Example 21

[0197] Preparation of compound **21** (**1R,3aR,5aR,6R,7S,9aR,9bR,11aR**)-1-[(2R)-6-(2,6-difluorophenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.

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[0198] Step 1: Reagent 2-bromo-1,3-difluorobenzene (270 mg, 1.40 mmol, 3.0 eq) was dissolved in tetrahydrofuran (5 mL) under a nitrogen atmosphere. The mixture was cooled to -78°C in a dry ice bath, followed by addition of *n*-butyllithium (2.5 M in *n*-hexane, 0.67 mL, 1.680 mmol, 3.6 eq). After stirring for approximately 0.5 hours, a solution of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **III** (200 mg, 0.467 mmol, 1.0 eq) in tetrahydrofuran (10 mL) was then added. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was almost completely consumed, the reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, and the crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluorophenyl)hexan-1-ol **21-1** (180 mg, purity: 90%, yield: 63.97%) as a white

solid. ¹H NMR (400 MHz) δ 7.21 (s, 1H), 6.87 (t, *J* = 8.2 Hz, 2H), 5.80 (d, *J* = 2.7 Hz, 1H), 5.03 (s, 1H), 4.40 (d, *J* = 5.8 Hz, 1H), 4.10 (d, *J* = 7.4 Hz, 1H), 2.12 (m, 1H), 2.00 (d, *J* = 13.4 Hz, 2H), 1.69 (m, 10H), 1.39 (m, 8H), 1.08 (m, 10H), 0.90 (dd, *J* = 14.8, 8.6 Hz, 5H), 0.68 (d, *J* = 3.9 Hz, 3H).

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[0199] Step 2: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluorophenyl)hexan-1-ol **21-1** (180 mg, 0.332 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL), followed by addition of acetic anhydride (0.093 mL, 0.995 mmol, 3.0 eq), triethylamine (0.230 mL, 1.658 mmol, 5.0 eq), and DMAP (8.10 mg, 0.066 mmol, 0.2 eq). The resulting reaction mixture was stirred at 25°C for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction mixture was quenched with methanol, washed with saturated sodium bicarbonate, washed with saturated brine (15 mL), dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluorophenyl)hexyl acetate **21-2** (150 mg, purity: 90%, yield: 69.61%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.23 (m, 1H), 6.86 (t, *J* = 8.0 Hz, 2H), 6.05 (t, *J* = 7.5 Hz, 1H), 5.80 (d, *J* = 2.6 Hz, 1H), 4.40 (d, *J* = 5.8 Hz, 1H), 4.10 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.11 (dd, *J* = 12.6, 4.2 Hz, 1H), 2.06 (s, 3H), 2.01 (m, 2H), 1.77 (m, 3H), 1.61 (m, 6H), 1.41 (d, *J* = 12.5 Hz, 4H), 1.30 (m, 6H), 1.06 (m, 11H), 0.87 (m, 5H), 0.67 (d, *J* = 4.0 Hz, 3H).

[0200] Step 3: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluorophenyl)hexyl acetate **21-2** (150 mg, 0.257 mmol, 1.0 eq) was dissolved in

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acetone (5 mL). N-Hydroxyphthalimide (8.37 mg, 0.051 mmol, 0.2 eq), *tert*-butyl hydroperoxide (0.205 mL, 1.026 mmol, 4.0 eq), and anhydrous cobalt(II) acetate (2.27 mg, 0.013 mmol, 0.05 eq) were added. The resulting mixture was stirred under N₂ at 25°C for 18 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 10:1). After the starting material was basically consumed, the reaction was quenched with saturated sodium sulfite. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, washed with saturated brine (15 mL), dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluorophenyl)hexyl acetate **21-3** (90 mg, purity: 90%, yield: 52.74%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.23 (s, 1H), 6.86 (t, *J* = 8.2 Hz, 2H), 6.04 (t, *J* = 7.4 Hz, 1H), 5.92 (s, 1H), 4.52 (d, *J* = 6.4 Hz, 1H), 4.33 (d, *J* = 5.6 Hz, 1H), 2.34 (d, *J* = 10.5 Hz, 2H), 2.06 (s, 3H), 1.82 (m, 3H), 1.63 (dd, *J* = 15.0, 9.3 Hz, 3H), 1.56 (d, *J* = 5.4 Hz, 8H), 1.37 (s, 4H), 1.28 (m, 9H), 1.07 (m, 4H), 0.87 (dd, *J* = 12.8, 6.4 Hz, 4H), 0.69 (d, *J* = 3.9 Hz, 3H).

[0201] Step 4: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluorophenyl)hexyl acetate **21-3** (90 mg, 0.150 mmol) was dissolved in methanol (5 mL). Palladium on carbon (10.99 mg) was added, and the mixture was purged with hydrogen three times. The resulting mixture was stirred under hydrogen at 25°C for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 3:1). After the starting material was completely consumed, the mixture was filtered and concentrated to obtain a crude product. The crude product was added with silica gel and purified by column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-

[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluorophenyl)hexyl acetate **21-4** (50 mg, 0.067 mmol, purity: 80%, yield: 44.30%). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 7.03 (s, 1H), 6.01 (dd, J = 10.9, 6.4 Hz, 1H), 3.98 (d, J = 3.4 Hz, 2H), 2.77 (s, 1H), 2.42 (s, 1H), 2.19 (dd, J = 12.7, 2.7 Hz, 2H), 2.08 (s, 3H), 1.74 (m, 9H), 1.53 (s, 3H), 1.38 (dd, J = 11.7, 7.8 Hz, 4H), 1.28 (d, J = 17.1 Hz, 10H), 0.95 (ddd, J = 10.8, 9.5, 6.5 Hz, 10H), 0.64 (d, J = 3.2 Hz, 3H).

[0202] Step 5: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluorophenyl)hexyl acetate **21-4** (800 mg, 1.332 mmol) was dissolved in DAST (30 mL). The resulting mixture was stirred under N₂ at 80°C for 3 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. The reaction mixture was cooled to room temperature and carefully added dropwise to an ice-water mixture. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The ethyl acetate layers were combined and washed with saturated brine (100 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated to obtain a crude product, which was monitored on a crude TLC plate (petroleum ether: ethyl acetate = 1:1). The crude product was added with silica gel and purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain (5R)-1-(2,6-difluorophenyl)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexyl acetate **21-5** (600 mg, purity: 10%) as a colorless transparent solid.

[0203] Step 6: Compound (5R)-1-(2,6-difluorophenyl)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-

cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexyl acetate **21-5** (600 mg, content: 10%) was dissolved in tetrahydrofuran (30 mL), then added to 3 mol/L hydrochloric acid solution (5 mL). The resulting mixture was stirred at 25°C for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 1:1). After the starting material was completely consumed, the reaction mixture was diluted with ethyl acetate (20 mL), washed with saturated brine, and the organic phase was dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to obtain a crude product. The crude product 4 was purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2,6-difluorophenyl)hexyl acetate **21-6** (420 mg, purity: 10%).

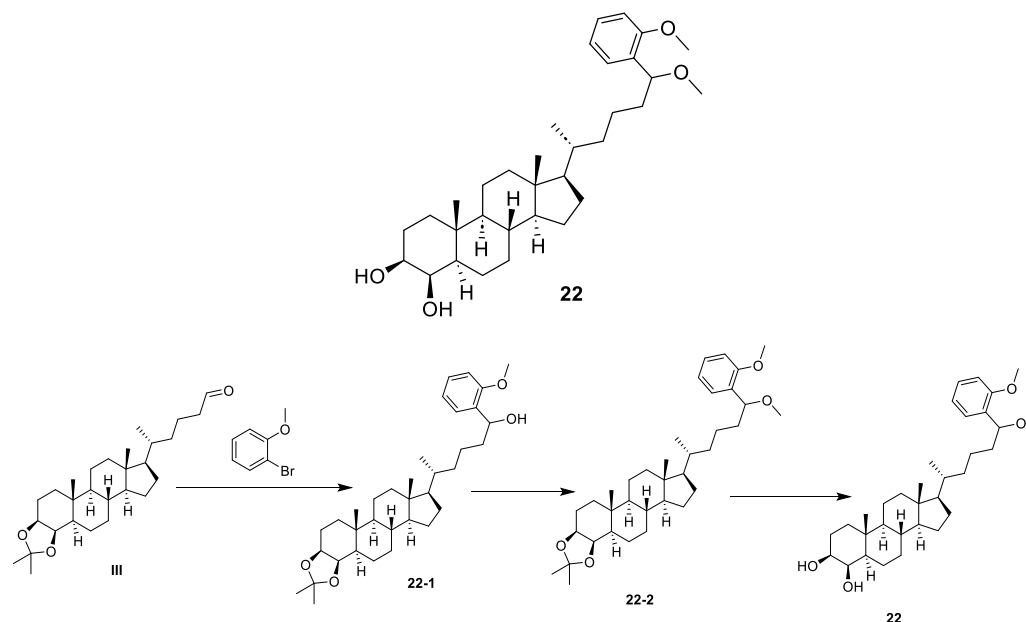
[0204] Step 7: Compound (5R)-1-(2,6-difluorophenyl)-5-[(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-6,7-dihydroxy-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexyl acetate **21-6** (420 mg, content: 10%) was dissolved in a mixed solvent of methanol (10 mL) and tetrahydrofuran (10 mL). Lithium hydroxide solution (3 mL) was added, and the resulting mixture was stirred at 25°C for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 1:1), and the starting material was completely consumed. Water (5 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The ethyl acetate layers were combined and washed with saturated brine (100 mL). The ethyl acetate layer was dried over Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 2:1). The resulting crude product was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C; retention time *t_R* = 1.738 min) to obtain 24-[(2,6-difluorophenyl)(hydroxy)methyl]-7-fluoro-5α-cholane-3β,4β-diol **21**

(30 mg, 0.055 mmol, 7.57%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.20 (m, 1H), 6.88 (m, 2H), 5.03 (m, 1H), 3.85 (s, 1H), 3.59 (dt, $J = 11.8, 4.1$ Hz, 1H), 2.66 (t, $J = 12.6$ Hz, 1H), 2.01 (m, 2H), 1.83 (ddd, $J = 33.4, 31.9, 12.6$ Hz, 13H), 1.61 (m, 2H), 1.46 (m, 3H), 1.37 (m, 3H), 1.09 (dd, $J = 12.7, 4.5$ Hz, 3H),
 5 1.04 (s, 3H), 0.90 (t, $J = 6.0$ Hz, 3H), 0.62 (d, $J = 3.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 151.96, 137.52, 128.96, 113.27, 111.86, 111.57, 108.65, 72.41, 72.36, 54.20, 53.47, 52.56, 49.59, 43.97, 43.45, 39.50, 36.79, 36.09, 35.44, 34.21, 32.98, 28.49, 27.56, 27.30, 25.37, 22.67, 22.50, 21.14, 18.85, 15.11, 12.56. ^{19}F NMR (377 MHz, CDCl_3) δ -89.26, -109.78, -115.39, -115.45. LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 503.7$.
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[0205] Example 22

[0206] Preparation of compound 22: 24-[methoxy(2-methoxyphenyl)methyl]-5 α -cholane-3 β ,4 β -diol

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[0207] Step 1: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetra Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **III** (58 mg, 0.058

mmol, 1.0 eq) was dissolved in tetrahydrofuran (5 mL). The reaction system was cooled to 0°C, and (2-methoxyphenyl)lithium (1.22 mL, 0.29 mmol, 5 eq) was slowly added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. 20 mL of water was added to the reaction system, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, washed with water (30 mL), dried, and concentrated to obtain a crude product. The crude product was subjected to silica gel column chromatography (petroleum ether: ethyl acetate = 88:12 to 85:15) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexan-1-ol **22-1** (7 mg, purity: 90%, yield: 20.14%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.27 (m, 1H), 7.25 – 7.21 (m, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 4.85 (dt, J = 9.9, 5.8 Hz, 1H), 4.02 – 3.94 (m, 2H), 3.85 (s, 3H), 1.95 (d, J = 12.7 Hz, 1H), 1.81 – 1.67 (m, 4H), 1.42 (s, 1H), 1.33 (s, 1H), 1.30 (s, 2H), 1.28 (s, 1H), 1.25 (s, 4H), 1.09 (dd, J = 16.1, 9.7 Hz, 2H), 1.04 (s, 2H), 0.89 (d, J = 4.0 Hz, 1H), 0.83 (dd, J = 16.6, 9.1 Hz, 1H), 0.65 (d, J = 2.7 Hz, 1H), 0.58 (d, J = 8.2 Hz, 1H).

[0208] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexan-1-ol **22-1** (50 mg, 0.093 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (5 mL). The reaction system was purged with a nitrogen atmosphere, and sodium hydride (11.14 mg, 0.278 mmol, 3.0 eq) was slowly added. The reaction system was stirred at room temperature for 30 min. Then iodomethane (39.51 mg, 0.278 mmol, 3.0 eq) was added, and the reaction system was stirred at 40°C for 2 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction

system, and the aqueous layer was extracted with ethyl acetate (3×25 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 94:6) to obtain

5 (3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-8-[(2R)-6-methoxy-6-(2-methoxyphenyl)hexan-2-yl]-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxole **22-2** (20 mg, purity: 95%, yield: 88.89%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.34 (d, $J = 7.5$ Hz, 1H), 7.24 – 7.20 (m, 1H), 6.98 (t, $J = 7.7$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 4.59 (dd, $J = 11.1, 5.1$ Hz, 1H), 4.05 – 3.91 (m, 2H), 3.82 (s, 3H), 3.22 (d, $J = 1.6$ Hz, 3H), 1.95 (d, $J = 12.2$ Hz, 1H), 1.76 (dd, $J = 15.0, 5.6$ Hz, 3H), 1.66 (dd, $J = 20.4, 8.4$ Hz, 4H), 1.51 (s, 3H), 1.41 (ddd, $J = 29.3, 15.8, 6.4$ Hz, 6H), 1.30 (s, 3H), 1.28 – 1.18 (m, 3H), 1.08 (d, $J = 9.2$ Hz, 2H), 1.04 (s, 3H), 1.01 – 0.96 (m, 2H), 0.88 (dd, $J = 6.4, 3.6$ Hz, 3H), 0.64 (t, $J = 2.5$ Hz, 3H), 0.62 – 0.55 (m, 1H).

10 **[0209] Step 3:** Reactant (3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-8-[(2R)-6-methoxy-6-(2-methoxyphenyl)hexan-2-yl]-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxole **22-2** (45 mg, 0.072 mmol, 1.0 eq) was dissolved in tetrahydrofuran (5 mL). Dilute hydrochloric acid (0.5 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 40 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 2:1). After the starting material was completely consumed, the reaction was

25 stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×25 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 73:27) to obtain 24-[methoxy(2-methoxyphenyl)methyl]-5 α -cholane-3 β ,4 β -diol **22** (21.37 mg, purity: 91.20%,

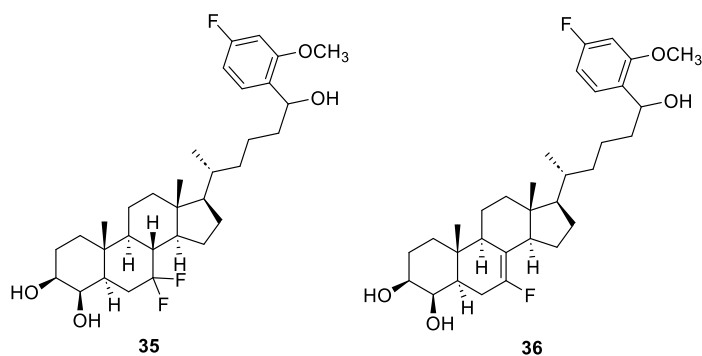
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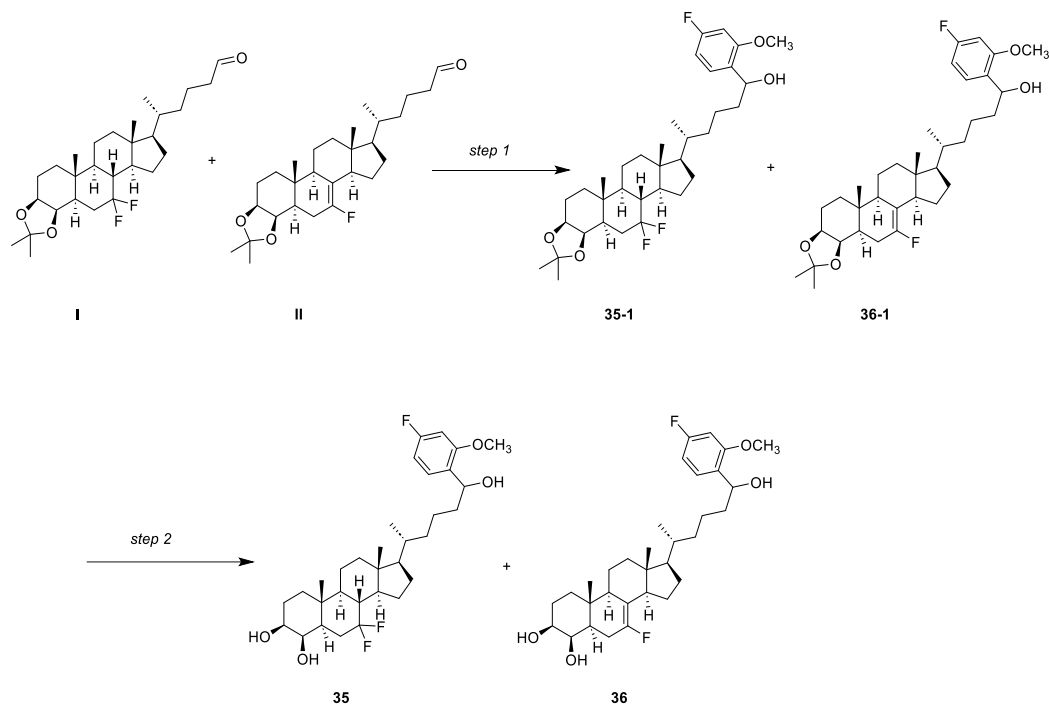
yield: 52.53%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.34 (d, J = 7.6 Hz, 1H), 7.25 – 7.19 (m, 1H), 6.98 (t, J = 7.8 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 4.59 (dd, J = 11.1, 5.1 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 1H), 3.55 (d, J = 11.2 Hz, 1H), 3.22 (d, J = 1.5 Hz, 3H), 1.95 (d, J = 12.0 Hz, 1H), 1.74 (dt, J = 15.2, 14.2 Hz, 6H), 1.54 (dd, J = 16.6, 7.5 Hz, 3H), 1.43 – 1.16 (m, 10H), 1.09 – 1.02 (m, 4H), 1.01 (s, 3H), 0.98 – 0.89 (m, 3H), 0.87 (dd, J = 6.4, 3.6 Hz, 3H), 0.63 (d, J = 1.1 Hz, 3H), 0.57 (dd, J = 16.8, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.13, 127.87, 126.52, 126.46, 120.68, 110.26, 74.86, 74.57, 72.30, 56.79, 56.57, 56.30, 55.31, 48.82, 42.59, 39.90, 37.48, 37.29, 36.85, 35.48, 35.39, 32.39, 28.22, 25.99, 25.86, 22.28, 20.58, 18.57, 14.67, 12.07.

[0210] Examples 35 & 36

[0211] Preparation of compound 35 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0212] Example 36 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





[0213] Step 1: Starting material 1-bromo-4-fluoro-2-methoxybenzene (107 mg, 0.5 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **35-1** and **36-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0214] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexan-1-ol **35-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexan-1-ol **36-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acuity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **35** (48.95 mg, purity: 100%, yield: 75%, retention time *t_R* = 1.420 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **36** (4.64 mg, purity: 99%, yield: 7%, retention time *t_R* = 2.015 min).

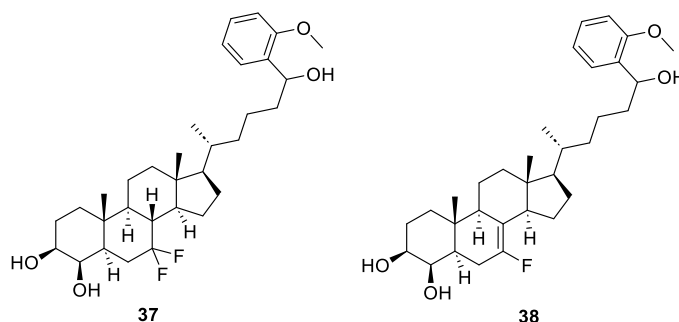
[0215] Compound **35**: ¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.16 (m, 1H), 6.62

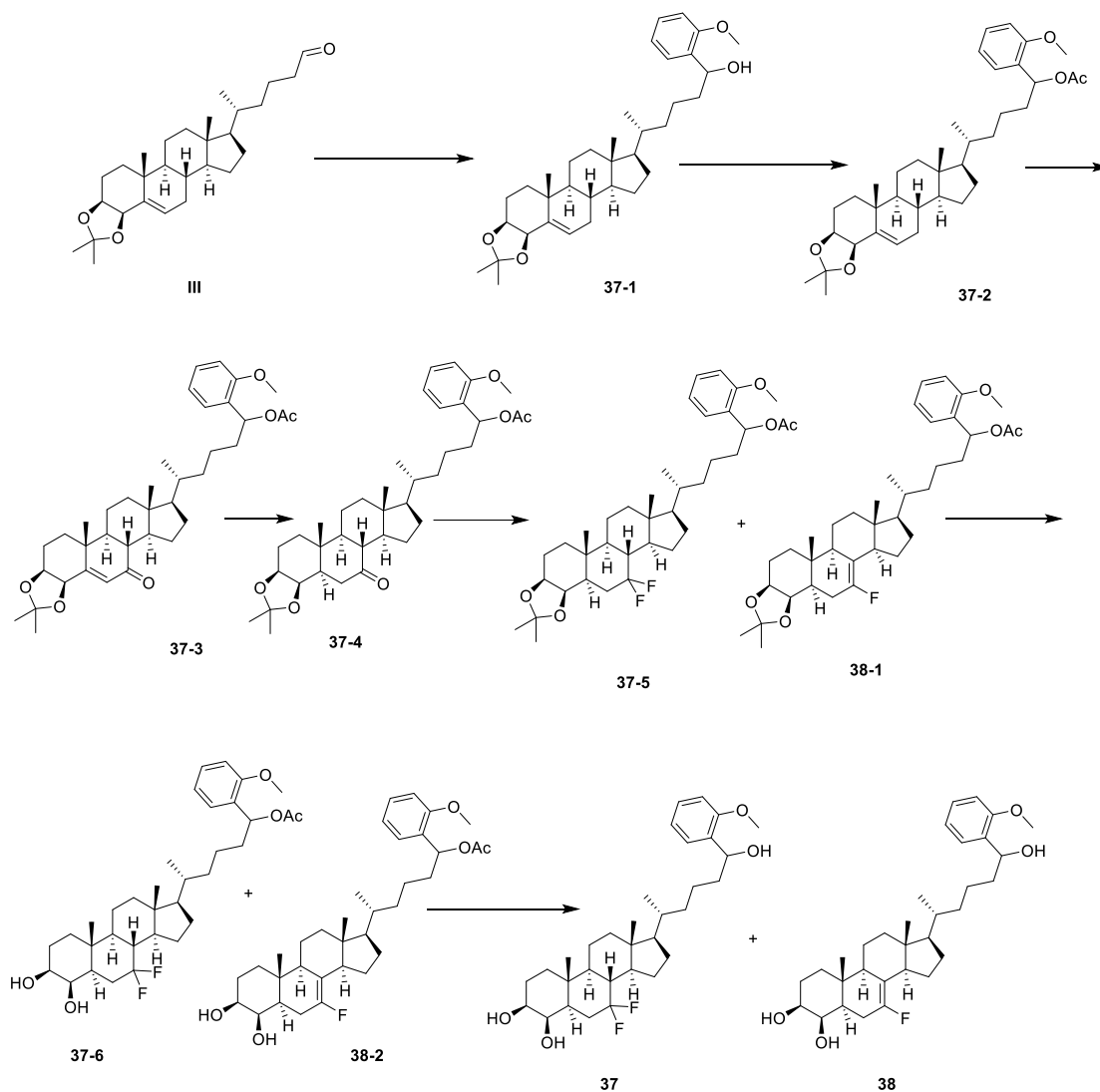
– 6.50 (m, 2H), 4.81 – 4.74 (m, 1H), 3.75 (d, $J = 13.2$ Hz, 3H), 3.67 (s, 1H), 3.56 – 3.49 (m, 1H), 2.22 – 2.05 (m, 1H), 1.90 (d, $J = 12.9$ Hz, 1H), 1.82 – 1.56 (m, 12H), 1.43 – 1.15 (m, 10H), 1.08 – 1.01 (m, 2H), 0.99 (s, 3H), 0.95 – 0.86 (m, 2H), 0.83 (dd, $J = 6.5, 4.1$ Hz, 3H), 0.59 (d, $J = 1.7$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.63, -89.25, -110.63, -111.25, -113.00, -113.06.

[0216] Compound 36: ^1H NMR (400 MHz, CDCl_3) δ 7.17 (d, $J = 4.3$ Hz, 1H), 6.64 – 6.47 (m, 2H), 4.82 – 4.74 (m, 1H), 3.78 (s, 1H), 3.77 (d, $J = 5.9$ Hz, 3H), 3.56 – 3.49 (m, 1H), 2.59 (s, 1H), 1.96 (d, $J = 11.9$ Hz, 1H), 1.90 – 1.73 (m, 6H), 1.68 – 1.51 (m, 11H), 1.42 – 1.16 (m, 10H), 1.06 – 0.99 (m, 3H), 0.97 (s, 3H), 0.84 (dd, $J = 6.5, 3.3$ Hz, 3H), 0.56 (d, $J = 1.9$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -109.80, -113.00, -113.06.

[0217] Examples 37 & 38

[0218] Preparation of compound 37 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
[0219] compound 38 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





[0220] Step 1: Compound 1-bromo-2-methoxybenzene (1309.01 mg, 6.999 mmol, 3.0 *eq*) was dissolved in tetrahydrofuran (50 mL). Under a nitrogen atmosphere, the solution was cooled to -78°C, and *n*-butyllithium (2.5 M in *n*-hexane, 3.359 mL, 8.398 mmol, 3.6 *eq*) was added. The mixture was stirred at this temperature for 1 hour. Then, a solution of (5*R*)-5-[(3*aS*,5*aR*,5*bS*,7*aR*,8*R*,10*aS*,10*bS*,12*bR*)-2,2,5*a*,7*a*-tetramethyl-4,5,5*a*,5*b*,6,7,7*a*,8,9,10,10*a*,10*b*,11,12*b*-tetradecahydro-3*aH*-cyclopenta[1',2':1,2]phenanthro[7,8-*d*][1,3]dioxol-8-yl]hexanal **III** (1000 mg, 2.333 mmol, 1.0 *eq*) in tetrahydrofuran (10 mL) was added, and the reaction mixture was stirred at this temperature for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1), and the starting material

was completely consumed. The reaction mixture was quenched with saturated ammonium chloride, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and washed with saturated brine (15 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 95:5) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexan-1-ol **37-1** (750 mg, purity: 90%, yield: 53.90%) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 7.30 (ddd, J = 7.4, 3.9, 1.6 Hz, 1H), 7.23 (m, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 5.74 (dd, J = 49.3, 2.9 Hz, 1H), 4.85 (d, J = 7.3 Hz, 1H), 4.40 (d, J = 5.8 Hz, 1H), 4.14 (d, J = 3.6 Hz, 0H), 3.85 (s, 3H), 3.56 (dd, J = 7.3, 3.8 Hz, 1H), 2.05 (m, 3H), 1.71 (m, 10H), 1.42 (d, J = 8.4 Hz, 4H), 1.17 (d, J = 6.5 Hz, 4H), 1.06 (ddd, J = 25.8, 14.6, 5.0 Hz, 6H), 0.90 (dt, J = 7.5, 3.7 Hz, 4H), 0.68 (dd, J = 4.6, 2.7 Hz, 3H).

[0221] Step 2: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexan-1-ol **37-1** (750 mg, 1.397 mmol, 1.0 eq) was dissolved in dichloromethane (50 mL). Acetic anhydride (0.197 mL, 2.096 mmol, 1.5 eq), triethylamine (0.388 mL, 2.794 mmol, 2.0 eq), and 4-dimethylaminopyridine (34.14 mg, 0.279 mmol, 0.2 eq) were added. The resulting mixture was stirred under N₂ at 25°C for 3 hours. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was quenched with methanol. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic phases were combined and washed with saturated brine (5 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was added with silica gel and purified by column chromatography (petroleum ether: ethyl acetate = 10:1)

to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-2** (750 mg, purity: 90%, yield: 83.46%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 5.5, 4.0 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.16 (m, 1H), 5.80 (d, J = 2.7 Hz, 1H), 4.40 (d, J = 5.8 Hz, 1H), 4.11 (m, 1H), 3.84 (d, J = 6.8 Hz, 3H), 3.55 (d, J = 12.1 Hz, 0H), 2.09 (t, J = 3.8 Hz, 3H), 2.00 (d, J = 12.6 Hz, 1H), 1.77(m, 5H), 1.62 (m, 5H), 1.53 (s, 3H), 1.35 (s, 3H), 1.26 (m, 3H), 1.16 (s, 3H), 1.02 (m, 5H), 0.86 (m, 7H), 0.67 (t, J = 3.5 Hz, 3H).

[0222] Step 3: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-2** (750 mg, 1.296 mmol, 1.0 eq) was dissolved in acetone (30 mL). N-Hydroxyphthalimide (42.27 mg, 0.259 mmol, 0.2 eq), *tert*-butyl hydroperoxide (1.037 mL, 5.183 mmol, 4.0 eq), and anhydrous cobalt(II) acetate (11.47 mg, 0.065 mmol, 0.05 eq) were added. The resulting mixture was stirred under N₂ at 25°C for 18 hours. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). The mixture was diluted with ethyl acetate and quenched with saturated sodium sulfite. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (15 mL). The ethyl acetate layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-3** (340 mg, purity: 90%, yield: 39.84%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.16 (s, 1H), 5.92

(s, 1H), 4.52(d, J = 6.4 Hz, 1H), 4.33 (d, J = 5.7 Hz, 1H), 3.84 (s, 3H), 2.35 (d, J = 10.3 Hz, 2H), 2.08 (d, J = 1.8 Hz, 3H), 2.05 (s, 1H), 1.80 (m, 4H), 1.63 (dd, J = 16.1, 10.4 Hz, 3H), 1.57 (s, 4H), 1.42 (m, 2H), 1.37 (s, 3H), 1.33 (s, 4H), 1.26 (m, 2H), 1.09 (dd, J = 38.3, 9.0 Hz, 4H), 0.88 (dt, J = 7.8, 3.9 Hz, 3H), 0.69 (d, J = 1.7 Hz, 3H).

[0223] Step 4: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetradecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-3** (340 mg, 0.574 mmol) was dissolved in methanol (20 mL). Palladium on carbon (100 mg, 0.940 mmol) was added, and the resulting mixture was stirred under H₂ at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). The mixture was filtered and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-4** (250 mg, purity: 90%, yield: 65.95%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.16 (t, J = 6.3 Hz, 1H), 3.99(dt, J = 8.4, 7.3 Hz, 2H), 3.84 (d, J = 6.9 Hz, 3H), 2.77 (t, J = 13.5 Hz, 1H), 2.42 (t, J = 11.2 Hz, 1H), 2.21 (d, J = 2.7 Hz, 1H), 2.08 (d, J = 0.9 Hz, 3H), 1.97 (d, J = 12.5 Hz, 1H), 1.87 (m, 2H), 1.74 (m, 3H), 1.63 (d, J = 14.5 Hz, 2H), 1.41 (m, 5H), 1.30 (s, 6H), 1.25 (m, 3H), 1.02 (m, 6H), 0.86 (m, 7H), 0.64 (d, J = 1.5 Hz, 3H).

[0224] Step 5: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-4** (180 mg, 0.303 mmol) was dissolved in DAST (5 mL, 0.333 mmol). The resulting mixture was stirred under N₂ at 80°C for 3

hours. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and carefully added dropwise to an ice-water mixture. The aqueous layer was
 5 extracted with dichloromethane (3 × 25 mL). The dichloromethane layers were combined and washed with saturated brine (15 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain the crude product of a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-
 10 4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-5** and (5R)-5-((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2-methoxyphenyl)hexyl
 15 acetate **38-1** (150 mg, purity: 80%, yield: 64.29%). The crude product was not further purified and was directly used in the next step.

[0225] Step 6: A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-5** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2-methoxyphenyl)hexyl
 20 acetate **38-1** (120 mg, 0.202 mmol) was dissolved in tetrahydrofuran (20 mL). Dilute hydrochloric acid (0.067 mL) was added, and the resulting mixture was stirred at 25°C for 3 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). The reaction mixture was diluted with ethyl acetate, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The ethyl
 25 acetate layers were combined and washed with saturated brine (15 mL). The

ethyl acetate layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain the crude product of a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-6** and (5R)-5-((3S,4R,5R,9R,10R,13R,14R,17R)-7-fluoro-3,4-dihydroxy-10,13-dimethyl-2,3,4,5,6,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-1-(2-methoxyphenyl)hexyl acetate **38-2** (80 mg, **37-6** purity: 80%). The crude product was directly used in the next step without further purification.

[0226] Step 7: A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxyphenyl)hexyl acetate **37-6** and (5R)-5-((3S,4R,5R,9R,10R,13R,14R,17R)-7-fluoro-3,4-dihydroxy-10,13-dimethyl-2,3,4,5,6,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-1-(2-methoxyphenyl)hexyl acetate **38-2** (80 mg, 0.139 mmol) was dissolved in a mixed solvent of methanol (1 mL) and tetrahydrofuran (1 mL). The resulting mixture was stirred at 25°C for 3 hours. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 1:1). The reaction mixture was cooled to room temperature and carefully added dropwise to an ice-water mixture. The aqueous layer was extracted with ethyl acetate (3 × 25 mL). The ethyl acetate layers were combined and washed with saturated brine (15 mL). The ethyl acetate layer was dried over anhydrous Na₂SO₄, filtered, and concentrated to obtain a crude product. The crude product was added with silica gel and purified by column chromatography (petroleum ether: ethyl acetate) to obtain a white solid. The resulting solid was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1%

DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **37** (42.6 mg, 0.074 mmol, purity: 93.24%, retention time t_R = 1.281 min) and (3S,4R,5R,9R,10R,13R,14R,17R)-7-fluoro-17-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-10,13-dimethyl-2,3,4,5,6,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,4-diol **38** (8.67 mg, 0.016 mmol, purity: 93.98%, yield: 11.34%, retention time t_R = 1.748 min).

[0227] Compound **37**: ^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.28 (m, 1H), 7.25 – 7.21 (m, 1H), 7.00 – 6.93 (m, 1H), 6.88 (dd, J = 8.1, 3.7 Hz, 1H), 4.85 (dt, J = 9.7, 5.9 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 1H), 3.64 – 3.57 (m, 1H), 2.35 – 1.94 (m, 4H), 1.88 – 1.78 (m, 5H), 1.40 (ddd, J = 18.9, 11.1, 7.2 Hz, 8H), 1.27 (t, J = 14.2 Hz, 4H), 1.16 – 1.07 (m, 3H), 1.06 (s, 3H), 1.02 – 0.93 (m, 2H), 0.90 (dd, J = 6.4, 4.1 Hz, 3H), 0.65 (d, J = 2.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.17, 127.21, 125.88, 124.00, 119.66, 109.53, 72.42, 70.88, 69.21, 54.56, 54.25, 49.92, 49.76, 47.44, 42.81, 42.20, 38.29, 36.76, 36.68, 35.21, 34.82, 34.63, 34.28, 33.87, 33.47, 27.43, 24.51, 21.51, 19.39, 17.68, 12.64, 10.83. ^{19}F NMR (377 MHz, CDCl_3) δ -88.63, -89.25, -110.62, -111.25.

[0228] Compound **38**: ^1H NMR (400 MHz, CDCl_3) δ 7.30 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 4.90 – 4.81 (m, 1H), 3.86 (s, 4H), 3.63 – 3.55 (m, 1H), 2.66 (s, 1H), 2.05 – 1.68 (m, 13H), 1.49 – 1.24 (m, 10H), 1.15 – 1.07 (m, 3H), 1.04 (s, 3H), 0.91 (dd, J = 6.5, 3.5 Hz, 3H), 0.62 (d, J = 2.5 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -119.83.

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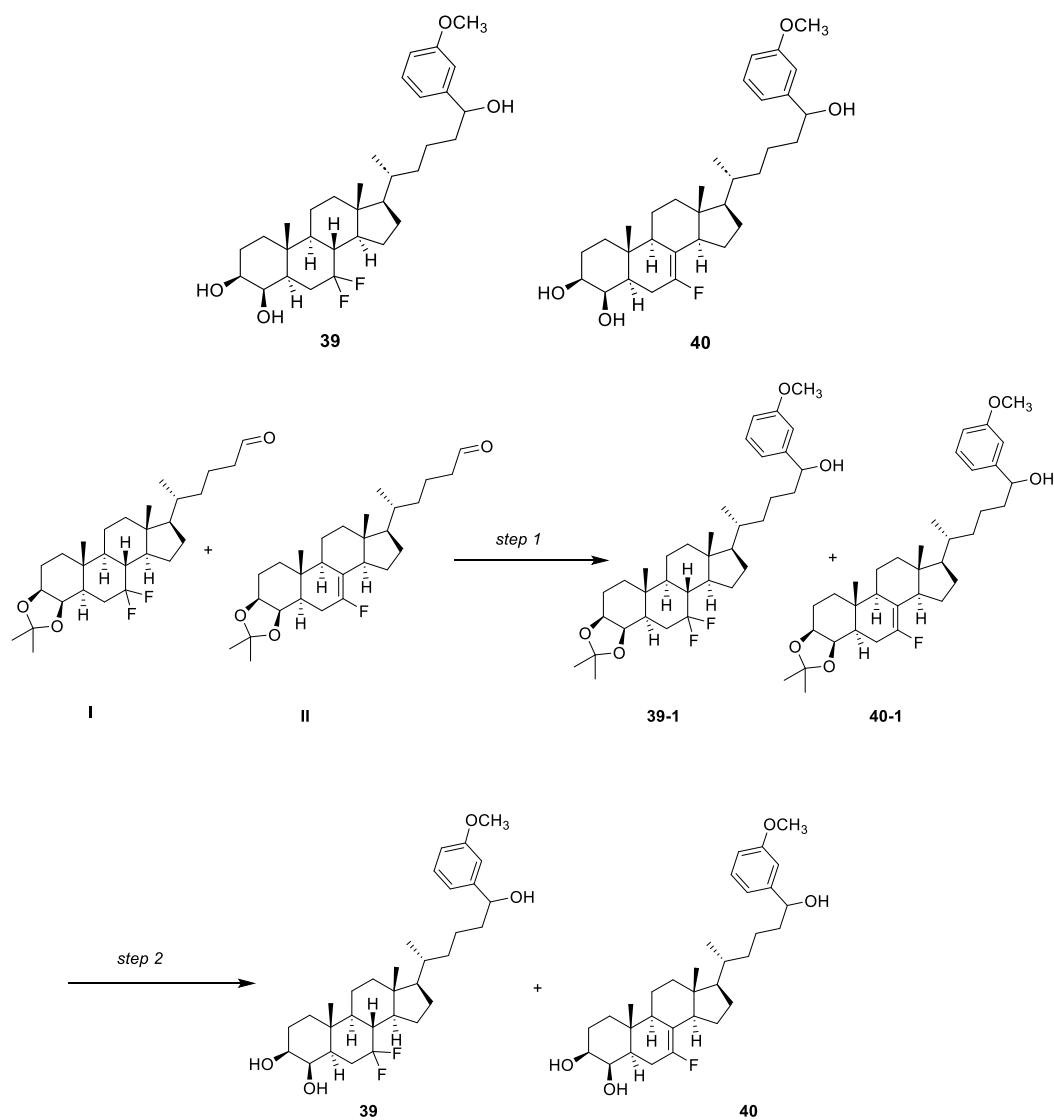
[0229] Examples **39** & **40**

[0230] Preparation of compound **39** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(3-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0231] compound **40** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(3-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-

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2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



- 5 **[0232]** Step 1: Starting material 1-bromo-3-methoxybenzene (98 mg, 0.5 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds
- 10 (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-

4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(3-methoxyphenyl)hexan-1-ol **39-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(3-methoxyphenyl)hexan-1-ol **40-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0233] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(3-methoxyphenyl)hexan-1-ol **39-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(3-methoxyphenyl)hexan-1-ol **40-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped.

Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0×150 mm, $3 \mu\text{m}$; mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(3-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **39** (48.27 mg, purity: 100%, yield: 74.12%, retention time $t_R = 2.218$ min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(3-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **40** (4.18 mg, purity: 100%, yield: 6%, retention time $t_R = 3.272$ min).

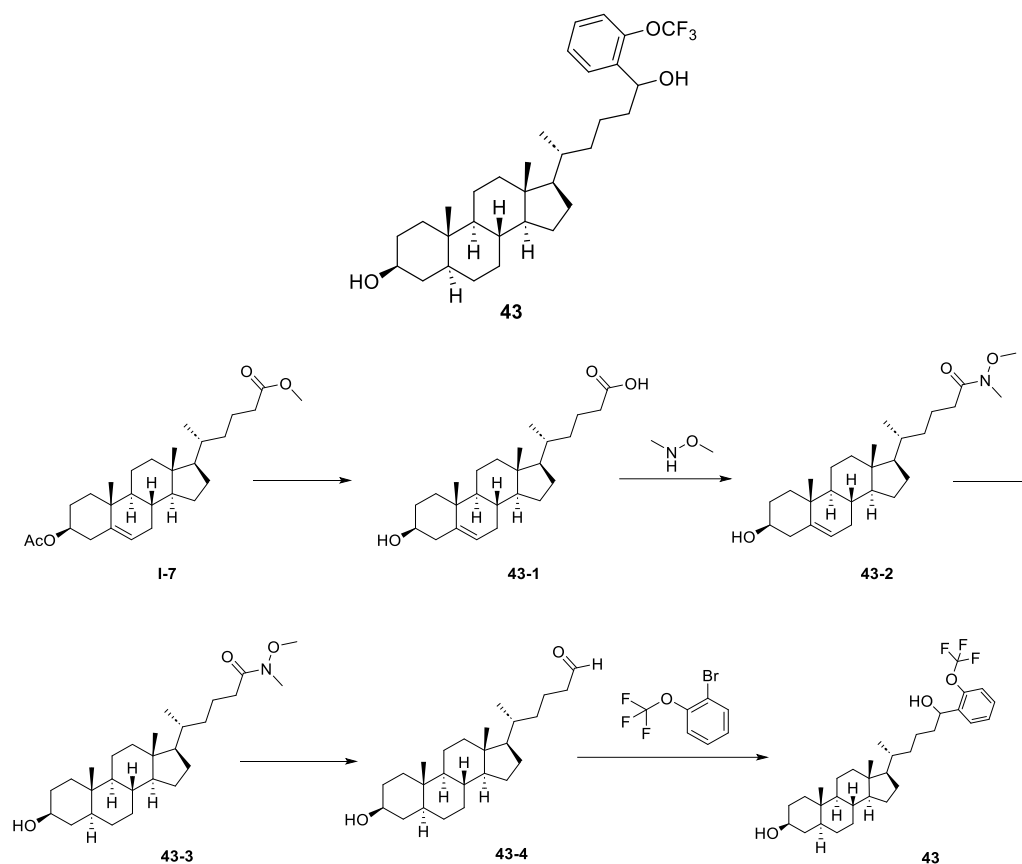
[0234] Compound **39**: ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 1H), 6.93 (d, $J = 6.9$ Hz, 2H), 6.82 (dd, $J = 8.6, 2.0$ Hz, 1H), 4.65 (dd, $J = 13.1, 6.0$ Hz, 1H), 3.83 (s, 3H), 3.75 (s, 1H), 3.64 – 3.57 (m, 1H), 1.97 (d, $J = 12.8$ Hz, 1H), 1.87 – 1.67 (m, 12H), 1.50 – 1.24 (m, 10H), 1.12 (dd, $J = 13.3, 4.4$ Hz, 2H), 1.06 (s, 3H), 1.03 – 0.94 (m, 2H), 0.92 – 0.88 (m, 3H), 0.66 (d, $J = 2.3$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.64, -89.26, -110.63, -111.26.

[0235] Compound **40**: ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 0H), 6.95 – 6.90 (m, 2H), 6.82 (dd, $J = 8.7, 2.0$ Hz, 1H), 4.66 (dd, $J = 13.3, 6.3$ Hz, 1H), 3.86 (s, 1H), 3.83 (s, 3H), 3.63 – 3.56 (m, 1H), 2.66 (t, $J = 13.5$ Hz, 1H), 1.78 (dddd, $J = 45.2, 31.3, 23.5, 11.4$ Hz, 17H), 1.49 – 1.42 (m, 4H), 1.28 (d, $J = 11.9$ Hz, 5H), 1.05 (s, 3H), 0.91 (dd, $J = 6.4, 4.2$ Hz, 3H), 0.63 (d, $J = 2.4$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -109.78.

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[0236] Example 43

[0237] Preparation of compound 43: 24-(hydroxy{2-[(trifluoromethyl)oxy]phenyl}methyl)-5 α -cholan-3 β -ol



- 5 **[0238] Step 1:** (1R,3aS,7S,9aR,11aR)-1-[(2R)-6-Methoxy-6-oxohexan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-7** (1.0 g, 2.2 mmol) was dissolved in a mixed solvent of anhydrous methanol (10 mL) and tetrahydrofuran (5 mL), followed by addition of 1 M lithium hydroxide aqueous solution (5 mL, 5 mmol).
- 10 The reaction was carried out at room temperature, and the reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. The organic solvent was removed by concentration, and the remaining crude product was extracted with water and ethyl acetate. The organic phase was separated, dried, and concentrated to obtain (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-
- 15 cyclopenta[1,2-a]phenanthren-1-yl]hexanoic acid **43-1** (800 mg, 2.06 mmol, 91.6%) as a white solid. ^1H NMR (399 MHz, Chloroform-d) δ 5.33 (s, 1H), 3.49

(d, $J = 12.8$ Hz, 1H), 2.36 – 2.17 (m, 5H), 2.04 – 1.91 (m, 3H), 1.82 (d, $J = 12.2$ Hz, 3H), 1.42 (d, $J = 5.2$ Hz, 5H), 1.20 – 1.14 (m, 2H), 1.11 – 1.05 (m, 3H), 0.99 (s, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.85 (d, $J = 10.0$ Hz, 3H), 0.66 (s, 3H).

[0239] Step 2: (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-Hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoic acid **43-1** (300 mg, 0.77 mmol) was dissolved in tetrahydrofuran (5 mL). After the addition of 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (354 mg, 0.93 mmol) and N,N-diisopropylethylamine (300 mg, 2.32 mmol), the mixture was stirred at room temperature for 30 minutes. Subsequently, dimethylhydroxylamine hydrochloride (150.2 mg, 1.54 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Ethyl acetate and water were added for extraction. The organic phase was separated, dried over anhydrous sodium sulfate, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 0 to 20%) to obtain (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-methoxy-N-methylhexanamide **43-2** (100 mg, 30%). ^1H NMR (399 MHz, Chloroform- d) δ 5.33 (d, $J = 5.1$ Hz, 1H), 3.66 (s, 3H), 3.49 (dq, $J = 10.9, 5.6, 4.9$ Hz, 1H), 3.16 (s, 3H), 2.35 (q, $J = 7.6$ Hz, 2H), 2.29 – 2.15 (m, 2H), 2.01 – 1.90 (m, 2H), 1.88 – 1.76 (m, 3H), 1.46 (d, $J = 8.3$ Hz, 5H), 1.43 – 1.36 (m, 3H), 1.21 (ddd, $J = 26.0, 13.5, 5.9$ Hz, 2H), 1.15 – 1.01 (m, 5H), 0.98 (s, 4H), 0.96 – 0.85 (m, 5H), 0.65 (s, 3H).

[0240] Step 3: (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-Hydroxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-methoxy-N-methylhexanamide **43-2** (200 mg, 0.51 mmol) was dissolved in methanol (5 mL), and Pd/C (20 mg, 10%) was added. The system was purged with H_2 , and the mixture was stirred overnight at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Ethyl acetate and water were added for extraction. The organic phase was separated, dried over anhydrous sodium

sulfate, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 0 to 20%) to obtain (5R)-5-[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-methoxy-N-methylhexanamide **43-3** (100 mg, 0.25 mmol, 50%). ¹H NMR (399 MHz, Chloroform-d) δ 3.66 (s, 3H), 3.57 (s, 1H), 3.16 (s, 3H), 2.35 (d, J = 7.7 Hz, 2H), 1.92 (s, 1H), 1.71 (dt, J = 37.0, 17.5 Hz, 5H), 1.49 (d, J = 30.3 Hz, 8H), 1.43 – 1.13 (m, 11H), 1.13 – 1.00 (m, 5H), 1.00 – 0.88 (m, 6H), 0.78 (s, 3H), 0.63 (s, 4H).

[0241] Step 4: (5R)-5-[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-Hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-methoxy-N-methylhexanamide **43-3** (100 mg, 0.25 mmol) was dissolved in tetrahydrofuran (10 mL) and cooled to -50°C. DIBAL-H (0.5 mL, 5.0 eq) was added, and the reaction was warmed to room temperature and stirred for 2 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Ethyl acetate and water were added for extraction. The organic phase was separated, dried over anhydrous sodium sulfate, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 0 to 20%) to obtain (5R)-5-[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanal **43-4** (60 mg, 0.16 mmol, 64%). ¹H NMR (399 MHz, Chloroform-d) δ 9.74 (s, 1H), 3.57 (s, 1H), 2.37 (d, J = 6.9 Hz, 1H), 1.96 – 1.62 (m, 5H), 1.55 (s, 11H), 1.45 – 1.21 (m, 14H), 1.07 (q, J = 8.5, 6.5 Hz, 5H), 1.00 – 0.84 (m, 7H), 0.78 (s, 3H), 0.63 (s, 3H), 0.60 (s, 1H).

[0242] Step 5: 2-(Trifluoromethoxy)bromobenzene (192.8 mg, 0.8 mmol) was weighed and dissolved in tetrahydrofuran (5 mL) and cooled to -78°C with a dry ice-acetone bath. *n*-Butyllithium (1.6 M, 1.15 mmol) was then added dropwise, and the mixture was stirred at -78°C for 1 hour. Separately, (5R)-5-[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanal **43-4** (60 mg, 0.16 mmol) was dissolved in tetrahydrofuran (10 mL), cooled to -78°C, and then the above *n*-butyllithium solution was added dropwise. The reaction

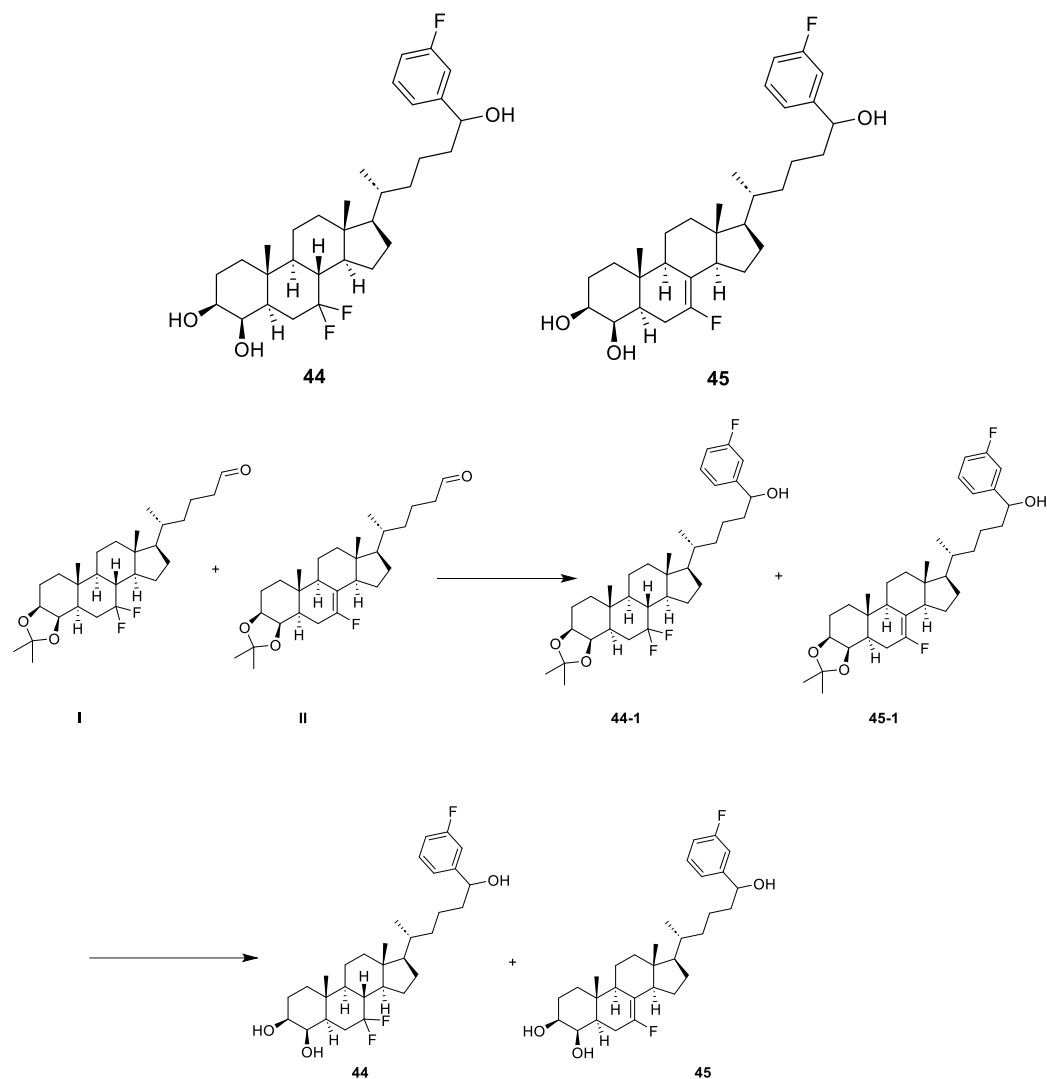
was stirred at -78°C for 1 hour and then slowly warmed to room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, saturated ammonium chloride aqueous solution was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 0 to 20%) to obtain 24-(hydroxy{2-[(trifluoromethyl)oxy]phenyl}methyl)-5 α -cholan-3 β -ol **43** (9 mg, 0.016 mmol, 10%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 7.57 (dt, J = 6.7, 2.3 Hz, 1H), 7.29 (td, J = 6.8, 6.2, 3.9 Hz, 2H), 7.22 – 7.17 (m, 1H), 5.04 (d, J = 6.8 Hz, 1H), 1.93 (d, J = 12.5 Hz, 1H), 1.77 (d, J = 11.6 Hz, 2H), 1.73 – 1.60 (m, 4H), 1.52 (s, 3H), 1.43 (d, J = 3.2 Hz, 1H), 1.39 (d, J = 18.7 Hz, 4H), 1.29 (dd, J = 18.1, 6.2 Hz, 4H), 1.24 (d, J = 3.9 Hz, 3H), 1.11 (s, 1H), 1.08 – 1.03 (m, 3H), 1.02 – 0.93 (m, 3H), 0.87 (dd, J = 6.5, 4.0 Hz, 3H), 0.78 (s, 3H), 0.62 (d, J = 1.5 Hz, 3H). ¹³C NMR (100 MHz, Chloroform-d) δ 128.44, 128.42, 127.40, 127.00, 119.93, 71.37, 68.11, 67.92, 56.43, 56.17, 54.29, 44.80, 42.57, 39.99, 38.54, 38.42, 38.17, 36.96, 35.67, 35.65, 35.62, 35.50, 35.46, 35.42, 32.05, 31.49, 30.95, 29.70, 28.70, 28.19, 24.17, 22.36, 22.23, 21.22, 18.50, 18.47, 12.30, 12.03. ¹⁹F NMR (376 MHz, Chloroform-d) δ -56.84 (dd, J = 4.0, 1.8 Hz). LC-MS: [M-OH]⁺ = 436.4.

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[0243] Examples 44 & 45

[0244] Preparation of compound **44** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(3-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0245] compound **45** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(3-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0246] Step 1: Starting material 1-bromo-3-fluorobenzene (92 mg, 0.5 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above

reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **44-1** and **45-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0247] Step 2: The crude product of reactants (5R)-5-
 10 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(3-fluorophenyl)hexan-1-ol **44-1** and (5R)-5-
 15 [(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(3-fluorophenyl)hexan-1-ol **45-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction
 20 progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated
 25 brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC_3, 3.0 ×
 30 150 mm, 3 µm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(3-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **44** (42.38 mg, purity: 96.53%, yield: 62.92%; retention time t_R = 1.302 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(3-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **45** (3.47 mg, purity: 91.52%, yield: 5%; retention time t_R = 1.730 min).

[0248] Compound **44**: ^1H NMR (400 MHz, CDCl_3) δ 7.23 (dd, J = 13.8, 7.9 Hz, 1H), 7.02 (dd, J = 12.2, 9.2 Hz, 2H), 6.89 (t, J = 8.4 Hz, 1H), 4.60 (dd, J = 12.9, 5.9 Hz, 1H), 3.67 (s, 1H), 3.53 (dt, J = 11.3, 4.1 Hz, 1H), 2.22 – 2.02 (m, 1H), 1.90 (d, J = 12.8 Hz, 1H), 1.80 – 1.55 (m, 13H), 1.43 – 1.14 (m, 10H), 1.04 (dd, J = 14.1, 5.4 Hz, 2H), 0.99 (s, 3H), 0.93 – 0.86 (m, 2H), 0.84 – 0.80 (m, 3H), 0.58 (d, J = 1.7 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.64, -89.26, -110.63, -111.26, -113.02.

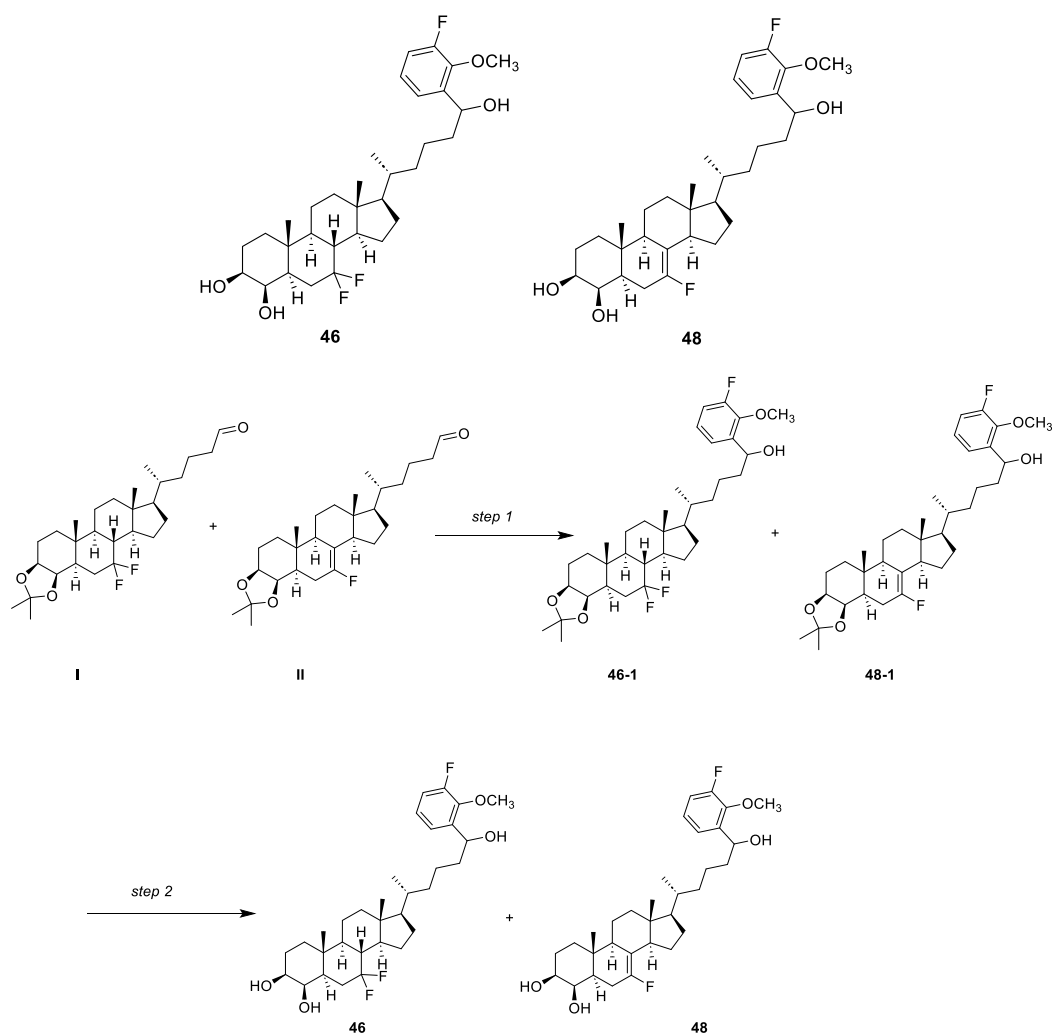
[0249] Compound **45**: ^1H NMR (400 MHz, CDCl_3) δ 7.27 – 7.20 (m, 1H), 7.02 (dd, J = 12.1, 9.3 Hz, 2H), 6.89 (t, J = 8.4 Hz, 1H), 4.61 (dd, J = 12.9, 5.9 Hz, 1H), 3.78 (s, 1H), 3.52 (dt, J = 11.7, 4.0 Hz, 1H), 2.58 (dd, J = 16.6, 8.1 Hz, 1H), 1.95 (d, J = 12.5 Hz, 1H), 1.67 (dddd, J = 32.2, 23.7, 10.5, 6.3 Hz, 17H), 1.42 – 1.16 (m, 13H), 1.05 – 0.99 (m, 4H), 0.97 (s, 3H), 0.83 (dt, J = 6.7, 3.4 Hz, 3H), 0.57 (dd, J = 14.6, 4.4 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -109.76, -113.02. LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 485.65$.

[0250] Examples **46** & **48**

[0251] Preparation of compound **46** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-methoxy-3-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0252] compound **48** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(3-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-

2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



- 5 **[0253]** Step 1: Starting material 1-bromo-3-fluoro-2-methoxybenzene (107 mg, 0.5 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15
- 10

mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **46-1** and **48-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0254] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(3-fluoro-2-methoxyphenyl)hexan-1-ol **46-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(3-fluoro-2-methoxyphenyl)hexan-1-ol **48-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(3-fluoro-2-

methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **46** (38.58 mg, purity: 100%, yield: 53%, retention time t_R = 1.341 min) and (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-methoxy-3-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-

5 dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **48** (3.464 mg, purity: 95.32%, yield: 5%, retention time t_R = 1.879 min).

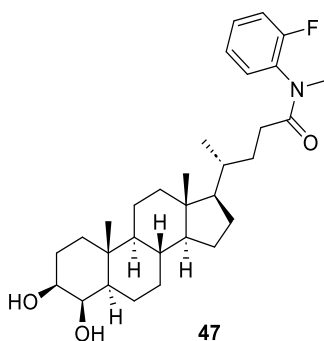
[0255] Compound **46**: ^1H NMR (400 MHz, CDCl_3) δ 7.04 (dd, J = 6.5, 3.2 Hz, 1H), 6.98 – 6.89 (m, 2H), 4.88 – 4.80 (m, 1H), 3.98 – 3.85 (m, 3H), 3.78 (s, 1H), 3.52 (s, 1H), 2.57 (d, J = 16.5 Hz, 1H), 1.95 (d, J = 15.1 Hz, 1H), 1.83 – 1.64 (m, 10H), 1.32 (ddd, J = 59.4, 28.0, 19.9 Hz, 12H), 1.10 – 1.00 (m, 4H), 0.98 (s, 3H), 0.85 (dd, J = 6.5, 3.3 Hz, 3H), 0.82 (d, J = 8.3 Hz, 2H), 0.56 (t, J = 4.6 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform- d) δ -88.63, -89.26, -110.63, -111.26, -130.48, -130.51.

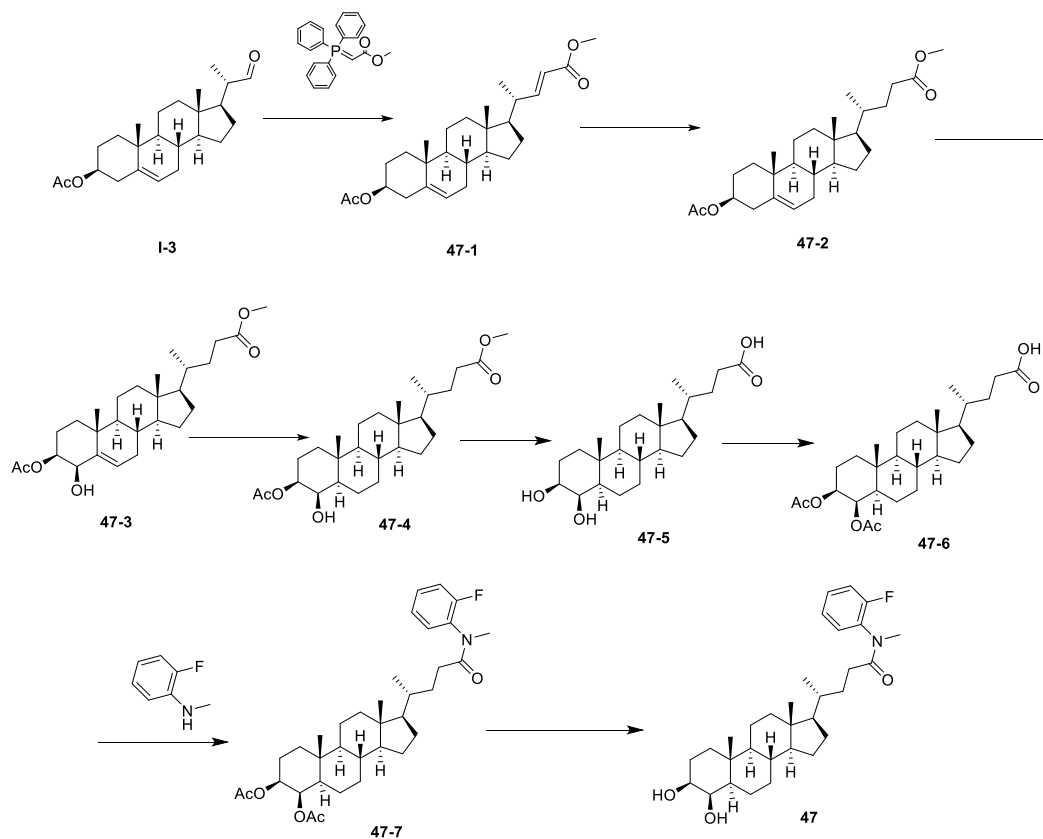
[0256] Compound **48**: ^1H NMR (400 MHz, CDCl_3) δ 7.07 – 6.99 (m, 1H), 6.97 – 6.88 (m, 2H), 4.84 (dt, J = 13.2, 5.9 Hz, 1H), 3.90 (d, J = 1.6 Hz, 3H), 3.67 (s, 1H), 3.53 (dt, J = 11.3, 4.0 Hz, 1H), 2.23 – 2.04 (m, 1H), 1.90 (d, J = 12.8 Hz, 1H), 1.68 (dddd, J = 19.3, 16.3, 8.7, 3.9 Hz, 12H), 1.40 – 1.18 (m, 9H), 1.07 – 1.00 (m, 2H), 0.99 (s, 3H), 0.97 – 0.86 (m, 2H), 0.83 (dd, J = 6.5, 3.8 Hz, 3H), 0.59 (d, J = 2.4 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform- d) δ -109.78, 130.48.

20 LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 515.70$.

[0257] Example 47

[0258] Preparation of compound **47** (3S,4R,5R,8S,9S,10R,13R,14S,17R,20R)-N-(2-fluorophenyl)-3,4-dihydroxy-N-methyl-5 α -cholan-24-amide





[0259] Step 1: (1R,3aS,3bS,7S,9aR,9bS,11aS)-1-[(1S)-1-Formylethyl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **I-3** (2 g, 5.368 mmol) was weighed and dissolved in tetrahydrofuran (30 mL), and methyl (triphenylphosphoranylidene)acetate (5.38 g, 16.105 mmol) was added at room temperature, followed by heating to 90°C with stirring. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. After cooling to room temperature, water and ethyl acetate were added for extraction. The organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 20:1 to 5:1) to obtain (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R,3E)-5-methoxy-5-oxopent-3-en-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-1** (1.4 g, 54.76%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 6.82 (dd, J = 15.6, 9.0 Hz, 1H), 5.72 (d, J = 15.6 Hz, 1H), 5.35 (d, J = 5.1 Hz, 1H), 4.64 – 4.52 (m, 1H), 3.70 (s, 3H), 2.30 (d, J = 7.8 Hz,

2H), 2.25 (d, $J = 6.8$ Hz, 1H), 2.01 (s, 3H), 1.97 (d, $J = 9.8$ Hz, 2H), 1.86 – 1.81 (m, 2H), 1.72 – 1.64 (m, 1H), 1.53 – 1.40 (m, 5H), 1.22 (dd, $J = 8.4, 3.8$ Hz, 3H), 1.18 – 1.09 (m, 2H), 1.07 (d, $J = 6.7$ Hz, 3H), 1.00 (s, 3H), 0.98 – 0.90 (m, 2H), 0.88 – 0.78 (m, 1H), 0.69 (s, 3H).

- 5 **[0260] Step 2:** (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R,3E)-5-Methoxy-5-oxopent-3-en-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-1** (1.4 g, 3.266 mmol) was weighed and dissolved in a mixed solvent of tetrahydrofuran (5 mL) and MeOH (3 mL). Nickel chloride (0.42 g, 3.266 mmol) and sodium
10 borohydride (0.19 g, 4.900 mmol) were added sequentially, and the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the reaction was completed, water and ethyl acetate were added for extraction. The organic phase was separated, dried, and concentrated. The residue was purified by column chromatography (petroleum
15 ether: ethyl acetate = 30:1 to 10:1) to obtain (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R)-5-methoxy-5-oxopentan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-2** (1.1 g, 66.47%) as a white solid. ^1H NMR (399 MHz, Chloroform- d) δ 5.35 (d, $J = 5.2$ Hz, 1H), 4.58 (d, $J = 9.8$ Hz, 1H), 3.64 (s, 3H), 2.30 (d, $J = 7.6$ Hz, 2H), 2.21 (td, $J = 9.8, 5.0$ Hz, 1H), 2.01 (s, 3H), 1.99 – 1.92 (m, 2H), 1.87 – 1.75 (m, 4H), 1.63 – 1.55 (m, 2H), 1.49 – 1.37 (m, 5H), 1.27 (d, $J = 10.5$ Hz, 3H), 1.18 – 1.02 (m, 5H), 0.99 (s, 3H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.66 (s, 3H).

- [0261] Step 3:** (1R,3aS,3bS,7S,9aR,9bS,11aR)-1-[(2R)-5-Methoxy-5-oxopentan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-2** (1.1 g, 2.554 mmol) was weighed and dissolved in chloroform (10 mL), followed by sequential addition of selenium dioxide (1.42 g, 12.772 mmol) and NMM (1.55 g, 15.326 mmol). The mixture was then heated to 75°C with stirring. The reaction was
30 monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the insoluble solids were removed by filtration through diatomite.

The filtrate was added with water and dichloromethane for extraction. The organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 30:1 to 2:1) to obtain (1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-6-hydroxy-1-[(2R)-5-methoxy-5-oxopentan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-3** (630 mg, 1.270 mmol, 49.70%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 5.73 – 5.63 (m, 1H), 4.70 (dt, J = 12.2, 3.9 Hz, 1H), 4.23 (d, J = 3.2 Hz, 1H), 3.67 (d, J = 22.0 Hz, 3H), 2.40 – 2.14 (m, 2H), 2.09 (s, 4H), 2.05 – 1.97 (m, 2H), 1.85 (d, J = 11.8 Hz, 3H), 1.65 (d, J = 10.5 Hz, 1H), 1.54 – 1.52 (m, 1H), 1.47 – 1.37 (m, 3H), 1.34 – 1.21 (m, 4H), 1.20 (d, J = 2.5 Hz, 3H), 1.13 (d, J = 15.9 Hz, 2H), 1.09 – 1.04 (m, 2H), 0.99 (t, J = 7.2 Hz, 1H), 0.90 (d, J = 6.3 Hz, 3H), 0.67 (d, J = 15.0 Hz, 3H).

[0262] Step 4: (1R,3aS,3bS,6R,7S,9aR,9bS,11aR)-6-Hydroxy-1-[(2R)-5-methoxy-5-oxopentan-2-yl]-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-3** (30 mg, 0.067 mmol) was weighed and dissolved in acetic acid (3 mL), and platinum dioxide (15.25 mg, 0.067 mmol) was added. The system was purged with hydrogen, and the mixture was heated to 40°C and stirred. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After the reaction was completed, the catalyst was removed by filtration, and most of the acetic acid was removed by concentration. The residue was extracted with saturated sodium bicarbonate and ethyl acetate. The organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 20:1 to 2:1) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6-hydroxy-1-[(2R)-5-methoxy-5-oxopentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-4** (8 mg, 0.016 mmol, 23.89%) as a white solid. ¹H NMR (399 MHz, Chloroform-d) δ 4.70 (dd, J = 11.8, 4.1 Hz, 1H), 3.81 (s, 1H), 3.65 (s, 3H), 2.40 – 2.17 (m, 2H), 2.07 (s, 3H), 1.97 – 1.78 (m, 4H), 1.77 – 1.71 (m, 3H), 1.65 (s, 2H), 1.32 (dd, J = 24.6, 13.3 Hz, 7H), 1.08 (q, J = 9.9, 8.1 Hz, 4H), 1.03 (s, 3H), 0.97 (d, J = 18.7 Hz, 1H), 0.89 (d, J = 6.4 Hz, 3H), 0.80 (d, J =

6.5 Hz, 1H), 0.63 (s, 3H), 0.58 (d, $J = 10.0$ Hz, 1H).

[0263] Step 5: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6-Hydroxy-1-[(2R)-5-methoxy-5-oxopentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-4** (100 mg, 0.223 mmol) was weighed and dissolved in a mixed solvent of tetrahydrofuran (3 mL) and methanol (2 mL). Lithium hydroxide (0.669 mL, 0.669 mmol) was added at room temperature, and the mixture was then stirred at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 1:1). After the reaction was completed, 1 N hydrochloric acid was added to adjust the pH to 3-4. Water and ethyl acetate were then added for extraction. The organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 5:1 to 0:1) to obtain 3 β -hydroxy-4 β -hydroxy-5 α -cholan-24-oic acid **47-5** (70 mg, 72.00%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 3.62 (d, $J = 3.3$ Hz, 1H), 3.50 – 3.41 (m, 1H), 2.28 (dd, $J = 9.8, 5.3$ Hz, 1H), 2.22 – 2.12 (m, 1H), 1.97 (d, $J = 12.6$ Hz, 1H), 1.81 (dd, $J = 14.5, 5.3$ Hz, 2H), 1.77 – 1.63 (m, 4H), 1.55 (t, $J = 12.5$ Hz, 2H), 1.40 (d, $J = 10.3$ Hz, 3H), 1.32 (d, $J = 3.8$ Hz, 3H), 1.16 – 1.03 (m, 4H), 1.01 (s, 4H), 0.97 (d, $J = 3.8$ Hz, 1H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.89 – 0.82 (m, 1H), 0.67 (s, 3H), 0.62 (d, $J = 12.6$ Hz, 1H).

[0264] Step 6: 3 β -Hydroxy-4 β -hydroxy-5 α -cholan-24-oic acid **47-5** (72 mg, 0.183 mmol) was weighed and dissolved in dichloromethane (5 mL), followed by addition of triethylamine (0.076 mL, 0.550 mmol) and DMAP (2.24 mg, 0.018 mmol). Under stirring at room temperature, acetic anhydride (0.034 mL, 0.367 mmol) was added, and then the mixture was stirred. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 1:1). After the reaction was completed, water and ethyl acetate were added for extraction. The organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 20:1 to 3:1) to obtain 4 β -acetoxy-3 β -acetoxy-5 α -cholan-24-oic acid **47-6** (81 mg, 83.39%) as a white solid. ¹H NMR (399 MHz, Chloroform-*d*) δ 5.18 (s, 1H), 4.77 (d, $J = 12.1$ Hz, 1H), 2.44 – 2.35 (m, 1H), 2.25 (q, $J = 9.7, 8.5$ Hz, 2H), 2.07 (s, 3H), 1.96 (s, 3H), 1.92 – 1.70 (m, 5H), 1.69 – 1.37 (m, 7H), 1.35 – 1.25 (m, 7H), 1.09 (q, $J = 18.1, 14.6$ Hz, 4H), 0.99 (s,

3H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.63 (s, 3H).

[0265] Step 7: 4 β -Acetoxy-3 β -acetoxy-5 α -cholan-24-oic acid **47-6** (50 mg, 0.105 mmol) was weighed and dissolved in dichloromethane (5 mL). SOCl_2 (0.015 mL, 0.210 mmol) was added dropwise at room temperature, and then the mixture was stirred at 40°C for 2 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After the reaction was completed, the solvent was removed by concentration. The residue was then diluted with dichloromethane, cooled in an ice bath, and added with diisopropylethylamine (0.017 mL, 0.105 mmol), followed by dropwise addition of (2-fluorophenyl)(methyl)amine (13.14 mg, 0.105 mmol). After the dropwise addition was completed, the mixture was gradually heated to 40°C and stirred overnight. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After the reaction was completed, the mixture was cooled to room temperature, and water and ethyl acetate were added for extraction. The organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 30:1 to 2:1) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6-acetoxy-1-[(2R)-5-[(2-fluorophenyl)(methyl)amino]-5-oxopentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-7** (20 mg, 29.39%) as a white solid.

[0266] Step 8: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6-Acetoxy-1-[(2R)-5-[(2-fluorophenyl)(methyl)amino]-5-oxopentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **47-7** (60 mg, 0.103 mmol) was weighed and dissolved in a mixed solvent of tetrahydrofuran (2 mL) and methanol (1 mL). Potassium carbonate (28.41 mg, 0.206 mmol) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 3:1). After the reaction was completed, water and ethyl acetate were added for extraction. The organic phase was separated, dried, concentrated, and purified by column chromatography (petroleum ether: ethyl acetate = 20:1 to 1:1) to obtain (3S,4R,5R,8S,9S,10R,13R,14S,17R,20R)-N-(2-fluorophenyl)-3,4-dihydroxy-N-

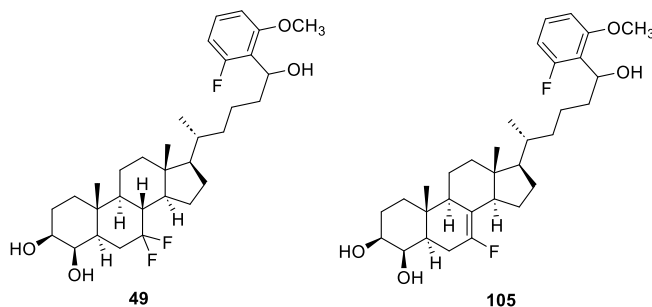
methyl-5 α -cholan-24-amide **47** (40 mg, 0.076 mmol, 74.10%) as a white solid.

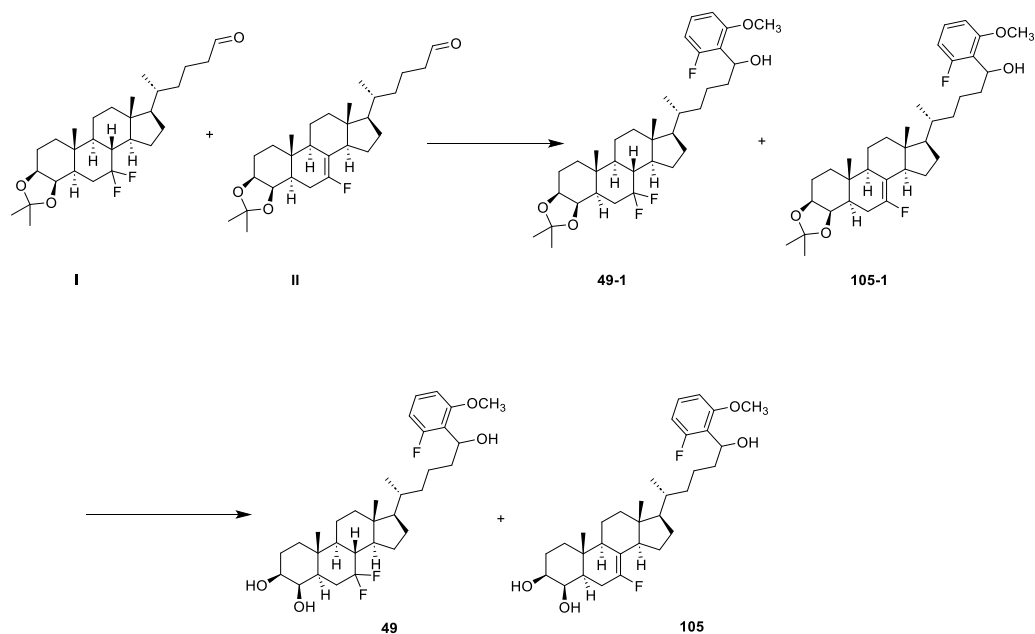
¹H NMR (399 MHz, Chloroform-d) δ 7.33 (d, J = 6.8 Hz, 1H), 7.18 (q, J = 9.8, 9.4 Hz, 3H), 3.71 (s, 1H), 3.53 (d, J = 10.6 Hz, 1H), 3.20 (s, 3H), 2.07 (s, 1H), 1.94 (s, 1H), 1.85 (d, J = 12.6 Hz, 1H), 1.71 – 1.58 (m, 6H), 1.50 (d, J = 9.4 Hz, 1H), 1.35 (d, J = 13.9 Hz, 3H), 1.28 (s, 1H), 1.21 (s, 3H), 1.06 – 0.99 (m, 3H), 0.98 (s, 3H), 0.97 – 0.82 (m, 5H), 0.67 (d, J = 5.6 Hz, 3H), 0.57 (s, 3H), 0.52 (s, 1H). ¹⁹F NMR (376 MHz, Chloroform-d) δ -121.32. LCMS: $[M+H]^+ = 500.45$.

[0267] Examples 49 & 105

[0268] Preparation of compound 49 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0269] compound 105 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





[0270] Step 1: Starting material 2-bromo-1-fluoro-3-methoxybenzene (107 mg, 0.5 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. A mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **49-1** and **105-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0271] Step 2: A mixture of reactants (5R)-5-

[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(6-fluoro-2-methoxyphenyl)hexan-1-ol **49-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(2-fluoro-6-methoxyphenyl)hexan-1-ol **105-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **49** (44.57 mg, purity: 100%, yield: 68.30%, retention time *t_R* = 1.876 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol (4.28 mg, purity: 93.67%, yield: 6.42%, retention time *t_R* = 2.785 min).

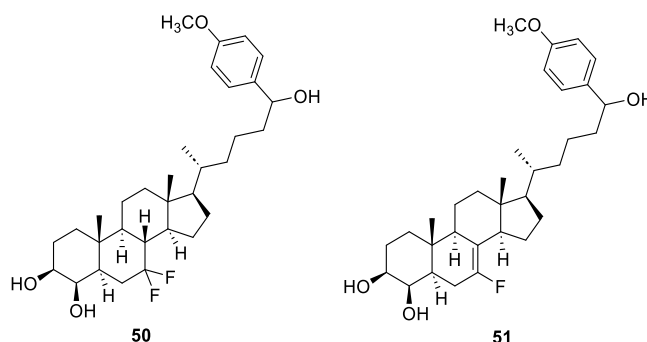
[0272] Compound **49**: ¹H NMR (400 MHz, CDCl₃) δ 7.18 (td, *J* = 8.3, 6.6 Hz, 1H), 6.74 – 6.67 (m, 2H), 5.01 (t, *J* = 6.1 Hz, 1H), 3.89 (s, 3H), 3.75 (s, 1H), 3.64

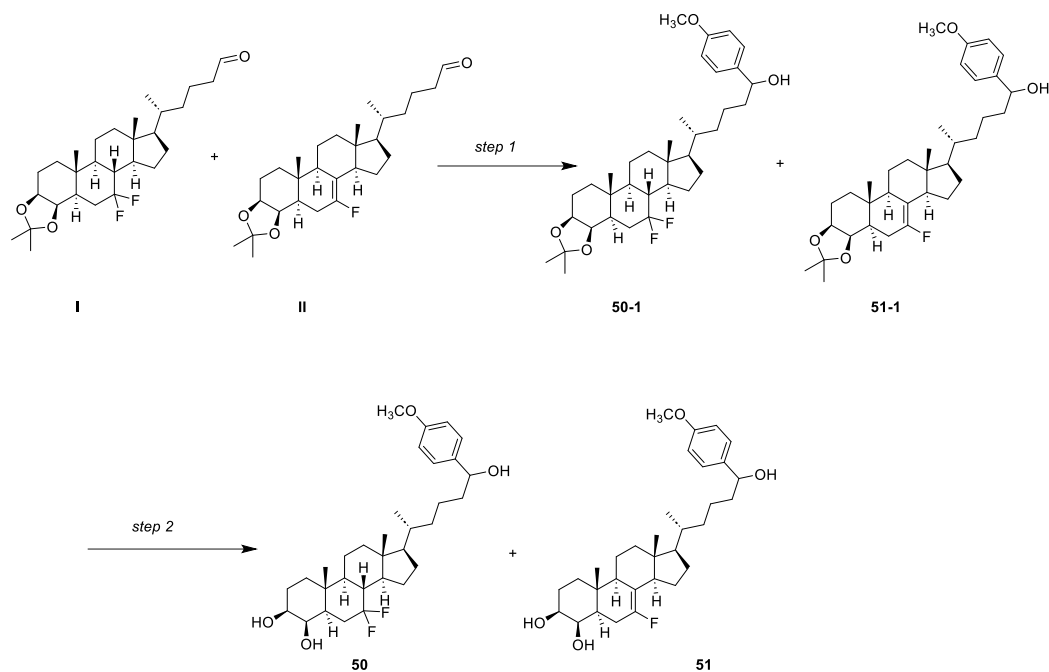
– 3.57 (m, 1H), 2.31 – 2.09 (m, 2H), 2.02 – 1.91 (m, 2H), 1.90 – 1.64 (m, 10H), 1.51 – 1.22 (m, 10H), 1.15 – 1.08 (m, 2H), 1.06 (s, 3H), 1.03 – 0.94 (m, 2H), 0.90 (dd, $J = 6.4, 4.5$ Hz, 3H), 0.66 (d, $J = 4.6$ Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.62, -89.25, -110.62, -111.24, -117.19, -117.26.

- 5 **[0273]** Compound **105**: ^1H NMR (100 MHz, CDCl_3) δ 7.17 (dd, $J = 14.9, 8.3$ Hz, 1H), 6.69 (dt, $J = 8.6, 4.5$ Hz, 2H), 5.01 (s, 1H), 3.88 (s, 3H), 3.85 (s, 1H), 3.63-3.56 (m, 1H), 2.66 (dd, $J = 16.9, 8.6$ Hz, 1H), 2.19 (s, 1H), 2.02 (t, $J = 6.0$ Hz, 1H), 1.97- 1.78 (m, 7H), 1.48 – 1.24 (m, 8H), 1.15-1.07 (m, 3H), 1.04 (s, 3H), 0.93 – 0.88 (m, 3H), 0.62 (d, $J = 5.0$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -109.83, -117.20, -117.28.
- 10

[0274] Examples **50** & **51**

- [0275]** Preparation of compound **50** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
- 15 **[0276]** compound **51** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(4-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





- [0277] Step 1: Starting material 4-bromo-1-methoxybenzene (98 mg, 0.5 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **50-1** and **51-1** (70 mg) as a colorless

oil, which was directly used in the next step.

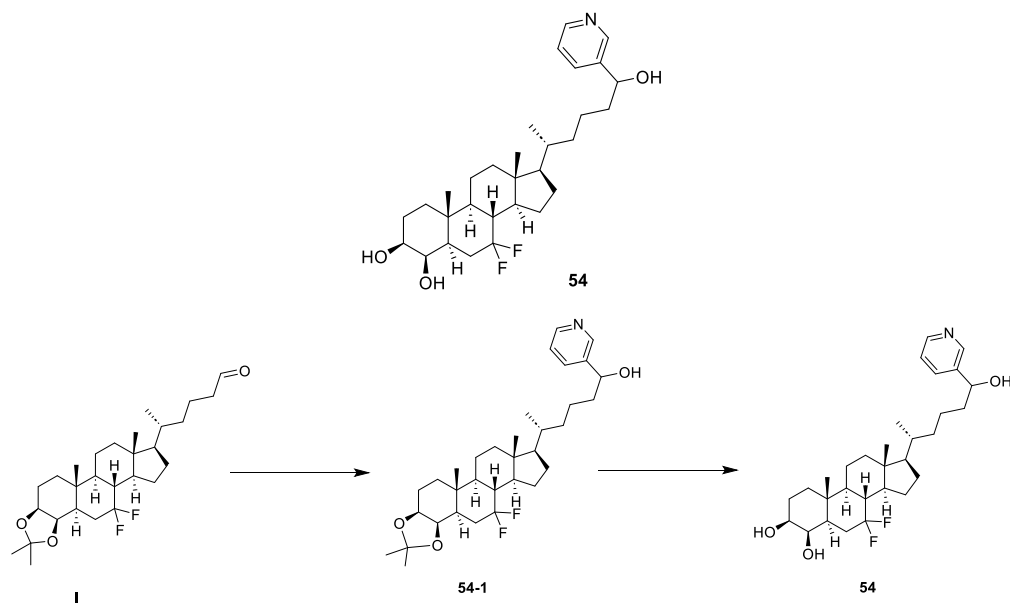
[0278] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-methoxyphenyl)hexan-1-ol **50-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(4-methoxyphenyl)hexan-1-ol **51-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(4-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **50** (43.21 mg, purity: 100%, yield: 66.35%, retention time t_R = 2.329 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(4-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **51** (3.77 mg, purity: 80.81%, yield: 4.85%, retention time t_R = 3.557 min).

[0279] Compound **50**: ^1H NMR (400 MHz, CDCl_3) δ 7.21 (s, 2H), 6.81 (d, $J = 8.6$ Hz, 2H), 4.54 (dd, $J = 12.2, 5.9$ Hz, 1H), 3.74 (s, 3H), 3.67 (s, 1H), 3.53 (dd, $J = 7.1, 4.2$ Hz, 1H), 2.22 – 1.99 (m, 2H), 1.89 (d, $J = 12.6$ Hz, 1H), 1.81 – 1.58 (m, 10H), 1.43 – 1.12 (m, 11H), 0.99 (s, 3H), 0.95 – 0.85 (m, 2H), 0.81 (t, $J = 6.3$ Hz, 3H), 0.58 (d, $J = 2.5$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.64, -89.26, -110.63, -111.26.

[0280] Compound **51**: ^1H NMR (400 MHz, CDCl_3) δ 7.28 (d, $J = 3.3$ Hz, 2H), 6.88 (t, $J = 6.0$ Hz, 2H), 4.62 (dd, $J = 12.8, 6.0$ Hz, 1H), 3.86 (d, $J = 9.2$ Hz, 1H), 3.81 (s, 3H), 3.63 – 3.55 (m, 1H), 2.66 (t, $J = 12.4$ Hz, 1H), 1.86 (ddt, $J = 46.3, 23.4, 12.1$ Hz, 12H), 1.64 – 1.56 (m, 5H), 1.48 – 1.36 (m, 6H), 1.14 – 1.05 (m, 4H), 1.04 (s, 3H), 0.91 – 0.87 (m, 3H), 0.62 (d, $J = 2.7$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -109.79. LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 497.60$.

[0281] Example 54

[0282] Preparation of compound **54** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(pyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0283] Starting material 3-bromopyridine (169 mg, 1.07 mmol, 5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL), and the system was cooled to -

78°C. *n*-Butyllithium (0.34 mL, 0.86 mmol, 4 *eq*) was added, and the mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.214 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a white solid **54-1**, which was dissolved in anhydrous tetrahydrofuran (3 mL). 3 M hydrochloric acid aqueous solution (1 mL) was added dropwise slowly. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 1:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(pyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **54** (36.95 mg, purity: 99.63%, yield: 34%) as a white solid.

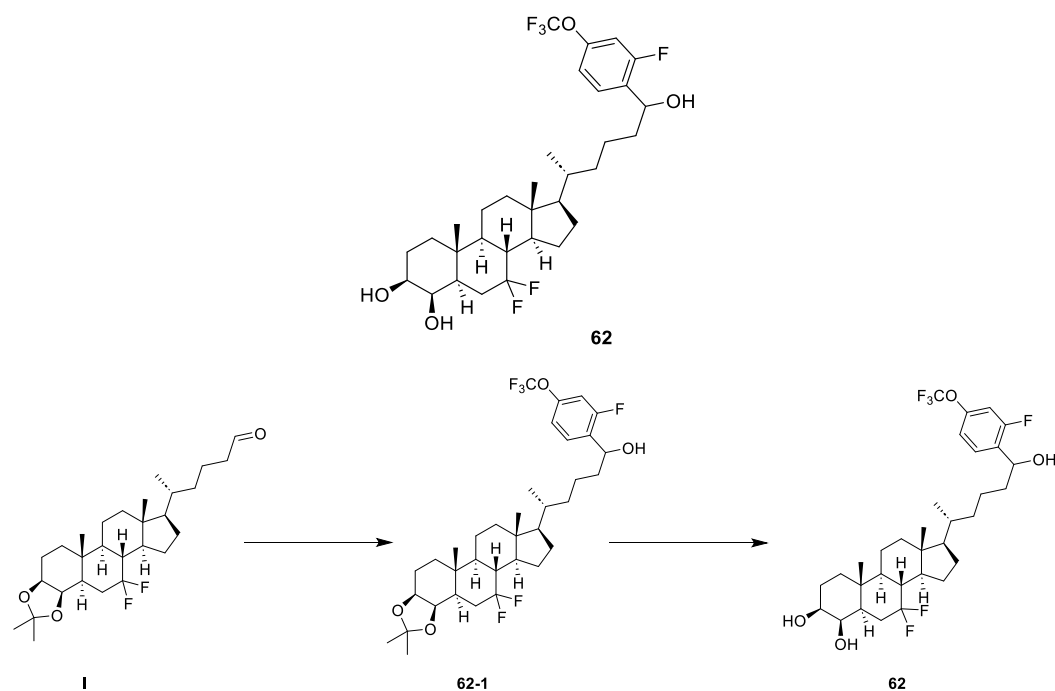
[0284] Compound **54**: ¹H NMR (400 MHz, CDCl₃) δ 8.55 (dd, *J* = 18.2, 3.1 Hz, 2H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.73 (d, *J* = 6.5 Hz, 1H), 3.74 (s, 1H), 3.60 (d, *J* = 10.9 Hz, 1H), 2.15 (s, 2H), 1.99 – 1.89 (m, 2H), 1.85 – 1.78 (m, 4H), 1.75 – 1.66 (m, 4H), 1.58 (s, 3H), 1.43 – 1.29 (m, 7H), 1.22 (s, 1H), 1.11 (dd, *J* = 13.1, 4.4 Hz, 2H), 1.06 (s, 3H), 1.02 – 0.92 (m, 2H), 0.89 (t, *J* = 6.0 Hz, 3H), 0.65 (d, *J* = 2.2 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.25.

30

[0285] Example 62

[0286] Preparation of compound **62** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-{2-fluoro-4-[(trifluoromethyl)oxy]phenyl}-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.

5



[0287] Step 1: Starting material 1-bromo-2-fluoro-4-[(trifluoromethyl)oxy]benzene (97 mg, 0.37 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.28 mL, 0.32 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain

the crude product of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{2-fluoro-4-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **62-1** (50 mg) as a colorless oil, which was directly used in the next step.

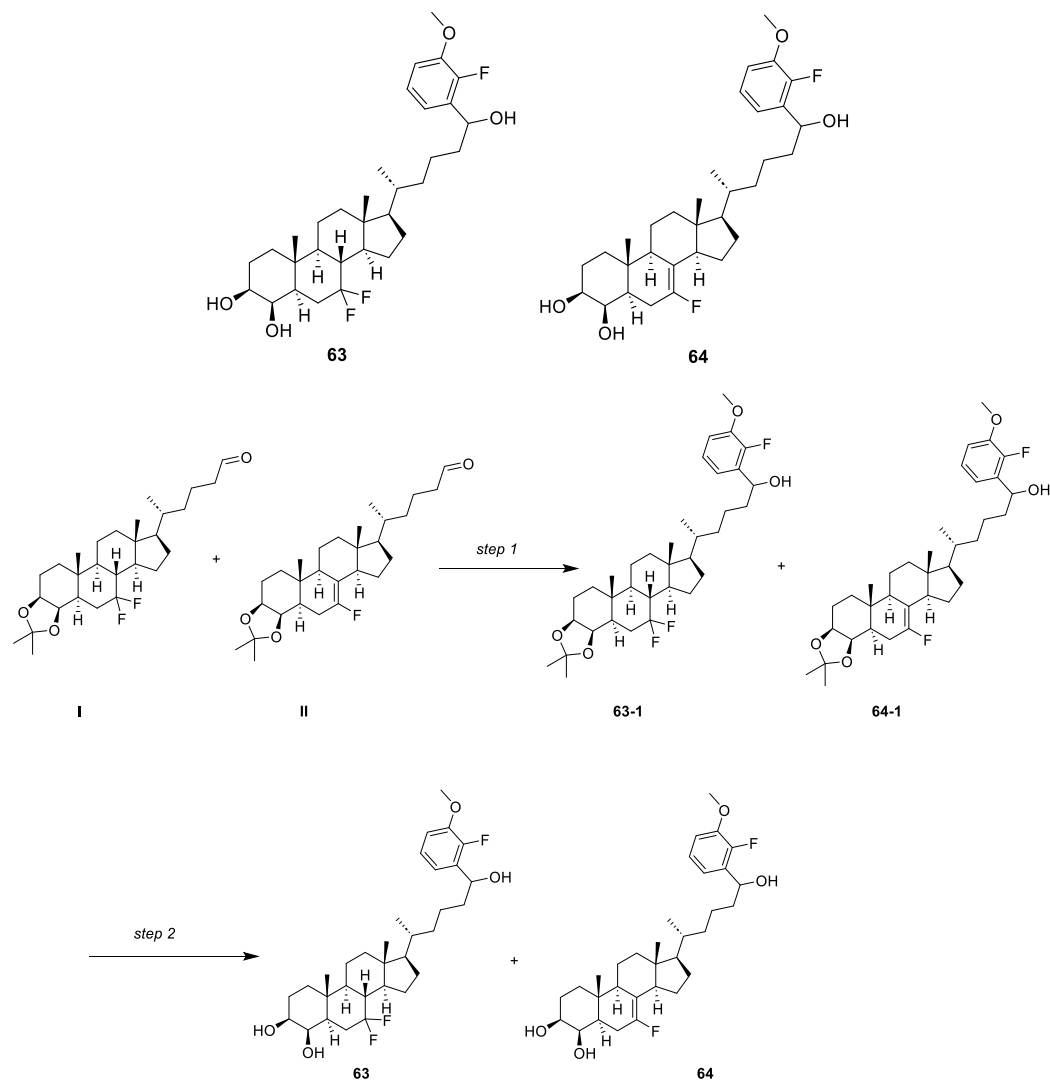
[0288] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{2-fluoro-4-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **62-1** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-{2-fluoro-4-[(trifluoromethyl)oxy]phenyl}-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **62** (19.80 mg, purity: 95.76%, yield: 50.53%).

[0289] Compound **62**: ¹H NMR (400 MHz, CDCl₃) δ 7.23 (dd, J = 13.8, 7.9 Hz, 1H), 7.02 (dd, J = 12.2, 9.2 Hz, 2H), 6.89 (t, J = 8.4 Hz, 1H), 4.60 (dd, J = 12.9, 5.9 Hz, 1H), 3.67 (s, 1H), 3.53 (dt, J = 11.3, 4.1 Hz, 1H), 2.22 – 2.02 (m, 1H), 1.90 (d, J = 12.8 Hz, 1H), 1.80 – 1.55 (m, 13H), 1.43 – 1.14 (m, 10H), 1.04 (dd, J = 14.1, 5.4 Hz, 2H), 0.99 (s, 3H), 0.93 – 0.86 (m, 2H), 0.84 – 0.80 (m, 3H), 0.58 (d, J = 1.7 Hz, 3H). ¹⁹F NMR (376 MHz, cdcl₃) δ -58.06, -58.07, -58.09, -88.65, -89.28, -110.65, -111.27, -115.89, -115.92.

[0290] Examples **63** & **64**

[0291] Preparation of compound **63** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-3-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0292] compound **64** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluoro-3-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0293] Step 1: Starting material 1-bromo-2-fluoro-3-methoxybenzene (77 mg,

0.37 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.28 mL, 0.32 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **63-1** and **64-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0294] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoro-3-methoxyphenyl)hexan-1-ol **63-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(4-methoxyphenyl)hexan-1-ol **64-1** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with

ethyl acetate (3×10 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0×150 mm, $3 \mu\text{m}$; mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 70/30; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-3-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **63** (29.11 mg, purity: 99.70%, yield: 77.81%, retention time $t_R = 1.966$ min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(2-fluoro-3-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **64** (2.06 mg, purity: 98.77%, yield: 5.70%, retention time $t_R = 2.943$ min).

[0295] Compound **63**: ^1H NMR (400 MHz, CDCl_3) δ 7.05 (dt, $J = 13.5, 7.9$ Hz, 2H), 6.91 – 6.85 (m, 1H), 5.05 – 4.98 (m, 1H), 3.89 (s, 3H), 3.74 (s, 1H), 3.60 (dt, $J = 11.2, 4.0$ Hz, 1H), 2.29 – 2.11 (m, 1H), 1.97 (d, $J = 13.2$ Hz, 1H), 1.89 – 1.63 (m, 13H), 1.39 (ddd, $J = 29.8, 17.0, 8.6$ Hz, 8H), 1.11 (dd, $J = 14.4, 5.4$ Hz, 2H), 1.05 (s, 3H), 1.02 – 0.93 (m, 2H), 0.89 (dd, $J = 6.4, 4.2$ Hz, 3H), 0.65 (d, $J = 2.3$ Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.64, -89.27, -110.63, -111.26, -142.59, -142.62.

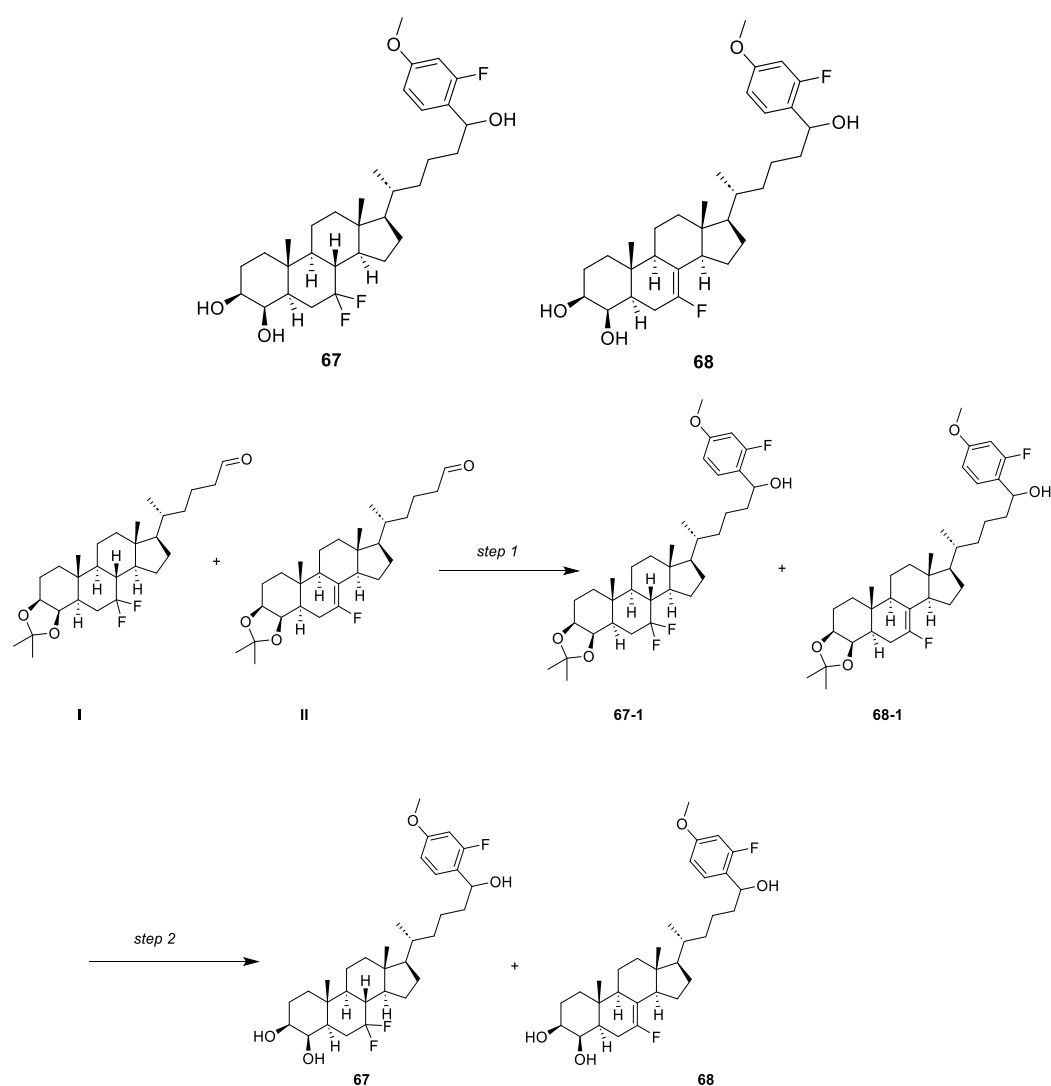
[0296] Compound **64**: ^1H NMR (400 MHz, CDCl_3) δ 7.14 – 7.04 (m, 2H), 6.95 – 6.89 (m, 1H), 5.06 (dd, $J = 12.2, 5.6$ Hz, 1H), 3.93 (s, 3H), 3.89 (s, 1H), 3.67 – 3.59 (m, 1H), 2.68 (d, $J = 13.8$ Hz, 1H), 2.06 (d, $J = 13.5$ Hz, 1H), 2.00 – 1.75 (m, 10H), 1.64 (d, $J = 12.3$ Hz, 4H), 1.52 – 1.44 (m, 5H), 1.14 (dd, $J = 18.2, 5.5$ Hz, 4H), 1.08 (s, 3H), 0.96 – 0.92 (m, 3H), 0.89 (dd, $J = 9.0, 5.2$ Hz, 2H), 0.66 (d, $J = 2.5$ Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -109.79, -142.59, -142.62.

30

[0297] Examples **67** & **68**

[0298] Preparation of compound **67** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

- 5 [0299] compound **68** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



10

[0300] Step 1: Starting material 1-bromo-2-fluoro-4-methoxybenzene (76 mg, 0.37 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.28 mL, 0.32 mmol, 3.0 eq) was

added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **67-1** and **68-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0301] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoro-4-methoxyphenyl)hexan-1-ol **67-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(2-fluoro-4-methoxyphenyl)hexan-1-ol **68-1** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a

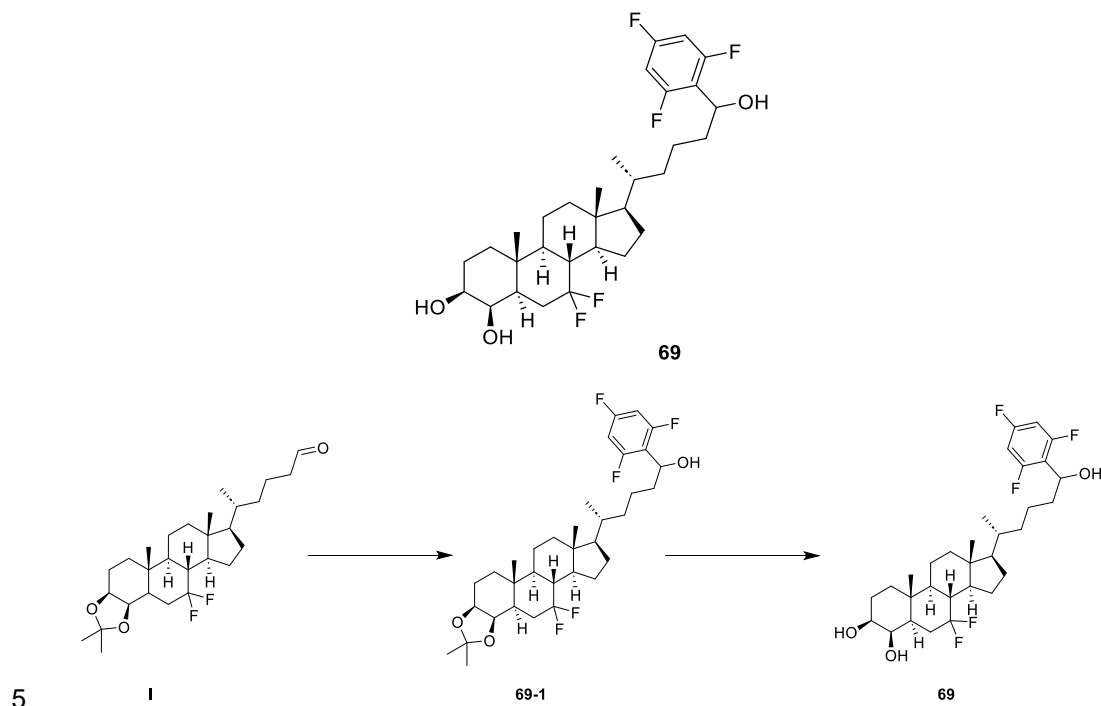
crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 65/35; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain
 5 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **67** (16 mg, purity: 100%, yield: 29.77%, retention time t_R = 1.135 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-
 10 1-[(2R)-6-(2-fluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **68** (1.17 mg, purity: 98.44%, yield: 2.57%, retention time t_R = 1.497 min).

[0302] Compound **67**: ¹H NMR (400 MHz, CDCl₃) δ 7.33 (td, J = 8.6, 1.7 Hz, 1H), 6.70 (dd, J = 8.6, 2.4 Hz, 1H), 6.58 (dd, J = 12.3, 2.5 Hz, 1H), 4.92 (m, 1H), 3.79 (s, 3H), 3.74 (s, 1H), 3.60 (m, 1H), 2.19 (m, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.82 (m, 5H), 1.68 (m, 4H), 1.38 (m, 10H), 1.08 (m, 6H), 0.96 (m, 2H), 0.89 (dd, J = 6.4, 4.5 Hz, 3H), 0.65 (d, J = 2.0 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.64, -89.26, -110.63, -111.25, -117.79, -117.83. LC-MS: [M+1-H₂O]⁺ =
 15 535.80.

[0303] Compound **68**: ¹H NMR (400 MHz, CDCl₃) δ 7.33 (td, J = 8.6, 2.0 Hz, 1H), 6.70 (dd, J = 8.5, 2.4 Hz, 1H), 6.58 (dd, J = 12.3, 2.5 Hz, 1H), 4.92 (dd, J = 13.1, 6.1 Hz, 1H), 3.85 (s, 1H), 3.79 (s, 3H), 3.59 (m, 1H), 2.66 (s, 1H), 2.02 (d, J = 10.7 Hz, 1H), 1.92 (s, 1H), 1.86 (s, 2H), 1.81 (s, 2H), 1.74 (d, J = 9.5 Hz, 3H),
 25 1.61 (d, J = 11.8 Hz, 4H), 1.45 (dd, J = 12.6, 5.6 Hz, 4H), 1.26 (s, 6H), 1.08 (d, J = 4.5 Hz, 2H), 1.04 (s, 3H), 0.90 (dd, J = 6.4, 4.3 Hz, 4H), 0.62 (d, J = 2.2 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -109.79, -117.80, -117.83. LC-MS: [M+H-H₂O]⁺ = 515.70.

30 **[0304]** Example **69**

[0305] Preparation of compound **69** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2,4,6-trifluorophenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0306] Step 1: Starting material 2-bromo-1,3,5-trifluorobenzene (79 mg, 0.37 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.28 mL, 0.32 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain the crude product of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-

4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4,6-trifluorophenyl)hexan-1-ol **69-1** (50 mg) as a colorless oil, which was directly used in the next step.

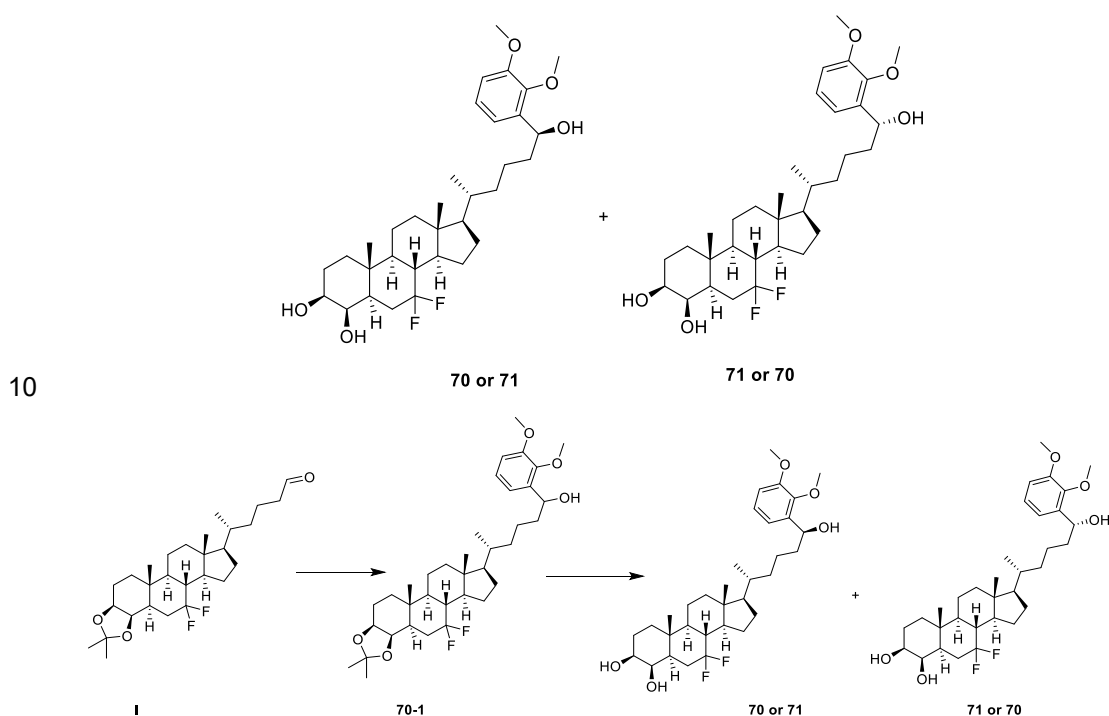
- 5 **[0307]** Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4,6-trifluorophenyl)hexan-1-ol **69-1** (50 mg, 0.1 mmol, 1.0 eq) was dissolved in
10 tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were
15 combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column:
20 Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 70/30; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2,4,6-trifluorophenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **69** (13.91 mg, purity: 98.75%, yield:
25 24.77%, retention time t_R = 1.107 min).

- [0308]** Compound **69**: ¹H NMR (400 MHz, CDCl₃) δ 6.65 (m, 2H), 4.98 (t, J = 6.9 Hz, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.2 Hz, 1H), 2.22 (m, 1H), 2.02 (m, 4H), 1.83 (m, 5H), 1.68 (ddd, J = 13.6, 10.8, 5.5 Hz, 3H), 1.35 (m, 9H), 1.11 (m, 2H), 1.06 (s, 3H), 0.98 (dd, J = 16.3, 5.7 Hz, 2H), 0.89 (t, J = 6.0 Hz, 3H), 0.65
30 (d, J = 2.9 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.64, -89.27, -109.16, -110.64, -111.26, -112.09, -112.16.

[0309] Examples **70** & **71**

[0310] Preparation of compound **70** or **71**
(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,3-
5 **dimethoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-**
dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0311] compound **71** or **70** **(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-**
[(2R,6R)-6-(2,3-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-
9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0312] Step 1: Starting material 1-bromo-2,3-dimethoxybenzene (81.4 mg, 0.38 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (0.13 mL, 0.32 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (50 mg, 0.11 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above

reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated sodium chloride (20 mL), dried, and concentrated to obtain the crude product of (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2,3-dimethoxyphenyl)hexan-1-ol as a colorless oil. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2,3-dimethoxyphenyl)hexan-1-ol **70-1** (32 mg, yield: 49%) as a white solid.

[0313] Step 2: Reactant (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2,3-dimethoxyphenyl)hexan-1-ol **70-1** (32 mg, 0.053 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 75:25) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK OZ3, 3 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain **70** (5.68 mg, purity: 94%, yield: 18%,

retention time $t_R = 1.909$ min) and **71** (5.06 mg, purity: 95%, yield: 16%, retention time $t_R = 2.840$ min).

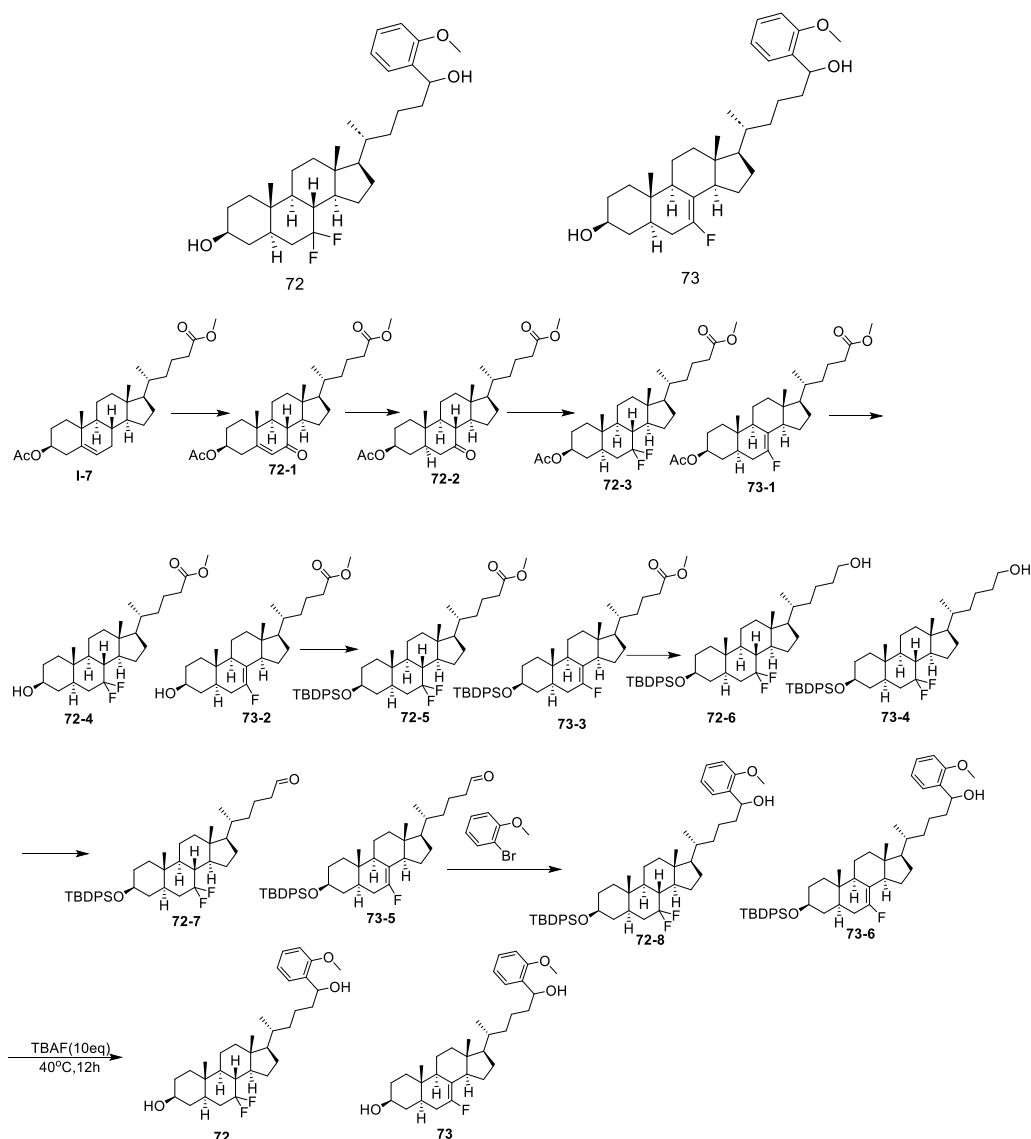
[0314] Compound **70**: ^1H NMR (400 MHz, CDCl_3) δ 7.05 (t, $J = 7.9$ Hz, 1H), 6.94 (d, $J = 6.6$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 4.91 (dd, $J = 8.1, 5.0$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 – 3.71 (m, 1H), 3.65 – 3.55 (m, 1H), 2.32 – 2.11 (m, 2H), 2.11 – 2.05 (m, 1H), 2.00 – 1.94 (m, 1H), 1.86 – 1.77 (m, 4H), 1.72 – 1.60 (m, 4H), 1.48 – 1.37 (m, 6H), 1.30 – 1.24 (m, 3H), 1.16 – 1.08 (m, 2H), 1.07 – 1.02 (m, 4H), 1.01 – 0.95 (m, 1H), 0.94 – 0.85 (m, 4H), 0.65 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.94 (d, $J = 235.7$ Hz, 1F), -110.94 (d, $J = 236.0$ Hz, 1F).

[0315] Compound **71**: ^1H NMR (400 MHz, CDCl_3) δ 7.05 (t, $J = 7.9$ Hz, 1H), 6.94 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.84 (dd, $J = 8.1, 1.4$ Hz, 1H), 4.90 (t, $J = 6.6$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 – 3.71 (m, 1H), 3.63 – 3.55 (m, 1H), 2.40 – 2.23 (m, 1H), 2.22 – 2.01 (m, 2H), 2.00 – 1.93 (m, 1H), 1.88 – 1.78 (m, 4H), 1.77 – 1.65 (m, 5H), 1.61 – 1.50 (m, 2H), 1.50 – 1.33 (m, 6H), 1.32 – 1.24 (m, 3H), 1.23 – 1.16 (m, 1H), 1.14 – 1.03 (m, 6H), 1.01 – 0.93 (m, 1H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.95 (d, $J = 236.5$ Hz, 1F), -110.94 (d, $J = 236.0$ Hz, 1F).

[0316] Examples 72 & 73

[0317] Preparation of compound 72 (1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol

[0318] Preparation of compound 73 (1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol



- [0319] **Step 1:** Methyl (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **I-7** (1 g, 2.25 mmol, 1 eq) was dissolved in tetrahydrofuran (10 mL). Cobalt acetate (80 mg, 0.45 mmol, 0.2 eq), N-hydroxyphthalimide (0.15 g, 0.90 mmol, 0.4 eq), and *tert*-butyl hydroperoxide (1.01 g, 11.25 mmol, 5 eq) were added to the solution, and the mixture was stirred at room temperature for 20 hours. After the reaction was completed, 30 mL of water was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The resulting organic phases were dried over anhydrous sodium sulfate and rotary evaporated to dryness to obtain a crude product, which

was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to obtain methyl (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-4-oxo-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-1** (0.6 g, 1.31 mmol, yield: 58%). ¹H NMR (400 MHz, CDCl₃) δ 5.70 (d, J = 1.5 Hz, 1H), 4.80 – 4.64 (m, 1H), 3.67 (s, 3H), 2.48 (dddd, J = 15.6, 12.1, 9.1, 2.4 Hz, 3H), 2.25 (ddd, J = 22.3, 12.9, 5.3 Hz, 3H), 2.05 (s, 3H), 2.01 – 1.95 (m, 2H), 1.93 – 1.84 (m, 1H), 1.79 – 1.65 (m, 2H), 1.65 – 1.46 (m, 5H), 1.40 (ddd, J = 11.6, 8.9, 4.3 Hz, 2H), 1.28 (ddd, J = 10.9, 10.5, 5.9 Hz, 3H), 1.21 (s, 3H), 1.18 – 1.05 (m, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.68 (s, 3H).

[0320] Step 2: Compound methyl (5R)-5-[(1R,3aS,3bS,7S,9aR,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-4-oxo-2,3,3a,3b,4,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-1** (0.6 g, 1.31 mmol, 1 eq) was dissolved in ethyl acetate (15 mL). Palladium on carbon (10%, 120 mg) was added thereto, and the mixture was stirred at room temperature for 12 hours. The mixture was filtered and rotary evaporated to dryness to remove the organic solvent to obtain the product methyl (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-4-oxohexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-2** (450 mg, 0.977 mmol, yield: 75%) as an oily compound. ¹H NMR (400 MHz, CDCl₃) δ 5.36 – 5.24 (m, 1H), 4.30 (s, 3H), 3.00 – 2.81 (m, 5H), 2.70 – 2.58 (m, 5H), 2.55 – 2.47 (m, 2H), 2.42 (dt, J = 13.4, 3.5 Hz, 1H), 2.35 – 2.26 (m, 2H), 2.22 – 2.10 (m, 6H), 2.09 – 1.99 (m, 3H), 1.86 (d, J = 12.4 Hz, 1H), 1.76 (s, 1H), 1.73 (s, 1H), 1.73 (s, 3H), 1.70 (s, 1H), 1.69 (d, J = 3.3 Hz, 1H), 1.67 – 1.60 (m, 1H), 1.56 (d, J = 6.5 Hz, 3H), 1.28 (s, 3H).

[0321] Step 3: Compound methyl (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-7-acetoxy-9a,11a-dimethyl-4-oxohexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-2** (150 mg, 0.326 mmol, 1.0 eq) and DAST (157 mg, 0.977 mmol, 3 eq) were dissolved in tetrahydrofuran (5 mL) and stirred at 80°C for 3 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, water was added to quench the

reaction, followed by extraction with ethyl acetate (50 mL). The organic phase was washed twice with saturated brine, dried over anhydrous sodium sulfate, filtered, and rotary evaporated to dryness to obtain a crude product, which was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 1:1) to obtain a mixture of methyl (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-7-acetoxy-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-3** and methyl (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-7-acetoxy-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **73-1** as a white solid (70 mg, 0.145 mmol, yield based on **72-3**: 45%).

[0322] Compound **72-3**: ^1H NMR (400 MHz, CDCl_3) δ 4.75 – 4.63 (m, 1H), 3.66 (s, 3H), 2.34 – 2.22 (m, 2H), 2.10 – 1.91 (m, 5H), 1.84 (ddd, $J = 9.3, 7.6, 3.7$ Hz, 3H), 1.78 – 1.65 (m, 5H), 1.57 – 1.49 (m, 3H), 1.45 – 1.22 (m, 7H), 1.09 (ddd, $J = 28.8, 14.4, 9.4$ Hz, 5H), 0.94 (t, $J = 5.4$ Hz, 3H), 0.85 (d, $J = 11.0$ Hz, 3H), 0.71 – 0.62 (m, 3H).

[0323] **Step 4:** A mixture of methyl (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-7-acetoxy-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-3** and methyl (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-7-acetoxy-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **73-1** (120 mg, 0.249 mmol, 1.0 eq) was dissolved in methanol (5 mL). Potassium carbonate (171 mg, 1.243 mmol, 5.0 eq) was added slowly, and the reaction system was stirred at room temperature for 5 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 2:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×25 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 5:1) to obtain a mixture of methyl (5R)-5-

[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-4** and methyl (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-7-hydroxy-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **73-2** as a white solid mixture (100 mg, purity: 95%, yield based on **72-4**: 91%). The crude product was directly used in the next step.

[0324] Step 5: A mixture of methyl (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-4** and methyl (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-7-hydroxy-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **73-2** (1.1 g, 2.496 mmol, 1.0 eq) was dissolved in dimethylformamide (10 mL). Chloro(2-methylpropan-2-yl)diphenylsilane (1.72 g, 6.24 mmol, 2.5 eq) and imidazole (0.84 g, 12.48 mmol, 5.0 eq) were added, and the reaction system was stirred at 40°C for 12 hours. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). 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 = 10:1) to obtain a mixture of methyl (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-[(2-methylpropan-2-yl)diphenylsilyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-5** and methyl (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-[(2-methylpropan-2-yl)diphenylsilyl]oxy}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **73-3** (1.65 g, purity: 95%, yield based on **72-5**: 92%) as a white solid.

[0325] Compound 72-5: ¹H NMR (400 MHz, CDCl₃) δ 7.63 – 7.56 (m, 4H), 7.36 – 7.26 (m, 6H), 3.55 (d, J = 27.4 Hz, 4H), 2.25 – 2.12 (m, 2H), 1.85 (d, J =

12.7 Hz, 1H), 1.74 (dd, $J = 13.6, 6.1$ Hz, 2H), 1.65 – 1.49 (m, 6H), 1.45 – 1.34 (m, 5H), 1.30 (dd, $J = 15.2, 11.1$ Hz, 4H), 1.23 – 1.13 (m, 5H), 1.04 – 1.00 (m, 2H), 0.97 (s, 9H), 0.84 (t, $J = 5.6$ Hz, 3H), 0.76 – 0.71 (m, 3H), 0.69 (d, $J = 3.3$ Hz, 1H), 0.55 (d, $J = 12.1$ Hz, 3H).

- 5 **[0326] Step 6:** A mixture of white solids methyl (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-[(2-methylpropan-2-yl)diphenylsilyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **72-5** and methyl (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-[(2-methylpropan-2-yl)diphenylsilyl]oxy}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **73-3** (2.5 g, 3.682 mmol, 1.0 eq) was dissolved in tetrahydrofuran (20 mL). Lithium aluminum hydride (0.42 g, 11.05 mmol, 3 eq) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by a
- 15 TLC plate (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was
- 20 purified by column chromatography (petroleum ether: ethyl acetate = 10:1) to obtain a mixture of (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-[(2-methylpropan-2-yl)diphenylsilyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexan-1-ol **72-6** and (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-[(2-methylpropan-2-yl)diphenylsilyl]oxy}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexan-1-ol **73-4** (1.7 g, purity: 95%, yield based on **72-6**: 72%) as a white solid.

[0327] Compound 72-6: $^1\text{H NMR}$ (400MHz, CDCl_3) δ 7.70 – 7.62 (m, 4H), 7.45 – 7.33 (m, 6H), 3.63 (s, 3H), 1.93 (d, $J = 12.7$ Hz, 1H), 1.81 (d, $J = 9.4$ Hz, 2H), 1.68 – 1.60 (m, 3H), 1.54 (s, 7H), 1.38 (ddd, $J = 23.8, 18.6, 8.6$ Hz, 8H), 1.25 (d, $J = 7.1$ Hz, 5H), 0.90 (d, $J = 6.5$ Hz, 4H), 0.82 (s, 4H), 0.63 (s, 3H)

30

- [0328] Step 7:** A mixture of white solids (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-{{(2-methylpropan-2-yl)diphenylsilyl}oxy}}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexan-1-ol **72-6** and (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-{{(2-methylpropan-2-yl)diphenylsilyl}oxy}}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexan-1-ol **73-4** (1.6 g, 2.46 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL). Dess-Martin periodinane (2.08 g, 4.92 mmol, 2.0 eq) was added, and the reaction system was stirred at room temperature for 2 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The ethyl acetate layers were combined and washed with saturated sodium sulfite (3 × 10 mL). The ethyl acetate layer 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 = 10:1) to obtain a mixture of (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-{{(2-methylpropan-2-yl)diphenylsilyl}oxy}}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanal **72-7** and (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-{{(2-methylpropan-2-yl)diphenylsilyl}oxy}}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanal **73-5** (1.4 g, purity: 95%, yield based on **72-7**: 87%) as a white solid.
- [0329] Compound 72-7:** ¹H NMR (400 MHz, CDCl₃) δ 9.75 (t, J = 1.7 Hz, 1H), 7.69 – 7.63 (m, 4H), 7.44 – 7.34 (m, 6H), 3.59 (td, J = 10.5, 5.3 Hz, 1H), 2.38 (d, J = 6.4 Hz, 2H), 1.55 (s, 6H), 1.04 (s, 10H), 0.92 (d, J = 6.5 Hz, 3H), 0.82 (s, 3H), 0.62 (d, J = 12.3 Hz, 3H).
- [0330] Step 8:** Starting material 1-bromo-2-methoxybenzene (173 mg, 0.9 mmol, 4 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.8 mL, 0.28 mmol, 3 eq) was added.

The mixture was stirred at this temperature for 30 min. A mixture of white solids (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-{[(2-methylpropan-2-yl)diphenylsilyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanal **72-7** and (5R)-5-[(1R,3aR,5aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-{[(2-methylpropan-2-yl)diphenylsilyl]oxy}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanal **73-5** (150 mg, 0.23 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain the crude product of (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-{[(2-methylpropan-2-yl)diphenylsilyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-methoxyphenyl)hexan-1-ol **72-8** and (5R)-5-[(1R,3aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-{[(2-methylpropan-2-yl)diphenylsilyl]oxy}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-methoxyphenyl)hexan-1-ol **73-6** (70 mg, 0.11 mmol) as a white solid, which was directly used in the next step.

[0331] Step 9: A mixture of white solids (5R)-5-[(1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-9a,11a-dimethyl-7-{[(2-methylpropan-2-yl)diphenylsilyl]oxy}hexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-methoxyphenyl)hexan-1-ol **72-8** and (5R)-5-[(1R,3aR,7S,9aS,9bR,11aR)-4-fluoro-9a,11a-dimethyl-7-{[(2-methylpropan-2-yl)diphenylsilyl]oxy}-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-methoxyphenyl)hexan-1-ol **73-6** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Tetrabutylammonium fluoride (1 mL, 1 mol/L) was added, and the reaction system was stirred at 40°C for 12 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was

added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IE_3, 3.0×150 mm, $3 \mu\text{m}$; mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol **72** (35 mg, purity: 100%, yield: 56%, retention time $t_R = 1.682$ min) and (1R,3aR,7S,9aS,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(2-methoxyphenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol **73** (5 mg, purity: 100%, yield: 8%, retention time $t_R = 2.241$ min).

[0332] 72: ^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.27 (m, 1H), 7.26 – 7.21 (m, 1H), 7.00 – 6.84 (m, 2H), 4.85 (dt, $J = 9.1, 5.9$ Hz, 1H), 3.85 (s, 3H), 3.68 – 3.58 (m, 1H), 1.98 (d, $J = 11.4$ Hz, 1H), 1.88 – 1.69 (m, 8H), 1.64 – 1.51 (m, 4H), 1.46 – 1.28 (m, 9H), 1.24 – 1.11 (m, 2H), 1.10 – 0.95 (m, 4H), 0.90 (dt, $J = 7.6, 3.8$ Hz, 3H), 0.84 (s, 3H), 0.65 (d, $J = 2.3$ Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.96, -89.59, -110.85, -111.48.

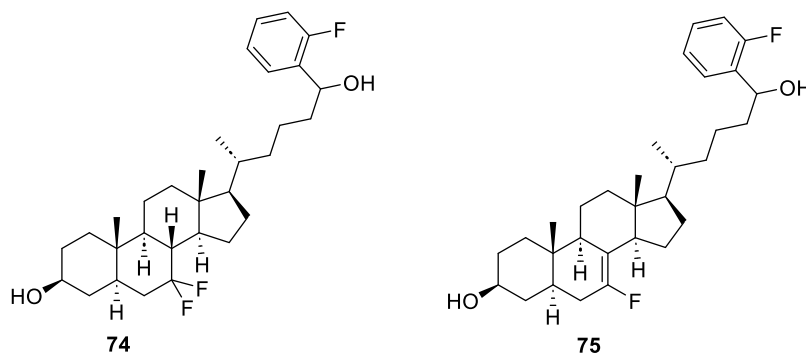
[0333] 73: ^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.28 (m, 1H), 7.24 (s, 1H), 6.92 (dd, $J = 32.7, 7.8$ Hz, 2H), 4.85 (dd, $J = 14.9, 8.1$ Hz, 1H), 3.86 (s, 3H), 3.68 – 3.54 (m, 1H), 2.02 (d, $J = 11.5$ Hz, 3H), 1.81 (ddd, $J = 17.2, 12.6, 8.5$ Hz, 6H), 1.64 (s, 2H), 1.54 (d, $J = 3.1$ Hz, 4H), 1.44 (dd, $J = 13.3, 4.6$ Hz, 3H), 1.34 – 1.28 (m, 5H), 1.13 – 1.02 (m, 4H), 0.91 (dd, $J = 6.5, 3.6$ Hz, 3H), 0.80 (d, $J = 10.7$ Hz, 3H), 0.71 – 0.60 (m, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -106.98, -110.64.

30

[0334] Examples 74 & 75

[0335] Preparation of **compound 74** (1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol

[0336] Preparation of **compound 75** (1R,3aR,7S,9aS,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol



[0337] Referring to Examples 72 & 73, 1-bromo-2-methoxybenzene was replaced with 1-bromo-2-fluorobenzene in Step 8, and the products were separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IE_3, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol **74** (35 mg, purity: 100%, yield: 56%, retention time t_R = 1.167 min) and (1R,3aR,7S,9aS,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol **75** (5 mg, purity: 100%, yield: 8%, retention time t_R = 1.410 min).

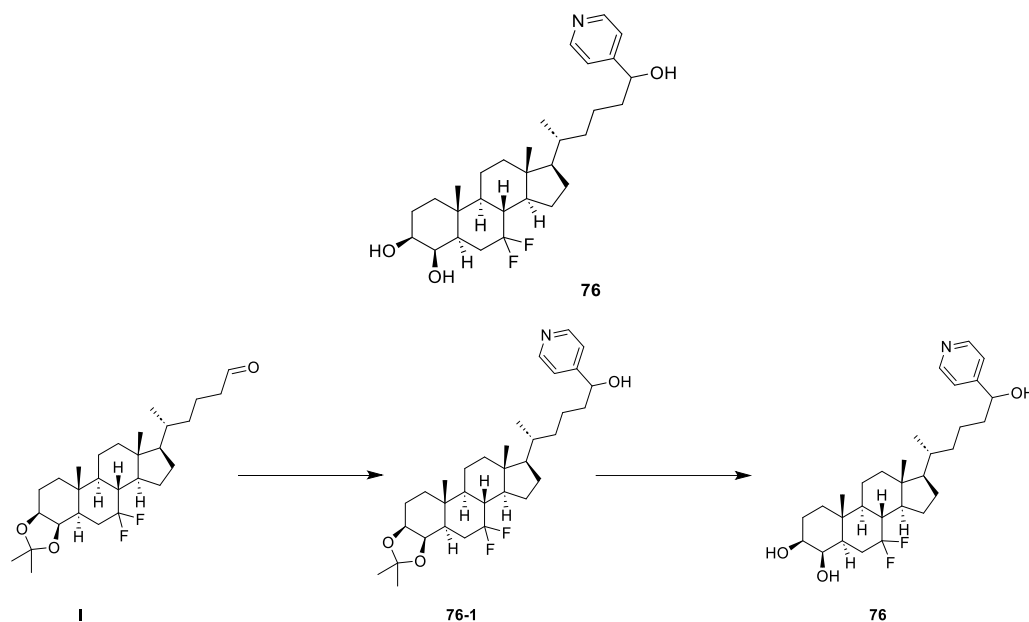
[0338] **Compound 74:** ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.27 (m, 1H), 7.26 – 7.21 (m, 1H), 7.00 – 6.84 (m, 2H), 4.85 (dt, J = 9.1, 5.9 Hz, 1H), 3.85 (s, 3H), 3.68 – 3.58 (m, 1H), 1.98 (d, J = 11.4 Hz, 1H), 1.88 – 1.69 (m, 8H), 1.64 – 1.51 (m, 4H), 1.46 – 1.28 (m, 9H), 1.24 – 1.11 (m, 2H), 1.10 – 0.95 (m, 4H), 0.90 (dt, J = 7.6, 3.8 Hz, 3H), 0.84 (s, 3H), 0.65 (d, J = 2.3 Hz, 3H). ¹⁹F NMR (376 MHz,

CDCl_3) δ -88.98, -89.60, -110.85, -111.48, -119.75, -119.78.

[0339] Compound 75: ^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.28 (m, 1H), 7.24 (s, 1H), 6.92 (dd, J = 32.7, 7.8 Hz, 2H), 4.85 (dd, J = 14.9, 8.1 Hz, 1H), 3.86 (s, 3H), 3.68 – 3.54 (m, 1H), 2.02 (d, J = 11.5 Hz, 3H), 1.81 (ddd, J = 17.2, 12.6, 8.5 Hz, 6H), 1.64 (s, 2H), 1.54 (d, J = 3.1 Hz, 4H), 1.44 (dd, J = 13.3, 4.6 Hz, 3H), 1.34 – 1.28 (m, 5H), 1.13 – 1.02 (m, 4H), 0.91 (dd, J = 6.5, 3.6 Hz, 3H), 0.80 (d, J = 10.7 Hz, 3H), 0.71 – 0.60 (m, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ 110.61, 105.12, 105.11.

[0340] Example 76

[0341] Preparation of compound **76** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(pyridin-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0342] Step 1: Starting material 4-bromopyridine (118.50 mg, 0.75 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (2.5 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-

yl)hexanal **I** (100 mg, 0.21 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product. The crude product was subjected to silica gel column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(pyridin-4-yl)hexan-1-ol **76-1** (24 mg, purity: 90%, yield: 18.8%) as a white solid.

[0343] ¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 2H), 7.39 (s, 2H), 4.75 (s, 1H), 4.02 (d, *J* = 15.0 Hz, 1H), 2.20 (dd, *J* = 22.6, 14.8 Hz, 1H), 2.09 – 1.93 (m, 3H), 1.82 (d, *J* = 7.0 Hz, 2H), 1.76 – 1.58 (m, 4H), 1.50 (s, 2H), 1.30 (s, 2H), 1.26 (s, 3H), 1.07 (s, 2H), 0.90 (dd, *J* = 7.0, 3.8 Hz, 2H), 0.65 (d, *J* = 11.8 Hz, 2H).

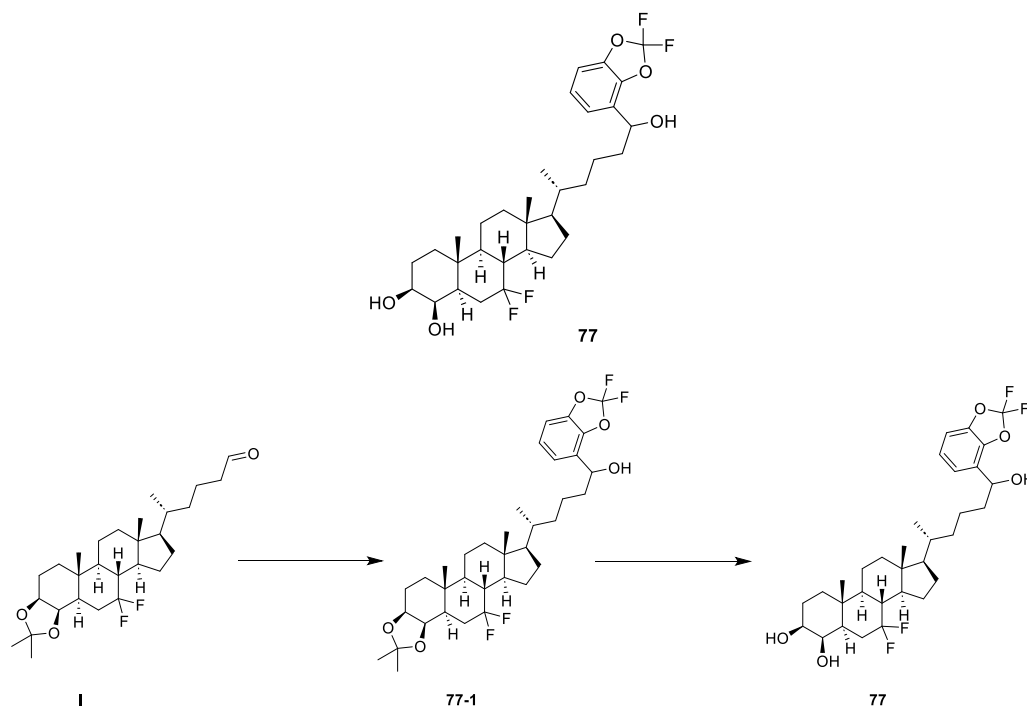
[0344] Step 2: Reactant (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(pyridin-4-yl)hexan-1-ol **76-1** (24 mg, 0.044 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 70:30) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 70/30; flow rate:

2.0 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(pyridin-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **76** (3.04 mg, purity: 100%, yield: 13.7%, retention time t_R = 1.965 min).

[0345] Compound **76**: ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, J = 5.9 Hz, 2H), 7.28 (s, 2H), 4.68 (t, J = 6.4 Hz, 1H), 3.73 (s, 1H), 3.64 – 3.55 (m, 1H), 2.23 – 2.14 (m, 1H), 1.96 (d, J = 12.7 Hz, 1H), 1.82 – 1.65 (m, 10H), 1.46 – 1.23 (m, 10H), 1.09 (d, J = 6.4 Hz, 2H), 1.05 (d, J = 5.2 Hz, 3H), 1.01 – 0.92 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.62, -89.25, -109.77, -110.65, -111.24.

[0346] Example 77

[0347] Preparation of compound **77** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0348] Step 1: Starting material 4-bromo-2,2-difluorobenzo[d][1,3]diazole

(177.8 mg, 0.75 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (4 mL). The system was cooled to -78°C, and *n*-butyllithium (0.26 mL, 0.64 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.21 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating) until completion. Water (20 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (20 mL × 2). The organic phases were combined, washed with saturated sodium chloride (30 mL), dried, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2,2-difluorobenzo[d][1,3]trioxol-4-yl)hexan-1-ol **77-1** (80 mg, yield: 60%) as a white solid.

[0349] Step 2: Reactant (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2,2-difluorobenzo[d][1,3]trioxol-4-yl)hexan-1-ol **77-1** (80 mg, 0.13 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 80:20) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 70/30; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain

5 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **77** (28.80 mg, purity: 97%, yield: 38%, retention time *t_R* = 0.921 min). ¹H NMR (400 MHz, CDCl₃) δ 7.13 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 4.94 – 4.83 (m, 1H), 3.77 – 3.71 (m, 1H), 3.65 – 3.54 (m, 1H), 2.30 – 2.05 (m, 2H), 2.02 – 1.90 (m, 2H), 1.89 – 1.76 (m, 6H), 1.75 – 1.63 (m, 3H), 1.50 – 1.39 (m, 4H), 1.38 – 1.32 (m, 3H), 1.31 – 1.20 (m, 2H), 1.16 – 1.08 (m, 2H), 1.07 – 1.02 (m, 4H), 1.01 – 0.94 (m, 1H), 0.92 – 0.85 (m, 3H), 0.65 (d, *J* = 1.9 Hz, 3H). ¹⁹F NMR (376MHz, CDCl₃) δ -49.75 (qd, *J* = 97.3, 9.6Hz, 2F), -

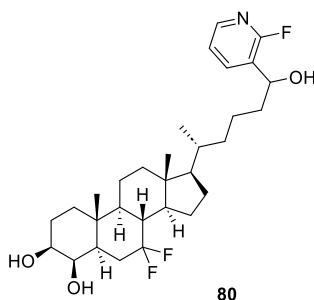
10 88.95 (d, *J* = 235.8Hz, 1F), -110.94 (d, *J* = 235.9Hz, 1F).

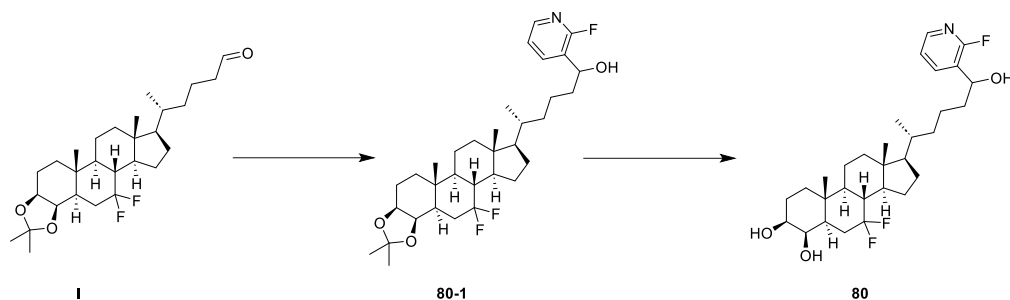
15

[0350] Example 80

[0351] Preparation of compound **80** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-

20 dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





[0352] Step 1: Starting material 3-bromo-2-methoxypyridine (141 mg, 0.75 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (0.26 mL, 0.64 mmol, 3.0 eq) was added.

5 The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.214 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above

10 reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain

15 the crude product of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoropyridin-3-yl)hexan-1-ol **80-1** (50 mg) as a colorless oil, which was directly used in the next

20 step. LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 594.3$.

[0353] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoropyridin-3-

25 yl)hexan-1-ol **80-1** (50 mg, 0.086 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction

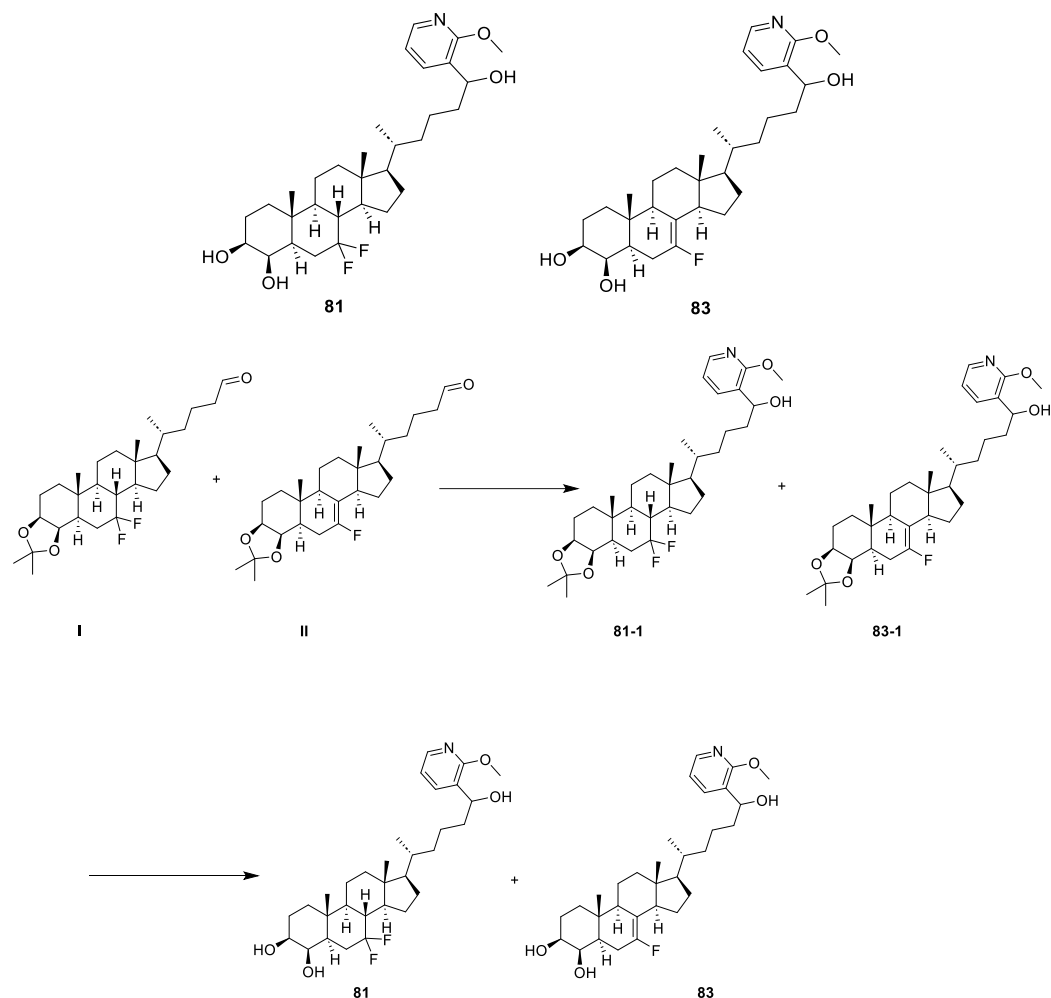
system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0×150 mm, $3 \mu\text{m}$; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **80** (4.06 mg, purity: 100%, yield: 8.07%, retention time $t_R = 1.683$ min).

[0354] Compound **80**: ^1H NMR (400 MHz, CDCl₃) δ 8.12 (d, $J = 4.5$ Hz, 1H), 7.92 (t, $J = 8.5$ Hz, 1H), 7.21 (m, 1H), 4.95 (m, 1H), 3.74 (s, 1H), 3.60 (m, 1H), 2.17 (m, 2H), 1.97 (d, $J = 12.9$ Hz, 4H), 1.82 (d, $J = 7.2$ Hz, 7H), 1.72 (s, 4H), 1.40 (s, 4H), 1.36 (m, 2H), 1.09 (s, 2H), 1.06 (s, 3H), 0.95 (m, 3H), 0.90 (dd, $J = 6.7, 2.3$ Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (377 MHz, CDCl₃) δ -72.48, -76.69, -88.63, -89.26, -110.61, -111.22. LC-MS: $[\text{M}+\text{H}]^+ = 524.35$.

[0355] Examples **81** & **83**

[0356] Preparation of compound **81** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0357] compound **83** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0358] Step 1: Starting material 3-bromo-2-methoxypyridine (141 mg, 0.75 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (0.26 mL, 0.64 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5*R*)-5-[(3*aS*,5*aR*,5*bS*,7*aR*,8*R*,10*aS*,10*bS*,12*aR*,12*bR*)-11,11-difluoro-2,2,5*a*,7*a*-tetramethyl-4,5,5*a*,5*b*,6,7,7*a*,8,9,10,10*a*,10*b*,11,12,12*a*,12*b*-hexadecahydro-3*aH*-cyclopenta[1',2':1,2]phenanthro[7,8-*d*][1,3]dioxol-8-yl]hexanal **I** and (5*R*)-5-[(3*aS*,5*aR*,5*bR*,7*aR*,8*R*,10*aR*,12*bR*)-11-fluoro-2,2,5*a*,7*a*-tetramethyl-4,5,5*a*,5*b*,6,7,7*a*,8,9,10,10*a*,12,12*a*,12*b*-tetradecahydro-3*aH*-cyclopenta[1',2':7,8]phenanthro[1,2-*d*][1,3]dioxol-8-yl]hexanal **II** (100 mg, 0.214 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min.

The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude mixture of **81-1** and **83-1** (80 mg) as a colorless oil, which was directly used in the next step. LC-MS: $[M+H-H_2O]^+ = 594.3$.

[0359] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aS,12bS)-11,11,12a-trifluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-methoxypyridin-3-yl)hexan-1-ol **81-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(2-methoxypyridin-3-yl)hexan-1-ol **83-1** (80 mg, 0.14 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 $\times$ 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 $\times$ 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IB 4.6 $\times$ 250 mm, 5 μ m; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aS,6S,7S,9aR,9bS,11aR)-4,4,5a-trifluoro-1-[(2R)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **81** (22.46 mg, purity: 99.06%, yield: 30.11%, retention time $t_R = 1.484$ min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(2-

methoxypyridin-3-yl)hexan-2-yl]hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **83** (1.98 mg, purity: 89.13%, yield: 2.75%, retention time t_R = 1.986 min).

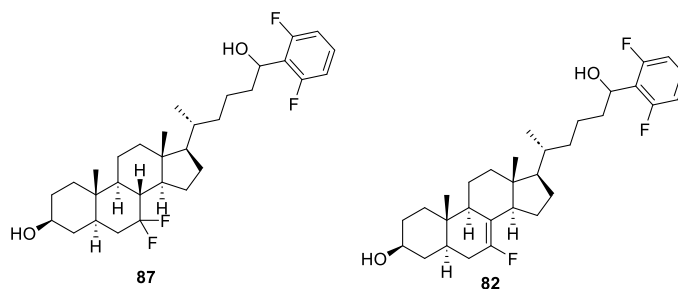
5 **[0360]** Compound **81**: ^1H NMR (400 MHz, CDCl_3) δ 8.08 (m, 1H), 7.62 (t, J = 5.2 Hz, 1H), 6.91 (dd, J = 7.2, 5.1 Hz, 1H), 4.79 (dt, J = 13.4, 6.7 Hz, 1H), 4.01 (s, 3H), 3.74 (s, 1H), 3.60 (m, 1H), 2.16 (m, 2H), 1.97 (d, J = 13.2 Hz, 1H), 1.82 (m, 4H), 1.70 (m, 4H), 1.36 (m, 11H), 1.10 (s, 2H), 1.06 (s, 3H), 0.98 (m, 2H), 0.90 (dd, J = 6.5, 3.3 Hz, 3H), 0.66 (d, J = 1.8 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.63, -89.26, -110.63, -111.26. LC-MS: $[\text{M}+\text{H}]^+ = 536.35$.

10 **[0361]** Compound **83**: ^1H NMR (400 MHz, CDCl_3) δ 8.11 (m, 1H), 7.68 (s, 1H), 6.95 (m, 1H), 4.81 (d, J = 4.9 Hz, 1H), 4.06 (s, 3H), 3.85 (s, 1H), 3.59 (d, J = 11.6 Hz, 1H), 2.66 (s, 1H), 2.02 (d, J = 11.3 Hz, 1H), 1.92 (s, 1H), 1.81 (dd, J = 20.6, 13.4 Hz, 6H), 1.77 (s, 3H), 1.61 (d, J = 9.5 Hz, 3H), 1.44 (m, 7H), 1.25 (s, 3H), 1.10 (m, 3H), 1.05 (s, 3H), 0.92 (dd, J = 6.5, 2.8 Hz, 3H), 0.63 (d, J = 1.5 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -109.77. LC-MS: $[\text{M}+\text{H}]^+ = 516.35$.

[0362] Examples 82 & 87

20 **[0363]** Preparation of compound **87** (1R,3aS,3bR,7S,9aS,9bS,11aR)-1-[(2R)-6-(2,6-difluorophenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol

[0364] Preparation of compound **82** (1R,3aR,7S,9aS,9bR,11aR)-1-[(2R)-6-(2,6-difluorophenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol



[0365] Referring to Examples 74 & 75, 1-bromo-2-methoxybenzene was replaced with 2-bromo-1,3-difluorobenzene in Step 8, and the products were separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IB 4.6 × 250 mm, 5 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bR,7S,9aS,9bS,11aR)-1-[(2R)-6-(2,6-difluorophenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol **87** (35 mg, purity: 100%, yield: 56%, retention time t_R = 1.293 min) and (1R,3aR,7S,9aS,9bR,11aR)-1-[(2R)-6-(2,6-difluorophenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol **82** (5 mg, purity: 100%, yield: 8%, retention time t_R = 1.646 min).

[0366] **87**: ¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.16 (m, 1H), 6.87 (t, J = 8.3 Hz, 2H), 5.03 (t, J = 7.2 Hz, 1H), 3.69 – 3.53 (m, 1H), 2.03 – 1.92 (m, 2H), 1.86 – 1.70 (m, 7H), 1.64 – 1.49 (m, 4H), 1.47 – 1.25 (m, 10H), 1.07 (ddd, J = 27.8, 15.1, 11.4 Hz, 5H), 0.89 (t, J = 6.0 Hz, 3H), 0.84 (s, 3H), 0.65 (d, J = 3.7 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.97, -89.60, -110.85, -111.48, -115.39, -115.46.

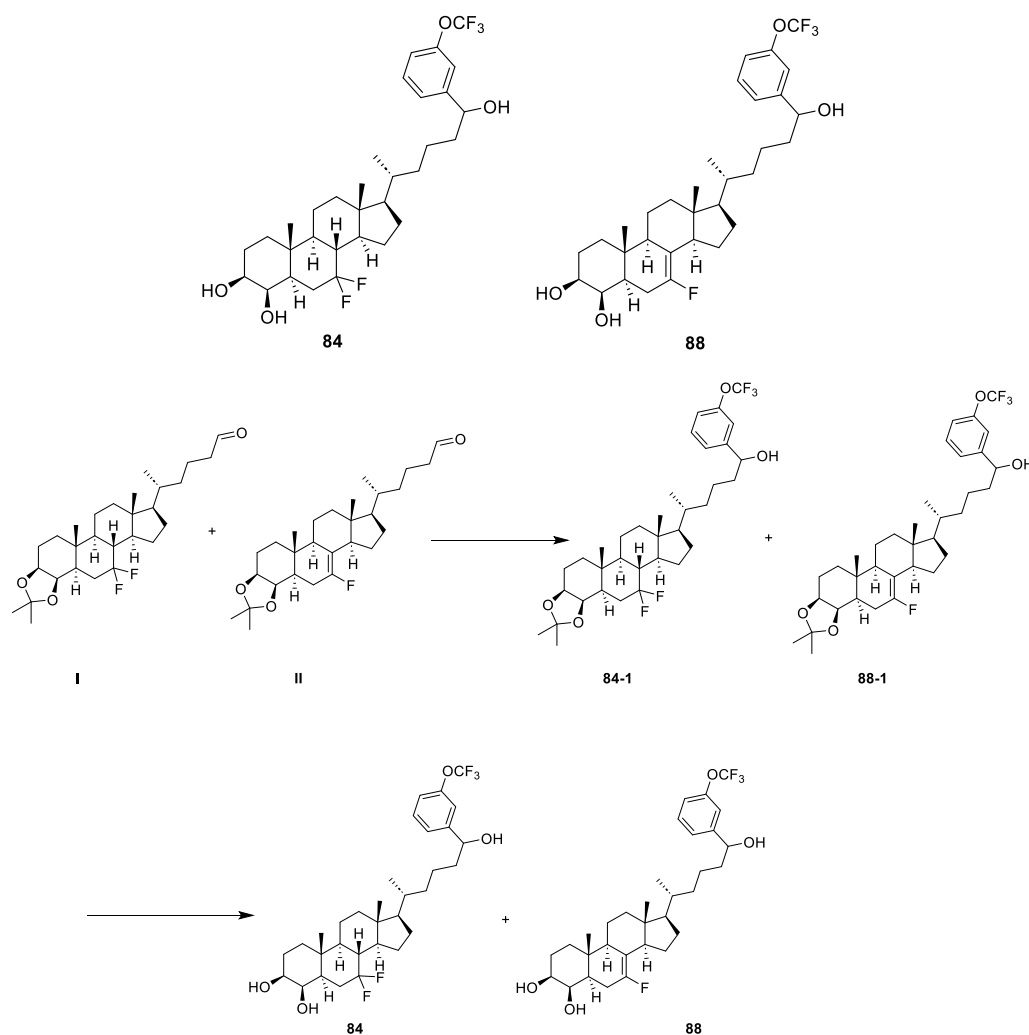
[0367] **82**: ¹H NMR (400 MHz, CDCl₃) δ 7.21 (t, J = 7.4 Hz, 1H), 6.87 (t, J = 8.2 Hz, 2H), 5.03 (s, 1H), 3.63 (d, J = 26.3 Hz, 1H), 2.01 (dd, J = 11.2, 8.9 Hz, 3H), 1.91 (s, 2H), 1.84 (s, 3H), 1.76 (s, 3H), 1.68 – 1.48 (m, 6H), 1.44 (dd, J = 10.8, 5.9 Hz, 2H), 1.38 (d, J = 5.0 Hz, 2H), 1.30 (dd, J = 11.6, 5.1 Hz, 4H), 1.13 (d, J = 12.9 Hz, 1H), 1.08 (d, J = 10.0 Hz, 2H), 1.02 (d, J = 11.9 Hz, 1H), 0.92 – 0.84 (m, 5H), 0.80 (d, J = 11.0 Hz, 3H), 0.66 (dd, J = 28.8, 3.7 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -110.61, -115.39, -115.46.

[0368] Examples 84 & 88

[0369] Preparation of compound **84** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-{3-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0370] compound **88** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-{3-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.

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[0371] Step 1: Starting material 1-bromo-3-[(trifluoromethyl)oxy]benzene (126.7 mg, 0.5 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-

10

tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude mixture of **84-1** and **88-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0372] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{3-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **84-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(3-[(trifluoromethyl)oxy]phenyl)hexan-1-ol **88-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 65/35; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain

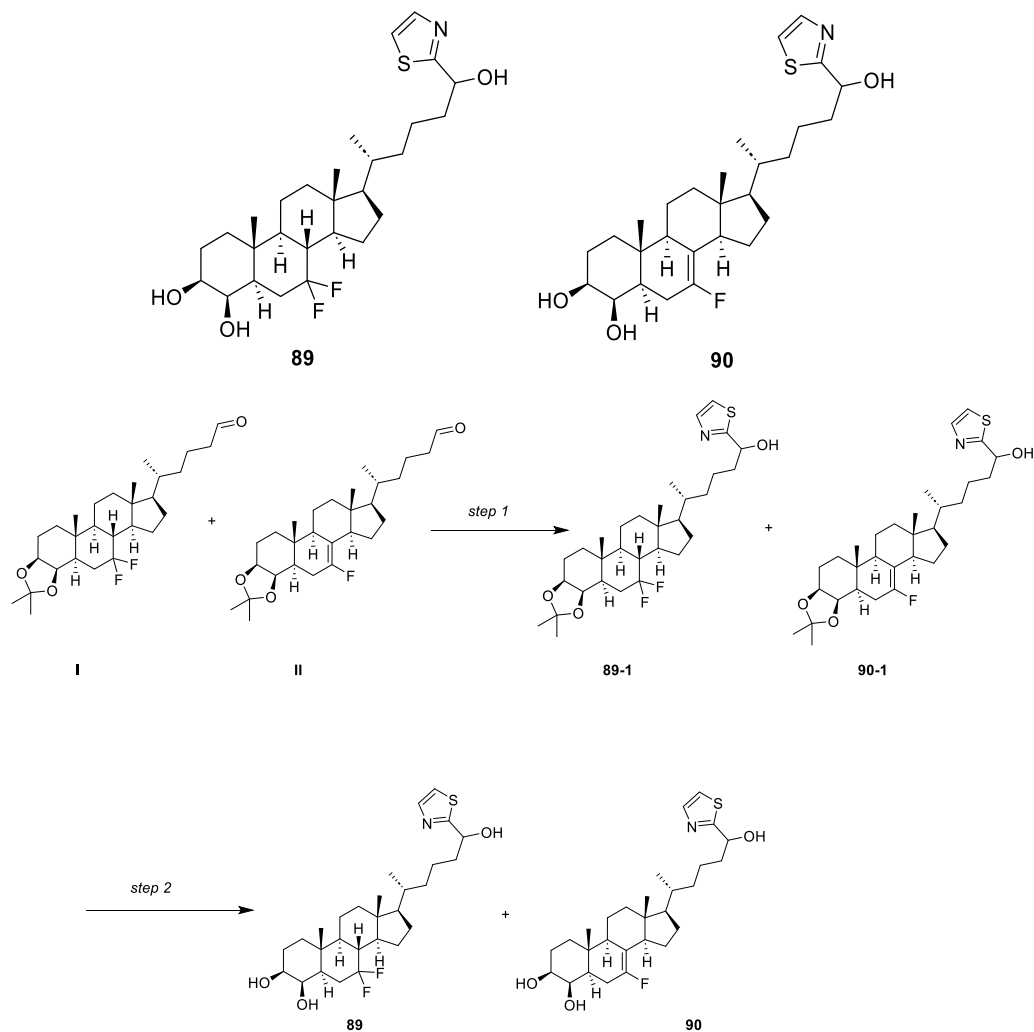
(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-{3-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **84** (33.05 mg, purity: 99.04%, yield: 49.94%, retention time t_R = 0.700 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(3-[(trifluoromethyl)oxy]phenyl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **88** (2.97 mg, purity: 97.97%, yield: 4.96%, retention time t_R = 0.927 min).

[0373] Compound **84**: ^1H NMR (400 MHz, CDCl_3) δ 7.37 (t, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.22 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.74 – 4.65 (m, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.0, 4.0 Hz, 1H), 2.29 – 2.07 (m, 1H), 1.97 (d, J = 12.9 Hz, 1H), 1.88 – 1.77 (m, 8H), 1.77 – 1.60 (m, 5H), 1.50 – 1.24 (m, 10H), 1.11 (dd, J = 14.1, 5.1 Hz, 2H), 1.06 (s, 3H), 1.02 – 0.92 (m, 2H), 0.89 (t, J = 5.9 Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -57.72, -88.64, -89.27, -110.64, -111.26.

[0374] Compound **88**: ^1H NMR (400 MHz, CDCl_3) δ 7.37 (t, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.22 (s, 1H), 7.12 (d, J = 7.9 Hz, 1H), 4.74 – 4.67 (m, 1H), 3.85 (s, 1H), 3.63 – 3.56 (m, 1H), 2.65 (t, J = 14.8 Hz, 1H), 2.02 (d, J = 14.1 Hz, 2H), 1.90 – 1.66 (m, 11H), 1.61 (d, J = 12.8 Hz, 4H), 1.45 (dd, J = 15.3, 7.8 Hz, 4H), 1.35 – 1.22 (m, 7H), 1.09 (dd, J = 12.2, 4.5 Hz, 3H), 1.04 (s, 3H), 0.90 (dd, J = 6.4, 4.4 Hz, 3H), 0.62 (d, J = 1.3 Hz, 3H). LC-MS: $[\text{M}+1-\text{H}_2\text{O}]^+ = 551.30$. ^{19}F NMR (376 MHz, CDCl_3) δ -57.72, -109.77.

[0375] Examples **89 & 90**

[0376] Preparation of compound **89** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(1,3-thiazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and **[0377]** compound **90** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(1,3-thiazol-2-yl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0378] Step 1: Starting material 1,3-thiazole (44.7 mg, 0.5 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (1.8 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of (5*R*)-5-[(3*aS*,5*aR*,5*bS*,7*aR*,8*R*,10*aS*,10*bS*,12*aR*,12*bR*)-11,11-difluoro-2,2,5*a*,7*a*-tetramethyl-4,5,5*a*,5*b*,6,7,7*a*,8,9,10,10*a*,10*b*,11,12,12*a*,12*b*-hexadecahydro-3*aH*-cyclopenta[1',2':1,2]phenanthro[7,8-*d*][1,3]dioxol-8-yl]hexanal **I** and (5*R*)-5-[(3*aS*,5*aR*,5*bR*,7*aR*,8*R*,10*aR*,12*bR*)-11-fluoro-2,2,5*a*,7*a*-tetramethyl-4,5,5*a*,5*b*,6,7,7*a*,8,9,10,10*a*,12,12*a*,12*b*-tetradecahydro-3*aH*-cyclopenta[1',2':7,8]phenanthro[1,2-*d*][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The

reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product of **89-1** and **90-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0379] Step 2: The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(1,3-thiazol-2-yl)hexan-1-ol **89-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(1,3-thiazol-2-yl)hexan-1-ol **90-1** (70 mg, 0.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 $\times$ 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 $\times$ 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 $\times$ 150 mm, 3 μ m; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(1,3-thiazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **89** (17.91 mg, purity: 93.50%, yield: 36.11%, retention time t_R = 1.209 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(1,3-thiazol-2-yl)hexan-2-yl]-9a,11a-dimethyl-

2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **90** (2.09 mg, purity: 98.75%, yield: 4.63%, retention time t_R = 1.618 min).

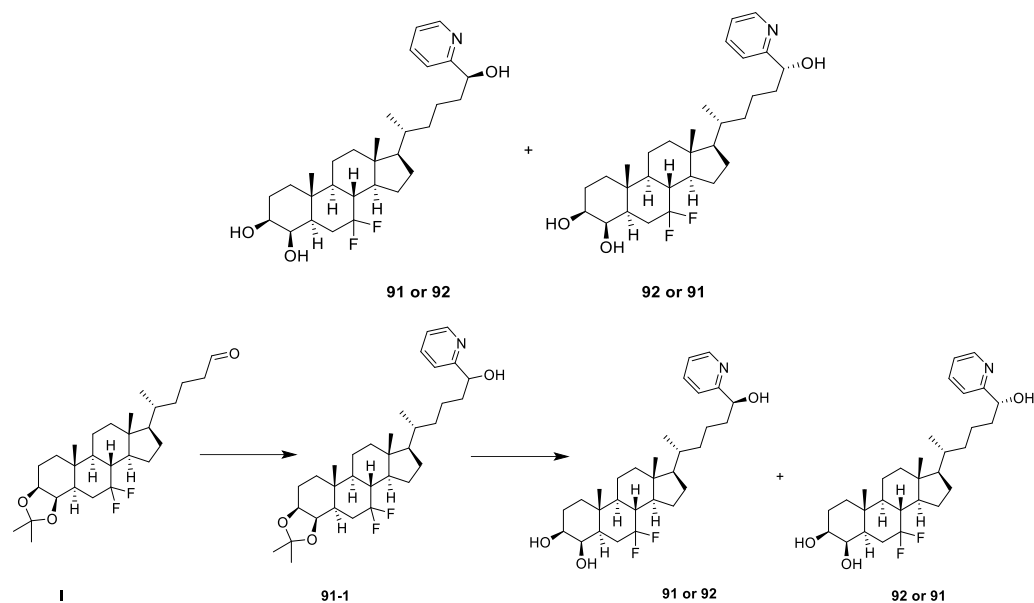
[0380] Compound **89**: ^1H NMR (400 MHz, DMSO) δ 7.72 – 7.69 (m, 1H), 7.58
5 (dd, J = 3.2, 1.8 Hz, 1H), 6.05 (dd, J = 5.2, 1.2 Hz, 1H), 4.78 (dt, J = 8.0, 3.9 Hz, 1H), 4.40 (d, J = 6.0 Hz, 1H), 4.24 (d, J = 3.4 Hz, 1H), 3.49 (d, J = 2.4 Hz, 1H), 3.35 (d, J = 6.6 Hz, 1H), 2.17 – 1.97 (m, 1H), 1.91 (d, J = 12.5 Hz, 1H), 1.85 – 1.54 (m, 8H), 1.43 (d, J = 9.9 Hz, 3H), 1.37 – 1.15 (m, 9H), 1.05 (t, J = 10.5 Hz, 3H), 0.98 (s, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.62 (s, 3H). LC-MS: $[\text{M}+1]^+ =$
10 512.37. ^{19}F NMR (377 MHz, DMSO) δ -86.66, -87.28, -108.65, -109.27.

[0381] Compound **90**: ^1H NMR (400 MHz, DMSO) δ 7.70 (d, J = 3.2 Hz, 1H), 7.58 (dd, J = 3.2, 1.7 Hz, 1H), 6.06 (d, J = 5.2 Hz, 1H), 4.77 (dt, J = 8.2, 4.8 Hz, 1H), 4.41 (d, J = 6.0 Hz, 1H), 4.24 (d, J = 3.4 Hz, 1H), 3.59 (d, J = 2.8 Hz, 1H), 3.29 (d, J = 4.2 Hz, 1H), 2.03 – 1.93 (m, 2H), 1.84 – 1.56 (m, 10H), 1.47 – 1.27
15 (m, 8H), 1.25 (d, J = 9.6 Hz, 4H), 1.07 (ddd, J = 35.6, 21.8, 13.4 Hz, 4H), 0.95 (s, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.57 (s, 3H). LC-MS: $[\text{M}+1]^+ = 492.25$. ^{19}F NMR (377 MHz, CDCl_3) δ -103.90.

[0382] Examples **91** & **92**

20 [0383] Preparation of compound **91** or **92**
(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(pyridin-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0384] compound **92** or **91** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(pyridin-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.
25



[0385] Step 1: Starting material 2-bromopyridine (118.50 mg, 0.750 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL). The system was cooled to -78°C , and *n*-butyllithium (0.257 mL, 0.643 mmol) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.214 mmol) was dissolved in tetrahydrofuran (5 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain the crude product of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(pyridin-2-yl)hexan-1-ol **91-1** (70 mg, 0.103 mmol, 47.88%) as a colorless oil.

[0386] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-

11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(pyridin-2-yl)hexan-1-ol **91-1** (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and
 5 dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The ethyl acetate layers were combined and washed with
 10 saturated brine (3×10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, $3.0 \times$
 15 150 mm, 3 μ m; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 65/35; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain compound **91** (4.46 mg, 0.009 mmol, 6.89%, retention time t_R = 1.776 min) and compound **92** (5.72 mg, 0.011 mmol, 8.25%, retention time t_R = 1.986 min).

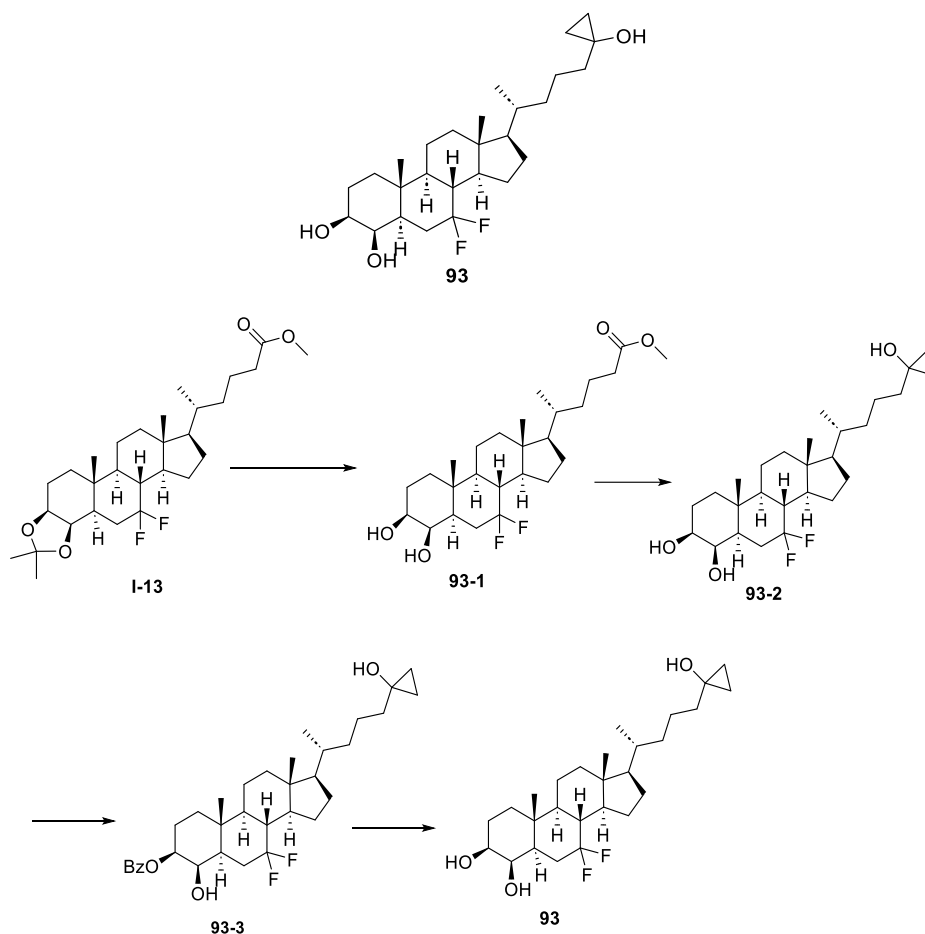
[0387] Compound **91**: ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, J = 4.7 Hz, 1H),
 20 7.71 (td, J = 7.7, 1.4 Hz, 1H), 7.29 (s, 1H), 7.25 – 7.21 (m, 1H), 4.74 (dd, J = 7.8, 4.4 Hz, 1H), 3.74 (s, 1H), 3.65 – 3.57 (m, 1H), 2.29 – 2.09 (m, 1H), 1.96 (dd, J = 9.5, 3.3 Hz, 0H), 1.85 – 1.77 (m, 1H), 1.76 – 1.70 (m, 1H), 1.56 – 1.45 (m, 1H), 1.40 (dd, J = 13.6, 8.8 Hz, 1H), 1.34 – 1.24 (m, 2H), 1.15 – 1.08 (m, 1H), 1.06 (s, 3H), 1.01 – 0.93 (m, 1H), 0.89 (t, J = 5.2 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376
 25 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.25.

[0388] Compound **92**: ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, J = 4.8 Hz, 1H),
 7.70 (td, J = 7.7, 1.5 Hz, 1H), 7.22 (dd, J = 7.2, 5.2 Hz, 1H), 4.74 (dd, J = 7.7, 4.2 Hz, 1H), 3.74 (s, 1H), 3.59 (m, 1H), 2.21 (ddd, J = 28.4, 13.8, 7.1 Hz, 1H), 1.97 (d, J = 12.7 Hz, 1H), 1.80 (dd, J = 16.2, 6.4 Hz, 4H), 1.70 (m, 6H), 1.33 (ddd, J =
 30 20.1, 16.0, 6.8 Hz, 11H), 1.11 (d, J = 5.4 Hz, 2H), 1.05 (s, 3H), 0.97 (m, 2H), 0.90 (d, J = 6.4 Hz, 3H), 0.63 (d, J = 11.0 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -

88.58, -89.21, -110.56, -111.19.

[0389] Example 93

[0390] Preparation of compound **93** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-
5 4,4-difluoro-1-[(2R)-5-(hydroxycyclopropyl)pentan-2-yl]-9a,11a-
dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0391] Step 1: Reactant methyl (5R)-5-
10 ((3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-11,11-difluoro-2,2,5a,7a-
tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-
yl)hexanoate **I-13** (400 mg, 0.805 mmol, 1.0 eq) was dissolved in tetrahydrofuran
(6 mL), and dilute hydrochloric acid (3 mL, 3 mol/L) was added. The reaction
system was stirred at room temperature for 1 hour. The reaction progress was
15 monitored by a TLC plate (petroleum ether: ethyl acetate = 10:1,

phosphomolybdic acid staining followed by heating). After the starting material was completely consumed, the reaction was stopped. Water (30 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The ethyl acetate layers were combined and washed with saturated brine (50 mL). The ethyl acetate layer 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 = 80:20) to obtain methyl (5R)-5-((3S,4R,8S,9S,10R,13R,14S,17R)-7,7-difluoro-3,4-dihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)hexanoate **93-1** (330 mg, purity: 90%, yield: 73.42%) as a white solid. Compound **93-1**: ¹H NMR (400 MHz, CDCl₃) δ 3.74 (s, 1H), 3.67 (s, 3H), 3.64 – 3.56 (m, 1H), 2.31 – 2.23 (m, 2H), 1.97 (d, *J* = 12.7 Hz, 1H), 1.89 – 1.77 (m, 5H), 1.75 – 1.66 (m, 4H), 1.55 – 1.43 (m, 4H), 1.43 – 1.33 (m, 5H), 1.15 – 1.07 (m, 3H), 1.06 (s, 3H), 1.01 (d, *J* = 3.0 Hz, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.96 (d, *J* = 235.9 Hz, 1F), -110.94 (d, *J* = 236.0 Hz, 1F).

[0392] Step 2: At room temperature, compound methyl (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexanoate **93-1** (300 mg, 0.66 mmol, 1.0 eq) was dissolved in tetrahydrofuran (15 mL). Under a nitrogen atmosphere, titanium isopropoxide (938 mg, 3.30 mmol, 5.0 eq) was added, followed by slow dropwise addition of ethylmagnesium bromide (1 M in tetrahydrofuran, 6.6 mL, 6.60 mmol, 10 eq), maintaining the temperature at 18–20°C. The mixture was then stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 2:1). The reaction was quenched with ammonium chloride solution, and ethyl acetate (30 mL) and water (20 mL) were added. The mixture was filtered through diatomite, and the aqueous phase was extracted with ethyl acetate (20 mL). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 2:1) to obtain

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-5-(hydroxycyclopropyl)pentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **93-2** (185 mg, purity: 90%, yield: 61.67%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 3.74 (s, 1H), 3.65 – 3.56 (m, 1H), 2.27 – 2.11 (m, 1H), 1.98 (d, *J* = 12.9 Hz, 1H), 1.91 – 1.78 (m, 5H), 1.77 – 1.65 (m, 4H), 1.54 (dd, *J* = 13.4, 9.8 Hz, 3H), 1.49 – 1.39 (m, 6H), 1.16 – 1.08 (m, 3H), 1.06 (s, 3H), 1.02 – 0.97 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.91 – 0.82 (m, 2H), 0.73 (t, *J* = 5.5 Hz, 2H), 0.67 (s, 3H), 0.47 – 0.41 (m, 2H).

[0393] Step 3: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-5-(hydroxycyclopropyl)pentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **93-2** (185 mg, 0.41 mmol, 1.0 eq) was dissolved in dichloromethane (4 mL) and tetrahydrofuran (2 mL) at room temperature. Triethylamine (41 mg, 1.23 mmol, 3 eq), 4-dimethylaminopyridine (40 mg, 0.33 mmol, 0.8 eq), and benzoyl chloride (58 mg, 0.62 mmol, 1.5 eq) were added at room temperature. The mixture was stirred at room temperature for 4 hours, and the reaction was monitored by TLC (petroleum ether: ethyl acetate = 1:1). After the reaction was completed, the reaction mixture was quenched with ice water (20 mL) and extracted with ethyl acetate (20 mL × 2). The organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 10:1) and SFC resolution (instrument: Waters Acquity UPCC column: Daicel CHIRALPAK IH_3, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 70/30; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6-hydroxy-1-[(2R)-5-(hydroxycyclopropyl)pentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl benzoate **93-3** (75 mg, purity: 95%, yield: 32.75%, retention time *t_R* = 1.171 min). ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 4.99 (d, *J* = 11.2 Hz, 1H), 3.98 (s, 1H), 2.25 (d, *J* = 35.4 Hz, 1H), 2.02 (dd, *J* = 17.0, 8.7 Hz, 2H), 1.83 (d, *J* = 10.0 Hz, 7H), 1.55 (s, 6H), 1.49 – 1.32 (m, 8H), 1.14 (s, 3H), 1.09 –

0.98 (m, 2H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.74 (t, $J = 5.5$ Hz, 2H), 0.68 (s, 3H), 0.50 – 0.37 (m, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -89.03 (d, $J = 236.3$ Hz, 1F), -110.80 (d, $J = 236.4$ Hz, 1F).

[0394] Step 4: At room temperature, (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-
 5 4,4-difluoro-6-hydroxy-1-[(2R)-5-(hydroxycyclopropyl)pentan-2-yl]-9a,11a-
 dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl benzoate **93-3**
 (20 mg, 0.036 mmol, 1.0 eq) was dissolved in tetrahydrofuran (1 mL) and
 methanol (1 mL). Potassium carbonate (25 mg, 0.18 mmol, 5.0 eq) and water
 (0.5 mL) were added at room temperature, and the mixture was stirred at room
 10 temperature for 4 hours. The reaction was monitored by TLC (petroleum ether:
 ethyl acetate = 4:1). After the reaction was completed, the mixture was diluted
 with water (10 mL) and extracted with ethyl acetate (10 mL $\times$ 2). The organic
 phase was washed with saturated brine (20 mL), dried over anhydrous sodium
 sulfate, and concentrated. The residue was purified by silica gel column
 15 chromatography (petroleum ether: ethyl acetate = 2:1) to obtain
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-5-
 (hydroxycyclopropyl)pentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-
 cyclopenta[1,2-a]phenanthrene-6,7-diol **93** (2.79 mg, purity: 100%, yield:
 17.01%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 3.76 – 3.72 (m, 1H),
 20 3.64 – 3.57 (m, 1H), 2.45 – 2.25 (m, 1H), 2.22 – 2.07 (m, 1H), 2.02 – 1.95 (m,
 1H), 1.91 – 1.77 (m, 5H), 1.76 – 1.73 (m, 2H), 1.72 – 1.64 (m, 3H), 1.49 – 1.43
 (m, 3H), 1.42 – 1.36 (m, 4H), 1.33 – 1.28 (m, 3H), 1.14 – 1.09 (m, 2H), 1.06 (s,
 3H), 1.03 – 0.97 (m, 1H), 0.95 – 0.92 (m, 3H), 0.73 (t, $J = 5.4$ Hz, 2H), 0.67 (s,
 3H), 0.44 (t, $J = 5.4$ Hz, 2H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.95 (d, $J = 235.7$
 25 Hz, 1F), -110.94 (d, $J = 235.7$ Hz, 1F).

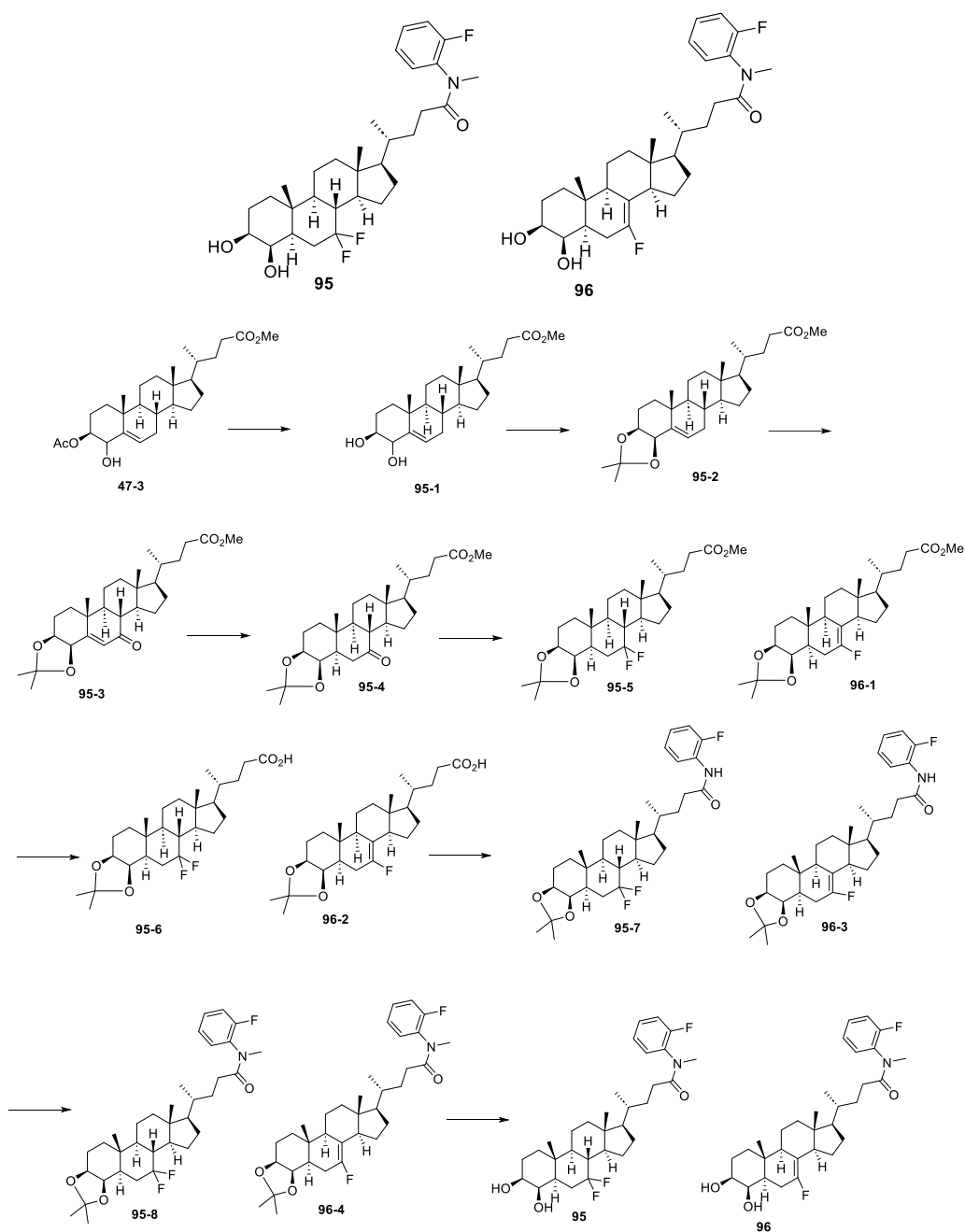
[0395] Examples **95** & **96**

[0396] Preparation of compound **95 (4R)-4-**

[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-
 30 **dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-(2-**
fluorophenyl)-N-methylpentanamide and

[0397] compound **96** (4R)-4-[(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-6,7-dihydroxy-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-(2-fluorophenyl)-N-methylpentanamide

5



[0398] Step 1: Reactant methyl (4R)-4-((3S,8S,9S,10R,13R,14S,17R)-3-acetoxy-4-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-

tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate **47-3** (4.5 g, 10.08 mmol, 1.0 eq) was dissolved in methanol (50 mL). Potassium carbonate (6.95 g, 50.38 mmol, 5.0 eq) was added, and the reaction system was stirred at room temperature for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (80 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 80 mL). The ethyl acetate layer 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 = 77:23 to 75:25) to obtain methyl (4R)-4-((3S,8S,9S,10R,13R,14S,17R)-3,4-dihydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate **95-1** (4.0 g, 9.89 mmol, purity: 80%, yield: 78.5%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.68 (d, *J* = 3.7 Hz, 1H), 4.14 (d, *J* = 3.3 Hz, 1H), 3.66 (s, 3H), 3.56 (d, *J* = 11.5 Hz, 1H), 2.39 – 2.18 (m, 3H), 2.13 – 1.96 (m, 3H), 1.91 – 1.77 (m, 4H), 1.68 – 1.52 (m, 5H), 1.45 (ddd, *J* = 15.1, 10.6, 4.8 Hz, 3H), 1.30 (dd, *J* = 19.1, 9.5 Hz, 3H), 1.18 (s, 3H), 1.09 (d, *J* = 9.3 Hz, 4H), 0.92 (d, *J* = 6.4 Hz, 4H), 0.68 (s, 3H).

[0399] Step 2: Reactant methyl (4R)-4-((3S,8S,9S,10R,13R,14S,17R)-3,4-dihydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate **95-1** (3.95 g, 9.76 mmol, 1 eq) was dissolved in acetone (60 mL). *p*-Toluenesulfonic acid (1.18 g, 6.83 mmol, 0.7 eq) and 4A molecular sieves were added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 10:1). The reaction was quenched with saturated sodium sulfite to stop the reaction. 20 mL of water was added to the reaction system, and the mixture was extracted with ethyl acetate (25 mL × 3). The organic phases were collected, dried over anhydrous sodium sulfate, and rotary evaporated to dryness under vacuum to obtain a crude product. The crude product was dissolved in ethyl acetate and purified by column chromatography

(petroleum ether: ethyl acetate = 95:5) to obtain methyl (R)-4-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetracontahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)pentanoate **95-2** (3.5 g, 7.87 mmol, purity: 90%, yield: 72.6%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.80 (d, *J* = 2.7 Hz, 1H), 4.41 (d, *J* = 5.8 Hz, 1H), 4.15 (s, 1H), 3.66 (s, 3H), 2.43 – 2.10 (m, 3H), 1.99 (s, 1H), 1.67 – 1.58 (m, 4H), 1.53 (s, 3H), 1.35 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 13H), 1.16 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.69 (s, 3H).

[0400] Step 3: Compound methyl (R)-4-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetracontahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)pentanoate **95-2** (3.4 g, 7.61 mmol, 1.0 eq) was dissolved in acetone (50 mL). N-Hydroxyphthalimide (0.99 g, 6.12 mmol, 0.8 eq), *tert*-butyl hydroperoxide (11 mL, 61.88 mmol, 8.0 eq), and anhydrous cobalt(II) acetate (0.27 g, 1.52 mmol, 0.2 eq) were added. The resulting mixture was stirred under N₂ at 25°C for 36 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 10:1). After the starting material was basically consumed, the reaction was quenched with saturated sodium sulfite. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, washed with saturated brine (15 mL), 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 = 87:13) to obtain methyl (R)-4-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-3a,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetrahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)pentanoate **95-3** (0.9 g, 1.96 mmol, purity: 90%, yield: 23.2%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.93 (s, 1H), 4.53 (d, *J* = 6.4 Hz, 1H), 4.33 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.67 (d, *J* = 5.3 Hz, 3H), 2.36 (ddd, *J* = 15.3, 10.0, 5.1 Hz, 3H), 2.28 – 2.18 (m, 1H), 1.88 (dddd, *J* = 16.7, 10.3, 9.6, 3.8 Hz, 5H), 1.59 – 1.55 (m, 4H), 1.50 – 1.42 (m, 2H),

1.33 (s, 5H), 1.18 – 1.06 (m, 2H), 0.94 (t, $J = 7.6$ Hz, 3H), 0.72 (d, $J = 10.0$ Hz, 3H).

[0401] Step 4: Compound methyl (R)-4-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-2,2,5a,7a-tetramethyl-11-oxo-5 3a,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12b-tetrahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)pentanoate **95-3** (2.4 g, 5.1 mmol, 1.0 eq) was dissolved in methanol (100 mL) and ethyl acetate (50 mL). Palladium on carbon (1.2 g, 11 mmol, 2.2 eq) was then added, and the reaction system was purged with hydrogen. The reaction mixture was stirred at room 10 temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. The reaction system was filtered, and the organic phase was collected and concentrated to obtain a crude product. The crude product was subjected to silica gel column chromatography (petroleum ether: ethyl acetate = 15 90:10) to obtain methyl (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl)pentanoate **95-4** (1.7 g, purity: 95%, yield: 67%) as a white solid.

[0402] ^1H NMR (400 MHz, CDCl_3) δ 4.07 – 4.00 (m, 1H), 4.00 – 3.95 (m, 1H), 20 3.66 (s, 3H), 2.81 – 2.70 (m, 1H), 2.46 – 2.32 (m, 3H), 2.26 – 2.17 (m, 4H), 1.98 – 1.74 (m, 5H), 1.65 (ddd, $J = 14.1, 6.7, 3.6$ Hz, 3H), 1.53 (s, 5H), 1.45 – 1.37 (m, 3H), 1.32 – 1.26 (m, 6H), 1.12 – 1.03 (m, 4H), 0.93 – 0.82 (m, 3H), 0.66 (s, 3H).

[0403] Step 5: Methyl (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-2,2,5a,7a-tetramethyl-11-oxo-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-25 hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl)pentanoate **95-4** (400 mg, 0.87 mmol) was dissolved in diethylaminosulfur trifluoride (5 mL). The resulting mixture was stirred at 80°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the starting material was completely consumed and a less polar spot 30 appeared, the reaction mixture was cooled to room temperature. Dichloromethane (50 mL) was added to dilute the reaction system, and ice water

was carefully added dropwise to quench the reaction. The organic phase was separated, and the aqueous layer was extracted with dichloromethane (3×30 mL). The organic phases were combined, washed with saturated brine (40 mL), filtered, and concentrated to obtain a crude product. The crude product was added with

5 silica gel and purified by column chromatography (petroleum ether: ethyl acetate = 93:7) to obtain a mixture of methyl (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]pentanoate **95-5** and

10 methyl (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]pentanoate **96-1** (300 mg, 0.62 mmol, purity: 90%, yield based on **95-5**: 64.3%) as a colorless transparent solid.

15 **[0404] Compound 95-5:** ^1H NMR (400 MHz, CDCl_3) δ 4.15 – 3.95 (m, 2H), 3.66 (s, 3H), 2.29 (dddd, $J = 21.8, 15.6, 9.8, 5.8$ Hz, 2H), 2.06 – 1.78 (m, 7H), 1.72 – 1.59 (m, 3H), 1.55 (s, 3H), 1.51 (s, 3H), 1.43 (ddd, $J = 20.7, 13.3, 5.9$ Hz, 3H), 1.34 – 1.25 (m, 8H), 1.14 – 1.05 (m, 4H), 0.93 (t, $J = 5.8$ Hz, 3H), 0.66 (d, $J = 12.0$ Hz, 3H).

20 **[0405] Step 6:** A mixture of methyl (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]pentanoate **95-5** and

25 methyl (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]pentanoate **96-1** (100 mg, 0.21 mmol) was dissolved in tetrahydrofuran (1 mL). 1 mol/L lithium hydroxide solution (0.5 mL) was added, and the resulting mixture was stirred at 25°C for 16 hours. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 1:1). After the starting material was completely consumed, the

30 reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated

brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 60:40) to obtain a mixture of (4R)-4-
 5 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]pentanoic acid **95-6** and (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-
 10 cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]pentanoic acid **96-2** (65 mg, 0.14 mmol, purity: 90%, yield based on **95-6**: 59.4%) as a white solid.

[0406] Compound 95-6: ¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H), 4.02 (s, 2H), 2.34 (ddd, J = 25.4, 17.2, 9.7 Hz, 2H), 1.99 (s, 2H), 1.96 – 1.57 (m, 8H), 1.51 (s, 3H), 1.40 (dd, J = 34.3, 11.9 Hz, 6H), 1.30 (s, 3H), 1.26 (s, 3H), 1.08 (t, J =
 15 16.2 Hz, 4H), 0.90 (dd, J = 28.7, 9.1 Hz, 5H), 0.69 (s, 3H).

[0407] Step 7: A mixture of (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]pentanoic acid **95-6** and
 20 (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]pentanoic acid **96-2** (50 mg, 0.11 mmol, 1.0 eq) was dissolved in DMF (3 mL), followed by sequential addition of HATU (2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium
 25 hexafluorophosphate) (50 mg, 0.13 mmol, 1.2 eq) and N,N-diisopropylethylamine (28 mg, 0.22 mmol, 2.0 eq). The mixture was stirred at room temperature for about 15 minutes, and then 2-fluoroaniline (12 mg, 0.11 mmol, 1.0 eq) was added. The mixture was stirred at room temperature for 2 hours, and the reaction was monitored by TLC (petroleum ether: ethyl acetate =
 30 5:1). After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed twice

with saturated brine, dried over anhydrous sodium sulfate, and purified by silica gel column chromatography (petroleum ether: ethyl acetate = 60:40) to obtain a mixture of (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)pentanamide **95-7** and (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)pentanamide **96-3** (30 mg, 0.053 mmol, purity: 90%, yield based on **95-7**: 48.2%). LC-MS: $[M+H]^+ = 562.3$.

[0408] Step 8: A mixture of starting materials (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)pentanamide **95-7** and (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)pentanamide **96-3** (30 mg, 0.053 mmol, 1.0 eq) was dissolved in DMF (2 mL), and the reaction system was purged with nitrogen. After the reaction system was cooled to 0°C, sodium hydride (60%, in paraffin) (2.26 mg, 0.056 mmol, 1.3 eq) was slowly added. The reaction was then stirred at room temperature for 30 minutes, followed by addition of iodomethane (8.00 mg, 0.056 mmol, 1.3 eq). The reaction system was stirred at room temperature for 2 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion, and the reaction was stopped. Water (10 mL) was added to the system for dilution, and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by flash chromatography (petroleum

ether: ethyl acetate = 90:10 to 80:20) to obtain a mixture of (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)-N-methylpentanamide **95-8** and (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)-N-methylpentanamide **96-4** (25 mg, purity: 90%, yield based on **95-8**: 90.3%) as a white solid. LC-MS: $[M+H]^+ = 576.4$.

[0409] Step 8: A mixture of reactants (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)-N-methylpentanamide **95-8** and (4R)-4-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-N-(2-fluorophenyl)-N-methylpentanamide **96-4** (25 mg, 0.043 mmol, 1.0 eq) was dissolved in tetrahydrofuran (1 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour.

The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 70:30) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: REGIS CHIRAL (S,S)-Whelk-O1 4.6 × 150 mm, 3.5 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (4R)-4-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-

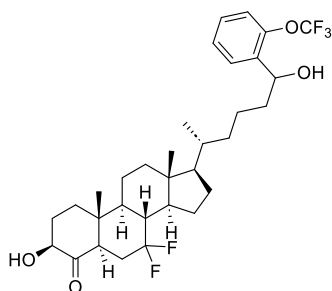
6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-(2-fluorophenyl)-N-methylpentanamide **95** (6.60 mg, purity: 100%, yield: 29%, retention time t_R = 2.907 min) and (4R)-4-[(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-6,7-dihydroxy-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-N-(2-fluorophenyl)-N-methylpentanamide **96** (0.68 mg, purity: 97%, yield: 3%, retention time t_R = 3.328 min).

[0410] Compound **95**: ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, J = 13.9, 6.3 Hz, 1H), 7.26 – 7.14 (m, 3H), 3.73 (s, 1H), 3.58 (dd, J = 11.4, 3.6 Hz, 1H), 3.22 (s, 3H), 2.26 – 2.05 (m, 2H), 2.02 – 1.89 (m, 2H), 1.89 – 1.75 (m, 6H), 1.72 – 1.60 (m, 4H), 1.45 – 1.30 (m, 4H), 1.25 (s, 3H), 1.04 (s, 3H), 1.00 – 0.86 (m, 3H), 0.72 (d, J = 5.5 Hz, 3H), 0.60 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -89.00 (d, J = 235.7 Hz, 1F), -110.96 (d, J = 236.0 Hz, 1F), -121.27 (d, J = 11.7 Hz, 1F).

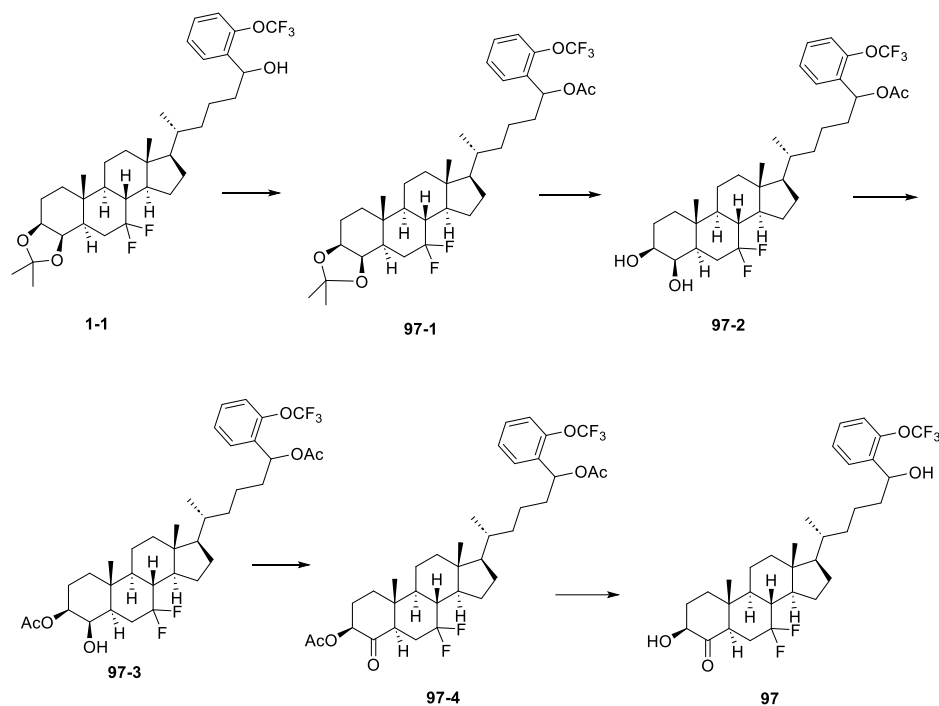
[0411] Compound **96**: ^1H NMR (400 MHz, CDCl_3) δ 7.36 (s, 1H), 7.20 (d, J = 7.4 Hz, 3H), 3.84 (s, 1H), 3.60 (s, 1H), 3.22 (s, 3H), 2.65 (s, 1H), 2.11 (s, 1H), 2.07 (s, 1H), 1.96 (s, 3H), 1.82 (s, 3H), 1.75 (s, 4H), 1.43 (s, 5H), 1.08 (d, J = 13.2 Hz, 2H), 1.02 (s, 3H), 0.88 (s, 4H), 0.73 (d, J = 5.7 Hz, 3H), 0.57 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -109.72 (s, 1F), -121.29 (s, 1F).

[0412] Example **97**

[0413] Preparation of compound **97** (**1R,3aS,3bS,5aR,7S,9aR,9bS,11aR**)-4,4-difluoro-7-hydroxy-1-[(2R)-6-hydroxy-6-{2-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one



97



- [0414]** Step 1: (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-11,11-Difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexan-1-ol **1-1** (220 mg, 0.35 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL). The reaction system was cooled to about 5°C in an ice-water bath, followed by sequential addition of acetic anhydride (0.1 mL, 1 mmol, 3.0 eq), 4-dimethylaminopyridine (8.55 mg, 0.07 mmol, 0.2 eq), and triethylamine (0.15 mL, 1 mmol, 3.0 eq). The reaction system was stirred at room temperature for 1 hour. After the reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion, the reaction mixture was washed with water (10 mL × 2) and saturated sodium bicarbonate (10 mL × 2). The aqueous phase was extracted with dichloromethane (10 mL × 2), and the organic phases were collected and concentrated under vacuum to obtain a crude product. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 92:8) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{2-

[(trifluoromethyl)oxy]phenyl}hexyl acetate **97-1** (190 mg, purity: 95%, yield: 72%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 7.7 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.23 (s, 1H), 6.08 – 6.00 (m, 1H), 4.05 – 3.98 (m, 2H), 2.13 (dd, J = 15.2, 5.1 Hz, 1H), 1.96 (dd, J = 12.6, 3.5 Hz, 2H), 1.87 – 1.55 (m, 13H),
 5 1.51 (s, 3H), 1.45 – 1.32 (m, 6H), 1.30 (s, 3H), 1.29 – 1.21 (m, 4H), 1.12 (dd, J = 12.9, 3.9 Hz, 2H), 1.07 (s, 4H), 1.04 – 0.90 (m, 4H), 0.87 (dd, J = 6.3, 4.3 Hz, 3H), 0.69 – 0.63 (m, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -56.48, -89.01, -89.64, -111.37, -112.00.

[0415] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12bR)-
 10 11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexyl acetate **97-1** (190 mg, 0.28 mmol, 1.0 eq) was dissolved in tetrahydrofuran (5 mL). Dilute hydrochloric acid (1.5 mL, 3
 15 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate
 20 layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 70:30) to obtain (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-{2-
 25 [(trifluoromethyl)oxy]phenyl}hexyl acetate **97-2** (180 mg, purity: 99%, yield: 90%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 7.3 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 6.08 – 5.98 (m, 1H), 3.74 (s, 1H), 3.60 (dd, J = 7.1, 4.0 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 2H), 1.96 (d, J = 12.8 Hz, 1H),
 30 1.89 – 1.55 (m, 13H), 1.49 – 1.29 (m, 9H), 1.16 – 1.08 (m, 2H), 1.05 (s, 4H), 0.95 (ddd, J = 12.4, 11.2, 2.5 Hz, 3H), 0.87 (dd, J = 6.3, 4.5 Hz, 3H), 0.67 – 0.61 (m,

3H).

[0416] Step 3: (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexyl acetate **97-2** (180 mg, 0.28 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL). The reaction system was placed in an ice-water bath, followed by sequential addition of acetic anhydride (0.04 mL, 0.34 mmol, 1.2 eq), 4-dimethylaminopyridine (6.97 mg, 0.06 mmol, 0.2 eq), and triethylamine (0.12 mL, 1 mmol, 3.0 eq). The reaction system was stirred at room temperature for 1 hour. After the reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion, the reaction mixture was washed with water (10 mL × 2) and saturated sodium bicarbonate (10 mL × 2). The aqueous phase was extracted with dichloromethane (10 mL × 2), and the organic phases were collected and concentrated under vacuum to obtain a crude product. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-6-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexyl acetate **97-3** (150 mg, purity: 95%, yield: 74%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 7.7 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.23 (s, 1H), 6.08 – 6.00 (m, 1H), 4.05 – 3.98 (m, 2H), 2.13 (dd, J = 15.2, 5.1 Hz, 1H), 1.96 (dd, J = 12.6, 3.5 Hz, 2H), 1.87 – 1.55 (m, 13H), 1.51 (s, 3H), 1.45 – 1.32 (m, 6H), 1.30 (s, 3H), 1.29 – 1.21 (m, 4H), 1.12 (dd, J = 12.9, 3.9 Hz, 2H), 1.07 (s, 4H), 1.04 – 0.90 (m, 4H), 0.87 (dd, J = 6.3, 4.3 Hz, 3H), 0.69 – 0.63 (m, 3H).

[0417] Step 4: Compound (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-6-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexyl acetate **97-3** (140 mg, 0.2 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL). Dess-Martin periodinane (176 g, 0.4 mmol, 2 eq) was added, and the resulting mixture was stirred under N₂ at 25°C for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the starting

material was basically consumed, saturated sodium bicarbonate (10 mL) was added to the reaction system. The organic phase was extracted with saturated sodium sulfite (3×10 mL), and the organic phase was collected and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 92:8) to obtain (5R)-5-[(1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-9a,11a-dimethyl-6-oxohexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexyl acetate **97-4** (150 mg, purity: 90%, yield: 96%) as a white solid. ^1H NMR (400MHz, CDCl_3) δ 7.43 (d, $J = 7.0$ Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 6.07 – 6.00 (m, 1H), 5.18 (dd, $J = 12.2, 7.4$ Hz, 1H), 2.53 (t, $J = 10.6$ Hz, 1H), 2.29 – 2.23 (m, 1H), 2.16 (d, $J = 2.8$ Hz, 3H), 2.08 (s, 3H), 2.03 – 1.78 (m, 8H), 1.60 (dd, $J = 23.4, 10.1$ Hz, 5H), 1.45 – 1.00 (m, 14H), 0.88 (dd, $J = 6.4, 3.8$ Hz, 3H), 0.79 (s, 3H), 0.66 – 0.60 (m, 3H).

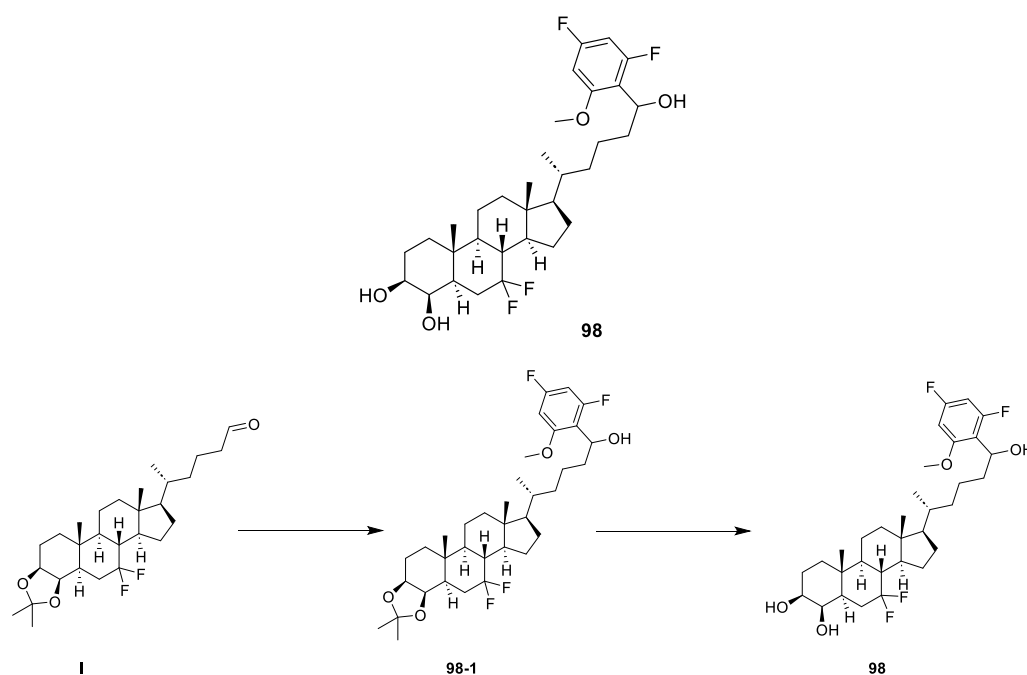
[0418] Step 5: Reactant (5R)-5-[(1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-7-acetoxy-4,4-difluoro-9a,11a-dimethyl-6-oxohexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-{2-[(trifluoromethyl)oxy]phenyl}hexyl acetate **97-4** (50 mg, 0.08 mmol, 1.0 eq) was dissolved in methanol (2 mL) and tetrahydrofuran (2 mL). Potassium carbonate (41 mg, 0.3 mmol, 4.0 eq) was added, and the reaction system was stirred at room temperature for 30 min. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 75:25) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0×150 mm, $3 \mu\text{m}$; mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-7-hydroxy-1-[(2R)-6-hydroxy-

6-{2-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one **97** (3.74 mg, purity: 99.64%, yield: 8.52%, retention time $t_R = 1.876$ min). ^1H NMR (400 MHz, CDCl_3) δ 7.62 – 7.56 (m, 1H), 7.35 – 7.28 (m, 2H), 7.24 – 7.19 (m, 1H), 5.11 – 5.03 (m, 1H), 4.15 (dd, $J = 11.0, 8.3$ Hz, 1H), 2.55 – 2.39 (m, 2H), 2.17 – 1.82 (m, 7H), 1.76 – 1.51 (m, 14H), 1.50 – 1.24 (m, 14H), 1.23 – 1.01 (m, 4H), 0.91 (dd, $J = 6.5, 3.8$ Hz, 3H), 0.76 (s, 3H), 0.66 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -56.78, -56.79, -56.81, -90.21, -90.85, -111.50, -112.14.

10 **[0419] Example 98**

[0420] Preparation of compound **98** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.

15



[0421] Step 1: Starting material 2-bromo-1,5-difluoro-3-methoxybenzene (123 mg, 0.5 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (0.18 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. Compound

20

(5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain the crude product of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4,6-difluoro-2-methoxyphenyl)hexan-1-ol **98-1** (70 mg) as a colorless oil, which was directly used in the next step.

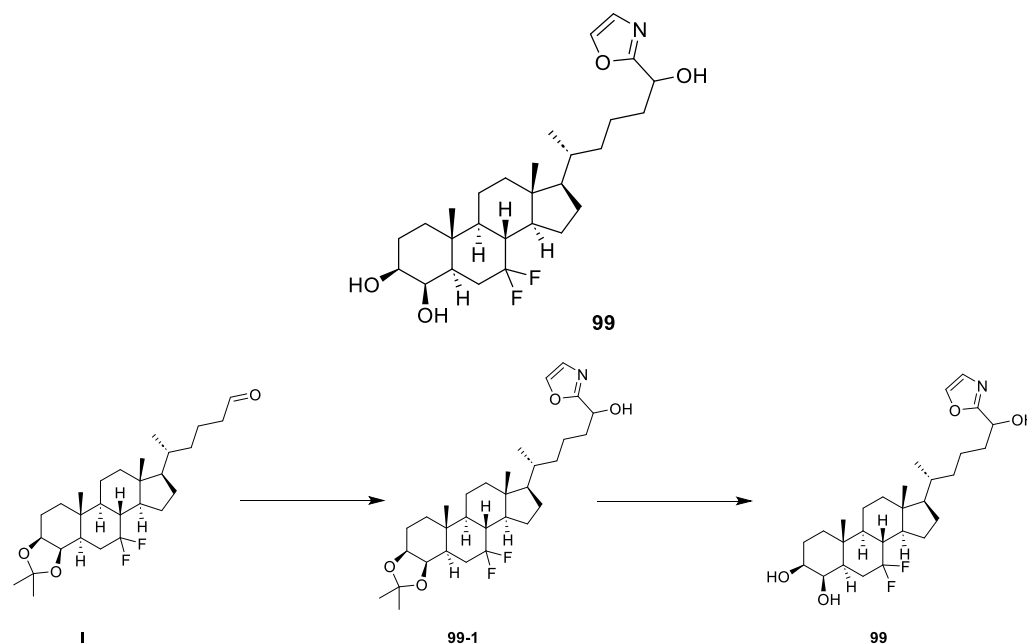
[0422] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4,6-difluoro-2-methoxyphenyl)hexan-1-ol (70 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1%

DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **98** (21.58 mg, purity: 100%, yield: 32.99%, retention time t_R = 1.486 min).

[0423] Compound **98**: ^1H NMR (400 MHz, CDCl_3) δ 6.44 (dd, J = 9.6, 8.0 Hz, 2H), 4.98 – 4.92 (m, 1H), 3.82 (d, J = 33.4 Hz, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.1 Hz, 1H), 2.30 – 2.11 (m, 2H), 1.97 (d, J = 12.6 Hz, 2H), 1.83 – 1.77 (m, 3H), 1.69 (ddd, J = 20.3, 13.9, 9.8 Hz, 5H), 1.46 – 1.24 (m, 10H), 1.11 (dd, J = 12.7, 4.3 Hz, 2H), 1.06 (s, 4H), 1.02 – 0.91 (m, 2H), 0.90 – 0.85 (m, 3H), 0.65 (d, J = 3.7 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.63, -89.25, -110.39, -110.41, -110.43, -110.62, -111.25, -113.84, -113.86, -113.91, -113.93, -114.31, -114.38.

[0424] Example 99

[0425] Preparation of compound **99** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(1,3-oxazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0426] **Step 1:** Starting material 1,3-oxazole (51.8 mg, 0.75 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C,

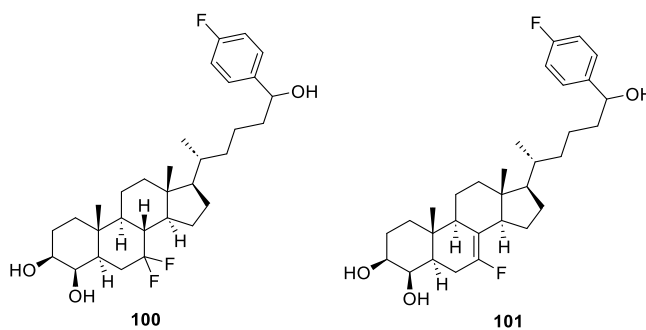
and *n*-butyllithium (0.25 mL, 0.64 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3a*S*,5a*R*,5b*S*,7a*R*,8*R*,10a*S*,10b*S*,12a*R*,12b*R*)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-*d*][1,3]dioxol-8-yl]hexanal **1** (100 mg, 0.21 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain the crude product of (5R)-5-[(3a*S*,5a*R*,5b*S*,7a*R*,8*R*,10a*S*,10b*S*,12a*R*,12b*R*)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-*d*][1,3]dioxol-8-yl]-1-(1,3-oxazol-2-yl)hexan-1-ol **99-1** (70 mg) as a colorless oil, which was directly used in the next step.

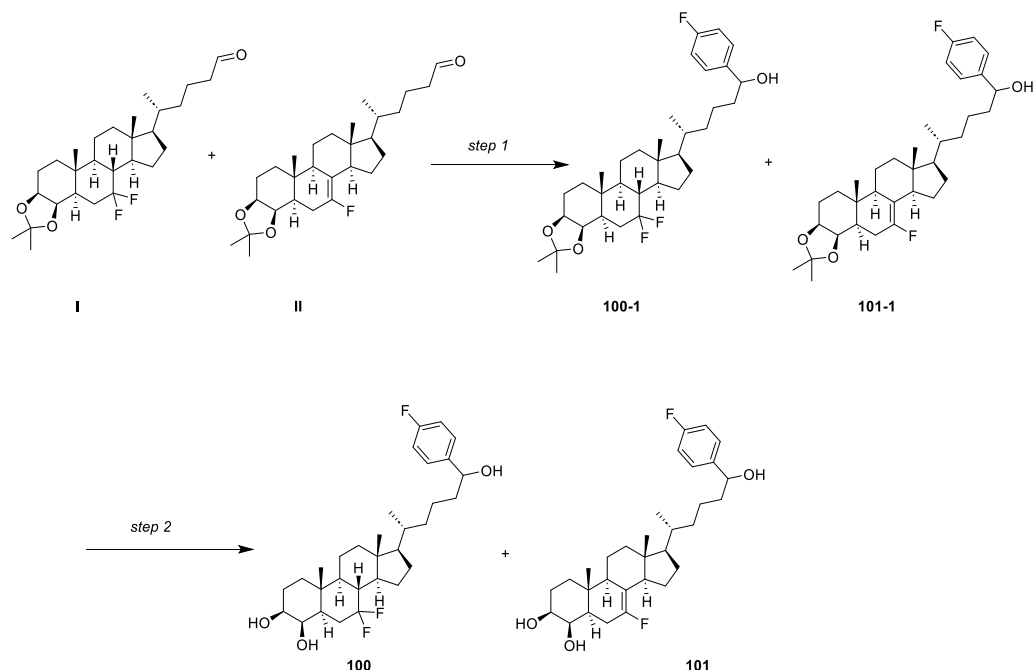
[0427] Step 2: Reactant (5R)-5-[(3a*S*,5a*R*,5b*S*,7a*R*,8*R*,10a*S*,10b*S*,12a*R*,12b*R*)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-*d*][1,3]dioxol-8-yl]-1-(1,3-oxazol-2-yl)hexan-1-ol **99-1** (70 mg, 0.1 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution

(instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(1,3-oxazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **99** (8.64 mg, purity: 94.39%, yield: 22.04%, retention time t_R = 1.684 min). ¹H NMR (400 MHz, DMSO) δ 8.25 (s, 1H), 7.85 (d, J = 2.6 Hz, 1H), 5.11 (dd, J = 5.2, 1.2 Hz, 1H), 4.46 (s, 1H), 4.40 (d, J = 6.0 Hz, 1H), 4.24 (d, J = 3.4 Hz, 1H), 3.49 (d, J = 2.2 Hz, 1H), 3.36 (s, 1H), 2.19 – 1.86 (m, 3H), 1.65 (ddd, J = 31.6, 22.1, 14.8 Hz, 9H), 1.43 (d, J = 9.8 Hz, 3H), 1.35 – 1.22 (m, 8H), 1.05 (t, J = 10.9 Hz, 3H), 0.98 (s, 3H), 0.87 (d, J = 5.8 Hz, 3H), 0.62 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -86.66, -87.28, -108.65, -109.27. LC-MS: [M+1]⁺ = 496.3.

[0428] Examples 100 & 101

[0429] Preparation of compound **100** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and **[0430]** compound **101** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(4-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





- [0431] Step 1:** Starting material 4-bromo-1-fluorobenzene (65.7 mg, 0.35 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (0.128 mL, 0.3 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (50 mg, 0.1 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating) until the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain the crude product of (5R)-5-

[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluorophenyl)hexan-1-ol **100-1** and (5R)-5-
 5 [(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(4-fluorophenyl)hexan-1-ol **101-1** (70 mg) as a colorless oil, which was directly used in the next step.

10 **[0432] Step 2:** The crude product of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluorophenyl)hexan-1-ol **100-1** and (5R)-5-
 15 [(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(4-fluorophenyl)hexan-1-ol **101-1** (70 mg, 0.09 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1.5 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction
 20 progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed
 25 with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel
 30 CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 65/35; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain

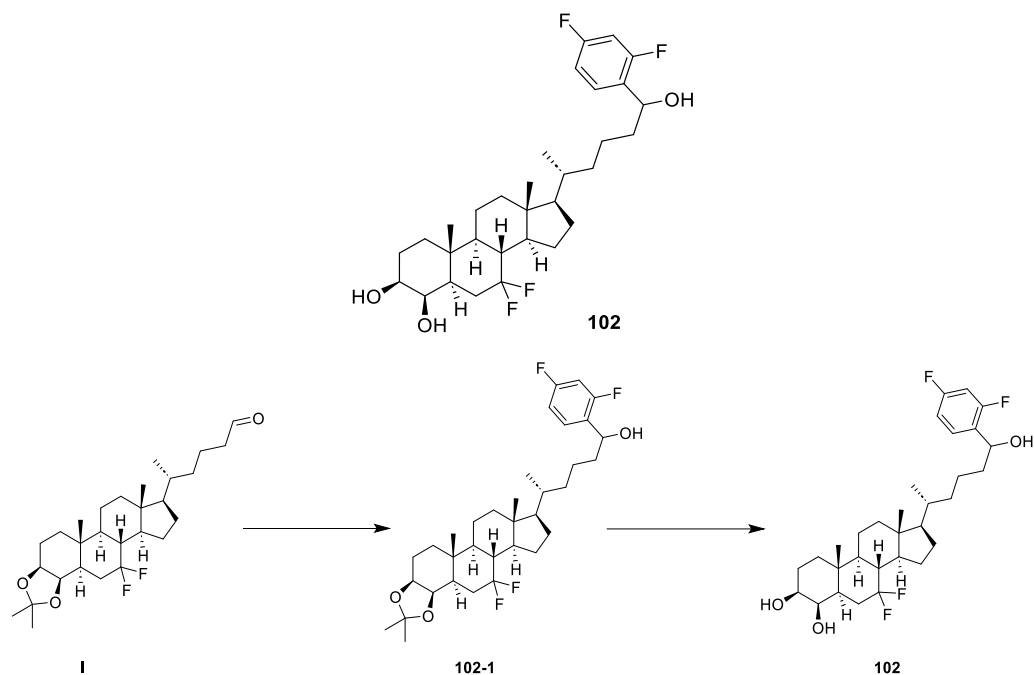
(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **100** (19.06 mg, purity: 99.68%, yield: 40.91%; retention time t_R = 1.154 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(4-fluorophenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **101** (1.72 mg, purity: 100%, yield: 3.85%; retention time t_R = 1.718 min).

[0433] Compound **100**: ^1H NMR (400 MHz, CDCl_3) δ 7.31 (dd, J = 8.6, 5.5 Hz, 2H), 7.03 (t, J = 8.7 Hz, 2H), 4.65 (dd, J = 12.6, 5.7 Hz, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.4, 4.3 Hz, 1H), 2.32 – 2.14 (m, 1H), 1.96 (d, J = 12.9 Hz, 1H), 1.89 – 1.77 (m, 5H), 1.76 – 1.58 (m, 10H), 1.46 – 1.36 (m, 5H), 1.14 – 1.07 (m, 2H), 1.06 (s, 3H), 0.98 (dd, J = 16.9, 5.9 Hz, 2H), 0.88 (t, J = 6.3 Hz, 3H), 0.65 (d, J = 2.2 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.64, -89.27, -110.63, -111.26, -115.21, -115.27.

[0434] Compound **101**: ^1H NMR (400 MHz, CDCl_3) δ 7.31 (s, 2H), 7.03 (s, 2H), 4.66 (dd, J = 12.7, 5.7 Hz, 1H), 3.85 (s, 1H), 3.62 – 3.56 (m, 1H), 2.66 (t, J = 12.5 Hz, 1H), 2.05 – 1.97 (m, 2H), 1.84 (s, 12H), 1.45 (dd, J = 12.4, 3.8 Hz, 7H), 1.33 – 1.24 (m, 10H), 1.07 (d, J = 8.8 Hz, 3H), 1.04 (s, 3H), 0.91 – 0.87 (m, 3H), 0.62 (d, J = 2.3 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -109.78, -115.21, -115.28.

[0435] Example **102**

[0436] Preparation of compound **102** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,4-difluorophenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0437] Step 1: Starting material 1-bromo-2,4-difluorobenzene (101 mg, 0.5 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (0.18 mL, 0.45 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion. Water (10 mL) was added to the reaction system, followed by extraction with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain the crude product of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4-difluorophenyl)hexan-1-ol **102-1** (70 mg) as a colorless oil, which was directly

used in the next step.

[0438] Step 2: Reactant (5R)-5-

[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-

tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-

5 **cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4-**

difluorophenyl)hexan-1-ol **102-1 (70 mg, 0.12 mmol, 1.0 eq) was dissolved in**

tetrahydrofuran (3 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added.

The reaction system was stirred at room temperature for 1 hour. The reaction

was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion.

10 Water (10 mL) was added to the reaction system, and the aqueous layer was

extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were

combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer

was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a

crude product. The crude product was purified by column chromatography

15 (petroleum ether: ethyl acetate = 65:35) to obtain a white solid, which was then

subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel

CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1%

DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,4-difluorophenyl)-6-

20 hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-

cyclopenta[1,2-a]phenanthrene-6,7-diol **102** (24.38 mg, purity: 100%, yield:

37.41%, retention time *t_R* = 1.306 min).

[0439] Compound **102:** ¹H NMR (400 MHz, , CDCl₃) δ 7.20 (td, *J* = 8.4, 4.2

Hz, 1H), 6.91 – 6.83 (m, 2H), 5.03 (t, *J* = 7.0 Hz, 1H), 3.74 (s, 1H), 3.60 (dt, *J* =

25 11.4, 4.2 Hz, 1H), 2.30 – 2.07 (m, 2H), 1.96 (d, *J* = 12.9 Hz, 2H), 1.82 (dd, *J* =

21.0, 13.2 Hz, 5H), 1.68 (ddd, *J* = 14.8, 7.5, 3.5 Hz, 4H), 1.39 (ddd, *J* = 36.8, 16.8,

8.5 Hz, 8H), 1.11 (dd, *J* = 13.3, 4.9 Hz, 3H), 1.05 (s, 3H), 0.98 (dd, *J* = 17.1, 6.1

Hz, 2H), 0.89 (t, *J* = 6.0 Hz, 3H), 0.65 (d, *J* = 3.7 Hz, 3H). ¹⁹F NMR (377 MHz,

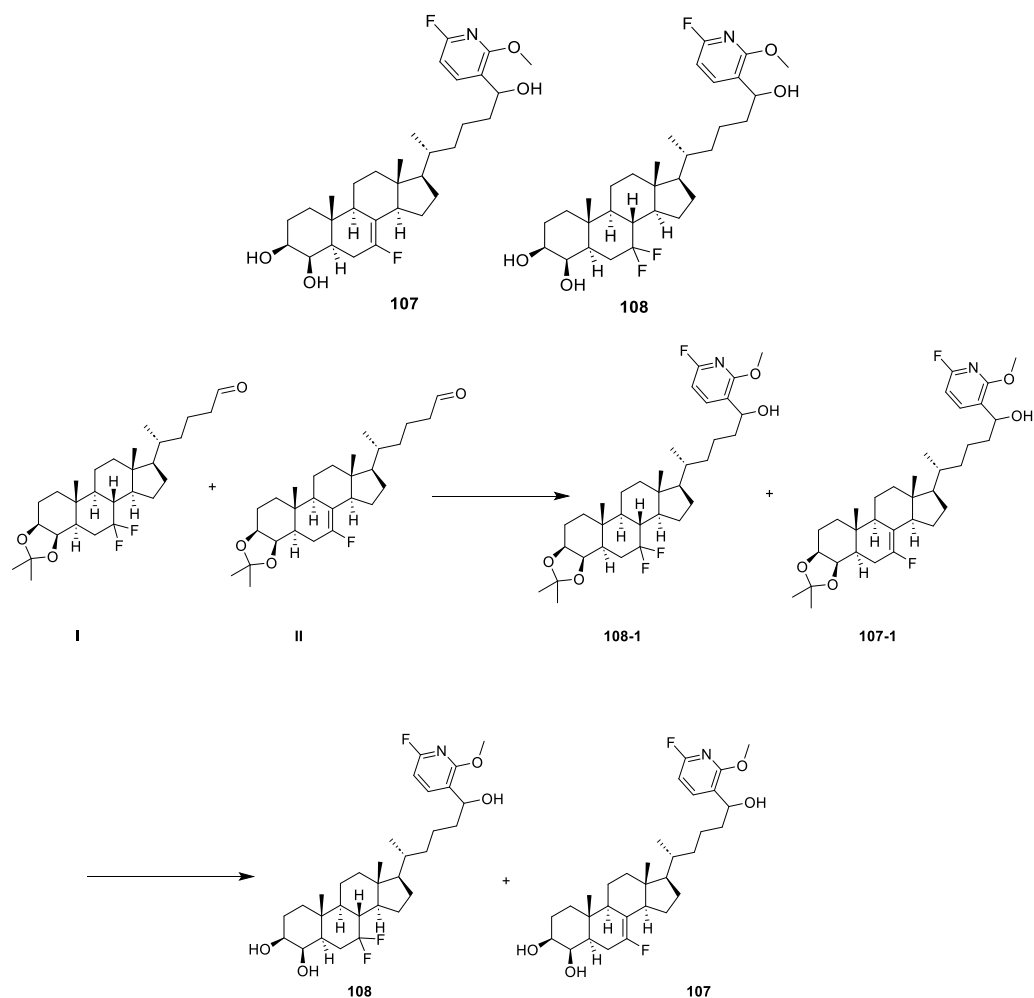
CDCl₃) δ -88.64, -89.27, -110.63, -111.26, -115.39, -115.46.

30

[0440] Examples **107 & 108**

[0441] Preparation of compound **107** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

- 5 [0442] compound **108** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



- 10 [0443] **Step 1:** Starting material 3-bromo-6-fluoro-2-methoxypyridine (123.61 mg, 0.6 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (0.2 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-

tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (80 mg, 0.17 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 87:13) to obtain a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(6-fluoro-2-methoxypyridin-3-yl)hexan-1-ol **108-1** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(6-fluoro-2-methoxypyridin-3-yl)hexan-1-ol **107-1** (60 mg, purity: 95%, yield based on **108-1**: 56%) as a white solid.

[0444] Compound 108-1: ¹H NMR (400 MHz, CDCl₃) δ 7.70 (td, J = 8.0, 4.1 Hz, 1H), 6.48 (dd, J = 7.9, 2.6 Hz, 1H), 4.82 (dd, J = 13.1, 7.5 Hz, 1H), 4.05 – 3.98 (m, 3H), 3.96 (s, 3H), 2.21 – 2.09 (m, 1H), 1.96 (dd, J = 14.7, 7.9 Hz, 2H), 1.89 – 1.55 (m, 17H), 1.51 (s, 4H), 1.44 – 1.34 (m, 6H), 1.30 (s, 3H), 1.29 – 1.24 (m, 5H), 1.13 (dd, J = 13.1, 4.2 Hz, 2H), 1.07 (s, 3H), 0.95 (dd, J = 16.5, 7.6 Hz, 2H), 0.90 (dd, J = 6.3, 3.2 Hz, 4H), 0.67 (s, 3H).

[0445] Step 2: A mixture of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-

tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(6-fluoro-2-methoxypyridin-3-yl)hexan-1-ol **108-1** and (5R)-5-((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(6-fluoro-2-methoxypyridin-3-yl)hexan-1-ol **107-1** (60 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1.5 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **108** (29.91 mg, purity: 90.01%, yield: 48.12%, SFC retention time t_R = 1.496 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **107** (2.63 mg, purity: 85.01%, yield: 4.15%, SFC retention time t_R = 2.090 min).

[0446] Compound **108**: ¹H NMR (400 MHz, DMSO) δ 7.87 (t, J = 7.8 Hz, 1H), 6.69 (dd, J = 7.9, 2.4 Hz, 1H), 5.16 (d, J = 4.9 Hz, 1H), 4.71 (s, 1H), 4.41 (d, J =

5.9 Hz, 1H), 4.26 (d, J = 3.2 Hz, 1H), 3.84 (s, 3H), 3.49 (s, 1H), 3.31 – 3.29 (m, 1H), 2.13 (s, 1H), 1.97 (dd, J = 47.3, 14.9 Hz, 2H), 1.73 – 1.54 (m, 6H), 1.42 (d, J = 10.3 Hz, 4H), 1.36 – 1.22 (m, 9H), 1.03 (d, J = 10.9 Hz, 3H), 0.98 (s, 3H), 0.94 (s, 1H), 0.86 (d, J = 6.3 Hz, 3H), 0.62 (s, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -74.51, -74.61, -86.66, -87.28, -108.65, -109.27. LC-MS: [M+H]⁺ = 554.35

5 [0447] Compound **107**: ¹H NMR (400 MHz, DMSO) δ 7.85 (t, J = 7.8 Hz, 1H), 6.68 (dd, J = 8.0, 2.5 Hz, 1H), 5.13 (s, 1H), 4.70 (s, 1H), 4.38 (s, 1H), 4.23 (s, 1H), 3.83 (s, 3H), 3.58 (s, 1H), 3.20 (s, 1H), 2.02 – 1.91 (m, 3H), 1.80 – 1.54 (m, 10H), 1.37 (d, J = 11.7 Hz, 6H), 1.13 – 0.96 (m, 6H), 0.94 (s, 3H), 0.85 (d, J = 6.3

10 Hz, 3H), 0.56 (d, J = 1.9 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -74.51, -108.66. LC-MS: [M+H-H₂O]⁺ = 516.35.

[0448] Examples **110 & 111 & 112 & 113**

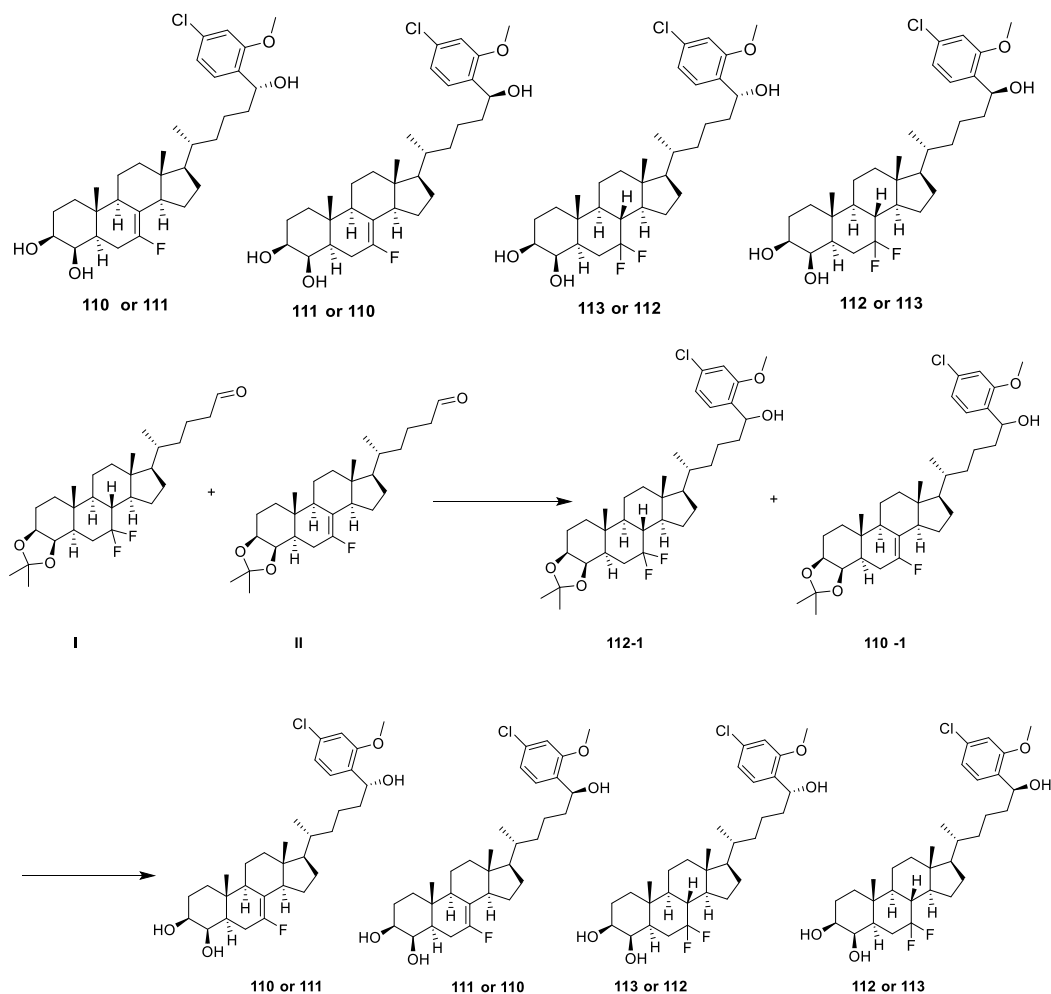
[0449] Preparation of compound **110** or **111**:

15 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R,6R)-6-(4-chloro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol;

[0450] compound **111** or **110**: (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R,6S)-6-(4-chloro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol;

20 [0451] compound **113** or **112**: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(4-chloro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol;

25 [0452] compound **112** or **113**: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(4-chloro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0453] Step 1: 2-Bromo-5-chloroanisole (116.28 mg, 0.525 mmol, 3.5 eq) was dissolved in tetrahydrofuran (5 mL). The reaction system was cooled to -78°C , and *n*-butyllithium (0.180 mL, 0.450 mmol, 2.5 mol/L, 3.0 eq) was added to the reaction system. After maintaining at -78°C for 30 min, a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.150 mmol, 1 eq) dissolved in tetrahydrofuran (1 mL) was added. After the addition was completed, nitrogen purging was performed three times, and the mixture was

stirred at -78°C for 30 min. After the reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1) until completion, the reaction was quenched with water (10 mL). The reaction mixture was washed with water (about 10 mL) three times, dried over anhydrous sodium sulfate, and concentrated to obtain a crude product. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 95:5 to 90:10) to obtain a mixture of (5R)-1-(4-chloro-2-methoxyphenyl)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **112-1** and (5R)-1-(4-chloro-2-methoxyphenyl)-5-(((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)hexan-1-ol **110-1** (65 mg, purity: 80.0%, yield based on **112-1**: 56.90%) as a white solid.

[0454] Compound 112-1: ¹H NMR (400MHz) δ 2.18 – 2.17 (m, 1H), 2.08 (dd, J = 2.4, 0.5Hz, 1H), 2.06 (s, 1H), 1.46 – 1.44 (m, 1H), 1.22 – 1.19 (m, 2H), 1.15 (d, J = 3.6Hz, 3H), 0.62 – 0.60 (m, 3H), 0.60 – 0.57 (m, 2H), 0.52 – 0.50 (m, 3H), 0.49 – 0.48 (m, 2H), 0.46 (d, J = 3.0Hz, 5H), 0.43 – 0.41 (m, 4H), 0.38 (dd, J = 2.7, 1.8Hz, 10H), 0.34 (dd, J = 3.3, 2.3Hz, 2H), 0.32 (d, J = 2.0Hz, 3H), 0.31 – 0.28 (m, 1H), 0.27 (dt, J = 3.7, 1.8Hz, 4H), 0.20 (dd, J = 3.5, 0.5Hz, 3H).

[0455] Step 2: A mixture of starting materials (5R)-1-(4-chloro-2-methoxyphenyl)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **112-1** and (5R)-1-(4-chloro-2-methoxyphenyl)-5-(((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)hexan-1-ol **110-1** (65 mg, 0.107 mmol, 1.0 eq) was dissolved in tetrahydrofuran (5 mL). Hydrochloric acid (1 mL, 3 mol/L) was slowly added dropwise, and nitrogen purging was performed three times. The mixture was stirred at room temperature for 1 hour.

The reaction was monitored by TLC (petroleum ether: ethyl acetate = 1:1), and a high-polarity spot appeared while the starting material spot disappeared. The reaction mixture was washed with saturated sodium bicarbonate solution (3 × 5 mL). The organic phases were combined, washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 90:10 to 80:20) to obtain a white solid. The white solid was separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK AD₃, 3 × 150mm, 3 μm; mobile phase: A/B: CO₂/EtOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain **112** (10.75 mg, purity: 98.85%, yield: 17.65%, retention time t_R = 1.487 min), **111** (1.43 mg, purity: 97.68%, yield: 2.38%, retention time t_R = 2.121 min), **113** (8.97 mg, purity: 95.13%, yield: 14.01%, retention time t_R = 1.698 min), **110** (2.26 mg, purity: 90.55%, yield: 3.48%, retention time t_R = 2.320 min).

[0456] Compound **112**: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (s, 1H), 6.94 (dd, J = 8.1, 1.9 Hz, 1H), 6.85 (d, J = 1.9 Hz, 1H), 4.85 (dd, J = 8.2, 5.1 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 1H), 3.63 – 3.57 (m, 1H), 2.29 – 2.14 (m, 1H), 2.08 – 1.94 (m, 2H), 1.91 – 1.80 (m, 4H), 1.77 – 1.69 (m, 5H), 1.49 (s, 1H), 1.44 (s, 1H), 1.42 – 1.36 (m, 5H), 1.33 (d, J = 14.1 Hz, 3H), 1.25 (s, 2H), 1.12 (s, 1H), 1.09 (s, 1H), 1.06 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63 (s, 1H), -89.26 (s, 1H), -110.62 (s, 1H), -111.25 (s, 1H).

[0457] Compound **111**: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (s, 1H), 6.94 (dd, J = 8.1, 1.9 Hz, 1H), 6.85 (d, J = 1.9 Hz, 1H), 4.86 (dd, J = 8.0, 5.0 Hz, 1H), 3.85 (s, 1H), 3.84 (s, 3H), 3.59 (d, J = 11.3 Hz, 1H), 2.64 (d, J = 13.1 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.85 (s, 4H), 1.74 (d, J = 13.3 Hz, 4H), 1.45 (d, J = 14.5 Hz, 4H), 1.39 (d, J = 8.2 Hz, 3H), 1.15 – 1.07 (m, 4H), 1.04 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.63 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -109.81 (s, 1H).

[0458] Compound **113**: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, J = 8.1 Hz, 1H), 6.94 (dd, J = 8.1, 1.9 Hz, 1H), 6.85 (d, J = 1.9 Hz, 1H), 4.83 (s, 1H), 3.84 (s, 3H), 3.74 (s, 1H), 3.64 – 3.55 (m, 1H), 2.29 – 2.11 (m, 1H), 2.00 – 1.94 (m, 1H), 1.76 (ddd, J = 17.5, 13.4, 5.3 Hz, 10H), 1.47 – 1.23 (m, 10H), 1.10 (d, J =

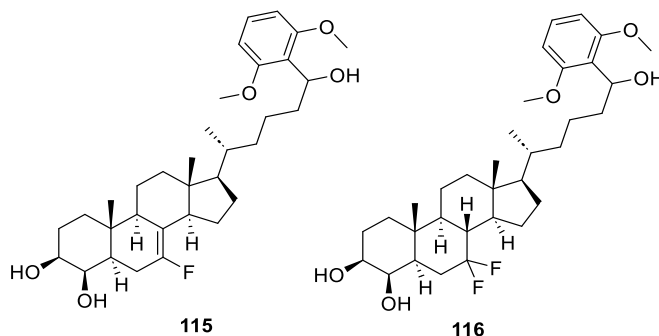
4.4 Hz, 2H), 1.06 (s, 3H), 1.02– 0.93 (m, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -109.81 (s, 1H).

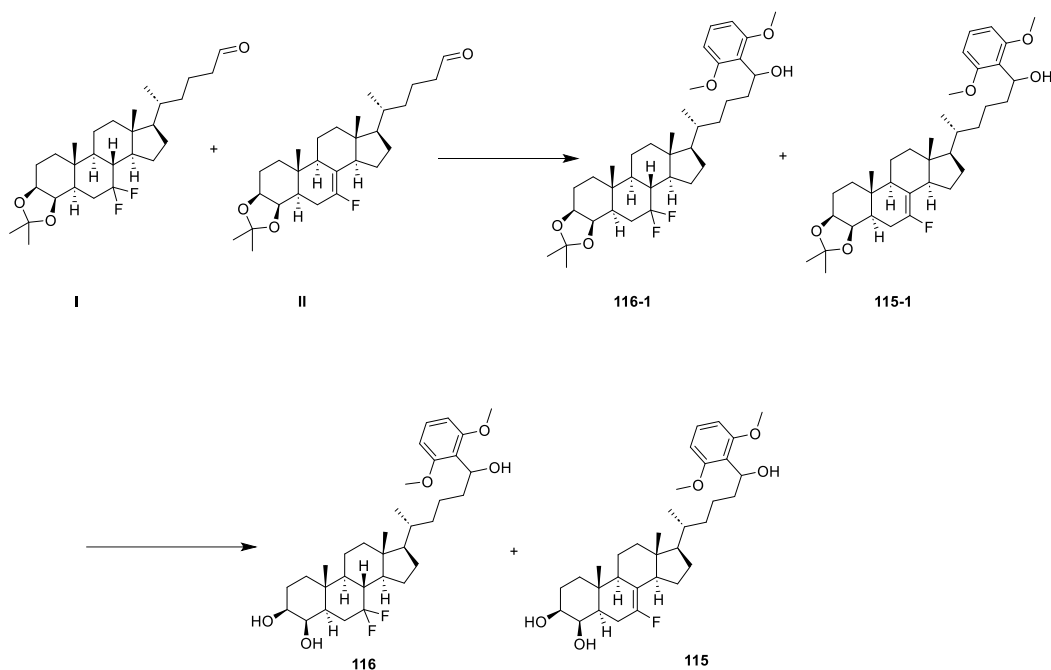
- [0459]** Compound **110**: ^1H NMR (400 MHz, CDCl_3) δ 7.23 (s, 1H), 6.96 – 6.92 (m, 1H), 6.86 (d, J = 1.9 Hz, 1H), 4.83 (t, J = 6.9 Hz, 1H), 3.85 (s, 1H),
 5 3.85 (s, 3H), 3.61 (s, 1H), 2.66 (s, 1H), 2.25 – 2.21 (m, 1H), 2.01 (d, J = 2.9 Hz, 4H), 1.83 (d, J = 10.2 Hz, 6H), 1.76 – 1.68 (m, 7H), 1.46 (d, J = 9.8 Hz, 3H), 1.32 (d, J = 13.0 Hz, 6H), 1.06 (s, 4H), 0.92 – 0.88 (m, 4H). ^{19}F NMR (377 MHz, CDCl_3) δ -109.81.

- 10 **[0460]** Examples **115** & **116**

[0461] Preparation of compound **115** (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R)-6-(2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

- 15 **[0462]** compound **116** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.





[0463] Step 1: Starting material 2-bromo-1,3-dimethoxybenzene (129.91 mg, 0.6 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (0.2 mL, 0.45 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. A mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (80 mg, 0.17 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl

acetate = 87:13) to obtain a mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-dimethoxyphenyl)hexan-1-ol **116-1** and (5R)-1-(2,6-dimethoxyphenyl)-5-((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)hexan-1-ol **115-1** (60 mg, purity: 95%, yield based on **116-1**: 56%) as a white solid.

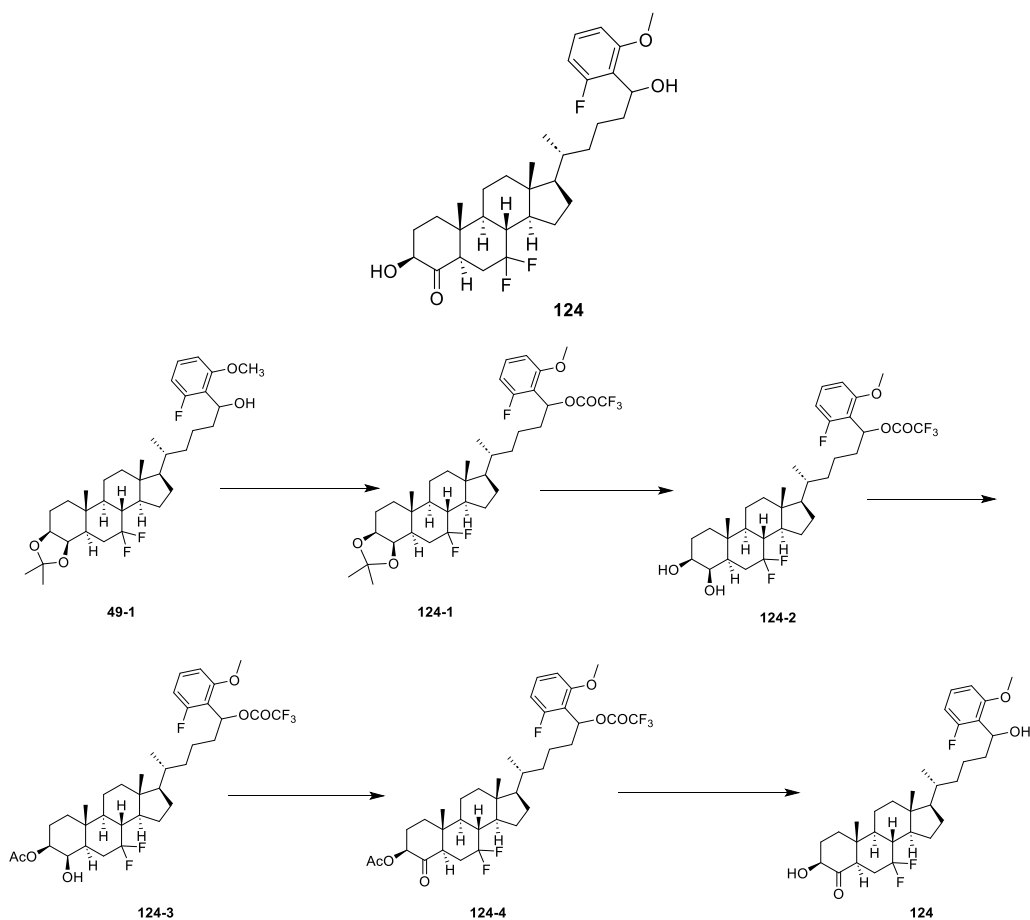
[0464] Compound 116-1: ^1H NMR (400 MHz, CDCl_3) δ 7.16 (t, J = 8.4 Hz, 1H), 6.56 (d, J = 8.4 Hz, 2H), 5.11 (s, 1H), 4.01 (d, J = 3.3 Hz, 2H), 3.83 (s, 6H), 2.12 (d, J = 16.6 Hz, 1H), 2.04 – 1.77 (m, 7H), 1.64 – 1.52 (m, 6H), 1.51 (s, 3H), 1.30 (s, 3H), 1.28 – 1.09 (m, 5H), 1.07 (s, 3H), 0.98 (d, J = 15.4 Hz, 1H), 0.92 – 0.89 (m, 3H), 0.65 (dd, J = 11.9, 4.4 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.98, -88.99, -89.61, -89.62, -109.70, -111.35, -111.36, -111.97, -111.99.

[0465] Step 2: A mixture of reactants (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-dimethoxyphenyl)hexan-1-ol **116-1** and (5R)-1-(2,6-dimethoxyphenyl)-5-((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)hexan-1-ol **115-1** (60 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1.5 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The ethyl acetate layers were combined and washed with saturated brine (3×10 mL). The ethyl acetate layer 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 = 65:35) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **116** (29.81 mg, purity: 100%, yield: 53.21%, retention time t_R = 1.498 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R)-6-(2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **115** (3.48 mg, purity: 88.44%, yield: 5.71%, retention time t_R = 2.091 min).
- [0466]** Compound **116**: ¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, J = 8.3 Hz, 1H), 6.56 (d, J = 8.4 Hz, 2H), 5.16 – 5.07 (m, 1H), 3.83 (s, 6H), 3.73 (s, 1H), 3.59 (d, J = 11.3 Hz, 1H), 2.27 – 2.08 (m, 2H), 2.00 (d, J = 8.7 Hz, 1H), 1.89 – 1.65 (m, 9H), 1.45 – 1.24 (m, 10H), 1.11 (dd, J = 13.0, 3.8 Hz, 2H), 1.05 (s, 3H), 1.03 – 0.94 (m, 2H), 0.89 (dd, J = 6.4, 3.8 Hz, 3H), 0.65 (d, J = 4.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 157.65, 128.10, 110.86, 104.28, 73.44, 71.94, 67.86, 55.70, 55.29, 50.89, 48.62, 43.96, 43.09, 39.27, 36.23, 35.76, 34.94, 28.49, 25.62, 22.64, 20.54, 18.67, 13.79, 11.87. ¹⁹F NMR (376 MHz, CDCl₃) δ -88.60, -89.23, -110.61, -111.24.
- [0467]** Compound **115**: ¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, J = 8.3 Hz, 1H), 6.56 (d, J = 8.4 Hz, 2H), 5.11 (s, 1H), 3.85 (s, 6H), 3.84 – 3.65 (m, 7H), 3.58 (s, 1H), 2.66 (t, J = 12.7 Hz, 1H), 2.25 – 2.13 (m, 1H), 2.06 – 1.80 (m, 9H), 1.76 – 1.60 (m, 5H), 1.50 – 1.30 (m, 9H), 1.15 – 1.07 (m, 3H), 1.05 (s, 3H), 0.93 – 0.88 (m, 3H), 0.64 (t, J = 9.1 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -109.88. ¹⁹F NMR (376 MHz, DMSO) δ -74.51, -108.66.
- LC-MS: [M+H-H₂O]⁺ = 527.35.

[0468] Example 124

[0469] Preparation of compound 124: (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one



[0470] Step 1: (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-Difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoro-6-methoxyphenyl)hexan-1-ol **49-1** (200 mg, 0.3 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL). The reaction system was placed in an ice-water bath and cooled to approximately 5°C. Trifluoroacetic anhydride (212 μ L, 1 mmol, 3.0 eq), 4-dimethylaminopyridine (8.24 mg, 0.07 mmol, 0.2 eq), and triethylamine (0.14 mL, 1 mmol, 3.0 eq) were sequentially added to the reaction system. The reaction system was stirred at room temperature for 1 hour. After

the reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion, the reaction mixture was washed with water (10 mL $\times$ 2) and saturated sodium bicarbonate (10 mL $\times$ 2). The aqueous phase was extracted with dichloromethane (10 mL $\times$ 2), and the organic phases were collected and concentrated under vacuum to obtain the crude product **124-1**. The crude product was directly used in the next step without further purification.

[0471] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-

4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-

cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoro-6-

methoxyphenyl)hexyl 2,2,2-trifluoroacetate **124-1** (200 mg, 0.3 mmol, 1.0 eq)

was dissolved in tetrahydrofuran (4 mL). Dilute hydrochloric acid (2 mL, 3 mol/L) was added, and the reaction mixture was stirred at room temperature for 1

hour. The reaction progress was monitored by TLC (petroleum ether: ethyl

acetate = 5:1). After the starting material was completely consumed, the

reaction was stopped. Water (10 mL) was added to the reaction system, and the

aqueous layer was extracted with ethyl acetate (3 $\times$ 10 mL). The ethyl acetate

layers were combined and washed with saturated brine (3 $\times$ 10 mL). The ethyl

acetate layer 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 = 73:27) to obtain (5R)-5-

[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-

dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluoro-6-

methoxyphenyl)hexyl 2,2,2-trifluoroacetate **124-2** (110 mg, purity: 95%, yield:

55%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 2H), 6.70 (s, 1H),

6.34 (s, 1H), 5.41 – 5.20 (m, 1H), 4.12 (q, J = 7.2 Hz, 1H), 3.86 (d, J = 4.8 Hz,

3H), 3.74 (s, 1H), 3.64 – 3.55 (m, 1H), 2.05 (s, 3H), 1.83 – 1.77 (m, 3H), 1.76 –

1.69 (m, 3H), 1.56 (s, 4H), 1.45 – 1.38 (m, 4H), 1.29 (d, J = 7.8 Hz, 4H), 1.27 –

1.19 (m, 5H), 1.05 (s, 3H), 0.87 (dd, J = 8.9, 4.4 Hz, 4H). ^{19}F NMR (376 MHz,

CDCl_3) δ -75.11, -75.12, -88.65, -89.28, -110.63, -111.26, -113.97, -114.07.

[0472] Step 3: (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluoro-6-methoxyphenyl)hexyl 2,2,2-trifluoroacetate **124-2** (80 mg, 0.12 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL).

5 The reaction system was placed in an ice-water bath, and acetic anhydride (25 mg, 0.25 mmol, 2 eq), 4-dimethylaminopyridine (3 mg, 0.003 mmol, 0.2 eq), and triethylamine (38 mg, 0.37 mmol, 3.0 eq) were sequentially added. The reaction mixture was stirred at room temperature for 1 hour. After the reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion, the
10 reaction mixture was washed with water (10 mL $\times$ 2) and saturated sodium bicarbonate (10 mL $\times$ 2). The aqueous phase was extracted with dichloromethane (10 mL $\times$ 2), and the organic phases were collected and concentrated under vacuum to obtain a crude product. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 80:20) to
15 obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-[(trifluoroacetyl)oxy]hexan-2-yl]-6-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **124-3** (80 mg, purity: 90%, yield: 84%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, J = 9.2 Hz, 0H), 7.27 (s, 1H), 6.70 (t, J = 7.7 Hz, 2H), 6.33 (t, J = 7.5 Hz, 1H), 4.75 – 4.67 (m, 1H), 3.86 (s, 3H), 3.83 (s, 1H), 2.35 (t, J = 7.5 Hz, 0H), 2.28 – 2.19 (m, 1H), 2.10 – 2.08 (m, 4H), 1.93 – 1.85 (m, 2H), 1.74 (s, 3H), 1.63 (d, J = 7.4 Hz, 2H), 1.55 – 1.52 (m, 5H), 1.42 (d, J = 4.9 Hz, 6H), 1.39 – 1.36 (m, 4H), 1.28 (s, 5H), 1.25 – 1.24 (m, 3H), 1.09 – 1.07 (m, 3H), 0.88 – 0.86 (m, 4H), 0.69 – 0.60 (m, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -75.11, -75.13, -88.74, -89.37, -
20 110.55, -111.18, -113.97, -114.07.

[0473] Step 4: Compound (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-[(trifluoroacetyl)oxy]hexan-2-yl]-6-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **124-3** (65 mg, 0.1 mmol, 1 eq) was dissolved in
30 dichloromethane (5 mL). Under a nitrogen atmosphere, tetrapropylammonium perruthenate (10 mg, 0.03 mmol, 0.3 eq), 4-methylmorpholine N-oxide (16.54

mg, 0.14 mmol, 1.5 eq), and 4A molecular sieves were sequentially added. The mixture was stirred at room temperature, and the reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. After the reaction was completed, the reaction mixture was filtered, and the filtrate was washed with water. The organic phase was dried and concentrated. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 88:12) to obtain a white solid, which was subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IB 4.6 × 250 mm, 5 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 70/30; flow rate: 2.0 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-[(trifluoroacetyl)oxy]hexan-2-yl]-9a,11a-dimethyl-6-oxohexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **124-4** (40 mg, purity: 80%, yield: 50%, retention time *t_R* = 0.761 min) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 13.2, 5.0 Hz, 2H), 6.34 (t, *J* = 7.4 Hz, 1H), 5.18 (dd, *J* = 12.2, 7.4 Hz, 1H), 3.86 (s, 3H), 2.54 (d, *J* = 11.2 Hz, 1H), 2.10 – 1.73 (m, 10H), 1.57 (dd, *J* = 15.5, 11.3 Hz, 5H), 1.26 (s, 6H), 0.88 (t, *J* = 6.5 Hz, 5H), 0.79 (s, 3H), 0.63 (dd, *J* = 15.5, 3.5 Hz, 3H).

[0474] Step 5: Reactant (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-[(trifluoroacetyl)oxy]hexan-2-yl]-9a,11a-dimethyl-6-oxohexadecahydro-1H-cyclopenta[1,2-i]phenanthren-7-yl acetate **124-4** (40 mg, 0.06 mmol, 1.0 eq) was dissolved in methanol (2 mL) and tetrahydrofuran (2 mL). Potassium carbonate (41 mg, 0.3 mmol, 4.0 eq) was added, and the reaction system was stirred at room temperature for 30 min. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were

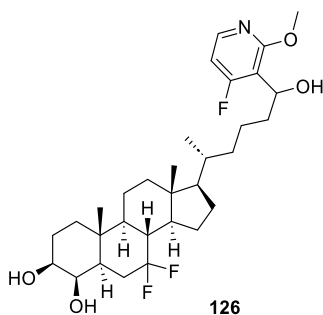
combined and washed with saturated brine (3×10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 75:25) to obtain
 5 (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one **124** (8.48 mg, purity: 96.50%, yield: 25.6%) as a white solid.

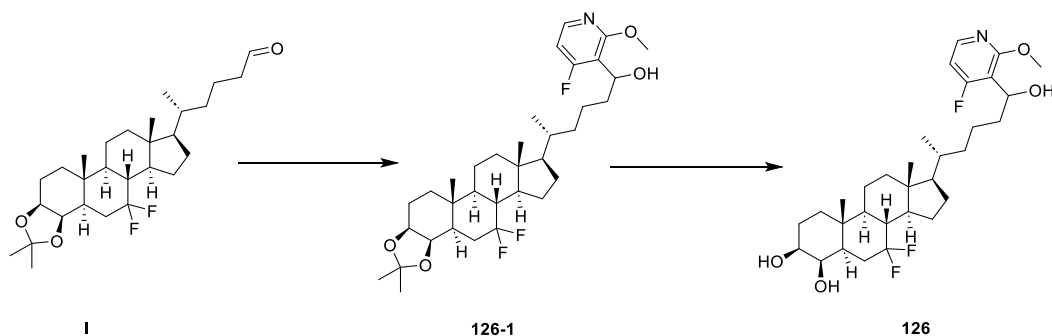
[0475] Compound **124**: ^1H NMR (400 MHz, DMSO) δ 7.22 (dd, $J = 15.4, 8.0$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H), 6.73 (dd, $J = 17.7, 7.5$ Hz, 1H), 4.95 (d, $J = 5.6$ Hz, 1H), 4.81 (s, 1H), 4.20 – 4.13 (m, 1H), 3.78 (s, 3H), 2.60 – 2.53 (m, 2H), 2.12 (s, 1H), 1.83 (ddd, $J = 45.3, 23.7, 15.5$ Hz, 8H), 1.52 (d, $J = 8.9$ Hz, 3H), 1.39 – 1.20 (m, 10H), 1.15 – 0.94 (m, 4H), 0.89 – 0.80 (m, 3H), 0.67 (s, 2H), 0.62 (d, $J = 1.8$ Hz, 3H). ^{19}F NMR (376 MHz, DMSO) δ -88.27, -88.90, -109.53, -110.16,
 15 -115.06, -115.09.

[0476] Example 126

[0477] Preparation of compound 126:

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol
 20





- [0478]** Step 1: Starting material 3-bromo-4-fluoro-2-methoxypyridine (108 mg, 0.5 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (0.18 mL, 0.45 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (70 mg, 2.57 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (2 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (30 mL), dried, and concentrated to obtain the crude product of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxypyridin-3-yl)hexan-1-ol **126-1** (70 mg) as a colorless oil.
- [0479]** Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxypyridin-3-yl)hexan-1-ol **126-1** (70 mg, 0.12 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1.5 mL, 3 mol/L) was

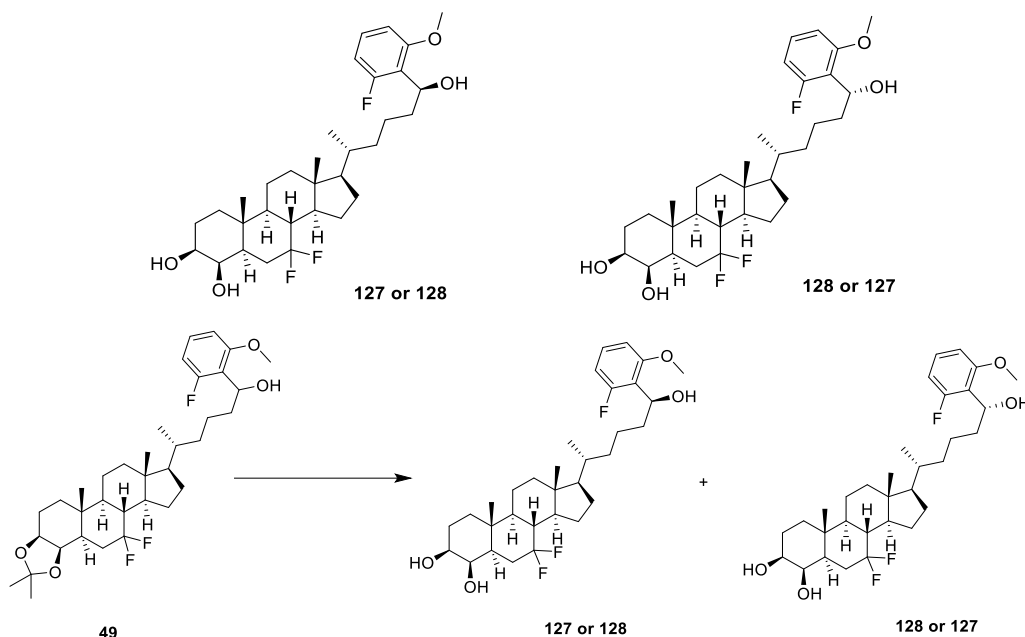
added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (30 mL) was added to the reaction system, and the aqueous layer was
 5 extracted with ethyl acetate (3 × 30 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 30 mL). The ethyl acetate layer 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 = 63:37) to obtain white solids, which were then
 10 subjected to chiral resolution to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **126** (17.47 mg, purity: 100%, yield: 26.76%) as a white solid.

[0480] Compound **126**: ¹H NMR (400 MHz, DMSO) δ 8.09 – 8.03 (m, 1H),
 15 6.88 (dd, *J* = 9.7, 5.8 Hz, 1H), 5.06 (s, 1H), 4.87 (t, *J* = 6.9 Hz, 1H), 4.38 (s, 1H), 4.29 – 4.13 (m, 1H), 3.89 – 3.84 (m, 3H), 3.51 – 3.46 (m, 1H), 3.34 (s, 1H), 1.75 – 1.55 (m, 7H), 1.46 – 1.15 (m, 14H), 1.03 (d, *J* = 16.2 Hz, 2H), 0.98 (s, 3H), 0.94 (s, 2H), 0.85 – 0.81 (m, 3H), 0.61 (s, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -86.66, -87.28, -105.55, -105.61, -108.65, -109.27. LCMS (ESI) [M+H]⁺ =
 20 554.35.

[0481] Examples 127 & 128

[0482] Preparation of compound **127** or **128**
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(2-fluoro-
 25 6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0483] compound **128** or **127** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0484] (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-Fluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-

2,3,3a,5,5a,6,7,8,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **49** was subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK AD₃, 3 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain **127** (retention time t_R = 3.006 min) and **128** (retention time t_R = 3.538 min).

[0485] Compound **127**: ¹H NMR (400 MHz, CDCl₃) δ 7.17 (td, J = 8.4, 6.6 Hz, 1H), 6.72 – 6.66 (m, 2H), 5.06 – 4.97 (m, 1H), 3.87 (d, J = 6.2 Hz, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.4, 4.2 Hz, 1H), 2.28 – 2.12 (m, 1H), 2.00 – 1.77 (m, 7H), 1.73 – 1.63 (m, 4H), 1.39 (ddd, J = 15.3, 9.8, 3.7 Hz, 8H), 1.24 (d, J = 8.1 Hz, 2H), 1.11 (dd, J = 14.1, 5.3 Hz, 2H), 1.06 (s, 3H), 1.02 – 0.94 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.39, 158.34, 119.60, 108.69, 108.45, 106.78, 106.75, 73.45, 71.95, 67.54, 55.88, 55.25, 50.89, 43.87, 43.10, 39.25, 37.86, 36.22, 35.63, 35.54, 34.93, 28.45, 25.63, 22.56, 20.52, 18.64, 13.77, 11.84. ¹⁹F NMR (376 MHz, CDCl₃) δ -208.10, -208.73, -230.29, -230.92, -236.99.

[0486] Compound **128**: ¹H NMR (400 MHz, CDCl₃) δ 1H NMR (400 MHz,

CDCl₃) δ 7.17 (td, J = 8.4, 6.6 Hz, 1H), 6.72 – 6.65 (m, 2H), 5.00 (t, J = 7.2 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 1H), 3.63 – 3.56 (m, 1H), 2.26 – 2.11 (m, 1H), 2.00 – 1.94 (m, 1H), 1.89 – 1.64 (m, 11H), 1.44 – 1.24 (m, 9H), 1.11 (dd, J = 11.2, 5.3 Hz, 2H), 1.05 (s, 3H), 1.02 – 0.93 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.64 (s, 3H).

5 ¹³C NMR (101 MHz, CDCl₃) δ 159.22, 158.41, 128.47, 119.54, 108.68, 108.44, 106.78, 73.44, 71.94, 67.64, 55.88, 55.23, 50.88, 48.57, 43.87, 43.09, 39.25, 38.03, 36.23, 35.74, 35.70, 34.93, 28.44, 25.62, 25.40, 22.68, 20.52, 18.63, 13.77, 11.84. ¹⁹F NMR (376 MHz, CDCl₃) δ -88.62, -89.25, -110.62, -111.24, -117.19.

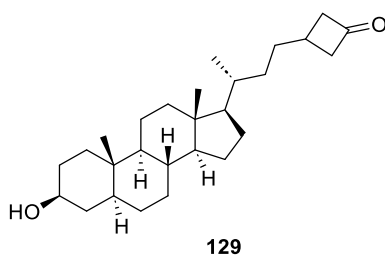
10 [0487] Example 129

[0488] Preparation of compound 129: 3-[(3R)-3-

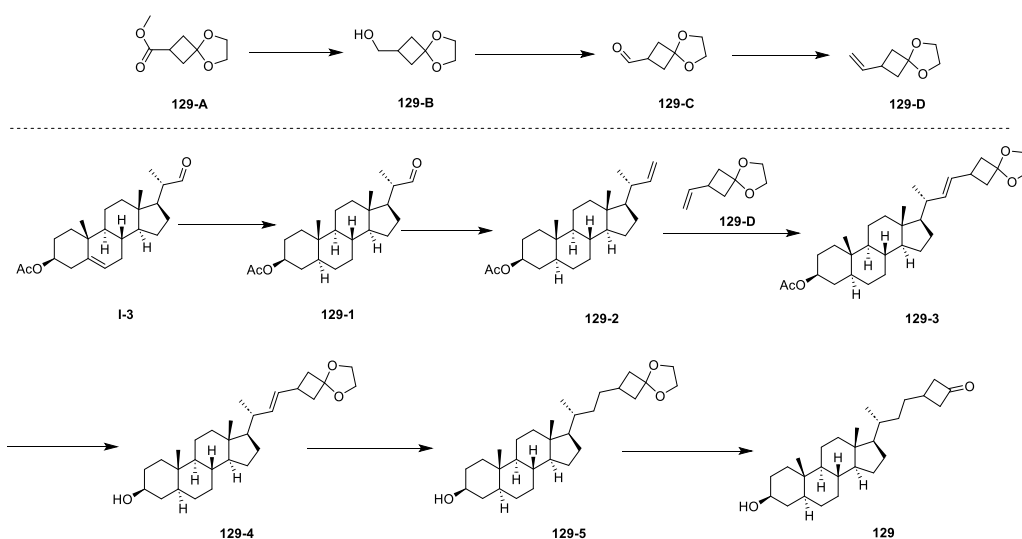
[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-hydroxy-9a,11a-

dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-

yl]butyl]cyclobutan-1-one



15



[0489] Step 1: At room temperature, methyl 5,8-dioxaspiro[3.4]octane-2-carboxylate **129-A** (1.5 g, 8.71 mmol) was dissolved in tetrahydrofuran (30 mL)

and cooled to 0°C in an ice bath. LiAlH₄ (0.66 g, 17.42 mmol) was added in portions. The mixture was stirred at 0°C for 1.5 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. Tetrahydrofuran (30 mL) was added to the reaction mixture, followed by sequential addition of water (0.66 mL), 15% NaOH (0.66 mL), and water (2 mL). The mixture was filtered through diatomite and rinsed with ethyl acetate (30 mL). The filtrate was concentrated to obtain a crude product. The crude product was purified by column chromatography (12 g, 0-30% ethyl acetate/petroleum ether, 30 mL/min) to obtain (5,8-dioxaspiro[3.4]octan-2-yl)methanol **129-B** (1.2 g, purity: 90%, yield: 86%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.94 – 3.85 (m, 4H), 3.68 (d, *J* = 6.7 Hz, 2H), 2.49 – 2.38 (m, 2H), 2.29 (dt, *J* = 17.0, 7.5 Hz, 1H), 2.10 (ddd, *J* = 12.7, 6.6, 3.0 Hz, 2H).

[0490] Step 2: Compound (5,8-dioxaspiro[3.4]octan-2-yl)methanol **129-B** (1.2 g, 8.32 mmol, 1 eq) was dissolved in dichloromethane (10 mL) and cooled to 0°C in an ice bath. Sodium bicarbonate (3.5 g, 41.62 mmol, 5 eq) and Dess-Martin periodinane (5.3 g, 12.49 mmol, 1.5 eq) were added. The mixture was stirred at room temperature for 3 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 1:1) until completion. Sodium thiosulfate solution (15 mL) and sodium bicarbonate solution (15 mL) were added to the reaction mixture. The mixture was stirred for 30 minutes until a clear solution formed, and then extracted with dichloromethane (20 mL × 2). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product of 5,8-dioxaspiro[3.4]octane-2-carbaldehyde **129-C** (620 mg, purity: 90%, yield: 47.16%), which was directly used in the next step without purification. ¹H NMR (400 MHz, CDCl₃) δ 9.74 (d, *J* = 2.6 Hz, 1H), 3.98 – 3.85 (m, 4H), 3.00 – 2.85 (m, 1H), 2.66 – 2.48 (m, 4H).

[0491] Step 3: At room temperature, methyltriphenylphosphonium bromide (2.51 g, 7.04 mmol, 2 eq) was dissolved in tetrahydrofuran (15 mL), cooled to 0°C in an ice bath, and NaHMDS (1 M in tetrahydrofuran, 7.0 mL, 7.0 mmol, 2 eq) was slowly added dropwise with stirring for 30 minutes. A solution of

starting material 5,8-dioxaspiro[3.4]octane-2-carbaldehyde **129-C** (500 mg, 3.52 mmol, 1.0 eq) in tetrahydrofuran (5 mL) was then added dropwise. The mixture was stirred in an ice bath for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 2:1) until completion. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL × 2). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated at low temperature to obtain a crude product. The crude product was purified by column chromatography (12 g, 0-5% dichloromethane/petroleum ether, 30 mL/min) to obtain 2-vinyl-5,8-dioxaspiro[3.4]octane **129-D** (390 mg, purity: 90%, yield: 71.19%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.93 (ddd, *J* = 17.2, 10.2, 7.1 Hz, 1H), 4.99 (ddt, *J* = 17.3, 10.2, 1.5 Hz, 2H), 3.95 – 3.84 (m, 4H), 2.71 (dt, *J* = 16.5, 8.2 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.26 – 2.15 (m, 2H).

[0492] Step 4: At room temperature, (3S,8S,9S,10R,13S,14S,17R)-10,13-dimethyl-17-((S)-1-oxopropan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta-phenanthren-3-yl acetate **I-3** (1.0 g, 2.68 mmol) was dissolved in ethyl acetate (20 mL). 10% Pd/C (700 mg) and acetic acid (0.5 mL) were added, and the mixture was stirred under a hydrogen atmosphere at room temperature for 40 hours. The reaction was monitored by HNMR. After the reaction was completed, the reaction mixture was diluted with ethyl acetate (30 mL), filtered through diatomite, and the filtrate was sequentially washed with saturated sodium bicarbonate solution (30 mL) and saturated brine (30 mL), 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 = 10:1) to obtain (3S,8R,9S,10S,13S,14S,17R)-10,13-dimethyl-17-((S)-1-oxopropan-2-yl)hexadecahydro-1H-cyclopenta-phenanthren-3-yl acetate **129-1** (430 mg, purity: 90%, yield: 38.50%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.56 (d, *J* = 3.3 Hz, 1H), 4.74 – 4.63 (m, 1H), 2.40 – 2.27 (m, 1H), 2.02 (s, 3H), 1.95 – 1.88 (m, 1H), 1.88 – 1.77 (m, 2H), 1.73 (dt, *J* = 13.2, 3.5 Hz, 1H), 1.58 (dddd, *J* = 29.5, 15.9, 12.8, 9.8 Hz, 7H), 1.44 – 1.29 (m, 4H), 1.19 (ddd, *J* = 12.2, 11.0, 4.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H),

1.08 – 0.96 (m, 3H), 0.94 – 0.86 (m, 1H), 0.84 – 0.81 (m, 3H), 0.70 (s, 3H), 0.66 (dd, $J = 10.5, 4.9$ Hz, 1H).

[0493] Step 5: At room temperature, methyltriphenylphosphonium bromide (357.22 mg, 2.30 mmol, 2 eq) was dissolved in tetrahydrofuran (15 mL), cooled to 0°C in an ice bath, and NaHMDS (1 M in tetrahydrofuran, 2.3 mL, 2.30 mmol, 2 eq) was slowly added dropwise with stirring for 30 minutes. A solution of starting material (3S,8R,9S,10S,13S,14S,17R)-10,13-dimethyl-17-((S)-1-oxopropan-2-yl)hexadecahydro-1H-cyclopenta-phenanthren-3-yl acetate **129-1** (430 mg, 1.15 mmol, 1.0 eq) in tetrahydrofuran (5 mL) was then added dropwise. The mixture was stirred in an ice bath for 30 minutes. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1) until completion. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (30 mL $\times$ 2). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (12 g, 0-10% ethyl acetate/petroleum ether, 30 mL/min) to obtain (3S,8R,9S,10S,13R,14S,17R)-17-((R)-but-3-en-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-3-yl acetate **129-2** (300 mg, purity: 90%, yield: 63.12%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 5.66 (ddd, $J = 17.1, 10.1, 8.4$ Hz, 1H), 4.89 (dd, $J = 17.1, 1.2$ Hz, 1H), 4.81 (ddd, $J = 10.2, 5.5, 2.0$ Hz, 1H), 4.74 – 4.63 (m, 1H), 2.13 – 2.03 (m, 1H), 2.02 (s, 3H), 1.94 (dt, $J = 12.4, 3.3$ Hz, 1H), 1.80 (d, $J = 9.3$ Hz, 1H), 1.76 – 1.55 (m, 5H), 1.53 – 1.46 (m, 2H), 1.38 – 1.05 (m, 10H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.98 (dd, $J = 8.5, 4.3$ Hz, 2H), 0.91 – 0.84 (m, 1H), 0.81 (d, $J = 7.0$ Hz, 3H), 0.67 (s, 3H), 0.65 – 0.60 (m, 1H).

[0494] Step 6: At room temperature, (3S,8R,9S,10S,13R,14S,17R)-17-((R)-but-3-en-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-3-yl acetate **129-2** (200 mg, 0.537 mmol, 1 eq), 2-vinyl-5,8-dioxaspiro[3.4]octane **129-D** (376 mg, 2.68 mmol, 5 eq), and Grubbs II (228 mg, 0.269 mmol, 0.5 eq) were dissolved in dichloromethane (10 mL). The mixture was heated to 50°C in a sealed tube and reacted for 10 hours. The reaction was monitored by TLC

(petroleum ether: ethyl acetate = 20:1), and a new spot was observed. Water (20 mL) was added to the reaction mixture, and dichloromethane was removed by concentration. The aqueous phase was extracted with ethyl acetate (20 mL $\times$ 2). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (12 g, 0-3% ethyl acetate/petroleum ether, 30 mL/min) to obtain (3S,5S,8R,9S,10S,13R,14S,17R)-17-((R,E)-4-(5,8-dioxaspiro[3.4]octan-2-yl)but-3-en-2-yl)-10,13-dimethylhexahydro-1H-cyclopenta-phenanthren-3-yl acetate **129-3** (60 mg, purity: 90%, yield: 20.77%) as a light brown solid. ¹H NMR (400 MHz, CDCl₃) δ 5.41 (dd, J = 15.2, 7.2 Hz, 1H), 5.23 (dd, J = 15.2, 8.4 Hz, 1H), 4.74 – 4.61 (m, 1H), 3.94 – 3.84 (m, 4H), 2.62 (dd, J = 16.0, 8.0 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.18 – 2.08 (m, 2H), 2.02 (s, 3H), 1.93 (d, J = 12.4 Hz, 1H), 1.85 – 1.58 (m, 6H), 1.53 – 1.43 (m, 3H), 1.37 – 1.28 (m, 5H), 1.23 – 1.01 (m, 7H), 0.98 (d, J = 6.6 Hz, 3H), 0.93 – 0.84 (m, 2H), 0.82 (s, 3H), 0.66 (d, J = 6.9 Hz, 3H).

[0495] Step 7: At room temperature, (3S,5S,8R,9S,10S,13R,14S,17R)-17-((R,E)-4-(5,8-dioxaspiro[3.4]octan-2-yl)but-3-en-2-yl)-10,13-dimethylhexahydro-1H-cyclopenta-phenanthren-3-yl acetate **129-3** (50 mg, 0.103 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and methanol (2 mL). Lithium hydroxide monohydrate (43 mg, 1.03 mmol, 10.0 eq) and water (1 mL) were added at room temperature, and the mixture was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 10:1). After the reaction was completed, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL $\times$ 2). The organic phase was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 10:1) to obtain (3S,5S,8R,9S,10S,13R,14S,17R)-17-((R,E)-4-(5,8-dioxaspiro[3.4]octan-2-yl)but-3-en-2-yl)-10,13-dimethylhexahydro-1H-cyclopenta-phenanthren-3-ol **129-4** (40 mg, purity: 90%, yield: 78.84%) as a white solid. ¹H NMR (400 MHz,

CDCl₃) δ 5.41 (dd, J = 15.2, 7.2 Hz, 1H), 5.23 (dd, J = 15.3, 8.5 Hz, 1H), 3.91 – 3.83 (m, 4H), 3.65 – 3.51 (m, 1H), 2.62 (dd, J = 16.2, 8.1 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.18 – 2.07 (m, 2H), 2.04 – 1.88 (m, 2H), 1.78 (s, 1H), 1.67 (ddd, J = 16.1, 13.0, 6.5 Hz, 3H), 1.52 – 1.38 (m, 5H), 1.35 – 1.28 (m, 4H), 1.16 – 1.04 (m, 4H),
 5 0.98 (d, J = 6.6 Hz, 3H), 0.97 – 0.82 (m, 4H), 0.80 (s, 3H), 0.66 (s, 3H), 0.63 – 0.57 (m, 1H).

[0496] Step 8: At room temperature, (3S,5S,8R,9S,10S,13R,14S,17R)-17-((R,E)-4-(5,8-dioxaspiro[3.4]octan-2-yl)but-3-en-2-yl)-10,13-dimethylhexahydro-1H-cyclopenta-phenanthren-3-ol **129-4** (40 mg, 0.090 mmol)
 10 was dissolved in ethyl acetate (5 mL). 10% Pd/C (40 mg) was added, and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 hours. The reaction was monitored by HNMR. After the reaction was completed, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through diatomite. The organic phase was concentrated and purified by silica gel column
 15 chromatography (petroleum ether: ethyl acetate = 10:1) to obtain (3S,5S,8R,9S,10S,13R,14S,17R)-17-((R)-4-(5,8-dioxaspiro[3.4]octan-2-yl)butan-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-3-ol **129-5** (35 mg, purity: 90%, yield: 78.39%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 3.87 (h, J = 5.9 Hz, 4H), 3.65 – 3.53 (m, 1H), 2.39 (d, J = 5.3 Hz, 2H),
 20 1.91 (dd, J = 25.9, 11.7 Hz, 4H), 1.78 (dd, J = 14.2, 10.3 Hz, 2H), 1.73 – 1.61 (m, 3H), 1.51 – 1.36 (m, 6H), 1.18 (d, J = 10.0 Hz, 4H), 1.15 – 0.94 (m, 8H), 0.89 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 12.0 Hz, 3H), 0.80 (s, 3H), 0.64 (s, 3H), 0.59 (d, J = 4.0 Hz, 1H).

[0497] Step 9: Reactant (3S,5S,8R,9S,10S,13R,14S,17R)-17-((R)-4-(5,8-dioxaspiro[3.4]octan-2-yl)butan-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-3-ol **129-5** (35 mg, 0.079 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 2 hours, then heated to 40°C and stirred for 1 hour. The reaction was monitored by ¹HNMR, and the
 30 reaction was completed. Water (20 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The ethyl

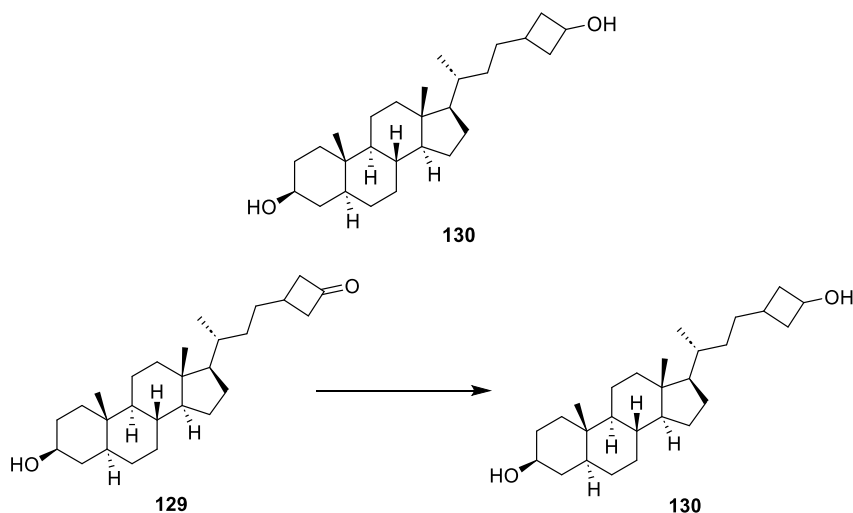
acetate layers were combined and washed with saturated brine (30 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 90:10) to obtain 3-
 5 [(3R)-3-[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]butyl]cyclobutan-1-one **129** (28 mg, purity: 98%, yield: 87.02%) as a white solid.

[0498] Compound **129**: ^1H NMR (400 MHz, CDCl_3) δ 3.65 – 3.54 (m, 1H), 3.20 – 3.04 (m, 2H), 2.70 – 2.57 (m, 2H), 2.36 – 2.22 (m, 1H), 1.96 (dd, J = 9.1, 3.5 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.74 – 1.62 (m, 2H), 1.61 – 1.52 (m, 4H), 1.49 – 1.44 (m, 2H), 1.37 (ddd, J = 23.3, 15.3, 9.6 Hz, 6H), 1.25 – 1.18 (m, 2H), 1.15 – 0.95 (m, 7H), 0.93 (d, J = 6.5 Hz, 3H), 0.87 (dd, J = 11.1, 7.3 Hz, 1H), 0.80 (s, 3H), 0.65 (s, 3H), 0.64 – 0.57 (m, 1H). LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 383.0$.

15

[0499] Example **130**

[0500] Preparation of compound **130**: (20R)-21-[(3-hydroxycyclobutyl)methyl]-20-methyl-5 α -pregnan-3 β -ol



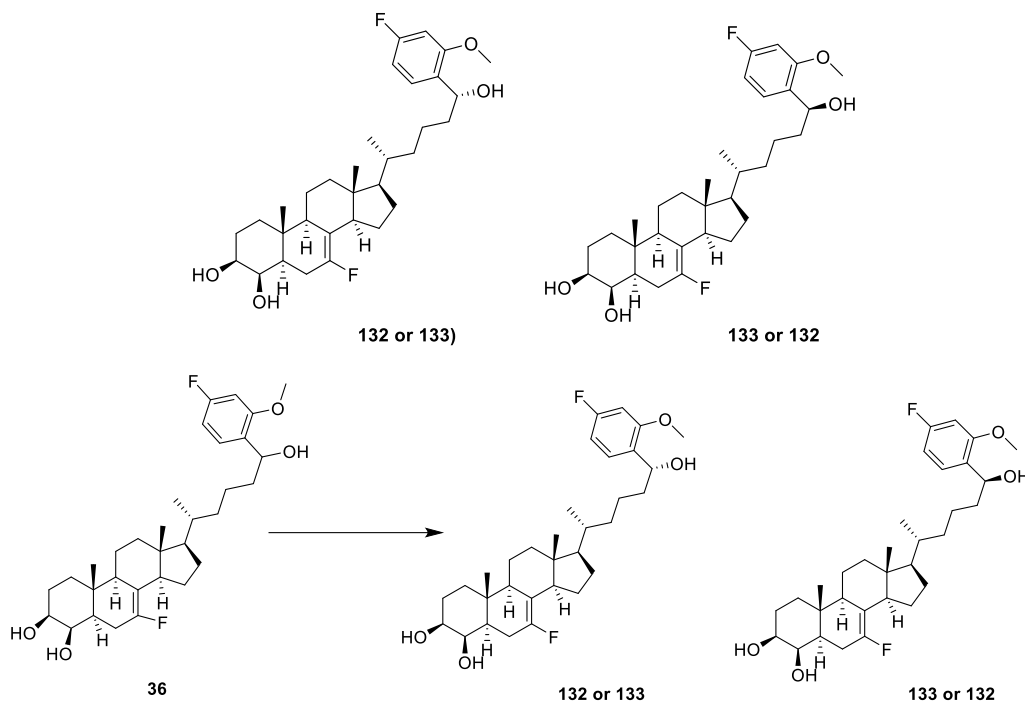
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[0501] Step 1: At room temperature, 3-((R)-3-((3S,5S,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-17-yl)butyl)cyclobutan-1-one (8 mg, 0.020 mmol,

1.0 eq) was dissolved in methanol (1 mL) and cooled to 0°C in an ice bath. Sodium borohydride (22.66 mg, 0.599 mmol, 3.0 eq) was added. The mixture was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 4:1) until completion. The reaction mixture was quenched with saturated ammonium chloride solution, and methanol was removed by concentration. Water (10 mL) was added, and the mixture was extracted with ethyl acetate (10 mL × 2). The organic phases were combined, washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-20% ethyl acetate/petroleum ether, 20 mL/min) to obtain (20R)-21-[(3-hydroxycyclobutyl)methyl]-20-methyl-5 α -pregnan-3 β -ol **130** (2.63 mg, purity: 84%, yield: 29.44%) as a white solid. Compound 130: ¹H NMR (400 MHz, CDCl₃) δ 4.09 (t, *J* = 7.3 Hz, 1H), 3.64 – 3.53 (m, 1H), 2.44 (dd, *J* = 6.9, 3.9 Hz, 2H), 2.04 – 1.56 (m, 8H), 1.46 – 1.28 (m, 10H), 1.25 – 0.92 (m, 11H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 1H), 0.80 (s, 3H), 0.64 (s, 3H), 0.59 (s, 1H). LC-MS: [M+H-2H₂O]⁺ = 367.0.

[0502] Examples 132 & 133:

[0503] Preparation of compound **133** or **132**:
 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6S)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
[0504] compound **132** or **133**: (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0505] Solid (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-

2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **36** (50 mg) was subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK AD₃, 3 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 55/45; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain **133** (16.49 mg, purity: 84%, yield: 34%, retention time t_R = 2.583 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **132** (22.05 mg, purity: 100%, yield: 44%, retention time t_R = 3.730 min).

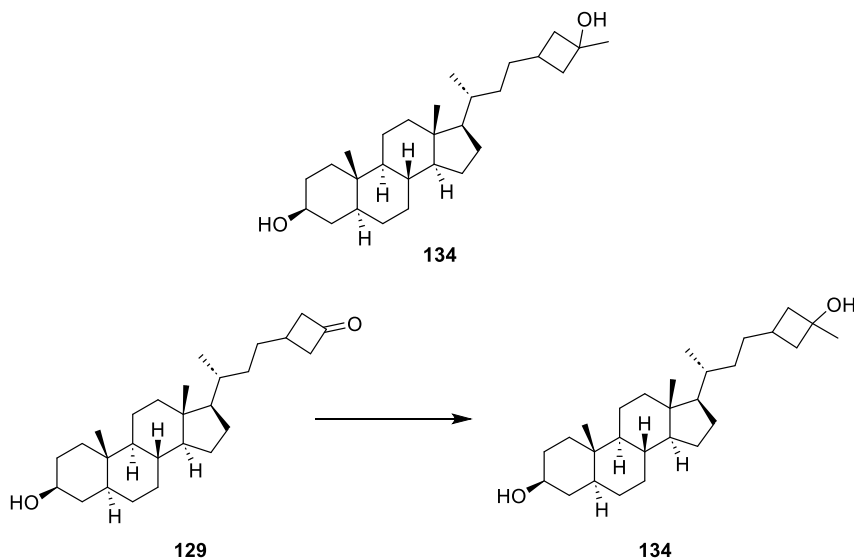
[0506] Compound **133**: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (s, 1H), 6.67 – 6.57 (m, 2H), 4.86 (s, 1H), 3.85 (s, 1H), 3.83 (s, 3H), 3.59 (d, J = 9.0 Hz, 1H), 2.66 (t, J = 12.5 Hz, 1H), 2.30 – 2.22 (m, 1H), 2.14 (s, 1H), 2.03 (d, J = 12.8 Hz, 1H), 1.86 (d, J = 4.1 Hz, 4H), 1.77 – 1.58 (m, 7H), 1.48 – 1.36 (m, 7H), 1.11 (dd, J = 18.2, 11.4 Hz, 4H), 1.04 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.64 (d, J = 6.9 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -109.80, -113.05. LCMS (ESI) [M+H-H₂O]⁺=

515.3.

[0507] Compound **132**: ^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, $J = 7.0$ Hz, 1H), 6.67 – 6.58 (m, 2H), 4.83 (s, 1H), 3.85 (s, 1H), 3.84 (s, 3H), 3.59 (d, $J = 11.6$ Hz, 1H), 2.65 (dd, $J = 16.4, 8.0$ Hz, 1H), 2.36 – 2.12 (m, 2H), 2.02 (dd, $J = 9.2, 3.5$ Hz, 1H), 1.89 – 1.79 (m, 5H), 1.76 – 1.68 (m, 4H), 1.60 (dd, $J = 14.9, 6.8$ Hz, 4H), 1.49 – 1.40 (m, 4H), 1.15 – 1.06 (m, 4H), 1.04 (s, 3H), 0.90 (d, $J = 6.5$ Hz, 3H), 0.62 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -109.80, -112.99. LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 515.35$.

10 [0508] **Example 134:**

[0509] Preparation of compound **134**: (20R)-21-[(3-hydroxy-3-methylcyclobutyl)methyl]-20-methyl-5 α -pregnan-3 β -ol



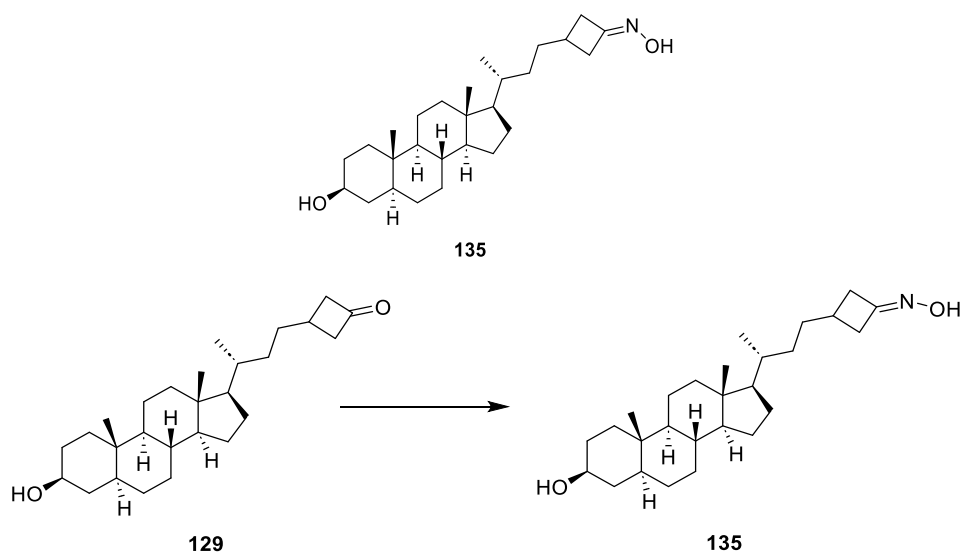
15 [0510] At room temperature, 3-((R)-3-((3S,5S,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-17-yl)butyl)cyclobutan-1-one **129** (30 mg, 0.075 mmol, 1 *eq*) was dissolved in tetrahydrofuran (3 mL). Under a nitrogen atmosphere, the solution was cooled to 0°C in an ice bath, and methylmagnesium bromide (3 M in tetrahydrofuran, 20 0.25 mL, 0.75 mmol, 10 *eq*) was added dropwise over 5 min. The mixture was stirred at room temperature for 1 hour. The mixture was cooled in an ice bath, quenched with ammonium chloride solution, and extracted with ethyl acetate (20

mL $\times$ 2). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-15% ethyl acetate/petroleum ether, 25 mL/min) to obtain (20R)-21-[(3-hydroxy-3-methylcyclobutyl)methyl]-20-methyl-5 α -pregnan-3 β -ol **134** (10.42 mg, purity: 96.3%, yield: 32.2%) as a white solid.

[0511] Compound **134**: ^1H NMR (400 MHz, CDCl_3) δ 3.64 – 3.53 (m, 1H), 2.17 (dd, J = 10.0, 6.0 Hz, 2H), 1.95 (d, J = 12.5 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.74 – 1.61 (m, 4H), 1.47 (dddd, J = 27.1, 17.7, 8.3, 5.1 Hz, 9H), 1.35 (s, 3H), 1.31 (dd, J = 12.5, 6.2 Hz, 4H), 1.21 (dd, J = 13.4, 3.7 Hz, 2H), 1.14 – 0.91 (m, 7H), 0.89 (dd, J = 6.5, 2.4 Hz, 3H), 0.87 – 0.82 (m, 1H), 0.80 (s, 3H), 0.64 (s, 3H), 0.60 (dd, J = 11.6, 3.3 Hz, 1H). LC-MS: $[\text{M}+\text{H}-2\text{H}_2\text{O}]^+ = 381.3$.

[0512] **Example 135:**

15 [0513] Preparation of compound **135**: {3-[(3R)-3-[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]butyl]cyclobutylidene}hydroxylamine



20

[0514] At room temperature, 3-((R)-3-((3S,5S,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-17-

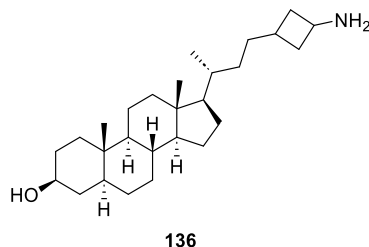
yl)butyl)cyclobutan-1-one **129** (30 mg, 0.075 mmol, 1 *eq*) was dissolved in ethanol (3 mL). Hydroxylamine hydrochloride (104 mg, 1.50 mmol, 20 *eq*) and sodium acetate (246 mg, 3.00 mmol, 40 *eq*) were added, and the mixture was stirred at room temperature for 3 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 4:1) until completion. The reaction mixture was concentrated, and water (20 mL) was added. The mixture was extracted with ethyl acetate (15 mL $\times$ 2), and the organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-15% ethyl acetate/petroleum ether, 25 mL/min) to obtain {3-[(3R)-3-[(1R,3aS,3bR,5aS,7S,9aS,9bS,11aR)-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]butyl]cyclobutylidene}hydroxylamine **135** (25 mg, purity: 90%, yield: 72.3%) as a white solid.

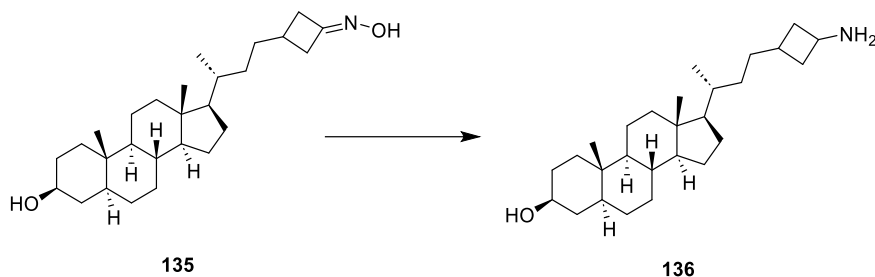
[0515] Compound **135**: ^1H NMR (400 MHz, CDCl_3) δ 3.65 – 3.53 (m, 1H), 3.02 (s, 2H), 2.54 – 2.42 (m, 2H), 2.33 – 2.22 (m, 1H), 1.95 (d, J = 12.5 Hz, 1H), 1.84 – 1.61 (m, 5H), 1.57 – 1.28 (m, 11H), 1.24 – 0.95 (m, 9H), 0.91 (d, J = 6.5 Hz, 3H), 0.89 – 0.83 (m, 1H), 0.80 (s, 3H), 0.65 (s, 3H), 0.63 – 0.57 (m, 1H). LC-MS: $[\text{M}+\text{H}]^+ = 416.35$.

20

[0516] Example 136:

[0517] Preparation of compound **136: (20R)-20-[2-(3-aminocyclobutyl)ethyl]-5 α -pregnan-3 β -ol**





[0518] At room temperature, 3-((R)-3-((3S,5S,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta-phenanthren-17-yl)butyl)cyclobutan-1-one oxime **135** (20 mg, 0.048 mmol, 1 *eq*) was dissolved in NH₃ in MeOH (3 mL, 7 M). Raney Ni (20 mg) was added, and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 4:1) until completion. The reaction mixture was diluted with methanol (10 mL) and filtered through diatomite. The organic phase was concentrated, and the crude product was purified by column chromatography (4 g, 0-10% methanol/dichloromethane, 25 mL/min) to obtain (20R)-20-[2-(3-aminocyclobutyl)ethyl]-5 α -pregnan-3 β -ol **136** (4.80 mg, purity: 95.47%, yield: 23.71%) as a white solid.

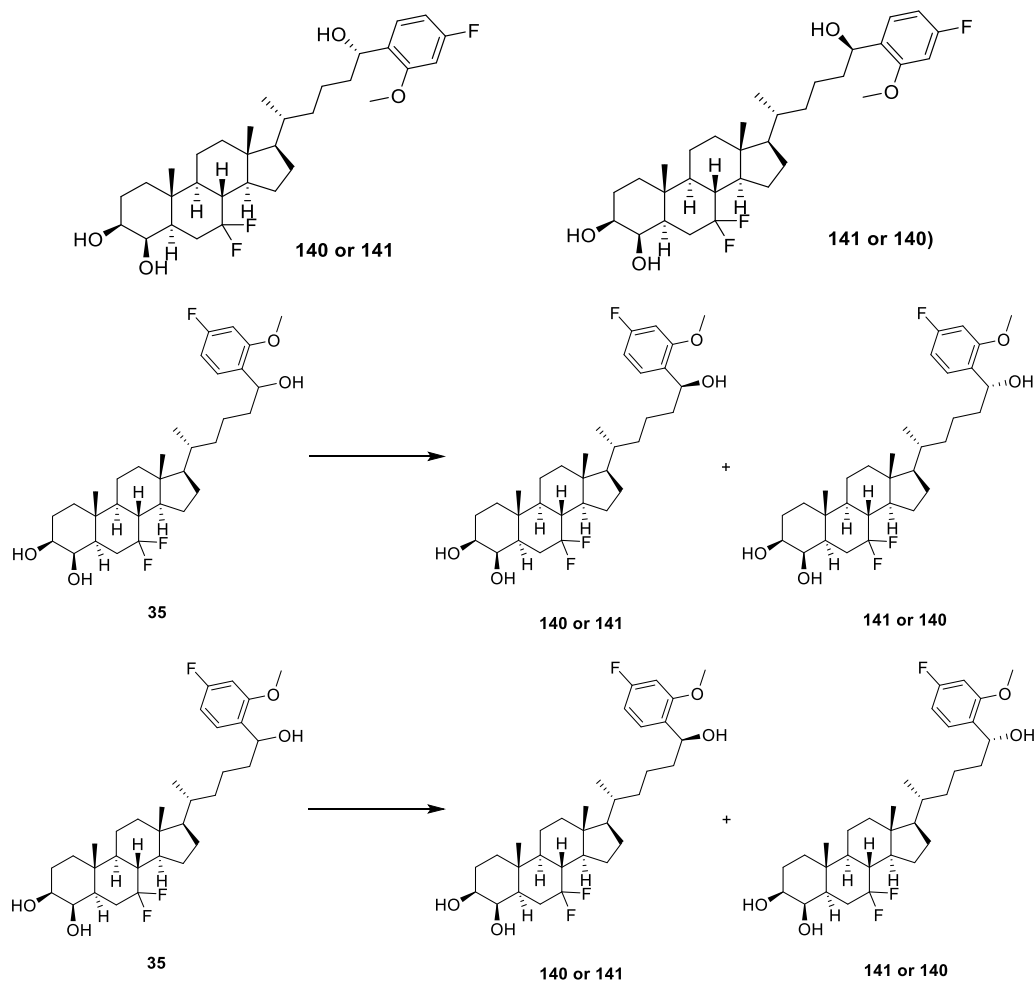
[0519] Compound **136**: ¹H NMR (400 MHz, MeOD) δ 3.79 – 3.42 (m, 2H), 2.52 – 1.94 (m, 5H), 1.90 (s, 1H), 1.83 (s, 1H), 1.62 (ddd, *J* = 62.9, 40.0, 13.7 Hz, 8H), 1.46 – 1.30 (m, 7H), 1.25 (t, *J* = 8.1 Hz, 3H), 1.15 – 1.06 (m, 3H), 1.04 – 0.87 (m, 7H), 0.83 (s, 3H), 0.68 (s, 3H), 0.64 (d, *J* = 11.3 Hz, 1H). LCMS (ESI) [M+H]⁺ = 402.35.

[0520] Example **140** or **141**

[0521] Preparation of compound **140** or **141**: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0522] compound **141** or **140**: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-

9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



- 5 **[0523]** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **35** was subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK AD₃, 3 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain
- 10 compounds **140** (retention time t_R = 3.112 min) and **141** (retention time t_R = 4.395 min).

- [0524]** Compound **140**: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (s, 1H), 6.68 – 6.57 (m, 2H), 4.85 (dd, J = 8.1, 5.1 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 1H), 3.59 (dt, J =
- 15 11.2, 4.1 Hz, 1H), 2.30 – 2.12 (m, 1H), 2.00 – 1.86 (m, 3H), 1.81 (dd, J = 15.1, 9.1 Hz, 4H), 1.72 – 1.63 (m, 3H), 1.50 – 1.24 (m, 11H), 1.15 – 1.07 (m, 2H), 1.06

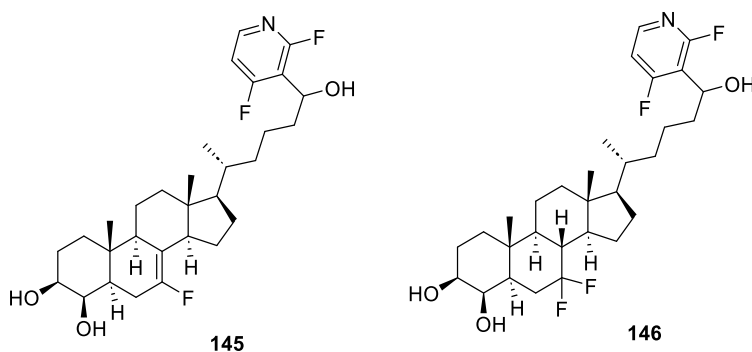
(s, 3H), 1.03 – 0.93 (m, 2H), 0.90 (d, $J = 6.5$ Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.61, -89.24, -110.61, -111.24, -113.05. LC-MS: $[\text{M-H}]^- = 551.45$.

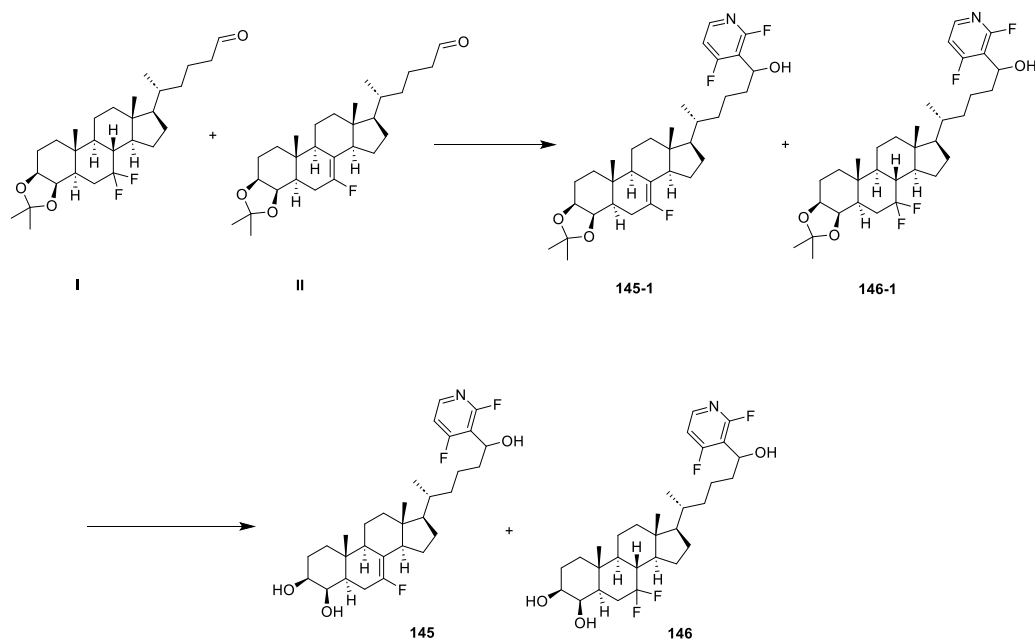
[0525] Compound **141**: ^1H NMR (400 MHz, CDCl_3) δ 7.26 – 7.22 (m, 1H), 6.67 – 6.56 (m, 2H), 4.83 (t, $J = 6.6$ Hz, 1H), 3.83 (s, 3H), 3.73 (s, 1H), 3.60 (dt, $J = 11.3, 4.1$ Hz, 1H), 2.29 – 2.12 (m, 2H), 1.97 (dd, $J = 9.5, 3.4$ Hz, 1H), 1.84 (ddd, $J = 23.1, 11.6, 5.0$ Hz, 5H), 1.76 – 1.66 (m, 6H), 1.40 (ddd, $J = 24.0, 13.7, 7.6$ Hz, 6H), 1.16 – 1.06 (m, 3H), 1.06 (s, 3H), 1.01 – 0.92 (m, 2H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.62, -89.25, -110.62, -111.25, -112.99.

[0526] Examples 145 & 146:

[0527] Preparation of compound **145**: (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R)-6-(2,4-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0528] compound **146**: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,4-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol





- [0529]** Step 1: Starting material 3-bromo-2,4-difluoropyridine (145 mg, 0.75 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (0.25 mL, 0.64 mmol, 3.0 *eq*) was added.
- 5 The mixture was stirred at this temperature for 30 min. A mixture of compounds (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-
- 10 4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (100 mg, 0.21 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1,
- 15 phosphomolybdic acid staining followed by heating). Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude mixture of (5R)-1-(2,4-difluoropyridin-3-yl)-5-(((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-
- 20 2,2,5a,7a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10a,12,12a,12b-tetradecahydro-

4H-cyclopenta[7,2]phenanthro[1,3]dioxol-8-ol)hexan-1-ol **145-1** and (5R)-5-
 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-
 tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-
 cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4-difluoropyridin-
 3-yl)hexan-1-ol **146-1** (20 mg) as a colorless oil, which was directly used in the
 next step.

[0530] Step 2: A mixture of reactants (5R)-1-(2,4-difluoropyridin-3-yl)-5-
 (((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a,7a-tetramethyl-
 3a,5,5a,5b,6,7,7a,8,9,10a,12,12a,12b-tetradecahydro-4H-
 cyclopenta[7,2]phenanthro[1,3]dioxol-8-ol)hexan-1-ol **145-1** and (5R)-5-
 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-
 tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-
 cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4-difluoropyridin-
 3-yl)hexan-1-ol **146-1** (20 mg, 0.04 mmol, 1.0 eq) was dissolved in
 tetrahydrofuran (3 mL). Dilute hydrochloric acid (1.5 mL, 3 mol/L) was added,
 and the reaction system was stirred at room temperature for 1 hour. The reaction
 was monitored by TLC (petroleum ether: ethyl acetate = 5:1). Water (10 mL)
 was added to the reaction system, and the aqueous layer was extracted with ethyl
 acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with
 saturated brine (3 × 10 mL). The ethyl acetate layer was dried over anhydrous
 sodium sulfate, filtered, and concentrated to obtain a crude product. The crude
 product was purified by thin-layer chromatography (petroleum ether: ethyl acetate
 = 1:1) to obtain a white solid, which was then subjected to chiral resolution
 (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 ×
 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate:
 1.5 mL/min; column temperature: 37°C) to obtain
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,4-difluoropyridin-3-yl)-6-
 hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-
 cyclopenta[1,2-a]phenanthrene-6,7-diol **146** (8.70 mg, purity: 97.42%, yield:
 43%, retention time t_R = 1.597 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-
 [(2R)-6-(2,4-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-

dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **145** (1.15 mg, purity: 96.12%, yield: 5%, retention time $t_R = 2.353$ min).

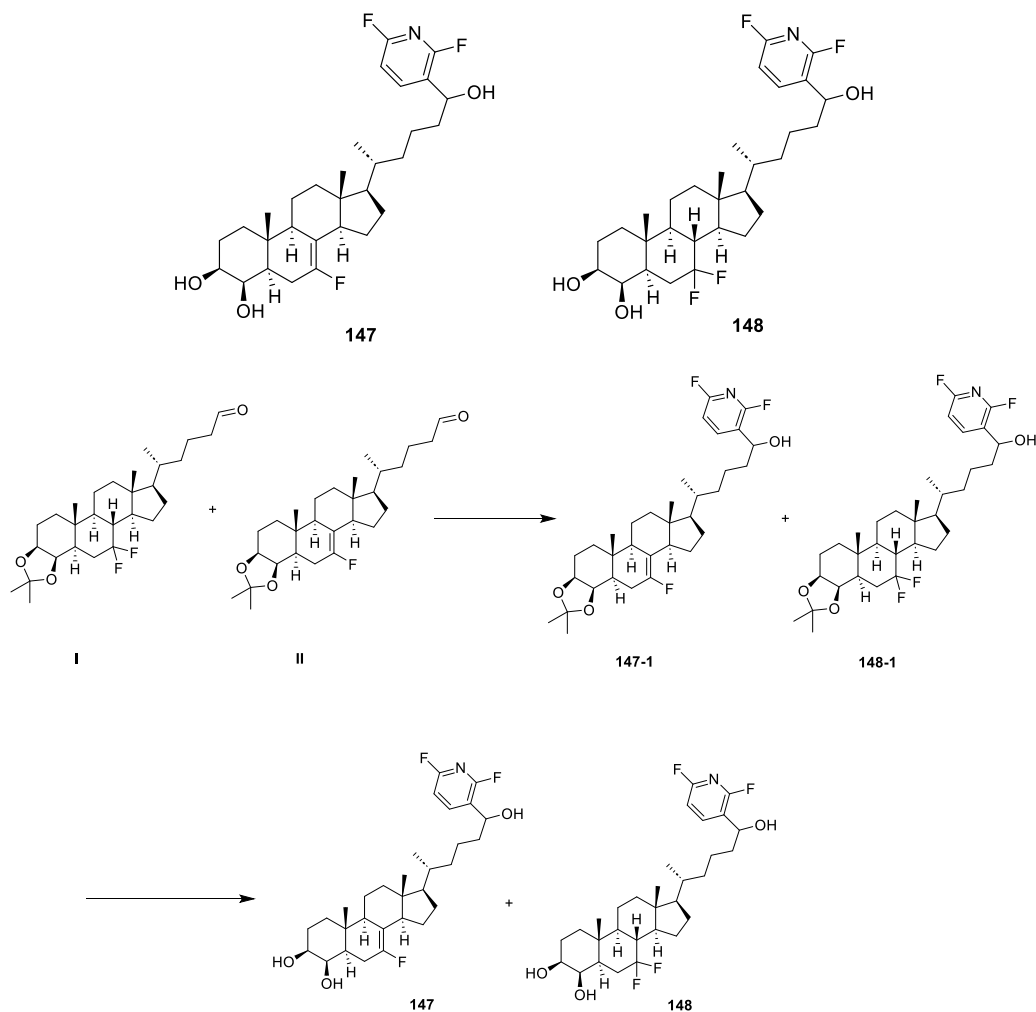
[0531] Compound 146: ^1H NMR (400 MHz, CDCl_3) δ 8.11 (dd, $J = 7.9, 5.7$ Hz, 1H), 6.96 (dd, $J = 8.6, 5.7$ Hz, 1H), 5.00 (t, $J = 6.6$ Hz, 1H), 3.74 (s, 1H), 3.60 (dt, $J = 11.3, 4.1$ Hz, 1H), 2.28 – 2.12 (m, 1H), 1.96 (d, $J = 13.7$ Hz, 2H), 1.84 – 1.70 (m, 10H), 1.46 – 1.25 (m, 10H), 1.10 (dd, $J = 10.2, 5.7$ Hz, 2H), 1.06 (s, 3H), 1.04 – 0.94 (m, 2H), 0.89 (t, $J = 5.9$ Hz, 3H), 0.65 (d, $J = 3.0$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -67.50, -67.56, -67.61, -88.64, -89.27, -102.16, -102.22, -102.23, -102.28, -110.63, -111.26. LC-MS: $[\text{M}+\text{H}]^+ = 542.00$, $t_R = 4.800$ min.

[0532] Compound 145: ^1H NMR (400 MHz, CDCl_3) δ 8.14 – 8.09 (m, 1H), 6.96 (dd, $J = 8.5, 5.7$ Hz, 1H), 5.00 (d, $J = 8.2$ Hz, 1H), 3.85 (s, 1H), 3.58 (s, 1H), 2.66 (s, 1H), 2.15 – 1.99 (m, 5H), 1.92 – 1.71 (m, 10H), 1.62 (s, 3H), 1.17 – 1.07 (m, 5H), 1.04 (s, 4H), 0.91 – 0.87 (m, 4H), 0.62 (d, $J = 3.1$ Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -67.50, -67.56, -67.60, -102.18, -102.25, -102.31, -109.75. LC-MS: $[\text{M}+\text{H}]^+ = 522.40$.

[0533] Examples 147 & 148:

[0534] Preparation of compound 147: (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0535] compound 148: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0536] Step 1: Starting material 3-bromo-2,6-difluoropyridine (102 mg, 0.52 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (0.18 mL, 0.45 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. A mixture of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (70 mg, 0.15 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The

reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude mixture of (5R)-1-(2,6-difluoropyridin-3-yl)-5-(((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,2]phenanthro[1,3]dioxol-8-ol)hexan-1-ol **147-1** and (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluoropyridin-3-yl)hexan-1-ol **148-1** (70 mg) as a colorless oil, which was directly used in the next step.

[0537] Step 2: A mixture of reactants (5R)-1-(2,6-difluoropyridin-3-yl)-5-(((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,2]phenanthro[1,3]dioxol-8-ol)hexan-1-ol **147-1** and (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluoropyridin-3-yl)hexan-1-ol **148-1** (70 mg, 0.09 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1.5 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 $\times$ 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 $\times$ 10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by thin-layer chromatography (petroleum ether: ethyl acetate = 1:1) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC_3, 3.0 $\times$

150 mm, 3 μ m; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **148** (24.76 mg, purity: 95.13%, yield: 36%, retention time t_R = 1.044 min) and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **147** (2.24 mg, purity: 86%, yield: 3%, retention time t_R = 1.398 min) as a white solid.

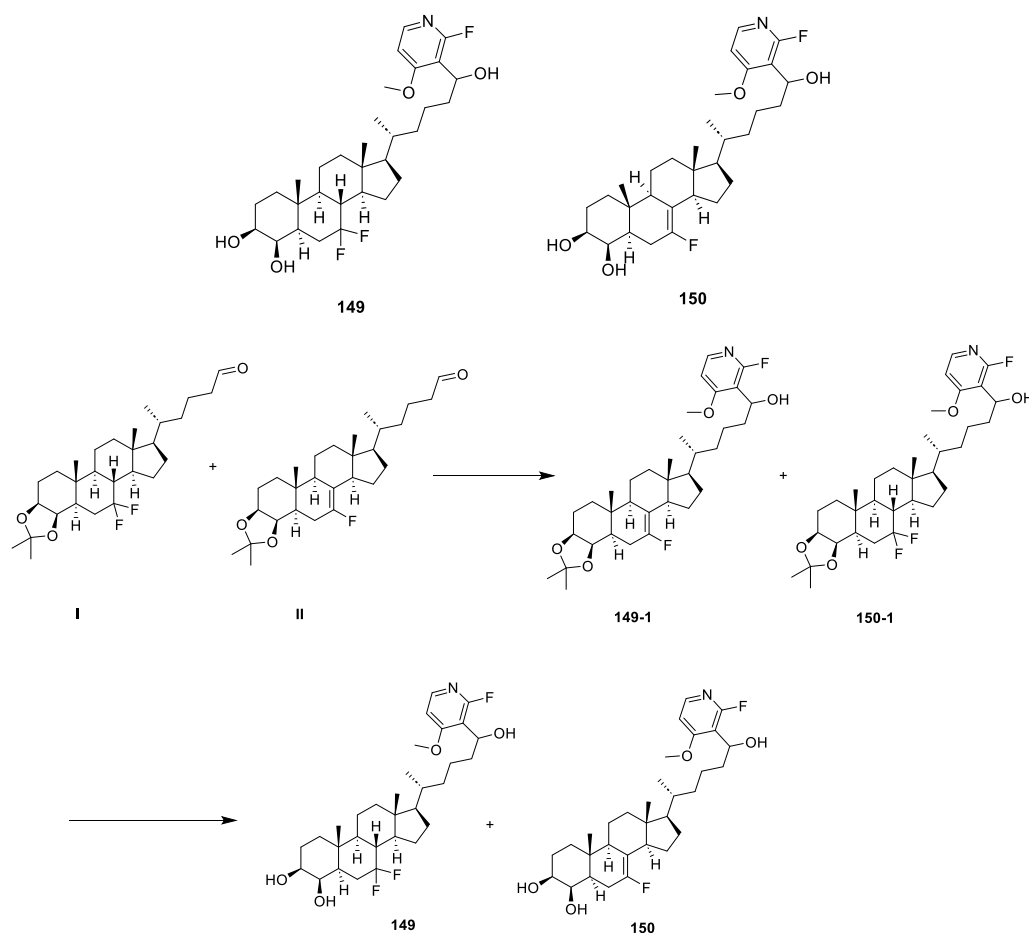
[0538] Compound **148**: ¹H NMR (400 MHz, DMSO) δ 8.16 (dd, J = 17.6, 8.3 Hz, 1H), 7.16 (dd, J = 8.1, 2.2 Hz, 1H), 5.47 (s, 1H), 4.72 (d, J = 6.2 Hz, 1H), 4.25 (s, 2H), 3.49 (s, 1H), 3.30 – 3.28 (m, 1H), 2.17 – 1.99 (m, 1H), 1.91 (d, J = 12.6 Hz, 1H), 1.81 – 1.63 (m, 5H), 1.43 (d, J = 10.4 Hz, 3H), 1.36 – 1.22 (m, 8H), 1.11 – 1.01 (m, 3H), 0.98 (s, 3H), 0.92 (d, J = 17.0 Hz, 1H), 0.85 (dd, J = 6.3, 2.7 Hz, 3H), 0.61 (d, J = 7.5 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -72.87, -72.90, -72.96, -72.99, -74.69, -74.72, -74.75, -86.66, -87.28, -108.66, -109.28.

[0539] Compound **147**: ¹H NMR (400 MHz, CDCl₃) δ 8.03 (q, J = 7.8 Hz, 1H), 6.85 (dd, J = 8.1, 2.7 Hz, 1H), 4.97 (dd, J = 11.1, 5.3 Hz, 1H), 3.85 (s, 1H), 3.63 – 3.56 (m, 1H), 2.66 (dd, J = 16.5, 8.1 Hz, 1H), 1.87 (dddd, J = 31.9, 28.4, 16.6, 5.7 Hz, 13H), 1.48 – 1.41 (m, 5H), 1.28 (dd, J = 9.4, 6.3 Hz, 6H), 1.13 – 1.07 (m, 3H), 1.05 (s, 3H), 0.91 (dd, J = 6.5, 3.6 Hz, 3H), 0.63 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -70.66, -70.69, -70.74, -70.77, -72.96, -72.99, -109.74.

[0540] Examples 149 & 150:

[0541] Preparation of compound **149**: (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and **[0542]** compound **150**: (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-

dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



- 5 **[0543]** Step 1: 3-Bromo-4-fluoro-2-methoxypyridine (139 mg, 0.68 mmol) was dissolved in tetrahydrofuran (3 mL). After purging with nitrogen three times, *n*-BuLi (37 mg, 0.58 mmol) was slowly added dropwise at -78°C, and the mixture was stirred at -78°C for 0.5 hours. After 0.5 hours, a solution of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-
- 10 tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** and (5R)-5-[(3aS,5aR,5bR,7aR,8R,10aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-
- 15 4,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]hexanal **II** (90 mg, 0.19 mmol) dissolved in tetrahydrofuran (2 mL) was added. The reaction mixture

was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the system was cooled to 0°C and quenched with saturated ammonium chloride aqueous solution (50 mL). The mixture was extracted with ethyl acetate (80 mL × 3), and the
 5 organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 93:7) to obtain a mixture of (5R)-5-((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-
 10 cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2-fluoro-4-methoxypyridin-3-yl)hexan-1-ol **149-1** and (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2']phenanthro[7,8-d][1,3]dioxole]-1-(4-fluoro-2-methoxypyridin-
 15 3-yl)hexanol **150-1** (63 mg, purity: 90%, yield based on **149-1**: 49.51%) as a white solid.

[0544] **149-1**: ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.33 (dd, *J* = 27.7, 2.2 Hz, 1H), 5.00 – 4.95 (m, 1H), 4.04 (s, 3H), 4.02 (dd, *J* = 6.9, 3.8 Hz, 2H), 2.03 – 1.95 (m, 3H), 1.84 (d, *J* = 7.0 Hz, 3H), 1.65 – 1.60 (m, 3H), 1.52 (s, 3H), 1.44
 20 (s, 3H), 1.38 (s, 3H), 1.35 (s, 1H), 1.31 (s, 4H), 1.30 (s, 5H), 1.27 (s, 4H), 1.08 (s, 3H), 0.91 (dd, *J* = 6.3, 4.9 Hz, 4H), 0.68 (d, *J* = 3.5 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -70.63, -88.99, -89.59, -89.65, -109.56, -111.35, -111.98.

[0545] Step 2: A mixture of reactants (5R)-5-((3aS,5aR,5bR,7aR,8R,10aR,12aR,12bR)-11-fluoro-2,2,5a,7a-tetramethyl-
 25 3a,5,5a,5b,6,7,7a,8,9,10,10a,12,12a,12b-tetradecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2-fluoro-4-methoxypyridin-3-yl)hexan-1-ol **149-1** and (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2']phenanthro[7,8-d][1,3]dioxole]-1-(4-fluoro-2-methoxypyridin-
 30 3-yl)hexanol **150-1** (63 mg, 0.11 mmol, 1.0 eq) was dissolved in tetrahydrofuran

(3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 70:30) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **149** (17.09 mg, purity: 100%, yield: 29.09%, retention time t_R = 2.090 min) and ((1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **150** (2.28 mg, purity: 100%, yield: 4.03%, retention time t_R = 3.142 min).

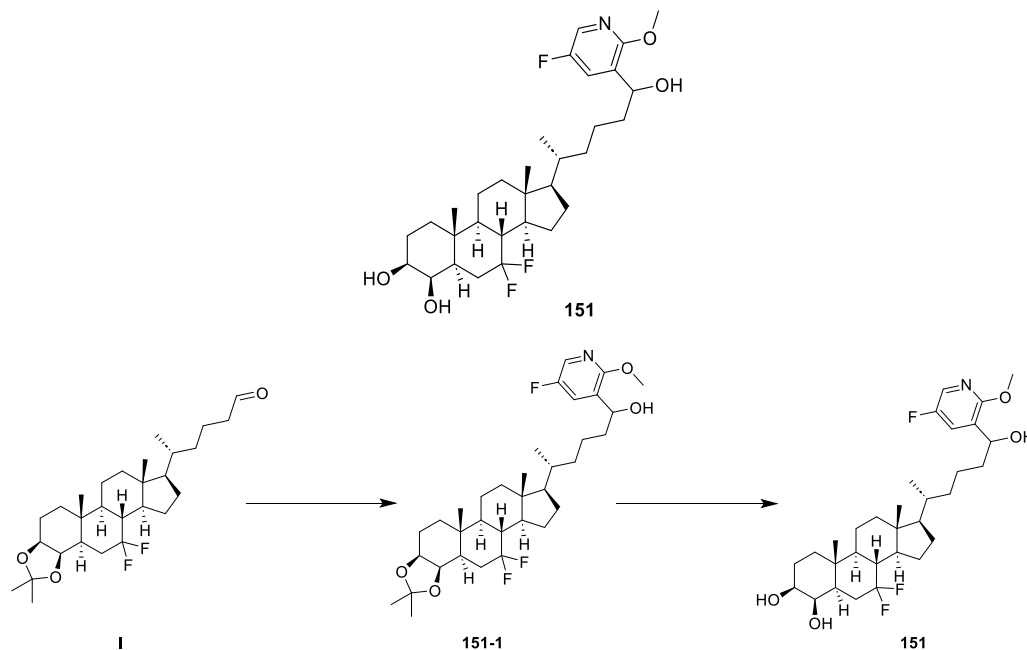
[0546] Compound **149**: ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 4.99 – 4.90 (m, 1H), 4.03 (s, 3H), 3.74 (s, 1H), 3.64 – 3.55 (m, 1H), 2.18 (ddd, J = 35.3, 12.4, 5.9 Hz, 2H), 1.97 (d, J = 13.1 Hz, 2H), 1.83 (ddd, J = 14.1, 12.7, 5.9 Hz, 6H), 1.76 – 1.65 (m, 4H), 1.38 (ddd, J = 16.4, 13.1, 6.1 Hz, 7H), 1.24 (d, J = 14.0 Hz, 3H), 1.11 (dd, J = 13.0, 4.3 Hz, 2H), 1.06 (s, 4H), 1.00 – 0.95 (m, 1H), 0.90 (dd, J = 6.3, 4.9 Hz, 3H), 0.65 (d, J = 3.4 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -70.65, -88.63, -89.26, -110.62, -111.25. LC-MS: [M+Na]⁺ = 576.3.

[0547] Compound **150**: ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 4.99 – 4.92 (m, 1H), 4.03 (s, 3H), 3.85 (s, 1H), 3.59 (d, J = 8.8 Hz, 1H), 2.64 (d, J = 13.1 Hz,

1H), 2.38 (d, *J* = 9.8 Hz, 1H), 2.25 – 2.19 (m, 1H), 2.15 (s, 1H), 2.04 – 1.99 (m, 2H), 1.88 – 1.84 (m, 3H), 1.80 (d, *J* = 6.7 Hz, 1H), 1.75 (s, 1H), 1.63 (d, *J* = 4.8 Hz, 1H), 1.56 (s, 3H), 1.47 – 1.43 (m, 3H), 1.41 (d, *J* = 4.2 Hz, 1H), 1.26 (s, 5H), 1.11 – 1.07 (m, 3H), 1.04 (s, 3H), 0.92 – 0.89 (m, 3H), 0.62 (d, *J* = 3.5 Hz, 3H).
 5 ¹⁹F NMR (376 MHz, CDCl₃) δ -70.65, -109.75. ¹⁹F NMR (376 MHz, CDCl₃) δ -70.65, -109.75.

[0548] Example 151:

[0549] Preparation of compound 151:
 10 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(5-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



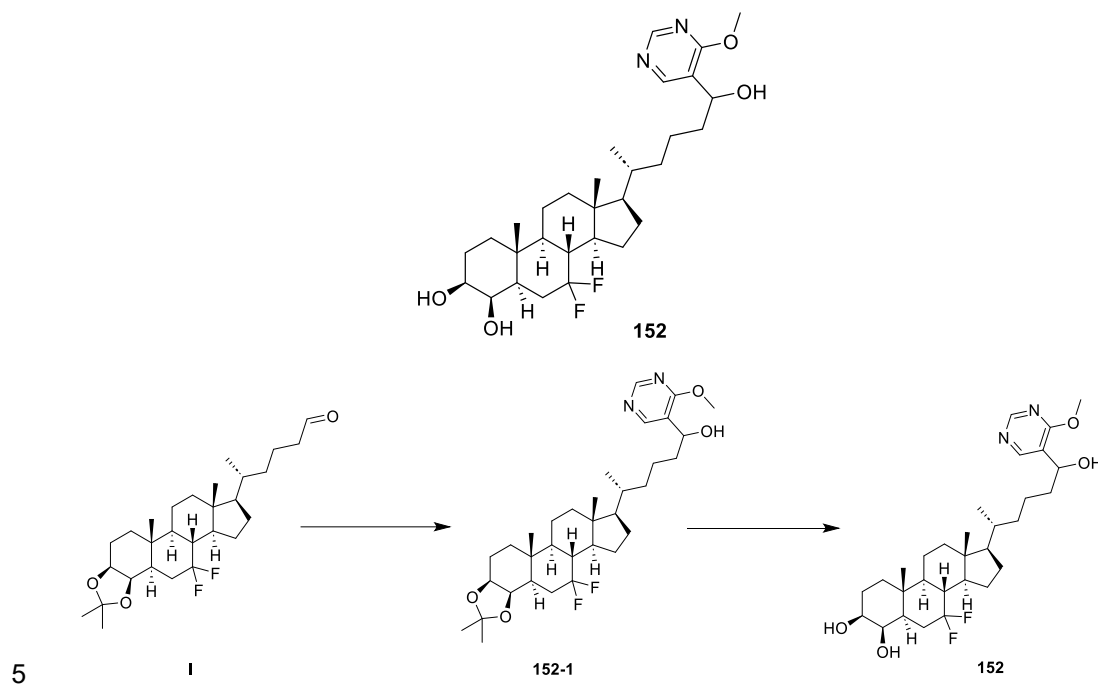
15 [0550] Starting material 3-bromo-5-fluoro-2-methoxypyridine (154 mg, 0.75 mmol, 3 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (0.25 mL, 0.75 mmol, 3 *eq*) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-
 20 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.214

mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a white solid **151-1**. The crude product **151-1** was dissolved in tetrahydrofuran (3 mL), and 3 M hydrochloric acid aqueous solution (1 mL) was slowly added dropwise. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 1:1). Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and the crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 100:0 to 50:50) and concentrated to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μm, mobile phase: A/B: CO₂/IPA (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(5-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **151** (39.82 mg, purity: 99.53%, yield: 34%, retention time *t_R* = 2.111 min).

[0551] Compound **151**: ¹H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 6.99 – 6.76 (m, 1H), 4.93 (d, *J* = 5.3 Hz, 1H), 3.90 (s, 3H), 3.74 (s, 1H), 3.60 (d, *J* = 11.1 Hz, 1H), 2.28 – 2.06 (m, 3H), 1.97 (d, *J* = 13.2 Hz, 1H), 1.82 (d, *J* = 7.7 Hz, 5H), 1.71 (dd, *J* = 19.1, 10.4 Hz, 5H), 1.43 (d, *J* = 22.3 Hz, 5H), 1.33 (d, *J* = 12.2 Hz, 3H), 1.23 (s, 1H), 1.09 (s, 2H), 1.06 (s, 3H), 1.02 – 0.94 (m, 2H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.64, -89.27, -110.63, -111.25, -146.23. LC-MS; [M+H]⁺ = 554.35.

[0552] Example **152**:

[0553] Preparation of compound **152** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(4-methoxypyrimidin-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0554] Step 1: Starting material 5-bromo-4-methoxypyrimidine (142 mg, 0.75 mmol, 3.5 *eq*) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C, and *n*-butyllithium (0.25 mL, 0.64 mmol, 3.0 *eq*) was added. The mixture was stirred at this temperature for 30 min. Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.2 mmol, 1.0 *eq*) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a crude product. The crude product was purified by thin-layer chromatography (petroleum ether: ethyl acetate = 2:1) to obtain (5R)-5-

[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-methoxypyrimidin-5-yl)hexan-1-ol **152-1** (2.0 mg, purity: 95%, yield: 15%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 8.52 (d, J = 4.9 Hz, 1H), 4.83 (s, 1H), 4.07 (s, 3H), 4.00 (s, 2H), 2.33 – 1.70 (m, 15H), 1.63 – 1.53 (m, 11H), 1.51 (s, 4H), 1.30 (s, 3H), 1.19 – 1.09 (m, 3H), 1.07 (s, 3H), 0.96 (dd, J = 14.6, 9.0 Hz, 3H), 0.93 – 0.90 (m, 3H), 0.66 (d, J = 11.6 Hz, 4H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.99, -89.62, -111.36, -111.98.

- [0555]** Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-methoxypyrimidin-5-yl)hexan-1-ol **152-1** (20 mg, 0.035 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1.5 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by thin-layer chromatography (petroleum ether: ethyl acetate = 1:1.8) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(4-methoxypyrimidin-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **152** (9.3 mg, purity: 99.10%, yield: 49%, retention time *t_R* = 1.613 min) as a white solid.

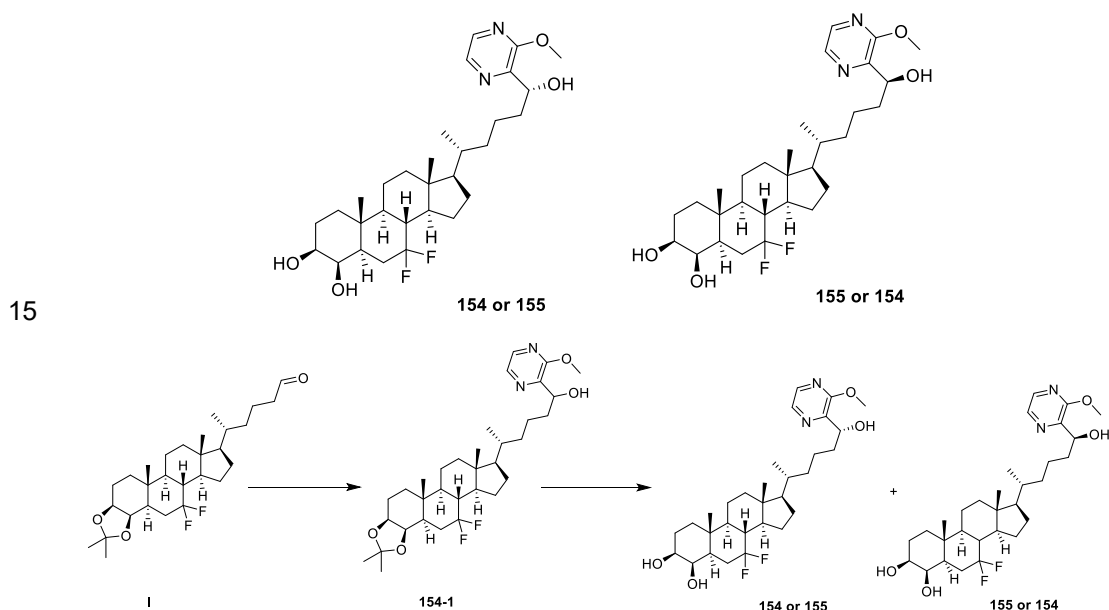
[0556] Compound **152**: ¹H NMR (400 MHz, DMSO) δ 8.67 (s, 1H), 8.49 (s,

1H), 5.27 (d, J = 4.9 Hz, 1H), 4.69 (d, J = 4.8 Hz, 1H), 4.41 (d, J = 6.0 Hz, 1H), 4.25 (d, J = 3.3 Hz, 1H), 3.93 (s, 3H), 3.48 (s, 1H), 3.30 (s, 1H), 2.18 – 1.88 (m, 3H), 1.79 – 1.51 (m, 8H), 1.43 (d, J = 12.9 Hz, 4H), 1.27 – 1.18 (m, 8H), 0.98 (s, 3H), 0.86 (d, J = 6.3 Hz, 3H), 0.62 (s, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -
 5 81.91, -82.53, -103.90, -104.52. LC-MS: [M+H]⁺ = 537.40.

[0557] Examples 154 & 155:

[0558] Preparation of compound 154 or 155
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-
 10 6-(3-methoxypyrazin-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-
 cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0559] compound 155 or 154 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-
 difluoro-1-[(2R,6S)-6-hydroxy-6-(3-methoxypyrazin-2-yl)hexan-2-yl]-
 9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0560] Step 1: 3-Bromo-2-methoxypyridine (60 mg, 0.32 mmol) was dissolved in tetrahydrofuran (3 mL). After purging with nitrogen three times, *n*-butyllithium (0.11 mL, 0.264 mmol) was slowly added dropwise at -78°C, and the
 20 mixture was stirred at -78°C for 0.5 hours. After 0.5 hours, a solution of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a,7a-

- tetramethyl-4,5,5,5a,5b,6,7,7a,8,9,10,10,10a,10b,12,12a,12b-hexadecahydro-3aH-cyclopenta[1':2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.21 mmol) dissolved in tetrahydrofuran (2 mL) was added. The reaction mixture was stirred at -78°C for 30 min. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). After the reaction was completed, the system was cooled to 0°C and quenched with saturated ammonium chloride aqueous solution (50 mL). The mixture was extracted with ethyl acetate (80 mL × 3), and the organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 93:7) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl]-1-(3-methoxypyrazin-2-yl)hexan-1-ol **154-1** (40 mg, purity: 90%, yield: 29.17%) as a white solid.
- [0561]** ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 2.8 Hz, 1H), 4.87 (s, 1H), 4.00 (s, 5H), 2.02 (ddd, J = 35.0, 22.2, 14.1 Hz, 5H), 1.82 (d, J = 6.9 Hz, 4H), 1.57 (s, 3H), 1.51 (s, 3H), 1.39 (d, J = 11.8 Hz, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.12 (d, J = 11.7 Hz, 2H), 1.07 (s, 3H), 0.92 (dd, J = 8.3, 4.1 Hz, 7H), 0.67 (s, 3H).
- [0562]** Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(3-methoxypyrazin-2-yl)hexan-1-ol (40 mg, 0.069 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL). Dilute hydrochloric acid (1 mL, 3 mol/L) was added, and the reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 70:30) to obtain a white solid, which was then separated by chiral resolution SFC (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain **155** (6.08 mg, 0.011 mmol, 15.89%, retention time *t_R* = 2.307 min) and **154** (6.39 mg, 0.012 mmol, 16.80%, retention time *t_R* = 4.428 min).

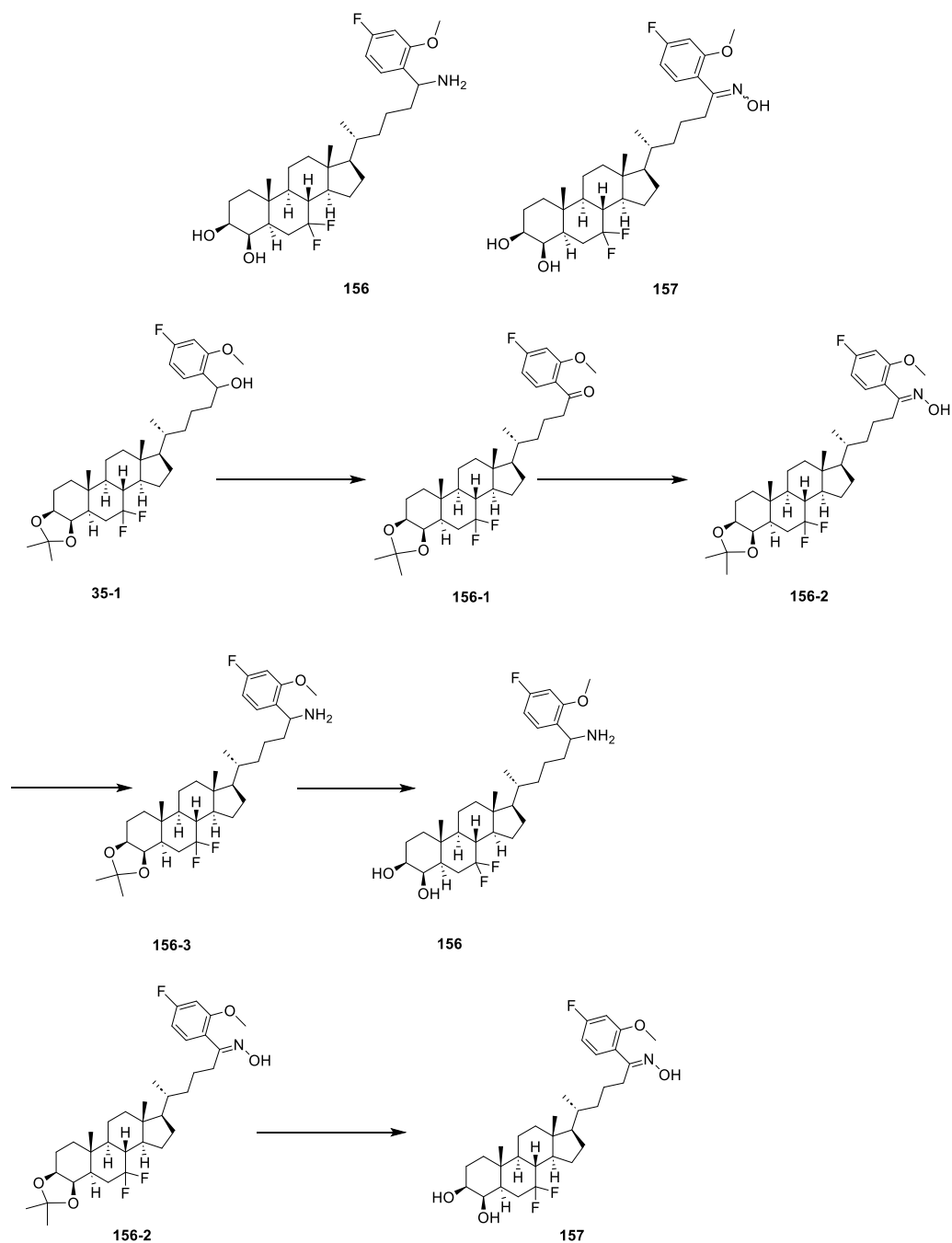
[0563] Compound **155**: ¹H NMR (400 MHz, CDCl₃) δ 8.05 (dd, *J* = 14.6, 2.8 Hz, 2H), 4.87 (dd, *J* = 7.6, 3.5 Hz, 1H), 4.00 (s, 3H), 3.74 (s, 1H), 3.60 (dt, *J* = 11.4, 4.1 Hz, 1H), 2.26 – 2.19 (m, 1H), 1.99 (dd, *J* = 15.8, 9.3 Hz, 3H), 1.86 – 1.79 (m, 6H), 1.72 (dd, *J* = 10.7, 7.3 Hz, 4H), 1.31 (d, *J* = 13.5 Hz, 6H), 1.26 (s, 4H), 1.15 – 1.08 (m, 2H), 1.06 (s, 4H), 0.97 (s, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.63, -89.25, -110.62, -111.25.

[0564] Compound **154**: ¹H NMR (400 MHz, CDCl₃) δ 8.05 (dd, *J* = 14.9, 2.8 Hz, 2H), 4.88 (d, *J* = 4.0 Hz, 1H), 4.00 (s, 3H), 3.74 (s, 1H), 3.61 (dd, *J* = 7.4, 3.9 Hz, 1H), 2.24 – 2.20 (m, 1H), 2.01 (dd, *J* = 11.5, 4.8 Hz, 3H), 1.86 – 1.78 (m, 6H), 1.72 (dd, *J* = 10.6, 7.3 Hz, 4H), 1.38 – 1.31 (m, 6H), 1.26 (s, 4H), 1.12 (d, *J* = 9.3 Hz, 2H), 1.06 (s, 4H), 0.97 (s, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.62, -89.25, -110.61, -111.24.

[0565] Examples **156 & 157**:

[0566] Preparation of compound **156** (**1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR**)-1-[(2R)-6-amino-6-(4-fluoro-2-methoxyphenyl)hexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0567] compound **157** [(1E,5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(4-fluoro-2-methoxyphenyl)hexylidene]hydroxylamine.



[0568] Step 1: Compound (5R)-5-

5 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexan-1-ol **35-1** (100 mg, 0.17 mmol, 1.0 eq) was dissolved in DCM (5 mL). Dess-Martin periodinane (143.10 mg, 0.337 mmol, 2.0 eq) was

added, and the resulting mixture was stirred under N₂ at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Saturated sodium bicarbonate (10 mL) was added to the reaction system, and the

5 dichloromethane layer was washed with saturated sodium sulfite. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was subjected to column chromatography (petroleum ether: ethyl acetate = 92:8) by wet loading to obtain (5R)-5-

10 [(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexan-1-one **156-1** (75 mg, purity: 95%, yield: 71.49%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, J = 8.6, 7.0 Hz, 1H), 6.68 (ddd, J = 13.2, 9.5, 2.3 Hz, 1H), 4.01 (dt, J = 8.5, 6.2 Hz, 2H), 3.89 (s, 3H), 2.89 (dt, J = 8.2, 6.1 Hz, 1H), 1.99 – 1.55 (m, 7H), 1.51 (s, 2H), 1.45 – 1.34 (m, 2H), 1.30 (s, 1H), 1.28 – 1.10 (m, 3H), 1.07 (s, 2H), 0.94 (d, J = 6.5 Hz, 2H), 0.66 (d, J = 11.9 Hz, 2H).

[0569] Step 2: Starting material (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-

20 tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexan-1-one **156-1** (75 mg, 0.128 mmol) and anhydrous sodium acetate (62 mg, 0.102 mmol, 6.0 eq) were dissolved in ethanol (5 mL), and hydroxylamine hydrochloride (53 mg, 0.77 mmol, 6.0 eq) was added. The

25 reaction mixture was stirred at 90°C under a nitrogen atmosphere for 5 hours. LCMS showed that the reaction had completed with the product, and the reaction was stopped. (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate,

30 filtered, and concentrated to obtain the crude product **156-2**. LC-MS: [M+H]⁺ = 606.7.

[0570] Step 3: [(1E,5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-Difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexylidene]hydroxylamine **156-2** (20 mg, 0.034 mmol) was dissolved in a solution of ammonia in methanol (5 mL). The reaction system was cooled to 0°C, and Raney nickel (20 mg) was slowly added. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 1 hour. LCMS monitoring showed complete consumption of the starting material and formation of a new spot. The mixture was filtered and concentrated to obtain a crude product. The crude product was added with silica gel and purified by column chromatography (dichloromethane: methanol = 10:1) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexan-1-amine **156-3** (10 mg, 0.014 mmol, 40.94%). Compound **156-3**: ¹H NMR (400 MHz, CDCl₃) δ 7.28 (s, 1H), 6.62 (dd, J = 12.9, 9.6 Hz, 2H), 4.29 (s, 1H), 4.01 (d, J = 14.7 Hz, 2H), 3.81 (s, 3H), 2.21 – 1.59 (m, 15H), 1.50 (s, 3H), 1.29 (s, 3H), 1.24 – 1.07 (m, 6H), 1.06 (s, 3H), 0.99 – 0.85 (m, 6H), 0.84 – 0.81 (m, 3H), 0.63 (t, J = 6.8 Hz, 3H).

[0571] Step 4: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexan-1-amine **156-3** (10 mg, 0.017 mmol) was dissolved in tetrahydrofuran (1 mL), and 3 N hydrochloric acid (0.5 mL) was added. The reaction was monitored by LCMS. After the reaction was completed, the reaction mixture was diluted with ethyl acetate. The pH was adjusted to approximately 8 with sodium bicarbonate, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate, and the organic phases were combined, dried over anhydrous sodium sulfate, and purified by silica gel column

chromatography (dichloromethane: methanol = 90:10) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-amino-6-(4-fluoro-2-methoxyphenyl)hexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **156** (5.52 mg, 0.009 mmol, 52.08%) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 2H), 7.42 (dd, J = 15.6, 8.1 Hz, 1H), 7.01 (m, 1H), 6.87 (td, J = 8.5, 2.4 Hz, 1H), 4.41 (s, 2H), 4.26 (s, 1H), 3.83 (s, 3H), 3.48 (s, 1H), 3.36 (s, 1H), 2.05 (m, 2H), 1.89 (d, J = 12.2 Hz, 1H), 1.67 (m, 6H), 1.58 (m, 2H), 1.42 (d, J = 9.2 Hz, 2H), 1.24 (d, J = 9.4 Hz, 10H), 0.97 (s, 3H), 0.83 (m, 6H), 0.60 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -81.91, -82.53, -103.92, -104.54, -105.60, -105.64. LCMS (ESI) [M+H-N₂H]⁺ = 536.3, t_R = 1.222 min.

[0572] Step 5: Compound [(1E,5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4-fluoro-2-methoxyphenyl)hexylidene]hydroxylamine **156-2** (15 mg, 0.041 mmol) was dissolved in tetrahydrofuran (1 mL), and 3 N hydrochloric acid (0.5 mL) was added. The reaction was monitored by LCMS. After the reaction was completed, the reaction mixture was diluted with ethyl acetate. The pH was adjusted to approximately 8 with sodium bicarbonate, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate, and the organic phases were combined, dried over anhydrous sodium sulfate, and purified by silica gel column chromatography (dichloromethane: methanol = 90:10) to obtain [(1E,5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(4-fluoro-2-methoxyphenyl)hexylidene]hydroxylamine **157** (5.52 mg, 0.009 mmol, purity: 83.46%, yield: 62.67%) as a brown solid.

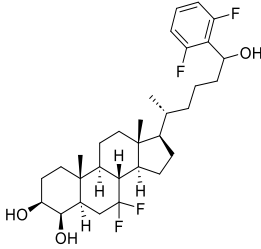
[0573] Compound **157**: ¹H NMR (400 MHz, CDCl₃) δ 10.90 (s, 1H), 7.20 (m, 1H), 6.94 (m, 1H), 6.76 (td, J = 8.4, 2.4 Hz, 1H), 3.76 (d, J = 16.2 Hz, 2H), 3.48 (s, 2H), 3.30 (m, 1H), 2.06 (ddd, J = 29.4, 20.8, 8.0 Hz, 2H), 1.87 (d, J = 12.6 Hz, 1H), 1.68 (s, 3H), 1.66 (s, 4H), 1.36 (m, 5H), 1.24 (d, J = 9.7 Hz, 8H), 1.03 (m,

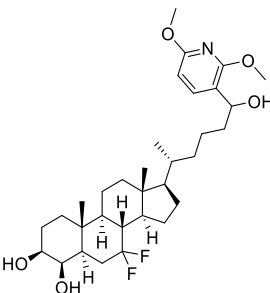
1H), 0.97 (s, 3H), 0.86 (m, 3H), 0.78 (d, J = 6.4 Hz, 2H), 0.59 (d, J = 8.4 Hz, 3H).

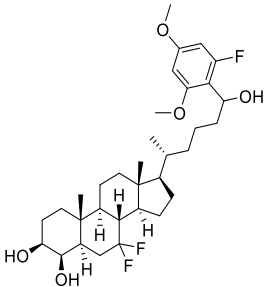
¹⁹F NMR (376 MHz, CDCl₃) δ -81.91, -82.53, -103.92, -104.54, -105.60, -105.64.

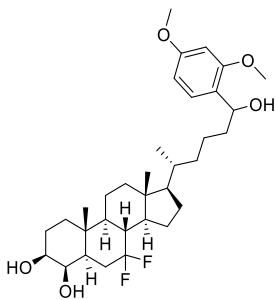
LCMS (ESI) [M+H]⁺ = 566.45, t_R = 5.734 min, 5.976 min.

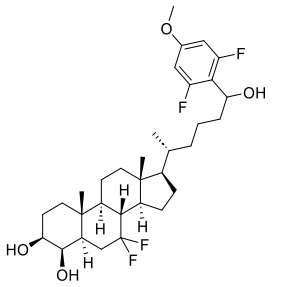
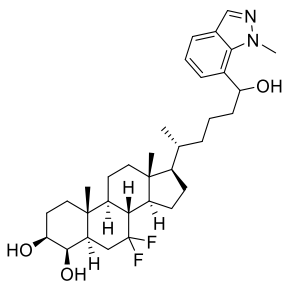
- 5 **[0574]** The following examples can be completed by referring to the synthetic method of Example **54**:

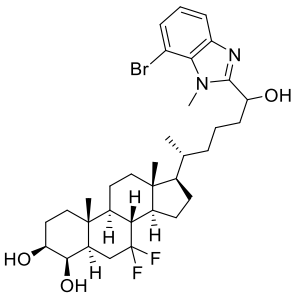
Exa- mple	Structural formula	Compound name	Characterization results
161		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-Difluorophenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.21 (m, 1H), 6.87 (t, J=8.3 Hz, 2H), 5.04 (d, J =7.2 Hz, 1H), 3.74 (s, 1H), 3.60 (d, J =11.3 Hz, 1H), 2.18 (m, 1H), 1.98 (m, 2H), 1.81 (m, 6H), 1.68 (m, 3H), 1.37 (ddd, J =42.4, 21.9, 12.6 Hz, 10H), 1.11 (dd, J =13.2, 4.6 Hz, 2H), 1.06 (s, 3H), 0.98 (m, 2H), 0.89 (t, J =6.0 Hz, 3H), 0.65 (d, J=3.7 Hz, 3H). ¹³ C NMR (101 MHz, CDCl ₃) δ 164.65, 163.79, 137.73, 131.82, 130.78, 111.87, 111.61, 73.43,

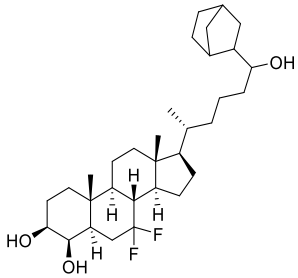
			71.94, 70.56, 55.18, 50.84, 43.10, 42.13, 41.93, 39.24, 37.87, 37.75, 36.23, 35.59, 35.39, 34.94, 28.98, 28.44, 25.63, 20.52, 18.65, 18.61, 18.47, 13.78, 11.84 ¹⁹ F NMR (377 MHz, CDCl ₃) δ - 88.64, -89.27, -89.29, -110.63, -111.26, -115.38, -115.40, -115.46.
177		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-Dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.49 (dd, J = 8.0, 3.4 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 4.73 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.74 (s, 1H), 3.60 (m, 1H), 2.15 (m, 2H), 1.97 (d, J = 13.0 Hz, 1H), 1.81 (dd, J = 17.2, 6.0 Hz, 5H), 1.68 (m, 5H), 1.37 (m, 6H), 1.25 (s, 2H), 1.09 (s, 2H), 1.06 (s, 4H), 1.01 (s, 2H), 0.90 (dd, J = 6.3, 4.2 Hz, 3H), 0.66 (s, 3H).

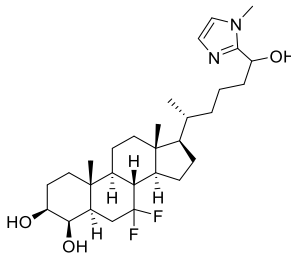
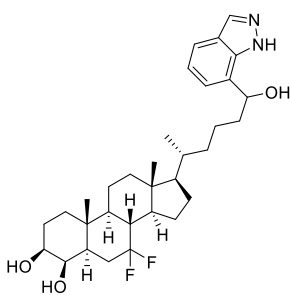
			¹⁹ F NMR (377 MHz, CDCl ₃) δ -88.62, -89.25, -110.62, -111.24, -115.52, -115.58. ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.63, -89.25, -110.62, -111.25. LC-MS: [M-H] ⁻ = 564.4.
182		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-(2-fluoro-4,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 6.24 (m, 2H), 4.92 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.74 (s, 1H), 3.60 (dd, J = 7.2, 4.1 Hz, 1H), 2.20 (m, 2H), 1.97 (d, J = 13.0 Hz, 1H), 1.83 (ddd, J = 20.3, 11.6, 4.0 Hz, 6H), 1.68 (m, 4H), 1.41 (m, 5H), 1.27 (dd, J = 20.3, 8.0 Hz, 4H), 1.11 (dd, J = 12.8, 4.5 Hz, 2H), 1.05 (s, 3H), 0.97 (m, 2H), 0.89 (dd, J = 6.4, 4.6 Hz, 3H), 0.65 (d, J = 3.9 Hz, 3H). ¹⁹ F NMR (377 MHz,

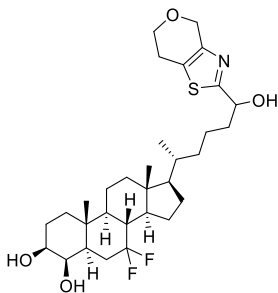
			CDCl_3) δ -88.62, -89.25, -110.62, -111.24, -115.52, -115.58. LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 565.50$.
183		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,4-Dimethoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	^1H NMR (400 MHz, CDCl_3) δ 7.19 (dd, $J = 8.3, 3.8$ Hz, 1H), 6.46 (m, 2H), 4.79 (d, $J = 6.7$ Hz, 1H), 3.82 (d, $J = 3.0$ Hz, 3H), 3.80 (s, 3H), 3.74 (s, 1H), 3.60 (m, 1H), 2.24 (m, 1H), 2.09 (s, 1H), 1.97 (d, $J = 12.6$ Hz, 1H), 1.83 (m, 5H), 1.69 (m, 5H), 1.36 (m, 10H), 1.09 (d, $J = 3.6$ Hz, 1H), 1.06 (s, 3H), 0.94 (m, 5H), 0.65 (m, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.63, -89.25, -110.66, -111.25. LC-MS: $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ = 547.45$.

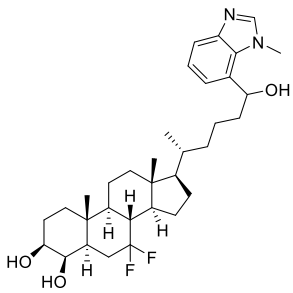
197		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-Difluoro-4-methoxyphenyl)-6-fluorohexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 6.43 (d, J = 10.2 Hz, 2H), 4.94 (t, J = 7.1 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 1H), 3.63 – 3.57 (m, 1H), 2.25 – 2.09 (m, 2H), 1.96 (d, J = 11.7 Hz, 2H), 1.86 – 1.78 (m, 6H), 1.75 – 1.70 (m, 5H), 1.48 – 1.31 (m, 11H), 1.06 (s, 3H), 1.01 – 0.94 (m, 2H), 0.88 (t, J = 5.9 Hz, 3H), 0.65 (d, J = 3.0 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -88.00, -88.63, -109.99, -110.62, -113.68, -113.74. LC-MS: [M-H] ⁻ = 569.50.
207		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahy	¹ H NMR (400 MHz, CDCl ₃) δ 8.11 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 5.30 (s, 1H), 4.48 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J =

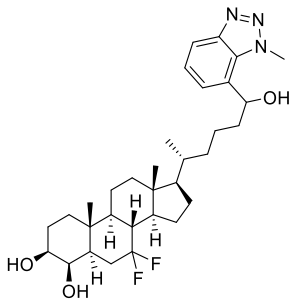
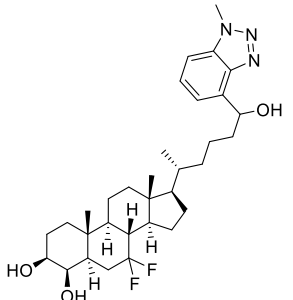
		dro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	11.3, 4.2 Hz, 1H), 2.19 (dd, J = 25.6, 9.4 Hz, 2H), 1.84 (s, 6H), 1.75 (s, 4H), 1.27 (s, 12H), 1.11 (t, J = 9.0 Hz, 2H), 1.06 (s, 3H), 0.92 (t, J = 5.9 Hz, 3H), 0.66 (d, J = 1.4 Hz, 3H). ¹⁹ F NMR (377 MHz) δ -275.52, -275.91, -289.12, -289.52. LC-MS: [M+H] ⁺ = 559.2.
212		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(7-Bromo-1-methylbenzo[d]imidazol-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.70 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 5.01 (m, 1H), 4.18 (d, J = 3.5 Hz, 3H), 3.74 (s, 1H), 3.61 (dd, J = 9.9, 6.1 Hz, 1H), 2.19 (dd, J = 25.5, 9.3 Hz, 3H), 1.97 (d, J = 14.2 Hz, 3H), 1.83 (m, 5H), 1.70 (d, J = 11.9 Hz, 3H), 1.42 (dd, J = 33.2, 11.1 Hz, 7H), 1.27 (m, 3H), 1.09 (s,

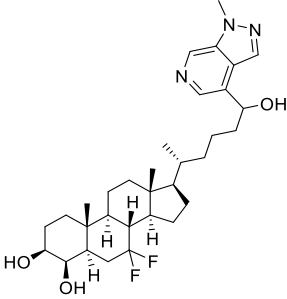
			2H), 1.05 (s, 3H), 0.91 (dd, J = 6.3, 2.3 Hz, 3H), 0.66 (d, J = 5.5 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ - 88.62, -89.25, -110.62, -111.22. LC-MS: [M+H] ⁺ = 637.2 [M+H+2] ⁺ = 639.2.
213		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(Bicyclo[2.2.1]heptan-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR(400 MHz, CDCl ₃) δ 3.74 (s, 1H), 3.59 (m, 2H), 2.19 (m, 1H), 1.98 (d, J = 12.9Hz, 1H), 1.81 (dt, J = 39.1, 11.7Hz, 9H), 1.39 (dd, J = 11.3, 6.6Hz, 13H), 1.32 (m, 4H), 1.27 (s, 3H), 1.11 (m, 2H), 1.06 (s, 3H), 0.99 (dd, J = 16.0, 5.6Hz, 2H), 0.92 (d, J = 6.5Hz, 5H), 0.66 (s, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ - 88.64, -89.26, -110.63, -111.26.

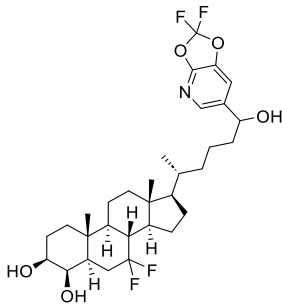
223		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(3-methylimidazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 7.07 (s, 1H), 6.86 (s, 1H), 4.78 (s, 1H), 3.73 (s, 4H), 3.58 (s, 1H), 1.83 (m, 7H), 1.73 (d, J = 15.0 Hz, 5H), 1.39 (d, J = 13.2 Hz, 8H), 1.25 (s, 6H), 1.09 (s, 3H), 1.06 (s, 3H), 0.91 (s, 5H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.55, -89.39, -110.71, -111.25. LC-MS: [M-H]⁻ = 507.45.
224		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(1H-indazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 12.98 (s, 1H), 8.11 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 6.9 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 5.35 (d, J = 4.2 Hz, 1H), 5.02 (s, 1H), 4.46 (d, J = 6.0 Hz, 1H), 4.29 (d, J = 3.3 Hz, 1H), 3.55 (s, 2H), 1.94 (s, 1H), 1.71

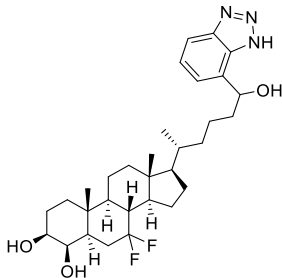
			(d, J = 11.3 Hz, 8H), 1.64 (d, J = 18.4 Hz, 3H), 1.53 – 1.38 (m, 6H), 1.15 (dd, J = 60.0, 9.4 Hz, 7H), 1.04 (s, 3H), 0.90 (t, J = 5.9 Hz, 4H), 0.65 (t, J = 9.6 Hz, 3H). ¹⁹ F NMR (376 MHz, DMSO) δ -86.65, -87.27, -108.67, -109.28. LC-MS: [M-H] ⁻ = 543.50.
257		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR(400 MHz, CDCl ₃) δ 5.02 (d,J = 5.3Hz, 1H), 4.82 (s, 2H), 4.03 (t,J = 5.6Hz, 2H), 3.74 (s, 1H), 3.59 (dd,J = 11.4, 3.5Hz, 1H), 2.96 (t,J = 5.4Hz, 2H), 2.29 – 2.05 (m, 2H), 1.97 (d,J = 12.7Hz, 2H), 1.85 (dd,J = 22.1, 7.5Hz, 6H), 1.76 – 1.68 (m, 4H), 1.44 – 1.36 (m, 5H), 1.29 (d,J = 20.9Hz, 4H), 1.11 (d,J = 11.8Hz, 2H), 1.07

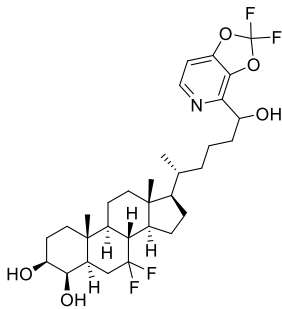
			(d, J = 7.6 Hz, 4H), 0.92 (d, J = 6.4 Hz, 3H), 0.66 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.63, -89.26, -110.62, -111.25. LC-MS: [M-H] ⁺ = 566.40.
261		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(3-methylbenzo[d]imidazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.58 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.19 (dt, J = 15.1, 7.2 Hz, 2H), 5.54 (t, J = 6.8 Hz, 1H), 4.82 (dd, J = 13.7, 6.9 Hz, 1H), 4.40 (d, J = 5.0 Hz, 1H), 4.24 (d, J = 3.3 Hz, 1H), 3.84 (s, 3H), 3.49 (s, 1H), 3.36 (s, 1H), 2.12 (d, J = 11.8 Hz, 1H), 1.85 (d, J = 37.6 Hz, 4H), 1.61 (dd, J = 33.1, 14.4 Hz, 5H), 1.45 – 1.23 (m, 10H), 1.07 (d, J = 10.6 Hz, 3H), 0.98 (s, 3H), 0.90 – 0.86 (m, 3H), 0.63 (d, J = 3.5 Hz, 3H).

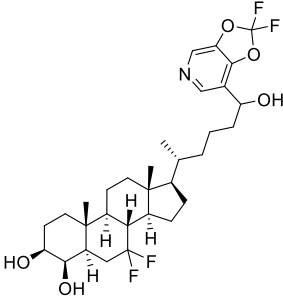
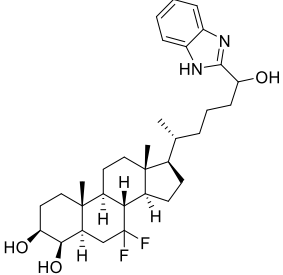
			¹⁹ F NMR (376 MHz, DMSO) δ -86.64, -87.27, -108.65, -109.27. LC-MS: [M-H] ⁻ = 557.55.
271		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(3-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 8.02 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 7.1 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H), 5.21 (s, 1H), 4.60 (s, 3H), 3.74 (s, 1H), 3.61 (s, 1H), 1.84 (s, 3H), 1.51 – 1.42 (m, 10H), 1.26 (d, J = 1.5 Hz, 10H), 1.06 (s, 5H), 0.92 (d, J = 6.4 Hz, 4H), 0.66 (d, J = 3.1 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -88.60, -89.24, -110.70, -111.26. LC-MS: [M+H] ⁺ = 560.45.
272		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(1-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.57 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 6.9 Hz, 1H), 5.31 – 5.24 (m, 1H), 4.40 (s,

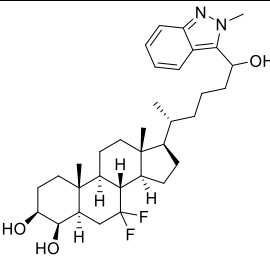
		3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	3H), 3.74 (s, 1H), 3.63 – 3.57 (m, 1H), 1.89 – 1.64 (m, 9H), 1.42 (d, J = 11.4 Hz, 7H), 1.27 (dd, J = 12.1, 4.9 Hz, 8H), 1.05 (s, 4H), 0.90 (dd, J = 6.4, 4.7 Hz, 4H), 0.65 (d, J = 3.6 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -88.51, -89.42, -110.45, -111.33. LC-MS: [M-H] ⁻ = 558.40.
275		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(1-methylpyrazolo[3,4-c]pyridin-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.43 (s, 1H), 8.24 (d, J = 0.9 Hz, 1H), 5.45 (s, 1H), 4.89 (dd, J = 13.2, 6.8 Hz, 1H), 4.41 (s, 1H), 4.25 (s, 1H), 4.16 (s, 3H), 3.49 (s, 1H), 3.21 (s, 1H), 2.17 – 1.99 (m, 2H), 1.89 (d, J = 14.2 Hz, 1H), 1.76 – 1.60 (m, 7H), 1.42 (d, J = 13.0 Hz, 3H), 1.27 (dd, J = 15.4, 8.9 Hz, 8H), 1.07

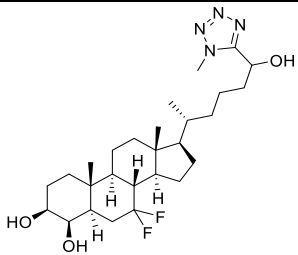
			– 0.99 (m, 3H), 0.97 (s, 3H), 0.92 (d, J = 15.9 Hz, 2H), 0.82 (t, J = 6.9 Hz, 3H), 0.59 (d, J = 4.2 Hz, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -69.20, -71.09, -86.67, -87.29, -108.66, -109.28. LC-MS: [M-H]⁻ = 558.40.
284		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,2-Difluoro[1,3]dioxolo[4,5-b]pyridin-6-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 1.7 Hz, 1H), 7.43 (d, J = 1.8 Hz, 1H), 4.74 (dd, J = 13.3, 6.2 Hz, 1H), 3.74 (s, 1H), 3.63 – 3.56 (m, 1H), 2.21 (dd, J = 19.0, 11.3 Hz, 2H), 1.99 (dd, J = 17.3, 9.5 Hz, 2H), 1.87 – 1.72 (m, 7H), 1.48 – 1.25 (m, 12H), 1.10 (dd, J = 10.5, 5.9 Hz, 2H), 1.06 (s, 3H), 0.98 (d, J = 10.4 Hz, 1H), 0.89 (dd, J = 6.3, 5.0 Hz, 3H), 0.65 (d, J = 2.3 Hz, 3H). ¹⁹F

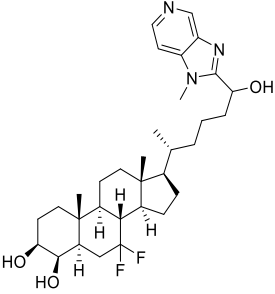
			NMR (377 MHz, CDCl₃) δ -49.24, -49.48, -49.52, -49.76, -88.65, -89.27, -110.63, -111.26. LC-MS: [M-H]⁻ = 584.70.
282		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(3H-benzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.23 (s, 3H), 5.16 (d, J = 6.1 Hz, 1H), 3.74 (s, 1H), 3.60 (d, J = 11.4 Hz, 1H), 2.18 (d, J = 16.8 Hz, 1H), 1.96 (d, J = 11.4 Hz, 2H), 1.85 (d, J = 19.8 Hz, 5H), 1.74 – 1.64 (m, 4H), 1.41 (dd, J = 22.6, 10.9 Hz, 6H), 1.30 (dd, J = 18.3, 9.5 Hz, 5H), 1.13 – 1.08 (m, 2H), 1.06 (s, 3H), 1.01 – 0.93 (m, 2H), 0.89 (s, 3H), 0.65 (d, J = 2.4 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.64, -89.27, -110.63, -

			111.26. LC-MS: [M+H] ⁺ = 546.3.
296		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,2-Difluoro[1,3]dioxolo[4,5-c]pyridin-4-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 8.36 (d, J = 5.2 Hz, 1H), 7.05 (d, J = 5.2 Hz, 1H), 4.96 – 4.83 (m, 1H), 3.74 (s, 1H), 3.60 (d, J = 10.9 Hz, 1H), 2.19 (dd, J = 25.9, 9.4 Hz, 1H), 1.97 (d, J = 11.8 Hz, 1H), 1.82 (dd, J = 13.9, 5.6 Hz, 4H), 1.69 (dd, J = 18.3, 6.5 Hz, 4H), 1.57 – 1.36 (m, 8H), 1.33 – 1.24 (m, 4H), 1.11 (d, J = 9.5 Hz, 2H), 1.06 (s, 3H), 0.98 (dd, J = 19.0, 7.3 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -49.26, -49.50, -49.56, -49.58, -49.82, -88.64, -89.27, -110.63, -111.26. LC-MS: [M+H] ⁺ = 586.3.

297		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,2-Difluoro[1,3]dioxolo[4,5-c]pyridin-7-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 8.46 (d, J = 3.4 Hz, 1H), 8.33 (s, 1H), 4.92 (s, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.1 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.02 – 1.93 (m, 2H), 1.83 (dd, J = 7.3, 4.6 Hz, 4H), 1.75 – 1.65 (m, 4H), 1.50 – 1.37 (m, 6H), 1.35 – 1.25 (m, 5H), 1.14 – 1.09 (m, 2H), 1.06 (s, 3H), 1.03 – 0.94 (m, 2H), 0.92 – 0.88 (m, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -49.18, -49.20, -49.42, -49.44, -49.57, -49.59, -49.81, -49.83, -88.65, -89.28, -110.64, -111.26. LC-MS: [M+H]⁺ = 586.2.
303		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(1H-benzo[d]imidazol-2-	¹H NMR (400MHz, DMSO) δ 12.19 (s, 1H), 8.19 (s, 1H), 7.47 (s, 2H), 7.11 (dd, J = 6.0, 3.1Hz, 2H), 5.69 (s, 1H), 4.74 (dd, J =

		yl)hexan-2-yl]- 9a,11a- dimethylhexadecahy dro-1H- cyclopenta[1,2- a]phenanthrene-6,7- diol	11.7, 5.8Hz, 1H), 4.40 (s, 1H), 4.24 (s, 1H), 3.49 (s, 1H), 3.34 (s, 1H), 2.15 – 2.03 (m, 1H), 1.90 (d, J = 12.0Hz, 1H), 1.66 (ddd, J = 34.9, 24.4, 9.7Hz, 8H), 1.47 – 1.20 (m, 11H), 1.10 – 1.00 (m, 3H), 0.98 (s, 3H), 0.97 – 0.88 (m, 2H), 0.86 (d, J = 4.1Hz, 3H), 0.62 (s, 3H). ¹⁹ F NMR (376MHz, DMSO) δ - 86.66, -87.28, - 108.65, -109.27. LC-MS [M-H] ⁻ = 543.35.
325		(1R,3aS,3bS,5aR,6R ,7S,9aR,9bS,11aR)- 4,4-Difluoro-1- [(2R)-6-hydroxy-6- (2-methylindazol-3- yl)hexan-2-yl]- 9a,11a- dimethylhexadecahy dro-1H- cyclopenta[1,2- a]phenanthrene-6,7-	¹ H NMR (400 MHz, CDCl ₃) δ 7.74 (s, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.29 (s, 1H), 7.08 (s, 1H), 5.25 (s, 1H), 4.24 (d, J = 3.5 Hz, 3H), 3.74 (s, 1H), 3.64 – 3.55 (m, 1H), 2.28 – 2.11 (m, 3H), 1.99 (dd, J = 28.5, 13.2 Hz, 5H), 1.82 – 1.67 (m, 9H),

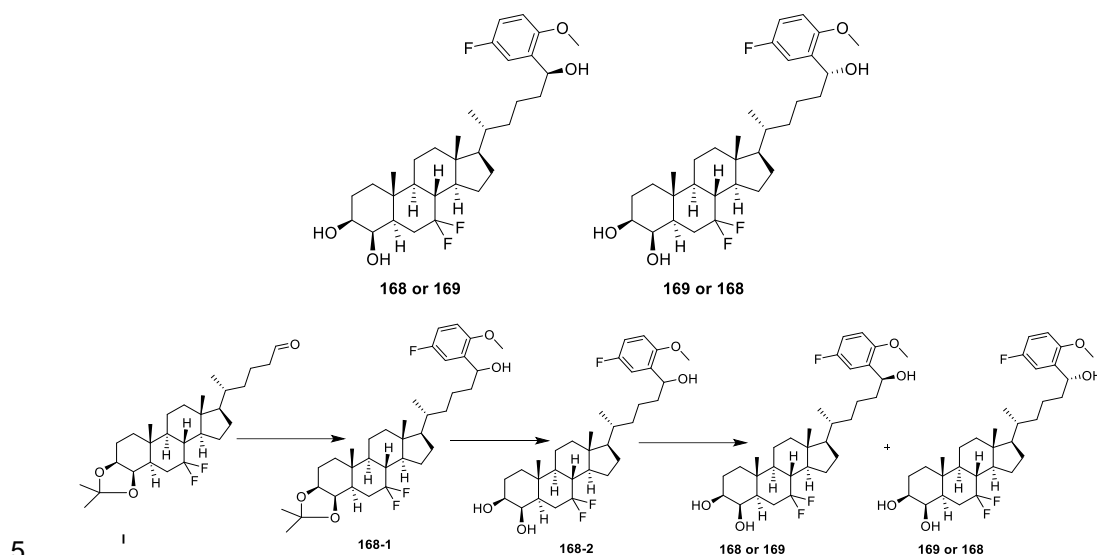
		diol	1.55 – 1.40 (m, 7H), 1.30 (s, 5H), 1.11 – 1.02 (m, 7H), 0.90 – 0.84 (m, 5H), 0.64 (d, J = 4.2 Hz, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.64, -89.26, -110.63, -111.25 LC-MS [M-H] ⁻ = 557.55.
384		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(1-methyl-1,2,3,4-tetrazol-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO) δ = 5.90 (dd, J=5.9, 3.9, 1H), 4.92 (dd, J=13.6, 5.9, 1H), 4.41 (d, J=6.0, 1H), 4.25 (d, J=3.3, 1H), 4.08 (s, 3H), 3.53 – 3.45 (m, 1H), 3.39 – 3.36 (m, 1H), 2.07 – 1.53 (m, 13H), 1.51 – 1.31 (m, 9H), 1.12 – 1.00 (m, 4H), 0.98 (s, 3H), 0.88 (dd, J=6.2, 3.5, 3H), 0.63 (s, 3H). ¹⁹ F NMR (377 MHz, DMSO) δ = -86.96 (d, J=233.6, 1F), -108.96 (d, J=233.6, 1F). LC-MS: [M-H] ⁻ = 509.60.

311		(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-6-hydroxy-6-(1-methylimidazo[5,4-c]pyridin-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, MeOD) δ 8.88 (s, 1H), 8.37 (d, J = 5.7 Hz, 1H), 7.66 (d, J = 5.7 Hz, 1H), 5.03 (dd, J = 8.0, 6.0 Hz, 1H), 4.01 (d, J = 1.1 Hz, 3H), 3.65 (s, 1H), 3.50 (dt, J = 8.3, 3.9 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.10 – 1.98 (m, 3H), 1.83 – 1.71 (m, 5H), 1.52 (s, 5H), 1.44 (d, J = 6.6 Hz, 2H), 1.41 – 1.30 (m, 6H), 1.19 – 1.13 (m, 2H), 1.10 (d, J = 7.2 Hz, 4H), 0.96 (t, J = 6.1 Hz, 4H), 0.71 (d, J = 4.3 Hz, 3H). ¹⁹F NMR (377 MHz, MeOD) δ -89.34, -89.97, -111.86, -112.49. LCMS: [M-H]⁻ = 558.75.
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[0575] Examples 168 & 169:

[0576] Preparation of compound 168 or 169 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(5-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0577] compound 169 or 168 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(5-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.



[0578] Step 1: 2-Bromo-4-fluoro-1-methoxybenzene (153.78 mg, 0.750 mmol) was dissolved in tetrahydrofuran (5 mL), and *n*-butyllithium (0.257 mL, 0.643 mmol) was slowly added at -78°C . The mixture was stirred at -78°C for 30 minutes, followed by addition of a solution of (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** (100 mg, 0.214 mmol) in tetrahydrofuran. The reaction mixture was stirred for an additional 30 minutes. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate = 7%) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(5-fluoro-2-methoxyphenyl)hexan-1-ol **168-1** (80 mg, 53.61%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.09 – 7.03 (m, 1H), 6.91 (td, J = 8.4, 3.1 Hz, 1H), 6.79 (dd,

$J = 9.2, 4.5$ Hz, 1H), 4.92 – 4.79 (m, 1H), 4.01 (d, $J = 3.1$ Hz, 2H), 3.82 (d, $J = 7.6$ Hz, 3H), 2.19 – 2.08 (m, 1H), 2.01 – 1.91 (m, 3H), 1.90 – 1.80 (m, 5H), 1.70 (dd, $J = 13.0, 3.5$ Hz, 4H), 1.61 (d, $J = 13.9$ Hz, 4H), 1.46 – 1.33 (m, 8H), 1.30 (s, 3H), 1.17 – 1.10 (m, 3H), 1.07 (s, 3H), 0.90 (dd, $J = 6.2, 3.0$ Hz, 4H), 0.67 (s, 3H).

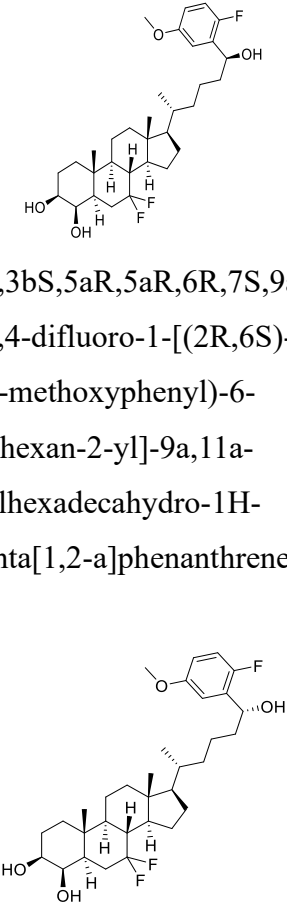
- 5 **[0579]** Step 2: (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-Difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(5-fluoro-2-methoxyphenyl)hexan-1-ol **168-1** (75 mg, 0.127 mmol) was dissolved in tetrahydrofuran (3 mL), and the mixture was stirred at room temperature for 1 hour. 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 then rotary evaporated to dryness. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate = 25-30%) to obtain
- 15 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(5-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol (45 mg) as a white solid **168-2**, followed by SFC resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IE_3, 3.0×150 mm, 3 μ m, mobile phase: A/B: CO₂/EtOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain white solid **168** (6 mg, 0.011 mmol, 8.55%, retention time: 1.548 min) and white solid **169** (7 mg, 0.012 mmol, 9.73%, retention time: 1.786 min).

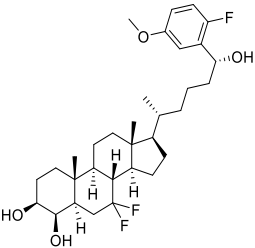
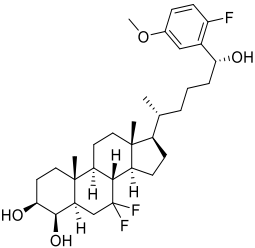
[0580] Compound **168**: ¹H NMR (400 MHz, CDCl₃) δ 7.06 (dd, $J = 9.1, 3.1$ Hz, 1H), 6.90 (td, $J = 8.5, 3.1$ Hz, 1H), 6.79 (dd, $J = 9.0, 4.3$ Hz, 1H), 4.87 (dd, $J = 8.0, 4.8$ Hz, 1H), 3.83 (s, 3H), 3.74 (s, 1H), 3.64 – 3.56 (m, 1H), 2.26 – 2.11 (m, 1H), 1.98 (d, $J = 13.1$ Hz, 1H), 1.89 – 1.78 (m, 5H), 1.73 (d, $J = 14.4$ Hz, 6H), 1.41 (dd, $J = 20.9, 10.5$ Hz, 8H), 1.16 – 1.07 (m, 3H), 1.06 (s, 3H), 0.98 (dd, $J = 18.1, 7.4$ Hz, 2H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.62, -89.25, -110.62, -111.25, -123.46. LC-MS: [M-H]⁻ = 551.50.

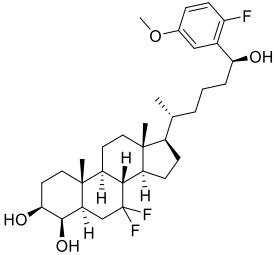
30 **[0581]** Compound **169**: ¹H NMR (400 MHz, CDCl₃) δ 7.05 (dd, $J = 9.1, 3.1$ Hz, 1H), 6.91 (td, $J = 8.3, 3.0$ Hz, 1H), 6.79 (dd, $J = 8.9, 4.3$ Hz, 1H), 4.88 – 4.80 (m,

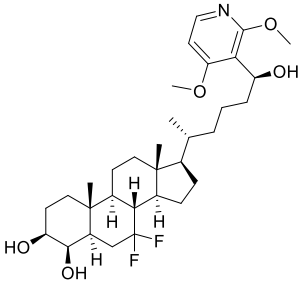
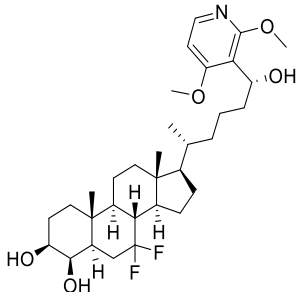
1H), 3.83 (s, 3H), 3.74 (s, 1H), 3.64 – 3.56 (m, 1H), 2.20 (ddd, J = 30.4, 13.8, 9.2 Hz, 1H), 1.97 (d, J = 12.6 Hz, 1H), 1.83 (dd, J = 22.3, 14.4 Hz, 5H), 1.76 – 1.68 (m, 6H), 1.50 – 1.34 (m, 8H), 1.15 – 1.07 (m, 3H), 1.06 (s, 3H), 0.98 (dd, J = 16.5, 5.9 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.25, -123.47. LC-MS: [M-H]⁻ = 551.50.

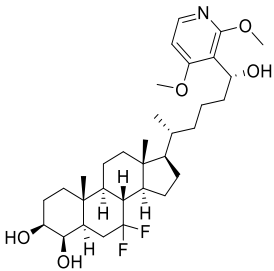
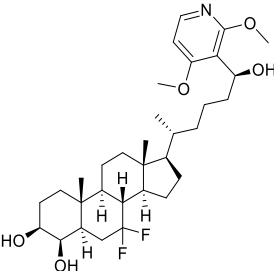
[0582] The following examples can be completed by referring to the synthesis method of Examples 168 & 169:

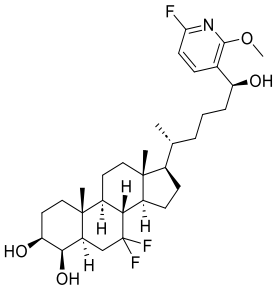
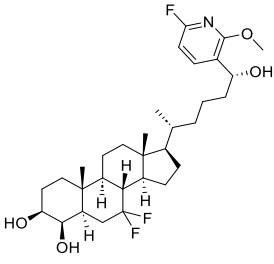
Example	Structural formula and compound name	Characterization results	SFC resolution method and results
166	 (1R,3aS,3bS,5aR,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(2-fluoro-5-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹ H NMR (400 MHz, CDCl ₃) δ 6.98 (dd, J = 5.8, 3.2 Hz, 1H), 6.93 (s, 1H), 6.77 – 6.71 (m, 1H), 4.97 (dd, J = 7.8, 5.1 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.5, 4.1 Hz, 1H), 2.19 (ddd, J = 18.3, 13.9, 7.1 Hz, 1H), 1.97 (d, J	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OJ_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 75/25, flow rate: 2.0 mL/min, column

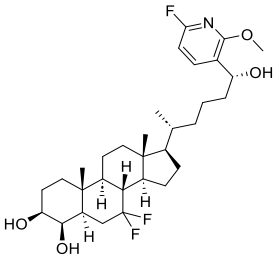
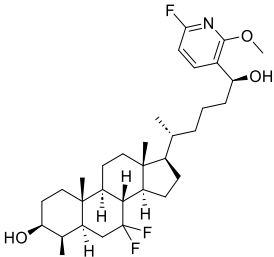
	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-5-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol 	= 12.8 Hz, 1H), 1.90 – 1.70 (m, 9H), 1.50 – 1.28 (m, 11H), 1.11 (dd, J = 13.6, 5.0 Hz, 2H), 1.06 (s, 3H), 0.98 (dd, J = 16.6, 5.6 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.63, -111.25, -130.42. LC-MS: [M-H]⁻ = 551.50.	temperature: 37°C, retention time: 2.084 min.
167	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-	¹H NMR (400 MHz, CDCl₃) δ 6.98 (dd, J = 5.8, 3.2 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.78 – 6.70	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA

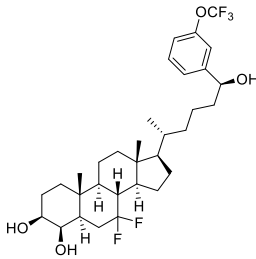
	5-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(2-fluoro-5-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(m, 1H), 4.96 (t, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 1H), 3.60 (d, J = 11.3 Hz, 1H), 2.29 – 2.13 (m, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.90 – 1.77 (m, 5H), 1.74 (d, J = 8.1 Hz, 4H), 1.55 – 1.27 (m, 11H), 1.11 (dd, J = 13.3, 4.2 Hz, 2H), 1.05 (s, 3H), 1.01 – 0.93 (m, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.25, -130.39. LC-	K OJ_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 75/25, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 2.858 min.
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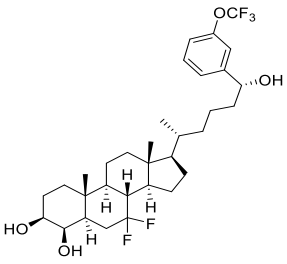
		MS: $[M-H]^- = 551.50$.	
171	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, 1H), 6.64 (s, 1H), 5.03 (m, 1H), 4.11 (s, 3H), 3.92 (s, 3H), 3.74 (s, 1H), 3.60 (dt, $J = 11.2, 4.1$ Hz, 1H), 2.19 (ddd, $J = 33.0, 13.6, 4.5$ Hz, 2H), 1.98 (d, $J = 12.6$ Hz, 2H), 1.83 (m, 7H), 1.72 (m, 4H), 1.37 (m, 7H), 1.09 (m, 7H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.61, -89.24, -110.61, -	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6×150 mm, $3.5 \mu\text{m}$, mobile phase: A/B: CO_2/EtOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C , retention time: 2.885 min.

		111.23. LC-MS: [M+H] ⁺ = 566.36.	
172	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 8.04 (s, 1H), 6.60 (s, 1H), 5.02 (t, J = 6.9 Hz, 1H), 4.06 (s, 3H), 3.90 (s, 3H), 3.74 (s, 3H), 3.60 (s, 1H), 3.60 (m, 1H), 2.18 (m, 2H), 1.97 (d, J = 12.8 Hz, 2H), 1.80 (m, 7H), 1.69 (m, 4H), 1.38 (m, 7H), 1.07 (m, 7H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -88.62, -89.25, -110.62, -	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μ m, mobile phase: A/B: CO ₂ /EtOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 3.300 min.

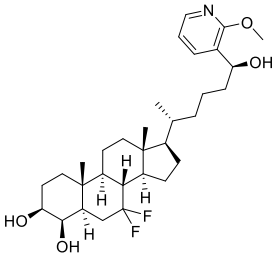
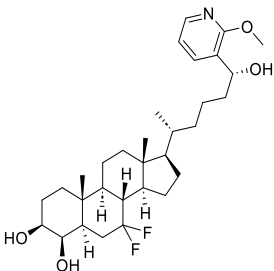
		111.25. LC-MS: $[M-H]^- = 564.55$.	
188	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	^1H NMR (400 MHz, CDCl_3) δ 7.70 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.83 (dd, J = 8.0, 5.0 Hz, 1H), 3.96 (s, 3H), 3.74 (s, 1H), 3.60 (dd, J = 7.2, 4.2 Hz, 1H), 2.12 (m, 3H), 1.80 (m, 7H), 1.66 (dd, J = 9.0, 4.5 Hz, 7H), 1.40 (dd, J = 12.1, 9.8 Hz, 6H), 1.26 (d, J = 4.5 Hz, 2H), 1.06 (s, 4H), 0.91 (d, J = 6.5 Hz, 3H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C , retention time: 1.220 min.

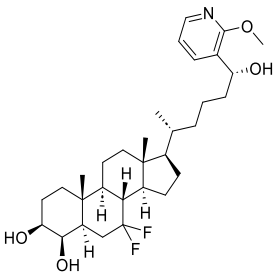
		0.66 (s, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -73.36, -88.63, -89.26, -110.63, -111.26.	
189	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-	¹ H NMR (400 MHz, CDCl ₃) δ 7.69 (s, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.84 – 4.76 (m, 1H), 3.96 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.4, 4.2 Hz, 1H), 2.18 (ddd, J = 35.1, 14.0, 4.4 Hz, 1H), 2.00 – 1.94 (m, 1H), 1.87 – 1.78 (m, 4H), 1.68 (dd, J = 11.3, 5.3 Hz, 8H), 1.39 (d, J = 15.8 Hz, 8H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 1.490 min.

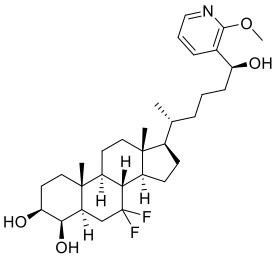
	cyclopenta[1,2-a]phenanthrene-6,7-diol	1.10 (s, 2H), 1.06 (s, 3H), 0.98 (dd, J = 16.2, 5.3 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -73.27, - 88.64, -89.27, -110.64, - 111.26. LC- MS: [M-H] ⁻ = 552.50.	
190	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-{3-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹ H NMR (400 MHz, CDCl ₃) δ 7.37 (t, J = 7.8 Hz, 1H), 7.28 (s, 1H), 7.22 (s, 1H), 7.12 (d, J = 7.9 Hz, 1H), 4.69 (t, J = 6.5 Hz, 1H), 3.74 (s, 1H), 3.60 (d, J = 11.5 Hz, 1H), 2.20 (d, J	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OJ_3, 3 × 150 mm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA)

	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-{3-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	= 35.0 Hz, 1H), 1.96 (d, J = 12.2 Hz, 1H), 1.79 (d, J = 11.5 Hz, 4H), 1.74 – 1.66 (m, 7H), 1.64 – 1.58 (m, 5H), 1.47 – 1.36 (m, 6H), 1.31 – 1.21 (m, 3H), 1.06 (s, 3H), 0.95 (s, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -57.72, -88.64, -89.27, -110.64, -111.27. LC-MS: [M-H]⁻ = 587.50.	= 85/15, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 2.893 min.
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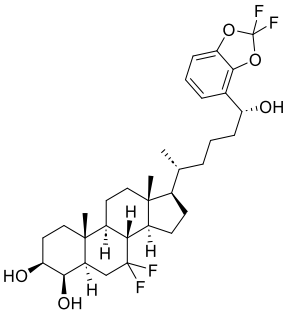
191	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-{3-[(trifluoromethyl)oxy]phenyl}hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.36 (d, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.22 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.70 (dd, J = 7.7, 5.1 Hz, 1H), 3.74 (s, 1H), 3.60 (dt, J = 8.5, 4.0 Hz, 1H), 2.28 – 2.12 (m, 1H), 1.97 (d, J = 12.7 Hz, 1H), 1.78 (d, J = 23.6 Hz, 7H), 1.68 – 1.63 (m, 4H), 1.60 – 1.54 (m, 4H), 1.51 – 1.36 (m, 7H), 1.26 (dd, J = 18.8, 11.0 Hz, 3H), 1.10 (d, J = 4.7 Hz, 1H), 1.06 (s, 3H), 1.01 – 0.95	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OJ_3, 3 × 150 mm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 85/15, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 3.702 min.
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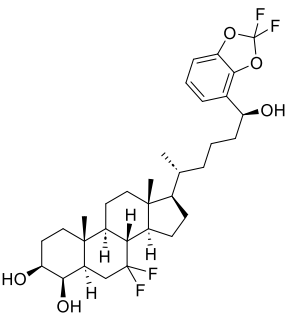
		(m, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -57.73, -88.65, -89.27, -110.65, -111.27. LC-MS: $[\text{M}-\text{H}]^-$ = 587.55.	
192	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)	^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 5.3 Hz, 1H), 7.79 (s, 1H), 7.02 (s, 1H), 4.83 (s, 1H), 4.15 (s, 3H), 3.74 (s, 1H), 3.64 – 3.56 (m, 1H), 2.28–2.10 (m, 2H), 1.97 (d, J = 13.0 Hz, 1H), 1.87 – 1.79 (m, 4H), 1.76 – 1.66 (m,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column

	)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	6H), 1.52 (d, J = 22.3 Hz, 3H), 1.42 (dd, J = 23.6, 12.8 Hz, 6H), 1.23 (dd, J = 18.4, 8.4 Hz, 3H), 1.11 (s, 1H), 1.06 (s, 3H), 1.01 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.62, -89.25, -110.62, -111.24. LC-MS: [M+H]⁺ = 536.45.	temperature: 37°C, retention time: 1.356 min.
193	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-	¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 5.0 Hz, 1H), 7.64 (s, 1H), 6.92 (t, J = 6.1 Hz, 1H), 4.87 – 4.74 (m,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 ×

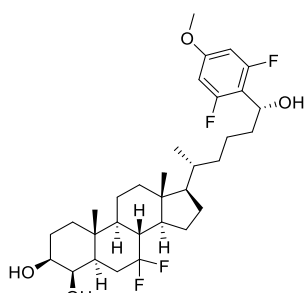
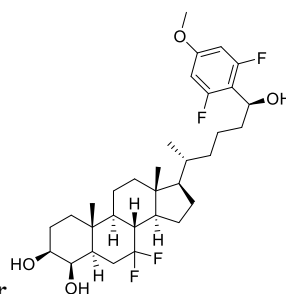
	yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1H), 4.01 (s, 3H), 3.74 (s, 1H), 3.64 – 3.57 (m, 1H), 2.28 – 2.08 (m, 2H), 2.00 – 1.96(m, 1H), 1.89 – 1.78 (m, 5H), 1.75 – 1.65 (m, 5H), 1.48 – 1.36 (m, 8H), 1.26 (d, J = 10.5 Hz, 2H), 1.11(dd, J = 9.0, 3.7 Hz, 2H), 1.06 (s, 3H), 1.03 – 0.94 (m, 2H), 0.91 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.62, -89.25, -110.62, -111.24. LC-MS: [M+H]⁺ = 536.45.	150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.900 min.
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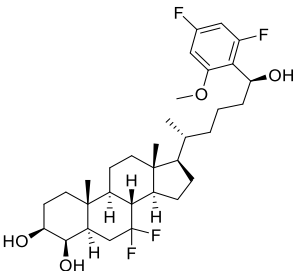
194	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ HNMR(400 MHz, CDCl ₃) δ 7.17 – 7.11 (m, 1H), 7.07 (t, J = 7.9 Hz, 1H), 6.97 (dd, J = 7.8, 1.3 Hz, 1H), 4.90 (dd, J = 7.9, 5.3 Hz, 1H), 3.74 (s, 1H), 3.63 – 3.56 (m, 1H), 2.30 – 2.11 (m, 1H), 1.97 (dt, J = 12.7, 3.3 Hz, 1H), 1.88 – 1.79 (m, 5H), 1.77 – 1.65 (m, 6H), 1.50 – 1.39 (m, 5H), 1.38 – 1.28 (m, 4H), 1.11 (dd, J = 13.3, 4.6 Hz, 2H), 1.06 (s, 3H), 1.03 – 0.93 (m, 2H), 0.90 (d, J = 6.5 Hz,	Instrument: SFC Acquity UPCC, column: Daicel CHIRALPA K AD-3 150 mm $\times$ 3 mm, 3.0 μ m, mobile phase: CO ₂ /MeOH (0.1% DEA)] = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.759 min.
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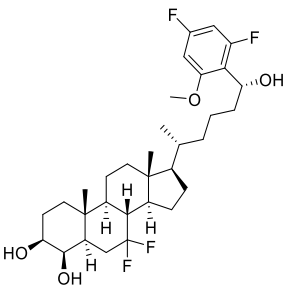
		3H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -49.39 – -50.16 (m, 2F), -88.95 (d, J = 236.0 Hz, 1F), -110.94 (d, J = 236.2 Hz, 1F). LC-MS: $[\text{M}-\text{H}]^-$ = 583.65.	
195	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	^1HNMR(400 MHz, CDCl_3) δ 7.16 – 7.11 (m, 1H), 7.07 (t, J = 7.9Hz, 1H), 6.97 (dd, J = 7.8, 1.2Hz, 1H), 4.88 (t, J = 6.7Hz, 1H), 3.73 (s, 1H), 3.63 – 3.57 (m, 1H), 2.26 – 2.11 (m, 1H), 2.00 – 1.92 (m, 3H), 1.82 (dd, J = 19.9,	Instrument: SFC Acquity UPCC, column: Daicel CHIRALPA K AD-3 150 mm $\times$ 3 mm, 3.0 μm, mobile phase: CO_2/MeOH (0.1% DEA)] = 60/40, flow rate: 1.5 mL/min, column

	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	9.8Hz, 5H), 1.69 (ddd, J = 15.5, 11.9, 7.8Hz, 5H), 1.46 (dd, J = 13.2, 3.0Hz, 2H), 1.41 – 1.30 (m, 5H), 1.15 (ddd, J = 17.7, 12.4, 6.1Hz, 3H), 1.05 (s, 3H), 1.01 – 0.93 (m, 2H), 0.89 (d, J = 6.5Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -49.78 (q, J = 97.0 Hz, 2F), -88.94 (d, J = 236.0 Hz, 1F), -110.92 (d, J = 235.8 Hz, 1F). LC-MS: [M-H]⁻ = 583.55.	temperature: 37°C, retention time: 3.470 min.
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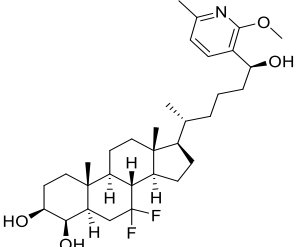
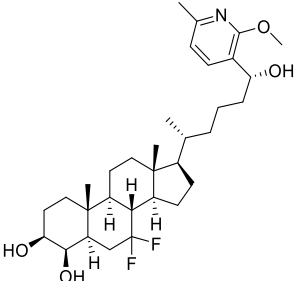
204	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,6-difluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7- diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,6-difluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 6.43 (d, J = 10.4 Hz, 2H), 4.94 (t, J = 7.3 Hz, 1H), 3.76 (d, J = 15.9 Hz, 4H), 3.60 (dt, J = 11.5, 4.2 Hz, 1H), 2.23–2.13 (m, 1H), 1.96 (d, J = 12.6 Hz, 2H), 1.88–1.77 (m, 6H), 1.75–1.63 (m, 5H), 1.49–1.40 (m, 4H), 1.32 (d, J = 12.7 Hz, 4H), 1.13–1.08 (m, 2H), 1.05 (s, 3H), 1.00 (d, J = 3.3 Hz, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃)	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OD_3, 3 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 80/20, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 3.690 min.
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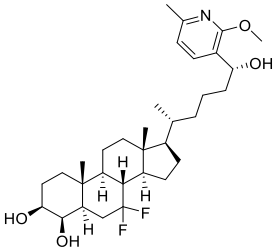
		δ -88.64, - 89.27, - 110.63, - 111.26, - 114.32. LC- MS: $[M-H]^-$ = 569.5.	
205	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,6-difluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,6-difluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-	^1H NMR (400 MHz, CDCl_3) δ 6.43 (d, J = 10.3 Hz, 2H), 4.94 (t, J = 7.1 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.2 Hz, 1H), 2.25–2.13 (m, 1H), 2.03 – 1.92 (m, 3H), 1.82 (d, J = 7.6 Hz, 4H), 1.73 (dd, J = 12.9, 5.9 Hz, 3H), 1.63 (d, J = 18.8 Hz, 2H), 1.44 – 1.26 (m, 10H), 1.09 (d, J = 4.5	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OD_3, 3 $\times$ 150 mm, 3 μm , mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 80/20, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 4.405 min.

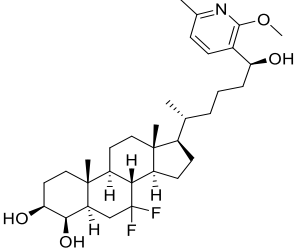
	cyclopenta[1,2-a]phenanthrene-6,7-diol	Hz, 1H), 1.06 (s, 3H), 0.98 (dd, J = 16.3, 5.6 Hz, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.64, -89.27, -110.63, -111.26, -114.38. LC-MS: [M-H]⁻ = 569.5.	
200	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹H NMR (400 MHz, CDCl₃) δ 6.44 (dd, J = 9.5, 7.8 Hz, 2H), 4.95 (t, J = 7.2 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 1H), 3.63 – 3.56 (m, 1H), 2.28 – 2.15 (m, 1H), 1.97 (d, J = 12.6 Hz, 1H),	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μm Mobile, mobile phase: A/B:

	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1.91 – 1.78 (m, 5H), 1.75 – 1.66 (m, 5H), 1.46 – 1.39 (m, 3H), 1.37 – 1.28 (m, 6H), 1.23 (s, 1H), 1.09 (d, J = 7.4 Hz, 2H), 1.06 (s, 3H), 0.98 (dd, J = 13.1, 8.7 Hz, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.63, -89.25, -110.42, -110.44, -110.62, -111.25, -113.91, -113.93. LC-MS: [M-H]⁻ = 569.50.	CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.721 min.
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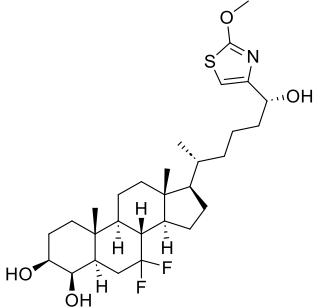
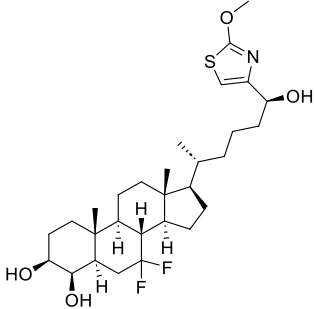
201	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7- diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,6-difluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 6.47 – 6.40 (m, 2H), 4.94 (d, J = 7.2 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 1H), 3.63 – 3.56 (m, 1H), 2.18 (dd, J = 36.8, 15.9 Hz, 2H), 1.95 (s, 1H), 1.82 (d, J = 7.0 Hz, 5H), 1.73 (d, J = 14.7 Hz, 5H), 1.53 – 1.42 (m, 4H), 1.38 – 1.29 (m, 5H), 1.10 (d, J = 4.6 Hz, 2H), 1.06 (s, 3H), 1.01 – 0.94 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.64, -	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μ m Mobile, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.893 min.
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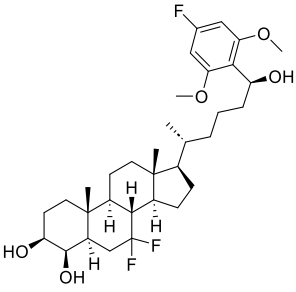
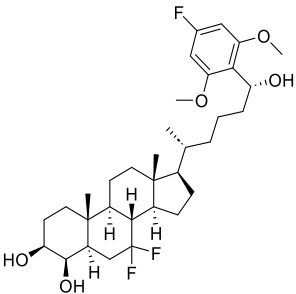
		89.26, - 110.39, - 110.41, - 110.63, - 111.25, - 113.85, - 113.87. LC- MS: $[M-H]^-$ = 569.45.	
217	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(2-methoxy-6-methylpyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(2-methoxy-6-methylpyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	^1H NMR (400 MHz, CDCl_3) δ 7.47 (d, J = 7.4 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 4.73 (t, J = 6.7 Hz, 1H), 4.01 (s, 3H), 3.74 (s, 1H), 3.63 – 3.57 (m, 1H), 2.47 (s, 3H), 2.26 – 2.12 (m, 1H), 1.97 (d, J = 12.7 Hz, 1H), 1.88 – 1.76 (m, 5H), 1.69 (dd, J = 10.6, 4.7 Hz, 5H), 1.44	Instrument: SFC Acquity UPCC, column: Daicel CHIRALPA K IC-3, 3 mm $\times$ 150 mm, 3 μm , mobile phase: CO_2/MeOH (0.1% DEA)] = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 1.632

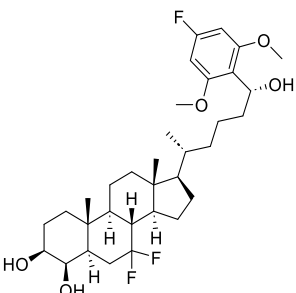
	yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(dd, $J = 20.1$, 14.2 Hz, 6H), 1.30 (dd, $J = 21.7$, 12.4 Hz, 4H), 1.16 – 1.09 (m, 2H), 1.06 (s, 3H), 0.98 (dd, $J = 18.6$, 7.6 Hz, 2H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.94 (d, $J = 235.8$ Hz, 1F), -110.94 (d, $J = 236.2$ Hz, 1F). LC-MS: $[\text{M}-\text{H}]^- = 548.5$.	min.
218	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(2-methoxy-6-methylpyridin-3-yl)hexan-2-yl]-9a,11a-	^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, $J = 7.3$ Hz, 1H), 6.84 (d, $J = 7.4$ Hz, 1H), 4.88 – 4.77 (m, 1H), 4.23 (s, 3H), 3.74 (s, 3H), 3.74 (s, 3H).	Instrument: SFC Acquity UPCC, column: Daicel CHIRALPA K IC-3, 3 mm $\times$ 150 mm, 3 μm , mobile

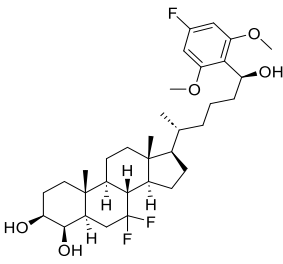
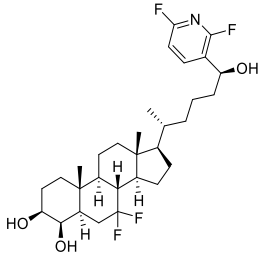
	dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(2-methoxy-6-methylpyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1H), 3.63 – 3.57 (m, 1H), 2.64 (s, 3H), 2.30 – 2.11 (m, 2H), 1.97 (d, $J = 12.6$ Hz, 1H), 1.83 (dd, $J = 21.7$, 14.4 Hz, 5H), 1.73 – 1.64 (m, 5H), 1.47 – 1.39 (m, 5H), 1.33 – 1.21 (m, 4H), 1.13 – 1.08 (m, 2H), 1.06 (s, 3H), 1.03 – 0.94 (m, 2H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.94 (d, $J = 236.0$ Hz, 1F), -110.94 (d, $J = 235.8$ Hz, 1F). LC-MS: $[\text{M}-\text{H}]^- = 548.5$.	phase: CO_2/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.042 min.
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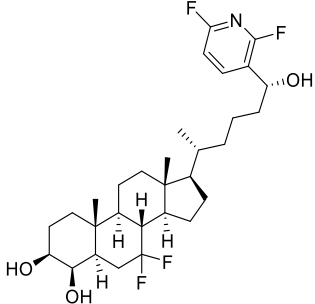
220	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(2-methoxy-1,3-thiazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(2-methoxy-1,3-thiazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR(400 MHz, CDCl ₃) δ 6.47 (s, 1H), 4.54 (m, 1H), 4.06 (s, 3H), 3.74 (s, 1H), 3.60 (d, J = 11.5Hz, 1H), 2.22 (m, 1H), 2.08 (s, 1H), 1.99 (m, 2H), 1.81 (m, 5H), 1.75 (s, 1H), 1.70 (dd, J = 11.2, 4.5Hz, 3H), 1.41 (dd, J = 14.5, 9.7Hz, 6H), 1.27 (s, 5H), 1.06 (s, 4H), 0.91 (d, J = 6.6Hz, 4H), 0.66 (s, 3H). ¹⁹ F NMR (376MHz, CDCl ₃) δ -88.64, -89.26, -110.63, -111.26. LC-MS: [M-H] ⁻ =	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OJ-3, 3 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 80/20, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 2.825 min.
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		540.50.	
221	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(2-methoxy-1,3-thiazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(2-methoxy-1,3-thiazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.69 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.81 (m, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.1 Hz, 1H), 2.19(m, 1H), 1.97 (m, 2H), 1.84 (ddd, J = 17.3, 7.5, 4.4 Hz, 6H), 1.74 (d, J = 7.5 Hz, 2H), 1.70 (m, 3H), 1.47 (m, 3H), 1.33 (m, 7H), 1.13 (m, 2H), 1.05 (d, J = 8.8 Hz, 4H), 0.98 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹ F NMR (376	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OJ-3, 3 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 80/20, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 3.326 min.

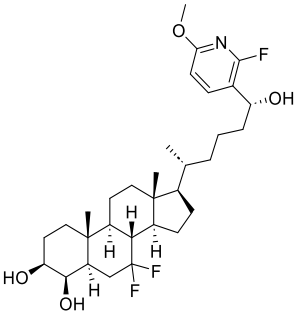
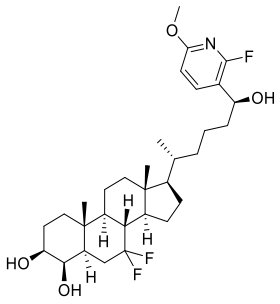
		MHz, CDCl₃) δ -73.27, -88.63, -89.26, -110.63, -111.25. LC-MS: [M-H]⁻ = 540.50.	
222	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(4-fluoro-2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(4-fluoro-2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-	¹H NMR (400 MHz, CDCl₃) δ 6.30 (d, J = 10.7 Hz, 2H), 5.12 – 4.97 (m, 1H), 3.81 (s, 7H), 3.74 (s, 1H), 3.60 (d, J = 11.4 Hz, 1H), 2.18 (dd, J = 37.3, 11.3 Hz, 2H), 1.97 (d, J = 12.7 Hz, 2H), 1.84 (s, 5H), 1.73 – 1.64 (m, 4H), 1.41 – 1.33 (m, 7H), 1.26 (s, 3H), 1.10 (s, 1H), 1.06 (s, 3H), 0.96 (d, J	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.247

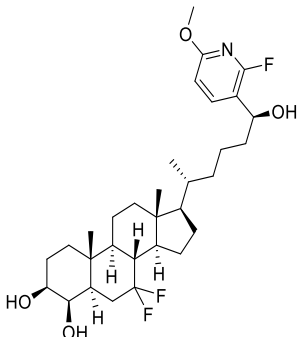
	dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	= 6.8 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.62, -89.24, -110.62, -111.24, -111.56. LC-MS: [M-H]⁻ = 581.50.	min.
225	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(4-fluoro-2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹H NMR (400 MHz, CDCl₃) δ 6.29 (d, J = 10.7 Hz, 2H), 5.04 (t, J = 7.1 Hz, 1H), 3.81 (s, 6H), 3.74 (s, 1H), 3.60 (dd, J = 10.1, 6.3 Hz, 1H), 2.23 – 1.95 (m, 3H), 1.88 – 1.77 (m, 5H), 1.69 (dd, J = 17.1, 7.4 Hz, 4H), 1.37	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50, flow rate: 1.5

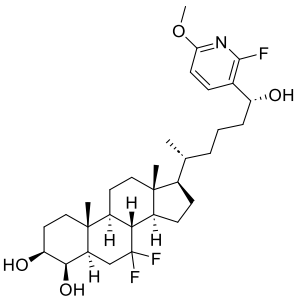
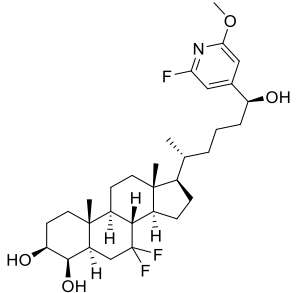
	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(4-fluoro-2,6-dimethoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(ddd, $J = 32.3$, 19.4, 10.0 Hz, 9H), 1.10 (d, $J = 10.0$ Hz, 2H), 1.06 (s, 3H), 0.98 (dd, $J = 16.7$, 5.8 Hz, 2H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ-88.62, -89.25, -110.63, -111.25, -111.53. LC-MS: $[\text{M}-\text{H}]^- = 581.45$.	mL/min, column temperature: 37°C, retention time: 2.634 min.
226	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	^1H NMR (400 MHz, CDCl_3) δ 8.02 (dd, $J = 17.1$, 8.0 Hz, 1H), 6.85 (dd, $J = 8.1$, 2.7 Hz, 1H), 4.95 (t, $J = 6.4$ Hz, 1H), 3.74 (s, 3H).	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K ID_3, 3.0 $\times$ 150 mm, 3

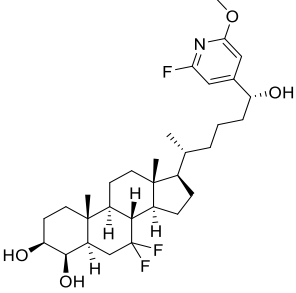
	dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1H), 3.60 (m, 1H), 2.19 (m, 2H), 1.97 (m, 1H), 1.79 (m, 7H), 1.67 (d, J = 5.7 Hz, 4H), 1.45 (d, J = 3.6 Hz, 3H), 1.39 (d, J = 13.6 Hz, 3H), 1.28 (s, 2H), 1.09 (s, 2H), 1.06 (s, 2H), 0.98 (dd, J = 17.8, 7.5 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -70.71, -72.98, -88.70, -89.28, 110.73, 111.33. LC-MS: [M-H]⁻ = 540.8.	μm mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50 flow rate: 1.5 mL/min column temperature: 37°C, retention time: 0.989 min.
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227	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,6-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 8.02 (d, J = 9.0 Hz, 1H), 6.85 (dd, J = 8.1, 2.7 Hz, 1H), 4.96 (d, J = 2.8 Hz, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.1 Hz, 1H), 2.08(m, 2H), 1.97 (d, J = 12.7 Hz, 1H), 1.82 (dd, J = 20.7, 13.0 Hz, 6H), 1.66 (m, 3H), 1.40 (m, 10H), 1.10 (d, J = 5.0 Hz, 2H), 1.06 (s, 3H), 1.00 (d, J = 3.4 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -70.73, -72.97, -88.64,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K ID_3, 3.0 × 150 mm, 3 μm mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min column temperature: 37°C, retention time: 1.429 min.
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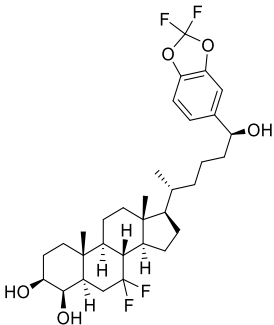
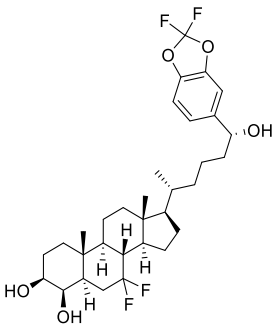
		-89.27, - 110.64, - 111.26. LC- MS: [M-H] ⁻ = 540.8.	
241	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(2-fluoro-6-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-	¹ H NMR (400 MHz, CDCl ₃) δ 7.77 (dd, J = 9.6, 8.4 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 4.90 (dd, J = 7.6, 5.5 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.4, 4.2 Hz, 1H), 2.29 – 2.11 (m, 1H), 1.99 – 1.93 (m, 1H), 1.88 – 1.78 (m, 8H), 1.72 – 1.61 (m, 3H), 1.37 (dddd, J = 26.6, 21.4, 17.5, 11.3 Hz, 11H), 1.13 – 1.09	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IA 4.6 × 250 mm, 5 μ m, mobile phase: A/B: CO ₂ /IPA (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 3.594 min.

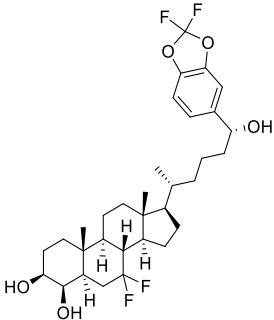
	cyclopenta[1,2-a]phenanthrene-6,7-diol	(m, 1H), 1.06 (s, 3H), 1.00 – 0.95 (m, 1H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -75.95, -88.64, -89.27, -110.63, -111.25. LC-MS: [M-H] ⁻ = 552.50.	
242	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(2-fluoro-6-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹ H NMR (400 MHz, CDCl ₃) δ 7.76 (dd, J = 9.6, 8.3 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 4.89 (t, J = 6.7 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 1H), 3.63 – 3.57 (m, 1H), 2.29 – 2.12 (m, 1H), 1.96 (dd, J = 9.4, 3.2 Hz, 1H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IA 4.6 × 250 mm, 5 μ m, mobile phase: A/B: CO ₂ /IPA (0.1% DEA) = 50/50, flow rate: 1.5

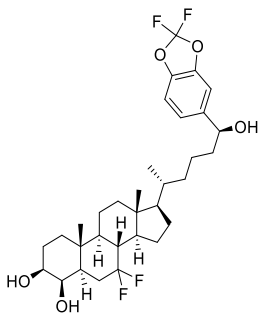
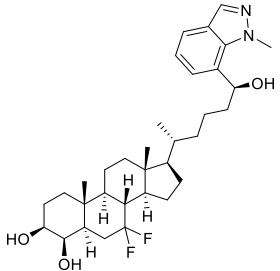
	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1.84 – 1.69 (m, 12H), 1.49 – 1.33 (m, 7H), 1.18 (dd, J = 43.1, 7.7 Hz, 3H), 1.06 (s, 3H), 1.01 – 0.91 (m, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -75.95, -88.64, -89.26, -110.62, -111.25. LC-MS: [M-H]⁻ = 552.50.	mL/min, column temperature: 37°C, retention time: 2.145 min.
247	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 6.58 (s, 1H), 6.46 (s, 1H), 4.67 (dd, J = 7.8, 4.8 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.1	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K AD_3, 3 × 150 mm, 3 μm, mobile

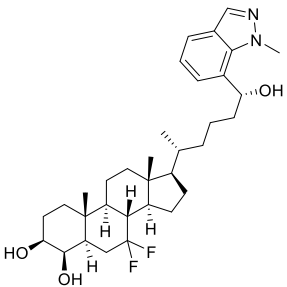
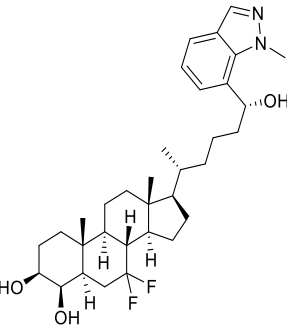
	dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-2-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	Hz, 1H), 2.30 – 2.12 (m, 1H), 1.97 (dt, J = 12.7, 3.3 Hz, 1H), 1.82 (dd, J = 15.1, 7.2 Hz, 7H), 1.73 – 1.60 (m, 4H), 1.46 – 1.27 (m, 9H), 1.11 (dd, J = 10.5, 5.9 Hz, 2H), 1.06 (s, 3H), 1.03 – 0.93 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ-71.06, -88.62, -89.25, -110.61, -111.24. LC-MS: [M-H]⁻ = 552.80.	phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 3.729 min.
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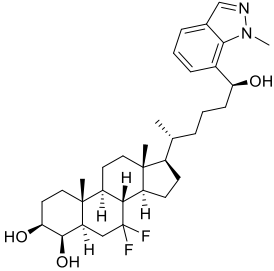
248	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-2-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 6.58 (s, 1H), 6.46 (s, 1H), 4.65 (t, J = 6.4 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.2, 4.0 Hz, 1H), 2.20 (dd, J = 34.9, 4.3 Hz, 1H), 1.99 – 1.94 (m, 1H), 1.90– 1.78 (m, 7H), 1.75 – 1.63 (m, 5H), 1.50 – 1.30 (m, 8H), 1.25 – 1.09 (m, 3H), 1.06 (s, 3H), 0.99 (d, J = 10.5 Hz, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -71.04, -88.64, -89.27,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K AD_3, 3 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 5.448 min.
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		-110.63, -111.25. LC-MS: $[M-H]^- = 552.75$.	
258	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-	^1H NMR (400 MHz, CDCl_3) δ 7.11 (s, 1H), 7.02 (m, 2H), 4.65 (s, 1H), 3.74 (s, 1H), 3.59 (m, 1H), 2.20 (m, 1H), 1.96 (dd, $J = 9.4, 3.1$ Hz, 1H), 1.80 (dd, $J = 14.6, 6.0$ Hz, 5H), 1.68 (m, 9H), 1.42 (dd, $J = 12.8, 8.6$ Hz, 4H), 1.35 (d, $J = 12.1$ Hz, 4H), 1.25 (s, 2H), 1.10 (d, $J = 4.7$ Hz, 2H), 1.06 (s, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.5$ Hz, 3H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K AZ_3, 3×150 mm, $3 \mu\text{m}$ mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C , retention time: 2.838 min.

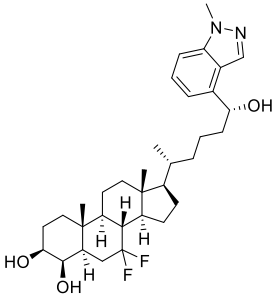
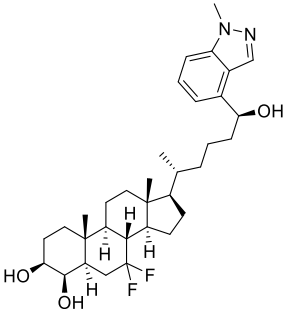
	diol	0.66 (d, J = 6.5 Hz, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃) δ -49.95, -49.97, -88.65, -89.27, -110.64, -111.27. LC-MS: [M-H] ⁻ = 583.60.	
259	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹ H NMR (400 MHz, CDCl ₃) δ 7.11 (s, 1H), 7.01 (m, 2H), 4.67 (dd, J = 7.7, 5.4 Hz, 1H), 3.74 (s, 1H), 3.60 (m, 1H), 2.19 (m, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.81 (m, 4H), 1.71 (dd, J = 7.9, 4.6 Hz, 3H), 1.65 (s, 5H), 1.41 (d, J = 10.8 Hz, 2H), 1.37	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K AZ_3, 3 × 150 mm, 3 μm mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column

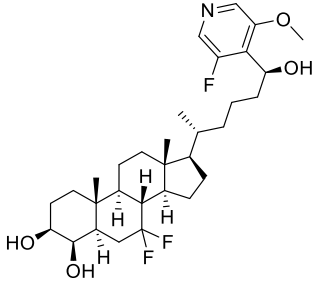
	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(s, 4H), 1.25 (s, 2H), 1.10 (m, 2H), 1.06 (s, 3H), 0.98 (dd, J = 17.9, 7.6 Hz, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -49.96, -49.97, -88.62, -89.32, 110.64, 111.22. LC-MS: [M-H]⁻ = 583.60.	temperature: 37°C, retention time: 3.420 min.
243	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.1 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 5.34 (dd, J = 8.1, 5.0 Hz, 1H), 4.37	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OZ_3, 3 × 150 mm, 3 μm, mobile

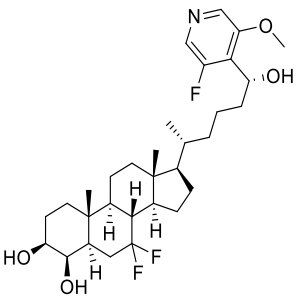
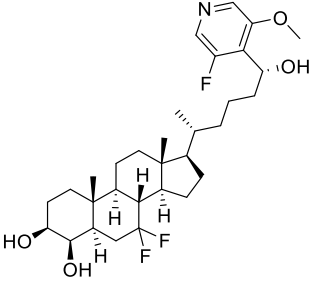
	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(s,3H), 3.73 (s, 1H), 3.60 (m, 1H), 2.20 (m, 1H), 1.96 (m, 2H), 1.85 (m, 5H), 1.67 (m, 5H), 1.46 (m, 3H), 1.32 (m, 6H), 1.11 (m, 2H), 1.06 (s, 3H), 0.98 (m, 2H), 0.91(d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.24. LC-MS: [M-H]⁻ = 557.50.	phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C. Retention time: 3.147 min.
244		¹H NMR (400 MHz, CDCl₃) δ 7.99 (s, 1H), 7.66 (m, 1H), 7.46 (d, J = 7.1 Hz, 1H), 7.13	Instrument: Waters Acquity UPCC, column: Daicel

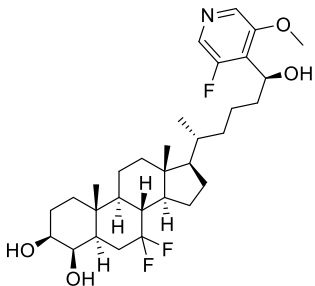
	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(m, 1H), 5.34 (dd, J = 8.2, 4.9 Hz, 1H), 4.37 (s, 3H), 3.73 (s, 1H), 3.59(dt, J = 11.3, 4.1 Hz, 1H), 2.19 (ddd, J = 23.4, 14.0, 7.0 Hz, 2H), 1.91 (m, 7H), 1.70 (m, 3H), 1.40 (m, 10H), 1.12 (ddd, J = 13.3, 11.2, 6.0 Hz, 3H), 1.06 (s, 3H), 0.99 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.69, -89.25, -110.59, -111.24. LC-MS: [M-H]⁻ = 557.45.	CHIRALPA K OZ_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C. Retention time: 4.153 min.
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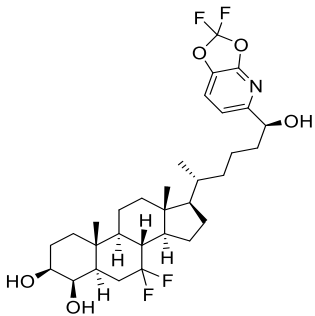
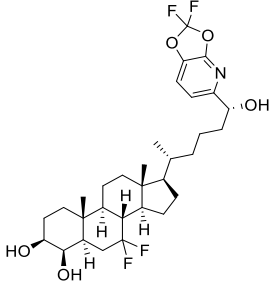
249	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ HNMR(400 MHz, CDCl ₃) δ 8.25 (s, 1H), 7.41 (t, J = 7.6Hz, 1H), 7.33 (d, J = 8.4Hz, 1H), 7.14 (d, J = 6.9Hz, 1H), 5.07 (dd, J = 7.6, 5.4Hz, 1H), 4.14 (s, 3H), 3.74 (s, 1H), 3.63 – 3.55 (m, 1H), 1.96 (dd, J = 9.2, 3.1Hz, 9H), 1.77 (dt, J = 20.6, 11.3Hz, 8H), 1.41 (d, J = 8.7Hz, 3H), 1.37 (s, 2H), 1.33 (s, 1H), 1.25 (s, 2H), 1.05 (s, 4H), 0.88 (d, J = 6.5Hz, 3H), 0.64 (s, 3H). ¹⁹ F NMR	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S) Whelk O1, 4.6 × 150 mm, 3.5 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 4.702 min.
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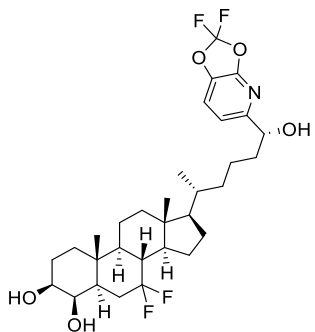
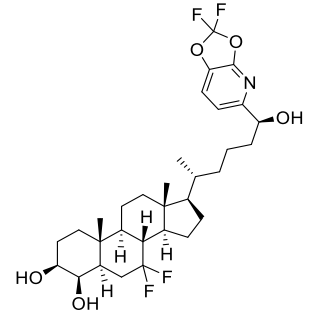
		(376MHz, CDCl ₃) δ - 88.64, -89.27, -110.63, -111.26. LC-MS: [M-H] ⁻ = 577.45.	
250	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-	¹ H NMR (400 MHz, CDCl ₃) δ 8.26 (s, 1H), 7.41 (dd, J = 8.4, 7.0 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 6.9 Hz, 1H), 5.05 (t, J = 6.6 Hz, 1H), 4.14 (s, 3H), 3.73 (s, 1H), 3.59 (dt, J = 11.3, 4.1 Hz, 1H), 2.24 (d, J = 4.4 Hz, 5H), 1.95 (d, J = 12.8 Hz, 1H), 1.84 (ddd, J = 20.6, 15.1, 7.9 Hz, 6H), 1.71 (m,	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S) Whelk O1, 4.6 × 150 mm, 3.5 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 5.339

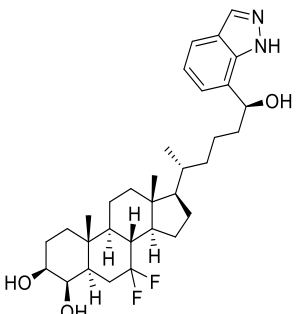
	cyclopenta[1,2-a]phenanthrene-6,7-diol	3H), 1.34 (m, 8H), 1.05 (s, 4H), 0.96 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H), 0.63 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.64, -89.27, -110.63, -111.26. LC-MS: [M-H] ⁻ = 577.40.	min.
251	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(3-fluoro-5-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.22 (s, 1H), 8.15 (s, 1H), 5.22 (s, 1H), 4.95 (s, 1H), 4.40 (d, J = 5.5 Hz, 1H), 4.24 (s, 1H), 3.91 (s, 3H), 3.49 (s, 1H), 3.33 (s, 1H), 2.16 – 2.03 (m, 1H), 1.90 (d, J = 12.4	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IA 4.6 × 250 mm, 5 μm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5

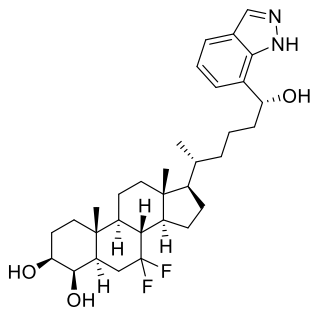
	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(3-fluoro-5-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	Hz, 1H), 1.81 – 1.65 (m, 6H), 1.58 (dd, J = 11.4, 7.6 Hz, 2H), 1.48 – 1.17 (m, 11H), 1.07 – 1.00 (m, 3H), 0.98 (s, 3H), 0.95 – 0.86 (m, 2H), 0.83 (d, J = 6.3 Hz, 3H), 0.61 (s, 3H). ¹⁹F NMR (376 MHz, DMSO) δ - 86.67, -87.29, -108.66, -109.28, -131.10. LC-MS: [M-H]⁻ = 552.50.	mL/min, column temperature: 37°C, retention time: 2.635 min.
252	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(3-fluoro-	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.22 (s, 1H), 8.16 (s, 1H), 5.22 (d, J = 5.3 Hz, 1H), 4.96 (dd, J =	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA

	5-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(3-fluoro-5-methoxypyridin-4-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	13.4, 5.6 Hz, 1H), 4.40 (d, J = 6.0 Hz, 1H), 4.25 (s, 1H), 3.91 (s, 3H), 3.49 (s, 1H), 3.34 (s, 1H), 2.11 (dd, J = 38.4, 12.4 Hz, 1H), 1.90 (d, J = 12.6 Hz, 1H), 1.86 – 1.73 (m, 3H), 1.73 – 1.51 (m, 6H), 1.42 (d, J = 10.5 Hz, 2H), 1.25 (d, J = 11.9 Hz, 8H), 1.10 – 1.00 (m, 3H), 0.98 (s, 3H), 0.92 (d, J = 20.6 Hz, 2H), 0.85 (d, J = 6.5 Hz, 3H), 0.62 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -86.66, -87.28, -	K IA 4.6 × 250 mm, 5 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 3.590 min.
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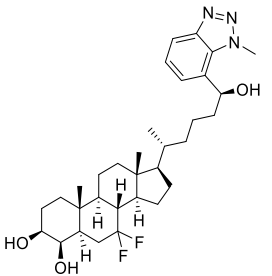
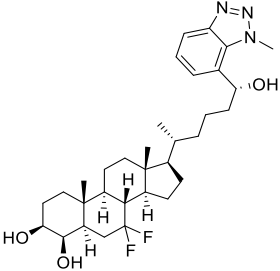
		108.65, - 109.27, - 131.08. LC- MS: [M-H] ⁻ = 552.45.	
265	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-5-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-5-yl)-6-hydroxyhexan-2-yl]-4,4-	¹ H NMR (400 MHz, CDCl ₃) δ 7.87 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 4.75 (dd, J = 7.6, 5.5 Hz, 1H), 3.74 (s, 1H), 3.64 – 3.56 (m, 1H), 2.22 (s, 1H), 2.04 – 1.98 (m, 3H), 1.81 (dd, J = 13.3, 6.7 Hz, 5H), 1.66 – 1.56 (m, 9H), 1.38 (dd, J = 17.0, 7.6 Hz, 8H), 1.06 (s, 3H), 0.89 (s, 3H), 0.66 (s, 3H). ¹⁹ F NMR (377 MHz, CDCl ₃)	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IG_3, 3.0 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 70/30, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 2.438 min.

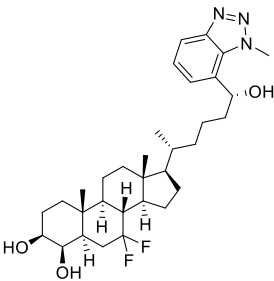
	difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	δ -49.26, -49.51, -49.54, -49.78, -88.64, -89.27, -110.63, -111.26. LC-MS: $[M-H]^- = 584.45$	
266	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-5-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)	^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, $J = 1.7$ Hz, 1H), 7.42 (d, $J = 1.8$ Hz, 1H), 4.73 (t, $J = 6.7$ Hz, 1H), 3.74 (s, 1H), 3.65 – 3.56 (m, 1H), 2.24 – 2.20 (m, 1H), 2.04 – 1.94 (m, 3H), 1.82 (d, $J = 8.0$ Hz, 4H), 1.71 (s, 6H), 1.42 (d, $J = 11.6$ Hz, 5H), 1.35 (d, $J = 15.2$ Hz, 7H), 1.06	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IG_3, 3.0×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 70/30, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 3.016

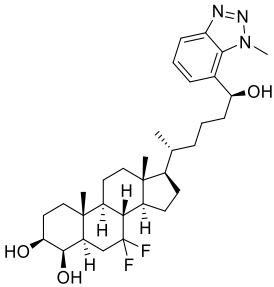
	)-1-[(2R,6S)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-5-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(s,3H), 0.89 (d, J = 6.6 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -49.27, -49.51, -49.54, -49.78, -88.64, -89.27, 110.64, 111.26. LC-MS: [M-H]⁻ = 584.45	min.
268	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1H-indazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 12.92 (s, 1H), 8.04 (s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.27 (d, J = 7.0 Hz, 1H), 7.08 – 7.03 (m, 1H), 5.28 (d, J = 4.2 Hz, 1H), 4.94 (s, 1H), 4.39 (d, J = 6.0 Hz, 1H), 4.23 (d, J = 3.3 Hz,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH = 50/50, flow rate: 1.5 mL/min,

	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1H-indazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1H), 3.49 (s, 1H), 3.29 (s, 1H), 2.14 – 2.02 (m, 1H), 1.89 (d, J = 12.5 Hz, 1H), 1.80 – 1.62 (m, 7H), 1.58 (dd, J = 11.4, 7.5 Hz, 2H), 1.42 (d, J = 9.7 Hz, 3H), 1.34 – 1.21 (m, 7H), 1.17 (d, J = 10.2 Hz, 2H), 0.99 (d, J = 10.4 Hz, 5H), 0.84 (t, J = 6.7 Hz, 4H), 0.60 (s, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -86.66, -87.28, -108.66, -109.28. LC-MS: [M-H]⁻ = 543.50.	column temperature: 37°C, retention time: 1.174 min.
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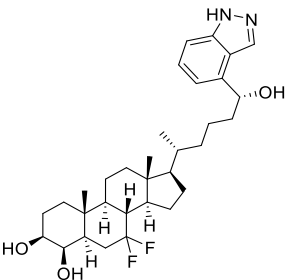
269	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1H-indazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1H-indazol-7-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.93 (s, 1H), 8.04 (s, 1H), 7.60 (d, <i>J</i> = 8.0 Hz, 1H), 7.28 (d, <i>J</i> = 6.9 Hz, 1H), 7.08 – 7.03 (m, 1H), 5.29 (d, <i>J</i> = 4.2 Hz, 1H), 4.97 (d, <i>J</i> = 3.4 Hz, 1H), 4.40 (d, <i>J</i> = 6.0 Hz, 1H), 4.24 (d, <i>J</i> = 3.4 Hz, 1H), 3.48 (s, 1H), 3.30 (s, 1H), 1.90 (d, <i>J</i> = 12.6 Hz, 1H), 1.63 (ddd, <i>J</i> = 22.9, 19.7, 16.7 Hz, 10H), 1.42 (d, <i>J</i> = 12.9 Hz, 3H), 1.34 – 1.21 (m, 9H), 1.03 (s, 1H), 0.98 (s, 4H), 0.84 (d, <i>J</i> = 6.4 Hz,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /MeOH = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 1.417 min.
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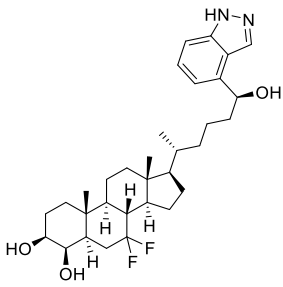
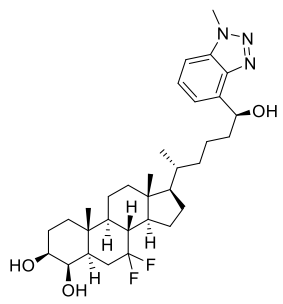
		4H), 0.60 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -86.66, -87.28, -108.67, -109.29. LC-MS: $[\text{M}-\text{H}]^- = 543.50$.	
277	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(3-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR	^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.2$ Hz, 1H), 7.46 (d, $J = 7.1$ Hz, 1H), 7.32 (dd, $J = 8.2, 7.3$ Hz, 1H), 5.21 (t, $J = 6.7$ Hz, 1H), 4.57 (s, 3H), 3.74 (s, 1H), 3.60 (dt, $J = 11.5, 4.2$ Hz, 1H), 2.25 – 2.15 (m, 1H), 1.88 – 1.78 (m, 5H), 1.76 – 1.65 (m, 6H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IH-3, 3.0×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 70/30, flow rate: 2.0 mL/min, column temperature: 37°C,

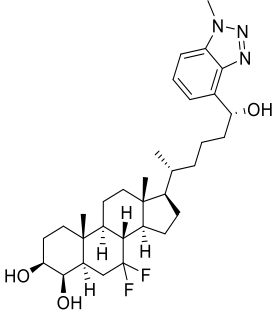
	)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(3-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1.45 (dd, J = 19.8, 8.1 Hz, 4H), 1.38–1.32 (m, 3H), 1.30 – 1.23 (m, 4H), 1.11 (dd, J = 11.1, 7.3 Hz, 3H), 1.06 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.64, -89.27, -110.64, -111.27. LC-MS: [MH]⁺ = 560.3.	retention time: 3.105 min.
278	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(3-methylbenzo[d][1,2,3]triazol-4-	¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 7.1 Hz, 1H), 7.35 – 7.30 (m, 1H), 5.22 (dd,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IH-3, 3.0 ×

	yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R,6S)-6-hydroxy-6-(3-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	J = 8.2, 5.2 Hz, 1H), 4.57 (s, 3H), 3.74 (s, 1H), 3.59 (dd, J = 8.0, 3.4 Hz, 1H), 2.01 (s, 3H), 1.84 (s, 3H), 1.70 (dd, J = 13.6, 5.2 Hz, 3H), 1.58 (s, 6H), 1.47 (d, J = 5.3 Hz, 3H), 1.25 (s, 8H), 1.06 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.64, -89.27, -110.64, -111.27. LC-MS: [M+H]⁺ = 560.40.	150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 70/30, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 4.636 min.
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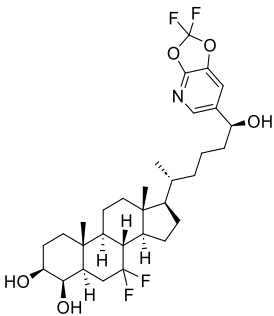
273	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1H-indazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1H-indazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 12.99 (s, 1H), 8.14 (s, 1H), 7.37 (d, J = 8.3Hz, 1H), 7.30 – 7.23 (m, 1H), 7.03 (d, J = 6.9Hz, 1H), 5.26 (d, J = 4.1Hz, 1H), 4.89 (dd, J = 7.8, 4.1Hz, 1H), 4.40 (d, J = 6.0Hz, 1H), 4.24 (d, J = 3.4Hz, 1H), 3.48 (s, 1H), 3.31 – 3.30 (m, 1H), 2.01 (dd, J = 15.0, 11.4Hz, 1H), 1.90 (d, J = 12.6 Hz, 1H), 1.78 – 1.55 (m, 8H), 1.42 (d, J = 9.8Hz, 2H), 1.23 (s, 11H), 1.07 –	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IG-3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 3.867 min.
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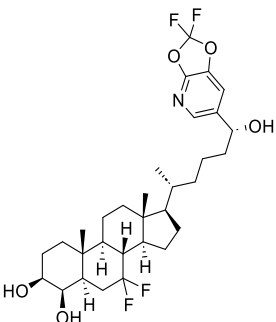
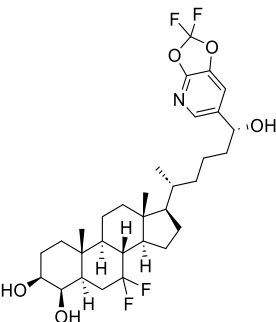
		1.01 (m, 2H), 0.98 (s, 3H), 0.83 (d, J = 6.4Hz, 4H), 0.60 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -86.71, - 87.28, - 108.71, - 109.28. LC- MS: [M-H]⁻ = 543.40	
274	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1H-indazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹H NMR (400MHz, DMSO-<i>d</i>₆) δ 12.98 (s, 1H), 8.15 (s, 1H), 7.37 (d, J = 8.3Hz, 1H), 7.29 – 7.23 (m, 1H), 7.02 (d, J = 6.9Hz, 1H), 5.26 (s, 1H), 4.87 (s, 1H), 4.24 (t, J = 5.9Hz, 1H), 4.17 – 4.08 (m, 1H), 3.48	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IG-3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min,

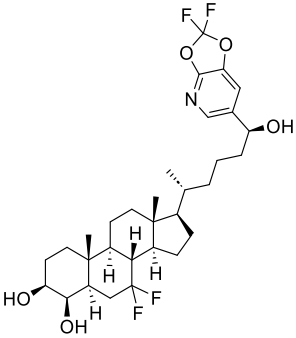
	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1H-indazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(s, 1H), 3.29 – 3.25 (m, 1H), 1.89 (d, J = 12.4Hz, 1H), 1.78 – 1.61 (m, 7H), 1.43 (d, J = 13.1Hz, 6H), 1.23 (s, 8H), 1.18 – 1.02 (m, 4H), 0.97 (s, 3H), 0.82 (d, J = 6.5Hz, 3H), 0.59 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -86.67, -87.29, -108.66, -109.28. LC-MS: [M-H]⁻ = 543.40	column temperature: 37°C, retention time: 4.246 min.
290	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1H-1,2,4-triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.49 (m, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 6.9 Hz, 1H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA

	)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	5.27 (dd, J = 8.0, 5.2 Hz, 1H), 4.35 (s, 3H), 3.74 (s, 1H), 3.60 (d, J = 11.2 Hz, 1H), 2.20 – 2.07 (m, 7H), 1.95 (s, 2H), 1.84 – 1.74 (m, 5H), 1.49 – 1.37 (m, 7H), 1.28 (d, J = 17.1 Hz, 3H), 1.05 (s, 4H), 0.90 (d, J = 6.5 Hz, 4H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.25. LC-MS: [M+H]⁺ = 560.30.	K OJ-3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 80/20, flow rate: 2 mL/min, column temperature: 37°C, retention time: 3.874 min.
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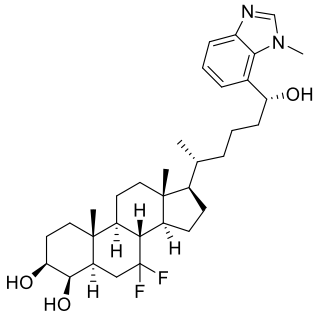
291	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylbenzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.67 (t, J = 8.0 Hz, 1H), 6.45 (dd, J = 7.9, 2.7 Hz, 1H), 4.82 – 4.78 (m, 1H), 4.39 (qd, J = 7.1, 1.3 Hz, 2H), 3.74 (s, 1H), 3.60 (d, J = 11.4 Hz, 1H), 2.20 (dd, J = 34.8, 4.5 Hz, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.85 – 1.78 (m, 4H), 1.70 (ddd, J = 15.5, 11.4, 6.4 Hz, 10H), 1.39 (t, J = 7.1 Hz, 7H), 1.26 (d, J = 3.7 Hz, 2H), 1.07 (d, J = 5.7 Hz, 5H), 1.02 – 0.94 (m, 2H), 0.90 (d, J	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OJ-3, 3.0 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 80/20, flow rate: 2 mL/min, column temperature: 37°C, retention time: 4.425 min.
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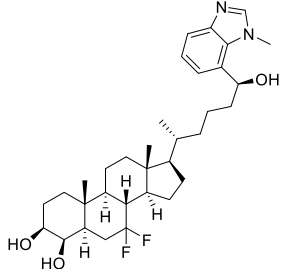
		= 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -73.22, - 88.64, -89.27, -110.64, - 111.27. LC- MS: [M+H]⁺ = 560.30	
285	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-6-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 5.5 Hz, 1H), 4.96 – 4.88 (m, 1H), 3.74 (s, 1H), 3.63 – 3.57 (m, 1H), 2.20 (dd, J = 34.9, 4.6 Hz, 1H), 1.99 – 1.94 (m, 1H), 1.84 (dd, J = 12.9, 7.1 Hz, 6H), 1.78 – 1.66 (m, 5H), 1.51 – 1.40 (m,	Instrument: SHIMADZU LC- 20ADXR, column: Daicel CHIRALPA K IC 4.6 mm × 250 mm, 5 μm, mobile phase: Hex/IPA (0.1% DEA) = 90/10, flow rate: 1.0 mL/min, wavelength: UV 214 & 254 nm,

	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-6-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	4H), 1.32 (ddd, J = 20.3, 13.8, 5.5 Hz, 5H), 1.18 – 1.09 (m, 2H), 1.06 (s, 3H), 1.03 – 0.93 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -49.06, -49.31, -49.47, -49.71, -88.64, -89.27, 110.63, 111.26. LC-MS: [M-H]⁻ = 584.65	column temperature: 30°C, retention time: 13.969 min.
286	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-6-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 4.75 (dd, J = 7.6, 5.5 Hz, 1H), 3.74	Instrument: SHIMADZU LC-20ADXR, column: Daicel CHIRALPA K IC 4.6 mm

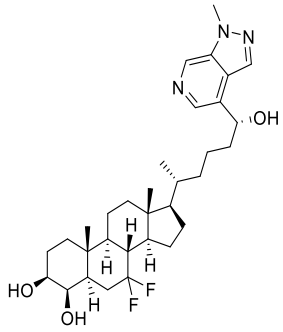
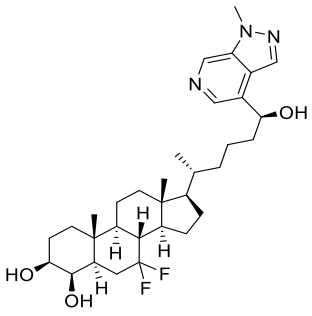
	difluoro[1,3]dioxolo[4,5-b]pyridin-6-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,2-difluoro[1,3]dioxolo[4,5-b]pyridin-6-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(s, 1H), 3.64 – 3.56 (m, 1H), 2.22 (s, 1H), 2.04 – 1.98 (m, 3H), 1.81 (dd, J = 13.3, 6.7 Hz, 5H), 1.66 – 1.56 (m, 9H), 1.38 (dd, J = 17.0, 7.6 Hz, 8H), 1.06 (s, 3H), 0.89 (s, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -49.26, -49.51, -49.54, -49.78, -88.64, -89.27, 110.63, 111.26. LC-MS: [M-H]⁻ = 584.65	× 250 mm, 5 μm, mobile phase: Hex/IPA (0.1% DEA) = 90/10, flow rate: 1.0 mL/min, wavelength: UV 214 & 254 nm, column temperature: 30°C, retention time: 17.829 min.
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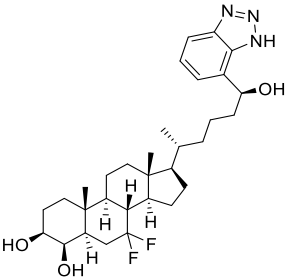
298	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(3-methylbenzo[d]imidazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(3-methylbenzo[d]imidazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.61 – 7.55 (m, 1H), 7.54 – 7.47 (m, 1H), 7.26 – 7.13 (m, 2H), 5.61 – 5.50 (m, 1H), 4.88 – 4.76 (m, 1H), 4.39 (dd, <i>J</i> = 5.9, 0.6 Hz, 1H), 4.29 – 4.17 (m, 1H), 3.87 – 3.80 (m, 3H), 3.49 (d, <i>J</i> = 1.0 Hz, 1H), 3.34 (s, 1H), 2.18 – 2.03 (m, 1H), 1.91 (d, <i>J</i> = 13.0 Hz, 2H), 1.79 (d, <i>J</i> = 13.6 Hz, 2H), 1.73 – 1.49 (m, 6H), 1.43 (d, <i>J</i> = 10.9 Hz, 3H), 1.27 (dt, <i>J</i> = 22.9, 10.8	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /IPA (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 1.367 min.
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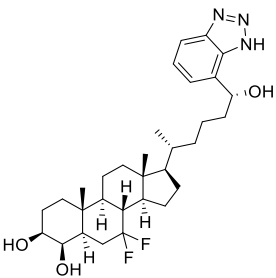
		Hz, 8H), 1.07 (d, J = 10.4 Hz, 3H), 0.98 (s, 3H), 0.92 (d, J = 17.2 Hz, 1H), 0.87 (d, J = 6.4 Hz, 3H), 0.62 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -86.65, -87.27, -108.66, -109.28. LC-MS: [M-H]⁻ = 557.35.	
299	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(3-methylbenzo[d]imidazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.58 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 24.0, 7.6 Hz, 2H), 5.53 (d, J = 6.2 Hz, 1H), 4.82 (dd, J = 13.6, 6.2 Hz, 1H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC₃, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/IPA

	diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(3-methylbenzo[d]imidazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	4.39 (d, J = 6.1 Hz, 1H), 4.23 (d, J = 3.2 Hz, 1H), 3.84 (s, 3H), 3.49 (s, 1H), 3.29 (s, 1H), 2.18 – 2.03 (m, 1H), 1.97 – 1.73 (m, 5H), 1.73 – 1.52 (m, 5H), 1.40 (d, J = 8.5 Hz, 7H), 1.25 (d, J = 11.3 Hz, 4H), 1.08 (d, J = 9.6 Hz, 3H), 0.98 (s, 3H), 0.94 (s, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.63 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -86.65, -87.27, -108.66, -109.28. LC-MS: [M-H]⁻ = 557.45.	(0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.071 min.
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287	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylpyrazolo[3,4-c]pyridin-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylpyrazolo[3,4-c]pyridin-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 8.24 (s, 1H), 8.14 (s, 1H), 5.44 (d, <i>J</i> = 4.1 Hz, 1H), 4.88 (d, <i>J</i> = 6.0 Hz, 1H), 4.40 (d, <i>J</i> = 5.9 Hz, 1H), 4.24 (d, <i>J</i> = 3.3 Hz, 1H), 4.16 (s, 3H), 3.48 (s, 1H), 2.07 (s, 1H), 1.89 (d, <i>J</i> = 12.3 Hz, 1H), 1.77 (s, 3H), 1.68 – 1.54 (m, 5H), 1.42 (d, <i>J</i> = 12.0 Hz, 2H), 1.25 (d, <i>J</i> = 10.2 Hz, 8H), 1.03 (d, <i>J</i> = 8.9 Hz, 4H), 0.98 (s, 3H), 0.95 – 0.85 (m, 2H), 0.83 (d, <i>J</i> = 6.4 Hz, 3H), 0.60	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Wheik O1 150 mm × 4.6 mm, 3.5 μm, 10 μm, mobile phase: CO ₂ /MeOH (0.1% DEA)] = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 4.668 min.
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		(s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -86.97 (d, J = 233.5 Hz, 1F), -108.96 (d, J = 233.3 Hz, 1F). LC-MS: $[\text{M}+\text{H}]^+ = 560.3$.	
288	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylpyrazolo[3,4-c]pyridin-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or 	^1H NMR (400 MHz, DMSO- d_6) δ 9.02 (s, 1H), 8.24 (s, 1H), 8.14 (s, 1H), 5.44 (s, 1H), 4.88 (s, 1H), 4.40 (d, J = 5.8 Hz, 1H), 4.24 (s, 1H), 4.16 (s, 3H), 3.49 (s, 1H), 2.17 – 2.00 (m, 1H), 1.88 (d, J = 12.2 Hz, 1H), 1.73 (d, J = 7.1 Hz, 3H), 1.62 (d, J = 34.8 Hz,	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 150 mm $\times$ 4.6 mm, 3.5 μm , 10 μm , mobile phase: CO_2/MeOH (0.1% DEA)] = 60/40, flow rate: 1.5 mL/min, column

	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylpyrazolo[3,4-c]pyridin-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	5H), 1.41 (s, 3H), 1.24 (d, J = 8.8 Hz, 7H), 1.14 (s, 4H), 0.97 (s, 3H), 0.85 (s, 2H), 0.81 (d, J = 6.0 Hz, 3H), 0.59 (s, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -86.97 (d, J = 233.4 Hz, 1F), -108.97 (d, J = 233.3 Hz, 1F). LC-MS: [M-H]⁻ = 558.40	temperature: 37°C, retention time: 5.241 min.
294	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(3H-benzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 15.62 (s, 1H), 7.76 (s, 1H), 7.40 – 7.35 (m, 2H), 5.42 (s, 1H), 5.07(s, 1H), 4.40 (d, J = 5.5 Hz, 1H), 4.24 (d, J = 3.3 Hz, 1H), 3.48	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K AS_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH

	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(3H-benzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(s, 1H), 3.31 – 3.27 (m, 1H), 2.07 (s, 1H), 1.89 (d, J = 12.5 Hz, 1H), 1.77 – 1.63 (m, 6H), 1.58 (dd, J = 11.5, 8.0 Hz, 2H), 1.42 (d, J = 10.2 Hz, 4H), 1.33 – 1.23 (m, 6H), 1.16 (d, J = 9.7 Hz, 2H), 1.03 (d, J = 7.9 Hz, 2H), 0.98 (s, 3H), 0.94 – 0.85 (m, 2H), 0.82 (d, J = 6.4 Hz, 3H), 0.59 (s, 3H). ¹⁹F NMR (376 MHz, DMSO) δ -86.67, -87.29, -108.66, -109.28. LC-MS: [M+H]⁺ = 546.3	(0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 4.596 min.
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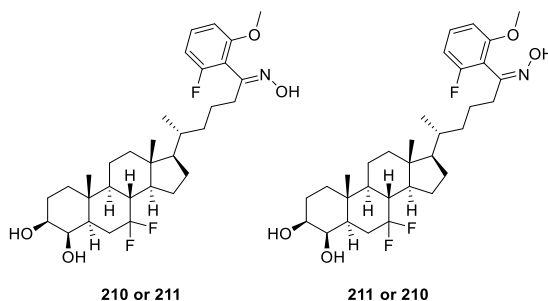
295	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(3H-benzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(3H-benzo[d][1,2,3]triazol-4-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 15.57 (s, 1H), 7.76 (d, <i>J</i> = 6.8 Hz, 1H), 7.46 – 7.26 (m, 2H), 5.42 (s, 1H), 5.10 (s, 1H), 4.40 (s, 1H), 4.24 (s, 1H), 3.49 (s, 1H), 3.31 – 3.23 (m, 1H), 2.15 – 1.99 (m, 1H), 1.90 (d, <i>J</i> = 12.7 Hz, 1H), 1.69 (dd, <i>J</i> = 32.2, 10.9 Hz, 6H), 1.59 – 1.55 (m, 1H), 1.42 (d, <i>J</i> = 13.3 Hz, 3H), 1.27 (ddd, <i>J</i> = 38.5, 22.9, 11.3 Hz, 10H), 1.04 (d, <i>J</i> = 6.3 Hz, 2H), 0.98 (s, 3H), 0.85 (dd, <i>J</i> =	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K AS_3, 3 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 5.254 min.
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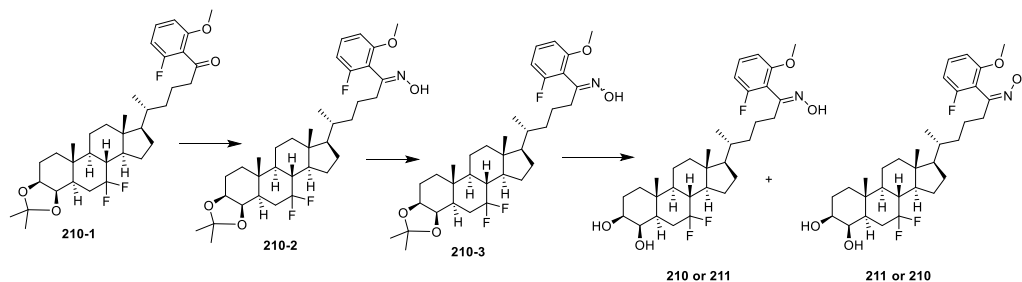
		16.7, 11.7 Hz, 5H), 0.60 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO) δ -86.66, - 87.28, - 108.65, - 109.27. LC- MS: [M+H] ⁺ = 546.3	
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[0583] Examples **210** & **211**:

[0584] Preparation of **compound 210 or 211** [(1E,5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluoro-6-methoxyphenyl)hexylidene]hydroxylamine

[0585] **compound 211 or 210** [(1Z,5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aS,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,9b,11a-trimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluoro-6-methoxyphenyl)hexylidene]hydroxylamine





[0586] Referring to Example 157, **156-1** was replaced with **210-1** to synthesize [(1E,5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-fluoro-6-methoxyphenyl)hexylidene]hydroxylamine **210-3** (20 mg). Chiral resolution was performed (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IH_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 70/30, flow rate: 2.0 mL/min, column temperature: 37°C) to obtain **210** (8.45 mg, yield: 91.95%, retention time: 2.135 min) and another isomer **211** (3.27 mg, purity: 95.02%, yield: 15.54%, retention time: 2.731 min).

[0587] **210**: ¹H NMR (400 MHz, CDCl₃) δ 7.30 (m, 1H), 6.74 (d, J = 8.5 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 1H), 3.60 (m, 1H), 2.67 (d, J = 8.7 Hz, 1H), 2.49 (dd, J = 14.7, 6.4 Hz, 1H), 2.18 (m, 2H), 1.96 (m, 2H), 1.80 (s, 5H), 1.71 (s, 2H), 1.51 (d, J = 27.9 Hz, 2H), 1.39 (m, 7H), 1.25 (s, 2H), 1.05 (s, 3H), 0.97 (m, 2H), 0.86 (dd, J = 11.9, 6.2 Hz, 3H), 0.64 (d, J = 4.6 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.24, -112.60, -112.81. LC-MS: [M+H]⁺ = 566.2.

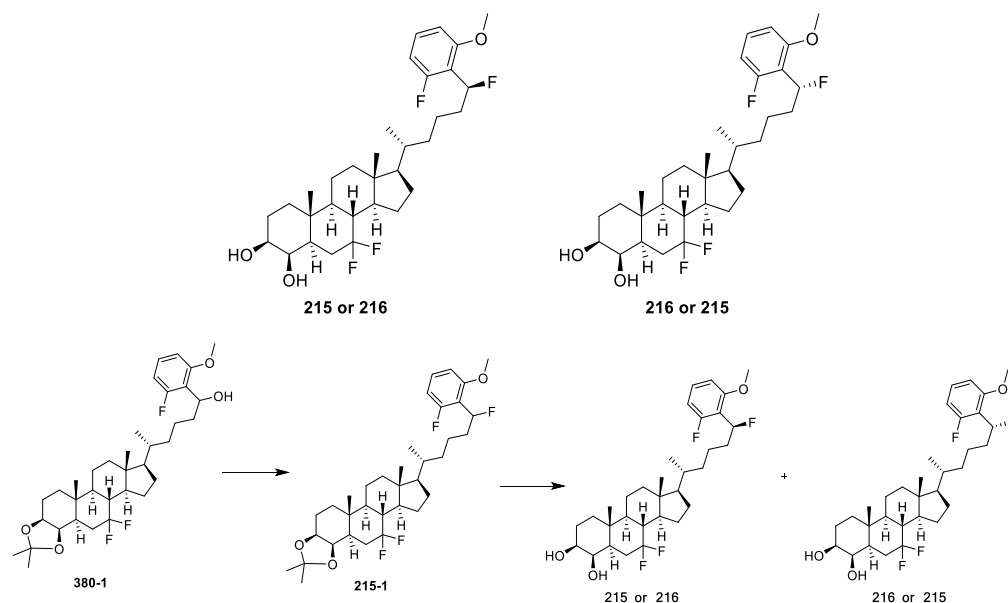
[0588] **211**: ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, J = 6.7 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.2, 4.1 Hz, 1H), 2.48 (m, 2H), 2.20 (m, 2H), 1.96 (d, J = 12.7 Hz, 1H), 1.80 (dd, J = 10.7, 4.5 Hz, 4H), 1.71 (s, 3H), 1.32 (dd, J = 20.5, 6.9 Hz, 7H), 1.25 (s, 3H), 1.08 (d, J = 2.7 Hz, 2H), 1.05 (s, 3H), 0.97 (m, 2H), 0.88 (m, 3H), 0.64 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.62, -111.24, -112.73, -112.94. LC-MS: [M+H]⁺ = 566.3.

[0589] Examples **215** & **216**

[0590] Preparation of compound **215** or **216**

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-fluoro-6-(2-fluoro-6-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol

[0591] compound 216 or 215 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-fluoro-6-(2-fluoro-6-methoxyphenyl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0592] Step 1: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoro-6-methoxyphenyl)hexan-1-ol (80 mg, 0.14 mmol) was dissolved in dichloromethane (5 mL), cooled to -65°C in a dry ice bath, and a solution of diethylaminosulfur trifluoride (65.26 mg, 0.41 mmol) in dichloromethane (1 mL) was slowly added dropwise. The reaction mixture was stirred at this temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 10:1). The starting material was completely consumed, and a less polar spot was formed. The reaction mixture was added dropwise to ice water and extracted with dichloromethane (20 mL × 2). The organic phases were combined, washed with saturated brine (30 mL), filtered, and concentrated

to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-10% ethyl acetate/petroleum ether, 20 mL/min) to obtain the product (3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-8-[(2R)-6-fluoro-6-(2-fluoro-6-methoxyphenyl)hexan-2-yl]-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxole **215-1** (50 mg, 56.06%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.20 (m, 1H), 6.69 (t, *J* = 9.8 Hz, 2H), 5.90 (dt, *J* = 13.7, 5.9 Hz, 1H), 4.06 – 3.97 (m, 2H), 3.84 (s, 3H), 2.32 – 2.04 (m, 3H), 2.01 – 1.91 (m, 2H), 1.83 (d, *J* = 3.7 Hz, 4H), 1.75 – 1.57 (m, 4H), 1.50 (s, 3H), 1.48 – 1.32 (m, 6H), 1.30 (s, 3H), 1.24 (s, 2H), 1.13 (dd, *J* = 14.6, 5.8 Hz, 2H), 1.07 (s, 3H), 1.01 – 0.85 (m, 6H), 0.65 (dd, *J* = 11.9, 2.3 Hz, 3H).

[0593] Step 2: Reactant (3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-8-[(2R)-6-fluoro-6-(2-fluoro-6-methoxyphenyl)hexan-2-yl]-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':7,8]phenanthro[1,2-d][1,3]dioxole **215-1** (45 mg, 0.076 mmol) was dissolved in tetrahydrofuran (2 mL) and water (1 mL), followed by addition of *p*-toluenesulfonic acid (6.51 mg, 0.038 mmol). The reaction system was heated at 70°C in an oil bath for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1, phosphomolybdic acid staining followed by heating). After the starting material was completely consumed, the reaction was stopped. Water (20 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (20 mL × 2). The ethyl acetate layers were combined and washed with saturated brine (40 mL). The ethyl acetate layer 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 = 80:20) to obtain a white solid, which was then subjected to chiral resolution (instrument: SFC Acuity UPCC, column: Daicel CHIRALCEL IF, 250 mm 30 mm I.D. 10 μm, mobile phase: CO₂/MeOH [0.2% NH₃ (7 M solution in MeOH)] = 50/50, flow rate: 70 g/min, wavelength: UV 214 nm) to obtain **215** (8.24 mg, purity: 92.0%, e.e. 100%, yield: 18.06%, retention time: 2.007 min) and another isomer (8.2 mg).

The another isomer was further subjected to chiral resolution (instrument: SFC Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1, 150 mm × 4.6 mm, 3.5 μm, 10 μm, mobile phase: CO₂/MeOH (0.1% DEA)] = 40/60, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain **216** (3.75 mg, purity: 100%, e.e. 100%, yield: 8.9%, retention time: 2.597 min).

[0594] 215: ¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.20 (m, 1H), 6.74 – 6.62 (m, 2H), 5.91 (ddd, *J* = 46.8, 8.6, 5.4 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 1H), 3.65 – 3.55 (m, 1H), 2.32 – 2.10 (m, 2H), 1.97 (dd, *J* = 9.4, 3.3 Hz, 1H), 1.91 – 1.81 (m, 3H), 1.77 (dd, *J* = 10.5, 5.5 Hz, 3H), 1.71 (d, *J* = 3.7 Hz, 3H), 1.51 – 1.38 (m, 6H), 1.37 – 1.22 (m, 4H), 1.12 (dd, *J* = 12.9, 4.0 Hz, 2H), 1.06 (s, 3H), 1.04 – 0.93 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.65 (d, *J* = 6.2 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.94 (d, *J* = 235.7 Hz, 1F), -110.94 (d, *J* = 235.6 Hz, 1F), -114.77 (d, *J* = 13.9 Hz, 1F), -180.21 (d, *J* = 13.8 Hz, 1F). LC-MS: [M-H]⁻ = 553.40.

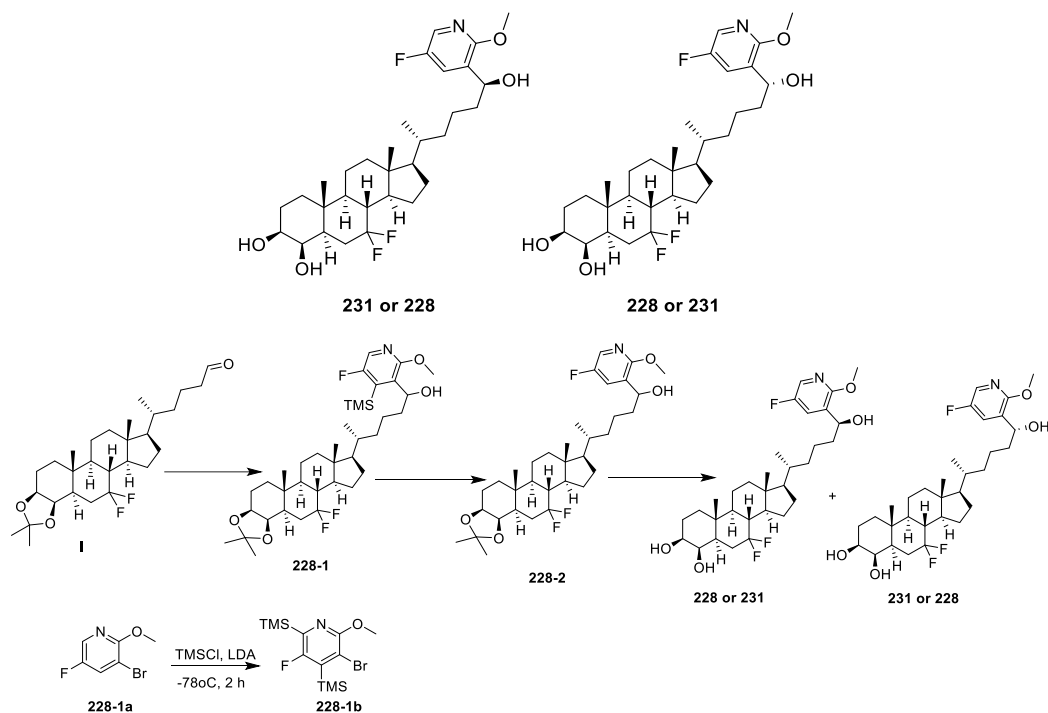
[0595] 216: ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, *J* = 7.2 Hz, 1H), 6.69 (t, *J* = 9.6 Hz, 2H), 6.00 – 5.79 (m, 1H), 3.84 (s, 3H), 3.74 (s, 1H), 3.60 (d, *J* = 11.4 Hz, 1H), 2.18 (dd, *J* = 29.0, 15.4 Hz, 2H), 1.97 (d, *J* = 12.8 Hz, 1H), 1.91 – 1.67 (m, 9H), 1.41 (dd, *J* = 23.4, 12.3 Hz, 6H), 1.26 (t, *J* = 16.0 Hz, 4H), 1.09 (s, 2H), 1.06 (s, 3H), 1.03 – 0.93 (m, 2H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.95 (d, *J* = 235.8 Hz, 1F), -110.94 (d, *J* = 235.9 Hz, -1F), -114.74 (d, *J* = 12.7 Hz, -1F), -179.22 (d, *J* = 12.8 Hz, 1F). LC-MS: [M-H]⁻ = 553.45.

[0596] Examples 228 & 231:

[0597] Preparation of

[0598] compound 231 or 228 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(5-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0599] compound 228 or 231 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(5-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0600] Step 1: 3-Bromo-5-fluoro-2-methoxypyridine (1 g, 4.854 mmol) was dissolved in tetrahydrofuran (30 mL), and the atmosphere was replaced with nitrogen. The mixture was stirred at -78°C , and lithium diisopropylamide (7.281 mL, 14.562 mmol) was added dropwise. After stirring for 30 minutes, trimethylsilyl chloride (1.846 mL, 14.562 mmol) was slowly added. The reaction mixture was stirred at -78°C for an additional 30 minutes and then quenched with saturated ammonium chloride aqueous solution (20 mL). The mixture was extracted with ethyl acetate ($30\text{ mL} \times 3$), and the organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and rotary evaporated to dryness. The residue was purified by silica gel column chromatography (pure petroleum ether) to obtain 5-bromo-3-fluoro-6-methoxy-2,4-bis(trimethylsilyl)pyridine **228-1b** (1.4 g, 3.396 mmol, 69.97%) as a colorless transparent solid. ^1H NMR (400 MHz, CDCl_3) δ 3.97 (s, 3H), 0.46 (d, $J = 2.5$ Hz, 9H), 0.32 (d, $J = 1.1$ Hz, 9H).

[0601] Referring to Examples **168** & **169**, 2-bromo-4-fluoro-1-methoxybenzene was replaced with 5-bromo-3-fluoro-6-methoxy-2,4-bis(trimethylsilyl)pyridine **228-1b** to obtain the crude product (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-

difluoro-1-[(2R)-6-(5-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol.

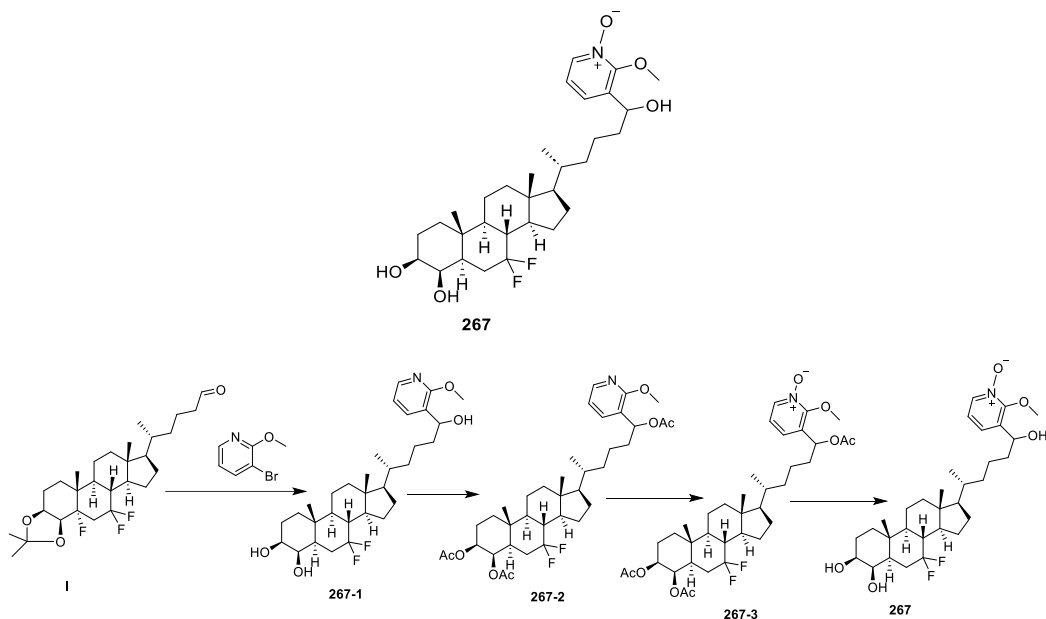
SFC was performed (instrument: Waters Acquity UPCC; column: Daicel CHIRALPAK IC₃, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO₂/MeOH (0.1% ethyl acetate) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C) to obtain compound **231** (27 mg, 0.049 mmol, 45.38%, retention time: 0.964 min) and compound **231** (29 mg, 0.052 mmol, 48.74%, retention time: 1.262 min) as a white solid.

[0602] Compound **231**: ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, J = 2.9 Hz, 1H), 7.49 (dd, J = 8.2, 2.9 Hz, 1H), 4.80 (dd, J = 7.8, 4.7 Hz, 1H), 4.02 (s, 3H), 3.74 (s, 1H), 3.64 – 3.56 (m, 1H), 2.27 – 2.15 (m, 1H), 2.00 – 1.95 (m, 2H), 1.85 – 1.79 (m, 4H), 1.76 – 1.68 (m, 4H), 1.52 – 1.34 (m, 7H), 1.32 – 1.20 (m, 3H), 1.11 (dd, J = 13.2, 9.1 Hz, 2H), 1.06 (s, 3H), 1.05 – 0.93 (m, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.64, -89.26, -110.63, -111.26, -137.83.
LC-MS: [M-H]⁻ = 552.40.

[0603] Compound **228**: ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 3.0 Hz, 1H), 7.48 (dd, J = 8.3, 2.9 Hz, 1H), 4.82 (t, J = 6.2 Hz, 1H), 3.99 (s, 3H), 3.74 (s, 1H), 3.59 (dd, J = 11.4, 3.6 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.98 (d, J = 12.5 Hz, 2H), 1.84 (d, J = 7.2 Hz, 4H), 1.69 (dd, J = 15.6, 4.7 Hz, 5H), 1.48 – 1.31 (m, 9H), 1.11 (dd, J = 15.7, 6.8 Hz, 3H), 1.06 (s, 3H), 1.03 – 0.94 (m, 2H), 0.91 (d, J = 6.5 Hz, 3H), 0.67 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -88.63, -89.26, -110.63, -111.26, -138.14. LC-MS: [M-H]⁻ = 552.40.

[0604] Example **267**:

[0605] Preparation of compound **267**: 3-[(5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-hydroxyhexyl]-2-methoxypyridine-1-oxide



[0606] Step 1: Referring to Examples 168 & 169, 2-bromo-4-fluoro-1-methoxybenzene was replaced with 3-bromo-2-methoxypyridine to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2-methoxypyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **267-1**.

[0607] Step 2: **267-1** (60 mg, 0.112 mmol, 1 eq) was dissolved in anhydrous tetrahydrofuran (5 mL), followed by sequential addition of triethylamine (170 mg, 1.68 mmol, 15 eq), DMAP (14 mg, 0.112 mmol, 1 eq), and acetic anhydride (114 mg, 1.12 mmol, 10 eq). The mixture was stirred at 60°C for 3 hours, and the reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). Water (100 mL) was added to the reaction system, which was then extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), and dried. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 10:1) and concentrated to obtain (5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-diacetoxy-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-(2-methoxypyridin-3-yl)hexyl acetate **267-2** (60 mg, purity: 90%, yield: 81%) as a white solid. LC-MS: $[M+H]^+ = 662.3$.

[0608] Step 3: **267-2** (20 mg, 0.030 mmol, 1 *eq*) was dissolved in anhydrous dichloromethane (3 mL), and *m*-chloroperoxybenzoic acid (32 mg, 0.181 mmol, 6 *eq*) was added. The mixture was stirred at room temperature for 72 hours, and the reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). Water (100 mL) was added to the reaction system, which was then extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), and dried. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 10:1) and concentrated to obtain 3-[(5R)-1-acetoxy-5-
 5 [(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-6,7-diacetoxy-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]hexyl]-2-methoxypyridine-1-oxide **267-3** (10 mg, purity: 90%, yield: 49%) as a white solid. LC-MS: [M+H]⁺ = 678.3.

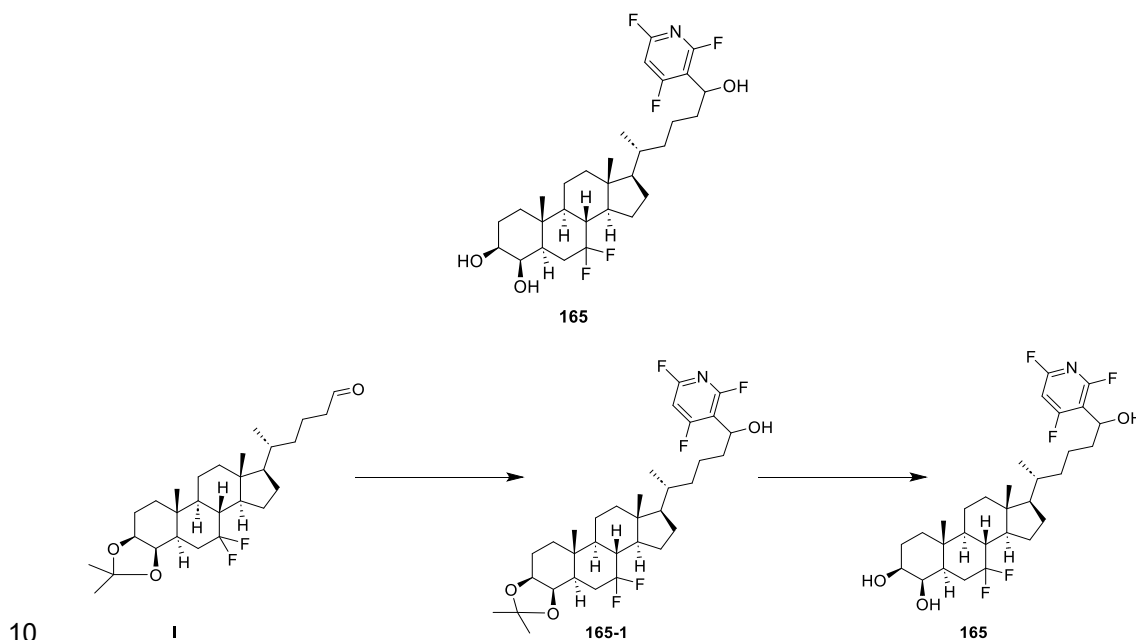
[0609] Step 4: Starting material **267-3** (40 mg, 0.059 mmol, 1 *eq*) was dissolved
 15 in tetrahydrofuran (2 mL) and water (2 mL), followed by addition of lithium hydroxide (14 mg, 0.590 mmol, 10 *eq*). The mixture was stirred at room temperature for 30 min, and the reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). Water (100 mL) was added to the reaction system, which was then extracted with ethyl acetate (100 mL × 3). The organic
 20 phases were combined, washed with saturated sodium chloride (10 mL), and dried. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 1:1) and concentrated to obtain 3-[(5R)-5-[(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-6,7-dihydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-1-yl]-1-
 25 hydroxyhexyl]-2-methoxypyridine-1-oxide **267** (12 mg, purity: 100%, yield: 34%) as a white solid.

[0610] Compound **267**: ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, J = 5.8 Hz, 1H), 7.63 (s, 1H), 7.14 (t, J = 6.9 Hz, 1H), 4.94 (dd, J = 12.6, 5.1 Hz, 1H), 4.30 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.0 Hz, 1H), 2.26 – 2.13 (m, 2H), 1.97 (d, J = 12.7
 30 Hz, 2H), 1.81 (dd, J = 15.7, 7.1 Hz, 4H), 1.73 – 1.63 (m, 5H), 1.42 (d, J = 13.9 Hz, 5H), 1.32 (dd, J = 12.5, 3.8 Hz, 4H), 1.10 (d, J = 4.8 Hz, 2H), 1.06 (s, 3H), 1.02 –

0.94 (m, 2H), 0.92 – 0.89 (m, 3H), 0.66 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -88.63, -89.26, -110.63, -111.25. LC-MS: $[\text{M}-\text{H}]^- = 550.45$.

[0611] Example 165:

5 [0612] Preparation of compound 165
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2,4,6-trifluoropyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0613] Step 1: Starting material 2,4,6-trifluoropyridine (199.61 mg, 1.500 mmol, 3.5 eq) was dissolved in anhydrous tetrahydrofuran (3 mL). The system was cooled to -78°C , and *n*-butyllithium (2.5 M, 0.514 mL, 1.286 mmol, 3.0 eq) was added. The mixture was stirred at this temperature for 30 min. Compound
 15 (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal (200 mg, 0.429 mmol, 1.0 eq) was dissolved in tetrahydrofuran (2 mL) and added to the above reaction mixture. The reaction system was stirred at -78°C for 30 min. The
 20 reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (2 mL) was

added to the reaction system, which was then extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (30 mL), dried, and concentrated to obtain a crude product as a colorless oil. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 15:1) to obtain the product (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4,6-trifluoropyridin-3-yl)hexan-1-ol **165-1** (227 mg, purity: 95%, yield: 83.90%) as a white solid.

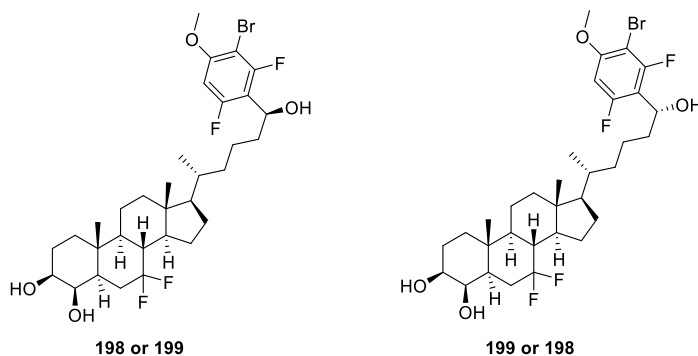
[0614] Step 2: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4,6-trifluoropyridin-3-yl)hexan-1-ol **165-1** (30 mg, 0.050 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1.5 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 $\times$ 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 $\times$ 10 mL). The ethyl acetate layer 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 = 63:37) to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IC₃, 3.0 $\times$ 150 mm, 3 μ m, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C; retention time: 1.070 min) to obtain the product (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(2,4,6-trifluoropyridin-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **165** (18.12

mg, purity: 99%, yield: 63.64%).

[0615] Compound **165**: ^1H NMR (400 MHz, CDCl_3) δ 6.59 (dd, $J = 8.6, 2.0$ Hz, 1H), 4.96 (s, 1H), 3.74 (s, 1H), 3.67 – 3.56 (m, 1H), 2.08 (d, $J = 4.0$ Hz, 2H), 2.04 – 1.91 (m, 3H), 1.89 – 1.77 (m, 5H), 1.76 – 1.61 (m, 5H), 1.47 – 1.30 (m, 8H),
 5 1.26 (dd, $J = 16.0, 6.9$ Hz, 3H), 1.10 (dd, $J = 10.6, 7.0$ Hz, 3H), 1.08-1.06 (m, 4H), 1.02 – 0.92 (m, 2H), 0.92 – 0.87 (m, 3H), 0.66 (d, $J = 2.3$ Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -65.80, -67.66, -88.64, -89.27, -95.83, -110.63, -111.25. LCMS: $[\text{M}+\text{Na}]^+ = 582.2$.

10 [0616] Examples **198 & 199**

[0617] Preparation of compound **198** or **199**
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(3-bromo-2,6-difluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol
 15 compound **199** or **198** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(3-bromo-2,6-difluoro-4-methoxyphenyl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0618] Referring to Example **165**, starting material 2,4,6-trifluoropyridine was replaced with 2-bromo-1,5-difluoro-3-methoxybenzene to obtain white solid **198-1**, which was purified by flash chromatography (PE: EtOAc = 100:0 to 50:50) and chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IH₃, 3.0 × 150 mm, 3 μm , mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 70/30, flow rate: 2.0 mL/min, column temperature: 37°C) to obtain white
 20 solid **198** (150 mg, purity: 99.53%, yield: 49%, retention time: 2.376 min) and
 25

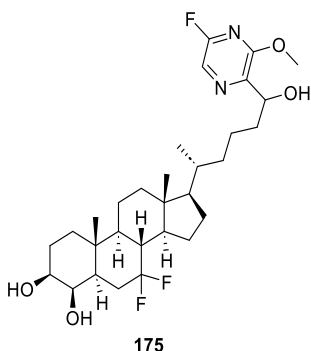
white solid **199** (70 mg, purity: 100%, yield: 20.42%, retention time: 2.980 min).

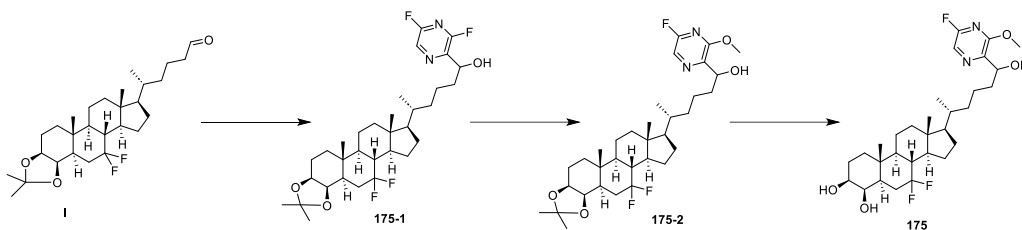
[0619] Compound 198: ^1H NMR (400 MHz, CDCl_3) δ 6.49 (dd, $J = 12.0, 1.9$ Hz, 1H), 4.97 (t, $J = 7.0$ Hz, 1H), 3.89 (s, 3H), 3.74 (s, 1H), 3.59 (dd, $J = 11.4, 3.6$ Hz, 1H), 2.21 (dd, $J = 16.7, 13.8$ Hz, 1H), 1.98 (dd, $J = 12.9, 8.4$ Hz, 3H), 1.82 (d, $J = 8.1$ Hz, 3H), 1.75 (s, 4H), 1.64 (s, 2H), 1.43 (s, 3H), 1.34 (dd, $J = 14.7, 7.6$ Hz, 5H), 1.25 (s, 2H), 1.08 (s, 1H), 1.06 (s, 3H), 1.01 – 0.94 (m, 2H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.64, -89.26, -106.90, -106.91, -110.63, -111.25, -114.67, -114.69. LC-MS: $[\text{M}-\text{H}]^- = 647.40$, $[\text{M}+2-\text{H}]^- = 649.45$.

[0620] Compound 199: ^1H NMR (400 MHz, CDCl_3) δ 6.49 (dd, $J = 12.0, 1.8$ Hz, 1H), 4.97 (t, $J = 7.2$ Hz, 1H), 3.89 (s, 3H), 3.74 (s, 1H), 3.60 (dt, $J = 11.3, 4.1$ Hz, 1H), 2.27–2.13 (m, 1H), 1.98 – 1.94 (m, 1H), 1.88 – 1.77 (m, 5H), 1.71 (dd, $J = 12.9, 9.5$ Hz, 4H), 1.46 – 1.26 (m, 11H), 1.13 – 1.08 (m, 2H), 1.06 (s, 3H), 0.98 (dd, $J = 16.5, 5.9$ Hz, 2H), 0.91 – 0.86 (m, 3H), 0.65 (d, $J = 3.2$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.64, -89.26, -106.86, -106.90, -110.62, -111.25, -114.61, -114.69. LC-MS: $[\text{M}-\text{H}]^- = 647.40$, $[\text{M}+2-\text{H}]^- = 649.40$.

[0621] Example 175:

[0622] Preparation of compound 175 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(5-fluoro-3-methoxypyrazin-2-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol





[0623] Step 1: Referring to Example **165**, starting material 2,4,6-trifluoropyridine was replaced with 2,6-difluoropyrazine to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a,7a-tetramethyl-4,5,55a,5b,6,7,7a,8,9,10,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxolyl-1-(3,5-difluoropyrazin-2-yl)hexanol **175-1** (20 mg, 41.18%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.33 (dd, *J* = 8.2, 2.9 Hz, 1H), 4.98 (s, 1H), 4.10 – 3.96 (m, 2H), 3.20 (s, 1H), 2.18 – 1.92 (m, 3H), 1.90 – 1.67 (m, 7H), 1.63 – 1.53 (m, 6H), 1.51 (s, 3H), 1.46 – 1.35 (m, 5H), 1.30 (d, *J* = 3.5 Hz, 3H), 1.26 – 1.19 (m, 2H), 1.18 – 1.09 (m, 2H), 1.07 (s, 3H), 0.96 (dd, *J* = 13.6, 7.2 Hz, 2H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.65 (d, *J* = 12.0 Hz, 3H).

[0624] Step 2: At room temperature, (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a,7a-tetramethyl-4,5,55a,5b,6,7,7a,8,9,10,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxolyl-1-(3,5-difluoropyrazin-2-yl)hexanol (45 mg, 0.077 mmol) was dissolved in anhydrous methanol (4 mL), cooled to 0°C, and sodium methoxide solution (30%, 42 mg, 0.23 mmol) was added. The mixture was stirred at room temperature for 2 hours. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL × 2). The organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-13% EtOAc/PE, 20 mL/min) to obtain the product (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a,7a-tetramethyl-4,5,55a,5b,6,7,7a,8,9,10,10b,11,12,12a,12b-

hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxolyl-1-(5-fluoro-3-methoxypyrazin-2-yl)hexanol **175-2** (15 mg, 0.025 mmol, 32.8%). ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.2 Hz, 1H), 4.89 (s, 1H), 4.07 – 3.96 (m, 5H), 3.56 (s, 1H), 2.19 – 1.60 (m, 6H), 1.51 (s, 3H), 1.47 – 1.34 (m, 5H), 1.30 (s, 4H), 1.24 (s, 2H), 1.12 (d, *J* = 12.6 Hz, 2H), 1.07 (s, 3H), 1.00 (dd, *J* = 19.3, 11.1 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.88 – 0.82 (m, 1H), 0.67 (s, 3H).

[0625] Step 3: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a,7a-tetramethyl-

4,5,5a,5b,6,7,7a,8,9,10,10b,11,12,12a,12b-hexadecahydro-3aH-

cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxolyl-1-(5-fluoro-3-methoxypyrazin-2-yl)hexanol **175-2** (15 mg, 0.025 mmol) was dissolved in tetrahydrofuran (1 mL), and dilute hydrochloric acid (0.5 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer 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 = 80:20) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(5-fluoro-3-methoxypyrazin-2-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **175** (2.46 mg, purity: 98.3%, 17.23%) as a white solid.

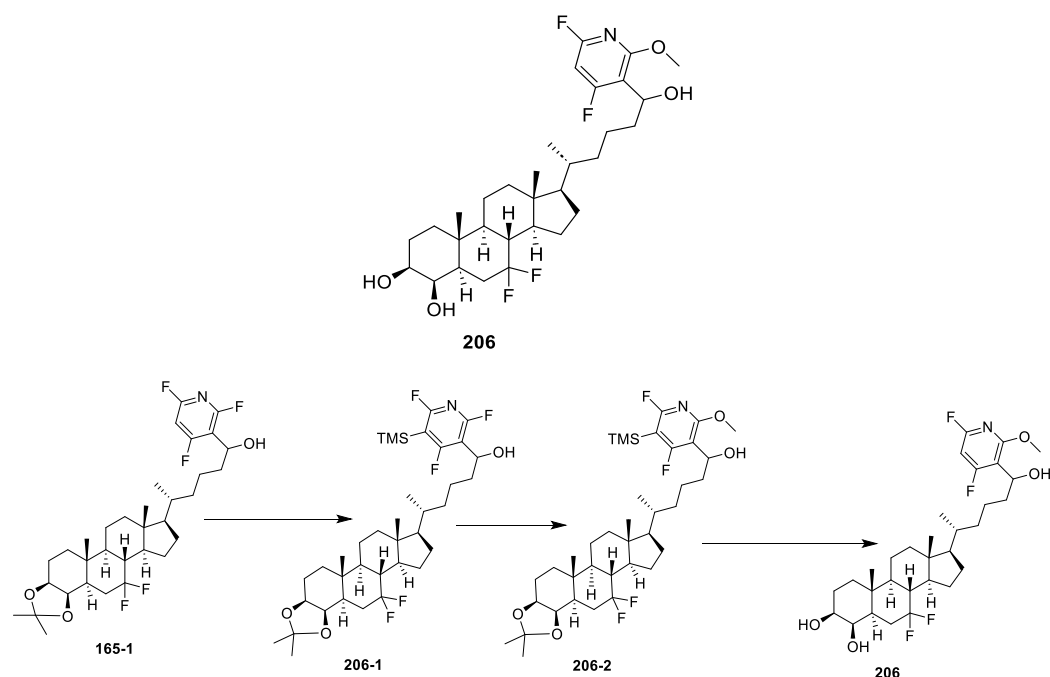
[0626] Compound **175**: ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.2 Hz, 1H), 4.89 (s, 1H), 3.99 (d, *J* = 13.7 Hz, 3H), 3.74 (s, 1H), 3.65 – 3.55 (m, 1H), 1.97 (d, *J* = 13.2 Hz, 3H), 1.78 (dd, *J* = 35.4, 11.1 Hz, 9H), 1.67 (s, 4H), 1.45 (s, 4H), 1.39 (d, *J* = 14.5 Hz, 4H), 1.10 (s, 2H), 1.06 (s, 3H), 1.02 – 0.94 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.64 (d, *J* = 12.1 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -87.71 (d, *J* = 25.9 Hz, 1F), -88.94 (d, *J* = 235.9 Hz, 1F), -110.94 (d, *J* = 236.1 Hz, 1F). LC-

MS: $[M-H]^- = 553.45$.

[0627] Example 206

[0628] Preparation of compound 206

- 5 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(4,6-difluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



- 10 [0629] Step 1: Referring to Example 165, starting material 2,4,6-trifluoropyridine was replaced with trimethylsilyl chloride to obtain the product (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-[2,4,6-trifluoro-5-
- 15 (trimethylsilyl)pyridin-3-yl]hexan-1-ol **206-1** (70 mg, purity: 95%, yield: 39.57%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 4.94 (s, 1H), 4.01 (dd, $J = 5.0$, 2.8 Hz, 2H), 2.26 – 1.93 (m, 3H), 1.82 (m, 6H), 1.49 (m, 5H), 1.34 – 1.24 (m, 9H), 1.12 – 1.06 (m, 12 H), 0.90 (d, $J = 5.7$ Hz, 3H), 0.67 (s, 3H), 0.38 (s, 9H).

- [0630] Step 2: Referring to Step 2 of Example 175, starting material **175-1** was
- 20 replaced with **206-1** to obtain the product (5R)-5-

[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-[4,6-difluoro-2-methoxy-5-(trimethylsilyl)pyridin-3-yl]hexan-1-ol **206-2** (60 mg, purity: 95%,
 5 yield: 80.00%).

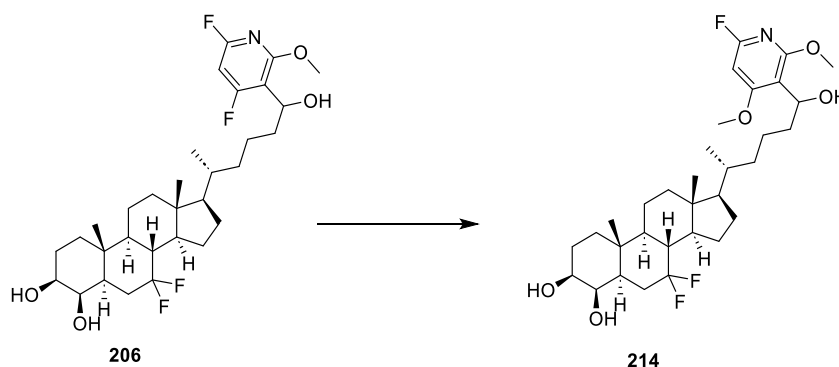
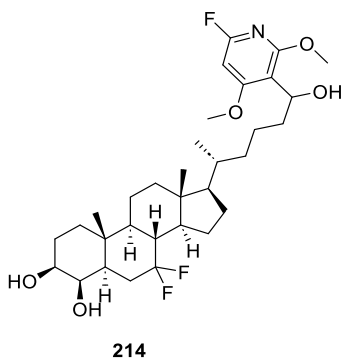
[0631] Step 3: Reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-[4,6-difluoro-2-methoxy-5-(trimethylsilyl)pyridin-3-yl]hexan-1-ol **206-2** (60 mg, 0.088 mmol,
 10 1.0 eq) was dissolved in tetrahydrofuran (5 mL), and TBAF (0.877 mL, 0.877 mmol, 10.0 eq) was added. The reaction system was stirred at room temperature for 0.5 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed,
 15 the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was then dissolved
 20 in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1.5 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 3 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 1:1). After the starting material was completely consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer
 25 was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by preparative chromatography to obtain the product (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(4,6-difluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-
 30 dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **206** (25 mg,

purity: 95%, yield: 47.35%).

[0632] Compound **206**: ^1H NMR (400 MHz, CDCl_3) δ 6.27 (dd, $J = 8.8, 2.0\text{Hz}$, 1H), 4.94 – 4.85 (m, 1H), 3.99 (s, 3H), 3.74 (s, 1H), 3.65 – 3.56 (m, 1H), 2.30 – 2.11 (m, 1H), 2.02 – 1.90 (m, 2H), 1.75 (s, 14H), 1.43 – 1.25 (m, 9H), 1.15 – 1.05 (m, 6H), 0.89 (dd, $J = 6.3, 5.0\text{Hz}$, 3H), 0.66 (d, $J = 3.0\text{Hz}$, 3H). ^{19}F NMR (376MHz, CDCl_3) δ -68.70, -88.62, -89.25, -101.23, -110.62, -111.24. LC-MS: $[\text{M}-\text{H}]^- = 570.50$.

[0633] Example **214**:

[0634] Preparation of compound **214**
(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0635] Step 1: Starting material (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(4,6-difluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol (20 mg, 0.035 mmol, 1 *eq*) was dissolved in anhydrous tetrahydrofuran (2

mL). Sodium methoxide (1.9 M) (0.11 mL, 0.21 mmol, 6 *eq*) was added at room temperature, and the mixture was stirred at this temperature for 12 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1), and the starting material was completely consumed. Water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (100 mL $\times$ 3). The organic phases were combined, washed with saturated sodium chloride (10 mL), dried, and concentrated to obtain a white solid. The crude product was purified by flash chromatography (petroleum ether: ethyl acetate = 50:50) and concentrated to obtain a white solid, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK OZ_3, 3 $\times$ 150 mm, 3 μ m, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 2.0 mL/min, column temperature: 37°C) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **214** (3.38 mg, purity: 99.23%, yield: 20.42%, retention time: 2.385 min).

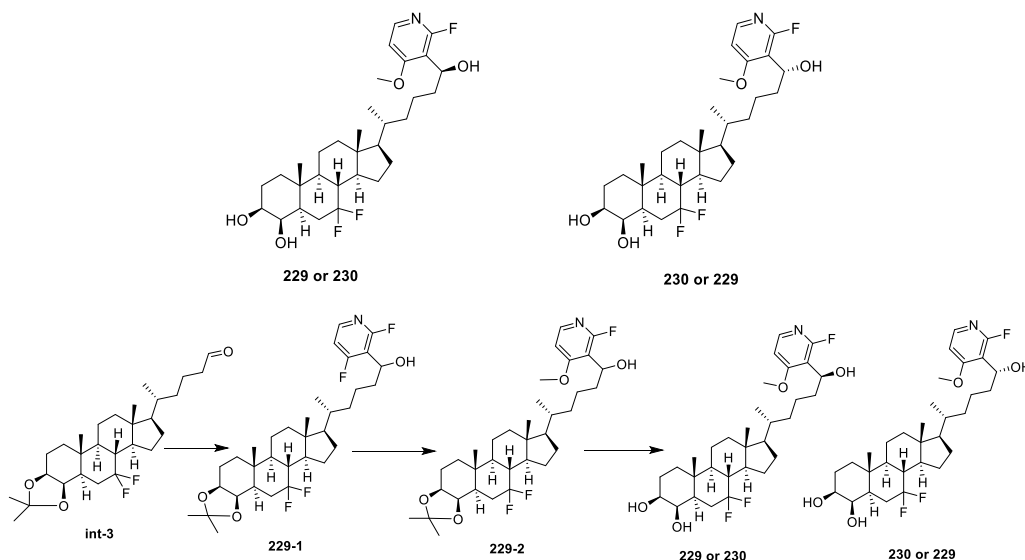
[0636] Compound **214**: ¹H NMR (400 MHz, CDCl₃) δ 6.10 (s, 1H), 4.95 (t, J = 7.1 Hz, 1H), 3.90 (d, J = 26.5 Hz, 6H), 3.74 (s, 1H), 3.59 (dd, J = 11.4, 3.4 Hz, 1H), 2.25 (t, J = 7.2 Hz, 1H), 1.99 (dd, J = 15.7, 9.4 Hz, 3H), 1.86 – 1.79 (m, 4H), 1.71 (s, 4H), 1.49 (s, 3H), 1.35 (d, J = 13.4 Hz, 7H), 1.09 (s, 1H), 1.06 (s, 3H), 1.02 – 0.95 (m, 2H), 0.89 (dd, J = 6.2, 4.2 Hz, 4H), 0.66 (d, J = 2.8 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -69.75, -88.63, -89.25, -110.63, -111.24. LC-MS: [M-H]⁻ = 582.50.

[0637] Examples **229 & 230**

[0638] Preparation of compound **229** or **230** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(2-fluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0639] compound **230** or **229** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-

9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0640] Step 1: Referring to Example 165, starting material 2,4,6-trifluoropyridine in Step 1 was replaced with 2,4-difluoropyridine to obtain (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexadecahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2,4-difluoropyridin-3-yl)hexan-1-ol **229-1** (68 mg, yield: 33.1%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 8.19 – 8.06 (m, 1H), 7.00 – 6.93 (m, 1H), 5.00 (t, *J* = 6.9 Hz, 1H), 4.02 (d, *J* = 15.0 Hz, 2H), 2.18 – 1.92 (m, 4H), 1.89 – 1.67 (m, 9H), 1.61 (d, *J* = 13.2 Hz, 3H), 1.50 (s, 3H), 1.45 – 1.34 (m, 5H), 1.30 (s, 3H), 1.12 (d, *J* = 12.7 Hz, 3H), 1.07 (s, 3H), 1.02 – 0.93 (m, 2H), 0.91 – 0.87 (m, 3H), 0.66 (t, *J* = 5.8 Hz, 3H).

[0641] Step 2: At room temperature, (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2,4-difluoropyridin-3-yl)hexan-1-ol **229-1** (68 mg, 0.12 mmol) was dissolved in anhydrous methanol (3 mL), sodium methoxide (30% in MeOH, 126.4 mg, 0.70 mmol) was added, and the mixture was stirred at room temperature for 6 hours. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1) until completion. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (20 mL × 2). The organic phase was washed

with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-20% ethyl acetate/petroleum ether, 20 mL/min) to obtain the product (5R)-5-((3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-

5 11,11-difluoro-2,2,5a,7a-tetramethylhexahydro-4H-cyclopenta[7,8]phenanthro[1,2-d][1,3]dioxol-8-yl)-1-(2-fluoro-4-methoxypyridin-3-yl)hexan-1-ol **229-2** (40 mg, yield: 57.6%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 5.3 Hz, 1H), 6.76 (d, *J* = 4.8 Hz, 1H), 4.97 (d, *J* = 5.8 Hz, 1H), 4.07 – 3.97 (m, 2H), 3.95 (s, 3H), 2.10 (s, 1H), 2.02 – 1.89 (m, 3H), 1.89 – 1.75 (m, 5H), 1.72 – 1.65 (m, 3H), 1.61 (d, *J* = 13.7 Hz, 3H), 1.50 (s, 3H), 1.39 (ddd, *J* = 22.2, 12.8, 7.4 Hz, 5H), 1.30 (d, *J* = 3.6 Hz, 3H), 1.25 – 1.20 (m, 2H), 1.15 – 1.09 (m, 2H), 1.03 – 0.92 (m, 2H), 0.89 (dd, *J* = 6.3, 4.3 Hz, 3H), 0.65 (dd, *J* = 12.0, 3.5 Hz, 3H).

[0642] Step 3: Referring to Step 2 of Example **165**, **165-1** was replaced with 15 **229-2** (40 mg, 0.067 mmol) to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 80:20) and SFC chiral resolution (instrument: SFC Acuity UPCC, column: Daicel CHIRALPAK IH-3, 3 mm × 150 mm, 3 μm, mobile phase: CO₂/MeOH (0.1% DEA)] = 80/20, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain white 20 solid compound **229** (7.17 mg, purity: 100%, e.e. 100%, yield: 27.6%, retention time: 3.969 min) and white solid compound **230** (5.83 mg, purity: 100%, e.e. 100%, yield: 22.4%, retention time: 4.626 min).

[0643] Compound **229**: ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 5.3 Hz, 1H), 6.76 (d, *J* = 4.9 Hz, 1H), 4.98 (d, *J* = 6.9 Hz, 1H), 3.95 (s, 3H), 3.74 (s, 25 1H), 3.60 (d, *J* = 10.8 Hz, 1H), 2.18 (dd, *J* = 32.6, 12.7 Hz, 1H), 1.97 (d, *J* = 13.0 Hz, 1H), 1.90 – 1.77 (m, 7H), 1.71 (s, 6H), 1.39 (dd, *J* = 29.3, 15.7 Hz, 7H), 1.09 (s, 2H), 1.06 (s, 3H), 1.02 – 0.93 (m, 2H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.30 (s, 1F), -88.94 (d, *J* = 235.5 Hz, 1F), -110.93 (d, *J* = 236.3 Hz, 1F). LC-MS: [M-H]⁺ = 552.60.

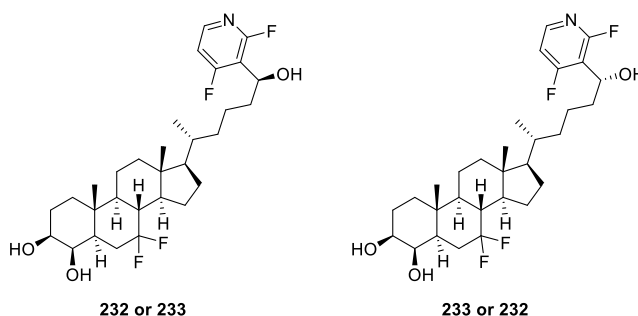
30 [0644] Compound **230**: ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 5.7 Hz, 1H), 6.75 (d, *J* = 5.8 Hz, 1H), 5.03 – 4.93 (m, 1H), 3.95 (s, 3H), 3.74 (s, 1H), 3.65 –

3.56 (m, 1H), 2.30 – 2.11 (m, 1H), 2.03 – 1.90 (m, 2H), 1.88 – 1.73 (m, 6H), 1.68 (dd, $J = 19.0, 6.4$ Hz, 5H), 1.44 – 1.38 (m, 3H), 1.37 – 1.29 (m, 5H), 1.16 – 1.07 (m, 2H), 1.06 (s, 3H), 1.03 – 0.93 (m, 2H), 0.90 (d, $J = 6.5$ Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -72.93 (s, 1F), -88.94 (d, $J = 236.0$ Hz, 1F), -110.93 (d, $J = 235.8$ Hz, 1F). LC-MS: $[\text{M}-\text{H}]^- = 552.60$.

[0645] Examples 232 & 233

[0646] Preparation of compound 232 or 233 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,4-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0647] compound 233 or 232 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,4-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0648] Referring to Example 165, starting material 2,4,6-trifluoropyridine was replaced with 2,4-difluoropyridine to obtain the crude product (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,4-difluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol, which was then subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK OD₃, 3×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 80/20, flow rate: 2.0 mL/min, column temperature: 37°C) to obtain the product compound 232 (40 mg, 0.07 mmol, yield: 28.62%, retention time: 3.241 min) and compound 233 (30 mg, 0.06 mmol, yield: 21.47%, retention time: 3.603 min).

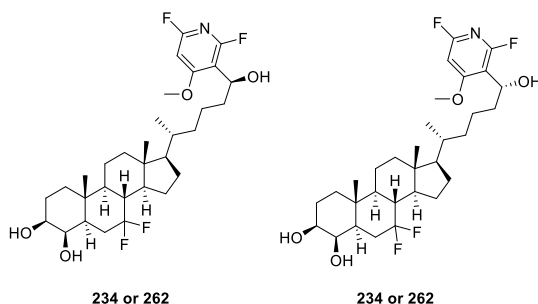
[0649] **Compound 232:** ^1H NMR (400 MHz, CDCl_3) δ 8.11 (dd, $J = 8.0, 5.7$ Hz,

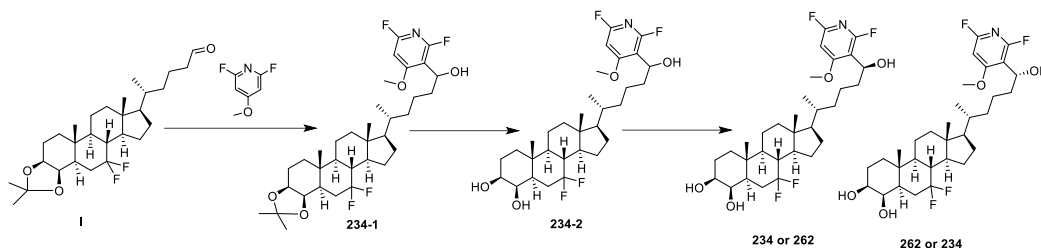
1H), 6.96 (dd, J = 8.6, 5.7 Hz, 1H), 5.00 (s, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.2 Hz, 1H), 2.31 – 2.08 (m, 2H), 1.96 (d, J = 13.1 Hz, 2H), 1.80 (dd, J = 13.5, 6.3 Hz, 6H), 1.71 (dd, J = 17.0, 13.3 Hz, 5H), 1.50 – 1.27 (m, 9H), 1.17 – 1.00 (m, 8H), 0.88 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -67.55, -88.65, -89.27, -102.23, -110.63, -111.26. LC-MS: [M-H]⁻ = 540.45.

[0650] Compound 233: ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, J = 7.8, 5.8 Hz, 1H), 7.00 – 6.93 (m, 1H), 5.05 – 4.97 (m, 1H), 3.74 (s, 1H), 3.66 – 3.56 (m, 1H), 2.29 – 2.11 (m, 2H), 2.07 – 1.93 (m, 4H), 1.90 – 1.67 (m, 10H), 1.45 – 1.30 (m, 11H), 1.06 (s, 5H), 0.90 (d, J = 6.5 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -67.45, -88.64, -89.27, -102.21, -110.73, -111.24. LCMS: [M-H]⁻ = 540.45.

[0651] Examples 234 & 262

[0652] Preparation of compound 234 or 262
(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,6-difluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
[0653] compound 262 or 234 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2,6-difluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol





[0654] Referring to Example 165, starting material 2,4,6-trifluoropyridine in Step 1 was replaced with 2,6-difluoro-4-methoxypyridine to obtain the crude compound (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,6-difluoro-4-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **234-2** (80 mg, 0.140 mmol), which was then subjected to chiral resolution (resolution conditions: instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IH_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/IPA (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain white solid compound **234** (20 mg, 0.035 mmol, 24.75%, retention time: 2.749 min) and white solid compound **262** (19 mg, 0.033 mmol, 54.29%, retention time: 3.838 min).

[0655] **Compound 234:** ¹H NMR (400 MHz, CDCl₃) δ 6.34 (s, 1H), 4.92 (s, 1H), 3.96 (s, 3H), 3.74 (s, 1H), 3.66 – 3.56 (m, 1H), 2.34 – 2.11 (m, 1H), 2.06 – 1.93 (m, 2H), 1.78 (ddd, J = 27.5, 15.2, 6.3 Hz, 12H), 1.41 – 1.24 (m, 11H), 1.06 (s, 5H), 0.89 (d, J = 6.5 Hz, 4H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -67.22, -67.25, -73.19, -73.22, -88.63, -89.26, -110.63, -111.25.

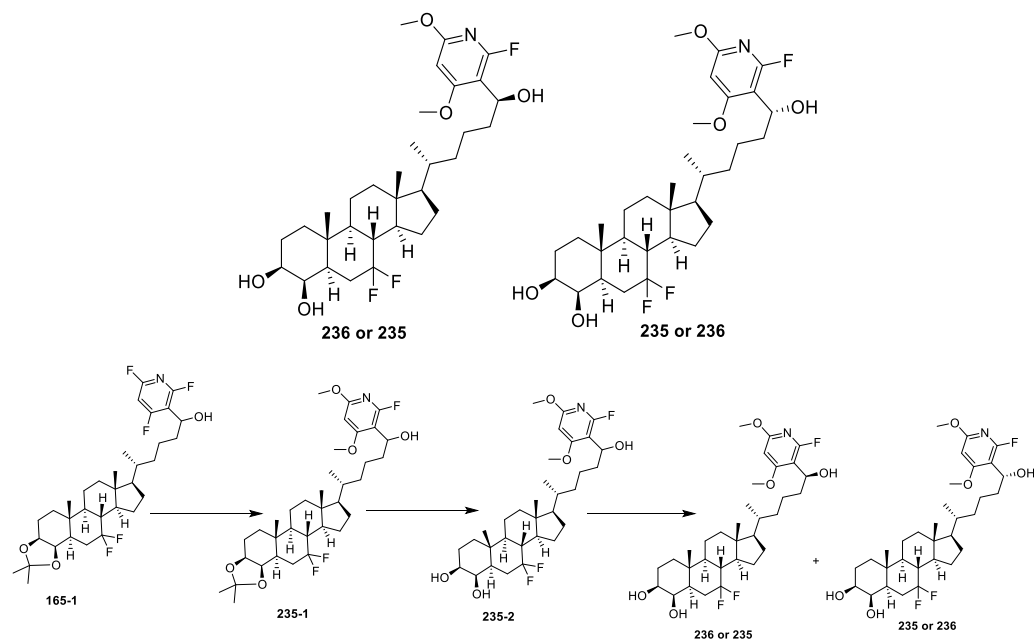
[0656] **Compound 262:** ¹H NMR (400 MHz, CDCl₃) δ 6.34 (s, 1H), 4.93 (dd, J = 8.1, 6.3 Hz, 1H), 3.96 (s, 3H), 3.74 (s, 1H), 3.60 (d, J = 11.4 Hz, 1H), 2.19 (dtd, J = 23.5, 14.0, 6.9 Hz, 1H), 1.93 – 1.65 (m, 13H), 1.49 – 1.28 (m, 10H), 1.19 – 0.96 (m, 8H), 0.90 (d, J = 6.5 Hz, 4H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -67.24, -67.28, -73.20, -73.24, -88.62, -89.25, -110.62, -111.24.

[0657] Examples **235 & 236**

[0658] Preparation of

[0659] compound **236 or 235** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-

difluoro-1-[(2R,6S)-6-(2-fluoro-4,6-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
[0660] compound 235 or 236 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-
5 difluoro-1-[(2R,6R)-6-(2-fluoro-4,6-dimethoxypyridin-3-yl)-6-
hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-
a]phenanthrene-6,7-diol



[0661] Step 1: At room temperature, reactant (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4,6-trifluoropyridin-3-yl)hexan-1-ol **165-1** (80 mg, 0.13 mmol) was dissolved in methanol (3 mL), and sodium methoxide (30% in methanol) (192 mg, 1.07 mmol) was added. The reaction was stirred for 48 hours. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was basically consumed, the reaction was stopped. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The ethyl acetate layers were combined and washed with saturated brine (10 mL). The ethyl acetate layer was dried over anhydrous

sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 15:1) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-

5 4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2-fluoro-4,6-dimethoxypyridin-3-yl)hexan-1-ol **235-1** (45 mg, 0.07 mmol, yield: 54.14%).

[0662] Referring to Examples **234** & **262**, starting material **234-1** in Step 2 was replaced with **235-1** to obtain compound
 10 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-4,6-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **235-2** (30 mg, 0.051 mmol), which was resolved by SFC (resolution conditions: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μm, mobile phase: A/B:
 15 CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain white solid compound **236** (7.73 mg, 0.013 mmol, yield: 25.77%, retention time: 3.140 min) and white solid compound **235** (4.62 mg, 0.008 mmol, yield: 14.90%, retention time: 3.395 min).

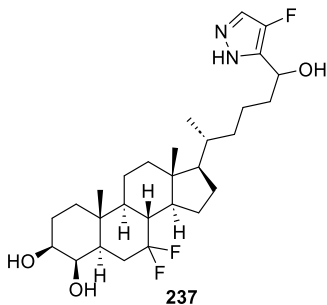
[0663] **236**: ¹H NMR (400 MHz, CDCl₃) δ 6.12 (s, 1H), 4.88 (dd, J = 7.8, 6.7 Hz, 1H), 3.88 (d, J = 2.4 Hz, 6H), 3.74 (s, 1H), 3.60 (d, J = 10.9 Hz, 1H), 2.23 (dd, J = 10.0, 5.6 Hz, 1H), 1.99 – 1.84 (m, 9H), 1.79 – 1.59 (m, 6H), 1.52 – 1.32 (m, 9H), 1.18 – 1.01 (m, 7H), 0.90 (t, J = 7.2 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -75.92, -88.62, -89.24, -110.61, -111.24. LC-MS: [M-H]⁻ = 582.45.

25 [0664] **235**: ¹H NMR (400 MHz, CDCl₃) δ 6.12 (s, 1H), 4.87 (t, J = 7.3 Hz, 1H), 3.88 (d, J = 1.7 Hz, 6H), 3.72 (d, J = 14.9 Hz, 1H), 3.66 – 3.57 (m, 1H), 2.31 – 2.09 (m, 1H), 2.01 (s, 2H), 1.82 – 1.71 (m, 13H), 1.49 – 1.33 (m, 8H), 1.06 (s, 8H), 0.88 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -75.90, -88.63, -89.25, -110.62, -111.24. LC-MS: [M-H]⁻ = 582.40.

30

[0665] Example **237**

[0666] Preparation of **compound 237** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2H-pyrazol-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



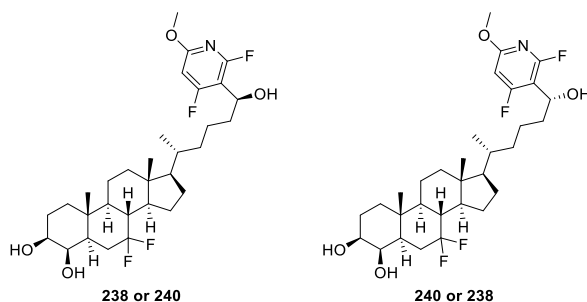
5 [0667] Referring to Example **165**, starting material 2,4,6-trifluoropyridine in Step 1 was replaced with 4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (162 mg, 0.75 mmol) to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-50% ethyl acetate/petroleum ether, 20 mL/min) and preparative liquid chromatography (wavelength: 214 nm,
10 instrument: Waters MS-triggered Prep-LC with SQD2 detector, column: Xbridge 5u C18 150 × 19 mm, flow rate: 20 mL/min), followed by lyophilization to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2H-pyrazol-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **237** (2.86 mg, 0.006 mmol, purity:
15 99.2%, yield: 15.29%) as a white solid.

[0668] Compound **237**: ¹H NMR (400 MHz, MeOD) δ 7.43 (d, *J* = 48.7 Hz, 1H), 4.73 (s, 1H), 3.63 (s, 1H), 3.51 – 3.44 (m, 1H), 2.28 – 2.06 (m, 1H), 2.00 (d, *J* = 12.9 Hz, 1H), 1.93 – 1.61 (m, 8H), 1.59 (d, *J* = 12.9 Hz, 1H), 1.36 (tdd, *J* = 26.4, 20.3, 11.0 Hz, 11H), 1.15 – 1.09 (m, 2H), 1.06 (s, 3H), 1.00 (d, *J* = 16.3 Hz, 2H),
20 0.93 – 0.89 (m, 3H), 0.69 (s, 3H). ¹⁹F NMR (377MHz, MeOD) δ -89.33, -89.96, -111.85, -112.48, -182.36. LCMS: [M-H]⁻ = 511.4.

[0669] Examples **238 & 240**

[0670] Preparation of **compound 238 or 240**
25 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(2,4-difluoro-6-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-

dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
[0671] compound 240 or 238 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-
[(2R,6R)-6-(2,4-difluoro-6-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-
difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-
5 a]phenanthrene-6,7-diol



[0672] Referring to Example **165**, starting material 2,4,6-trifluoropyridine in Step 1 was replaced with 4,6-difluoro-2-methoxypyridine to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-(2,4-difluoro-6-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol, which was subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IG-3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain white solid compound **238** (5 mg, 0.009 mmol, 31.25%, retention time: 3.5 min) and white solid compound **240** (4 mg, 0.007 mmol, 25.00%, retention time: 4.489 min).

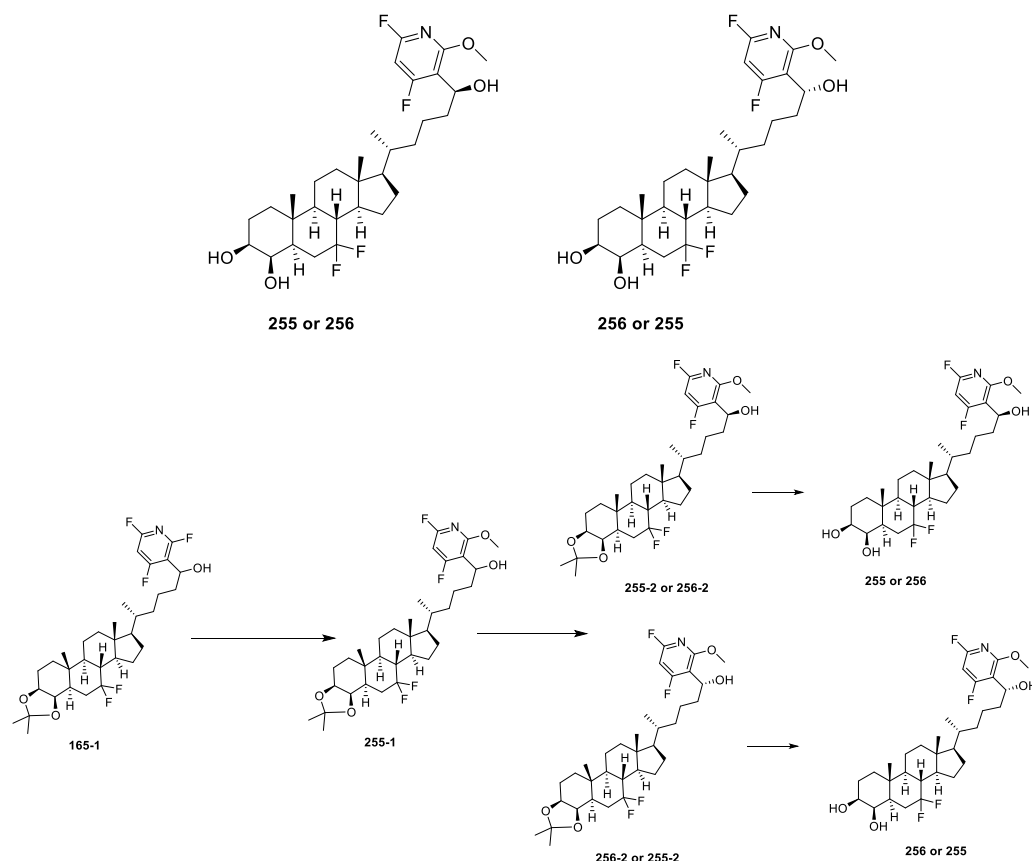
[0673] Compound **238**: ¹H NMR (400 MHz, CDCl₃) δ 6.33 (d, J = 10.1 Hz, 1H), 4.90 (t, J = 7.4 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 1H), 3.60 (m, 1H), 2.23 (m, 1H), 1.99 (dd, J = 19.8, 8.2 Hz, 2H), 1.81 (s, 5H), 1.71 (d, J = 3.7 Hz, 11H), 1.41 (d, J = 10.3 Hz, 2H), 1.27 (s, 11H), 1.09 (m, 3H), 1.06 (s, 3H), 0.88 (d, J = 6.5 Hz, 4H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -70.72, -70.77, -88.65, -89.28, -101.74, -101.79, -110.64, -111.26. LCMS: [M-H]⁻ = 570.45

[0674] Compound **240**: ¹H NMR (400 MHz, CDCl₃) δ 6.33 (d, J = 10.1 Hz, 1H), 4.90 (t, J = 7.3 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 1H), 3.60 (m, 1H), 2.21 (dd, J = 21.3, 13.3 Hz, 1H), 1.95 (s, 3H), 1.81 (m, 5H), 1.70 (d, J = 8.7 Hz, 6H), 1.35 (m,

5H), 1.26 (s, 4H), 1.06 (s, 4H), 0.90 (d, $J = 6.5$ Hz, 4H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -70.76, -70.81, -88.65, -89.27, -101.80, -101.85, -110.64, -111.27. LCMS: $[\text{M}-\text{H}]^- = 570.45$.

[0675] Examples 255 & 256

- 5 [0676] Preparation of compound 255 or 256
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(4,6-difluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
 [0677] compound 255 or 256 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-
 10 [(2R,6R)-6-(4,6-difluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



- 15 [0678] Step 1: At 0°C , compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-

cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,4,6-trifluoropyridin-3-yl)hexan-1-ol **165-1** (300 mg, 0.500 mmol) was dissolved in anhydrous diethyl ether (15 mL), and sodium methoxide (21.62 mg, 0.120 mmol) was added. The mixture was reacted at 0°C under a nitrogen atmosphere for 30 minutes. The reaction system was quenched with water (20 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phases were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 1:0 to 15:1) to obtain **255-1** (233 mg, 0.305 mmol, 60.91%) as a white solid. ¹H NMR(400 MHz, CDCl₃) δ 6.27 (dd, J = 8.7, 2.0 Hz, 1H), 4.94 – 4.85 (m, 1H), 4.07 – 3.96 (m, 5H), 2.16 – 2.06 (m, 1H), 2.05 – 1.91 (m, 4H), 1.82 (ddd, J = 21.6, 14.0, 6.5 Hz, 6H), 1.69 – 1.61 (m, 4H), 1.53 – 1.43 (m, 6H), 1.34 – 1.25 (m, 10H), 1.15 – 1.07 (m, 4H), 0.88 (dd, J = 6.8, 1.8 Hz, 4H), 0.66 (dd, J = 7.8, 3.6 Hz, 3H). ¹⁹F NMR(376 MHz, CDCl₃) δ -68.67, -68.68, -68.72, -68.74, -89.00, -89.62, -101.19, -101.26, -101.31, -111.36, -111.99.

[0679] Step 2: Compound (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(4,6-difluoro-2-methoxypyridin-3-yl)hexan-1-ol **255-1** (80 mg, 0.131 mmol) was resolved (resolution method: instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK OD_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 90/10, flow rate: 2.0 mL/min, column temperature: 37°C) to obtain **255-2** (30 mg, 0.049 mmol, 37.40%, retention time: 3.798 min) and **256-2** (35 mg, 0.057 mmol, 43.51%, retention time: 4.344 min) as a solid.

[0680] Step 3: **255-2** (30 mg, 0.049 mmol) was dissolved in tetrahydrofuran (3 mL), and dilute hydrochloric acid (1.5 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 1:1). After the starting material was completely consumed, the reaction was stopped. Water (10

mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layers were combined and washed with saturated brine (3 × 10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product.

- 5 The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 63:37) to obtain the product **255** (15 mg, 0.026 mmol, 53.50%, retention time: 1.534 min) as a white solid.

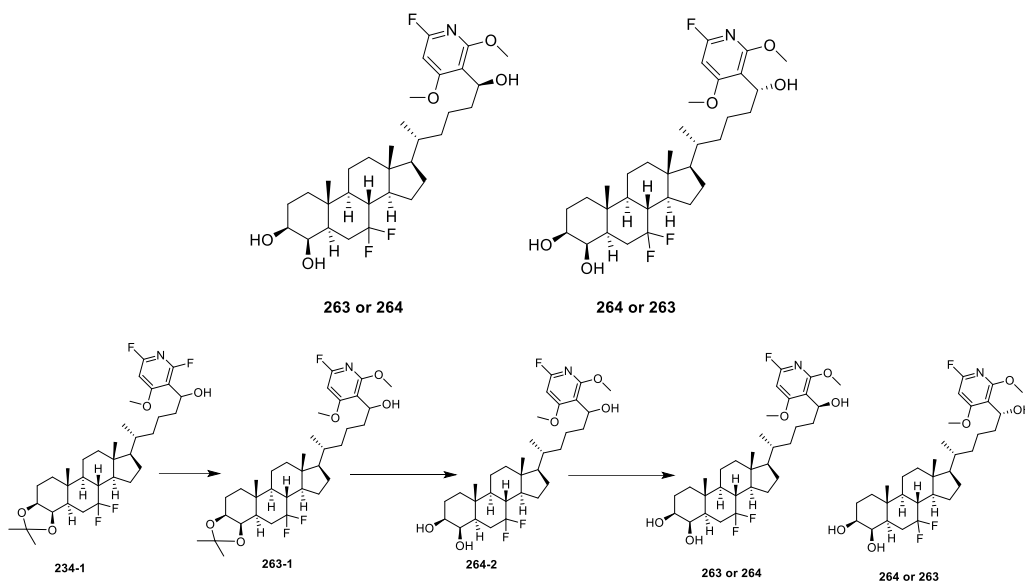
[0681] Compound **255**: ¹H NMR (400 MHz, CDCl₃) δ 6.26 (dd, J = 8.8, 2.1 Hz, 1H), 4.88 (d, J = 7.3 Hz, 1H), 3.99 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.4, 4.1 Hz, 1H), 2.20 (dtd, J = 34.9, 14.0, 4.5 Hz, 1H), 1.97 (d, J = 12.7 Hz, 1H), 1.91 – 1.66 (m, 12H), 1.50 – 1.21 (m, 12H), 1.10 – 1.04 (m, 6H), 0.89 (d, J = 6.5 Hz, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -68.67, -68.72, -88.64, -89.26, -101.19, -101.25, -110.63, -111.26. LC-MS: [M-H]⁻ = 570.55.

- [0682] Similarly, **255-2** was replaced with **256-2** to obtain the product **256** (20 mg, 0.035 mmol, 61.15%, retention time: 1.701 min) as a white solid.

[0683] Compound **256**: ¹H NMR (400 MHz, CDCl₃) δ 6.27 (dd, J = 8.8, 2.1 Hz, 1H), 4.90 (dd, J = 7.9, 6.5 Hz, 1H), 3.99 (s, 3H), 3.74 (s, 1H), 3.60 (dt, J = 11.4, 4.2 Hz, 1H), 2.24 (s, 1H), 1.99 – 1.94 (m, 1H), 1.91 – 1.58 (m, 12H), 1.48 – 1.26 (m, 12H), 1.09 – 1.01 (m, 6H), 0.89 (t, J = 5.1 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -68.68, -68.74, -88.63, -89.26, -101.26, -101.31, -110.63, -111.25. LC-MS: [M-H]⁻ = 570.50.

[0684] Examples **263** & **264**

- [0685] Preparation of compound **263** or **264**
 25 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
 [0686] compound **264** or **263** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol
 30



[0687] Referring to Example 206, **206-1** was replaced with **234-1** to obtain the crude product (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2,4-dimethoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol (80 mg, 0.123 mmol), which was subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IG_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain the crude product **263** (40 mg, 0.068 mmol, 57.10%, retention time: 2.749 min) and the crude product **264** (35 mg, 0.059 mmol, 39.81%, retention time: 3.838 min).

[0688] Compound 263: (30 mg, 0.051 mmol, 75.01 %). ¹H NMR(400 MHz, CDCl₃) δ 6.10 (s, 1H), 5.00 – 4.91 (m, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.74 (s, 1H), 3.60 (dd, J = 7.4, 4.0 Hz, 1H), 2.34 – 2.12 (m, 2H), 2.01 – 1.83 (m, 5H), 1.77 – 1.58 (m, 8H), 1.47 – 1.31 (m, 11H), 1.06 (s, 5H), 0.90 (d, J = 6.5 Hz, 4H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -69.77, -88.61, -89.24, -110.61, -111.24. LC-MS: [M-H]⁻ = 582.45.

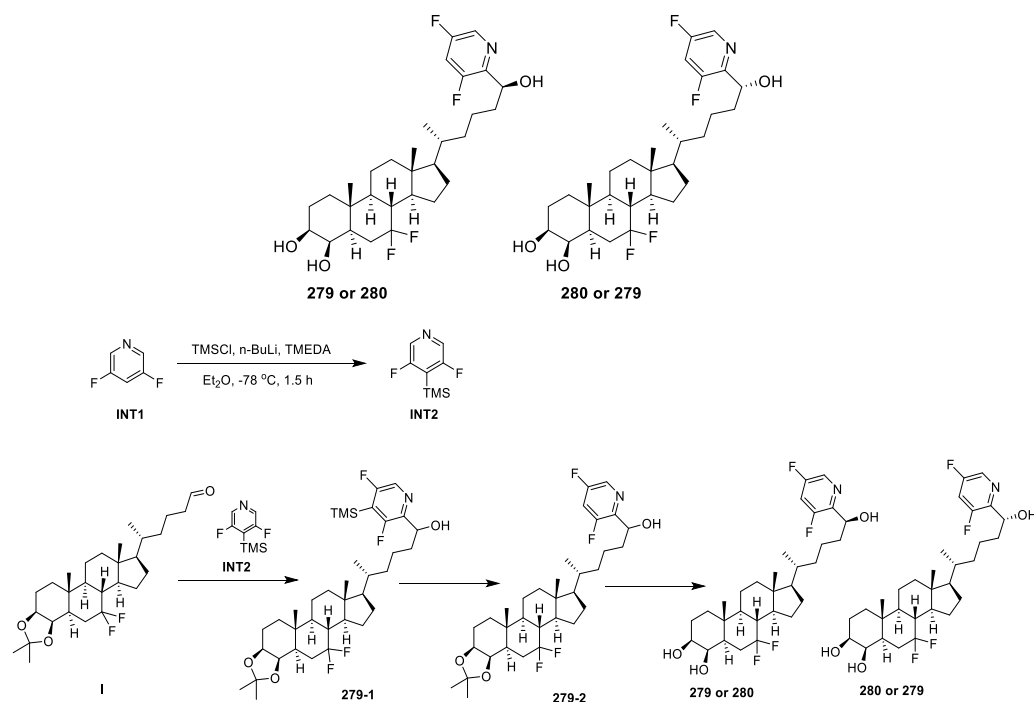
[0689] Compound 264: (20 mg, 0.033 mmol, 58.07 %). ¹H NMR(400 MHz, CDCl₃) δ 6.10 (s, 1H), 4.94 (d, J = 9.5 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.74 (s, 1H), 3.60 (d, J = 10.9 Hz, 1H), 2.19 (dd, J = 30.1, 22.6 Hz, 2H), 2.01 – 1.94 (m, 2H), 1.89 – 1.66 (m, 10H), 1.43 – 1.26 (m, 11H), 1.10 – 1.03 (m, 6H), 0.88 (t, J = 6.4 Hz,

4H), 0.65 (s, 3H). ^{19}F NMR (376MHz, CDCl_3) δ -69.75, -88.62, -89.25, -110.62, -111.25, -157.57, -218.57. LC-MS: $[\text{M}-\text{H}]^- = 582.45$.

[0690] Examples 279 & 280

5 **[0691] Preparation of compound 279 or 280**
(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(3,5-difluoropyridin-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0692] compound 280 or 279 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(3,5-difluoropyridin-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0693] Step 1: At -78°C , N,N,N',N'-tetramethylethylenediamine (151.47 mg, 1.303 mmol) was dissolved in anhydrous diethyl ether (10 mL), and *n*-butyllithium (2.5 M solution in *n*-hexane, 0.487 mL, 1.217 mmol) was added. The mixture was stirred at this temperature for 30 min. Compound 3,5-difluoropyridine (100 mg, 0.869 mmol) was dissolved in anhydrous diethyl ether (1 mL) and slowly added to the above reaction mixture. The reaction system was stirred at -78°C for 0.5 hours, then (0.121 mL, 0.956 mmol) was added, and

the mixture was stirred for an additional 1.5 hours. Water (10 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (10 mL $\times$ 3). The ethyl acetate layers were combined and washed with saturated brine (10 mL $\times$ 3). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether) to obtain the product 3,5-difluoro-4-(trimethylsilyl)pyridine (80 mg, 0.406 mmol, yield: 46.71%) as a pale yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 2H), 0.33 (s, 9H). ^{19}F NMR (376MHz, CDCl_3) δ 113.14.

[0694] Referring to Example **237**, 4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole was replaced with 3,5-difluoro-4-(trimethylsilyl)pyridine to obtain a crude product. The crude product was subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IA 4.6×250 mm, 5 μm , mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain compound **279** (13 mg, 0.024 mmol, 32.50%, retention time: 2.374 min) and compound **280** (15 mg, 0.028 mmol, yield: 37.50%, retention time: 2.953 min).

[0695] Compound **279**: ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, $J = 2.2$ Hz, 1H), 7.26 – 7.25 (m, 1H), 5.01 – 4.93 (m, 1H), 3.74 (s, 1H), 3.60 (d, $J = 11.4$ Hz, 1H), 2.32 – 2.09 (m, 2H), 1.97 (d, $J = 12.7$ Hz, 1H), 1.89 – 1.77 (m, 4H), 1.77 – 1.65 (m, 5H), 1.55 – 1.39 (m, 4H), 1.38 – 1.19 (m, 8H), 1.14 – 1.00 (m, 7H), 0.89 (t, $J = 5.9$ Hz, 4H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.63, -89.26, -110.62, -111.25, -122.52, -124.93. LC-MS: $[\text{M-H}]^- = 540.40$.

[0696] Compound **280**: ^1H NMR (400 MHz, CDCl_3) δ 8.31 (s, 1H), 7.23 (t, $J = 8.7$ Hz, 1H), 4.95 (s, 1H), 3.74 (s, 1H), 3.60 (dt, $J = 11.2, 4.0$ Hz, 1H), 2.28 – 2.08 (m, 1H), 1.99 (dd, $J = 20.5, 17.4$ Hz, 1H), 1.89 – 1.60 (m, 9H), 1.53 – 1.40 (m, 4H), 1.40 – 1.20 (m, 9H), 1.13 – 0.98 (m, 7H), 0.89 (t, $J = 9.1$ Hz, 4H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.63, -89.25, -110.62, -111.25, -122.96, -125.34. LC-MS: $[\text{M+H}]^+ = 542.40$.

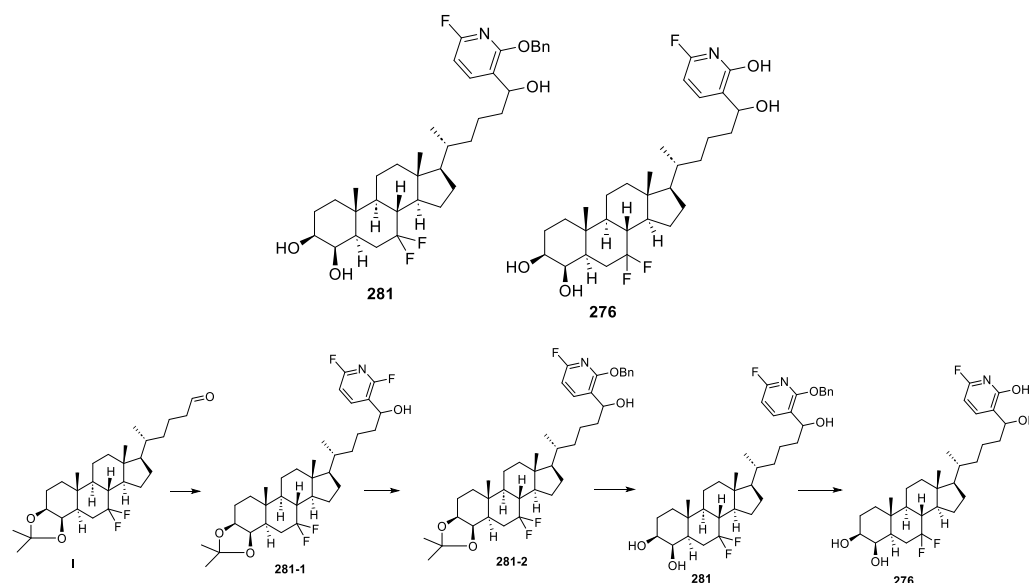
30

[0697] Examples **281 & 276**

[0698] Preparation of compound 281

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-(benzyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

- 5 **[0699] compound 276 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2-hydroxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol**



- 10 **[0700] Step 1:** Referring to Example 165, starting material 2,4,6-trifluoropyridine was replaced with 2,6-difluoropyridine to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(2,6-difluoropyridin-3-yl)hexan-1-ol **281-1**.

- 15 **[0701] Step 2:** **281-1** (110 mg, 0.19 mmol, 1.0 eq) was dissolved in diethyl ether (5 mL), and sodium benzyloxide (1.89 mL, 0.1 mol/L, 10 eq) was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Water (20 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The ethyl acetate layers were combined and washed

with saturated brine (20 mL $\times$ 3). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 15:1) to obtain the product (5R)-1-[2-(benzyloxy)-6-fluoropyridin-3-yl]-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexan-1-ol **281-2** (60 mg, yield: 42.63%) as a white solid. LC-MS: $[M-H]^+ = 692.7$.

[0702] Step 3: Compound **281-1** (40 mg, 0.06 mmol, 1.0 eq) was dissolved in water (1 mL) and anhydrous tetrahydrofuran (4 mL), followed by addition of *p*-toluenesulfonic acid (11.36 mg, 0.06 mmol, 1.0 eq). The mixture was heated to 70°C and refluxed for 60 minutes. The reaction was monitored by TLC (petroleum ether: ethyl acetate = 5:1). The reaction mixture was quenched with saturated sodium bicarbonate, extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80:20) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-(benzyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **281** (22.02 mg, 0.035 mmol, purity: 100%, yield: 58.55%) as a white solid.

[0703] Compound **281**: ^1H NMR (400 MHz, CDCl_3) δ 7.74 (td, $J = 8.0, 1.3$ Hz, 1H), 7.38 (m, 5H), 6.51 (dd, $J = 7.9, 2.7$ Hz, 1H), 5.39 (s, 2H), 4.87 (m, 1H), 3.74 (s, 1H), 3.60 (d, $J = 11.4$ Hz, 1H), 2.20 (m, 1H), 1.96 (d, $J = 10.0$ Hz, 2H), 1.77 (m, 11H), 1.38 (m, 8H), 1.20 (s, 2H), 1.06 (s, 3H), 0.98 (m, 2H), 0.87 (t, $J = 6.7$ Hz, 3H), 0.64 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -73.15, -73.23, -88.62, -89.26, -110.62, -111.24. LC-MS: $[M+H]^+ = 630.35$.

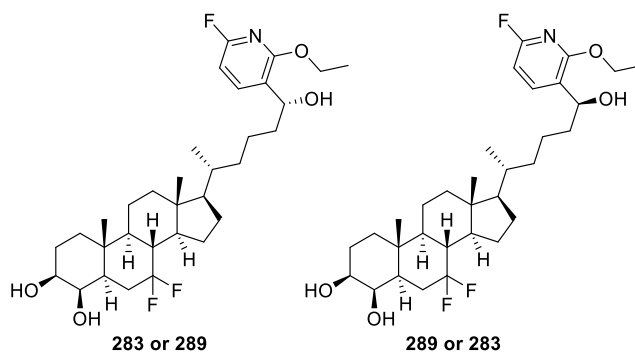
[0704] Step 4: Compound **281** (30 mg, 0.048 mmol, 1.0 eq) was dissolved in methanol (5 mL), and palladium on carbon (Pd/C, 10%) (10 mg) was added. After purging with hydrogen three times, the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours. The mixture was concentrated to

obtain a crude product, which was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 60:40) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2-hydroxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-
 5 1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **276** (15 mg, 0.026 mmol, purity: 94.64%, yield: 55.22%) as a white solid.

[0705] Compound **276**: ^1H NMR (400 MHz, CDCl_3) δ 7.70 (td, J = 8.0, 2.4 Hz, 1H), 6.46 (m, 1H), 4.85 (d, J = 7.4 Hz, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.1 Hz, 1H), 2.19 (m, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.77 (m, 9H), 1.34 (m, 11H),
 10 1.12 (dd, J = 10.2, 6.7 Hz, 2H), 1.06 (s, 3H), 0.98 (m, 2H), 0.91 (dd, J = 6.5, 2.9 Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -76.83, -76.89, -88.65, -89.25, -110.59, -111.28. LC-MS: $[\text{M}+\text{H}]^+ = 538.35$.

[0706] Examples **283** & **289**

15 [0707] Preparation of compound **283** or **289**
 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(2-ethoxy-6-fluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and
 [0708] compound **289** or **283** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-
 20 [(2R,6S)-6-(2-ethoxy-6-fluoropyridin-3-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



25 [0709] Referring to Example **281**, starting material sodium benzyloxide was

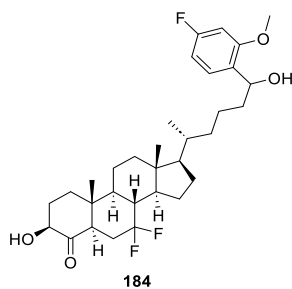
replaced with sodium ethoxide to obtain a crude product, which was subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK AD-3, 3.0×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain
 5 compound **289** (27 mg, 0.046 mmol, yield: 28.80%, retention time: 3.216 min) and **283** (35 mg, 0.062 mmol, yield: 38.89%, retention time: 4.126 min).

[0710] **Compound 289**: ^1H NMR (400 MHz, CDCl_3) δ 7.68 (t, $J = 8.1$ Hz, 1H), 6.46 (dd, $J = 7.9, 2.7$ Hz, 1H), 4.81 (dd, $J = 7.9, 5.1$ Hz, 1H), 4.39 (q, $J = 6.8$ Hz, 2H), 3.74 (s, 1H), 3.62 – 3.58 (m, 1H), 2.20 (dd, $J = 35.0, 4.4$ Hz, 1H), 1.97 (d, $J = 12.6$ Hz, 1H), 1.86 – 1.79 (m, 4H), 1.76 – 1.65 (m, 10H), 1.39 (t, $J = 7.1$ Hz, 9H), 1.26 (s, 1H), 1.07 (d, $J = 5.5$ Hz, 5H), 0.91 (d, $J = 6.5$ Hz, 4H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -73.29, -88.64, -89.26, -110.63, -111.26. LC-MS: $[\text{M-H}]^- = 566.45$.

[0711] **Compound 283**: ^1H NMR (400 MHz, CDCl_3) δ 7.67 (t, $J = 8.0$ Hz, 1H), 6.45 (dd, $J = 7.9, 2.7$ Hz, 1H), 4.82 – 4.78 (m, 1H), 4.39 (qd, $J = 7.1, 1.3$ Hz, 2H), 3.74 (s, 1H), 3.60 (d, $J = 11.4$ Hz, 1H), 2.20 (dd, $J = 34.8, 4.5$ Hz, 1H), 1.97 (d, $J = 12.8$ Hz, 1H), 1.85 – 1.78 (m, 4H), 1.70 (ddd, $J = 15.5, 11.4, 6.4$ Hz, 10H), 1.39 (t, $J = 7.1$ Hz, 7H), 1.26 (d, $J = 3.7$ Hz, 2H), 1.07 (d, $J = 5.7$ Hz, 5H), 1.02 – 0.94 (m, 2H), 0.90 (d, $J = 6.5$ Hz, 3H), 0.66 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ
 15 -73.22, -88.64, -89.27, -110.64, -111.27. LC-MS: $[\text{M-H}]^- = 566.50$.
 20

[0712] Example 184

[0713] Preparation of **compound 184 (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one**
 25



[0714] Referring to the synthesis of Example **97**, (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(4-fluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-7-hydroxy-9a,11a-

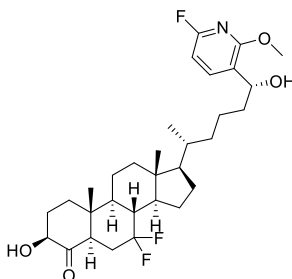
5 dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one **184** (5 mg, 0.008 mmol, 5.11%) was obtained as a white solid.

[0715] Compound **184**: ^1H NMR (400 MHz, CDCl_3) δ 7.28 (m, 1H), 6.63 (ddd, J = 13.2, 9.6, 4.1 Hz, 2H), 4.84 (m, 1H), 4.15 (dd, J = 11.1, 8.3 Hz, 1H), 3.83 (s, 3H), 2.48(m, 2H), 2.01 (d, J = 10.3 Hz, 2H), 1.88 (m, 4H), 1.57 (m, 5H), 1.37 (s, 10 4H), 1.33 (s, 2H), 1.29 (s, 4H), 1.08 (d, J = 10.6 Hz, 2H), 0.90 (dd, J = 6.4, 4.0 Hz, 4H), 0.76 (s, 3H), 0.66 (d, J = 1.6 Hz, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -90.20, -90.84, -111.49, -112.13, -112.95, -113.01. LC-MS: $[\text{M}-\text{H}]^-$ = 549.50.

[0716] Example **260**

15 **[0717]** Compound **260**

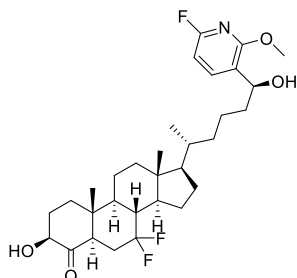
[0718] Preparation of (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-7-hydroxy-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one or



20

[0719] (1R,3aS,3bS,5aR,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-7-hydroxy-9a,11a-

dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-6-one

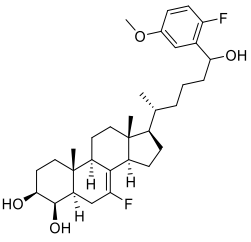


[0720] Referring to the synthesis of Example **97**, **189** was used as the starting material to obtain a crude product (12 mg, purity: 85%, yield: 43.54%) as a white solid. The crude product was subjected to chiral resolution (instrument: Gilson281, column: Daicel CHIRALCEL IG, 250 mm × 30 mm I.D., 10 μm, mobile phase: Hex/EtOH [0.2% NH₃ (7 M solution in MeOH)] = 60/40, flow rate: 20 mL/min, wavelength: UV 214 nm, column temperature: 35°C) to obtain **260** (8 mg, retention time: 10.7 min; purity: 100%, yield: 66.67%) as a white solid.

- [0721]** Compound **260**: ¹H NMR (400 MHz, CDCl₃) δ 7.69 (t, J=8.0, 1H), 6.48 (dd, J=7.9, 2.7, 1H), 4.85 – 4.78 (m, 1H), 4.15 (dd, J=11.0, 8.2, 1H), 3.96 (s, 3H), 2.54 – 2.40 (m, 2H), 2.28 – 1.82 (m, 9H), 1.75 – 1.40 (m, 10H), 1.11 (dddd, J=19.3, 15.6, 6.5, 4.1, 5H), 0.91 (d, J=6.5, 3H), 0.76 (s, 3H), 0.67 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.22 (s, 1F), -90.52 (d, J=240.0, 1F), -111.81 (d, J=240.0, 1F). LC-MS: [M+H]⁺ = 552.3.

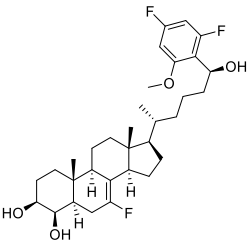
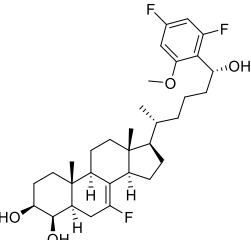
[0722] The following examples can be prepared by referring to the synthesis of Example **2**

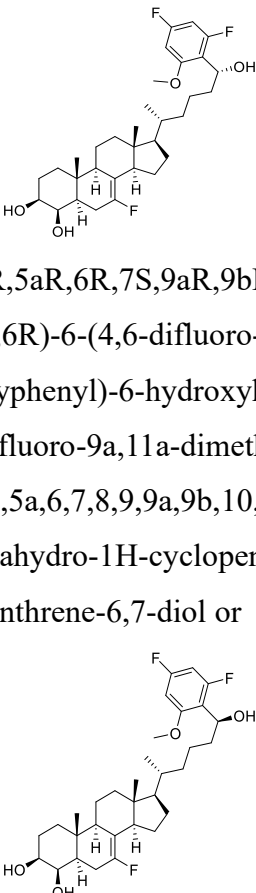
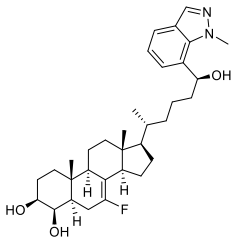
Exa- mple	Structural formula and compound name	Characterization results	SFC resolution method and results
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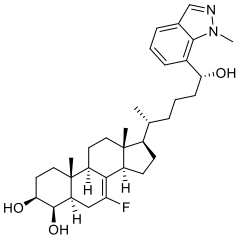
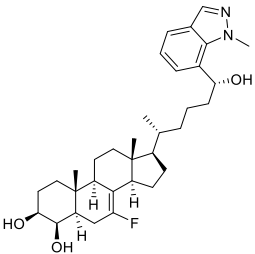
174	 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-(2-fluoro-5-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 6.98 (d, J = 2.7 Hz, 1H), 6.93 (t, J = 9.6 Hz, 1H), 6.77 – 6.70 (m, 1H), 4.97 (d, J = 5.6 Hz, 1H), 3.85 (s, 1H), 3.79 (s, 3H), 3.59 (d, J = 10.8 Hz, 1H), 2.65 (s, 1H), 2.02 (d, J = 12.1 Hz, 2H), 1.87 (t, J = 27.7 Hz, 9H), 1.77 – 1.69 (m, 5H), 1.45 (d, J = 10.1 Hz, 6H), 1.12 (s, 3H), 1.04 (s, 3H), 0.95 – 0.89 (m, 3H), 0.63 (d, J = 8.8 Hz, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -109.79, -130.39. LC-MS: [M+H-H ₂ O] ⁺ = 515.50.	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OJ_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 75/25, flow rate: 2.0 mL/min, column temperature: 37°C, retention time: 2.501 min.
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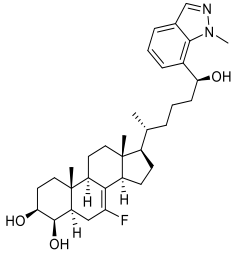
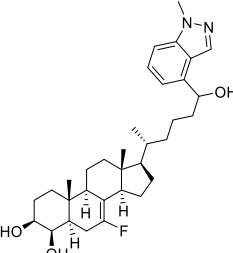
163	(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6S)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.17 (dd, J = 15.3, 8.1 Hz, 1H), 6.73 – 6.63 (m, 2H), 5.01 (d, J = 7.3 Hz, 1H), 3.86 (d, J = 13.8 Hz, 4H), 3.59 (d, J = 11.1 Hz, 1H), 3.19 (d, J = 10.7 Hz, 4H), 2.66 (s, 1H), 2.15 – 2.00 (m, 2H), 1.91 – 1.74 (m, 9H), 1.62 (s, 3H), 1.48 – 1.31 (m, 7H), 1.09 (d, J = 10.1 Hz, 4H), 1.04 (s, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.61 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -109.83, -117.19. LC-MS: [M+Na] ⁺ = 531.50.	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 × 150 mm, 3 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.826 min.
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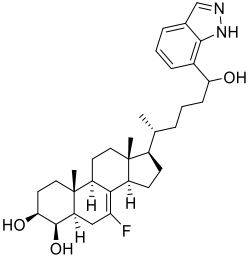
164	(1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6S)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.17 (dd, J = 15.0, 8.3 Hz, 1H), 6.72 – 6.64 (m, 2H), 5.01 (s, 1H), 3.88 (s, 3H), 3.86 (s, 1H), 3.59 (d, J = 11.1 Hz, 1H), 2.66 (s, 1H), 2.05 (dd, J = 22.9, 9.0 Hz, 2H), 1.93 (dd, J = 13.6, 6.1 Hz, 2H), 1.88 – 1.80 (m, 4H), 1.74 (d, J = 9.4 Hz, 2H), 1.61 (d, J = 11.8 Hz, 4H), 1.46 (d, J = 9.4 Hz, 3H), 1.41 – 1.32 (m, 4H), 1.14 – 1.07 (m, 3H), 1.04 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.63 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -109.83, -117.27. LC-MS:	Instrument: Waters Acquity UPC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μ m, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 2.931 min.
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		$[M+Na]^+ = 531.45.$	
202	 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R,6S)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R,6R)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (d, $J = 10.2$ Hz, 2H), 4.96 (s, 1H), 3.86 (s, 4H), 3.59 (d, $J = 11.3$ Hz, 1H), 2.66 (s, 1H), 2.10 – 1.99 (m, 4H), 1.84 (s, 5H), 1.75 (s, 2H), 1.67 (d, $J = 6.8$ Hz, 3H), 1.41 (dd, $J = 19.3, 9.6$ Hz, 6H), 1.11 (s, 4H), 1.04 (s, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.63 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.81, -110.43, -110.45, -113.92, -113.94. LC-MS: $[M-H]^- = 549.50.$	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6×150 mm, $3.5 \mu m$ Mobile, mobile phase: A/B: $CO_2/MeOH$ (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: $37^\circ C$, retention time: 3.131 min.

203	 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R,6R)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-1-[(2R,6S)-6-(4,6-difluoro-2-methoxyphenyl)-6-hydroxyhexan-2-yl]-4-fluoro-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 6.45 (d, J = 9.8 Hz, 2H), 4.95 (s, 1H), 3.85 (d, J = 6.1 Hz, 4H), 3.62 – 3.56 (m, 1H), 2.66 (s, 1H), 2.02 (d, J = 13.3 Hz, 3H), 1.84 (s, 5H), 1.71 (s, 6H), 1.47 – 1.40 (m, 5H), 1.09 (d, J = 5.3 Hz, 4H), 1.04 (s, 3H), 0.89 (d, J = 6.6 Hz, 4H), 0.62 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -109.81, -110.39, -110.41, -113.84, -113.86. LC-MS: [M-H] ⁻ = 549.50.	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S)-Whelk O1 4.6 × 150 mm, 3.5 μ m Mobile, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 3.356 min.
245		¹ H NMR (400 MHz, CDCl ₃) δ 8.11 (s, 1H), 7.72 (d, J = 7.9 Hz,	Instrument: Waters Acquity UPCC,

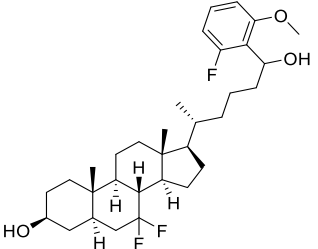
	(1R,3aR,5aR,6R,7S,9aR,9bR,11aR) -4-fluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aR,5aR,6R,7S,9aR,9bR,11aR) -4-fluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1H), 7.53 (t, J = 5.9 Hz, 1H), 7.21 (m, 1H), 5.31 (dd, J = 8.1, 5.1 Hz, 1H), 4.48 (s, 3H), 3.85 (s, 1H), 3.60 (m, 1H), 2.64 (d, J = 13.3 Hz, 1H), 1.88 (m, 12H), 1.61 (d, J = 9.8 Hz, 2H), 1.39 (m, 7H), 1.12 (m, 4H), 1.04 (s, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.65 (d, J = 13.8 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -109.52. LC-MS: [M-H]⁻ = 537.50	column: Daicel CHIRALPA K OZ_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 4.831 min.
246	 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR) -4-fluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 6.6 Hz, 1H), 7.22 (s, 1H), 5.30 (dd, J = 8.5, 4.8 Hz,	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K OZ_3, 3 ×

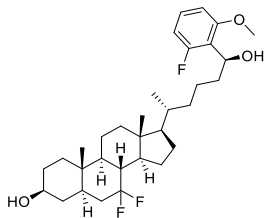
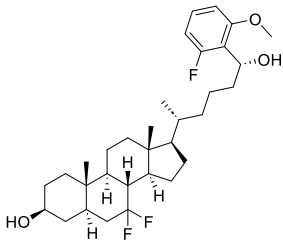
	9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-7-yl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1H), 4.52 (s, 3H), 3.85 (s, 1H), 3.59 (d, J = 11.5 Hz, 1H), 2.66 (s, 1H), 2.02 (d, J = 10.9 Hz, 3H), 1.87 (dd, J = 19.3, 15.1 Hz, 8H), 1.73 (m, 2H), 1.63 (s, 3H), 1.47 (m, 6H), 1.10 (d, J = 12.3 Hz, 3H), 1.05 (s, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.63 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -109.71. LC-MS: [M-H]⁻ = 537.50.	150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 6.853 min.
253	 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-4-yl)hexan-2-yl]-9a,11a-dimethyl-	¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 7.0 Hz, 1H), 5.06 (s, 1H), 4.15 (s, 3H),	Instrument: Waters Acquity UPCC, column: REGIS CHIRAL (S,S) Whelk O1, 4.6 × 150

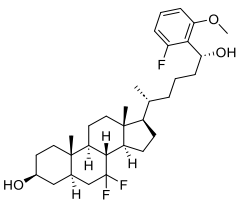
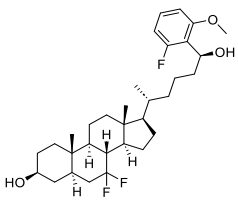
	2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	3.85(s, 1H), 3.59 (dd, J = 11.4, 3.6 Hz, 1H), 1.85 (m, 18H), 1.44 (m, 4H), 1.26 (s, 3H), 1.04 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.60 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -109.77. LC-MS: [M-H] ⁻ = 537.55	mm, 3.5 μm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C, retention time: 6.346 min.
270	 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-6-hydroxy-6-(1H-indazol-7-yl)hexan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.93 (s, 1H), 8.04 (s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 6.9 Hz, 1H), 7.08 – 7.04 (m, 1H), 5.29 (d, J = 4.2 Hz, 1H), 4.96 (s, 1H), 4.41 (d, J = 6.0 Hz, 1H), 4.24 (d, J = 3.3 Hz, 1H), 3.58 (s, 1H), 3.30 (s, 1H), 2.03	Instrument: Waters Acquity UPCC, column: Daicel CHIRALPA K IC_3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /MeOH = 50/50, flow rate: 1.5 mL/min,

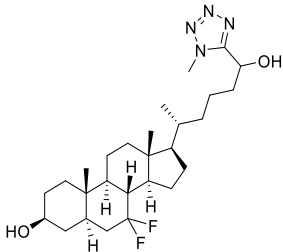
		– 1.92 (m, 2H), 1.72 (s, 6H), 1.62 (d, J = 12.9 Hz, 4H), 1.36 (d, J = 7.7 Hz, 2H), 1.23 (s, 5H), 0.98 (s, 5H), 0.95 (s, 3H), 0.84 (d, J = 6.4 Hz, 4H), 0.55 (s, 3H). ¹⁹ F NMR (377 MHz, DMSO) δ - 108.68. LC- MS: [M-H] ⁻ = 523.50	column temperature: 37°C, retention time: 1.977 min.
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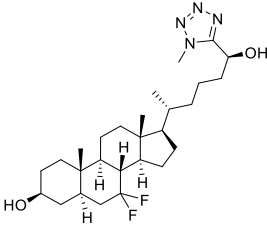
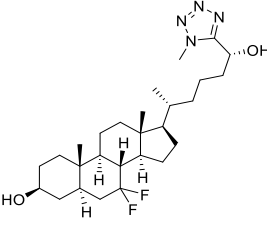
[0723] The following examples can be completed by referring to the synthesis method of Example 73, and the chiral compound is further resolved:

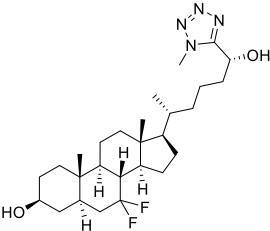
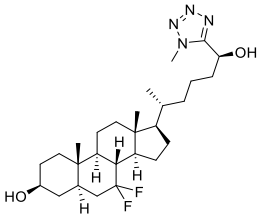
Exa- mple	Structural formula and compound name	Characterization results
302	 (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol	¹ H NMR (400 MHz, CDCl ₃) δ 7.17 (td, J = 8.4, 6.6 Hz, 1H), 6.69 (dt, J = 8.6, 4.5 Hz, 2H), 5.06 – 4.93 (m, 1H), 3.88 (s, 3H), 3.62 (s, 1H), 1.97 (d, J = 12.9 Hz, 1H), 1.89 – 1.78 (m, 4H), 1.71 (ddd, J = 23.3, 11.2, 5.2 Hz, 4H), 1.62 – 1.50 (m, 3H), 1.48

		– 1.18 (m, 11H), 1.13 – 0.97 (m, 5H), 0.89(dd, J = 6.5, 4.2 Hz, 3H), 0.84 (s, 3H), 0.65 (d, J = 4.5 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.96, -89.59, -110.84, -111.47, -117.20, -117.26.
314	 (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol or  (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol	¹H NMR (400 MHz, CDCl₃) δ 7.21 – 7.13 (m, 1H), 6.69 (dt, J = 8.6, 4.5 Hz, 2H), 5.01 (dd, J = 8.1, 6.3 Hz, 1H), 3.88 (s, 3H), 3.62 (s, 1H), 2.06 – 1.90 (m, 3H), 1.85 – 1.70 (m, 7H), 1.60 (dd, J = 10.8, 3.4 Hz, 3H), 1.46 – 1.37 (m, 5H), 1.30 (dd, J = 16.2, 10.6 Hz, 6H), 1.13– 1.00 (m, 4H), 0.89 (t, J = 4.9 Hz, 3H), 0.84 (s, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.96, -89.59, -110.85, -111.48, -117.25. SFC resolution method: Instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK

		OX_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 65/35, flow rate: 2.0 mL/min, column temperature: 37°C, wavelength: UV 214 nm; SFC retention time: 1.473 min.
315	 (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol or  (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(2-fluoro-6-methoxyphenyl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol	¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, J = 6.6 Hz, 1H), 6.69 (dd, J = 8.5, 3.5 Hz, 2H), 5.01 (s, 1H), 3.88 (s, 3H), 3.69 – 3.56 (m, 1H), 2.01 (s, 2H), 1.83 (dd, J = 9.8, 5.3 Hz, 4H), 1.76 – 1.69 (m, 4H), 1.62 – 1.53 (m, 4H), 1.43 (dd, J = 12.6, 8.0 Hz, 3H), 1.35 – 1.26 (m, 6H), 1.14 – 1.07 (m, 3H), 1.02 (d, J = 13.5 Hz, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.84 (s, 3H), 0.65 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.96, -89.59, -110.85, -111.48, -117.20. SFC resolution method: Instrument: Waters

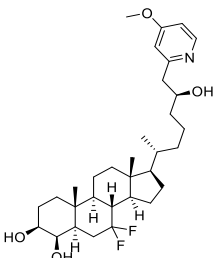
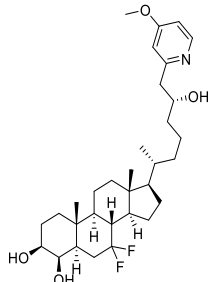
		Acquity UPCC, column: Daicel CHIRALPAK OX_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 65/35, flow rate: 2.0 mL/min, column temperature: 37°C, wavelength: UV 214 nm; SFC retention time: 1.694 min
373	 (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R)-6-hydroxy-6-(1-methyl-1,2,3,4-tetrazol-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol	¹H NMR (400 MHz, CDCl₃) δ 5.09 (dd, <i>J</i> = 8.0, 5.7 Hz, 1H), 4.16 (d, <i>J</i> = 0.6 Hz, 3H), 3.70 – 3.54 (m, 1H), 2.04 – 1.90 (m, 3H), 1.82 (s, 2H), 1.78 – 1.66 (m, 6H), 1.63 – 1.52 (m, 4H), 1.45 (d, <i>J</i> = 11.9 Hz, 5H), 1.36 – 1.28 (m, 3H), 1.17 – 1.07 (m, 3H), 1.05 – 0.95 (m, 2H), 0.91 (dd, <i>J</i> = 6.5, 3.4 Hz, 3H), 0.85 (s, 3H), 0.66 (s, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -89.29 (d, <i>J</i> = 237.1 Hz, 1F), -111.17 (d, <i>J</i> = 237.0 Hz, 1F). LC-MS: [M+H]⁺ = 495.45.

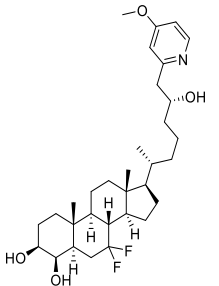
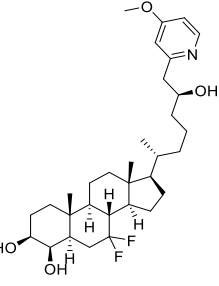
380	 (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methyl-1,2,3,4-tetrazol-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol or  (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methyl-1,2,3,4-tetrazol-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol	¹H NMR (400 MHz, CDCl₃) δ 5.10 (s, 1H), 4.16 (s, 3H), 3.62 (dd, <i>J</i> = 13.5, 8.5 Hz, 1H), 2.01 (dd, <i>J</i> = 26.0, 8.5 Hz, 3H), 1.86 – 1.68 (m, 6H), 1.65 – 1.57 (m, 3H), 1.45 (dd, <i>J</i> = 23.4, 11.5 Hz, 8H), 1.31 (dd, <i>J</i> = 18.9, 7.1 Hz, 3H), 1.12 (t, <i>J</i> = 15.1 Hz, 3H), 1.01 (t, <i>J</i> = 11.9 Hz, 2H), 0.92 (d, <i>J</i> = 6.3 Hz, 3H), 0.85 (s, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -89.29 (d, <i>J</i> = 237.1 Hz, 1F), -111.16 (d, <i>J</i> = 237.1 Hz, 1F). LC-MS: [M+H]⁺ = 495.50. SFC chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IB 4.6 × 250 mm, 5 μm, mobile phase: CO₂/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C); retention time: 3.655 min.
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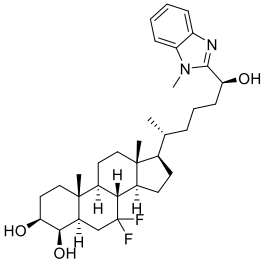
381	 (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methyl-1,2,3,4-tetrazol-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol or  (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methyl-1,2,3,4-tetrazol-5-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol	^1H NMR (400 MHz, CDCl_3) δ 5.10 (t, J = 11.4 Hz, 1H), 4.16 (s, 3H), 3.64 (dd, J = 23.3, 13.7 Hz, 1H), 2.05 – 1.91 (m, 3H), 1.88 – 1.77 (m, 4H), 1.76 – 1.62 (m, 5H), 1.45 (t, J = 26.1 Hz, 6H), 1.32 (d, J = 23.3 Hz, 5H), 1.12 (t, J = 15.0 Hz, 3H), 1.01 (t, J = 12.4 Hz, 2H), 0.91 (d, J = 6.6 Hz, 3H), 0.85 (s, 3H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -89.29 (d, J = 237.1 Hz, 1F), -111.17 (d, J = 237.2 Hz, 1F). LC-MS: $[\text{M}+\text{H}]^+ = 495.45$. SFC chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IB 4.6×250 mm, 5 μm, mobile phase: CO_2/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C); retention time: 4.240 min.
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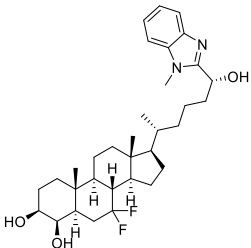
[0724] The following examples can be completed by referring to the

synthesis method of Examples 168 & 169:

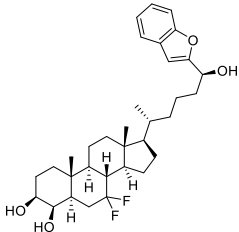
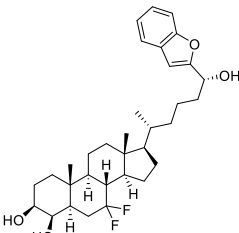
Example	Structural formula	Compound name	Characterization results	SFC resolution method and results
304	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-7-(4-methoxypyridin-2-yl)heptan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-7-(4-methoxypyridin-2-yl)heptan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, J = 5.8 Hz, 1H), 6.71 (dd, J = 5.8, 2.2 Hz, 1H), 6.67 (d, J = 2.1 Hz, 1H), 3.99 (d, J = 6.9 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 1H), 3.66 – 3.55 (m, 1H), 2.84 (ddd, J = 23.5, 14.8, 5.6 Hz, 2H), 2.19 (ddd, J = 23.2, 13.6, 6.9 Hz, 2H), 1.98 (d, J = 12.7 Hz, 1H), 1.90 – 1.78 (m, 4H), 1.77 – 1.61 (m, 4H), 1.60 – 1.37 (m, 8H), 1.35 – 1.18	Instrument : Waters Acquity UPCC, column: Daicel CHIRAL CEL IG, 250 mm × 4.6 mm 5 μm, mobile phase: MeOH/D NH₃ (7 M solution in MeOH)] = 90/10, flow rate: 1.0 mL/min, column temperature	

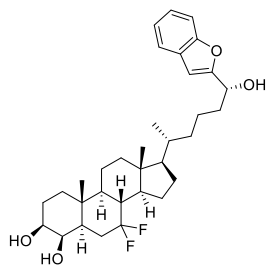
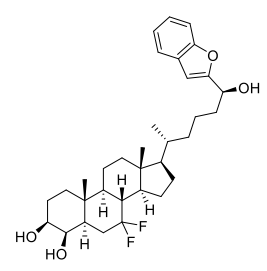
		(m, 5H), 1.14 – 0.98 (m, 7H), 0.93 (d, J = 6.5 Hz, 4H), 0.66 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.61, -89.24, -110.60, -111.23. LC-MS [M-H] ⁻ = 548.50	e: 30°C, retention time: 9.513 min.
305	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-7-(4-methoxypyridin-2-yl)heptan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or 	¹ H NMR (400 MHz, CDCl ₃) δ 8.31 (d, J = 5.9 Hz, 1H), 6.74 (dd, J = 5.9, 2.4 Hz, 1H), 6.69 (d, J = 2.2 Hz, 1H), 3.99 (d, J = 3.5 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 1H), 3.60 (dd, J = 7.2, 4.0 Hz, 1H), 2.87 (dd, J = 10.8, 5.7 Hz, 2H), 2.33 – 2.09 (m, 2H), 1.98	Instrument : Waters Acquity UPCC, column: Daicel CHIRAL CEL IG, 250 mm × 4.6 mm 5 μm, mobile phase: MeOH/D CM [0.2% NH ₃ (7 M solution in

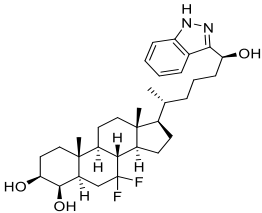
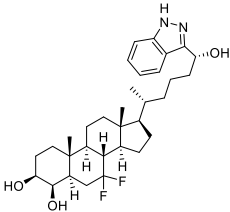
	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-7-(4-methoxypyridin-2-yl)heptan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	(d, J = 12.6 Hz, 1H), 1.83 (dd, J = 19.5, 13.0 Hz, 4H), 1.77 – 1.51 (m, 5H), 1.51 – 1.20 (m, 12H), 1.18 – 0.99 (m, 7H), 0.93 (d, J = 6.4 Hz, 4H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.60, -89.23, -110.60, -111.22. LC-MS [M-H]⁻ = 548.50	MeOH)] = 90/10, flow rate: 1.0 mL/min, column temperature: 30°C, retention time: 12.407 min.
306	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylbenzo[d]imidazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or 	¹H NMR (400 MHz, DMSO) δ 7.58 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.19 (dt, J = 23.9, 7.0 Hz, 2H), 5.55 (d, J = 6.0 Hz, 1H), 4.82 (d, J = 7.0 Hz, 1H), 4.40 (d, J = 5.9 Hz,	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IC_3, 3.0 × 150 mm, 3 μm; mobile phase:

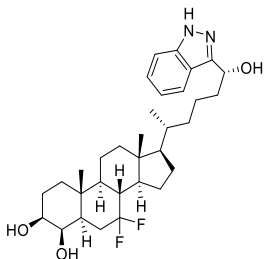
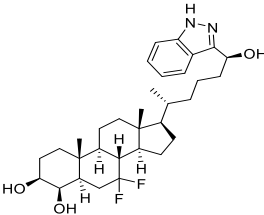
	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylbenzo[d]imidazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	1H), 4.24 (d, J = 3.2 Hz, 1H), 3.84 (s, 3H), 3.49 (s, 1H), 3.33 (s, 1H), 2.20 – 2.00 (m, 1H), 1.92 (t, J = 11.6 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.73 – 1.62 (m, 3H), 1.61 – 1.49 (m, 2H), 1.46 – 1.38 (m, 3H), 1.27 (dt, J = 20.4, 7.9 Hz, 8H), 1.09 – 0.96 (m, 6H), 0.87 (d, J = 6.4 Hz, 4H), 0.62 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -86.65, -87.27, -108.66, -109.28. LC-MS [M-H]⁻ = 557.45.	A/B: CO₂/EtOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C. Retention time: 1.818 min.
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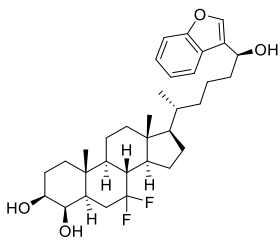
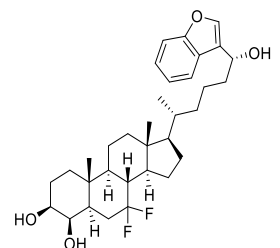
307	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylbenzo[d]imidazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylbenzo[d]imidazol-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.74 (d, J = 6.8 Hz, 1H), 7.38 – 7.28 (m, 3H), 5.00 (dd, J = 8.2, 4.7 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 1H), 3.60 (dd, J = 7.3, 3.8 Hz, 1H), 2.24 (s, 1H), 2.09 – 1.94 (m, 3H), 1.85 (ddd, J = 18.7, 10.4, 4.1 Hz, 5H), 1.70 (ddd, J = 23.2, 12.6, 7.2 Hz, 4H), 1.46 (dd, J = 11.8, 5.6 Hz, 4H), 1.37 – 1.20 (m, 6H), 1.17 – 0.96 (m, 8H), 0.95 – 0.87 (m, 4H), 0.65 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.61, -89.23, -	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IC ₃ , 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO ₂ /EtOH (0.1% DEA) = 60/40; flow rate: 1.5 mL/min; column temperature: 37°C. Retention time: 2.423 min.
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		110.58, -111.21. LC-MS [M-H] ⁻ = 557.60.	
316	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -1-[(2R,6S)-6-(1-benzofuran-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -1-[(2R,6R)-6-(1-benzofuran-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.54 (d, <i>J</i> = 7.5 Hz, 1H), 7.46 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 (t, <i>J</i> = 7.4 Hz, 2H), 6.62 (s, 1H), 4.81 (s, 1H), 3.74 (s, 1H), 3.61 (s, 1H), 2.17 (dd, <i>J</i> = 40.3, 19.8 Hz, 2H), 1.99 (dd, <i>J</i> = 22.8, 11.8 Hz, 3H), 1.90 – 1.67 (m, 9H), 1.50 – 1.30 (m, 8H), 1.12 – 1.02 (m, 6H), 0.90 (d, <i>J</i> = 6.3 Hz, 4H), 0.65 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.63, -89.26, -	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IE_3, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C). Retention time: 2.034 min.

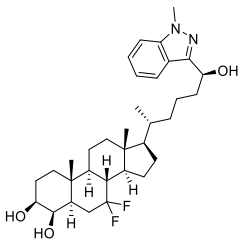
		110.61, -111.24. LC-MS [M-H] ⁻ = 543.40	
317	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -1-[(2R,6R)-6-(1-benzofuran-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -1-[(2R,6S)-6-(1-benzofuran-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, CDCl ₃) δ 7.54 (d, <i>J</i> = 6.9 Hz, 1H), 7.46 (d, <i>J</i> = 7.8 Hz, 1H), 7.22 (d, <i>J</i> = 7.3 Hz, 2H), 6.61 (s, 1H), 4.82 (s, 1H), 3.74 (s, 1H), 3.60 (s, 1H), 2.31 – 2.05 (m, 2H), 2.04 – 1.86 (m, 5H), 1.80 – 1.64 (m, 5H), 1.48 – 1.27 (m, 10H), 1.17 – 1.03 (m, 6H), 0.91 (d, <i>J</i> = 6.0 Hz, 4H), 0.66 (s, 3H). ¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.63, -89.26, -110.62, -111.24. LC-	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IE_3, 3.0 × 150 mm, 3 μm; mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C). Retention time: 2.632 min.

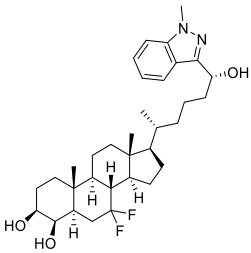
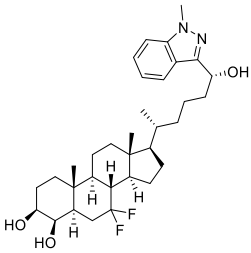
		MS[M-H] ⁻ = 543.50	
319	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1H-indazol-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1H-indazol-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO) δ 7.87 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 7.04 (s, 1H), 5.22 (s, 1H), 4.88 (s, 1H), 4.39 (s, 1H), 4.24 (s, 1H), 3.49 (s, 1H), 3.07 – 2.98 (m, 1H), 2.11 (dd, J = 31.4, 17.5 Hz, 1H), 1.89 (d, J = 11.4 Hz, 2H), 1.82 – 1.51 (m, 9H), 1.42 (d, J = 12.9 Hz, 2H), 1.27 (dd, J = 21.1, 8.3 Hz, 7H), 1.03 – 0.96 (m, 5H), 0.85 (d, J = 6.4 Hz, 4H), 0.61 (s,	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IA 4.6 × 250 mm, 5 μm; mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C. Retention time: 3.417 min.

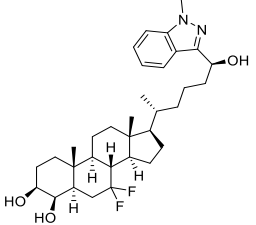
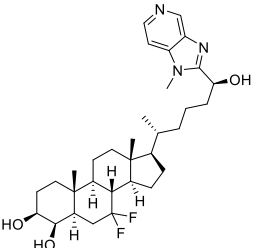
		3H). ^{19}F NMR (376 MHz, DMSO) δ -86.65, -87.27, - 108.65, - 109.27. LC- MS $[\text{M}-\text{H}]^- =$ 543.45.	
320	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -4,4-difluoro-1-[(2R,6R)-6-hydroxy-6- (1H-indazol-3-yl)hexan-2-yl]-9a,11a- dimethylhexadecahydro-1H- cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -4,4-difluoro-1-[(2R,6S)-6-hydroxy-6- (1H-indazol-3-yl)hexan-2-yl]-9a,11a- dimethylhexadecahydro-1H- cyclopenta[1,2-a]phenanthrene-6,7-diol	^1H NMR (400 MHz, CDCl_3) δ 7.86 (s, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.40 (t, $J = 7.4$ Hz, 1H), 7.17 (t, $J =$ 7.1 Hz, 1H), 5.17 (s, 1H), 3.73 (s, 1H), 3.60 (d, $J = 11.2$ Hz, 1H), 2.31 – 2.09 (m, 2H), 1.96 (s, 2H), 1.74 (dd, $J =$ 22.0, 9.8 Hz, 8H), 1.41 – 1.24 (m, 10H), 1.05 (s, 6H), 0.89 – 0.84 (m, 4H), 0.63 (s, 3H).	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IA 4.6 $\times 250$ mm, 5 μm ; mobile phase: A/B: CO_2/MeO H (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column

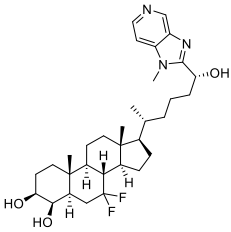
		¹⁹ F NMR (376 MHz, CDCl ₃) δ -88.62, -89.24, -110.60, -111.23. LC-MS [M-H] ⁻ = 543.45.	temperature: 37°C. Retention time: 4.973 min.
321	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6S)-6-(1-benzofuran-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R,6R)-6-(1-benzofuran-2-yl)-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400MHz, CDCl ₃) δ 7.71 (d, J = 7.0Hz, 1H), 7.56 (s, 1H), 7.48 (d, J = 8.0Hz, 1H), 7.33 – 7.29 (m, 1H), 7.25 – 7.22 (m, 1H), 4.97 – 4.86 (m, 1H), 3.74 (s, 1H), 3.63 – 3.56 (m, 1H), 2.25 – 2.13 (m, 1H), 1.98 (d, J = 24.1Hz, 2H), 1.82 (d, J = 6.6Hz, 4H), 1.71 (dd, J = 16.9, 13.3Hz, 11H), 1.38 (d, J = 12.1Hz, 4H), 1.26 (s, 3H),	Instrument: Waters Acquity UPCC, column: Daicel CHIRALP AK OJ_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C,

		1.05 (s, 4H), 0.89 (d, J = 6.6 Hz, 3H), 0.65 (s, 3H) ¹⁹F NMR (376 MHz, CDCl₃) δ -88.64, -89.27, - 110.63, -111.26. LC-MS [M-H]⁻ = 543.45.	retention time: 2.829 min.
322	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -1-[(2R,6R)-6-(1-benzofuran-2-yl)-6- hydroxyhexan-2-yl]-4,4-difluoro- 9a,11a-dimethylhexadecahydro-1H- cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -1-[(2R,6S)-6-(1-benzofuran-2-yl)-6- hydroxyhexan-2-yl]-4,4-difluoro- 9a,11a-dimethylhexadecahydro-1H-	¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 7.0 Hz, 1H), 7.56 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.30 (dd, J = 8.1, 1.3 Hz, 1H), 7.25 (d, J = 0.9 Hz, 1H), 4.95 (d, J = 1.7 Hz, 1H), 3.74 (s, 1H), 3.60 (dt, J = 11.3, 4.0 Hz, 1H), 2.32 – 2.19 (m, 1H), 2.07 (dd, J = 11.2,	Instrument : Waters Acquity UPCC, column: Daicel CHIRALP AK OJ_3, 3 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeO H (0.1% DEA) = 60/40, flow rate: 1.5

	cyclopenta[1,2-a]phenanthrene-6,7-diol	9.0Hz, 1H), 1.95 (s, 2H), 1.89 – 1.81 (m, 4H), 1.71 (dd, J = 17.1, 13.6Hz, 6H), 1.40 (s, 5H), 1.26 (s, 6H), 1.06 (s, 4H), 0.90 (d, J = 6.5Hz, 3H), 0.65 (s, 3H). ¹⁹ F NMR (376MHz, CDCl ₃) δ - 88.64, -89.26, - 110.63, - 111.26. LC-MS [M-H] ⁻ = 543.45.	mL/min, column temperature: 37°C, retention time: 3.112 min.
323	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or	¹ H NMR (400 MHz, CDCl ₃) δ 7.83 (d, J = 8.2 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.14 (t, J = 7.3 Hz, 1H), 5.13 (s, 1H), 4.02 (s, 3H), 3.73 (s, 1H), 3.59 (d, J =	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IC_3, 3.0 × 150 mm, 3 μm;

	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	10.6 Hz, 1H), 2.20 (ddd, J = 20.8, 12.1, 4.0 Hz, 2H), 2.09 – 1.93 (m, 4H), 1.86 – 1.68 (m, 6H), 1.33 (ddd, J = 26.3, 18.3, 9.5 Hz, 9H), 1.12 – 1.02 (m, 6H), 0.94 – 0.85 (m, 4H), 0.64 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.61, -89.23, -110.59, -111.22. LC-MS [M-H]⁻ = 557.50	mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C. Retention time: 1.762 min.
324	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylindazol-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 8.2 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.14 (t, J = 7.3 Hz, 1H), 5.17 – 5.09 (m, 1H), 4.02 (s, 3H), 3.73 (s, 1H),	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK IC_3, 3.0 × 150 mm, 3 μm;

	or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylindazol-3-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	3.59 (dt, $J = 11.3, 4.1$ Hz, 1H), 2.29 – 2.11 (m, 2H), 2.08 – 1.90 (m, 5H), 1.84 – 1.75 (m, 3H), 1.72 – 1.55 (m, 3H), 1.47 – 1.26 (m, 9H), 1.14 – 1.03 (m, 6H), 0.89 (t, $J = 8.3$ Hz, 4H), 0.63 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.61, -89.24, -110.60, -111.23. LC-MS(M-H)$^-$ = 557.45	mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 50/50; flow rate: 1.5 mL/min; column temperature: 37°C. Retention time: 2.046 min.
318	 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylimidazo[5,4-c]pyridin-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-	^1H NMR (400 MHz, DMSO) δ 8.90 (s, 1H), 8.33 (s, 1H), 7.61 (s, 1H), 5.68 (d, $J = 6.2$ Hz, 1H), 4.86 (dd, $J = 13.6, 6.4$ Hz, 1H), 4.39 (d, $J = 6.0$	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK OZ_3, 3 × 150 mm, 3 μm;

cyclopenta[1,2-a]phenanthrene-6,7-diol or  (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR) -4,4-difluoro-1-[(2R,6R)-6-hydroxy-6- (1-methylimidazo[5,4-c]pyridin-2- yl)hexan-2-yl]-9a,11a- dimethylhexadecahydro-1H- cyclopenta[1,2-a]phenanthrene-6,7-diol	Hz, 1H), 4.24 (d, $J = 3.4$ Hz, 1H), 3.87 (s, 3H), 3.49 (s, 1H), 2.18 – 1.96 (m, 2H), 1.95 – 1.76 (m, 4H), 1.66 (d, $J =$ 13.7 Hz, 3H), 1.60 – 1.50 (m, 2H), 1.43 (d, $J = 11.0$ Hz, 3H), 1.25 (d, $J = 10.0$ Hz, 8H), 1.13 – 1.02 (m, 3H), 0.98 (s, 3H), 0.88 (d, $J = 6.4$ Hz, 4H), 0.62 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -86.65, -87.27, - 108.66, - 109.28. LC- MS $[\text{M}-\text{H}]^- =$ 558.80.	mobile phase: A/B: CO₂/MeO H (0.1% DEA) = 45/55; flow rate: 1.5 mL/min; column temperatur e: 37°C. Retention time: 2.281 min.
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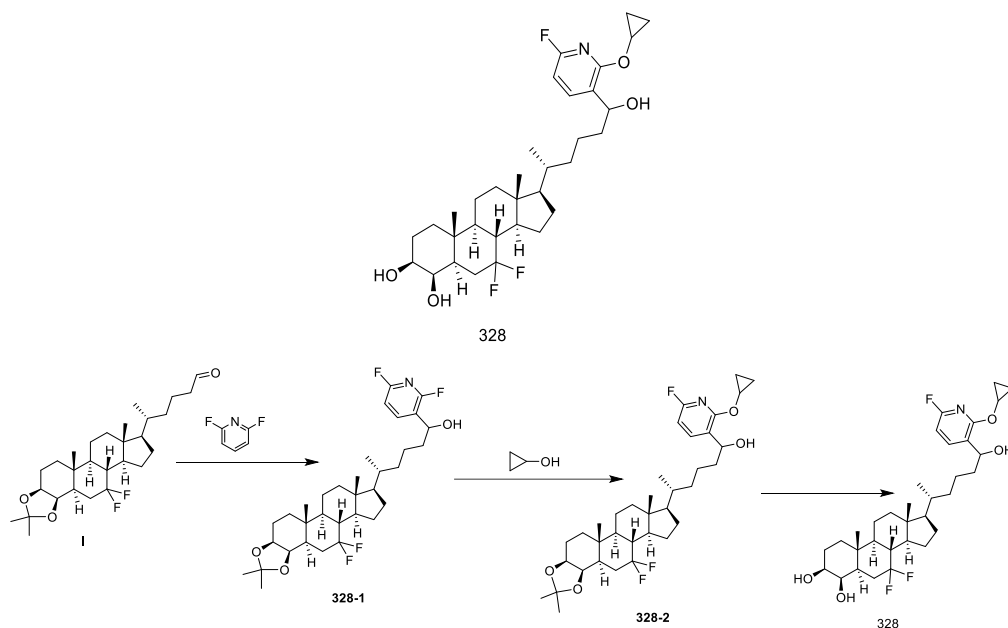
326	(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-hydroxy-6-(1-methylimidazo[5,4-c]pyridin-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol or (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-hydroxy-6-(1-methylimidazo[5,4-c]pyridin-2-yl)hexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol	¹ H NMR (400 MHz, DMSO) δ 8.87 (s, 1H), 8.32 (d, J = 5.5 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 5.66 (d, J = 6.4 Hz, 1H), 4.85 (dd, J = 13.9, 6.0 Hz, 1H), 4.40 (d, J = 6.0 Hz, 1H), 4.24 (d, J = 3.4 Hz, 1H), 3.87 (s, 3H), 3.49 (s, 1H), 2.18 – 2.01 (m, 1H), 1.91 (d, J = 7.9 Hz, 3H), 1.80 – 1.70 (m, 2H), 1.67 – 1.55 (m, 3H), 1.40 (dd, J = 25.5, 21.1 Hz, 7H), 1.24 (s, 6H), 0.98 (s, 7H), 0.89 (d, J = 6.5 Hz, 5H), 0.63 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO) δ	Instrument : Waters Acquity UPCC; column: Daicel CHIRALP AK OZ_3, 3 $\times$ 150 mm, 3 μ m; mobile phase: A/B: CO ₂ /MeOH (0.1% DEA) = 45/55; flow rate: 1.5 mL/min; column temperature: 37°C. Retention time: 2.410 min.
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		-86.64, -87.26, -108.65, -109.27 LC-MS [M-H] ⁻ = 558.35	
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[0725] Example 328

[0726] Preparation of compound 328:

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-(cyclopropyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0727] Referring to Example 206, 206-1 was replaced with 328-1 to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-(cyclopropyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol 328 (13.82 mg, yield: 32.18%) as a white solid.

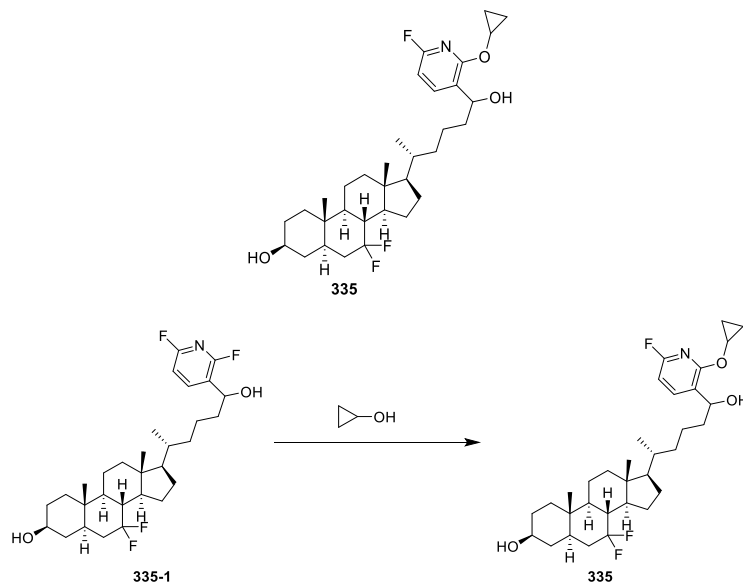
[0728] **Compound 328:** ¹H NMR (400 MHz, CDCl₃) δ 7.70 (td, *J* = 8.0, 2.2 Hz, 1H), 6.51 (dd, *J* = 8.0, 2.7 Hz, 1H), 4.79 – 4.72 (m, 1H), 4.36 – 4.27 (m, 1H), 3.74 (s, 1H), 3.60 (dt, *J* = 11.6, 4.2 Hz, 1H), 2.29 – 2.11 (m, 1H), 1.97 (d, *J* = 12.4 Hz,

1H), 1.82 (dd, $J = 20.8, 12.9$ Hz, 5H), 1.71 (dd, $J = 10.7, 7.1$ Hz, 4H), 1.66 (d, $J = 9.8$ Hz, 3H), 1.49 – 1.39 (m, 4H), 1.37 – 1.30 (m, 4H), 1.12 (dd, $J = 13.1, 4.3$ Hz, 2H), 1.06 (s, 3H), 0.98 (dd, $J = 16.3, 5.3$ Hz, 2H), 0.89 (dd, $J = 6.4, 3.8$ Hz, 3H), 0.86 – 0.77 (m, 2H), 0.76 – 0.70 (m, 2H), 0.66 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -72.52 (d, $J = 20.5$ Hz, 1F), -88.95 (d, $J = 235.9$ Hz, 1F), -110.94 (d, $J = 235.6$ Hz, 1F). LC-MS: $[\text{M}-\text{H}]^- = 578.50$.

[0729] Example 335

[0730] Preparation of compound 335:

10 (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-(cyclopropyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



15 [0731] Referring to Example 328, 328-1 was replaced with 335-1 to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-(cyclopropyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol 335 (31 mg, yield: 40.36%) as a white solid.

20 [0732] Compound 335: ^1H NMR (400 MHz, CDCl_3) δ = 7.71 (td, $J=8.0, 2.1$, 1H), 6.51 (dd, $J=8.0, 2.7$, 1H), 4.78 – 4.73 (m, 1H), 4.34 – 4.29 (m, 1H), 3.63 (td, $J=11.0, 5.5$, 1H), 1.98 (dt, $J=6.0, 3.2$, 1H), 1.89 – 1.67 (m, 8H), 1.60 – 1.52 (m,

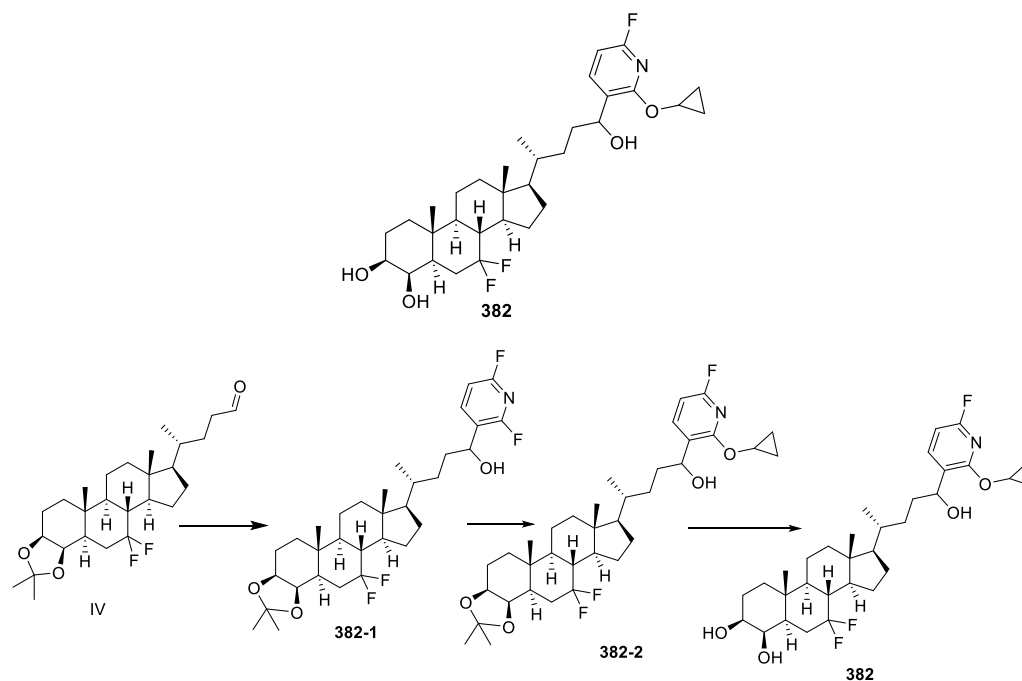
3H), 1.48 – 1.27 (m, 10H), 1.17 – 0.96 (m, 6H), 0.90 (dd, $J=6.4, 3.9$, 3H), 0.84 (s, 3H), 0.84 – 0.70 (m, 4H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) $\delta = -72.52$ (d, $J=20.5$, 1F), -89.28 (d, $J=237.0$, 1F), -111.16 (dd, $J=236.9, 2.4$, 1F).

5 **[0733] Example 382**

[0734] Preparation of compound **382**:

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-5-[2-(cyclopropyloxy)-6-fluoropyridin-3-yl]-5-hydroxypentan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol

10



15

[0735] Referring to Example **328**, compound **I** was replaced with compound **IV** to obtain **(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-5-[2-(cyclopropyloxy)-6-fluoropyridin-3-yl]-5-hydroxypentan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol** **382** (31 mg, yield: 40.36%) as a white solid.

20

[0736] Compound **382**: ^1H NMR (400 MHz, CDCl_3) δ 7.70 (t, $J = 8.0$ Hz, 1H), 6.51 (dd, $J = 7.9, 2.7$ Hz, 1H), 4.69 (t, $J = 6.5$ Hz, 1H), 4.32 (tt, $J = 6.3, 3.1$ Hz, 1H), 3.74 (s, 1H), 3.63 – 3.56 (m, 1H), 2.28 – 2.12 (m, 1H), 1.95 (d, $J = 12.5$ Hz, 1H), 1.81 (d, $J = 20.7$ Hz, 5H), 1.70 (d, $J = 11.1$ Hz, 5H), 1.58 – 1.44 (m, 4H),

1.35 (dd, $J = 24.4, 11.9$ Hz, 5H), 1.12 – 1.07 (m, 1H), 1.06 (s, 3H), 0.97 (dd, $J = 12.1, 7.8$ Hz, 2H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.82 (t, $J = 5.9$ Hz, 2H), 0.76 – 0.70 (m, 2H), 0.65 (s, 3H). ^{19}F NMR (377 MHz, CDCl_3) δ -72.46 (s, 1F), -88.97 (d, $J = 235.9$ Hz, 1F), -110.96 (d, $J = 235.8$ Hz, 1F). LC-MS: $[\text{M}-\text{H}]^- = 564.50$.

5

[0737] Example 383

[0738] Preparation of compound 383:

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-{6-fluoro-2-[(oxetan-3-ylmethyl)oxy]pyridin-3-yl}-6-hydroxyhexan-2-yl]-9a,11a-

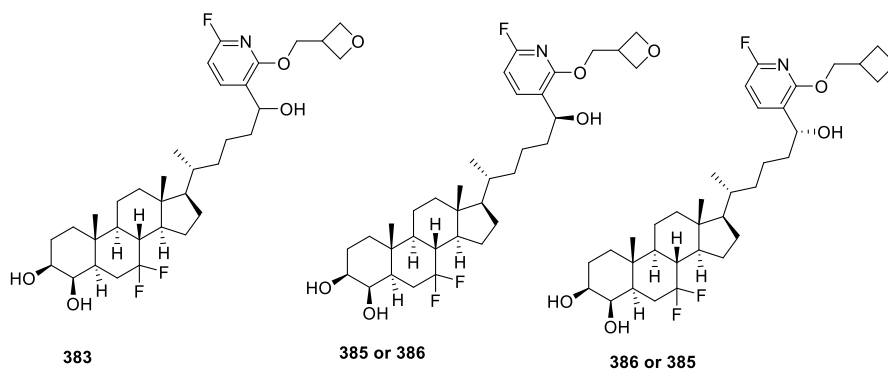
10 dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0739] compound 385 or compound 386:

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-{6-fluoro-2-[(oxetan-3-ylmethyl)oxy]pyridin-3-yl}-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

15 [0740] compound 386 or compound 385:

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-{6-fluoro-2-[(oxetan-3-ylmethyl)oxy]pyridin-3-yl}-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



20 [0741] Referring to Example 382, cyclopropanol was replaced with oxetan-3-ylmethanol to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-{6-fluoro-2-[(oxetan-3-ylmethyl)oxy]pyridin-3-yl}-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol 383 (31 mg, yield: 40.36 %) as a white solid.

25 [0742] Compound 383: ^1H NMR (400 MHz, CDCl_3) δ 7.73 (t, $J = 8.0$ Hz, 1H),

6.51 (dd, $J = 7.9, 2.6$ Hz, 1H), 4.91 – 4.86 (m, 2H), 4.83 (s, 1H), 4.56 (dd, $J = 8.2, 4.3$ Hz, 4H), 3.74 (s, 1H), 3.60 (d, $J = 11.7$ Hz, 1H), 3.45 – 3.38 (m, 1H), 2.27 – 2.17 (m, 2H), 1.98 (s, 2H), 1.82 (d, $J = 8.2$ Hz, 4H), 1.56 (s, 7H), 1.37 – 1.36 (m, 1H), 1.25 (s, 7H), 1.06 (s, 4H), 0.89 (d, $J = 6.8$ Hz, 4H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -73.21, -73.26, -88.64, -89.27, -110.63, -111.26. LC-MS $[\text{M-H}]^- = 608.70$.

[0743] Compound **383** (70 mg, 0.115 mmol) was subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IG-3, 3.0×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain white solid **385** (28 mg, 0.046 mmol, 40.00%, retention time: 2.910 min) and white solid **386** (24 mg, 0.039 mmol, 34.02%, retention time: 3.926 min).

[0744] Compound **385**: ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 7.9$ Hz, 1H), 6.51 (dd, $J = 8.0, 2.6$ Hz, 1H), 4.90 – 4.86 (m, 2H), 4.84 – 4.81 (m, 1H), 4.57 (d, $J = 6.3$ Hz, 4H), 3.74 (s, 1H), 3.60 (d, $J = 10.7$ Hz, 1H), 3.41 (t, $J = 5.8$ Hz, 1H), 2.20 (d, $J = 34.3$ Hz, 2H), 1.97 (d, $J = 12.9$ Hz, 1H), 1.84 – 1.78 (m, 4H), 1.73 (d, $J = 13.3$ Hz, 5H), 1.40 – 1.33 (m, 8H), 1.27 (d, $J = 11.8$ Hz, 4H), 1.06 (s, 4H), 0.90 (d, $J = 6.5$ Hz, 4H), 0.66 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -73.27, -88.64, -89.27, -110.63, -111.26. LC-MS $[\text{M-H}]^- = 608.0$.

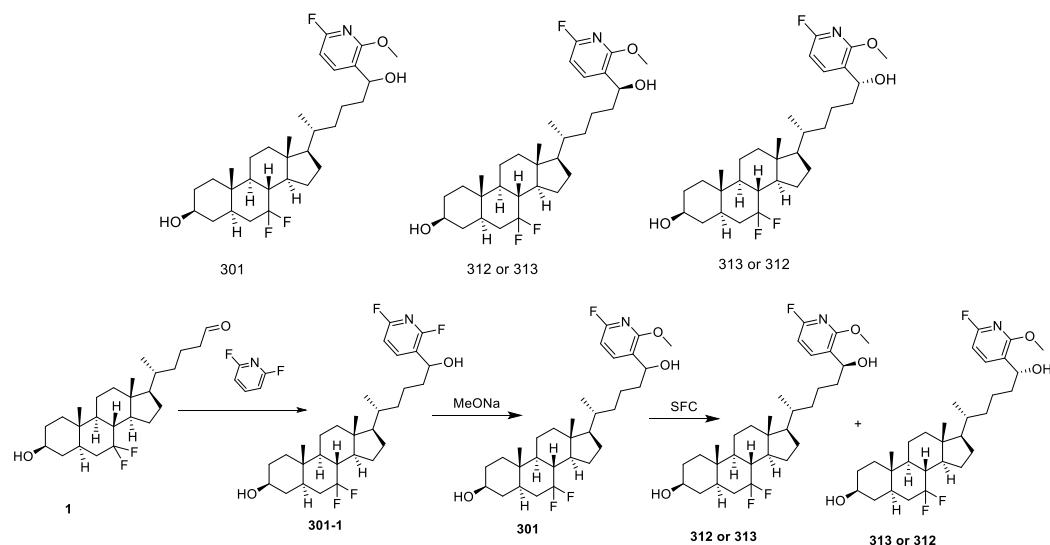
[0745] Compound **386**: ^1H NMR (400 MHz, CDCl_3) δ 7.73 (t, $J = 8.0$ Hz, 1H), 6.51 (dd, $J = 8.0, 2.6$ Hz, 1H), 4.91 – 4.86 (m, 2H), 4.82 (s, 1H), 4.56 (dd, $J = 8.6, 4.3$ Hz, 4H), 3.74 (s, 1H), 3.61 (s, 1H), 3.46 – 3.36 (m, 1H), 2.24 (s, 1H), 1.97 (d, $J = 12.2$ Hz, 1H), 1.82 (d, $J = 8.5$ Hz, 4H), 1.71 (dd, $J = 19.4, 10.0$ Hz, 6H), 1.39 (d, $J = 12.6$ Hz, 9H), 1.25 (s, 3H), 1.06 (s, 4H), 0.89 (d, $J = 6.5$ Hz, 4H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -73.22, -88.65, -89.27, -111.26. LC-MS: $[\text{M-H}]^- = 608.60$.

[0746] Examples **301, 312 & 313**

[0747] Preparation of compound **301**: **(1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol,**

[0748] compound 312 or 313: (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol and

- 5 [0749] compound 313 or 312: (1R,3aS,3bR,5aR,7S,9aS,9bS,11aR)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyhexan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthren-7-ol



- 10 [0750] Referring to Example 206, 206-1 was replaced with 301-1 to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-(cyclopropyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol 301 (13.82 mg, yield: 32.18%) as a white solid.
- 15 [0751] **Compound 301:** ^1H NMR (400 MHz, CDCl_3) δ 7.74 – 7.65 (m, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.82 (d, J = 5.5 Hz, 1H), 3.96 (s, 3H), 3.62 (s, 1H), 1.98 (d, J = 12.8 Hz, 1H), 1.83 (d, J = 7.5 Hz, 3H), 1.72 (dd, J = 9.7, 3.6 Hz, 5H), 1.66 – 1.52 (m, 4H), 1.47 – 1.39 (m, 4H), 1.32 (ddd, J = 23.5, 14.5, 4.9 Hz, 6H), 1.15 – 0.98 (m, 5H), 0.90 (dd, J = 6.5, 3.3 Hz, 3H), 0.84 (s, 3H), 0.66 (d, J = 0.9 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -73.27, -73.35, -88.96, -89.59, -110.85, -111.48.
- 20 [0752] (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-1-[(2R)-6-[2-

(Cyclopropyloxy)-6-fluoropyridin-3-yl]-6-hydroxyhexan-2-yl]-4,4-difluoro-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **301** was subjected to SFC separation (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK AD-3, 3.0 × 150 mm, 3 μm, mobile phase: A/B: CO₂/MeOH (0.1% DEA) = 50/50, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain **312** (retention time: 1.661 min) and **313** (retention time: 1.950 min).

[0753] Compound **312**: ¹H NMR (400 MHz, CDCl₃) δ 7.70 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.82 (dd, J = 8.1, 4.9 Hz, 1H), 3.96 (s, 3H), 3.66 – 3.59 (m, 1H), 1.98 (d, J = 12.9 Hz, 1H), 1.84 (d, J = 7.1 Hz, 3H), 1.73 (dd, J = 15.0, 5.9 Hz, 4H), 1.61 (d, J = 3.9 Hz, 2H), 1.48 – 1.25 (m, 13H), 1.10 (dd, J = 10.8, 6.8 Hz, 3H), 1.01 (d, J = 3.6 Hz, 2H), 0.91 (d, J = 6.5 Hz, 3H), 0.85 (s, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.35, -88.96, -89.59, -110.85, -111.48.

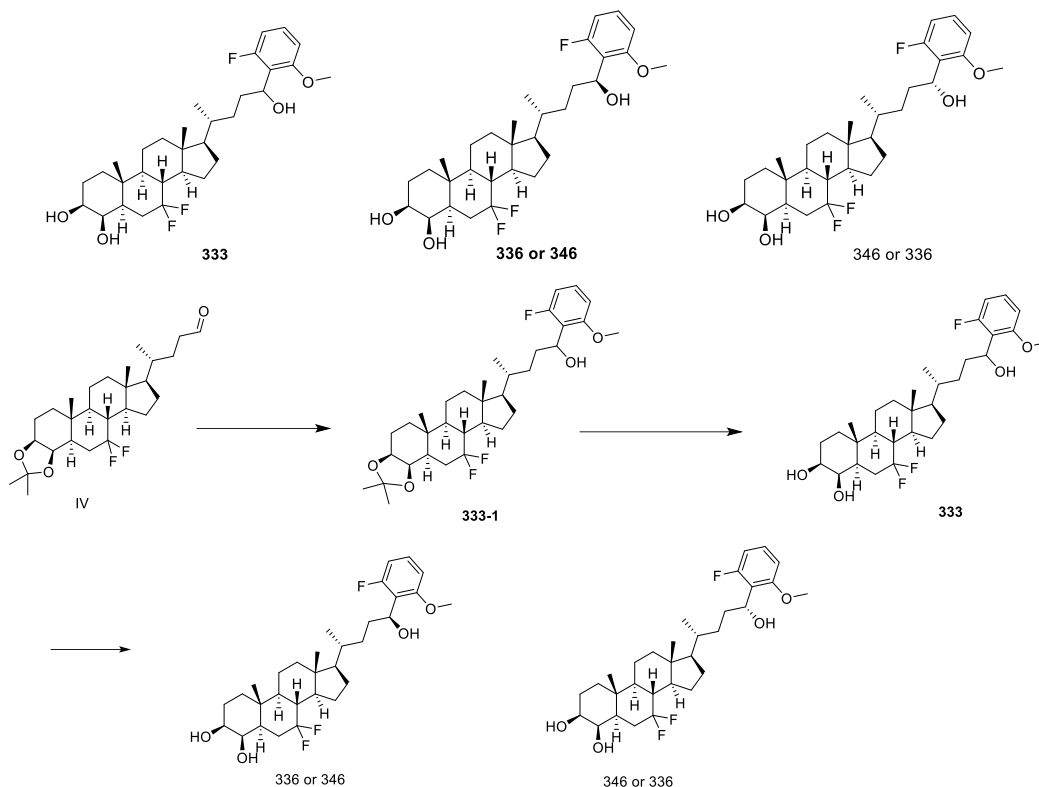
[0754] Compound **313**: ¹H NMR (400 MHz, CDCl₃) δ 7.69 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.84 – 4.77 (m, 1H), 3.96 (s, 3H), 3.66 – 3.59 (m, 1H), 1.98 (d, J = 12.7 Hz, 1H), 1.82 (s, 3H), 1.76 – 1.67 (m, 5H), 1.54 (s, 2H), 1.49 – 1.39 (m, 5H), 1.31 (dd, J = 26.0, 14.7 Hz, 6H), 1.05 (dd, J = 28.2, 11.7 Hz, 6H), 0.90 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 10.1 Hz, 3H), 0.65 (d, J = 10.0 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.27, -88.97, -89.60, -110.85, -111.48.

[0755] Examples **333**, **336** & **346**

[0756] Preparation of compound **333** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-5-(2-fluoro-6-methoxyphenyl)-5-hydroxypentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol,

[0757] compound **336** or compound **346** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,5S)-5-(2-fluoro-6-methoxyphenyl)-5-hydroxypentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0758] compound **346** or compound **336** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,5R)-5-(2-fluoro-6-methoxyphenyl)-5-hydroxypentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol



[0759] Referring to Example 49, (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]hexanal **I** was replaced with (4R)-4-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]pentanal **IV** to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-5-(2-fluoro-6-methoxyphenyl)-5-hydroxypentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **333** (120 mg, 0.200 mmol, 77.36%) as a white solid.

[0760] Compound **333**: ^1H NMR (400 MHz, CDCl_3) δ 7.20 – 7.14 (m, 1H), 6.71 – 6.66 (m, 2H), 4.96 (t, J = 7.2 Hz, 1H), 3.88 (d, J = 0.6 Hz, 3H), 3.74 (s, 1H), 3.62 – 3.57 (m, 1H), 2.19 (ddd, J = 23.1, 13.9, 7.1 Hz, 1H), 1.96 (d, J = 12.9 Hz, 2H), 1.80 (dd, J = 15.2, 6.3 Hz, 4H), 1.75 (s, 1H), 1.70 (dd, J = 9.4, 6.0 Hz, 4H), 1.46 – 1.23 (m, 10H), 1.05 (d, J = 5.4 Hz, 4H), 0.90 (d, J = 6.5 Hz, 4H), 0.64

(d, $J = 5.4$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.65, -89.27, -110.63, -110.65, -111.26, -111.27, -117.00, -117.27. LC-MS: $[\text{M-H}]^- = 537.45$,

[0761] (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-Difluoro-1-[(2R)-5-(2-fluoro-6-methoxyphenyl)-5-hydroxypentan-2-yl]-9a,11a-

5 dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **333** (180 mg, 0.334 mmol) was subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IH₃, 3.0×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 60/40, flow rate: 1.5 mL/min, column temperature: 37°C) to obtain **336** (77.05 mg, 0.143 mmol, 42.81%, retention time: 1.850 min) and **346** (53.79 mg, 0.100 mmol, 29.88%, retention time: 2.408 min).

[0762] Compound **336**: ^1H NMR (400 MHz, CDCl_3) δ 7.23 – 7.14 (m, 1H), 6.72 – 6.65 (m, 2H), 4.96 (t, $J = 7.3$ Hz, 1H), 3.88 (s, 3H), 3.73 (s, 1H), 3.59 (dt, $J = 11.4, 4.2$ Hz, 1H), 2.20 (dd, $J = 35.1, 4.6$ Hz, 1H), 1.96 (d, $J = 12.7$ Hz, 1H), 1.76 (d, $J = 9.2$ Hz, 8H), 1.61 (d, $J = 10.6$ Hz, 4H), 1.41 – 1.25 (m, 6H), 1.05 (s, 4H), 1.00 – 0.93 (m, 2H), 0.90 (d, $J = 6.6$ Hz, 4H), 0.65 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.66, -89.28, -110.65, -111.28, -117.00. LC-MS $[\text{M-H}]^- = 537.40$.

[0763] Compound **346**: ^1H NMR (400 MHz, CDCl_3) δ 7.20 – 7.13 (m, 1H), 6.71 – 6.66 (m, 2H), 4.96 (dd, $J = 8.1, 6.2$ Hz, 1H), 3.88 (s, 3H), 3.74 (s, 1H), 3.60 (dt, $J = 11.4, 4.1$ Hz, 1H), 2.20 (dd, $J = 34.9, 4.8$ Hz, 1H), 2.01 – 1.93 (m, 2H), 1.87 – 1.77 (m, 4H), 1.63 (dd, $J = 12.6, 5.2$ Hz, 8H), 1.42 – 1.23 (m, 9H), 1.05 (s, 3H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.64 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.64, -89.27, -110.63, -111.26, -117.27. LC-MS $[\text{M-H}]^- = 537.45$.

25 **[0764]** Examples **341**, **337**, **338**, **339** & **340**

[0765] Preparation of compound **341** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-5-(6-fluoro-2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol,

30 **[0766]** compound **337** or compound **338** (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,5S)-5-(6-fluoro-

2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-9a,11a-

dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol,

[0767] compound 338 or compound 337

(1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R,5R)-5-(6-fluoro-

5 2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-9a,11a-

dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol,

[0768] compound 339 or compound 340 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-

4-fluoro-1-[(2R,5S)-5-(6-fluoro-2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-

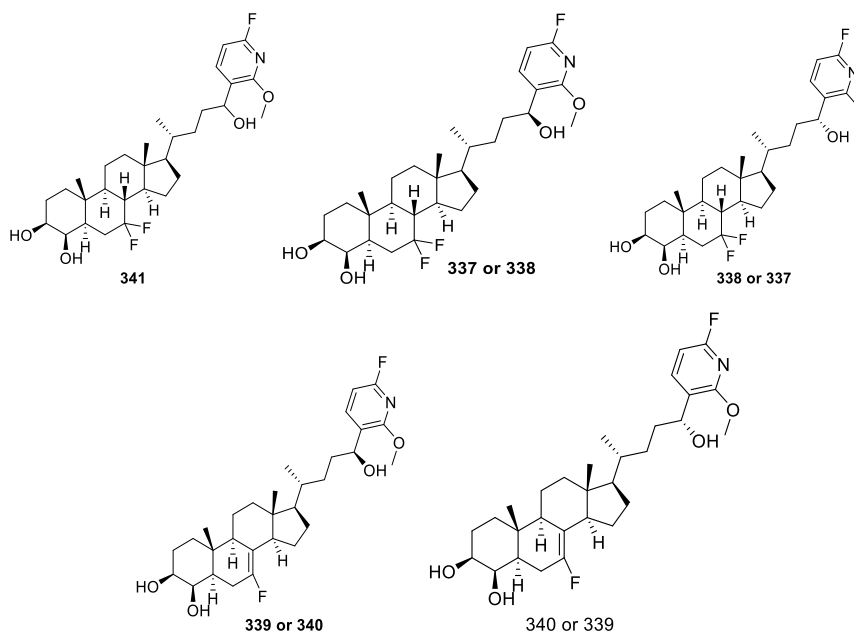
10 cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0769] compound 340 or compound 339 (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-

4-fluoro-1-[(2R,5R)-5-(6-fluoro-2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-

cyclopenta[1,2-a]phenanthrene-6,7-diol

15

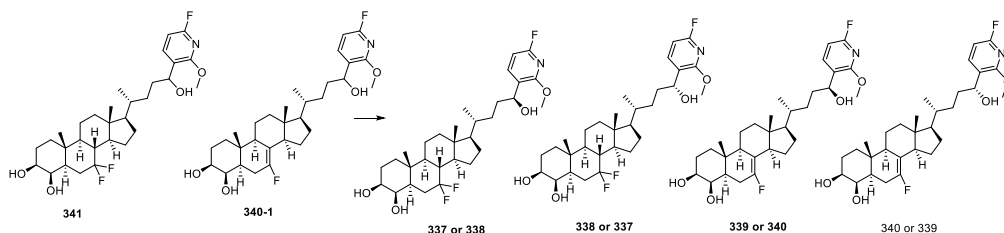


[0770] Referring to Examples 81, 83 & 301, the mixture of I and II was replaced with VI and V to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-5-(6-fluoro-2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-

20 9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol 341

(120 mg, 89.25%) as a white solid.

[0771] Compound 341: ^1H NMR (400 MHz, CDCl_3) δ 7.69 (t, J = 7.9 Hz, 1H), 6.48 (dd, J = 8.0, 2.7 Hz, 1H), 4.82 – 4.73 (m, 1H), 3.96 (s, 3H), 3.74 (s, 1H), 3.60 (d, J = 11.2 Hz, 1H), 2.18 (dd, J = 33.0, 12.3 Hz, 1H), 1.96 (d, J = 13.0 Hz, 1H), 1.80 (d, J = 6.6 Hz, 4H), 1.75 (s, 3H), 1.58 (s, 7H), 1.38 (d, J = 14.4 Hz, 5H), 1.06 (s, 6H), 0.92 (d, J = 6.5 Hz, 3H), 0.66 (d, J = 2.0 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -73.19, -73.40, -88.65, -89.27, -89.28, -110.64, -110.65, -111.26, -111.27. LCMS: $[\text{M}-\text{H}]^-$ = 538.50,



[0772] A mixture of (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-5-(6-fluoro-2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **341** and (1R,3aR,5aR,6R,7S,9aR,9bR,11aR)-4-fluoro-1-[(2R)-5-(6-fluoro-2-methoxypyridin-3-yl)-5-hydroxypentan-2-yl]-9a,11a-dimethyl-2,3,3a,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **340-1** (150 mg, 0.278 mmol) was subjected to chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK IG-3, 3.0×150 mm, $3 \mu\text{m}$, mobile phase: A/B: CO_2/MeOH (0.1% DEA) = 70/30, flow rate: 2.0 mL/min, column temperature: 37°C , retention times: P1 retention time: 1.335 min, P2 retention time: 1.678 min, P3 retention time: 2.117 min, P4 retention time: 2.672 min) to obtain white solids **337** (51.76 mg, 0.096 mmol, 34.51%, retention time: 1.335 min), **338** (58.12 mg, 0.102 mmol, 36.67%, retention time: 1.678 min), **339** (5.32 mg, 0.010 mmol, 3.65%, retention time: 2.117 min), and **340** (7.67 mg, 0.013 mmol, 4.84%, retention time: 2.672 min).

[0773] Compound **337:** ^1H NMR (400 MHz, CDCl_3) δ 7.69 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.76 (t, J = 6.4 Hz, 1H), 3.96 (s, 3H), 3.74 (s, 1H), 3.60 (dd, J = 7.3, 4.0 Hz, 1H), 2.26 – 2.11 (m, 1H), 1.96 (d, J = 12.8 Hz, 1H), 1.84 – 1.77 (m, 4H), 1.60 (s, 8H), 1.35 (ddd, J = 37.9, 22.1, 10.5 Hz, 8H), 1.06 (s, 3H),

1.03 – 0.96 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.19, -88.66, -89.28, -110.65, -111.27. LC-MS: [M-H]⁻ = 538.50,

[0774] Compound **338**: ¹H NMR (400 MHz, CDCl₃) δ 7.71 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 8.0, 2.7 Hz, 1H), 4.78 (dd, J = 8.1, 4.8 Hz, 1H), 3.96 (s, 3H), 3.74 (s, 1H), 3.62 – 3.58 (m, 1H), 2.20 (dd, J = 35.1, 4.5 Hz, 1H), 1.97 (d, J = 13.0 Hz, 1H), 1.85 – 1.80 (m, 3H), 1.75 (s, 2H), 1.60 (s, 9H), 1.41 (s, 3H), 1.29 – 1.19 (m, 3H), 1.06 (s, 4H), 0.92 (d, J = 6.5 Hz, 4H), 0.66 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.40, -88.65, -89.27, -110.64, -111.26. LC-MS: [M-H]⁻ = 538.50,

[0775] Compound **339**: ¹H NMR (400 MHz, CDCl₃) δ 7.69 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.8, 2.7 Hz, 1H), 4.75 (d, J = 7.3 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 1H), 3.62 – 3.56 (m, 1H), 2.66 (s, 1H), 2.00 (s, 1H), 1.89 – 1.78 (m, 6H), 1.60 (s, 8H), 1.46 (s, 4H), 1.25 (s, 3H), 1.04 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.63 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.19, -109.71. LC-MS: [M-H]⁻ = 518.45,

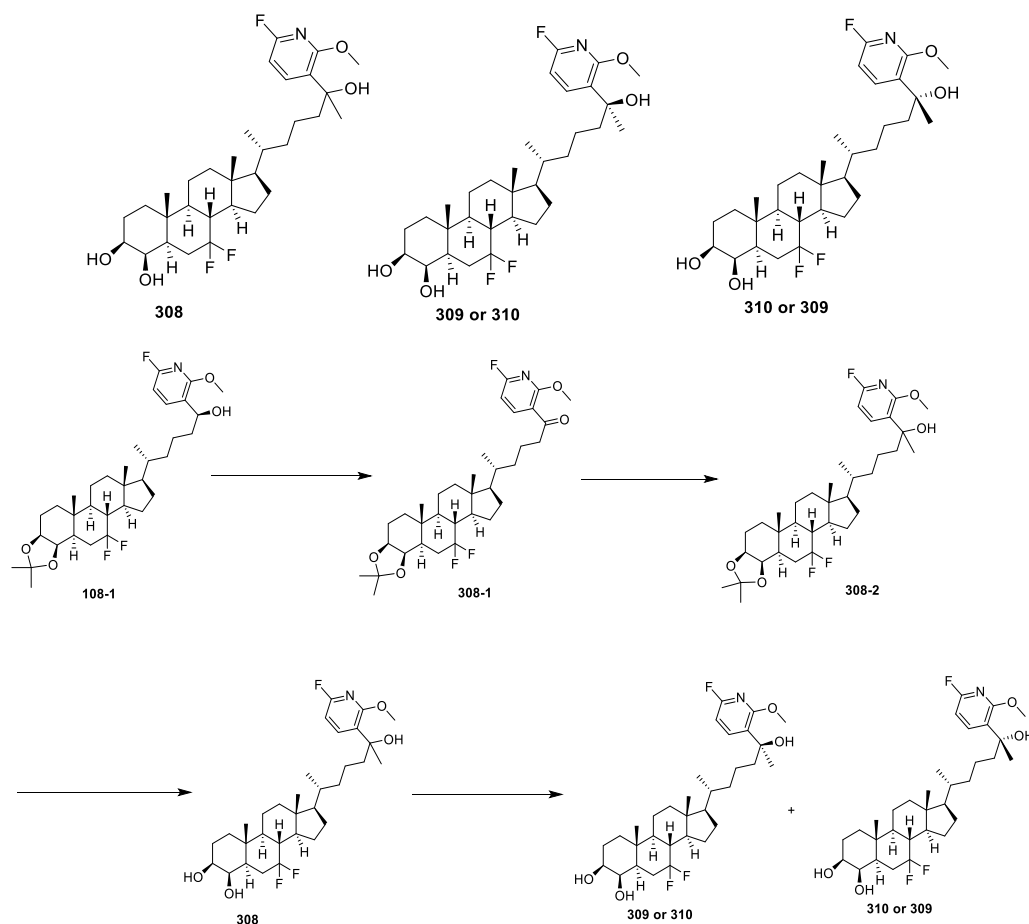
[0776] Compound **340**: ¹H NMR (400 MHz, CDCl₃) δ 7.71 (t, J = 8.0 Hz, 1H), 6.48 (dd, J = 7.9, 2.7 Hz, 1H), 4.79 (dd, J = 7.9, 4.8 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 1H), 3.59 (d, J = 11.4 Hz, 1H), 2.66 (s, 1H), 2.04 (s, 2H), 1.89 – 1.76 (m, 7H), 1.59 (s, 8H), 1.26 (s, 5H), 1.04 (s, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.63 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -73.39, -109.71. LC-MS: [M-H]⁻ = 518.45,

[0777] Examples **308**, **309** & **310**

[0778] Preparation of compound **308** (**1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR**)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyheptan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol,

[0779] compound **309** or compound **310** (**1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR**)-4,4-difluoro-1-[(2R,6S)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyheptan-2-yl]-9a,11a-dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol and

[0780] compound **310** or compound **309** (**1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR**)-4,4-difluoro-1-[(2R,6R)-6-(6-fluoro-



5 **[0781]** Step 1: Compound (1S,5R)-5-
[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-
tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-
cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(6-fluoro-2-
methoxypyridin-3-yl)hexan-1-ol **108-1** (150 mg, 0.253 mmol) was dissolved in
10 dichloromethane (6 mL), cooled in an ice bath, and Dess-Martin periodinane
(214.30 mg, 0.505 mmol) was added, then stirred at room temperature for 2 hours.
The reaction was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1)
until completion. 20% sodium thiosulfate solution and sodium bicarbonate
solution were added to the reaction mixture, stirred for 10 min, and extracted with
15 ethyl acetate (10 mL × 2). The organic phases were combined, washed with
saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered, and

concentrated to obtain a crude product, which was purified by column chromatography (4 g, 0-15% ethyl acetate/petroleum ether, 20 mL/min) to obtain (5R)-5-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-1-(6-fluoro-2-methoxypyridin-3-yl)hexan-1-one **308-1** (120 mg, 56.19%) as a white solid.

[0782] Compound **308-1**: ^1H NMR (400 MHz, CDCl_3) δ 8.25 (t, $J = 8.1$ Hz, 1H), 6.55 (dd, $J = 8.2, 3.0$ Hz, 1H), 4.04 (s, 3H), 4.01 (dd, $J = 5.0, 2.9$ Hz, 2H), 2.95 – 2.89 (m, 2H), 2.16 – 2.06 (m, 1H), 1.97 (dd, $J = 15.5, 6.0$ Hz, 2H), 1.92 – 1.79 (m, 6H), 1.71 (ddd, $J = 13.0, 10.1, 5.0$ Hz, 3H), 1.66 – 1.57 (m, 3H), 1.51 (s, 3H), 1.46 – 1.39 (m, 4H), 1.30 (s, 3H), 1.13 (dt, $J = 16.4, 5.9$ Hz, 4H), 1.07 (s, 3H), 0.98 (d, $J = 8.5$ Hz, 1H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.68 (s, 3H).

[0783] Step 2: At room temperature, compound **308-1** (130 mg, 0.220 mmol) was dissolved in tetrahydrofuran (5 mL), cooled to 0°C in an ice bath under a nitrogen atmosphere, and methylmagnesium bromide (0.220 mL) was slowly added dropwise over 5 min. The mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with ammonium chloride solution and extracted with ethyl acetate (20 mL $\times$ 2). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-10% ethyl acetate/petroleum ether, 20 mL/min) to obtain (6R)-6-[(3aS,5aR,5bS,7aR,8R,10aS,10bS,12aR,12bR)-11,11-difluoro-2,2,5a,7a-tetramethyl-4,5,5a,5b,6,7,7a,8,9,10,10a,10b,11,12,12a,12b-hexadecahydro-3aH-cyclopenta[1',2':1,2]phenanthro[7,8-d][1,3]dioxol-8-yl]-2-(6-fluoro-2-methoxypyridin-3-yl)heptan-2-ol **308-2** (82 mg, 55.27%) as a white solid.

[0784] Compound **308-2**: ^1H NMR (400 MHz, CDCl_3) δ 7.71 (q, $J = 8.0$ Hz, 1H), 6.48 (dd, $J = 8.1, 3.0$ Hz, 1H), 4.01 (dd, $J = 12.6, 6.7$ Hz, 5H), 2.17 – 2.02 (m, 1H), 1.95 (d, $J = 12.6$ Hz, 2H), 1.80 (d, $J = 7.5$ Hz, 5H), 1.65 (ddd, $J = 33.0, 13.5, 3.9$ Hz, 5H), 1.54 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.24 (dd, $J = 13.9, 6.6$ Hz, 3H), 1.16 – 1.08 (m, 2H), 1.07 (s, 3H), 1.03 – 0.90 (m, 5H), 0.84

(d, $J = 6.5$ Hz, 3H), 0.65 (s, 3H).

[0785] Step 3: Compound **308-2** (80 mg, 0.132 mmol) was dissolved in tetrahydrofuran (2 mL), and dilute hydrochloric acid (1 mL, 3 mol/L) was added. The reaction system was stirred at room temperature for 1 hour and then stirred
 5 in a 40°C water bath for 30 min. The reaction progress was monitored by a TLC plate (petroleum ether: ethyl acetate = 5:1). After the starting material was completely consumed, the reaction was stopped. Sodium bicarbonate solution (20 mL) was added to the reaction system, and the aqueous layer was extracted with ethyl acetate (2×20 mL). The organic phases were combined, washed with
 10 saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (4 g, 0-30% ethyl acetate/petroleum ether, 20 mL/min) to obtain (1R,3aS,3bS,5aR,6R,7S,9aR,9bS,11aR)-4,4-difluoro-1-[(2R)-6-(6-fluoro-2-methoxypyridin-3-yl)-6-hydroxyheptan-2-yl]-9a,11a-
 15 dimethylhexadecahydro-1H-cyclopenta[1,2-a]phenanthrene-6,7-diol **308** (56 mg, 0.089 mmol, 67.45%) as a white solid.

[0786] Compound **308**: ^1H NMR (400 MHz, CDCl_3) δ 7.71 (q, $J = 8.0$ Hz, 1H), 6.48 (dd, $J = 8.1, 3.0$ Hz, 1H), 3.99 (d, $J = 1.9$ Hz, 3H), 3.74 (s, 1H), 3.63 – 3.56 (m, 1H), 2.18 (dd, $J = 32.8, 11.8$ Hz, 1H), 1.95 (d, $J = 12.2$ Hz, 2H), 1.80 (d, $J =$
 20 8.4 Hz, 5H), 1.70 (dd, $J = 23.3, 12.0$ Hz, 6H), 1.54 (s, 3H), 1.35 (dd, $J = 25.8, 14.1$ Hz, 7H), 1.09 (d, $J = 13.1$ Hz, 1H), 1.05 (s, 3H), 1.02 – 0.88 (m, 4H), 0.84 (d, $J = 6.5$ Hz, 3H), 0.64 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -74.29 (d, $J = 33.0$ Hz, 1F), -88.95 (d, $J = 235.9$ Hz, 1F), -110.95 (d, $J = 236.2$ Hz, 1F). LC-MS: $[\text{M-H}]^- = 566.30$.

[0787] Step 4: Compound **308** (68 mg, 0.120 mmol) was subjected to SFC chiral resolution (instrument: Waters Acquity UPCC, column: Daicel CHIRALPAK OD_3, 3×150 mm, 3 μm , mobile phase: CO_2/IPA (0.1% DEA) = 75/25, flow rate: 2 mL/min, wavelength: UV 214 nm) to obtain white solid **309** (15.47 mg, purity: 100%, e.e. 100%, yield: 22.75%, retention time: 2.045 min) and white solid **310**
 30 (16.47 mg, purity: 100%, e.e. 100%, yield: 24.22%, retention time: 2.590 min).

[0788] Compound **309**: ^1H NMR (400 MHz, CDCl_3) δ 7.72 (t, $J = 8.1$ Hz, 1H),

6.47 (dd, $J = 8.1, 3.0$ Hz, 1H), 3.99 (s, 3H), 3.74 (s, 1H), 3.60 (dt, $J = 11.4, 4.1$ Hz, 1H), 2.29 – 2.11 (m, 1H), 1.95 (dd, $J = 18.5, 6.5$ Hz, 2H), 1.89 – 1.76 (m, 5H), 1.75 – 1.64 (m, 5H), 1.54 (s, 3H), 1.50 – 1.35 (m, 4H), 1.32 – 1.18 (m, 5H), 1.10 (dd, $J = 13.1, 4.4$ Hz, 1H), 1.05 (s, 3H), 1.02 – 0.94 (m, 3H), 0.84 (d, $J = 6.5$ Hz, 3H), 0.64 (s, 3H). ^{19}F NMR (377MHz, CDCl_3) δ -74.34 (s, 1F), -88.95 (d, $J = 236.1$ Hz, 1F), -110.95 (d, $J = 236.1$ Hz, 1F). LC-MS: $[\text{M-H}]^- = 566.40$.

[0789] Compound **310**: ^1H NMR (400 MHz, CDCl_3) δ 7.70 (t, $J = 8.0$ Hz, 1H), 6.48 (dd, $J = 8.1, 3.0$ Hz, 1H), 3.99 (s, 3H), 3.74 (s, 1H), 3.63 – 3.55 (m, 1H), 2.27 – 2.09 (m, 1H), 1.95 (d, $J = 12.9$ Hz, 1H), 1.83 (dd, $J = 25.4, 11.9$ Hz, 6H), 1.75 – 1.60 (m, 4H), 1.54 (s, 3H), 1.46 – 1.28 (m, 7H), 1.25 – 1.16 (m, 2H), 1.09 (d, $J = 13.6$ Hz, 1H), 1.05 (s, 3H), 1.03 – 0.89 (m, 4H), 0.84 (d, $J = 6.4$ Hz, 3H), 0.64 (s, 3H). ^{19}F NMR (376MHz, CDCl_3) δ -74.25 (s, 1F), -88.95 (d, $J = 235.8$ Hz, 1F), -110.94 (d, $J = 235.9$ Hz, 1F). LC-MS: $[\text{M-H}]^- = 566.50$.

[0790] Effect Example 1: Inhibitory effect of the compounds of the present disclosure on the SREBP pathway

[0791] 1.1 SREBP luciferase reporter gene system

[0792] Huh-7/SRE-luc cells were incubated in sterol-deficient medium (5% lipoprotein deficient serum, 2 μM lovastatin, 10 μM mevalonic acid) with corresponding concentrations of compounds for 16 hours. The Huh-7/SRE-luc cells were human hepatoma cell line Huh-7 stably expressing LDLR promotor-luciferase and green fluorescent protein (GFP). These cells were obtained by transfecting Huh-7 with pLDLR-promotor-luciferase and pEGFP-N1 plasmids, followed by screening under G418 antibiotic selection pressure. The Huh-7 cells were purchased from ATCC, the pLDLR-promotor-luciferase plasmid was obtained by molecular cloning methods, and the pEGFP-N1 plasmid was purchased from Addgene.

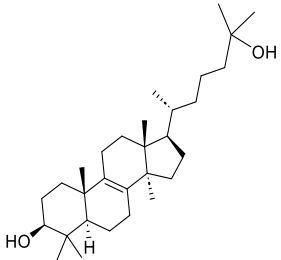
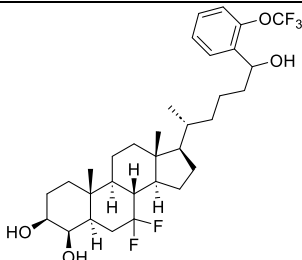
[0793] After compound treatment, the cells were lysed with lysis buffer (E397A, Promega). After the addition of luciferase substrate (E1500, Promega), the activity of SRE-driven luciferase was measured using a BioTek Synergy HTX microplate reader (including but not limited to this type of instrument). The

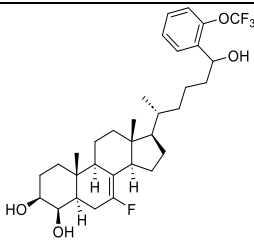
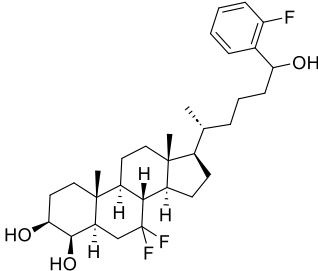
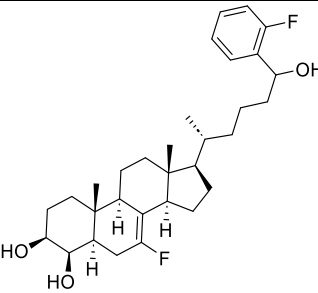
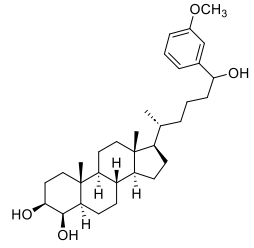
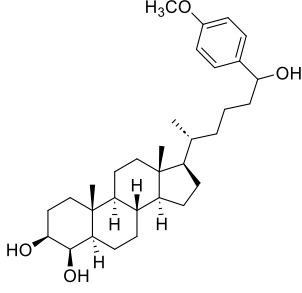
fluorescence intensity of green fluorescent protein (EGFP) was also measured using the above BioTek microplate reader (including but not limited to this type of instrument) and served as an internal control. The ratio of SRE-driven luciferase activity divided by the fluorescence intensity of green fluorescent protein was used as an indicator of SREBP pathway activity. The test data for each test compound were analyzed using Prism software (with the DMSO-treated group as the reference to calculate the compound inhibition rate, fitted using the Prism log(inhibitor) vs. response--Variable slope (four-parameter) model, calculation formula: $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) \times \text{HillSlope}))})$), to obtain the IC_{50} parameters of the compounds.

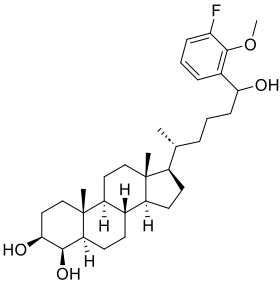
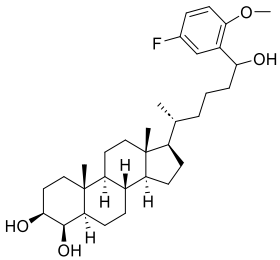
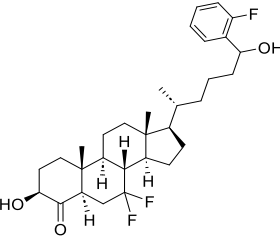
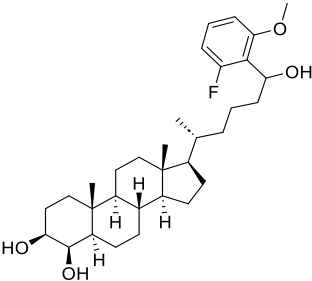
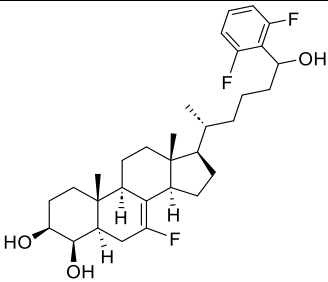
[0794] 1.2 Inhibitory effect of the compounds of the present disclosure on the SREBP pathway

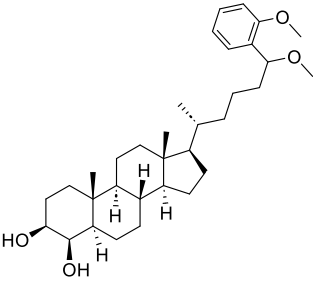
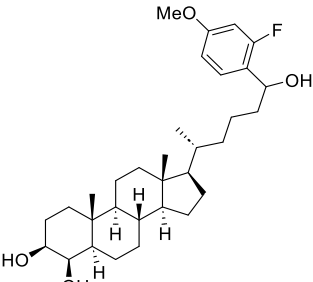
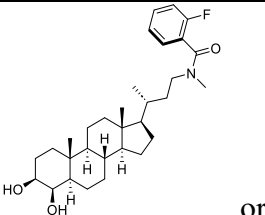
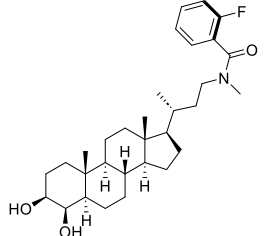
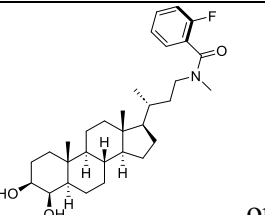
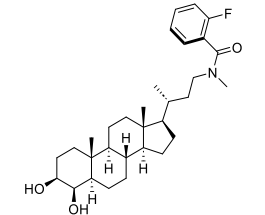
[0795] Using the method described in 1.1, the inhibitory effect of the compounds of the present disclosure on the SREBP pathway was tested. The concentration gradient for each compound was designed as 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, and 10 μM , with the vehicle DMSO as the control. The IC_{50} values for some compounds are shown in Table 1.

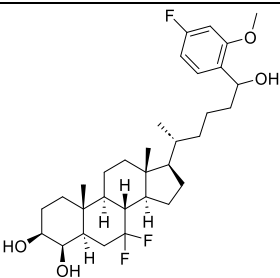
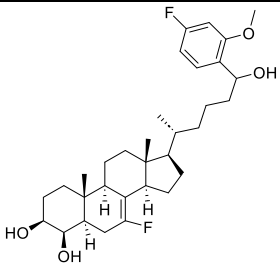
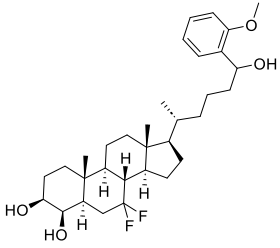
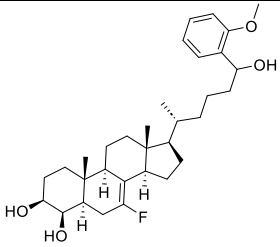
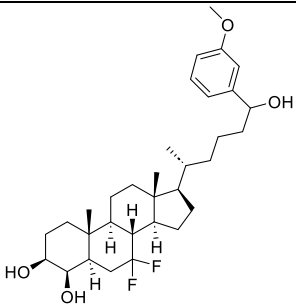
[0796] Table 1

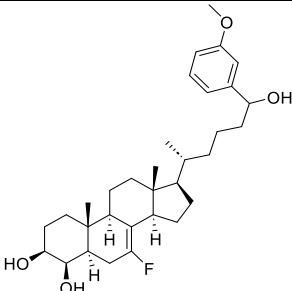
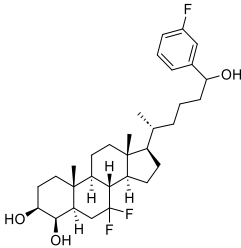
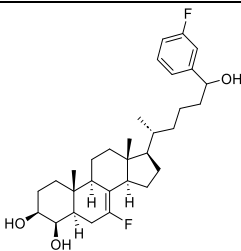
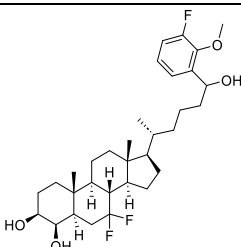
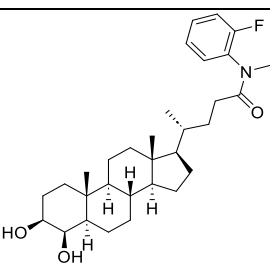
Example ID	Structural formula	SRE-luciferase assay ($\text{IC}_{50} \mu\text{M}$)
Comparative compound 1		0.293
1		0.330

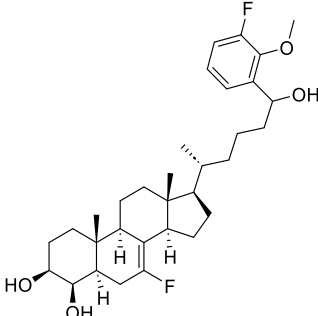
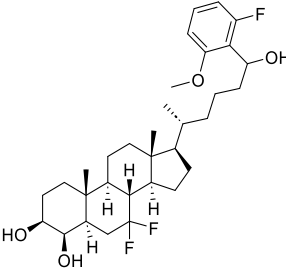
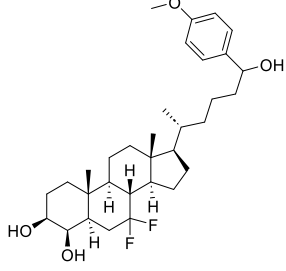
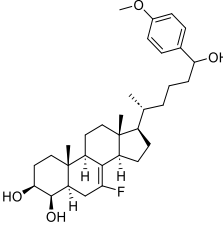
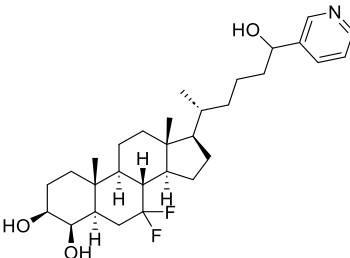
2	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and a fluorine atom at C6. The side chain at C17 is a 4-(trifluoromethoxy)phenyl group.	0.450
3	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and two fluorine atoms at C6 and C7. The side chain at C17 is a 4-fluorophenyl group.	0.03
4	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and a fluorine atom at C6. The side chain at C17 is a 4-fluorophenyl group.	0.09
5	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14. The side chain at C17 is a 4-methoxyphenyl group.	0.13
6	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14. The side chain at C17 is a 4-methoxyphenyl group.	0.13

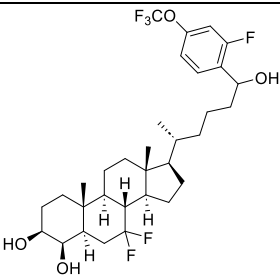
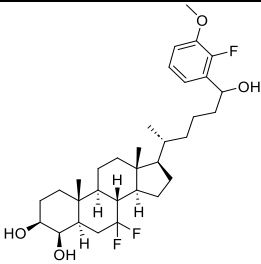
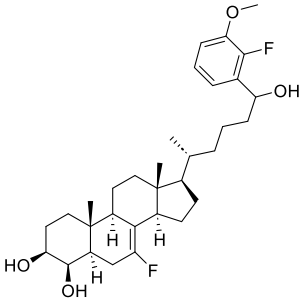
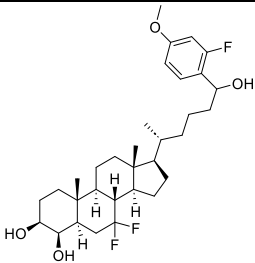
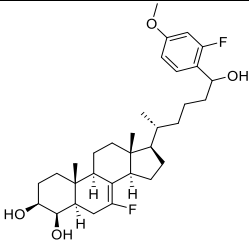
7		0.07
8		0.33
11		0.19
20		0.23
21		0.23

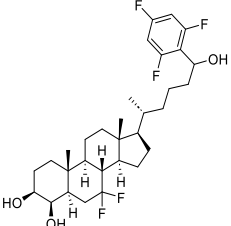
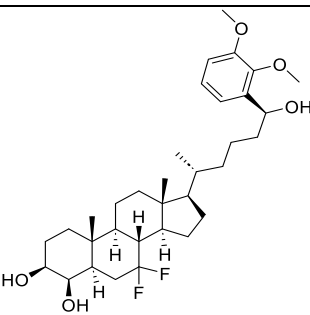
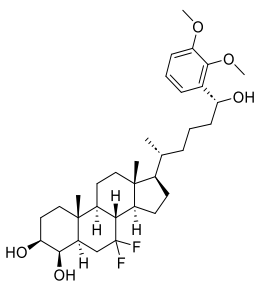
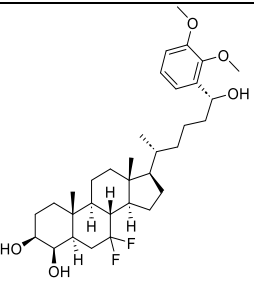
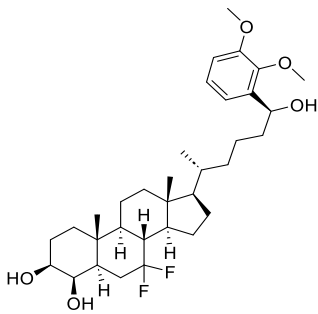
22	 <chem>COc1ccc(OC)cc1CCCC[C@H]2[C@@H]3CC[C@H]4[C@@H](C)[C@H](O)[C@@H](O)[C@H]4CC[C@@]3(C)CC[C@H]2C</chem>	2.01
28	 <chem>COc1cc(F)ccc1C(O)CCCC[C@H]2[C@@H]3CC[C@H]4[C@@H](C)[C@H](O)[C@@H](O)[C@H]4CC[C@@]3(C)CC[C@H]2C</chem>	0.26
15A	 or  <chem>CN(C)CCCC[C@H]2[C@@H]3CC[C@H]4[C@@H](C)[C@H](O)[C@@H](O)[C@H]4CC[C@@]3(C)CC[C@H]2C</chem>	0.37
15B	 or  <chem>CN(C)CCCC[C@H]2[C@@H]3CC[C@H]4[C@@H](C)[C@H](O)[C@@H](O)[C@H]4CC[C@@]3(C)CC[C@H]2C</chem>	0.32

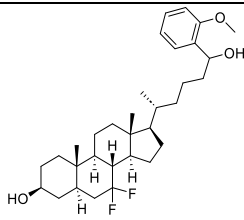
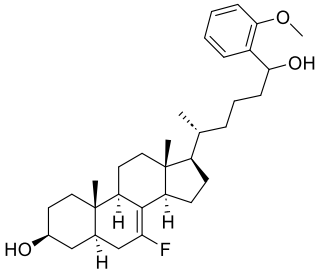
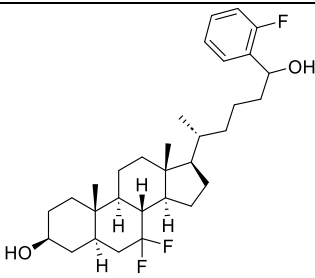
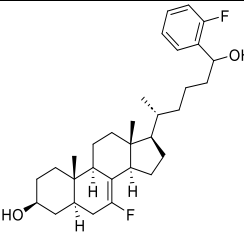
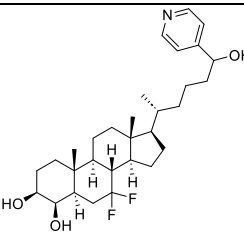
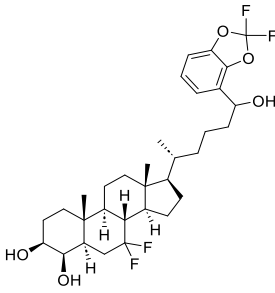
35		0.051
36		0.2
37		0.03
38		0.11
39		0.19

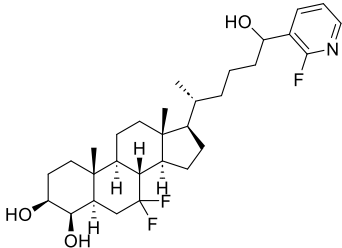
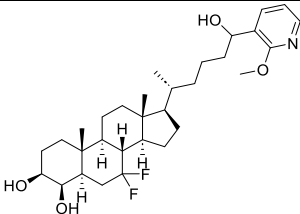
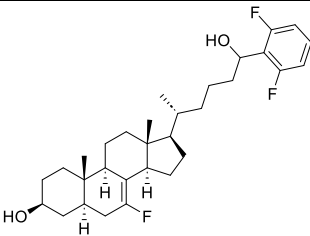
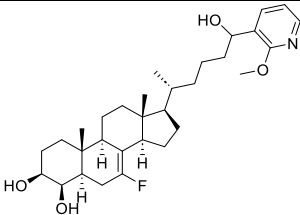
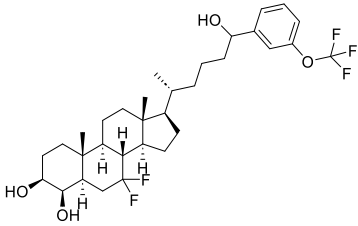
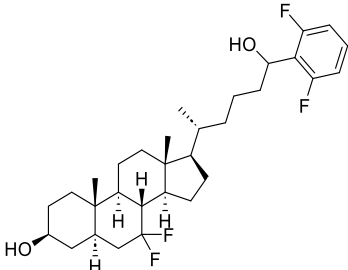
40		0.25
44		0.1522
45		0.1983
46		0.07
47		0.05

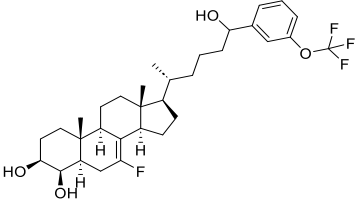
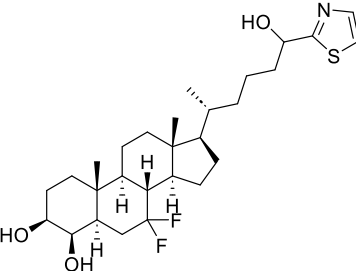
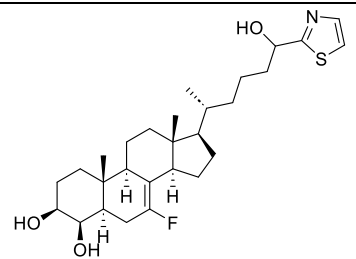
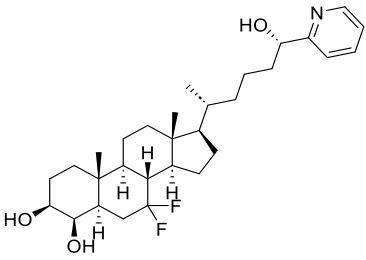
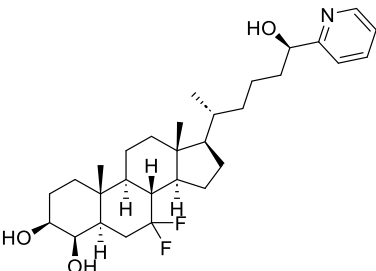
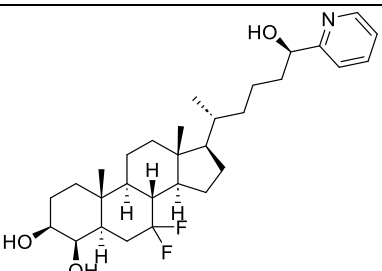
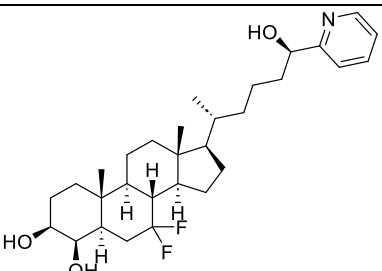
48	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and a fluorine atom at C6. At C17, there is a side chain consisting of a propyl group and a 2-fluoro-3-methoxyphenyl group.	0.2025
49	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and fluorine atoms at C6 and C7. At C17, there is a side chain consisting of a propyl group and a 2-fluoro-4-methoxyphenyl group.	0.06
50	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and fluorine atoms at C6 and C7. At C17, there is a side chain consisting of a propyl group and a 4-methoxyphenyl group.	0.1875
51	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and fluorine atoms at C6 and C7. At C17, there is a side chain consisting of a propyl group and a 4-methoxyphenyl group.	0.2122
54	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C3 and C14, and fluorine atoms at C6 and C7. At C17, there is a side chain consisting of a propyl group and a 3-pyridyl group.	0.35

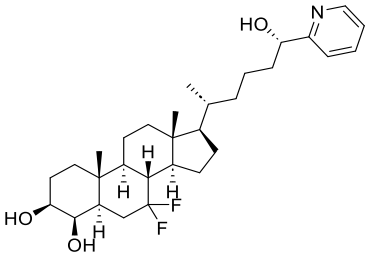
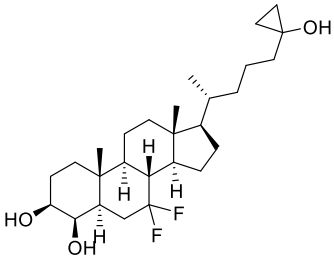
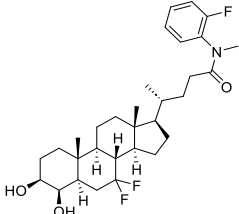
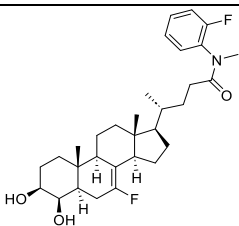
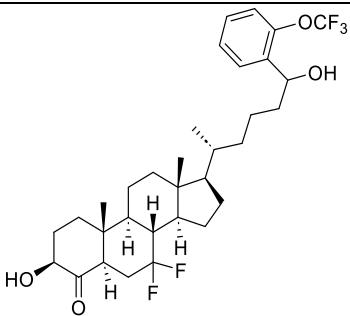
62		0.728
63		0.121
64		0.318
67		0.203
68		0.434

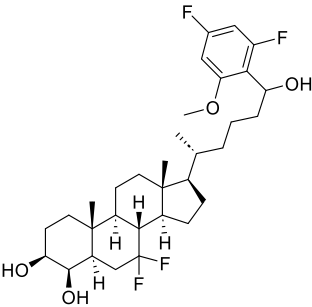
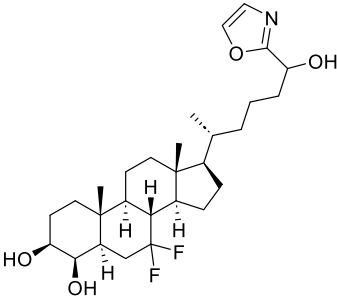
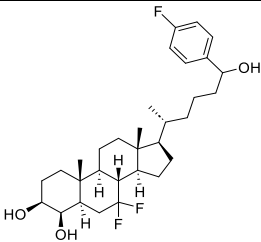
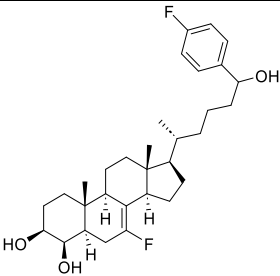
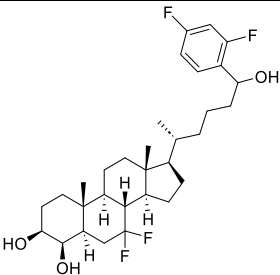
69		0.086
70	 or 	0.211
71	 or 	0.083

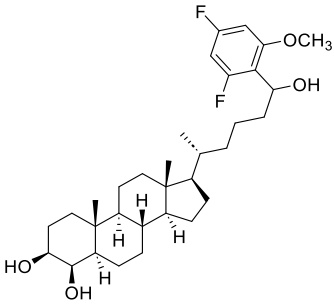
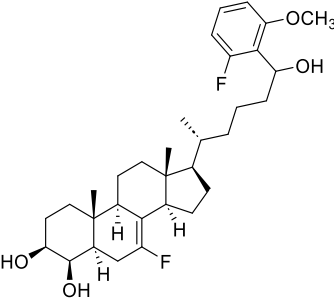
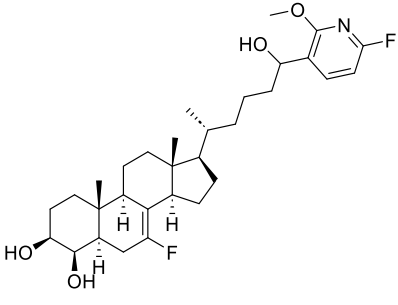
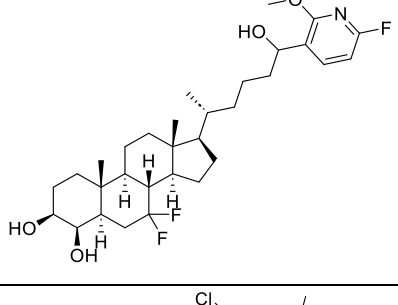
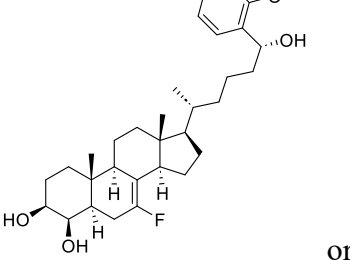
72		0.14
73		0.55
74		0.68
75		0.37
76		0.90
77		0.17

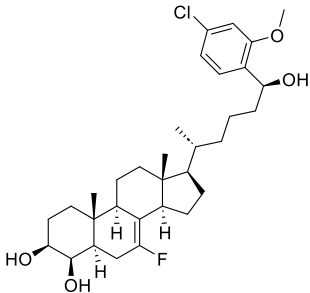
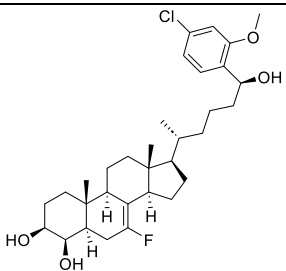
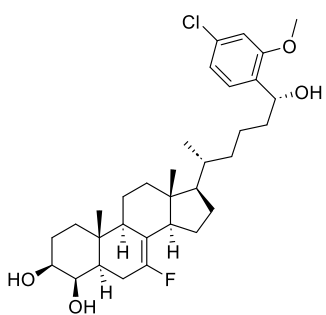
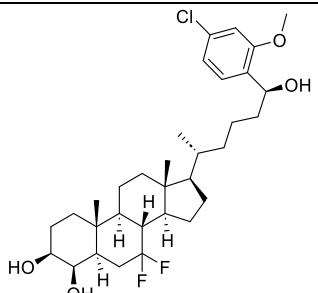
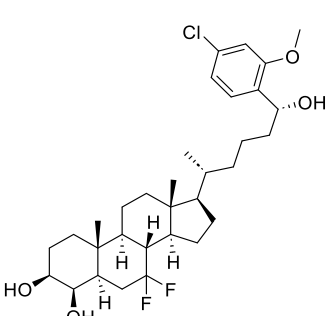
80		0.5137
81		0.1097
82		0.3566
83		0.092
84		0.2042
87		0.055

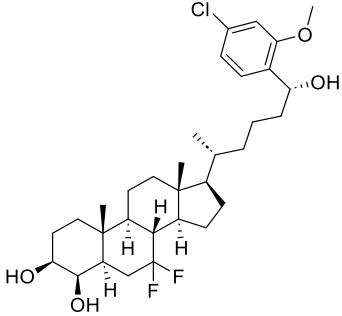
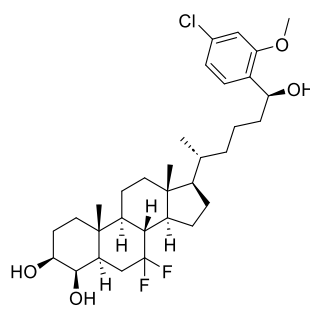
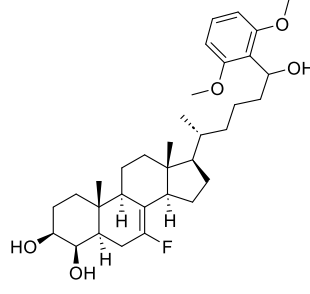
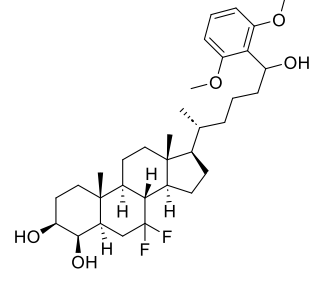
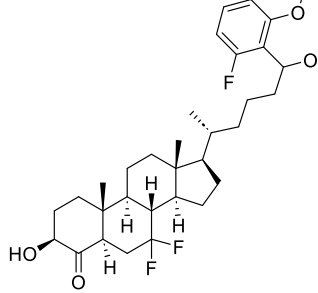
88		0.6223
89		0.1827
90		0.3793
91	 or 	0.3782
92	 or 	0.3706

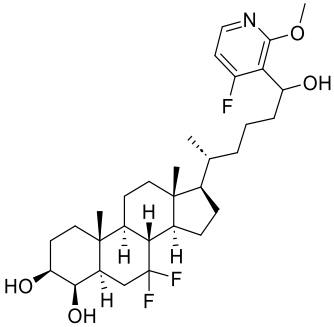
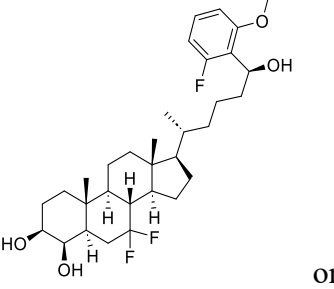
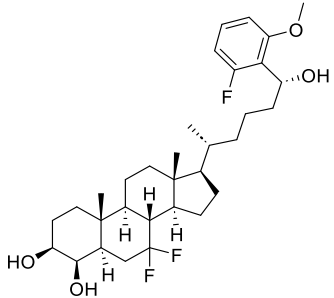
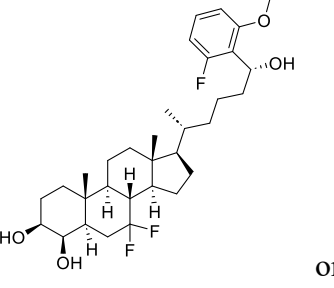
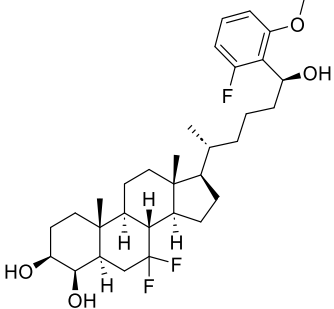
	 Chemical structure of a steroid derivative. The steroid core has a hydroxyl group at C3, a fluorine atom at C17, and a side chain at C13 consisting of a propyl group and a 2-pyridylmethyl group.	
93	 Chemical structure of a steroid derivative. The steroid core has a hydroxyl group at C3, a fluorine atom at C17, and a side chain at C13 consisting of a propyl group and a cyclopropylmethyl group.	0.6126
95	 Chemical structure of a steroid derivative. The steroid core has a hydroxyl group at C3, a fluorine atom at C17, and a side chain at C13 consisting of a propyl group and a 2-fluorophenyl group.	0.08
96	 Chemical structure of a steroid derivative. The steroid core has a hydroxyl group at C3, a fluorine atom at C17, and a side chain at C13 consisting of a propyl group and a 2-fluorophenyl group.	0.3404
97	 Chemical structure of a steroid derivative. The steroid core has a hydroxyl group at C3, a fluorine atom at C17, and a side chain at C13 consisting of a propyl group and a 2-(trifluoromethoxy)phenyl group.	0.07414

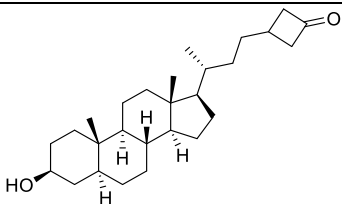
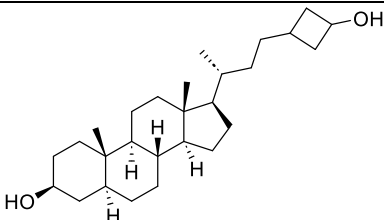
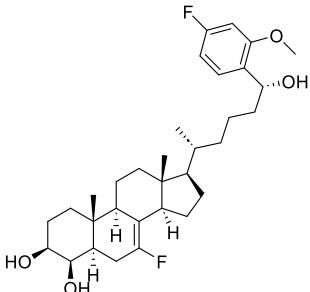
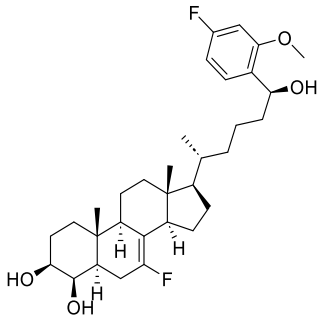
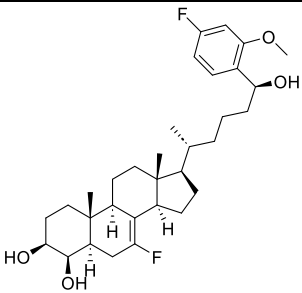
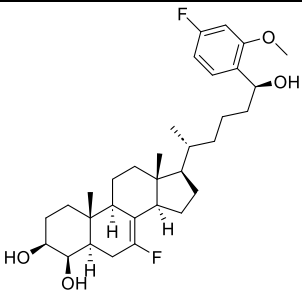
98		0.095
99		0.2426
100		0.1791
101		0.2976
102		0.1403

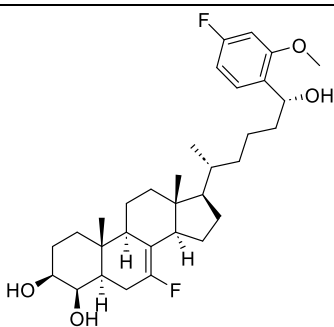
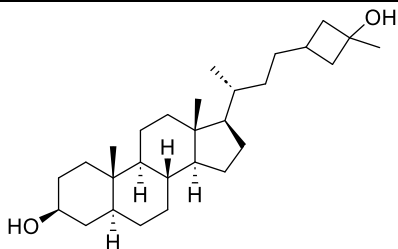
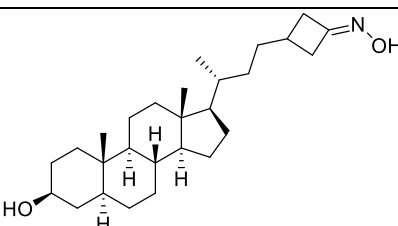
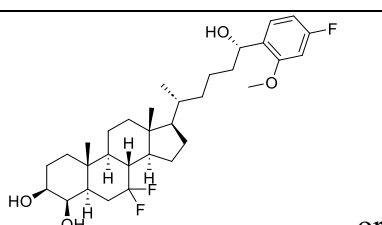
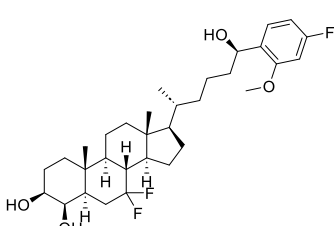
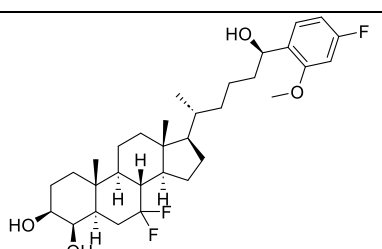
104	 <chem>COc1cc(F)ccc1C[C@H](CCCC[C@H]2[C@@H]3[C@H]([C@@H]([C@H]2O)O)C[C@H]3O)C[C@H]4[C@@H]([C@@H]([C@H]([C@H]4O)O)O)F</chem>	0.25
105	 <chem>COc1cc(F)ccc1C[C@H](CCCC[C@H]2[C@@H]3[C@H]([C@@H]([C@H]2O)O)C[C@H]3O)C[C@H]4[C@@H]([C@@H]([C@H]([C@H]4O)O)O)F</chem>	0.1094
107	 <chem>COc1cc(F)ccc1C[C@H](CCCC[C@H]2[C@@H]3[C@H]([C@@H]([C@H]2O)O)C[C@H]3O)C[C@H]4[C@@H]([C@@H]([C@H]([C@H]4O)O)O)F</chem>	0.0777
108	 <chem>COc1cc(F)ccc1C[C@H](CCCC[C@H]2[C@@H]3[C@H]([C@@H]([C@H]2O)O)C[C@H]3O)C[C@H]4[C@@H]([C@@H]([C@H]([C@H]4O)O)O)F</chem>	0.0359
110	 <chem>COc1cc(Cl)ccc1C[C@H](CCCC[C@H]2[C@@H]3[C@H]([C@@H]([C@H]2O)O)C[C@H]3O)C[C@H]4[C@@H]([C@@H]([C@H]([C@H]4O)O)O)F</chem> or	1.129

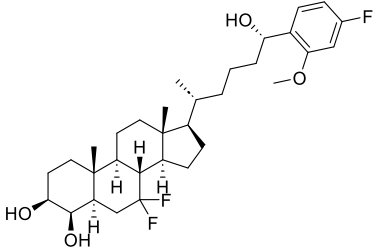
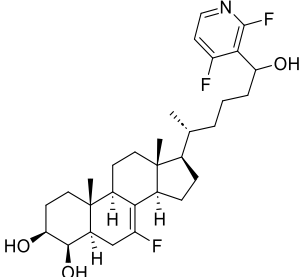
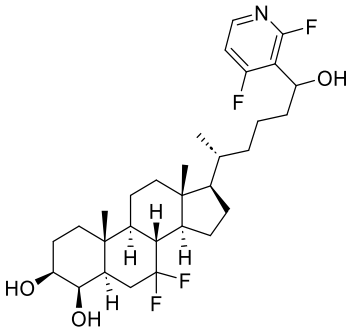
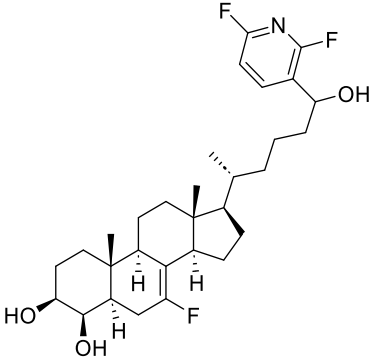
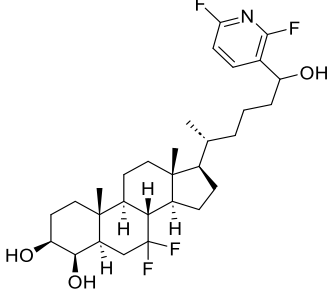
		
111	 or 	1.475
112	 or 	0.3176

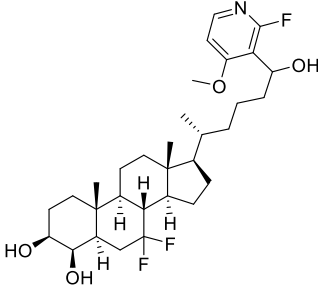
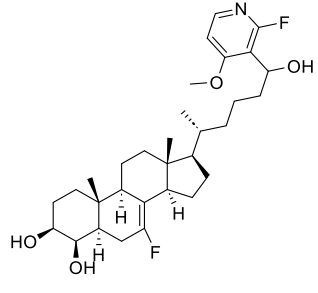
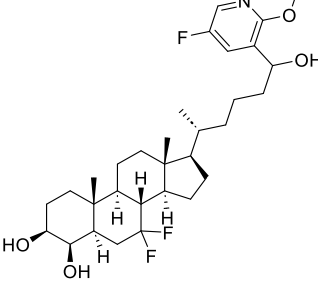
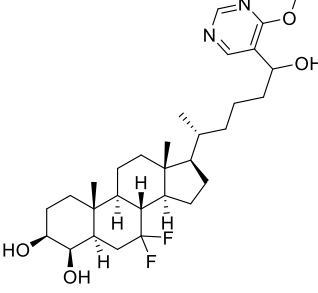
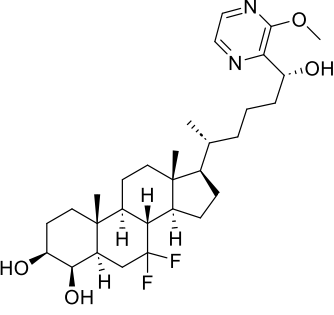
113	 or 	0.2275
115		0.6133
116		0.1766
124		0.064

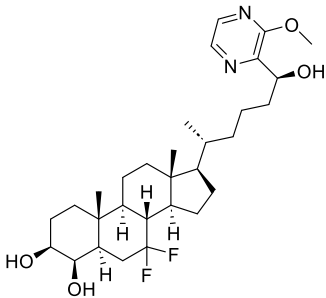
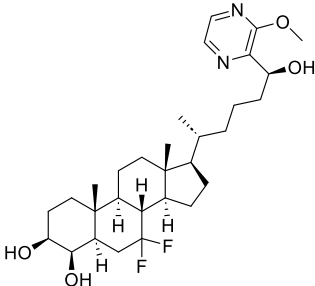
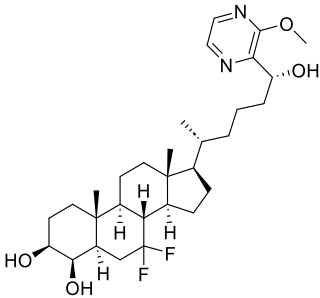
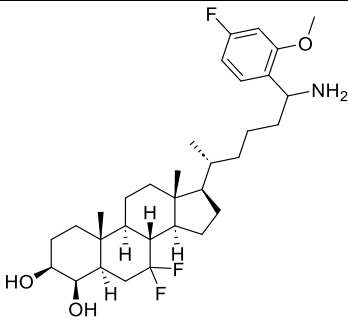
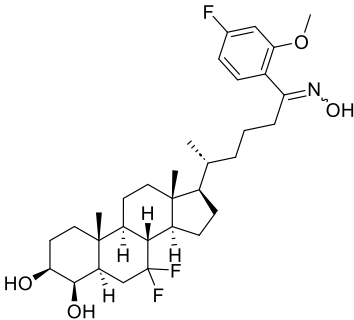
126		0.153
127	 or 	0.07
128	 or 	0.139

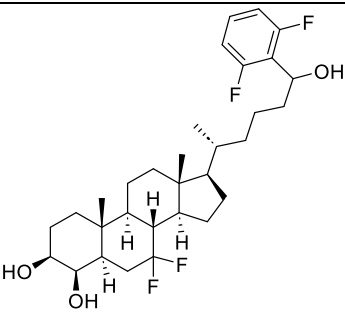
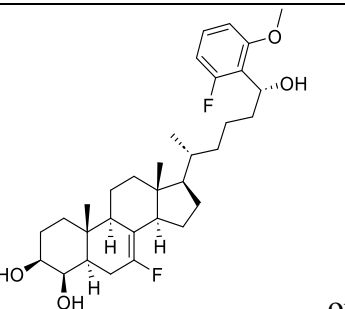
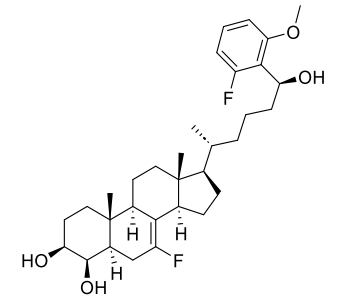
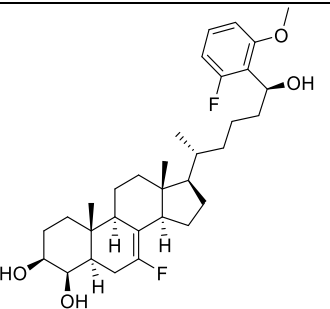
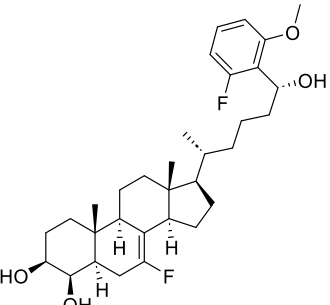
129		0.32
130		1.055
132	 or 	0.096
133	 or 	0.095

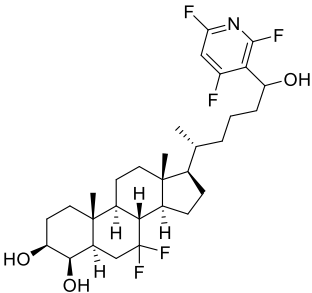
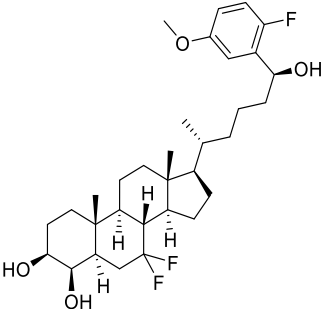
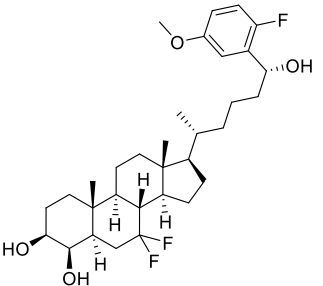
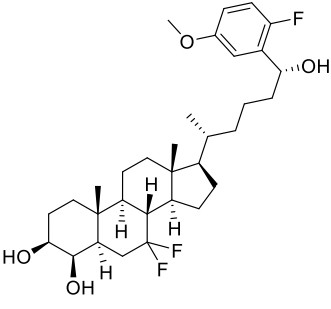
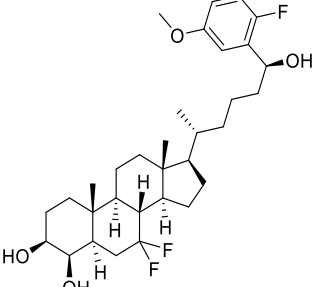
		
134		0.997
135		4.03
140	 or 	0.11
141	 or	0.017

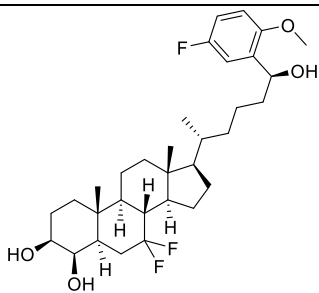
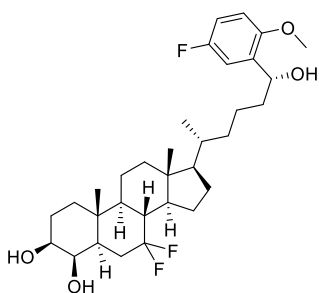
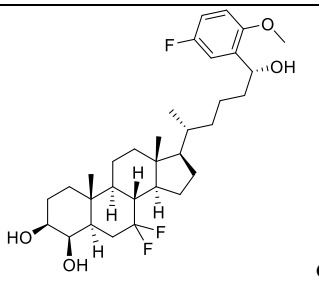
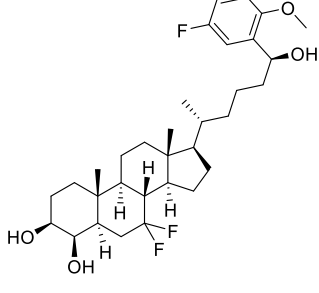
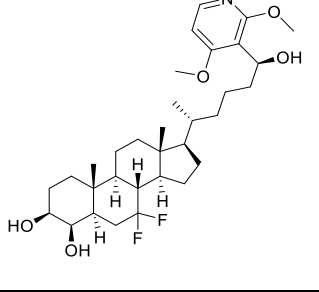
	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-11, and a fluorine atom at C-13. At C-14, there is a side chain consisting of a propyl group attached to a 4-fluorophenyl ring via an ether linkage.	
145	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-11, and a fluorine atom at C-13. At C-14, there is a side chain consisting of a propyl group attached to a 2,6-difluorophenyl ring via an ether linkage.	0.35
146	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-11, and a fluorine atom at C-13. At C-14, there is a side chain consisting of a propyl group attached to a 2,6-difluorophenyl ring via an ether linkage.	0.16
147	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-11, and a fluorine atom at C-13. At C-14, there is a side chain consisting of a propyl group attached to a 2,6-difluorophenyl ring via an ether linkage.	0.19
148	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-11, and a fluorine atom at C-13. At C-14, there is a side chain consisting of a propyl group attached to a 2,6-difluorophenyl ring via an ether linkage.	0.08

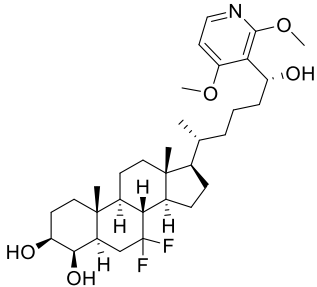
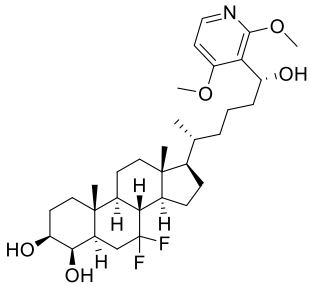
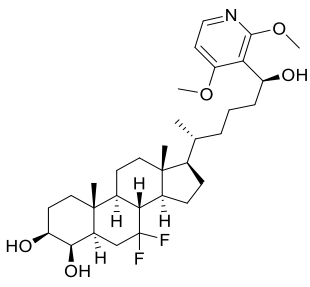
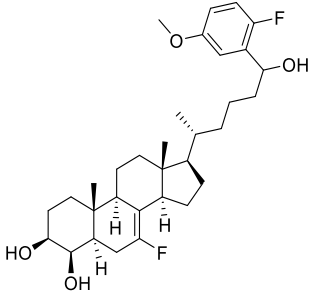
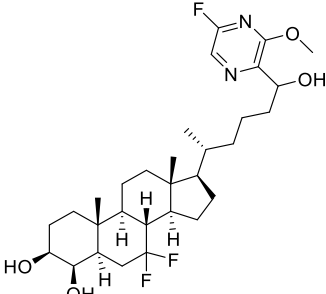
149		0.14
150		0.19
151		0.18
152		0.14
154	 or	0.2425

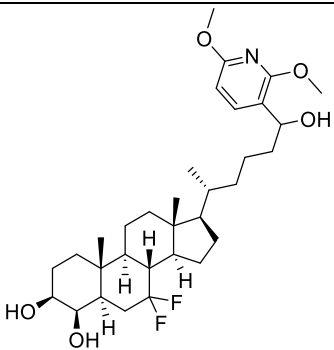
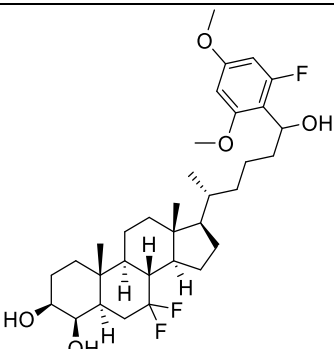
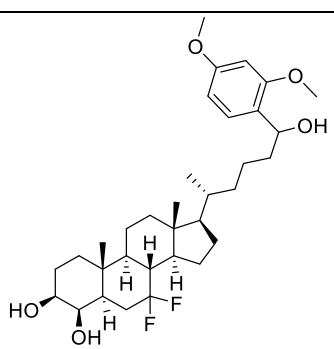
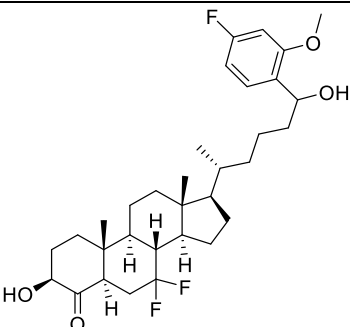
		
155	 or 	0.1876
156		1.323
157		0.053

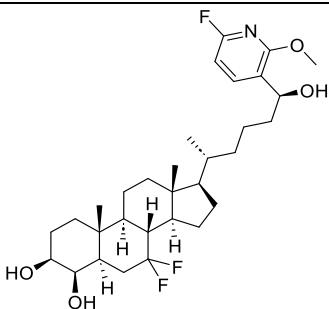
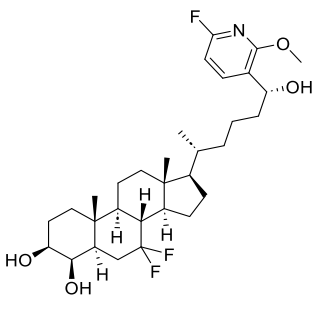
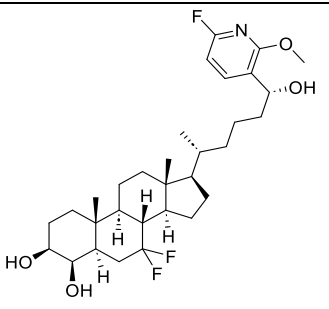
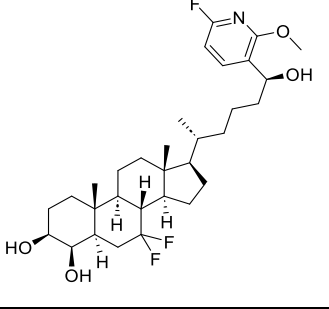
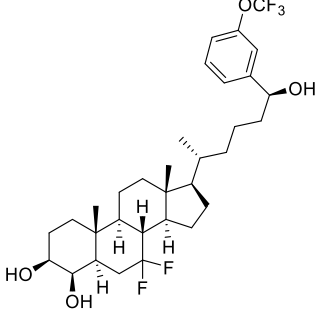
Compound 161		0.10
163	 or 	0.201
164	 or 	0.295

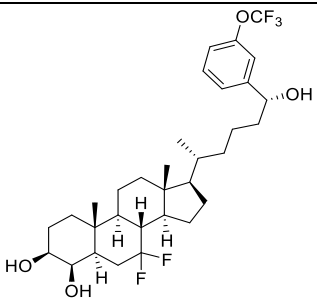
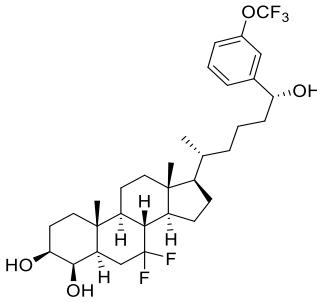
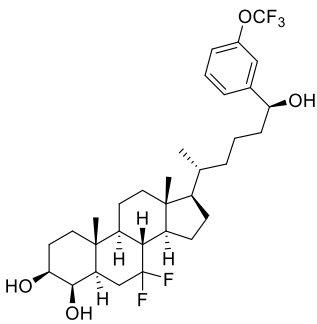
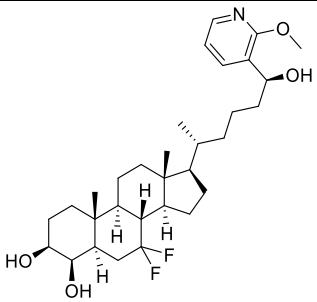
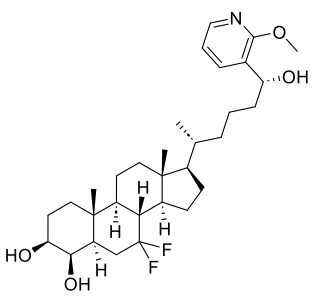
165		0.099
166	 or 	0.138
167	 or 	0.880

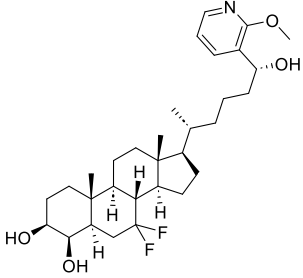
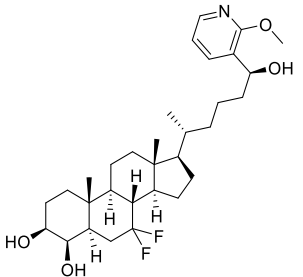
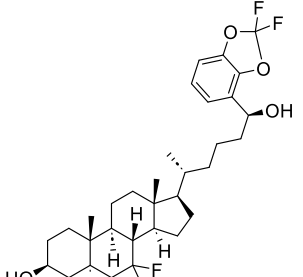
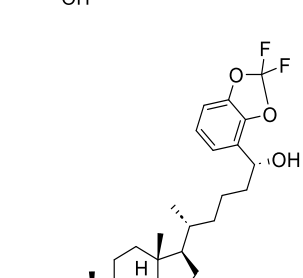
168	 or 	0.092
169	 or 	0.075
171	 or 	0.013

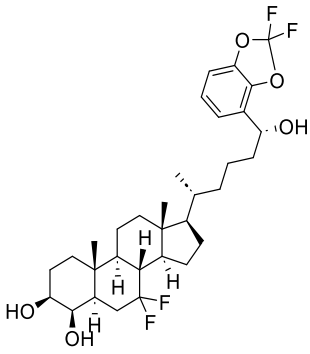
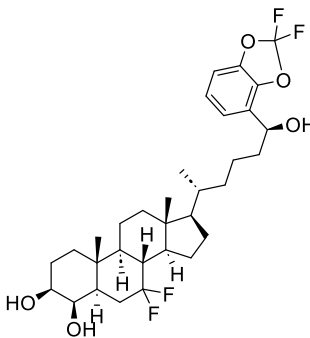
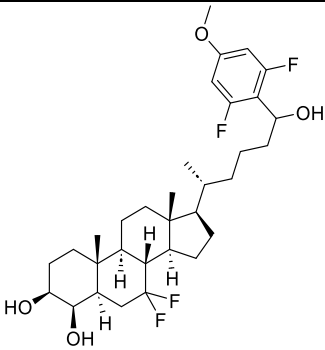
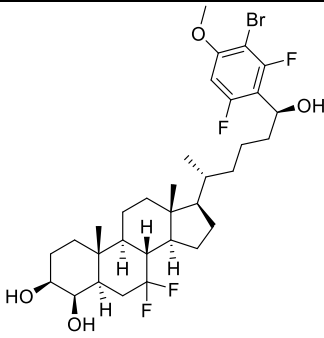
		
172	 or 	0.113
174		0.148
175		0.285

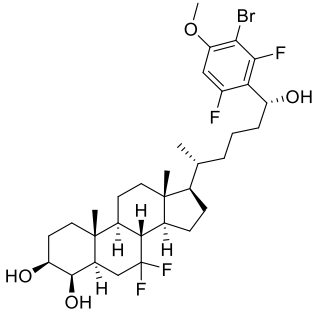
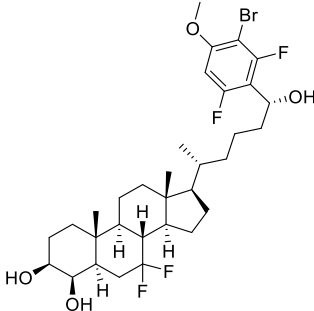
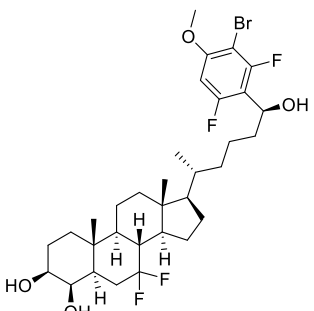
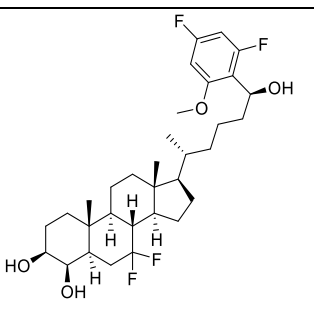
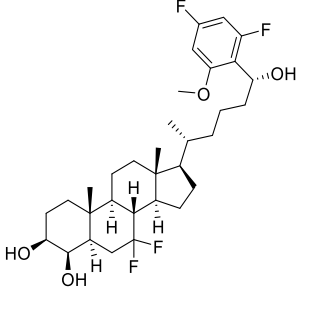
177		0.186
182		0.121
183		0.141
184		0.031

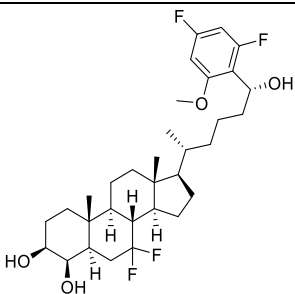
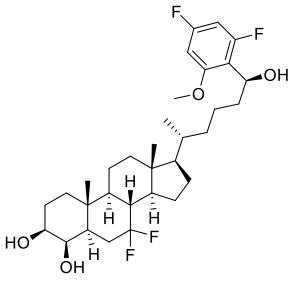
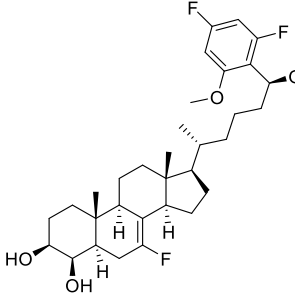
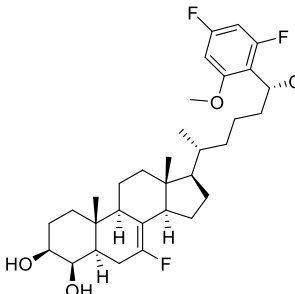
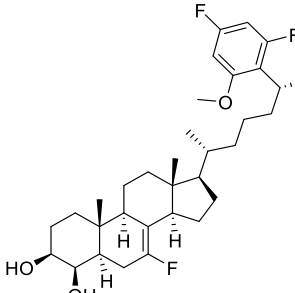
188	 or 	0.142
189	 or 	0.0231
190	 or 	0.355

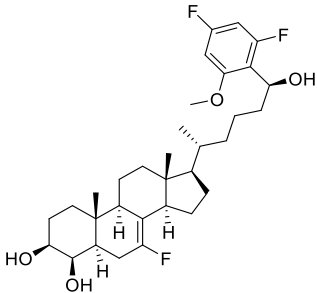
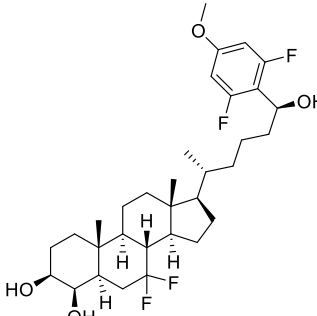
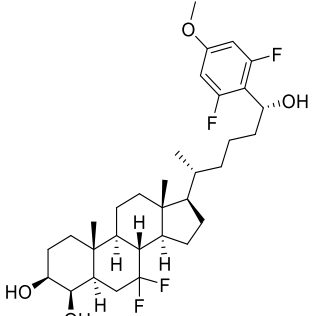
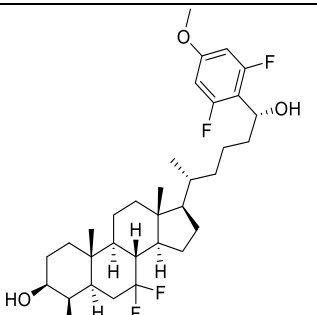
		
191	 or 	0.246
192	 or 	0.053

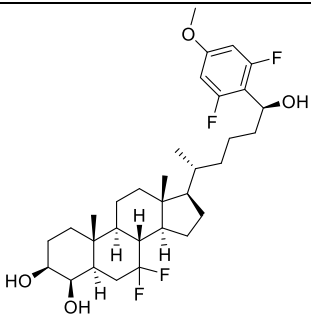
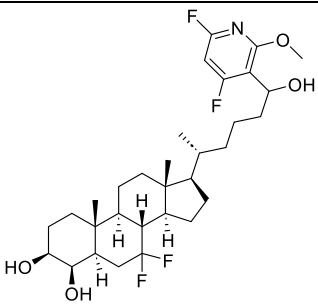
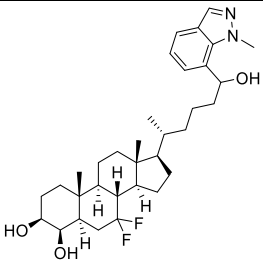
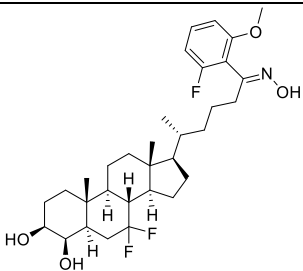
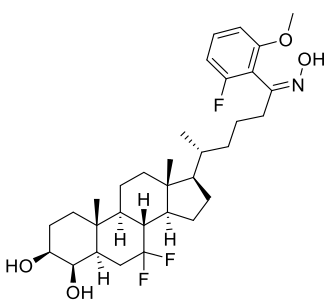
193	 or 	0.072
194	 or 	0.102

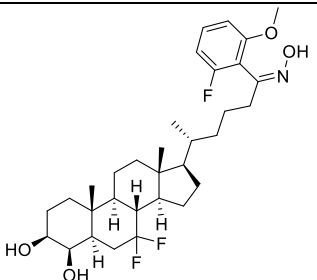
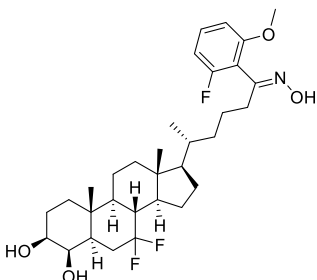
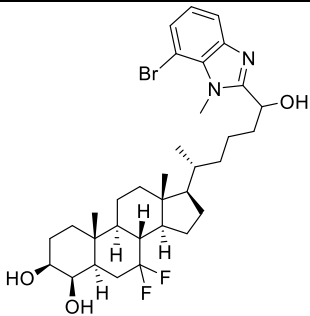
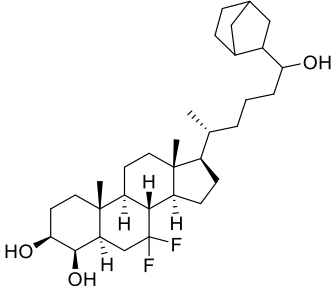
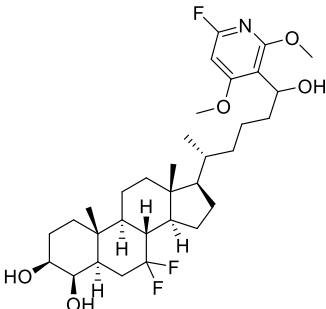
195	 or 	0.067
197		0.073
198	 or 	0.058

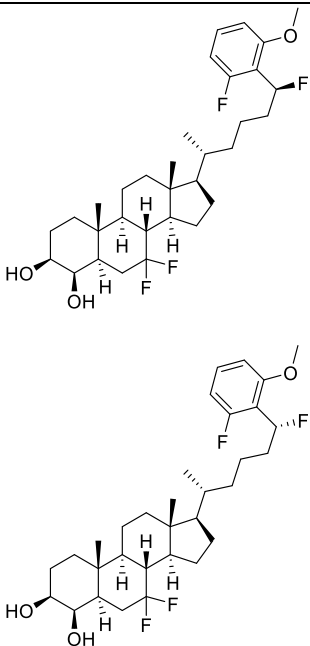
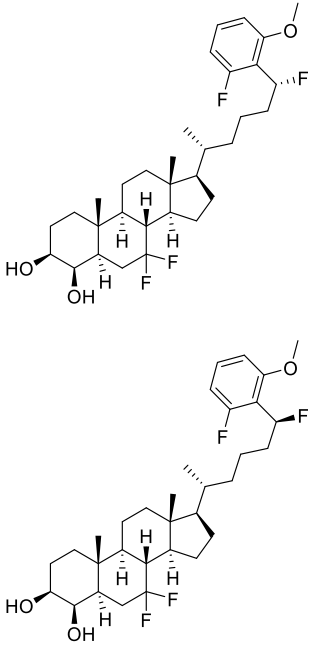
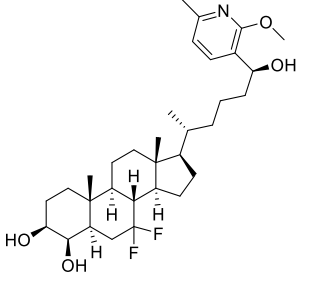
		
199	 or 	0.152
200	 or 	0.053

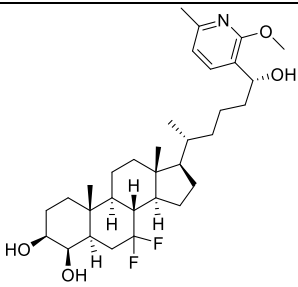
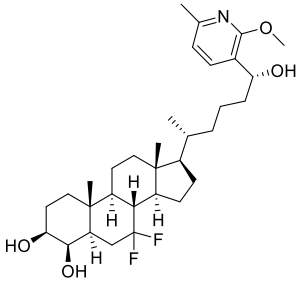
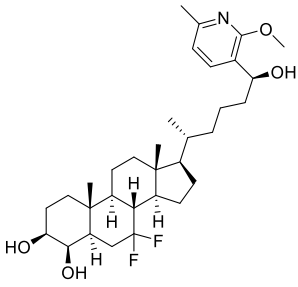
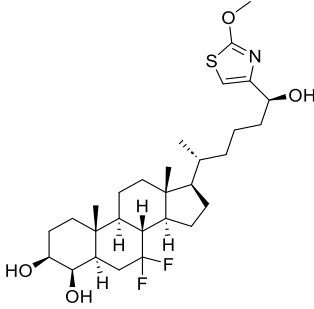
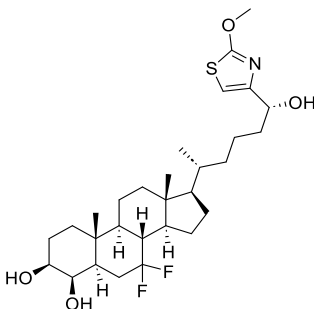
201	 or 	0.030
202	 or 	0.411
203	 or 	0.174

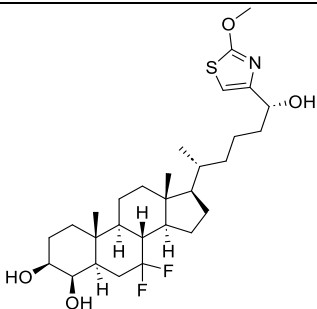
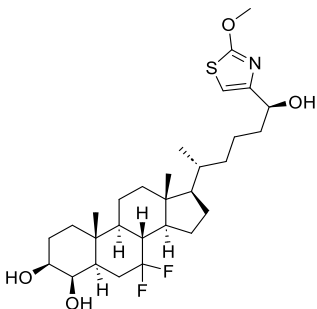
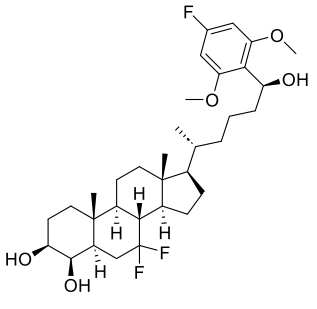
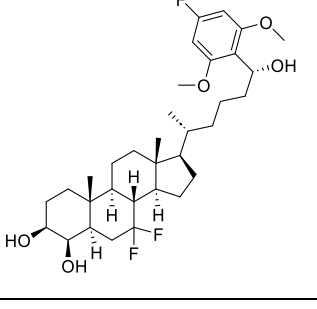
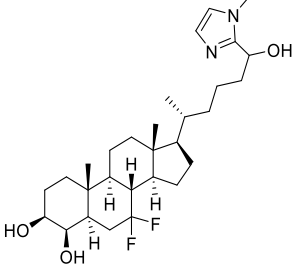
		
204	 or 	0.145
205	 or	0.107

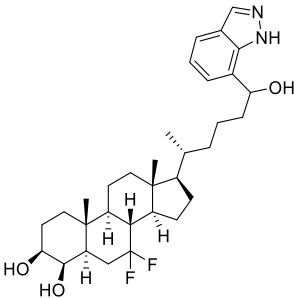
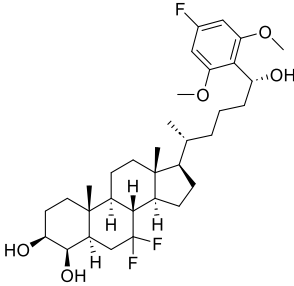
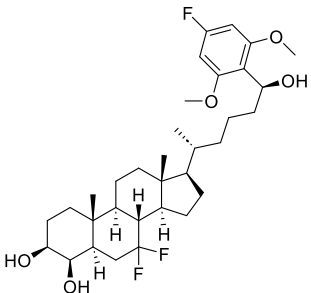
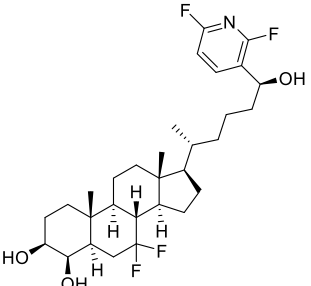
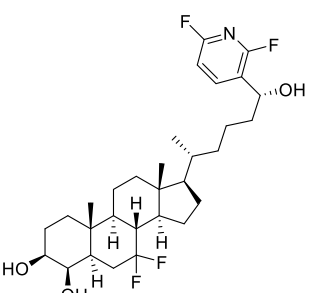
		
206		0.145
207		0.206
210	 or 	0.017

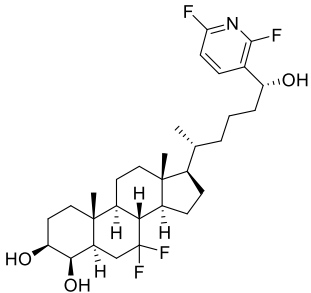
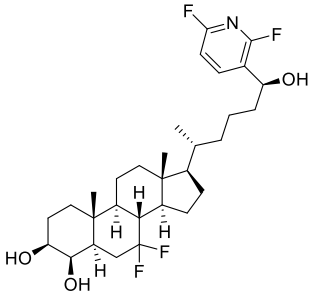
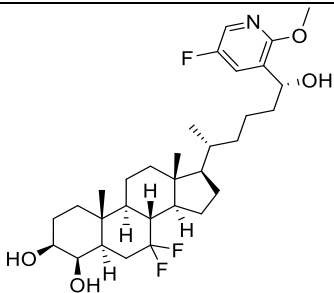
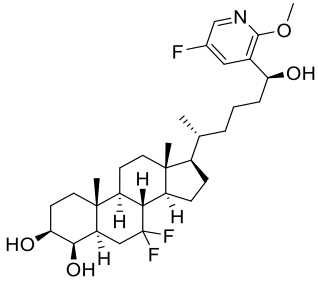
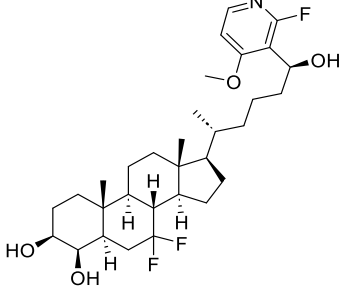
211	 or 	0.080
212		0.080
213		0.569
214		0.183

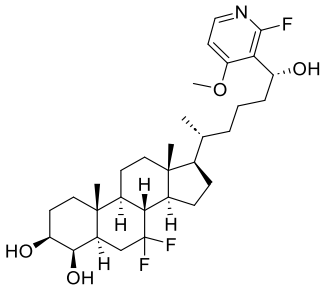
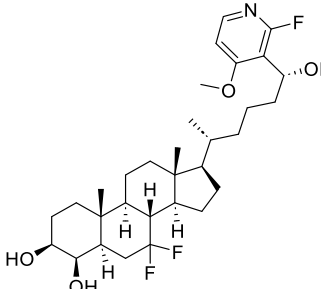
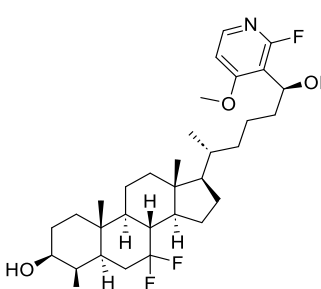
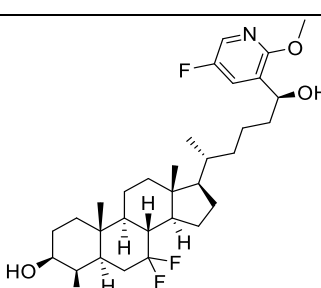
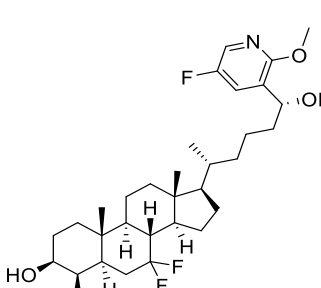
215	 or	3.569
216	 or	2.647
217	 or	0.210

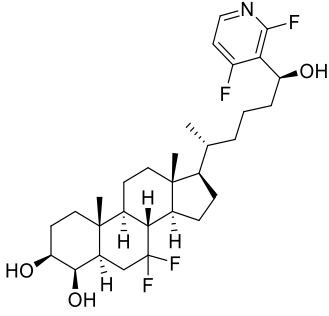
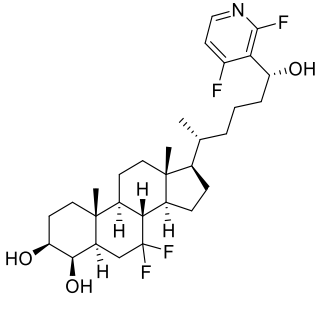
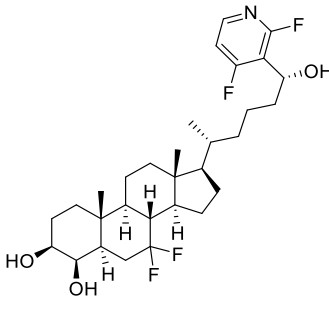
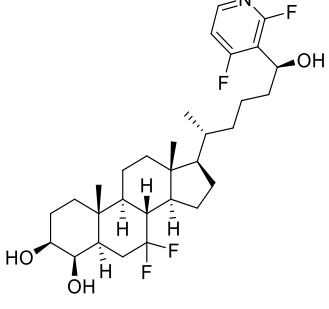
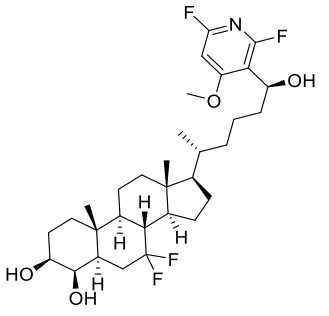
		
218	 or 	0.141
220	 or 	0.040

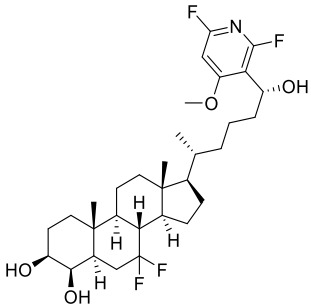
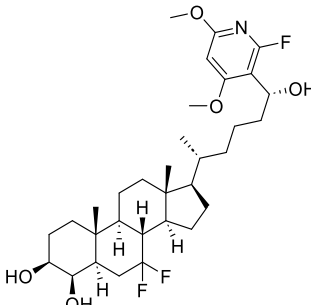
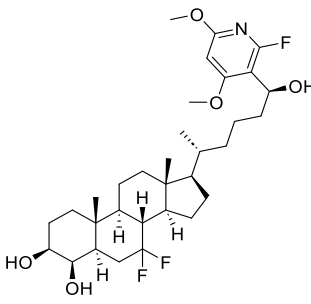
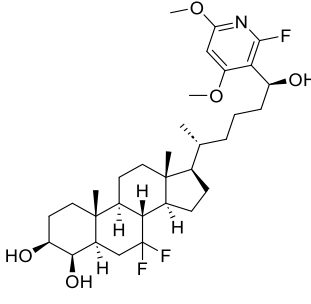
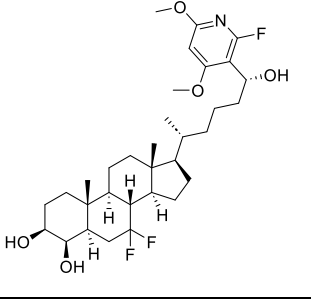
221	 or 	0.183
222	 or 	0.137
223		0.093

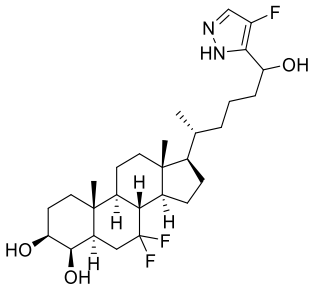
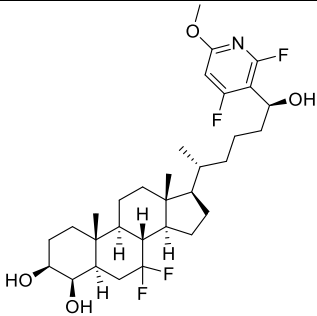
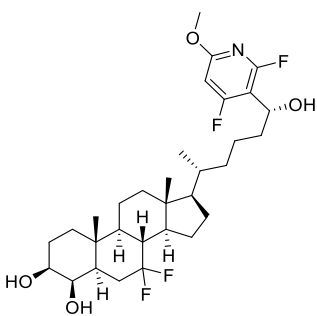
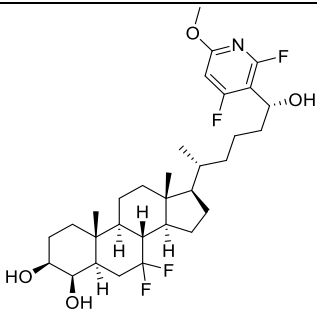
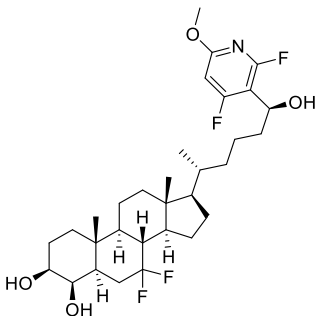
224	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H]([C@@H]([C@H](C4)F)F)O)O[C@H]3CC[C@H]([C@H]2C)CC[C@H]17Cc1c[nH]c2ccccc12</chem>	0.055
225	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H]([C@@H]([C@H](C4)F)F)O)O[C@H]3CC[C@H]([C@H]2C)CC[C@H]17Cc1cc(OC)c(F)c(OC)c1</chem> or  <chem>CC12CCC3C(C1CC[C@H]4[C@@H]([C@@H]([C@H](C4)F)F)O)O[C@H]3CC[C@H]([C@H]2C)CC[C@H]17Cc1cc(OC)c(F)c(OC)c1</chem>	0.175
226	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H]([C@@H]([C@H](C4)F)F)O)O[C@H]3CC[C@H]([C@H]2C)CC[C@H]17Cc1cc(F)c(F)cn1</chem> or  <chem>CC12CCC3C(C1CC[C@H]4[C@@H]([C@@H]([C@H](C4)F)F)O)O[C@H]3CC[C@H]([C@H]2C)CC[C@H]17Cc1cc(F)c(F)cn1</chem>	0.100

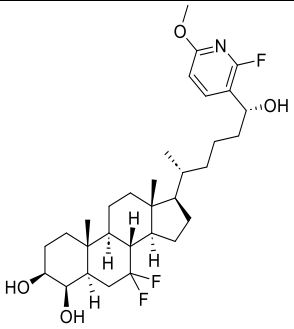
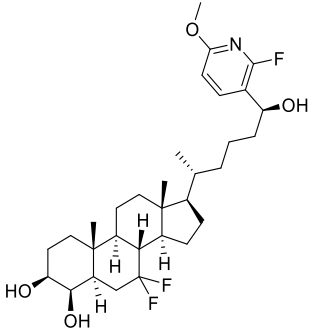
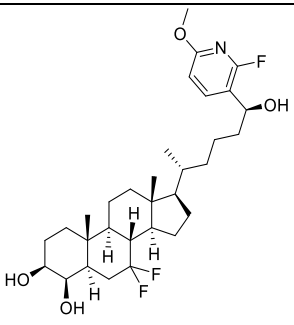
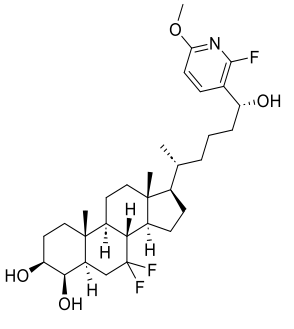
227	 or 	0.014
228	 or 	1.424
229	 or	0.049

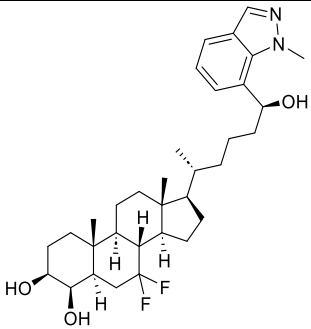
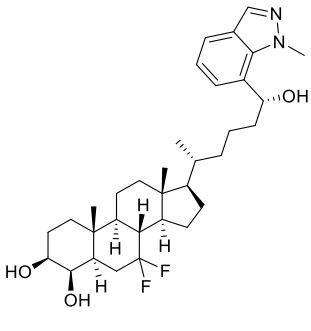
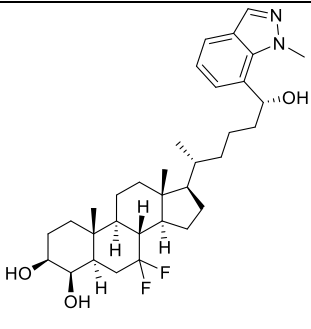
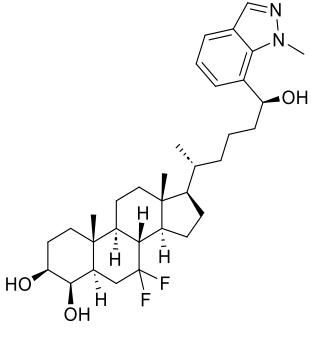
		
230	 or 	0.062
231	 or 	0.062

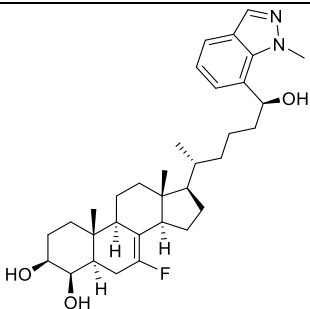
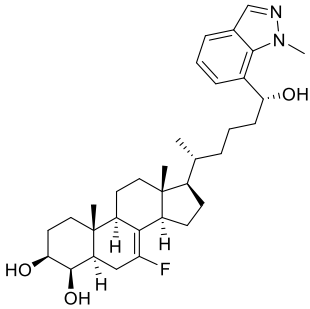
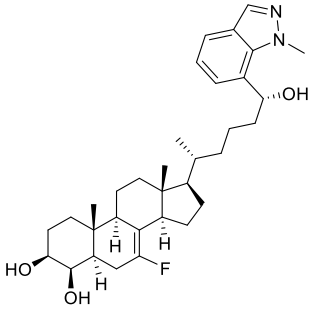
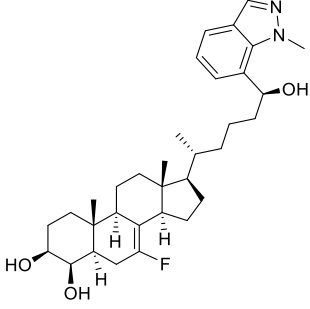
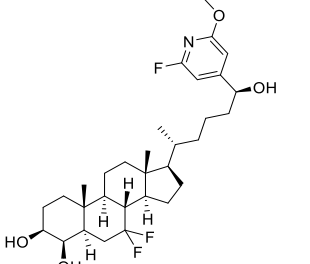
232	 or 	0.151
233	 or 	0.106
234	 or	0.029

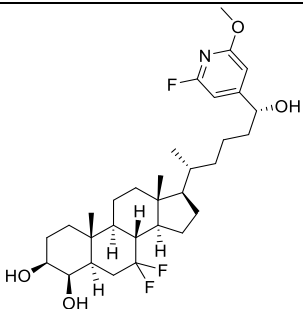
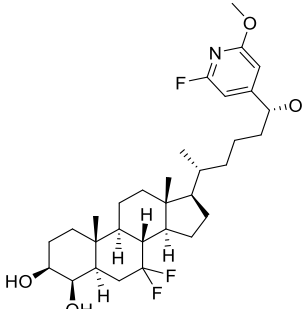
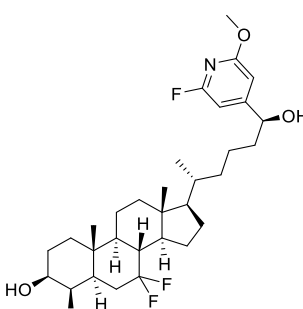
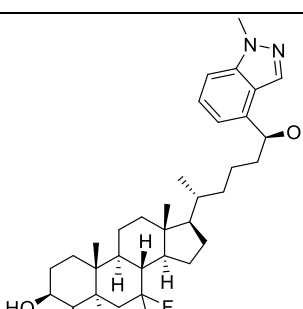
		
235	 or 	0.115
236	 or 	0.079

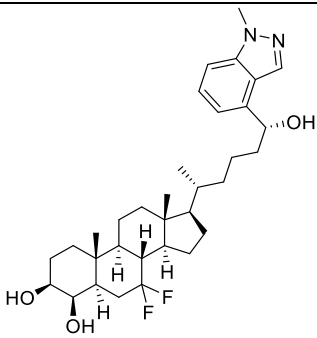
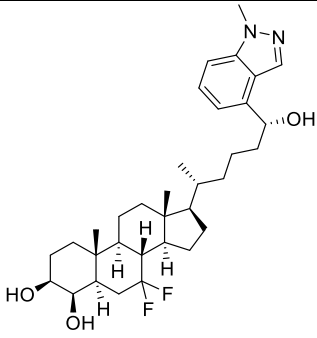
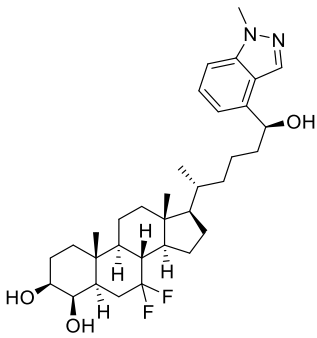
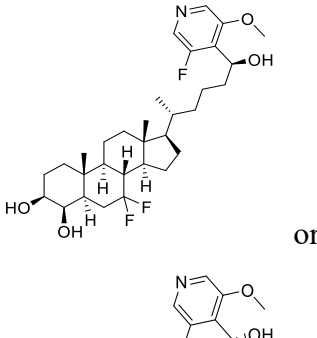
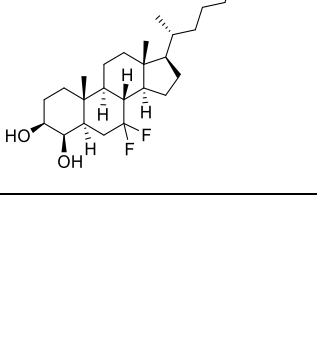
237		0.726
238	 or 	0.289
240	 or 	0.042

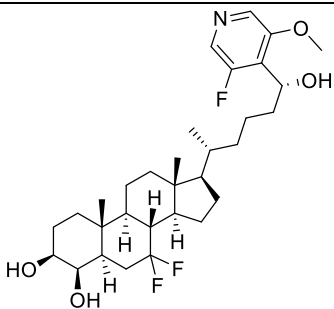
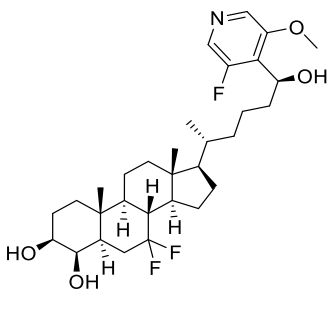
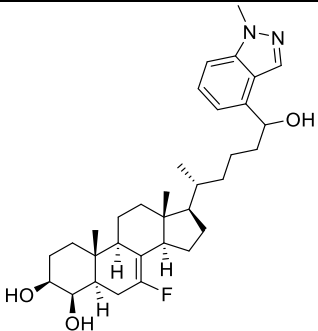
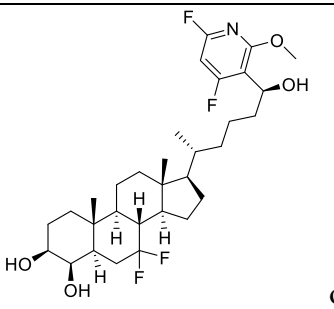
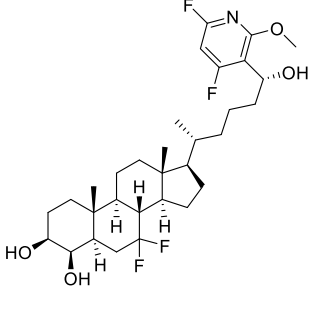
241	 	0.140
242	 or 	0.205

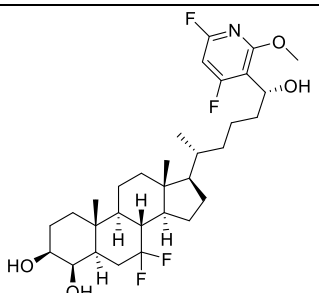
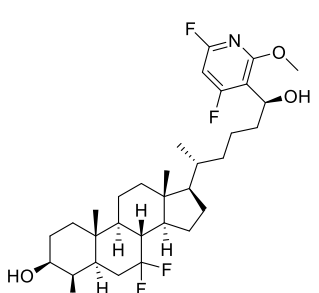
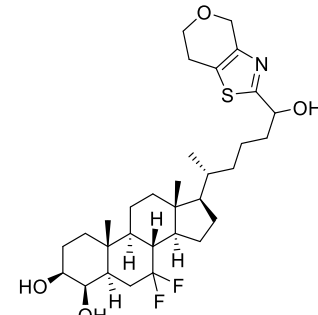
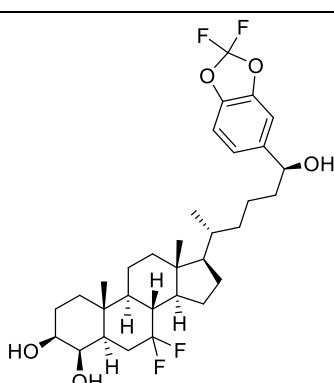
243	 or 	0.134
244	 or 	0.060

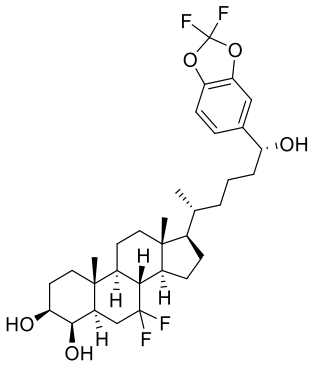
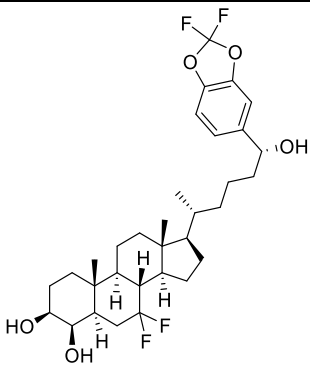
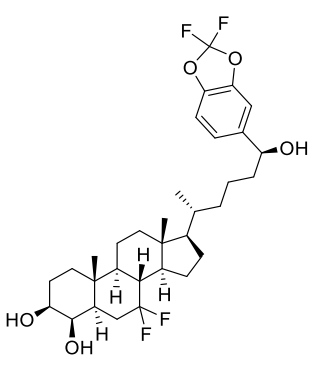
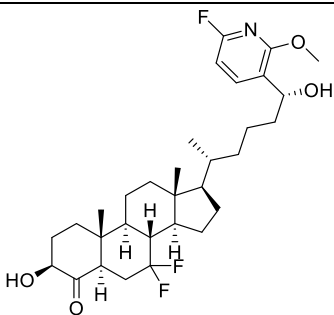
245	 or 	0.159
246	 or 	0.139
247	 or	0.040

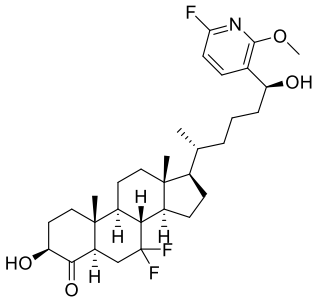
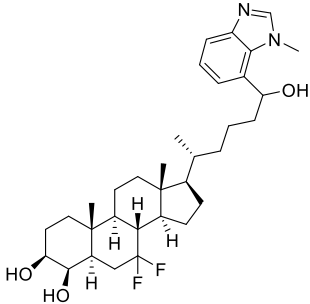
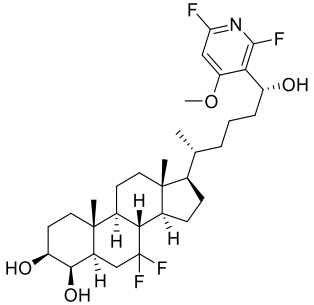
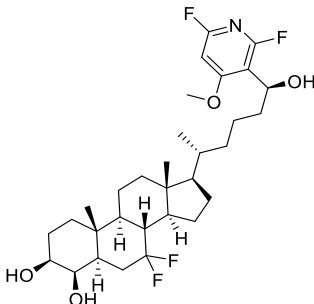
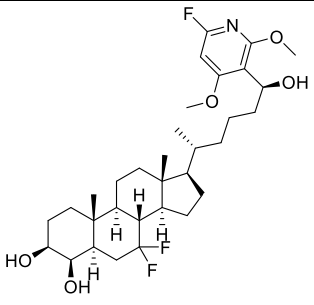
		
248	 or 	0.035
249	 or	0.058

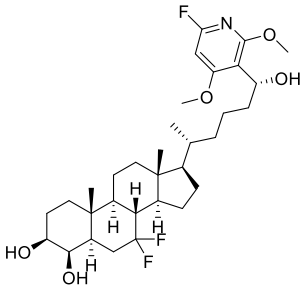
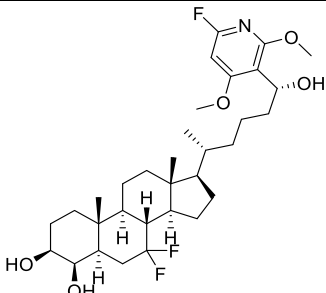
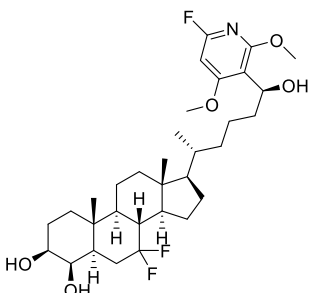
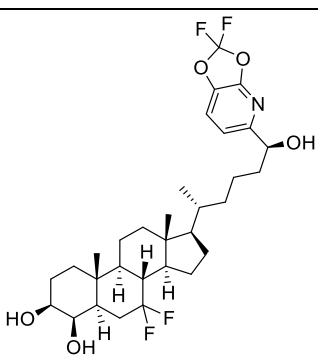
		
250	 or 	0.066
251	 or 	0.042

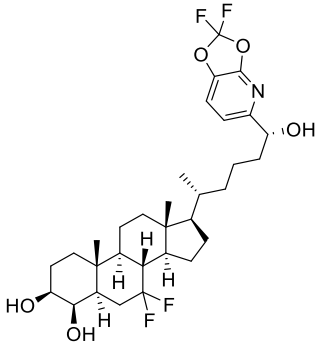
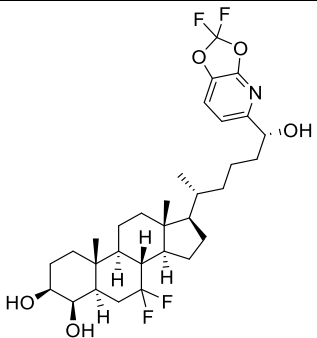
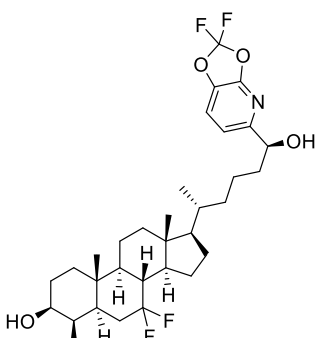
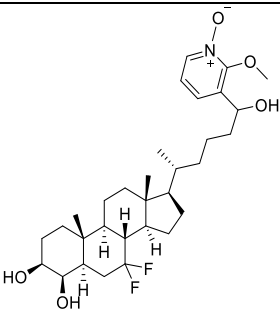
252	 or 	0.031
253		0.016
255	 or 	0.107

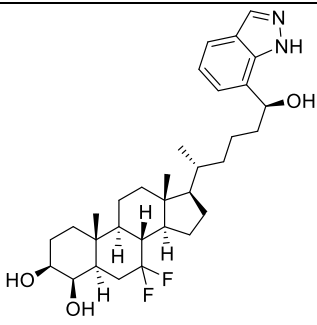
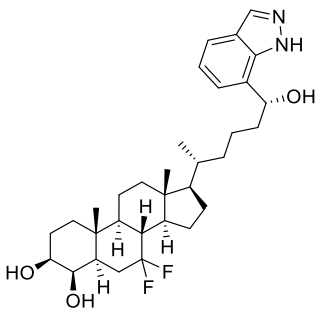
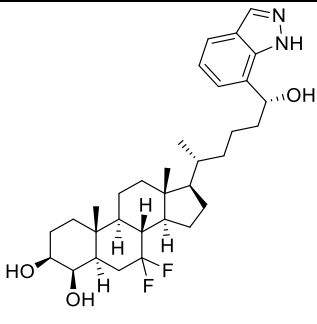
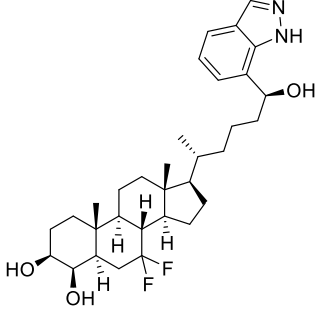
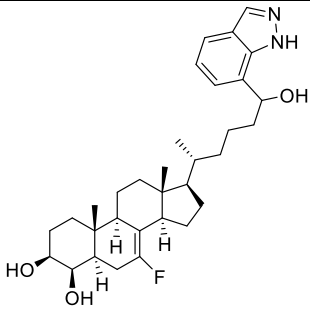
256	 or 	0.099
257		0.154
258	 or 	0.454

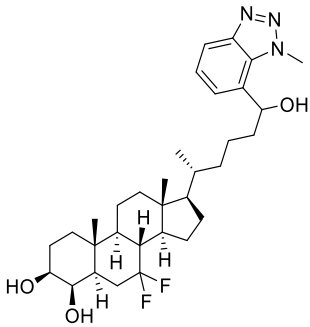
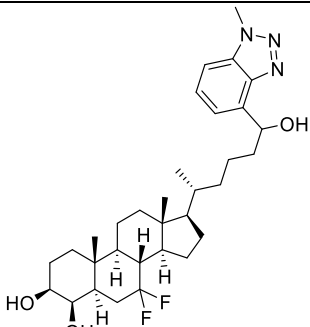
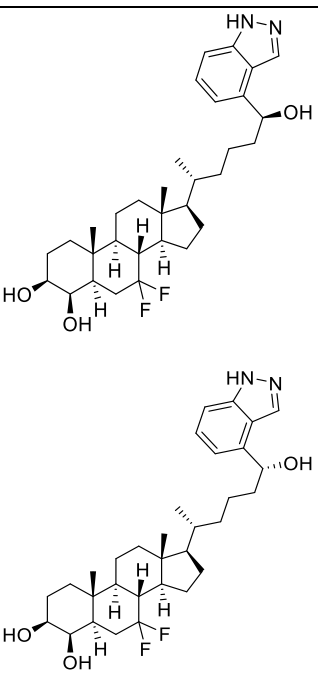
		
259	 or 	0.249
260	 or	0.030

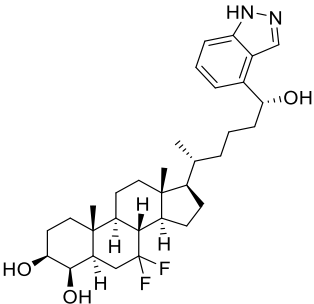
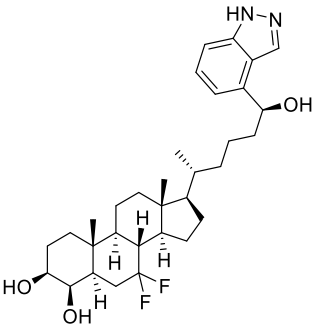
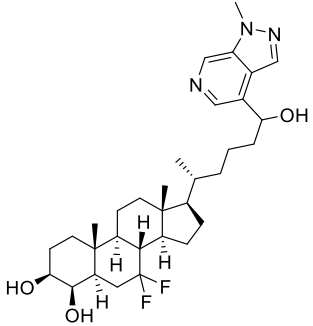
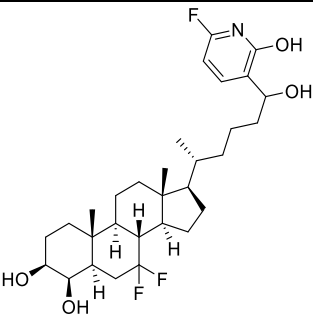
		
261		0.001
262	 or 	0.017
263	 or	0.032

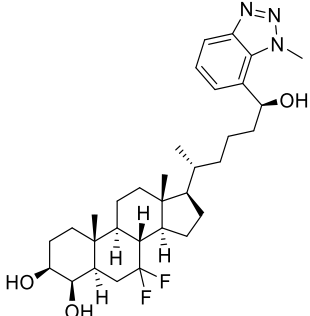
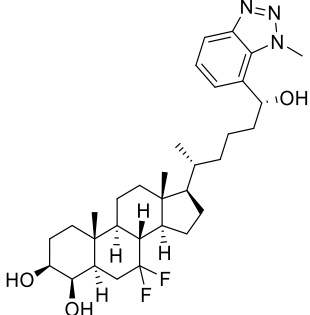
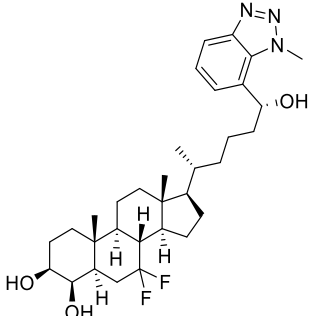
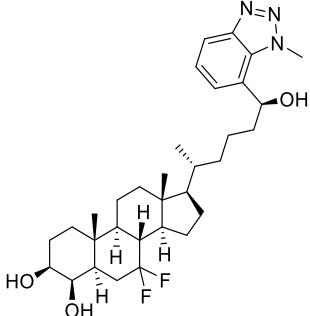
		
264	 or 	0.189
265	 or	0.006

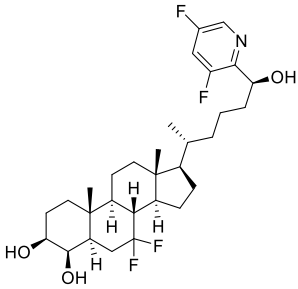
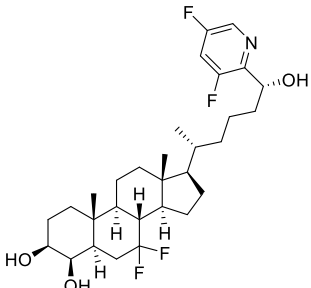
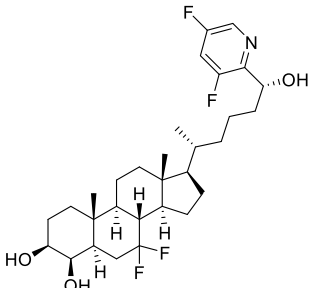
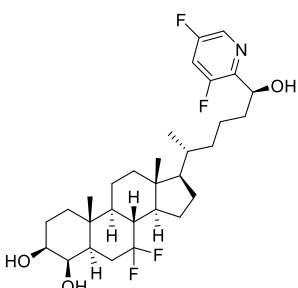
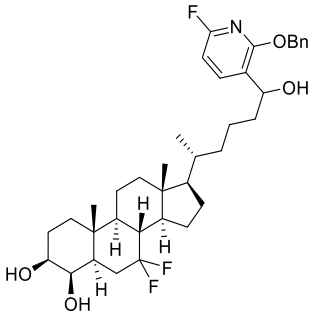
		
266	 or 	0.099
267		0.424

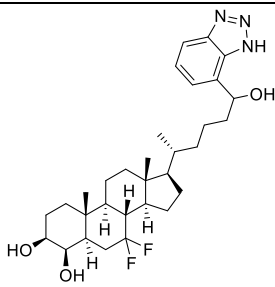
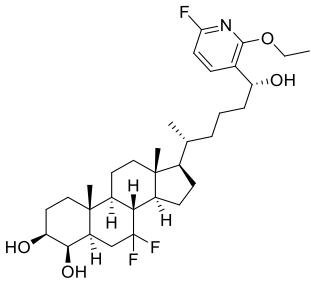
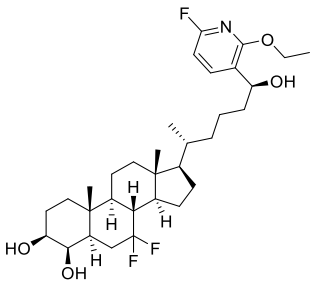
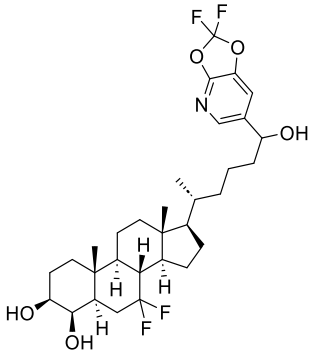
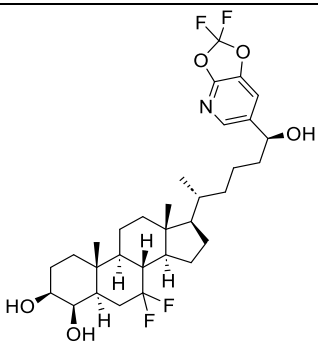
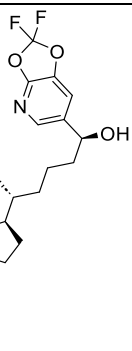
268	 or 	0.141
269	 or 	0.800
270		0.259

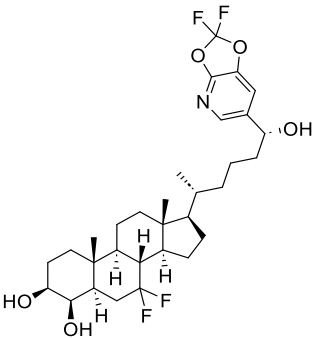
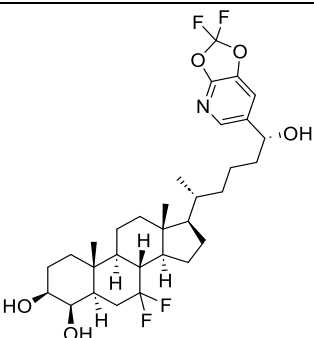
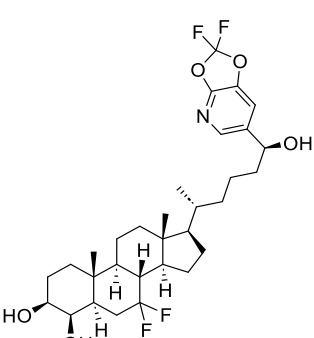
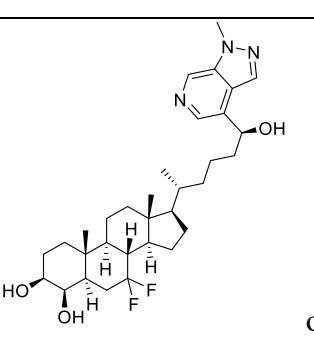
271	 The structure shows a steroid nucleus with a 1,2,3-triazole ring attached to the side chain at C-17. The triazole ring has a methyl group at the 4-position and a hydroxyl group at the 5-position. The steroid has hydroxyl groups at C-3 and C-14, and fluorine atoms at C-20 and C-21.	0.207
272	 The structure shows a steroid nucleus with a 1,2,3,4-tetrazole ring attached to the side chain at C-17. The tetrazole ring has a methyl group at the 5-position and a hydroxyl group at the 6-position. The steroid has hydroxyl groups at C-3 and C-14, and fluorine atoms at C-20 and C-21.	0.116
273	 The structure shows a steroid nucleus with a 1,2,3,4-tetrazole ring attached to the side chain at C-17. The tetrazole ring has a hydroxyl group at the 5-position. The steroid has hydroxyl groups at C-3 and C-14, and fluorine atoms at C-20 and C-21. The structure is shown in two enantiomeric forms, separated by the word "or".	0.361

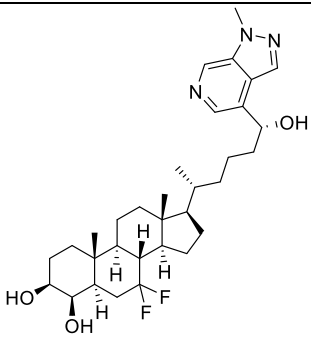
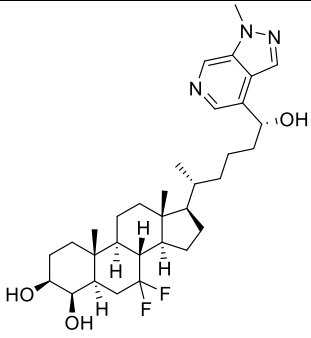
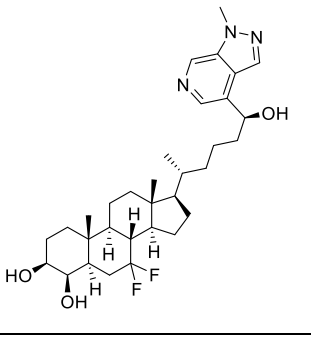
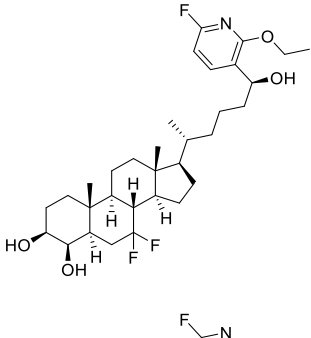
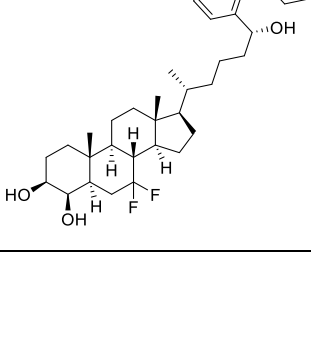
274	 or 	0.758
275		0.260
276		0.925

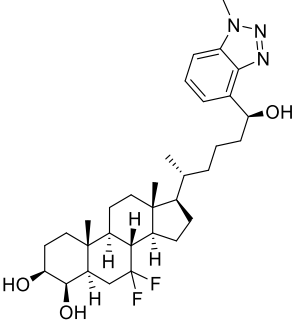
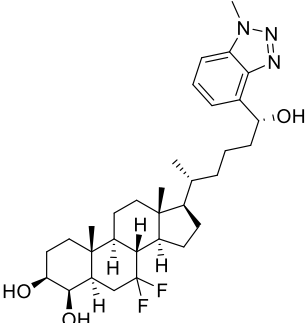
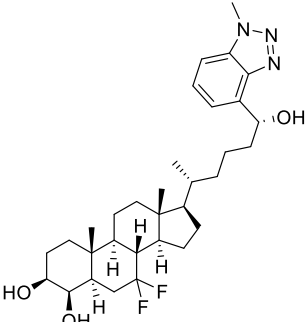
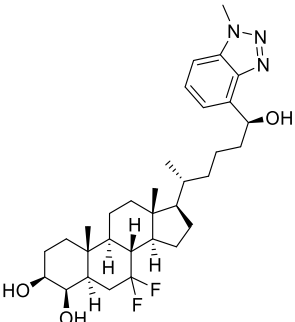
277	 or 	0.369
278	 or 	0.189

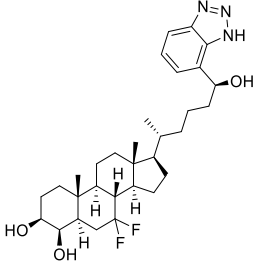
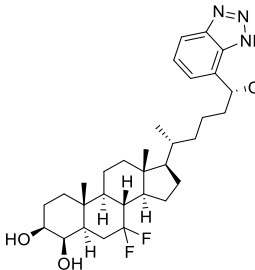
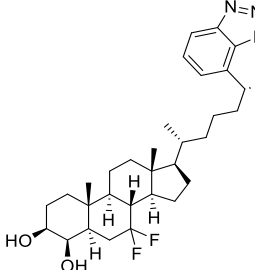
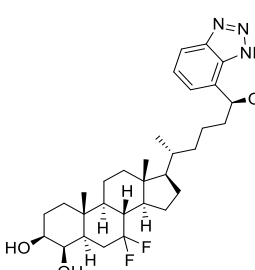
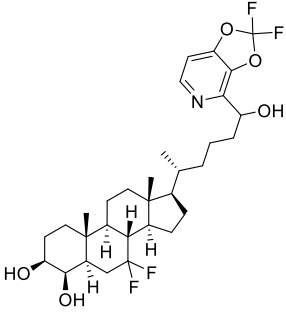
279	 or 	0.202
280	 or 	0.238
281		0.479

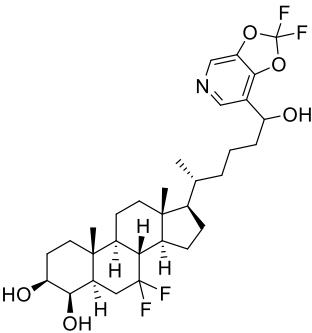
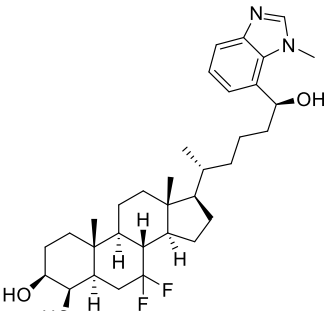
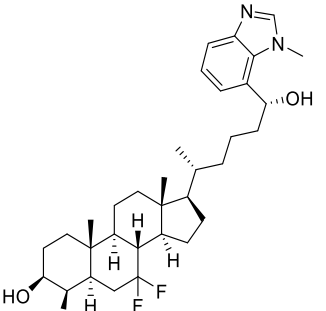
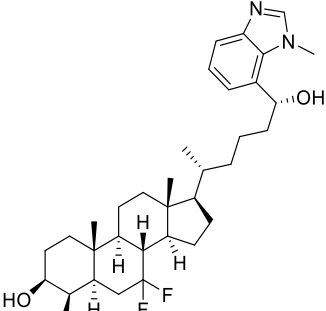
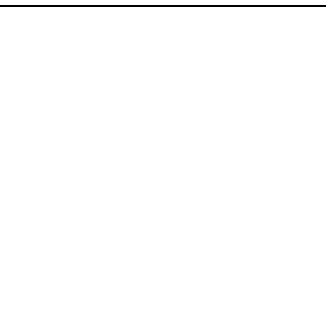
282	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)C[C@@H](C3)C(F)(F)C[C@H]4O)CC[C@H](C5=CC=C(C=C5)N=[N+]N)CO</chem>	0.389
283	 or  <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)C[C@@H](C3)C(F)(F)C[C@H]4O)CC[C@H](C5=CC=C(C=C5)F)OC</chem>	0.027
284	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)C[C@@H](C3)C(F)(F)C[C@H]4O)CC[C@H](C5=CC(=C(C=C5)OC(F)F)O)CO</chem>	0.309
285	 or  <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)C[C@@H](C3)C(F)(F)C[C@H]4O)CC[C@H](C5=CC(=C(C=C5)OC(F)F)O)CO</chem>	0.253

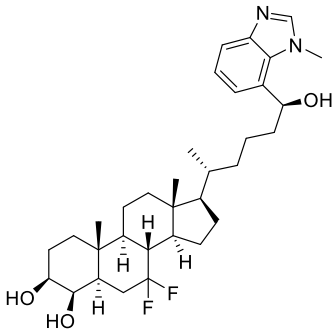
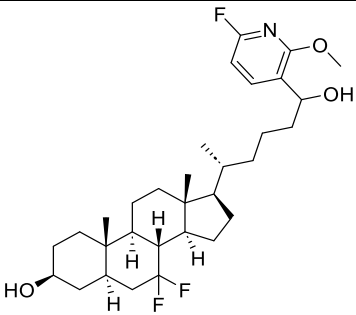
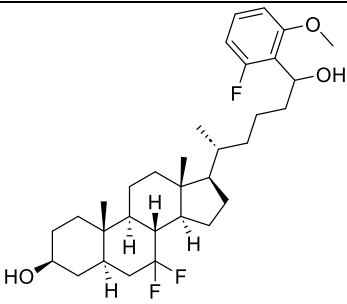
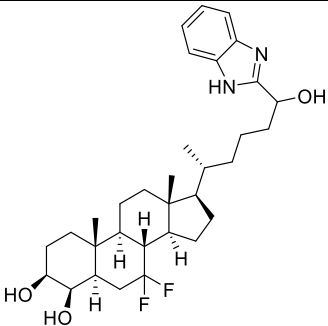
	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)CC[C@H](C4)C(F)(F)C)CC[C@H](C3)CC[C@H](C)CC[C@H](C)C1=CC=C2C(=C1)OC(F)(F)O</chem>	
286	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)CC[C@H](C4)C(F)(F)C)CC[C@H](C3)CC[C@H](C)CC[C@H](C)C1=CC=C2C(=C1)OC(F)(F)O</chem> or  <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)CC[C@H](C4)C(F)(F)C)CC[C@H](C3)CC[C@H](C)CC[C@H](C)C1=CC=C2C(=C1)OC(F)(F)O</chem>	0.260
287	 <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)CC[C@H](C4)C(F)(F)C)CC[C@H](C3)CC[C@H](C)CC[C@H](C)C1=CC=C2C(=C1)OC(F)(F)O</chem> or  <chem>CC12CCC3C(C1CC[C@H]4[C@@H](C2)CC[C@H](C4)C(F)(F)C)CC[C@H](C3)CC[C@H](C)CC[C@H](C)C1=CC=C2C(=C1)OC(F)(F)O</chem>	0.131

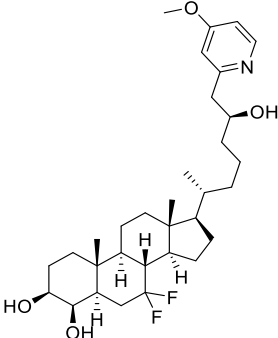
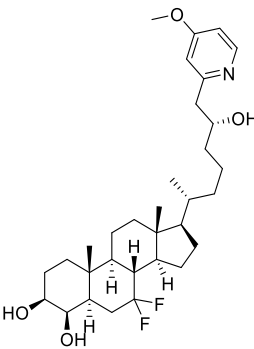
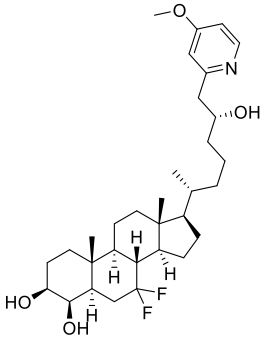
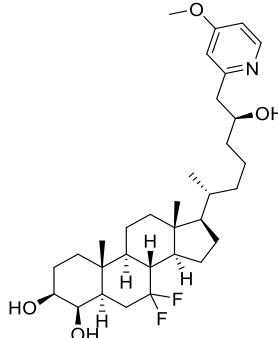
		
288	 or 	0.388
289	 or 	0.342

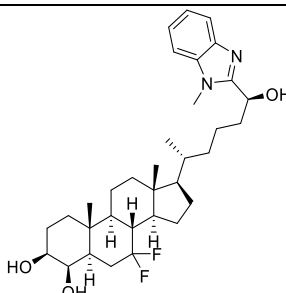
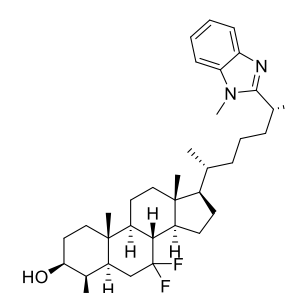
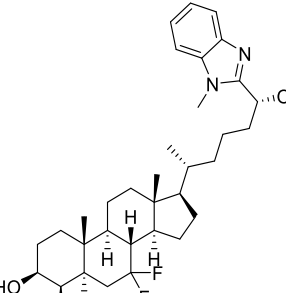
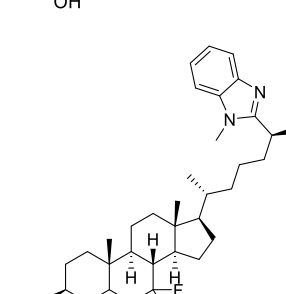
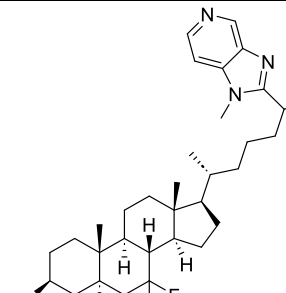
290	 or 	0.137
291	 or 	0.141

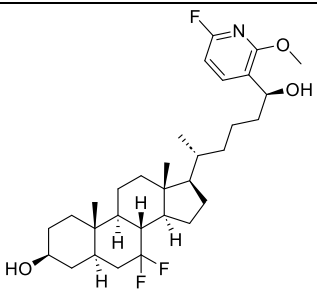
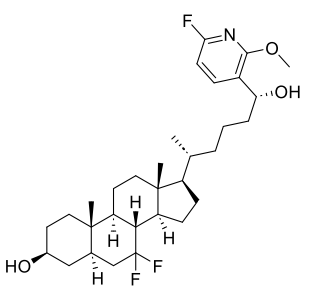
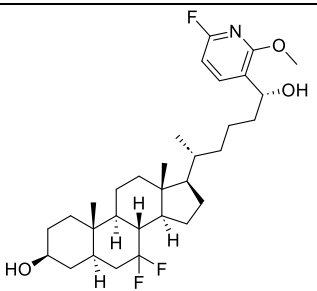
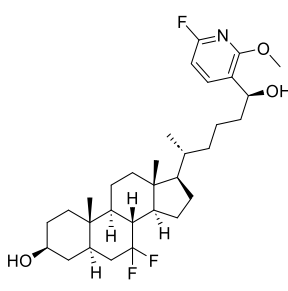
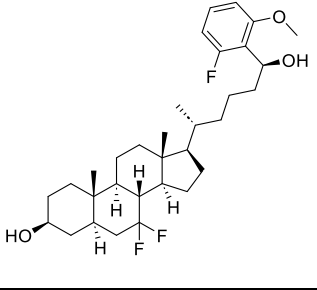
294	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-14, and fluorine atoms at C-6 and C-10. At C-17, there is a side chain with a methyl group at C-18 and a 1H-benzotriazol-4-yl group at C-19. The stereochemistry at C-13 is (1R,2R,3R,4R,5R,6R,10R,13R,14R,17R). or  Chemical structure of a steroid derivative, similar to the one above, but with a different stereochemistry at C-13 (1R,2R,3R,4R,5R,6R,10R,13S,14R,17R).	0.424
295	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-14, and fluorine atoms at C-6 and C-10. At C-17, there is a side chain with a methyl group at C-18 and a 1H-benzotriazol-4-yl group at C-19. The stereochemistry at C-13 is (1R,2R,3R,4R,5R,6R,10R,13R,14R,17R). or  Chemical structure of a steroid derivative, similar to the one above, but with a different stereochemistry at C-13 (1R,2R,3R,4R,5R,6R,10R,13S,14R,17R).	0.275
296	 Chemical structure of a steroid derivative. The steroid core has hydroxyl groups at C-3 and C-14, and fluorine atoms at C-6 and C-10. At C-17, there is a side chain with a methyl group at C-18 and a 2,2,2-trifluoro-1H-benzotriazol-4-yl group at C-19. The stereochemistry at C-13 is (1R,2R,3R,4R,5R,6R,10R,13R,14R,17R).	0.226

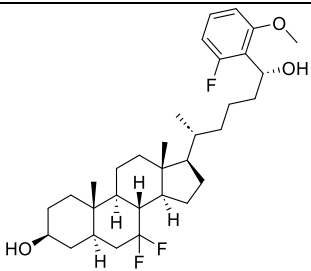
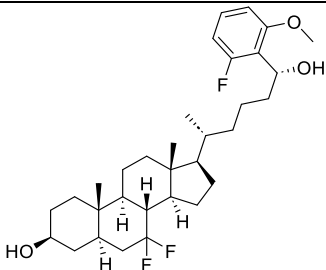
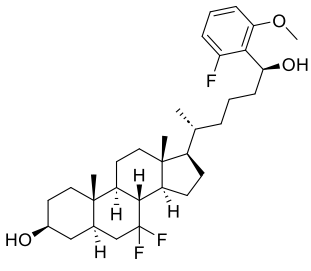
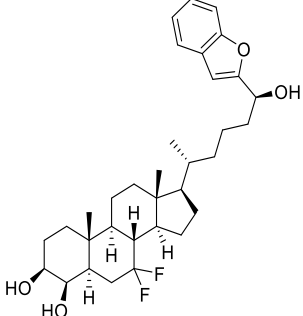
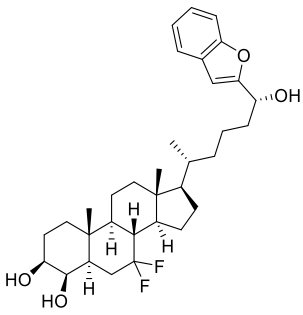
297		0.197
298	 or 	0.093
299	 or 	0.033

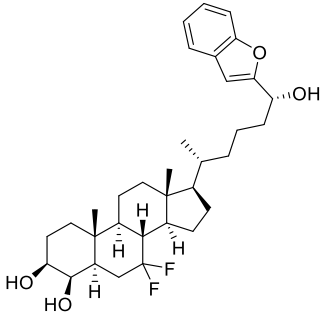
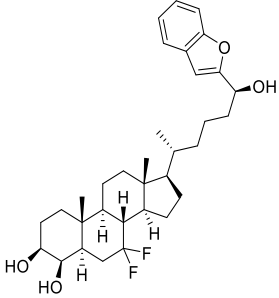
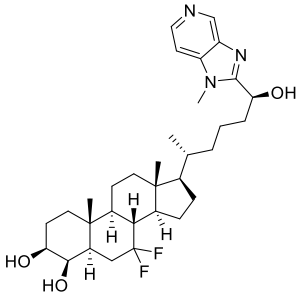
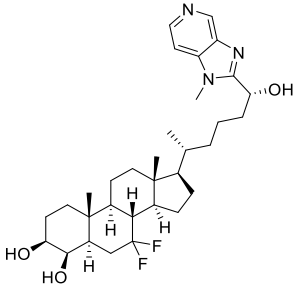
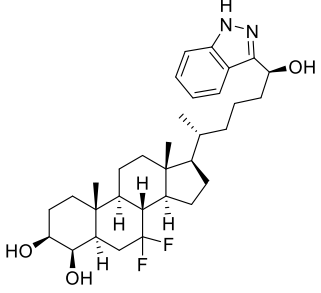
		
301		0.076
302		0.085
303		0.109

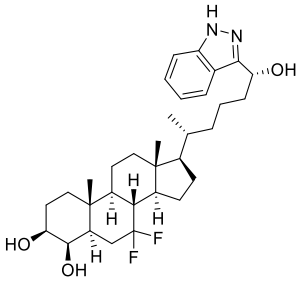
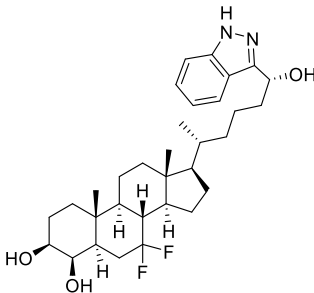
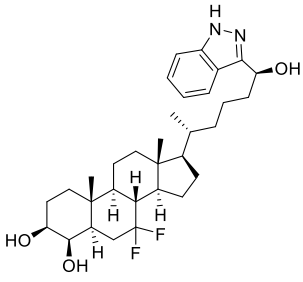
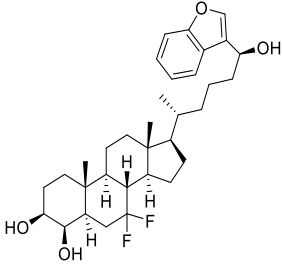
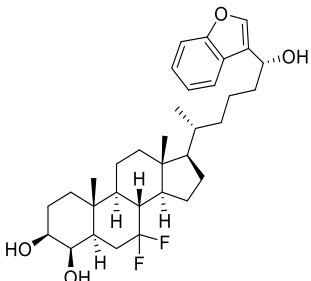
304	 or 	0.243
305	 or 	0.253

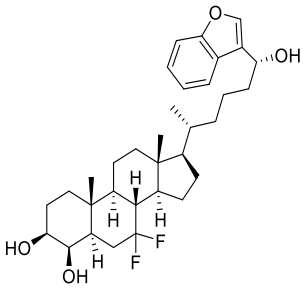
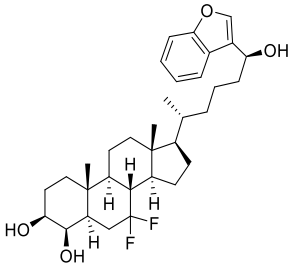
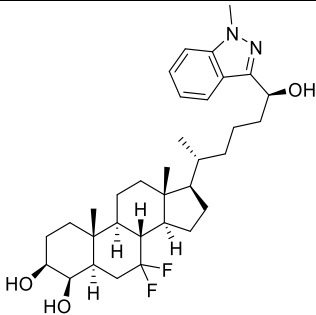
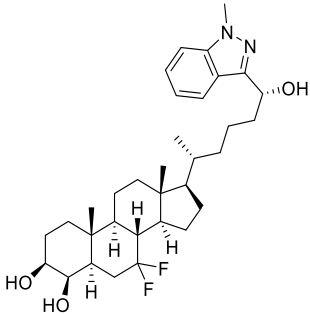
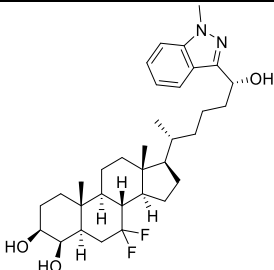
306	 or 	0.121
307	 or 	0.054
311		0.072

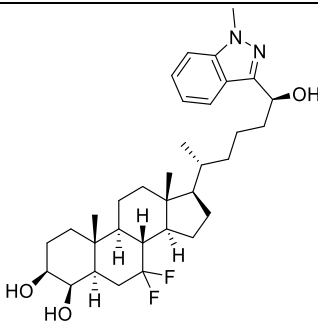
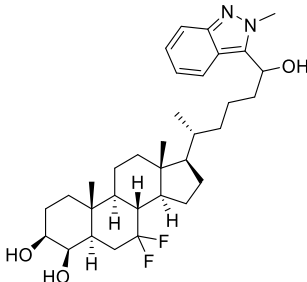
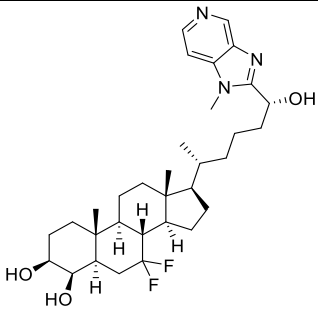
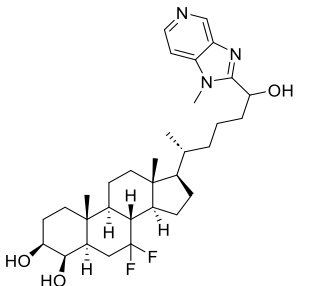
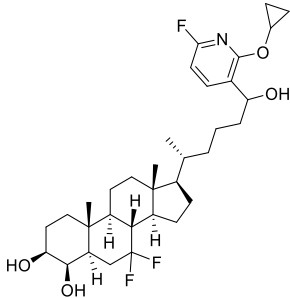
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313	 or 	0.076
314	 or 	0.140

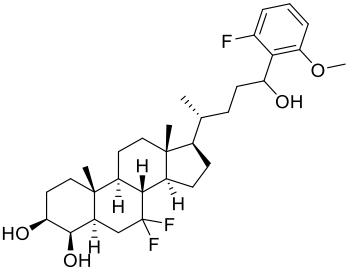
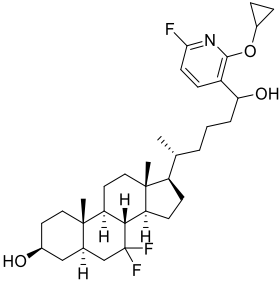
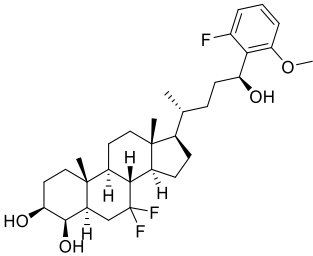
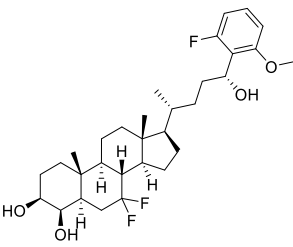
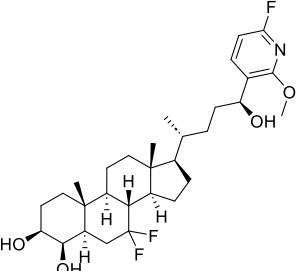
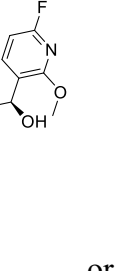
		
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316	 or 	0.145

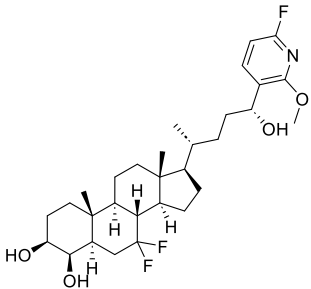
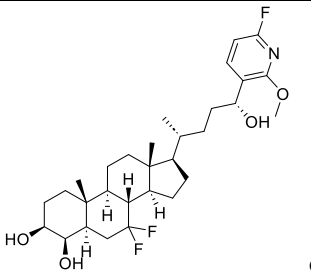
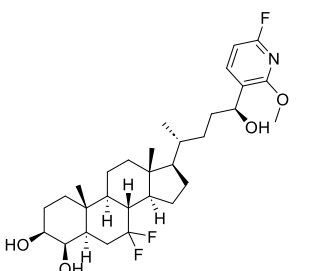
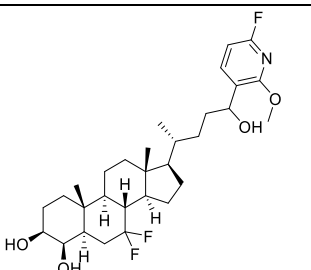
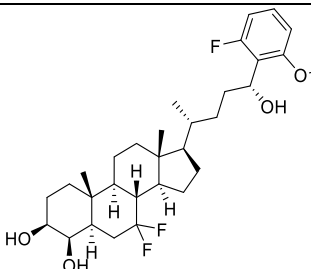
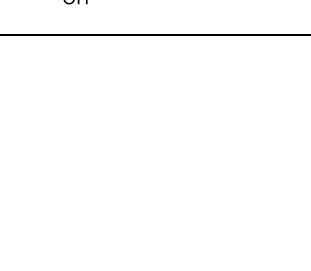
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319	 or 	0.104

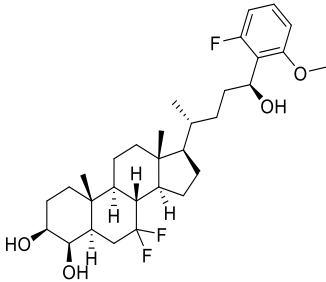
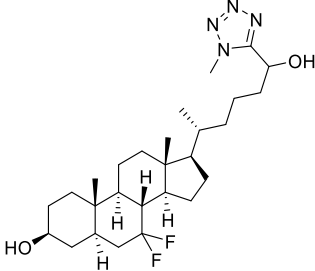
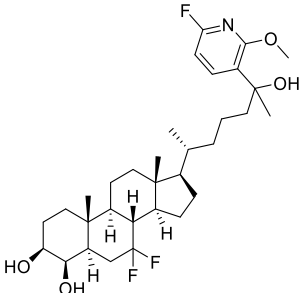
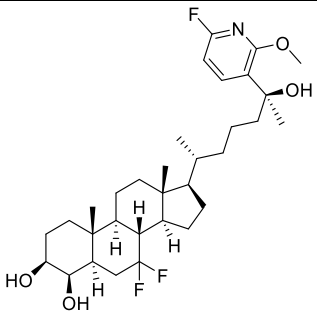
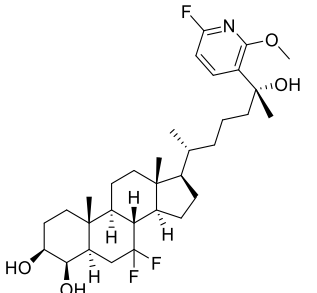
		
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321	 or 	0.114

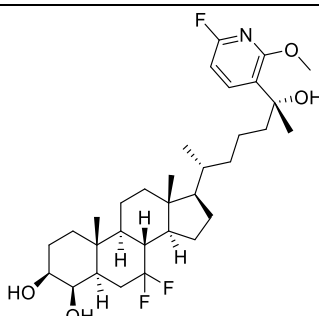
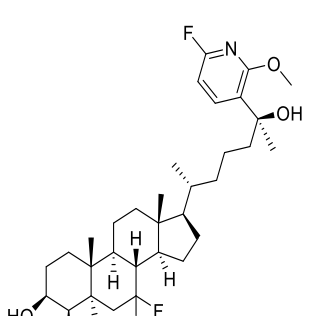
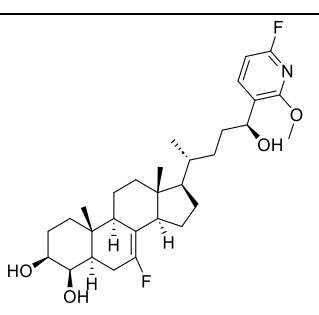
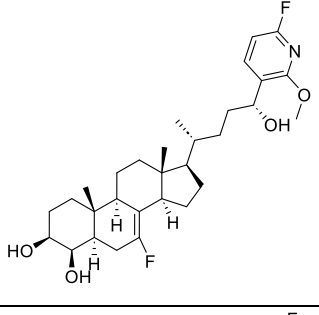
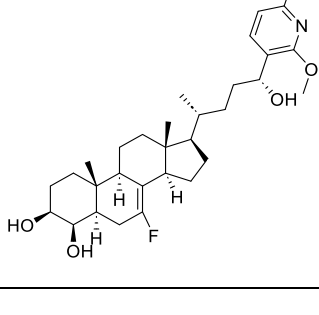
322	 Chemical structure of a steroid derivative. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. The side chain is a 6,7-epoxy side chain. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. or  Chemical structure of a steroid derivative. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. The side chain is a 6,7-epoxy side chain. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13.	0.339
323	 Chemical structure of a steroid derivative. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. The side chain is a 6,7-epoxy side chain. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. or  Chemical structure of a steroid derivative. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. The side chain is a 6,7-epoxy side chain. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13.	0.262
324	 Chemical structure of a steroid derivative. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. The side chain is a 6,7-epoxy side chain. The steroid core has a 6,7-epoxy side chain at C-13, a 19-fluoro group at C-13, and a 19-fluoro group at C-13. or	1.507

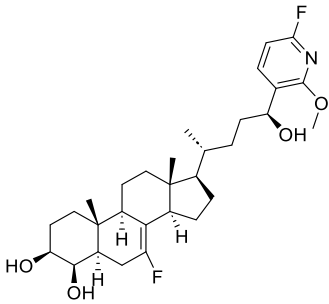
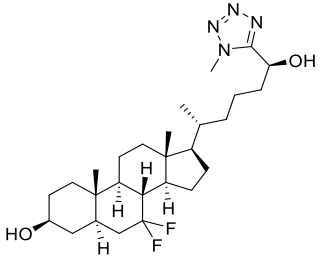
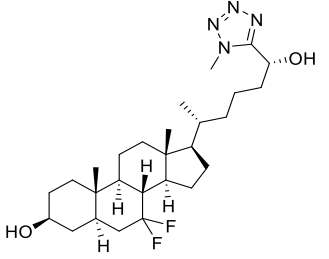
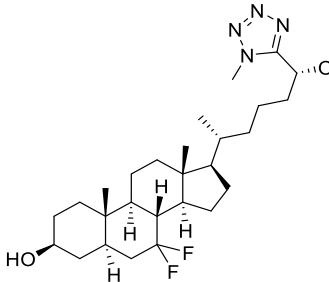
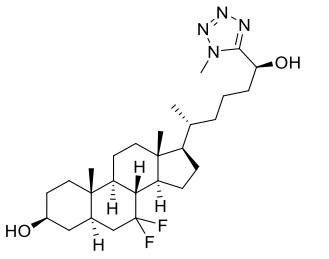
		
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326	 or 	0.011
328		0.043

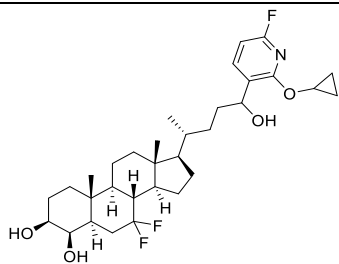
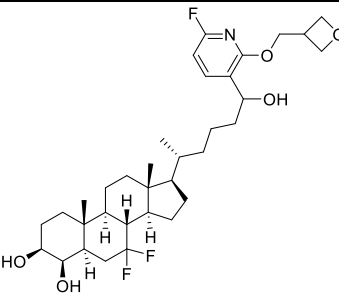
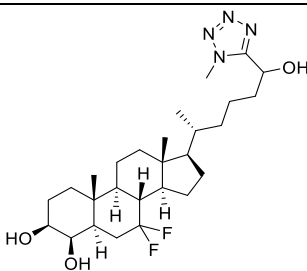
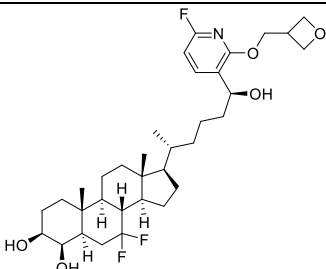
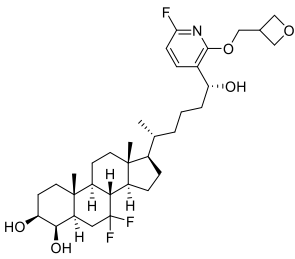
333		0.118
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336	 or 	0.31
337	 or 	0.155

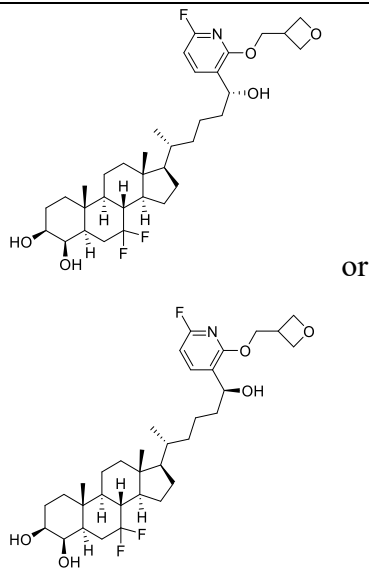
		
338	 or 	0.143
341		0.206
346	 or 	0.056

		
373		0.078
308		0.112
309	 or 	0.143

310	 or 	0.209
339	 or 	0.143
340	 or 	0.108

		
380	 or 	0.152
381	 or 	0.285

382		0.057
383		0.041
384		0.185
385	 or 	0.332

386		0.026
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[0797] Effect Example 2: Metabolic stability experiment of mouse liver microsomes

[0798] PB solution (100 mM), MgCl_2 solution (300 mM), NADPH solution (2.04 mM), and mouse liver microsome (SHQY catalog number: M1000, batch number: 2110330) solution (1.00 mg/mL) were prepared respectively. Stock solutions of the compounds and testosterone (positive control, half-life of 3.1 minutes) were prepared with dimethyl sulfoxide (DMSO) respectively and diluted to 100 μM with methanol for sample incubation, stored at -10 to -30°C . Then, 100 μL of mouse liver microsome solution was added to a 96-well sample plate. For the 0 min sample, acetonitrile solution containing the internal standard was first added; then, 2 μL of 100 μM working solution was added; followed by the addition of 98 μL of pre-warmed 2.04 mM NADPH at 37°C . For the 5 min, 15 min, 30 min, 45 min, and 60 min samples, 2 μL of 100 μM working solution was first added; followed by the addition of 98 μL of pre-warmed 2.04 mM NADPH at 37°C to initiate the reaction; upon reaching the respective time points, a solution of acetonitrile containing the internal standard was added to terminate the reaction. For the NCF60 sample, 2 μL of 100 μM working solution was first added; followed by the addition of 98 μL of pre-warmed PB at 37°C to initiate the reaction; upon reaching the respective time points, a solution of acetonitrile

containing the internal standard was added to terminate the reaction. During the experiment, all samples were incubated in a 37°C water bath. All samples were shaken on an oscillator at 800 rpm for 10 min, then centrifuged at 3200 g for 20 min. The supernatant was aspirated, diluted with deionized water at the corresponding ratio, and analyzed by LC-MS/MS. The remaining percentage of the compound at each time point was obtained by dividing the peak area ratio of the compound at 5, 15, 30, 45, and 60 min by the peak area ratio at 0 min. The half-life (T_{1/2}) of the compound was then calculated using Excel.

[0799] Table 2: Mouse liver microsome stability results of compounds from some examples

Example	Mouse liver microsomal half-life (minutes)
Comparative compound 1	7.85
1	167
7	37.43
8	39.21
11	49.12
20	29.86
21	161.39
28	> 184.78
35	> 186
36	> 186
37	131.65
38	12.18
39	117
44	> 186
46	155.87
49	112.74
50	107.96
63	> 184.78

64	69.67
70	34.86
71	63.3
77	> 184.78
81	114.69
84	> 184.78
97	106.96
98	250
108	184.78
126	107.65
72	82.8
87	135.87
127	112.10
128	> 186
134	27.26
136	96.24
140	321
141	291

[0800] Effect Example 3: Testing the solubility of the compounds of the present disclosure in fasted-state simulated intestinal fluid (FaSSIF)

[0801] Compound powder was dissolved in DMSO to prepare a 10.0 mM stock solution for later use. 0.021 g NaOH, 0.198 g NaH₂PO₄, and 0.309 g NaCl were weighed and added to 50.0 mL of ultrapure water. After thorough mixing, the pH was adjusted to 6.5 using HCl or NaOH. Then, 0.112 g of FaSSIF powder was added. After complete dissolution, the solution was allowed to stand at room temperature for 2 hours for later use. A certain volume of the compound stock solution was added to a certain volume of FaSSIF to prepare a 300 μ M sample solution, which was mixed at room temperature under 1000 rpm for 1 hour. After 1 hour, the sample was centrifuged, and a certain volume of supernatant was

taken. The termination solution was added to precipitate the sample, which was then thoroughly mixed and centrifuged for 20 minutes. The supernatant was then taken again, diluted with dilution solution, and then analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The concentration of the test compound in the samples was quantitatively determined using LC-MS/MS.

[0802] Table 3: FaSSIF solubility results of compounds from some examples

Example	FaSSIF solubility (μM)
Comparative compound 1	105
1	140
3	247.42
21	246.04
35	160
37	207.10
38	184.19
39	177
44	225
46	276.69
49	280.65
50	247.50
63	146.66
81	279.29
98	199
108	303.34
127	209
128	199
140	178
141	150
Comparative compound 161	18.04

165	87.38
188	138.93
189	157.08
195	244.44
197	327.8
223	305.03
236	305.47
240	145.85
249	38.65
250	32.95
234	49.29
263	62.96
265	107.36
283	287.59
298	18.21
175	279.55
224	47.99
296	69.29
297	19.53
272	225
328	262.62
333	148.01
338	34.74
337	245.75

[0803] Effect Example 4: Experiment for inhibitory effects of compounds on FASN gene expression

[0804] Huh-7 cells (purchased from ATCC) were cultured in DMEM medium (containing 10% fetal bovine serum LONSERA S711-001S) at 37°C in a 5% CO₂ incubator. After 24 hours, the original medium was aspirated and replaced with

DMEM starvation medium (containing 5% lipoprotein deficient serum (LPDS), 2 μ M lovastatin, and 10 μ M mevalonate). The control group was treated with dimethyl sulfoxide (DMSO), while the compound treatment groups were treated with different concentrations of compounds. The highest concentration of the compound was 3000 nM, with 3-fold dilutions, totaling 5 concentrations. The cells were cultured for 16 hours. Cell lysis was performed, followed by reverse transcription from cells to cDNA, and qPCR was performed to detect the expression of the SREBP target gene Fatty Acid Synthase (FASN) gene (FASN gene forward primer sequence: 5'-AAGGACCTGTCTAGGTTTGATGC-3', reverse primer sequence: 5'-TGGCTTCATAGGTGACTTCCA-3'). The IC_{50} was calculated. The test data for each test compound were analyzed using Prism software (with the DMSO-treated group as the reference to calculate the compound inhibition rate, fitted using the Prism log(inhibitor) vs. response--Variable slope (four-parameter) model, calculation formula: $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) \times \text{HillSlope}))})$), to obtain the IC_{50} parameters of the compounds.

[0805] Table 4: Inhibition results of FASN gene expression by compounds from some examples

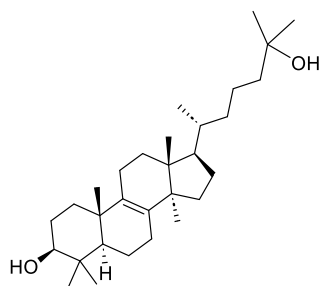
Example	FASN IC_{50} A: < 200 nM; B: 200-500 nM; C: 500-900 nM
Comparative compound 1	959 nM
37	B
7	B
11	B
28	B
35	B
49	B
54	B
63	A

64	A
67	B
68	B
69	A
70	A
71	A
72	A
75	A
77	A
81	A
82	B
83	B
84	B
87	A
89	A
92	A
95	A
97	A
98	A
100	B
101	B
102	A
104	B
105	B
107	B
108	A
113	B
127	B
128	B
140	A

141	A
Comparative compound 161	B
206	B
171	A
184	A
188	A
189	A
191	B
192	B
193	B
194	B
195	A
200	A
201	A
210	A
227	B
230	A
232	B
233	B
234	A
255	B
260	A
261	A
262	A
263	A
265	A
266	A
177	A
198	A

199	B
212	B
241	A
244	A
272	A
283	A
289	A
299	A
301	B
302	A
303	A
307	A
311	A
313	C
314	C
326	A
333	B
336	A
337	A
338	A
335	A
346	A
373	A

[0806] In the present disclosure, the structure of comparative compound 1 is



[0807] Effect Example 5: Microsomal stability

[0808] 1 μ M test compound or verapamil (positive control) was incubated with 0.5 mg/mL (mouse, rat, dog, and human) liver microsomes in 1 mM NADPH with and without cofactor. After incubation at 37°C for 0.5, 5, 15, 30, and 60 minutes, the reaction was terminated by adding an internal standard solution. All samples were centrifuged, analyzed by UPLC-MS/MS, and the remaining percentage was calculated to determine *in vitro* intrinsic clearance (CL_{int}) and half-life (T_{1/2}).
[0809] The compounds of the present disclosure exhibit good metabolic stability in mouse, rat, dog, and human liver microsomes.

[0810] Effect Example 6: Hepatocyte stability

[0811] 1 μ M test compound or verapamil (positive control) was incubated with incubation medium containing mouse, rat, dog, monkey, or human hepatocytes (0.5 $\times$ 10⁶ cells/mL). After incubation at 37°C for 0.5, 15, 30, 60, 90, and 120 minutes, the reaction was terminated by adding an internal standard solution. All samples were centrifuged to aspirate the supernatant. The samples were analyzed by UPLC-MS/MS, and the remaining percentage, intrinsic clearance (*in vitro* CL_{int}), and half-life (T_{1/2}) were calculated.
[0812] The compounds of the present disclosure exhibit good metabolic stability in mouse, rat, dog, monkey, and human hepatocytes.

[0813] Effect Example 7: CYP inhibition

[0814] A system containing 0.2 mg/mL human liver microsomes in 0.1 M phosphate buffer (pH 7.4) was used to evaluate the inhibitory potential of test compounds on cytochrome P450 enzymes 1A2, 2C9, 2C19, 2D6, and 3A4. The test compounds and specific substrates were co-incubated for different reaction times (incubation times for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4-M, and CYP3A4-T systems were 20, 5, 20, 20, 5, and 10 minutes, respectively). After incubation, an internal standard solution was immediately added to all samples to terminate the reaction. All samples were centrifuged to take the

supernatant, and the metabolites formed from specific substrates were detected by UPLC-MS/MS to calculate the half-maximal inhibitory concentration (IC₅₀) of specific substrate metabolism.

[0815] The compounds of the present disclosure exhibit weak inhibitory effects on cytochrome P450 enzymes 1A2, 2C9, 2C19, 2D6, and 3A4.

[0816] Effect Example 8: Mouse PK assay C57BL/6JL

[0817] C57BL/6J mice aged 6-8 weeks, male, 3 per group, were subjected to pharmacokinetic studies of new molecules via intravenous, gavage, intraperitoneal injection routes, *etc.* All animals were fasted before administration and fed 4 hours after administration. Whole blood samples were collected at 5 min, 15 min, 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h after administration. Plasma was obtained by centrifugation, and concentrations were detected using LC-MS/MS. Pharmacokinetic parameters were calculated using WinNonlin (PhoenixTM, version 8.3) or higher versions.

[0818] The compounds of the present disclosure exhibit low systemic clearance after intravenous administration and good oral and intraperitoneal bioavailability in mice.

[0819] Effect Example 9: Rat PK assay in Sprague Dawley rat

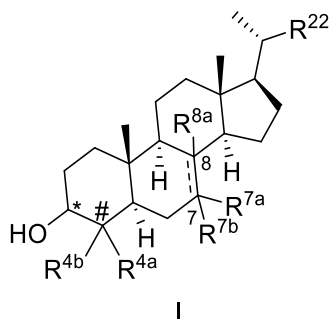
[0820] SD rats aged 6-8 weeks, male, 3 per group, were subjected to pharmacokinetic studies of new molecules via intravenous, gavage, or intraperitoneal injection routes, *etc.* All animals were fasted before administration and fed 4 hours after administration. Whole blood samples were collected at 5 min, 15 min, 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h after administration, then centrifuged to obtain plasma. Concentrations were detected by LC-MS/MS, and pharmacokinetic parameters were calculated using WinNonlin (PhoenixTM, version 8.3) or higher versions.

[0821] The compounds of the present disclosure exhibit low systemic clearance after intravenous administration and good oral and intraperitoneal bioavailability in rats.

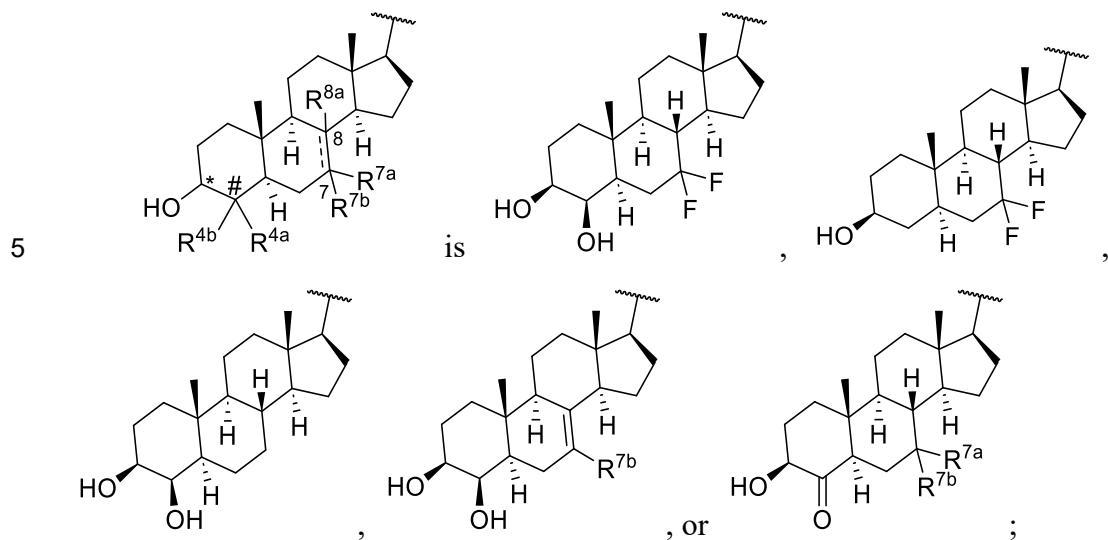
[0822] Although specific embodiments of the present disclosure have been described above, it should be understood by those skilled in the art that these are merely illustrative examples, and various modifications or changes may be made to these embodiments without departing from the principles and essence of the present disclosure. Therefore, the scope of protection of the present disclosure shall be defined by the appended claims.

CLAIMS

1. A compound of Formula I or a pharmaceutically acceptable salt thereof:

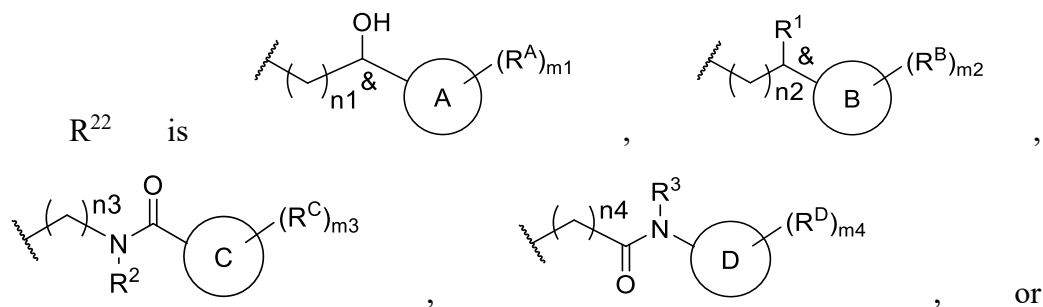


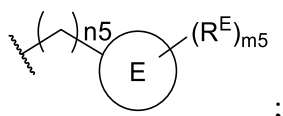
wherein



when the bond between carbon atom 7 and carbon atom 8 is a single bond,
 R^{7a} and R^{7b} are independently H or halogen;

when the bond between carbon atom 7 and carbon atom 8 is a double bond,
 10 R^{7b} is halogen;





;

$n_1, n_2, n_3, n_4,$ and n_5 are independently 2, 3, 4, or 5;

$m_1, m_2, m_3,$ and m_4 are independently 0, 1, 2, 3, 4, or 5;

- ring A, ring B, ring C, and ring D are independently C_6 - C_{10} aryl, 5- to 10-
 5 membered heteroaryl with 1, 2, or 3 heteroatoms selected from the group
 consisting of 1, 2, or 3 kinds of N, O, and S, or C_3 - C_6 cycloalkyl;

R^1 is C_1 - C_6 alkoxy, , or $NR^{1a}R^{1b}$;

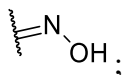
R^2 and R^3 are independently H or C_1 - C_6 alkyl;

- $R^A, R^B, R^C,$ and R^D are independently halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl,
 10 C_1 - C_6 alkoxy, or C_1 - C_6 haloalkoxy;

ring E is C_3 - C_6 cycloalkyl;

m_5 is 0, 1, 2, or 3;

R^E is independently OH, $NR^{e1}R^{e2}$, COOH, C_1 - C_6 alkyl, oxo ($=O$), or



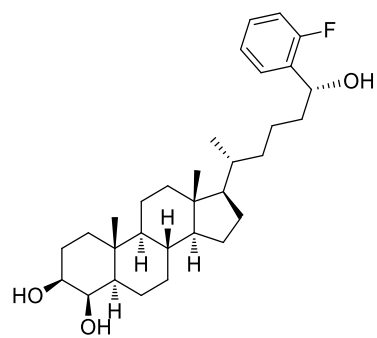
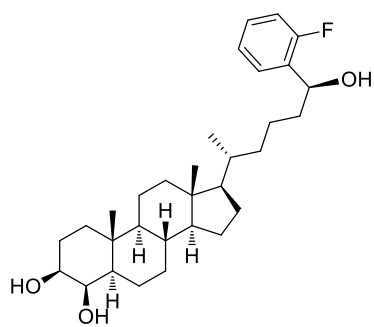
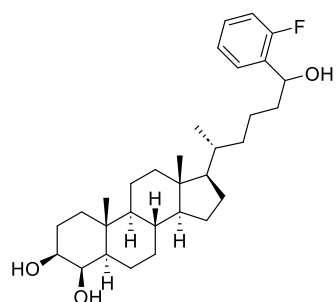
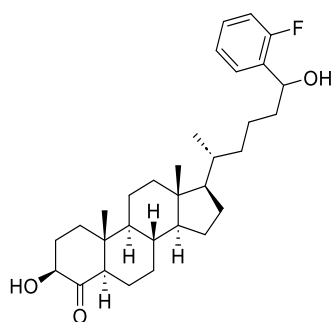
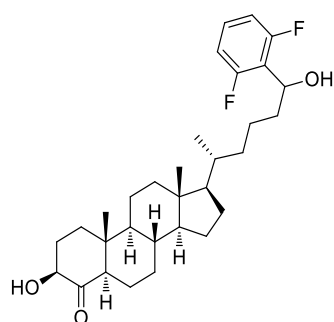
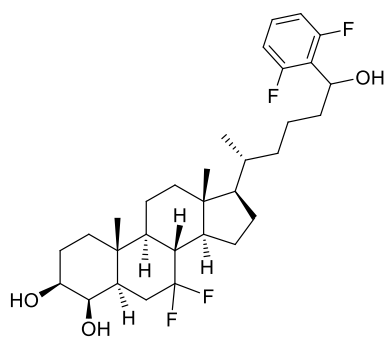
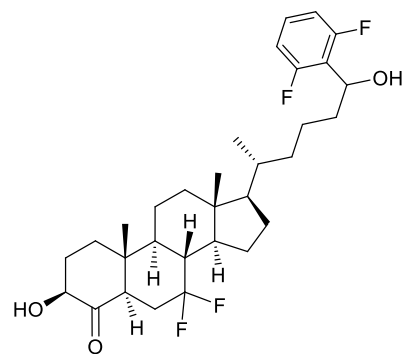
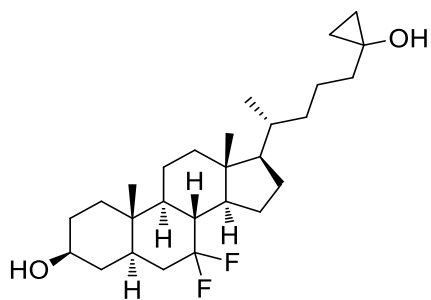
- 15 $R^{1a}, R^{1b}, R^{e1},$ and R^{e2} are independently H or C_1 - C_6 alkyl;

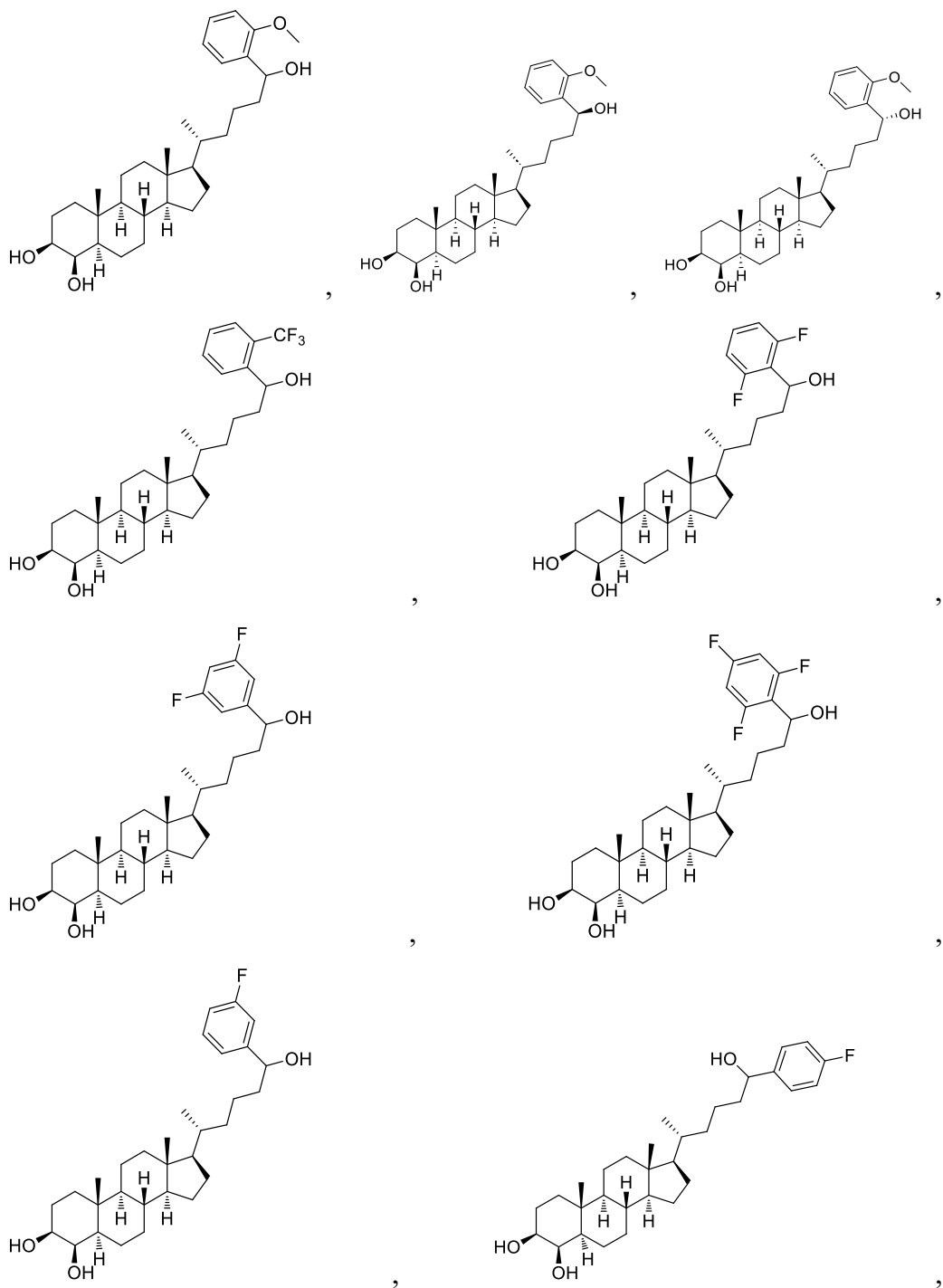
the carbon atom marked with "*" indicates that when it is a chiral carbon atom, it is in the R configuration, S configuration, or a mixture of both;

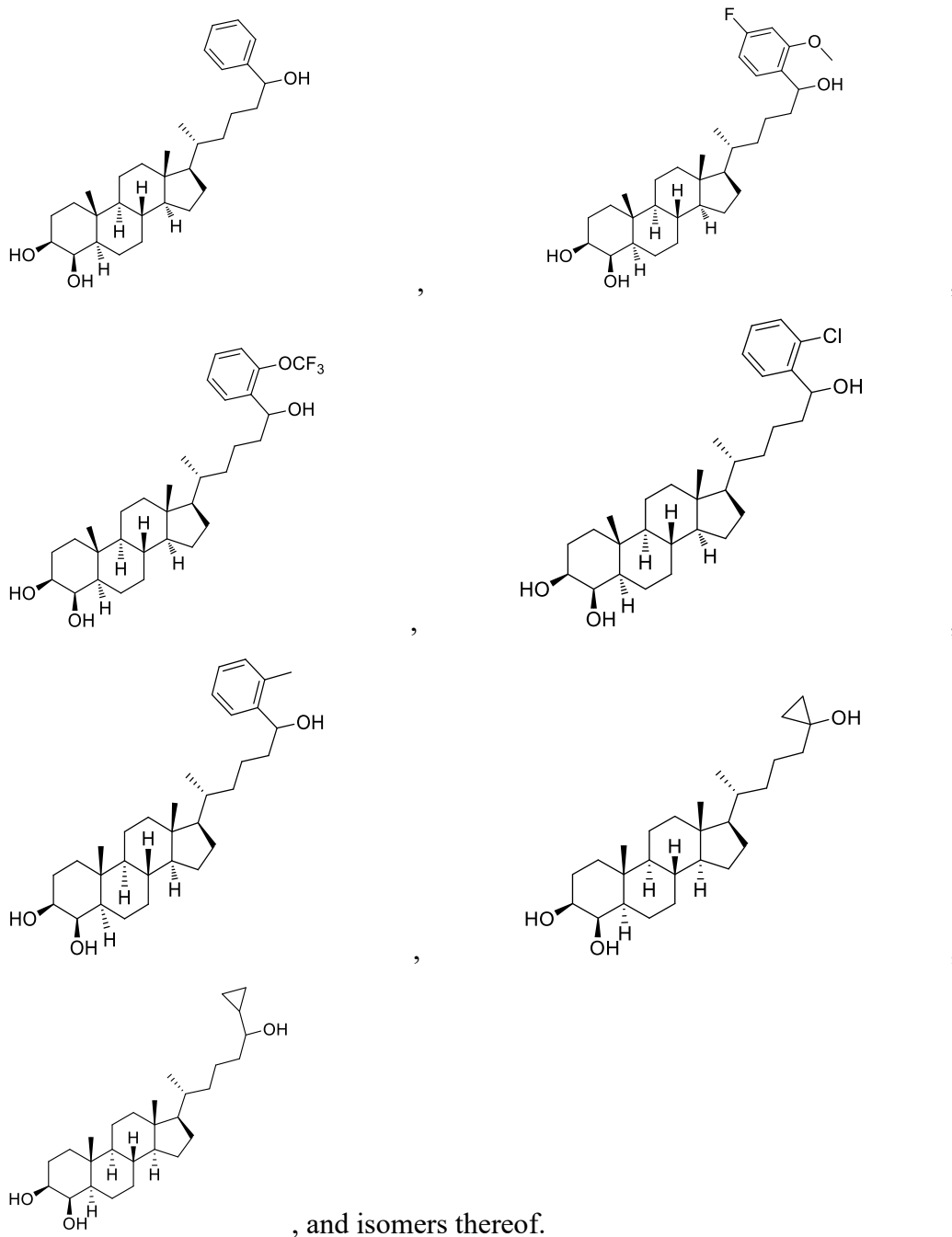
the carbon atom marked with "#" indicates that when it is a chiral carbon atom, it is in the R configuration, S configuration, or a mixture of both;

- 20 the carbon atom marked with "&" indicates that when it is a chiral carbon atom, it is in the R configuration, S configuration, or a mixture of both;

the compound of Formula I is not any of the following compounds:







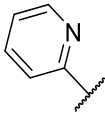
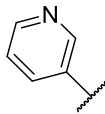
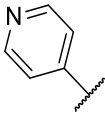
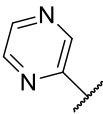
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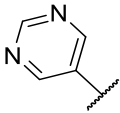
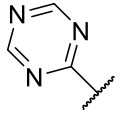
2. The compound of Formula I or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound of Formula I or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

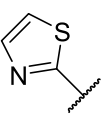
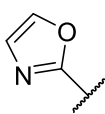
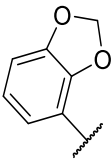
10 (1) in R^{7a} and R^{7b} , the halogen is independently F, Cl, Br, or I; preferably F;

(2) in ring A, ring B, ring C, and ring D, the C₆-C₁₀ aryl is independently phenyl or naphthyl, preferably phenyl;

(3) in ring A, ring B, ring C, and ring D, the 5- to 10-membered heteroaryl with 1, 2, or 3 heteroatoms selected from the group consisting of 1, 2, or 3 kinds of N, O, and S is independently 5- to 6-membered heteroaryl with 1 or 2 heteroatoms selected from the group consisting of 1, 2, or 3 kinds of N, O, and S or 9- to 10-membered heteroaryl with 1 or 2 heteroatoms being O, preferably

pyridyl (e.g., , , or ) , pyrazinyl (e.g., ) ,

pyrimidinyl (e.g., ) , triazinyl (e.g., ) , thiazolyl (e.g.,

) , oxazolyl (e.g., ) , or  ;

(4) in ring A, ring B, ring C, and ring D, the C₃-C₆ cycloalkyl is independently cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or

bicyclo[1.1.1]pentyl (e.g., ) , preferably  ;

(5) in R¹, the C₁-C₆ alkoxy is independently methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, or *tert*-butoxy, preferably methoxy;

(6) in R² and R³, the C₁-C₆ alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl; preferably methyl;

(7) in R^A, R^B, R^C, and R^D, the halogen is independently F, Cl, Br, or I; preferably F or Cl, for example, F;

(8) in R^A, R^B, R^C, and R^D, the C₁-C₆ alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl;

(9) in R^A, R^B, R^C, and R^D, the C₁-C₆ haloalkyl is independently CHF₂, CH₂F, or CF₃;

(10) in R^A, R^B, R^C, and R^D, the C₁-C₆ alkoxy is independently methoxy,

ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, or *tert*-butoxy, preferably methoxy or ethoxy;

(11) in R^A , R^B , R^C , and R^D , the C_1 - C_6 haloalkoxy is independently $-OCHF_2$, $-OCH_2F$, or $-OCF_3$; preferably $-OCF_3$;

5 (12) in ring E, the C_3 - C_6 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl,

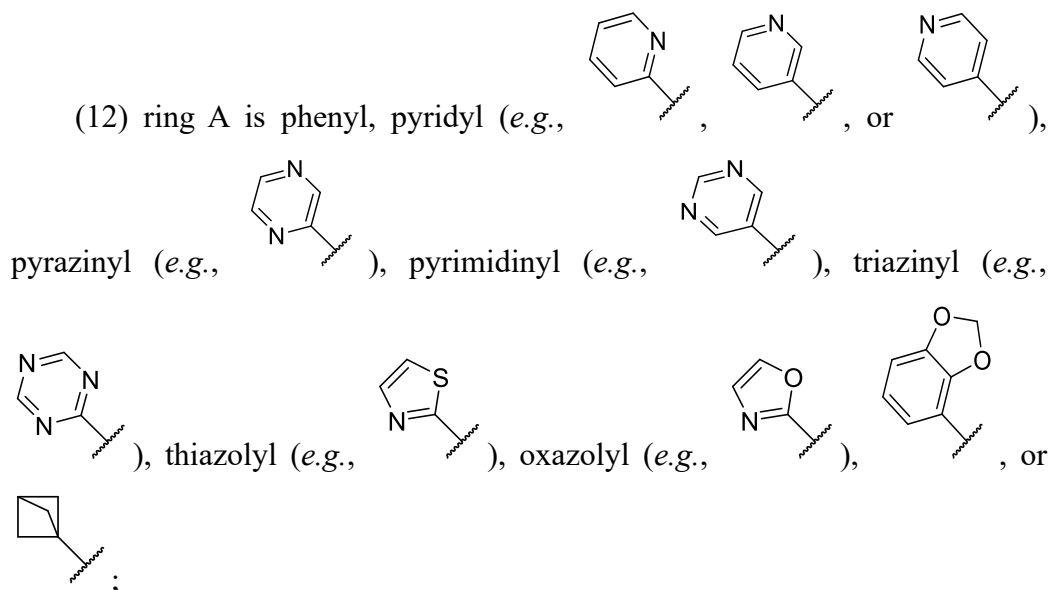
cyclohexyl, or bicyclo[1.1.1]pentyl (e.g., , preferably cyclopropyl or cyclobutyl;

(13) in R^E , the C_1 - C_6 alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl, for example, methyl; and

10 (14) in R^{1a} , R^{1b} , R^{e1} , and R^{e2} , the C_1 - C_6 alkyl is independently methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl, for example, methyl.

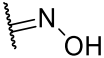
3. The compound of Formula I or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound of Formula I or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

- 20 (1) n_1 is 3;
 (2) n_2 is 3;
 (3) n_3 is 2;
 (4) n_4 is 2;
 (5) n_5 is 2;
 (6) m_1 is 0, 1, 2, or 3;
 (7) m_2 is 0, 1, 2, or 3, for example, 2;
 25 (8) m_3 is 1;
 (9) m_4 is 1;
 (10) m_5 is 1 or 2;
 (11) R^A is independently halogen, C_1 - C_6 alkoxy, or C_1 - C_6 haloalkoxy;



5 (13) R^B is independently halogen, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy; for example, halogen or C₁-C₆ alkoxy;

(14) ring B is phenyl;

(15) R¹ is methoxy, , or NH₂;

(16) R^{1a} and R^{1b} are independently H;

10 (17) R^C and R^D are independently halogen;

(18) ring C is phenyl;

(19) ring D is phenyl;

(20) ring E is cyclopropyl or cyclobutyl;

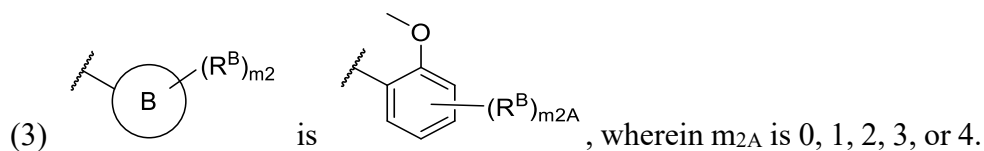
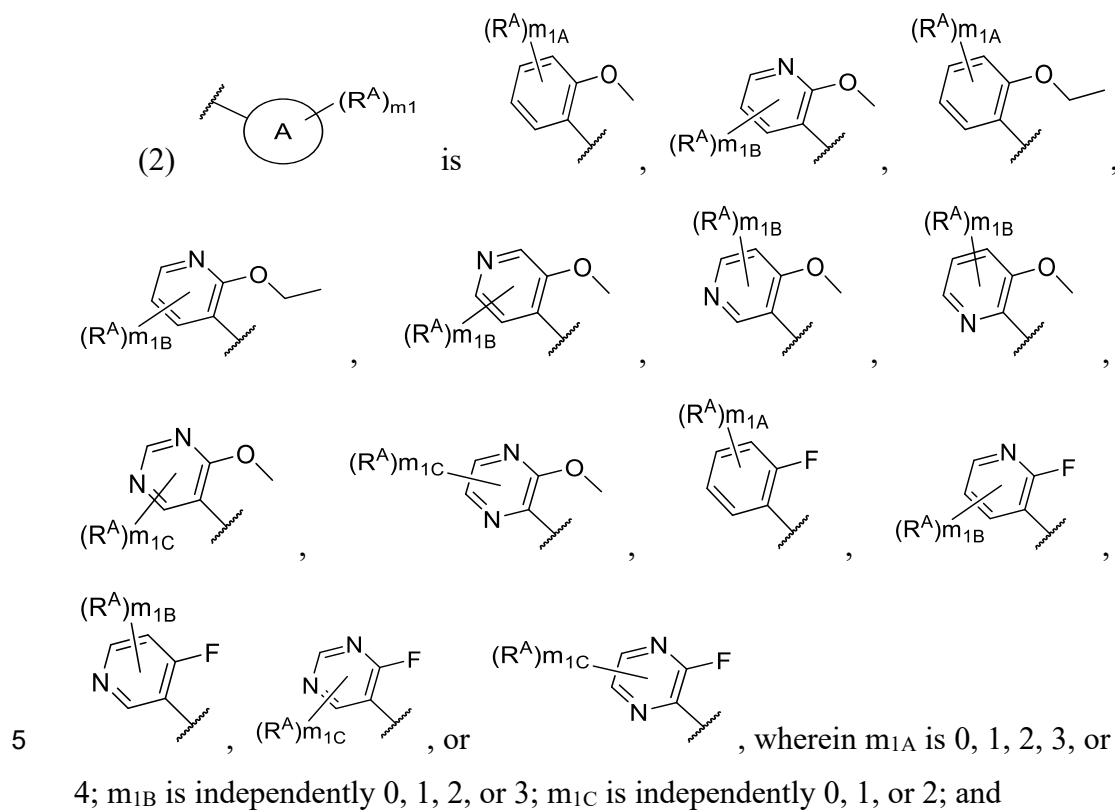
(21) R^{e1} and R^{e2} are independently C₁-C₆ alkyl (e.g., methyl);

15 (22) the carbon atom marked with "*" indicates that when it is a chiral carbon atom, it is in the S configuration; and

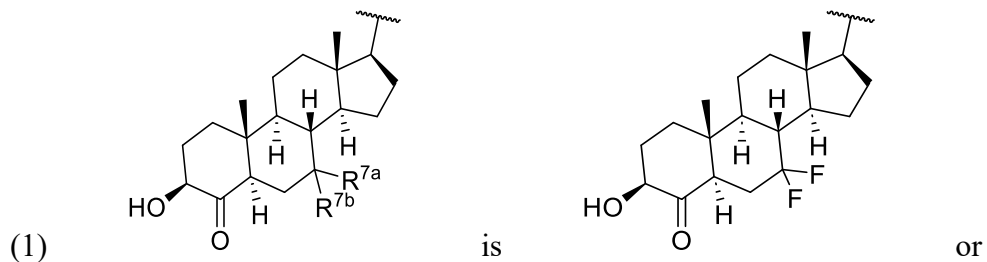
(23) the carbon atom marked with "#" indicates that when it is a chiral carbon atom, it is in the R configuration.

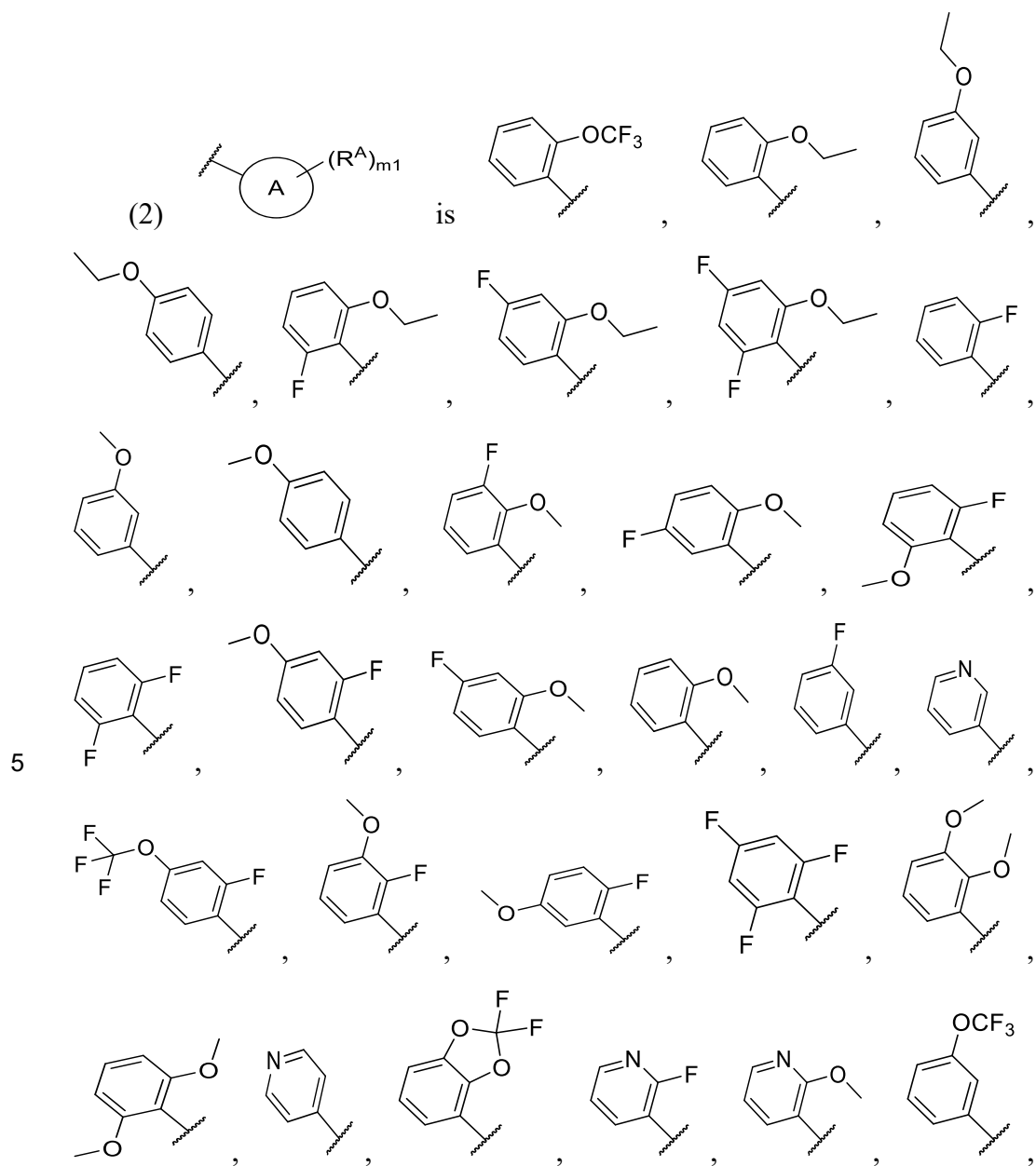
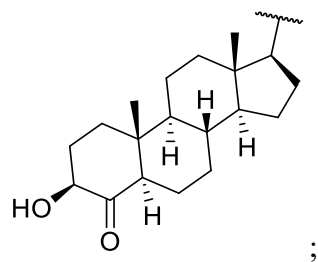
20 4. The compound of Formula I or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound of Formula I or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

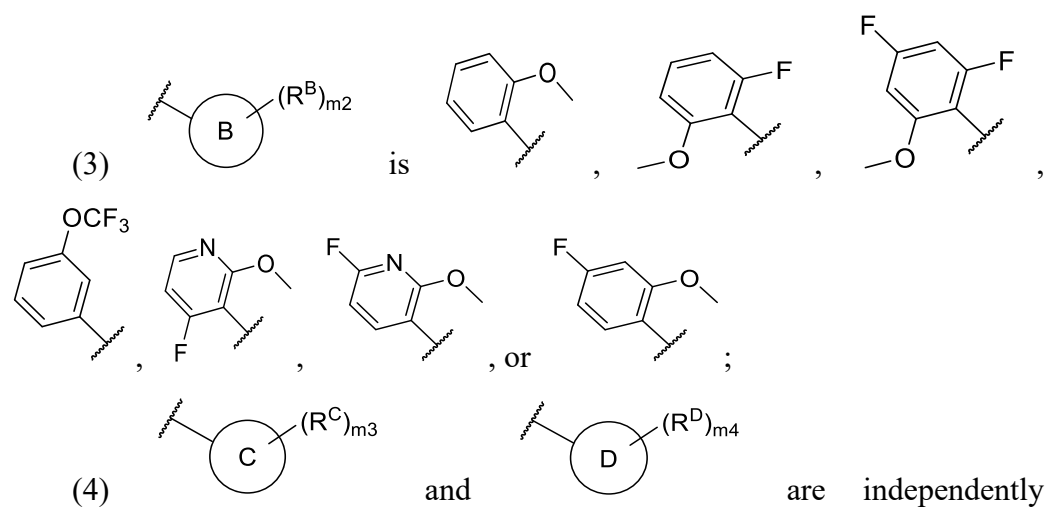
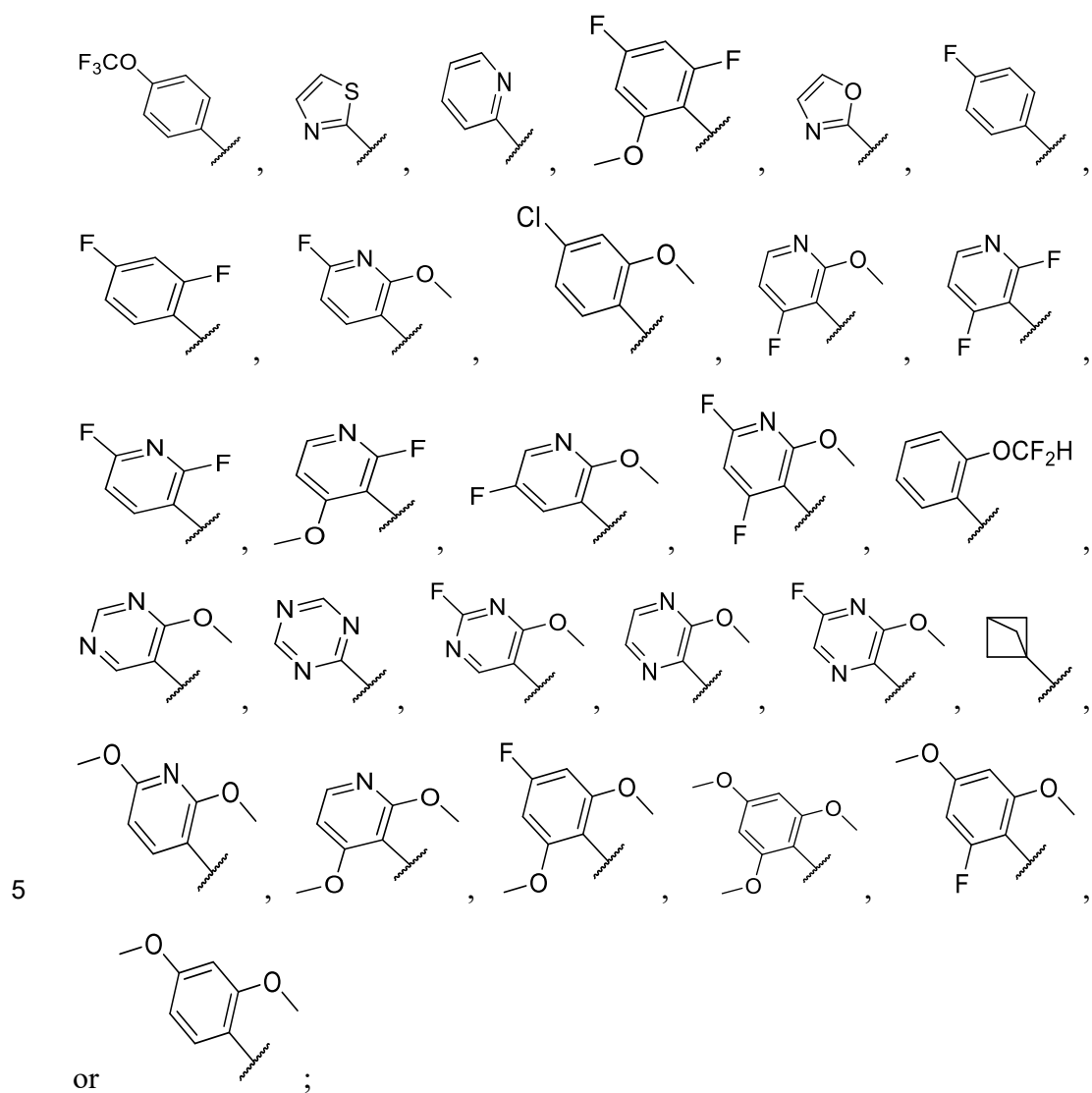
(1) R^{7a} and R^{7b} are independently halogen (*e.g.*, F);

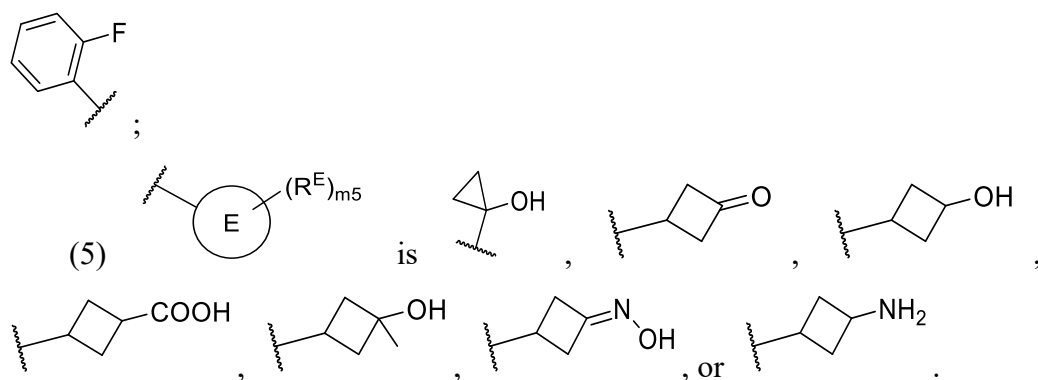


5. The compound of Formula I or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound of Formula I or the pharmaceutically acceptable salt thereof satisfies one or more of the following conditions:

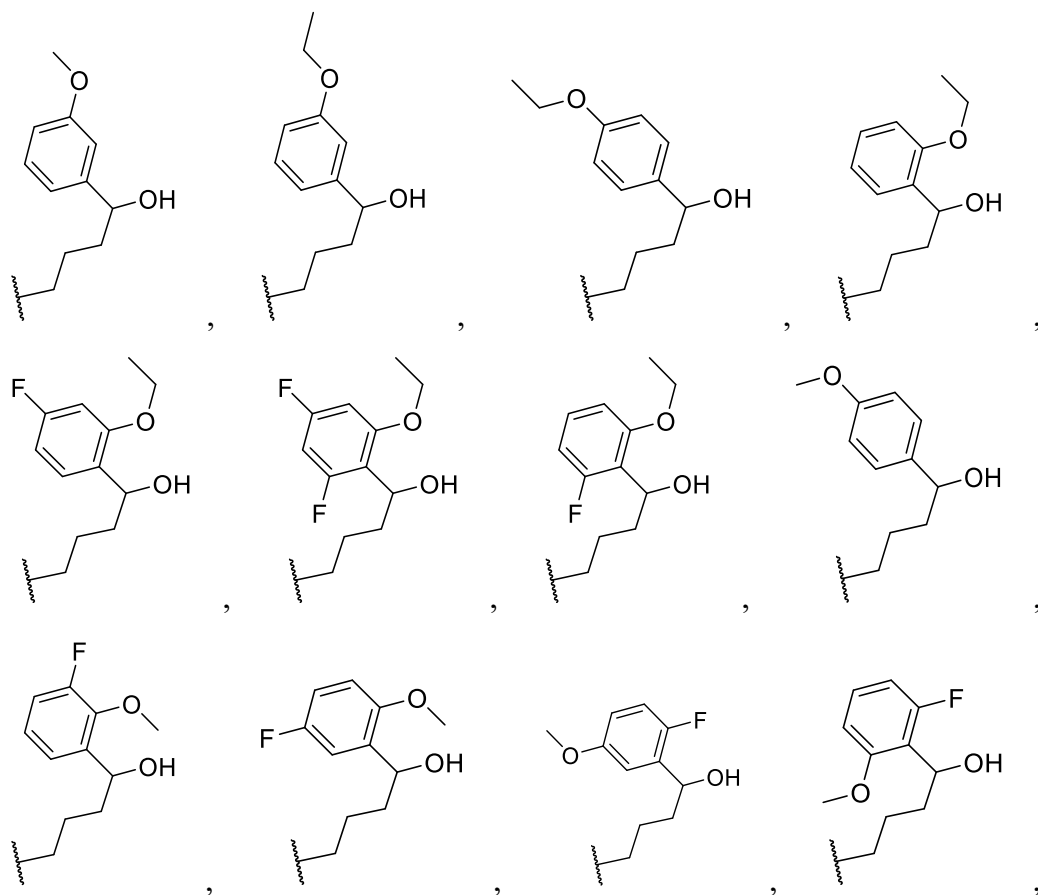
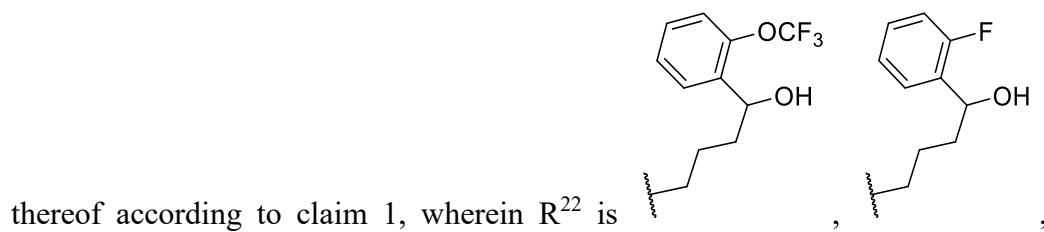


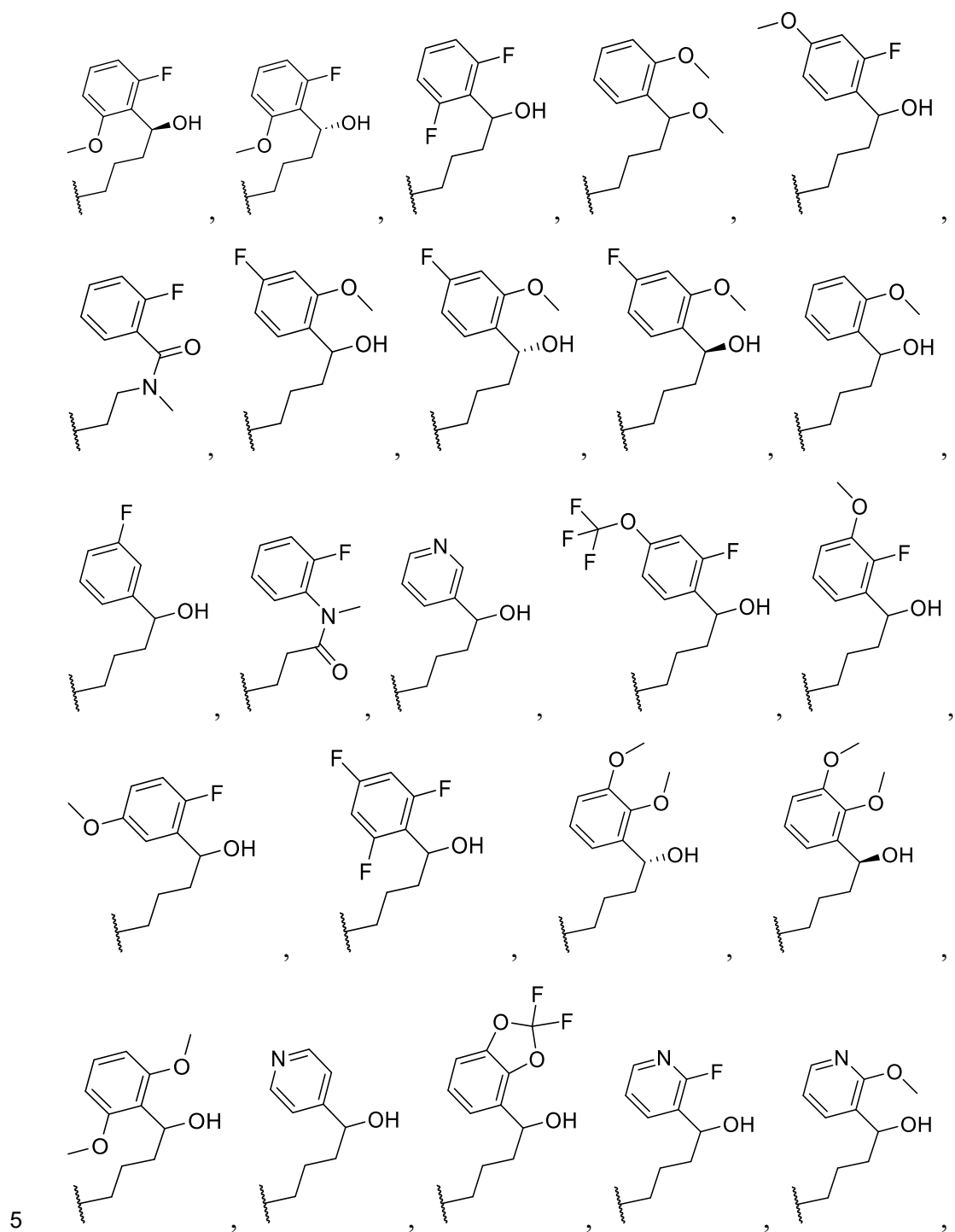


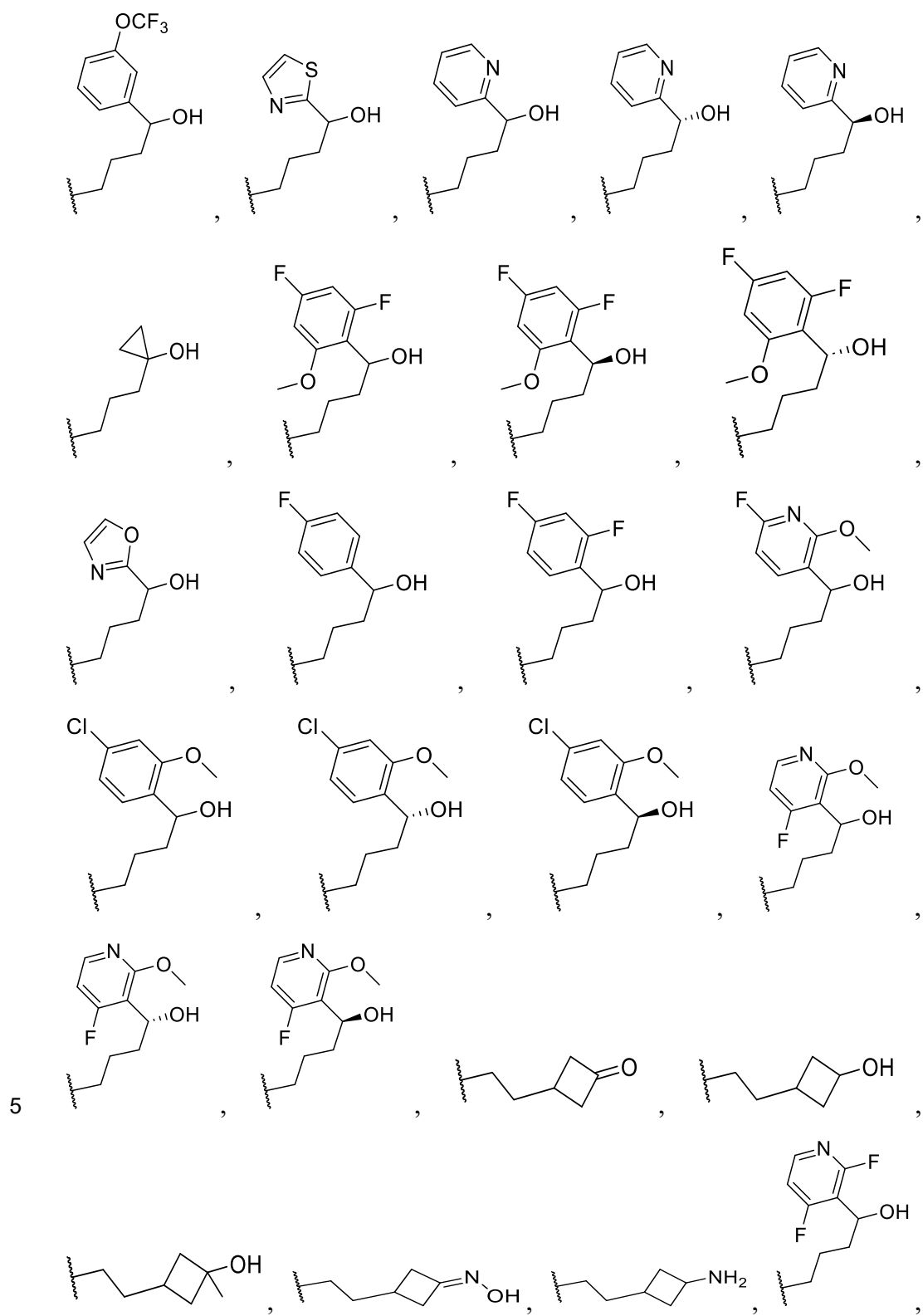


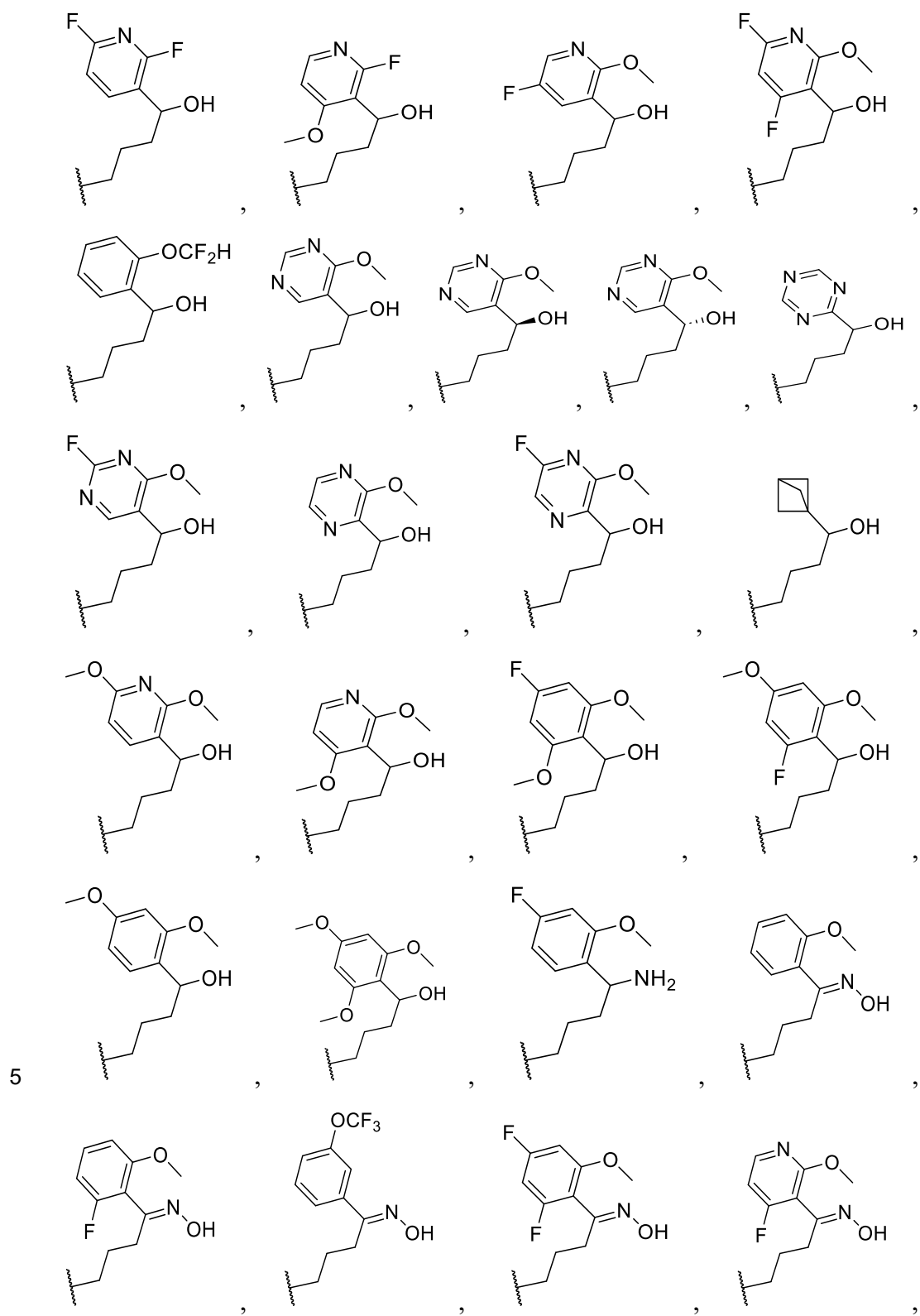


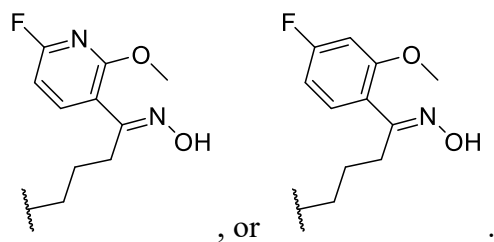
5 6. The compound of Formula I or the pharmaceutically acceptable salt



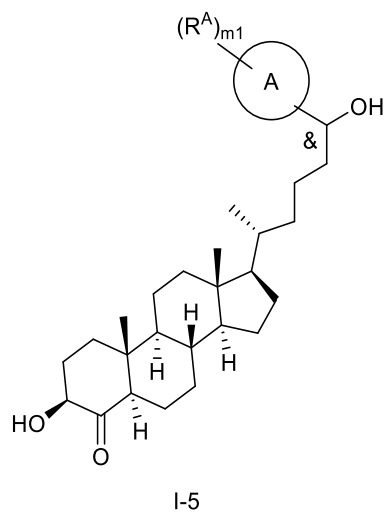
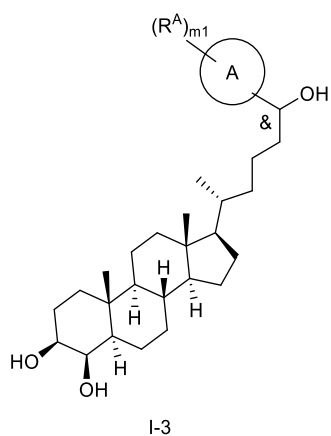
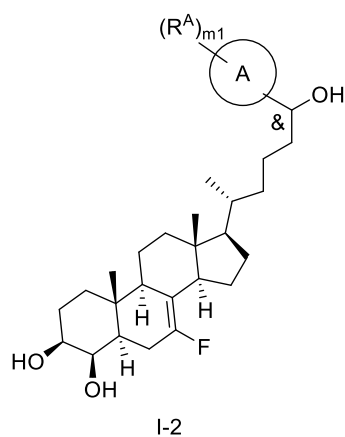
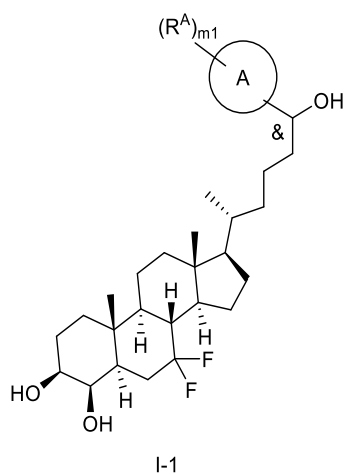


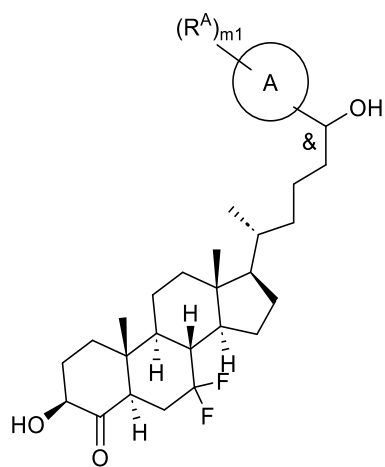




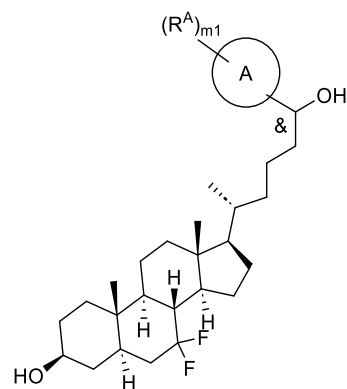


7. The compound of Formula I or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound of Formula I is a compound of Formula I-1, I-2, I-3, I-5, I-6, I-7, I-8, I-9, or I-10:

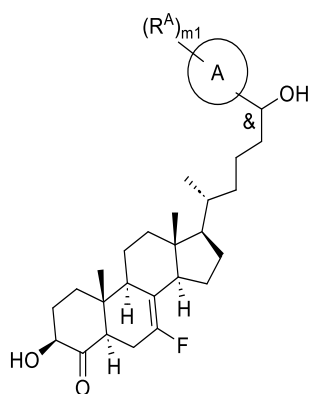




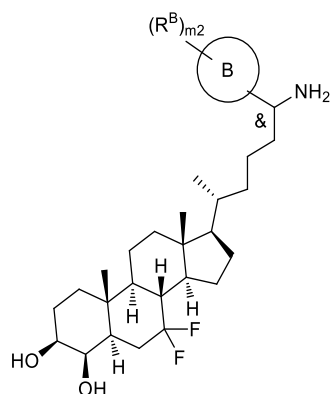
I-6



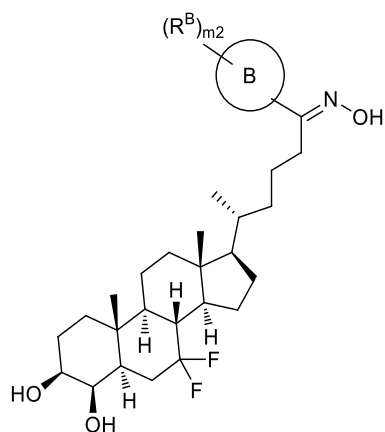
I-7



I-8



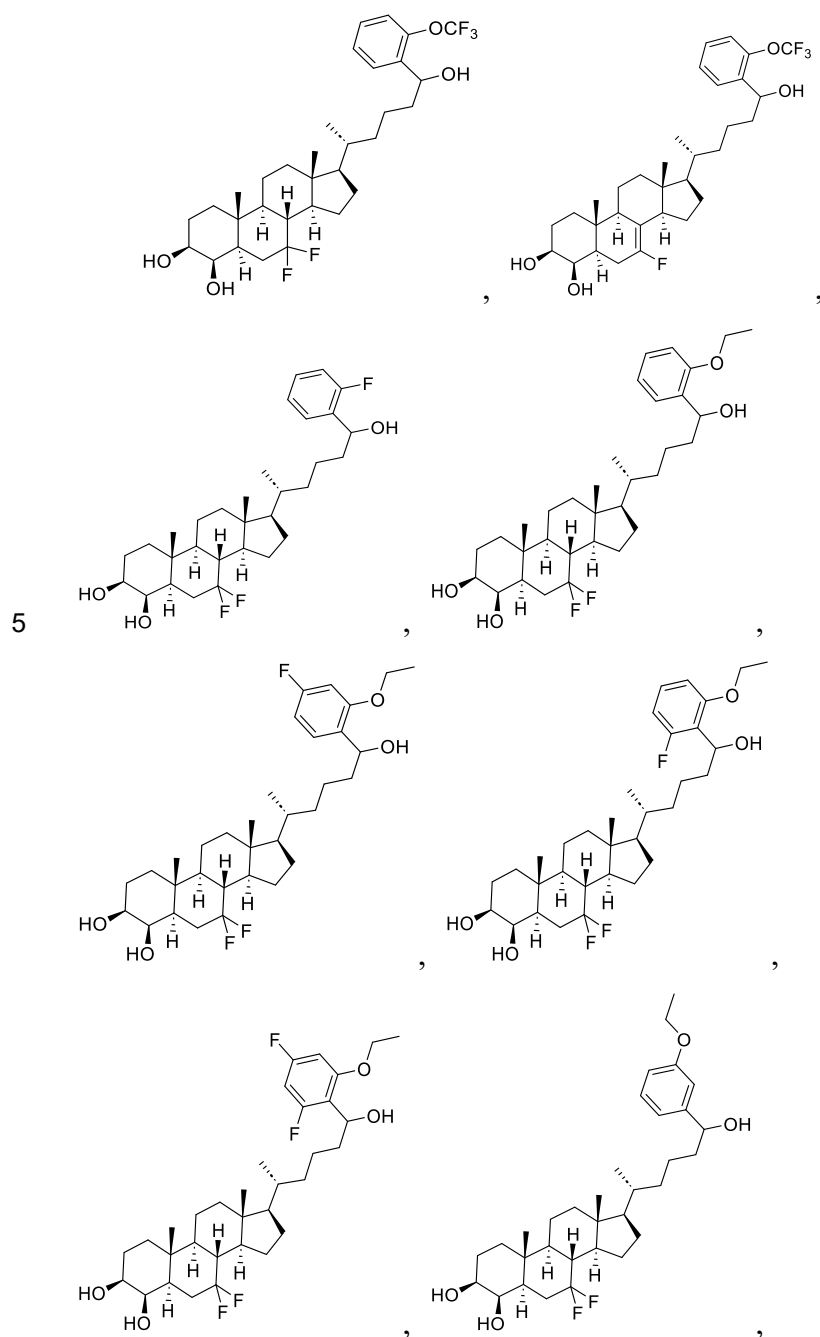
I-9

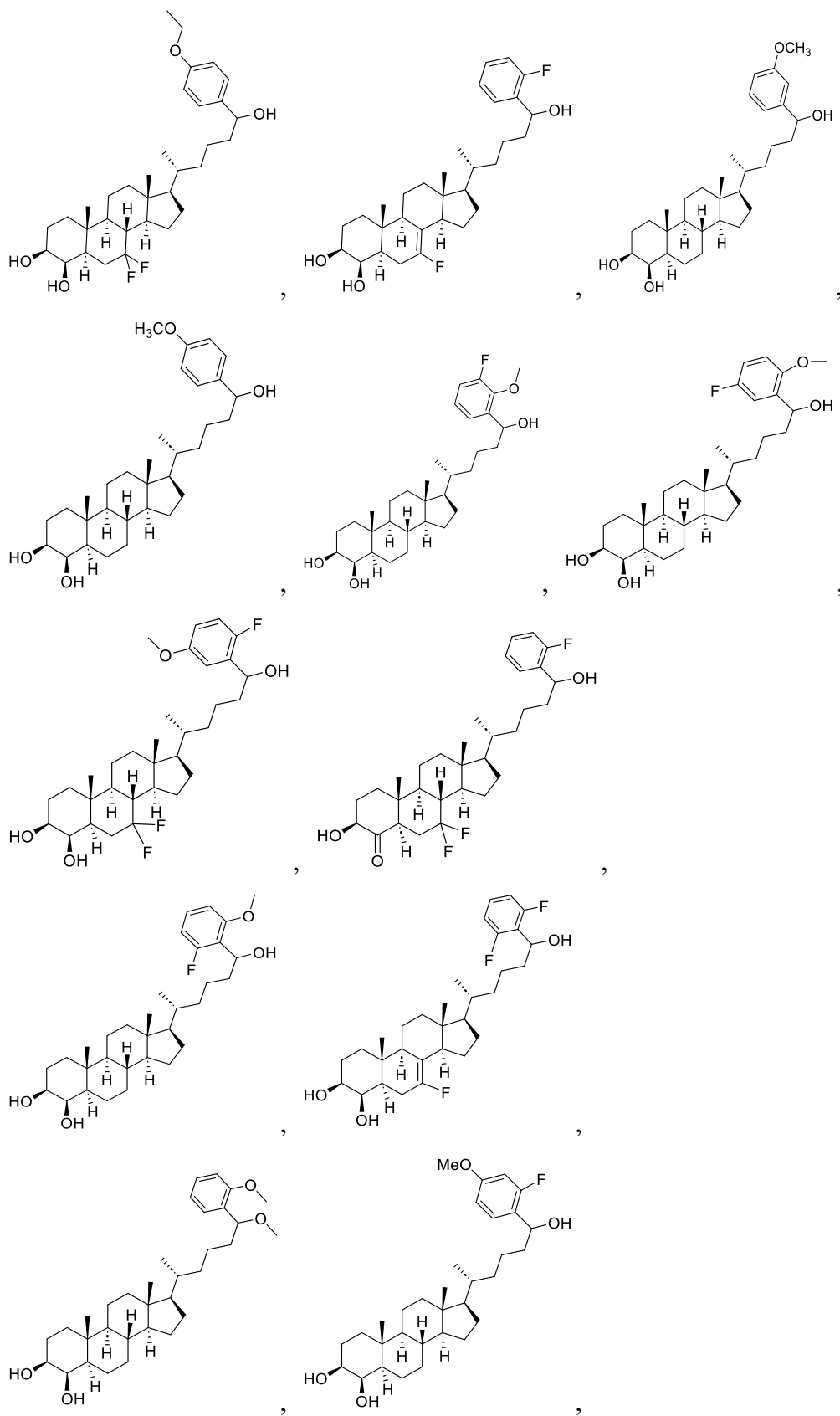


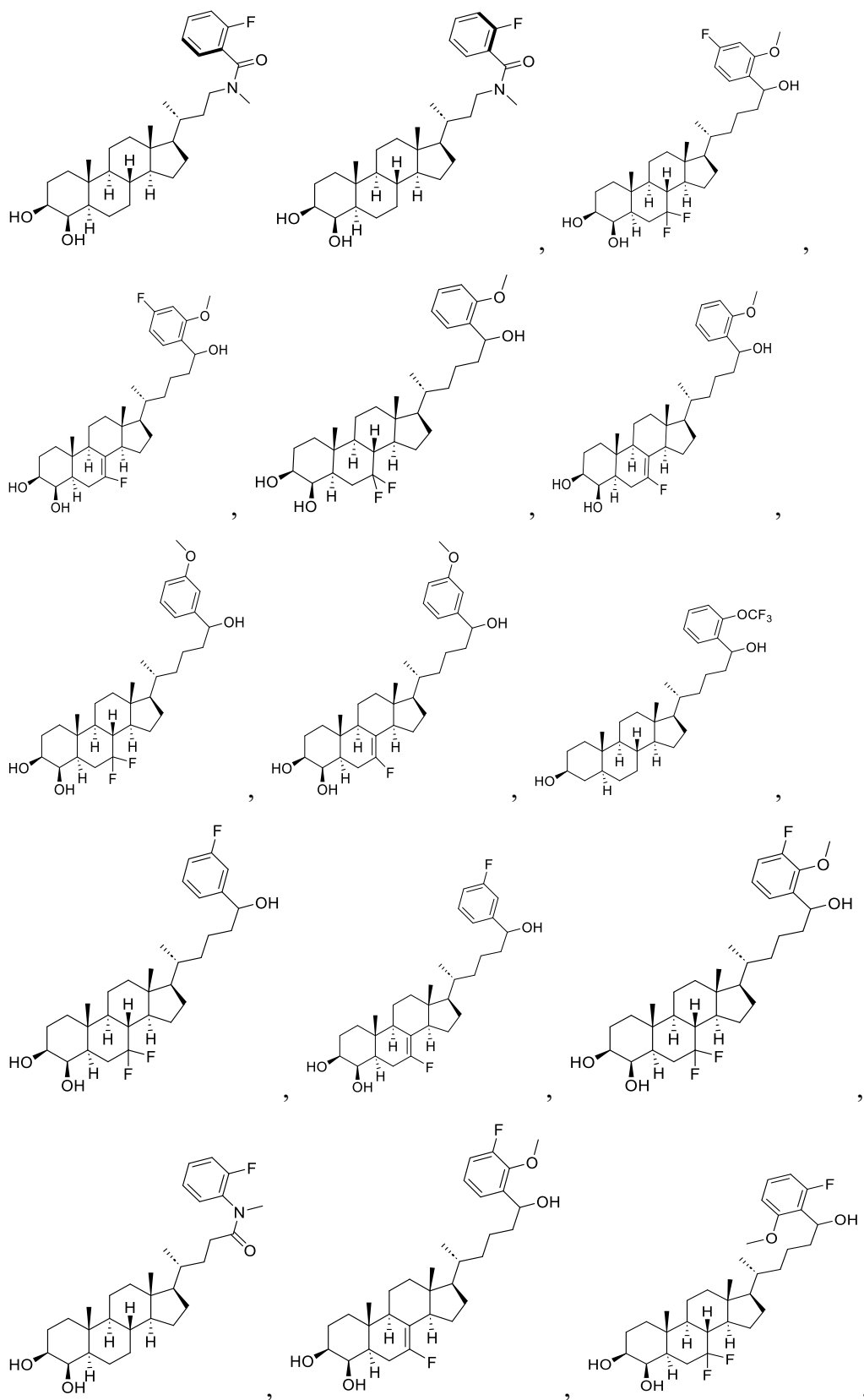
I-10

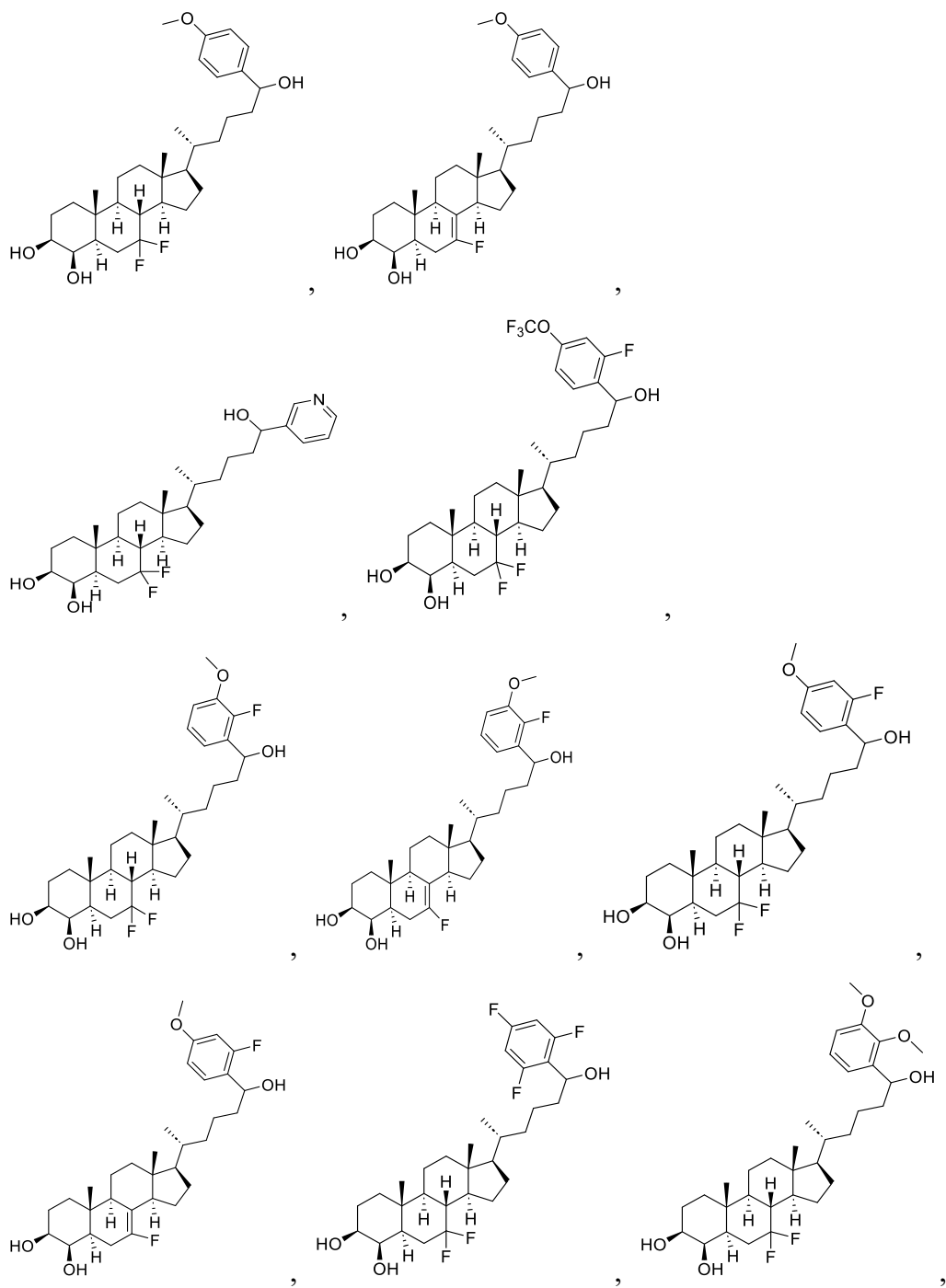
wherein the carbon atom marked with "&" indicates that when it is a chiral
 5 carbon atom, it is in the R configuration, S configuration, or a mixture of both;
 ring A, ring B, R^A , R^B , m_1 , and m_2 are as defined in any one of claims 1-6.

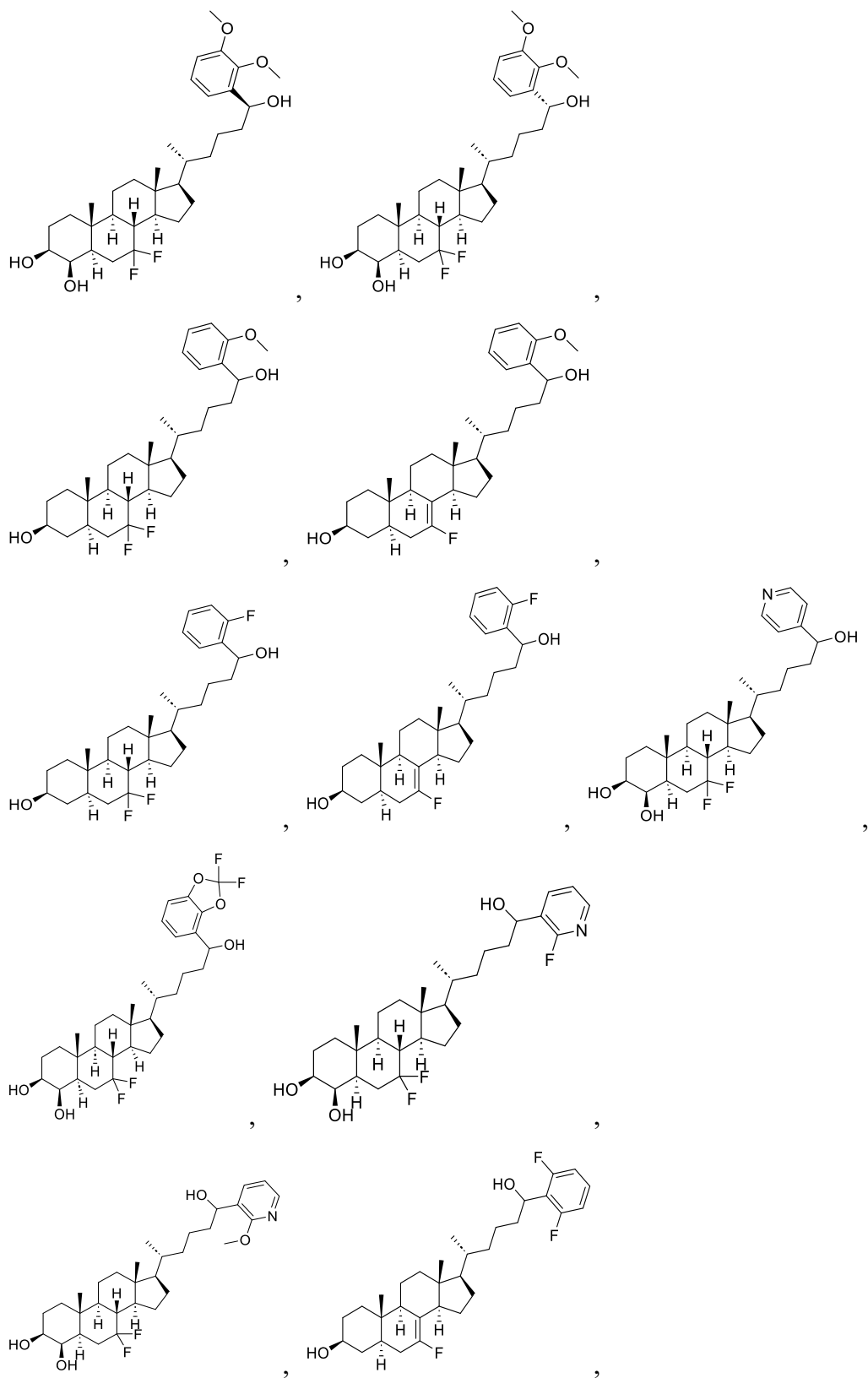
8. A compound as shown in any of the following or a pharmaceutically acceptable salt thereof:

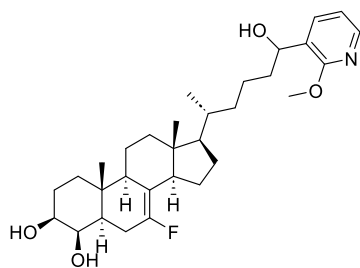




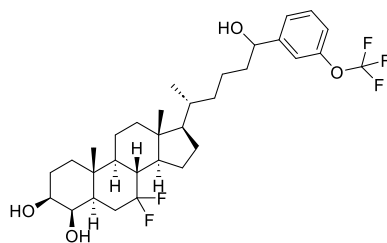




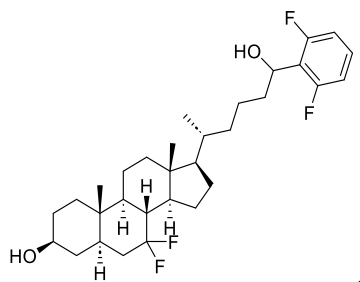




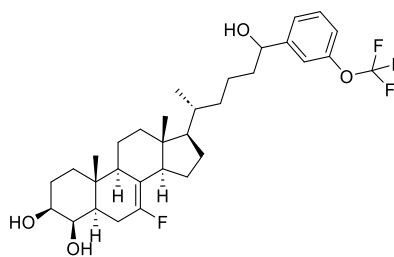
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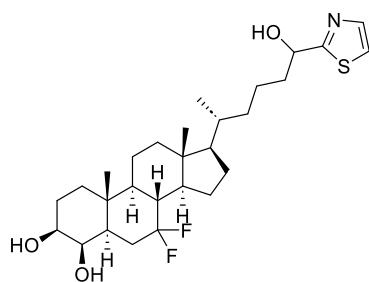
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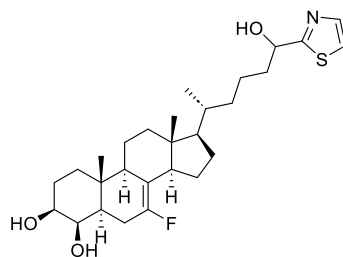
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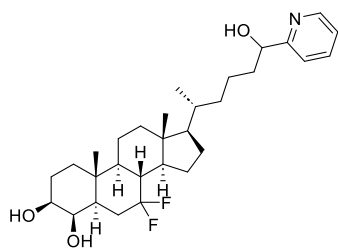
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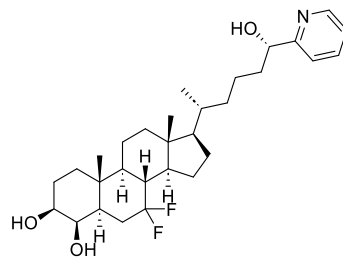
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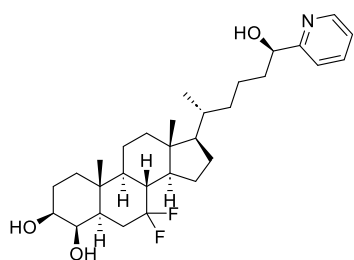
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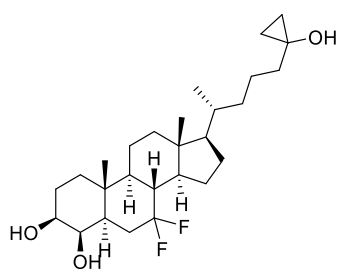
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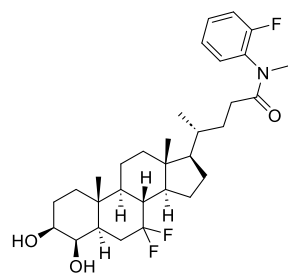
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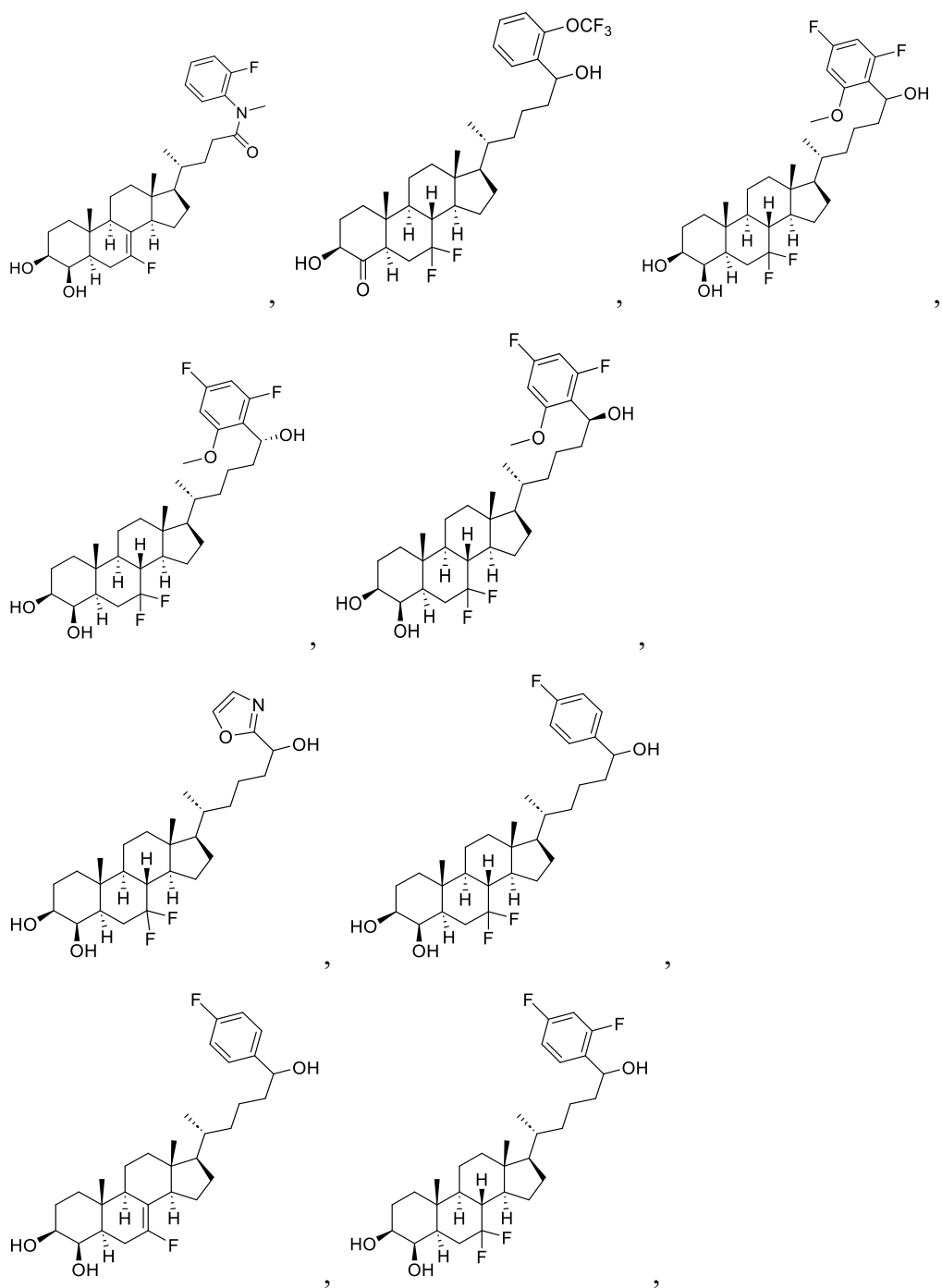
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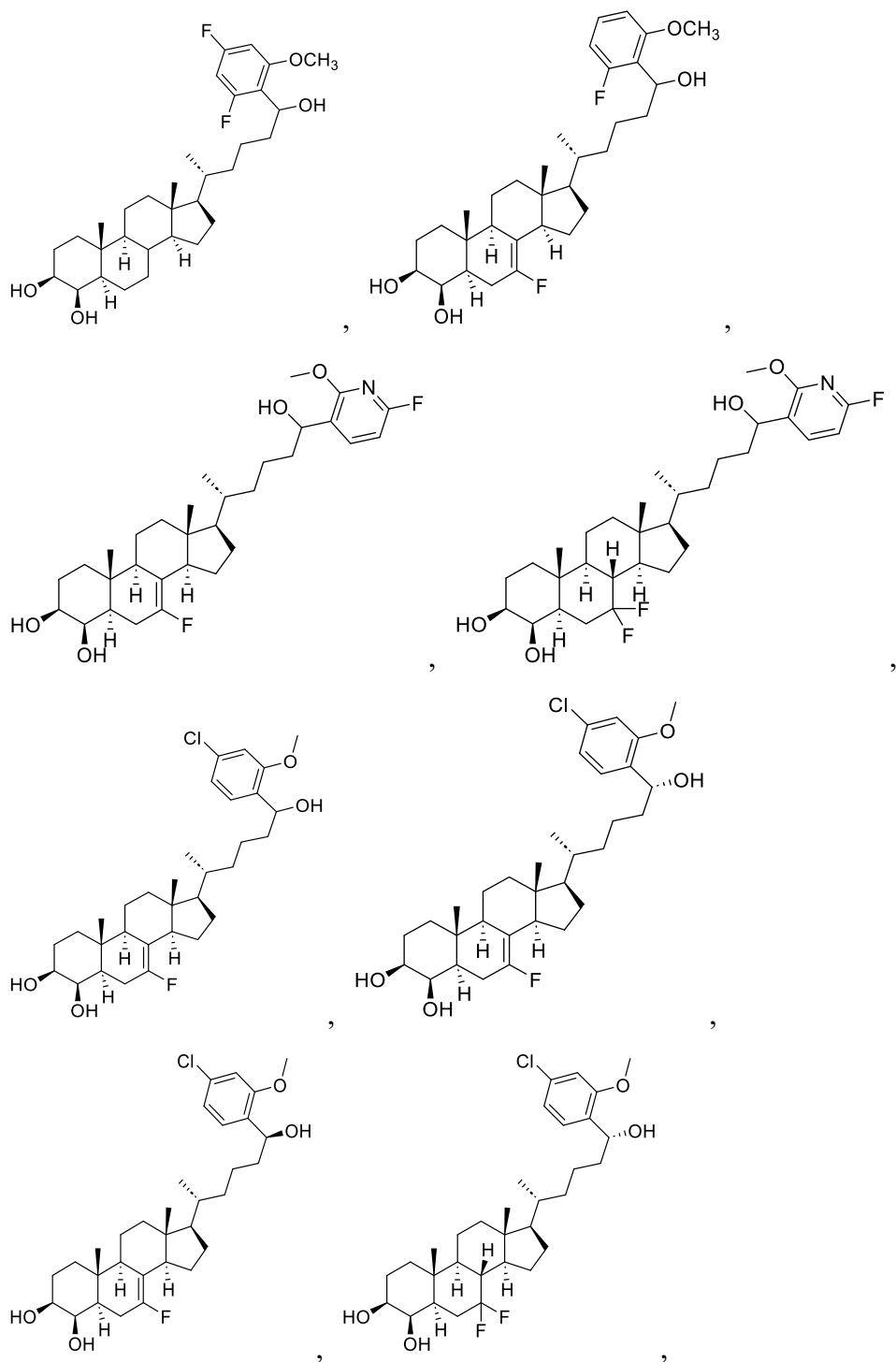


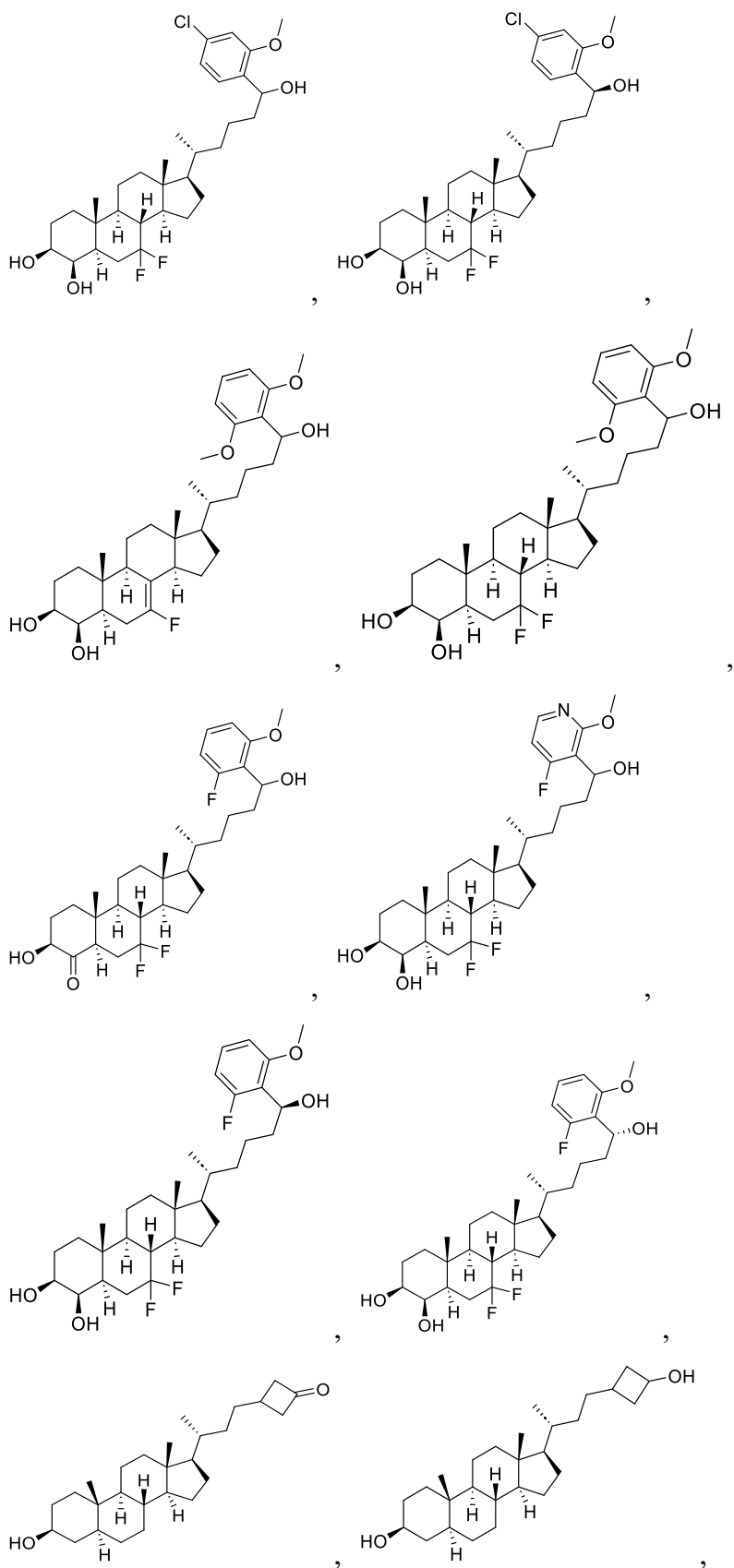
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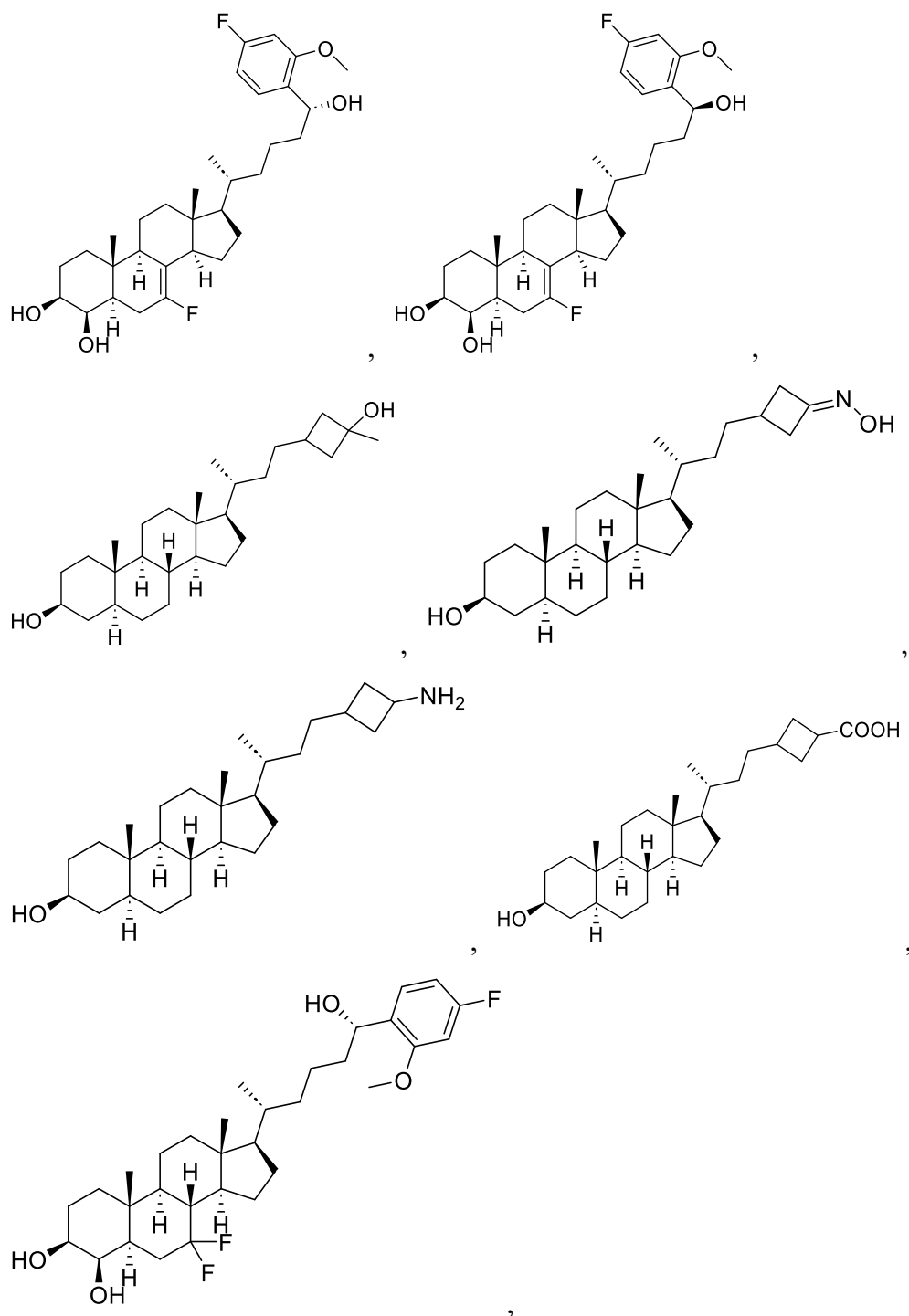


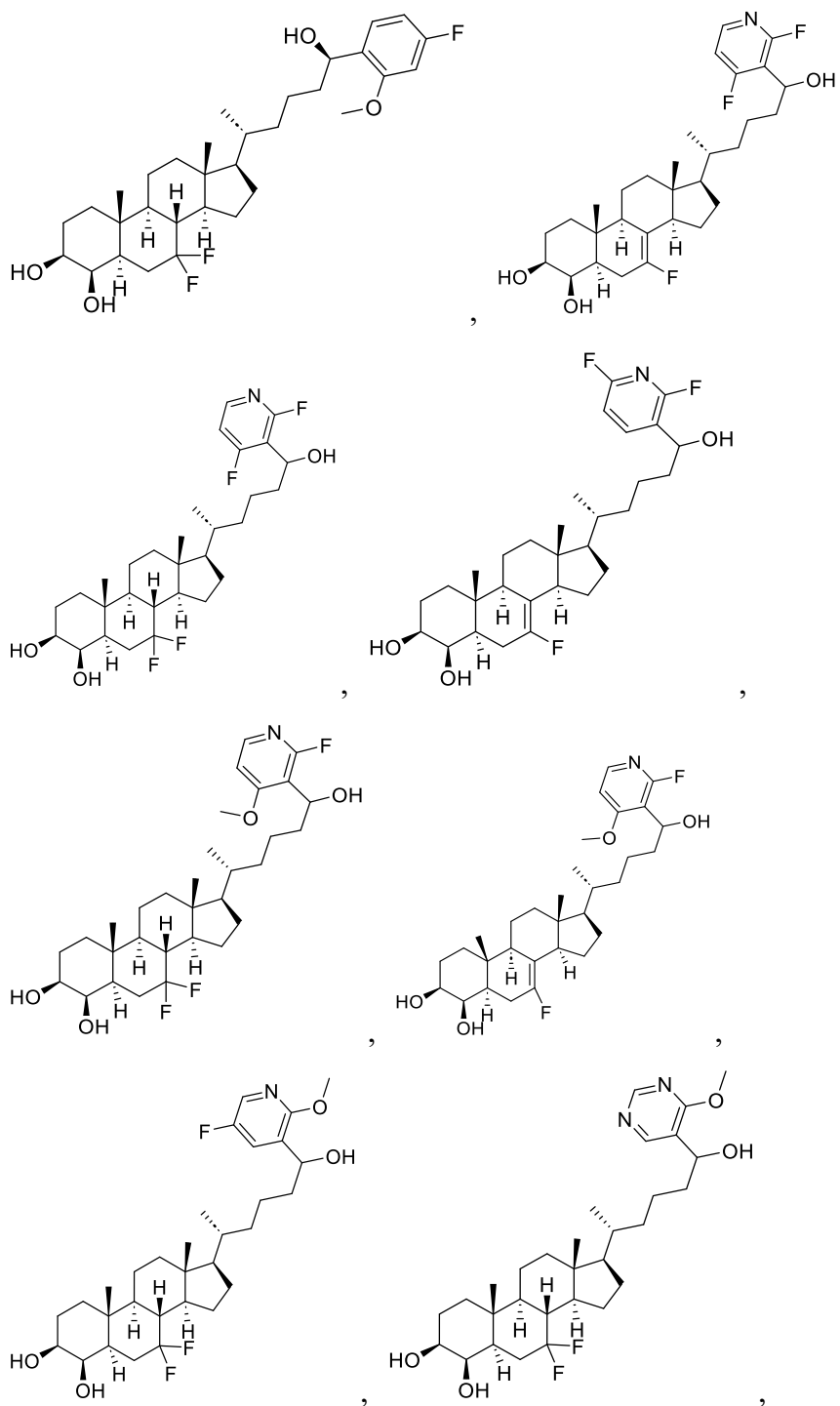
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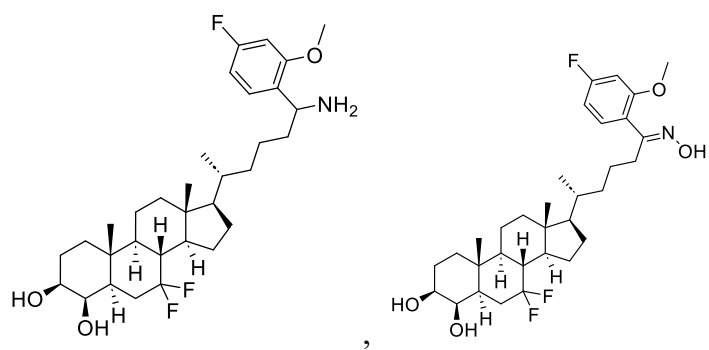
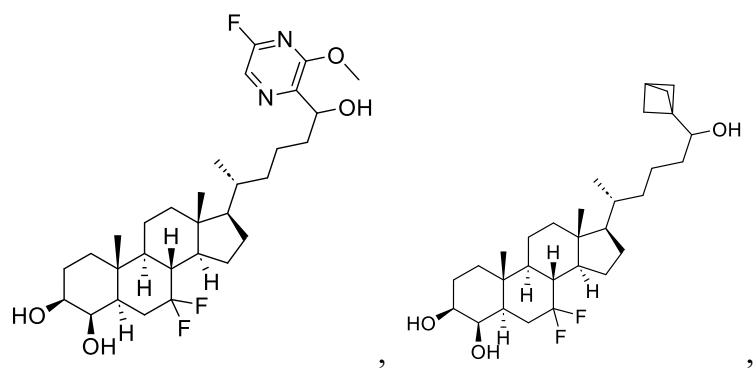
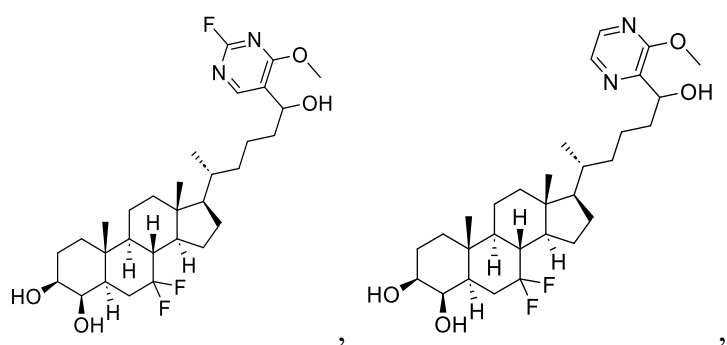
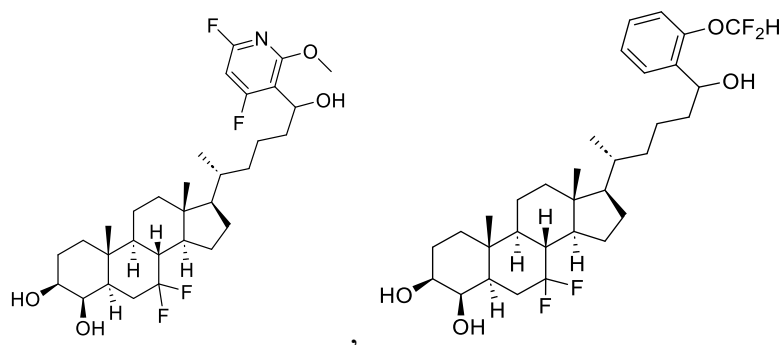


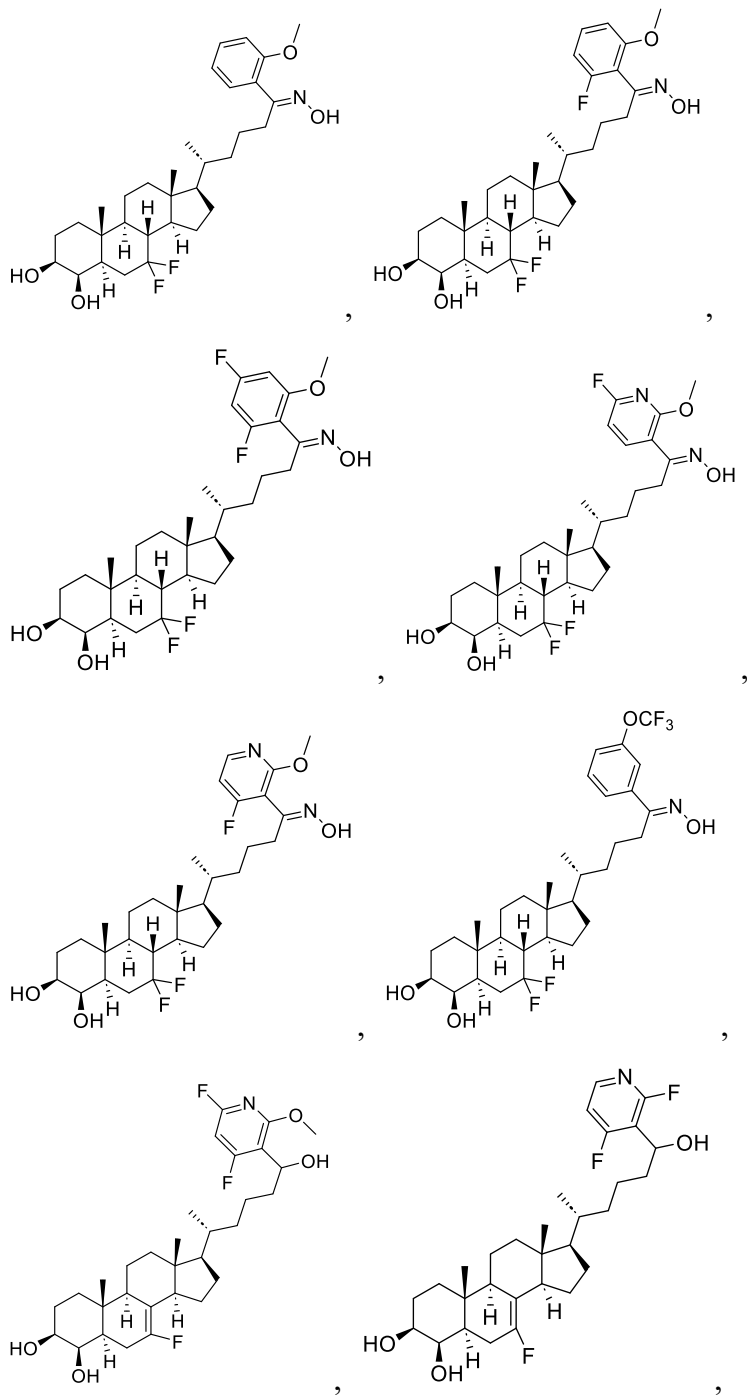


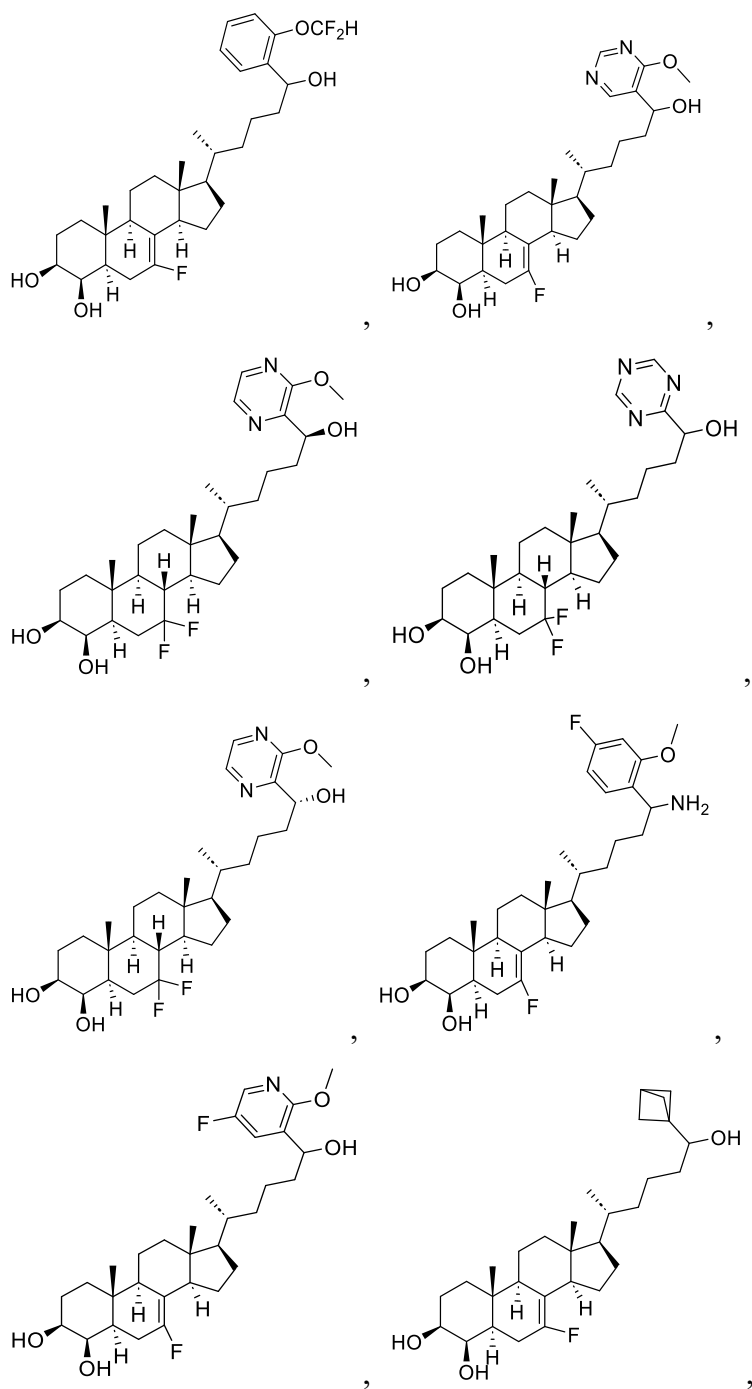


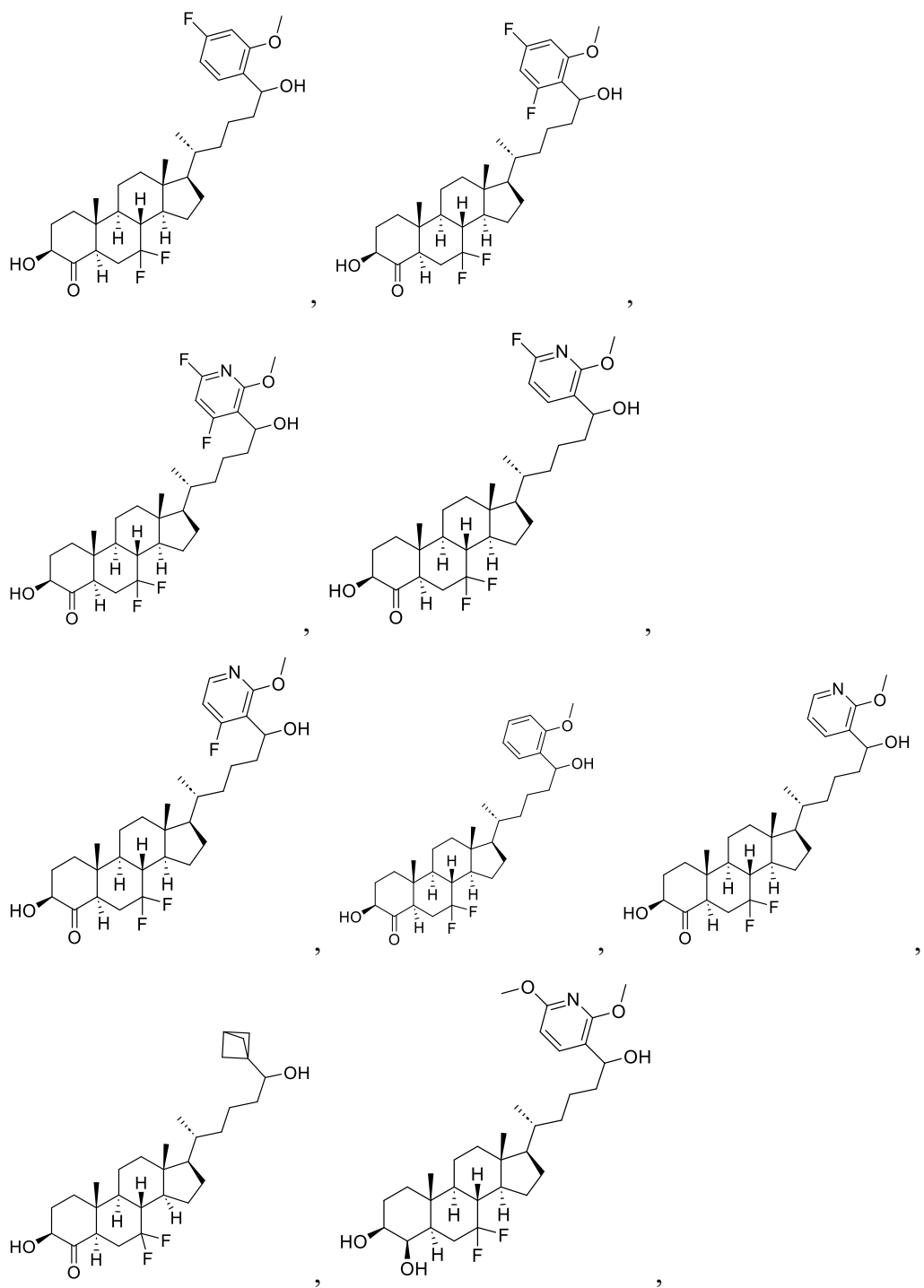


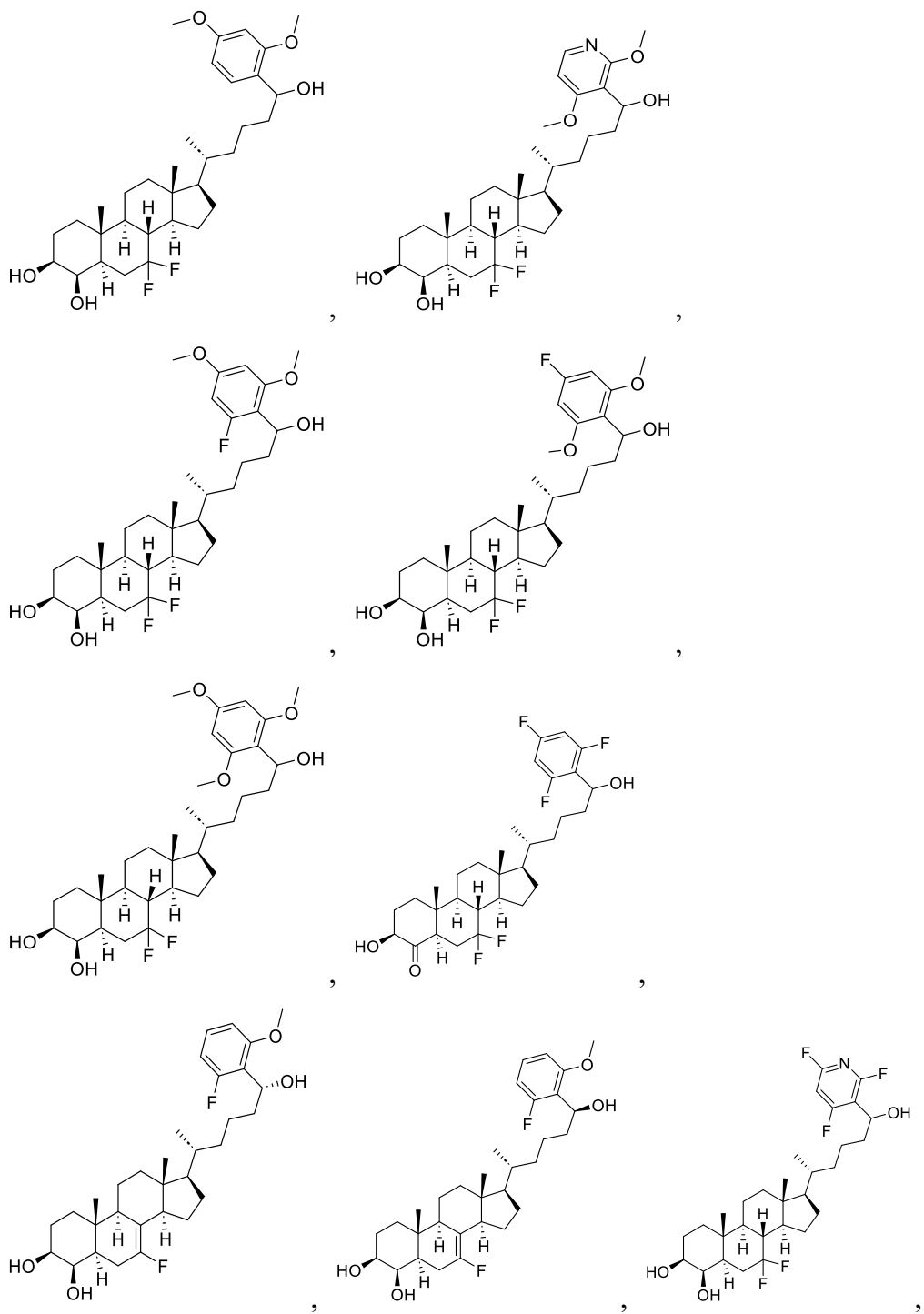


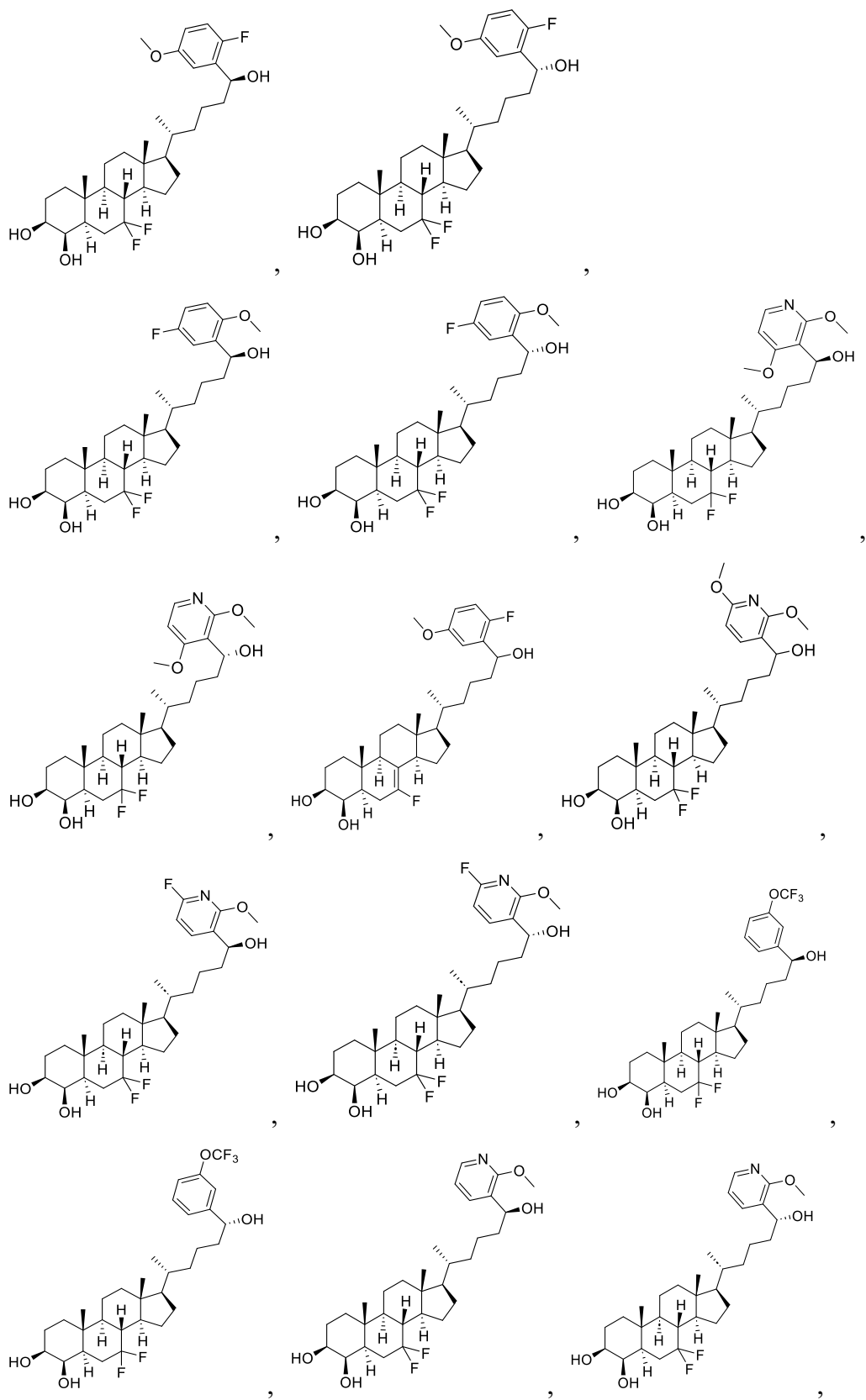


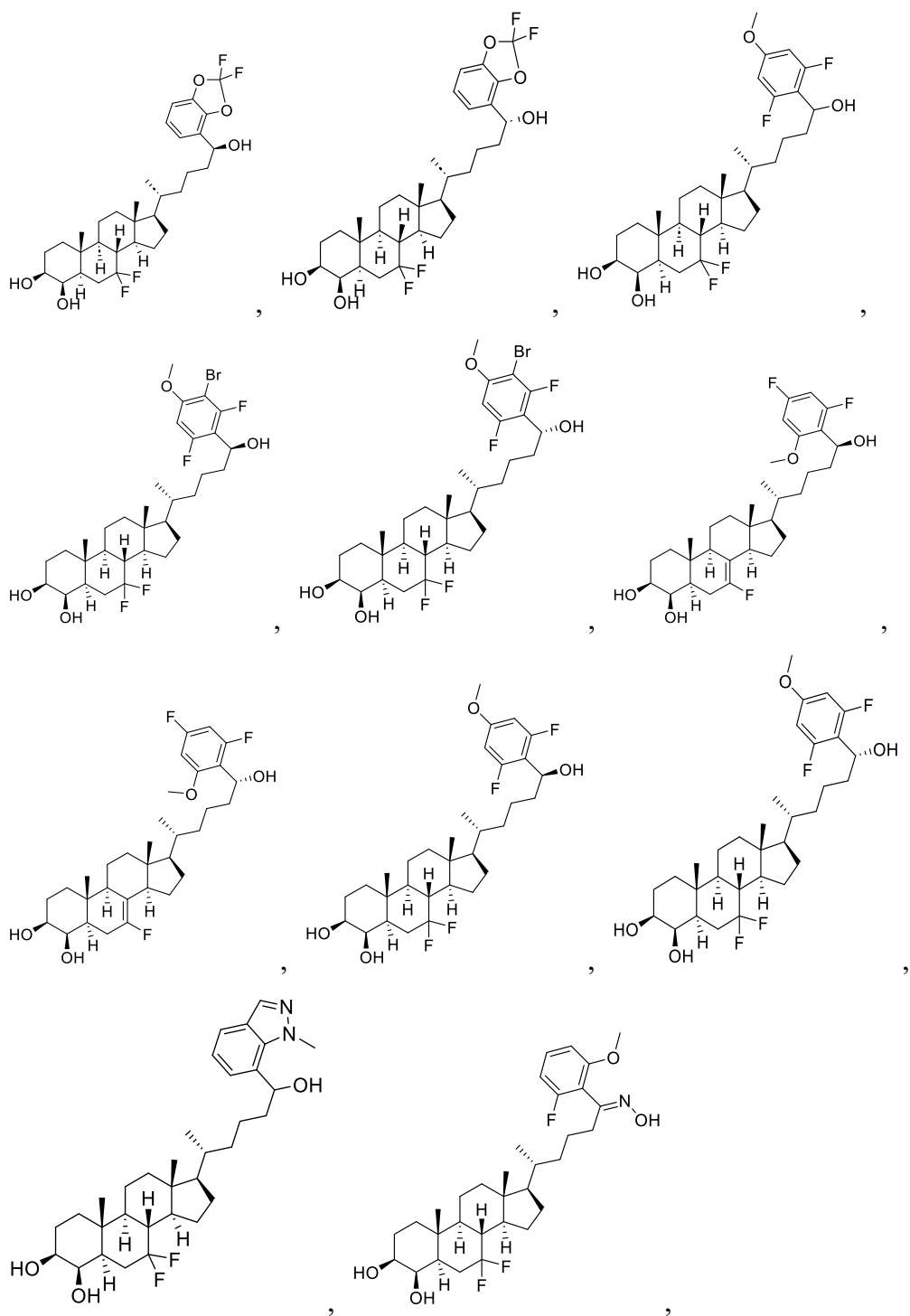


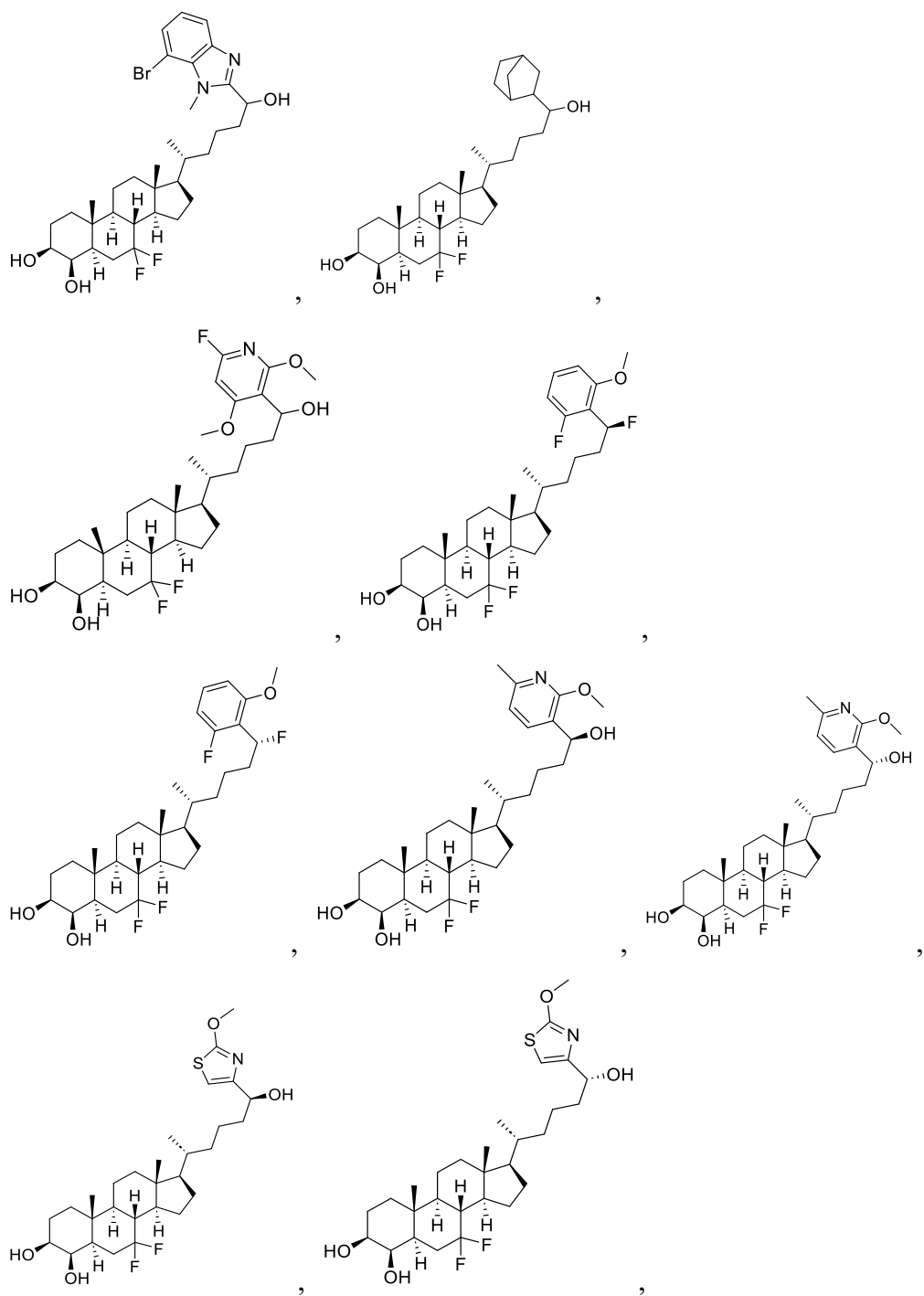


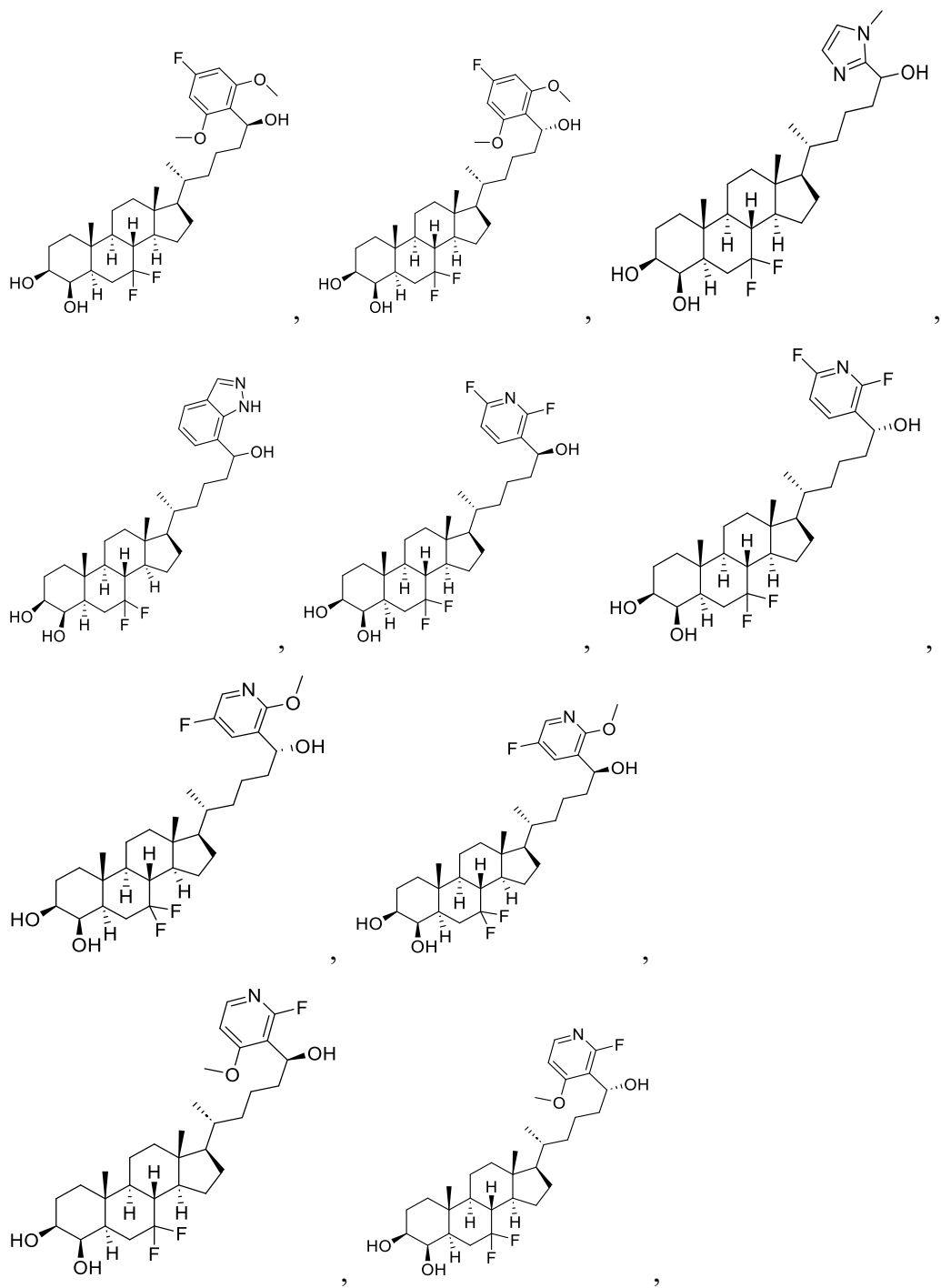


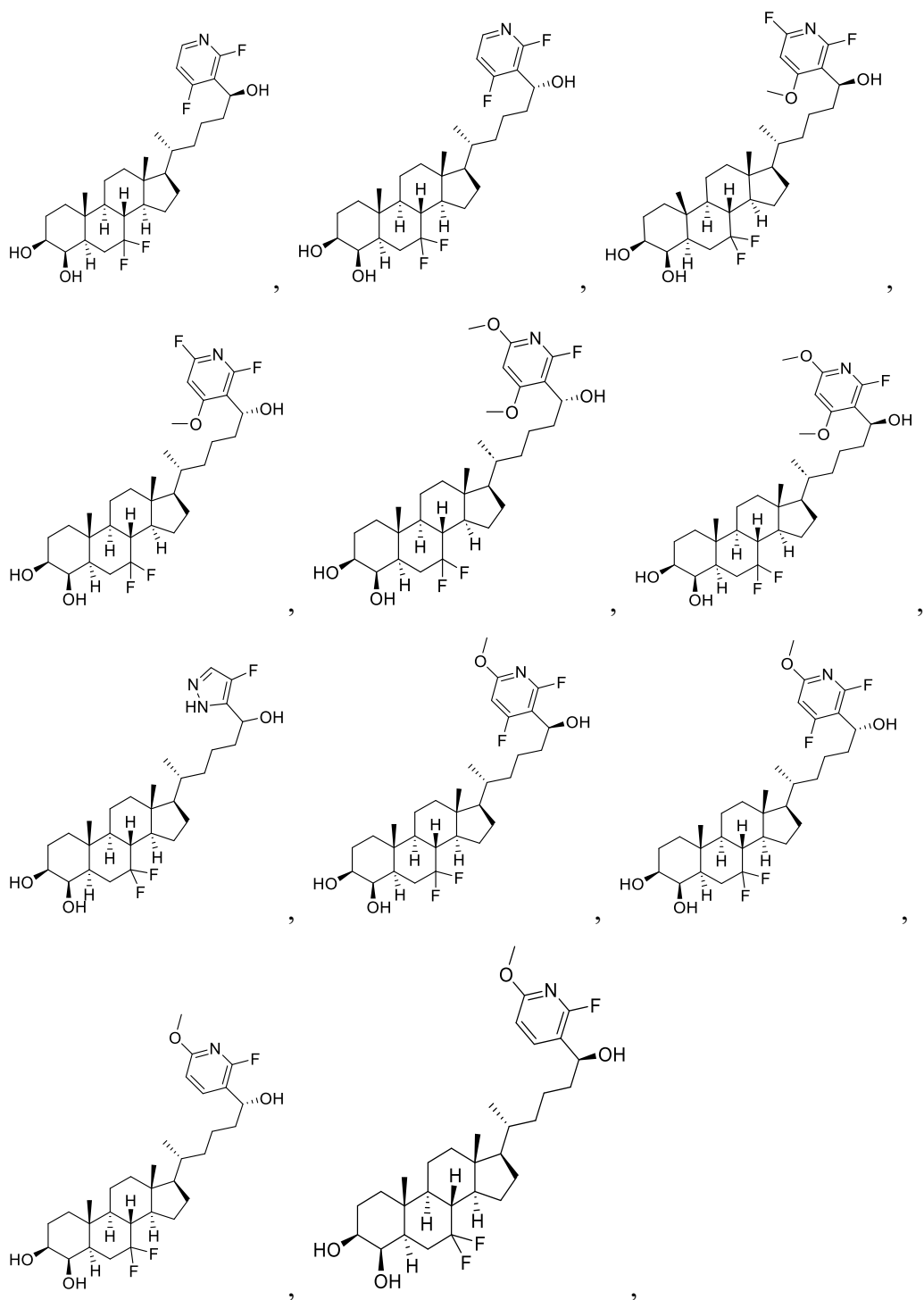


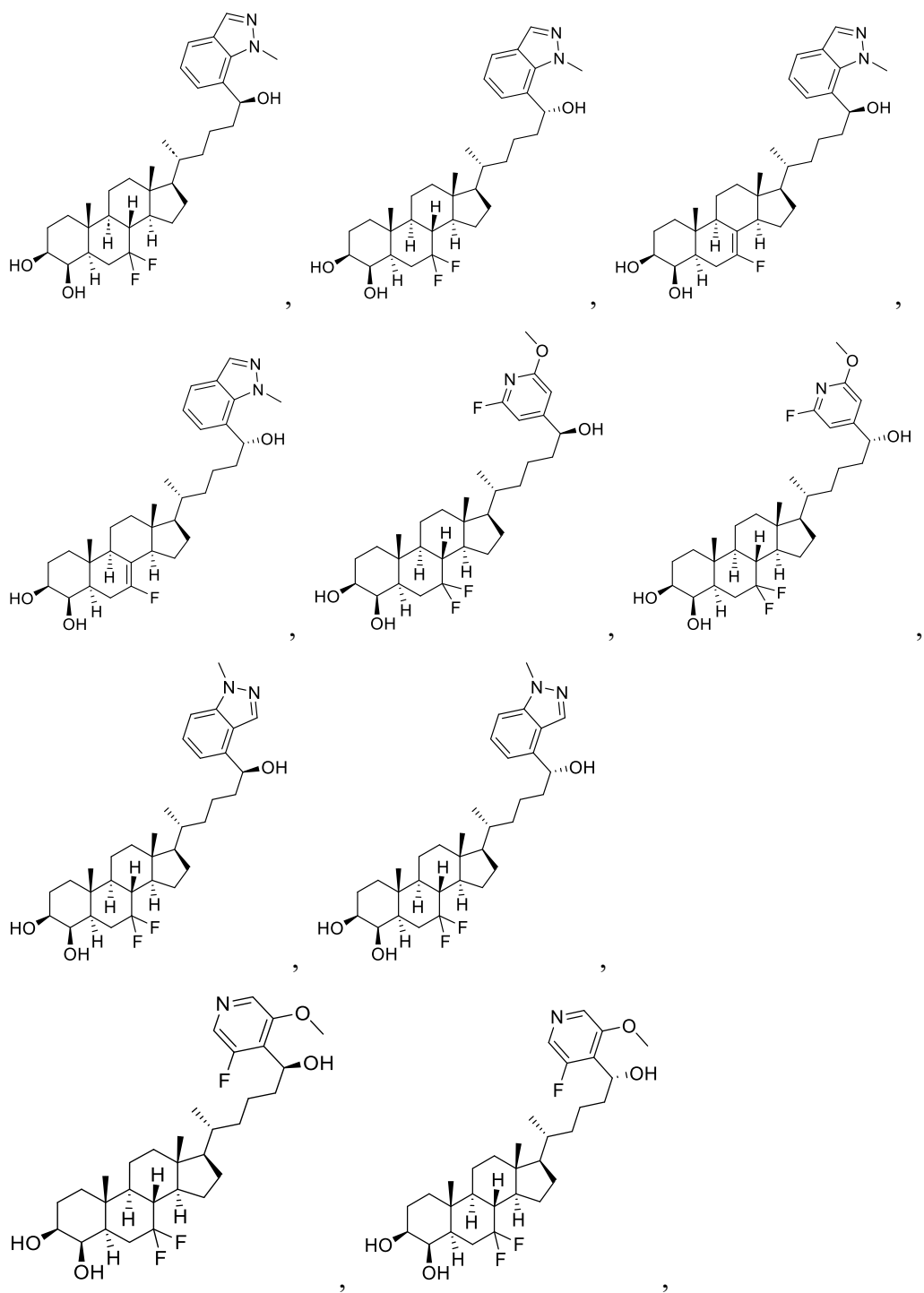


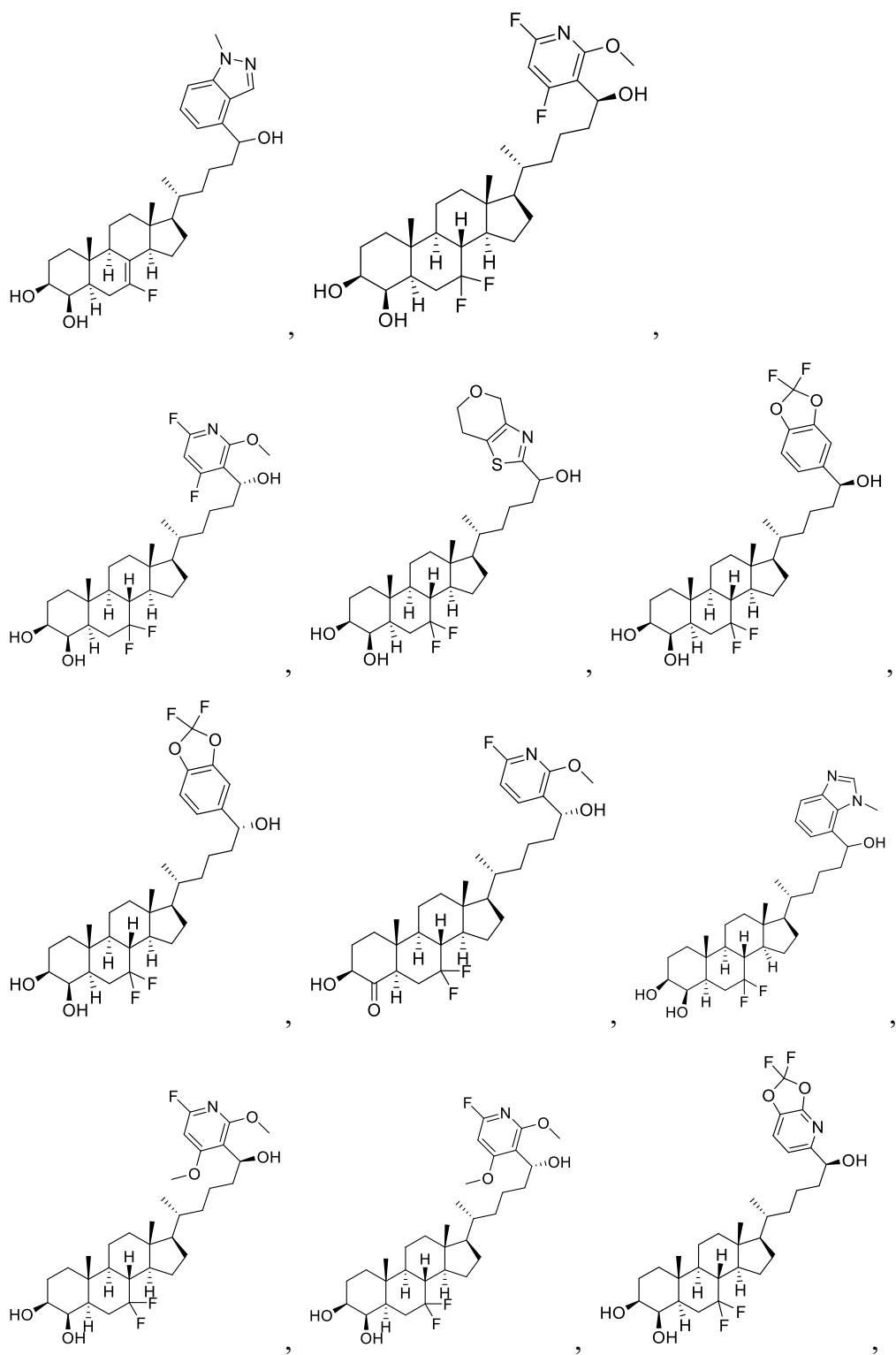


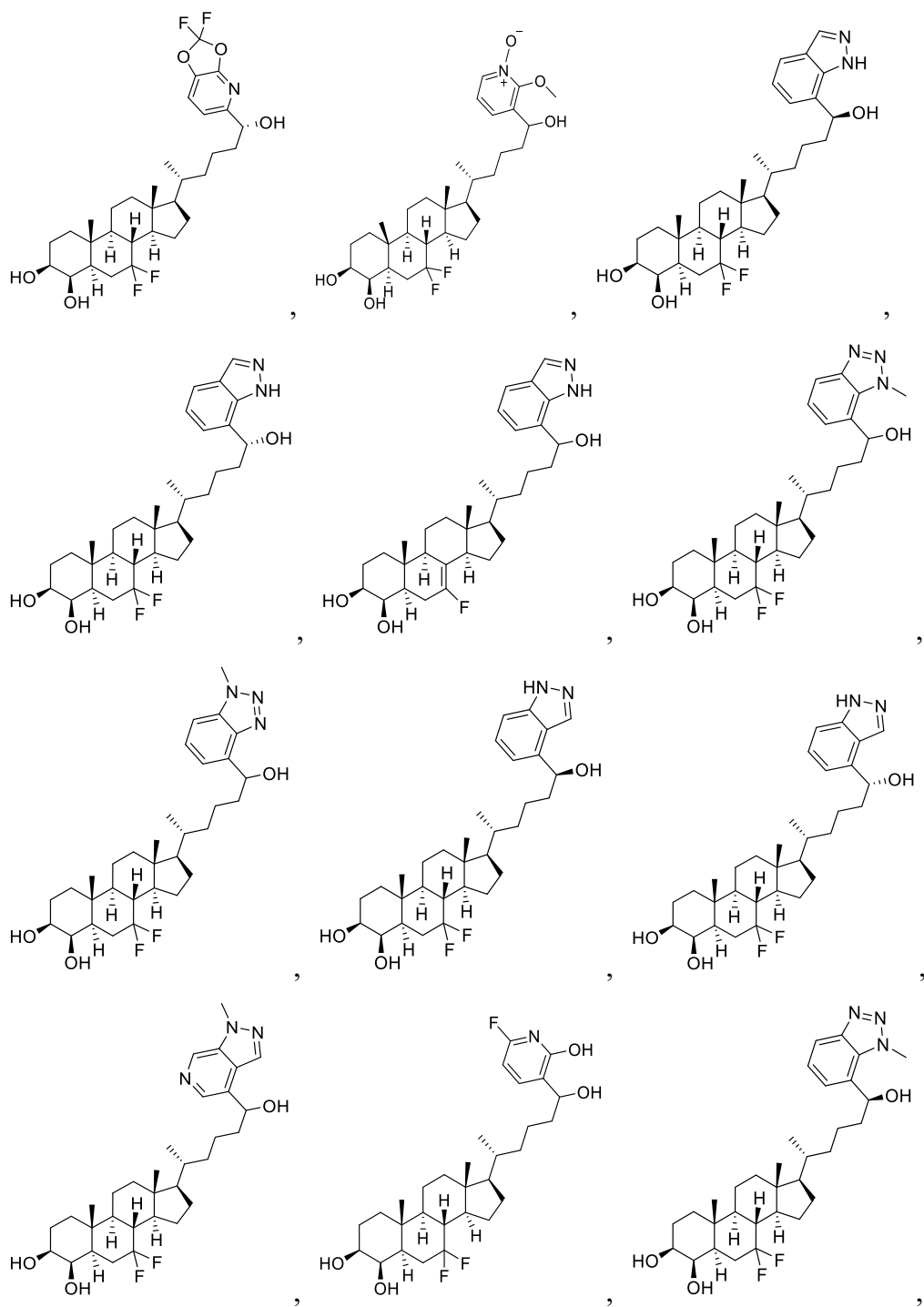


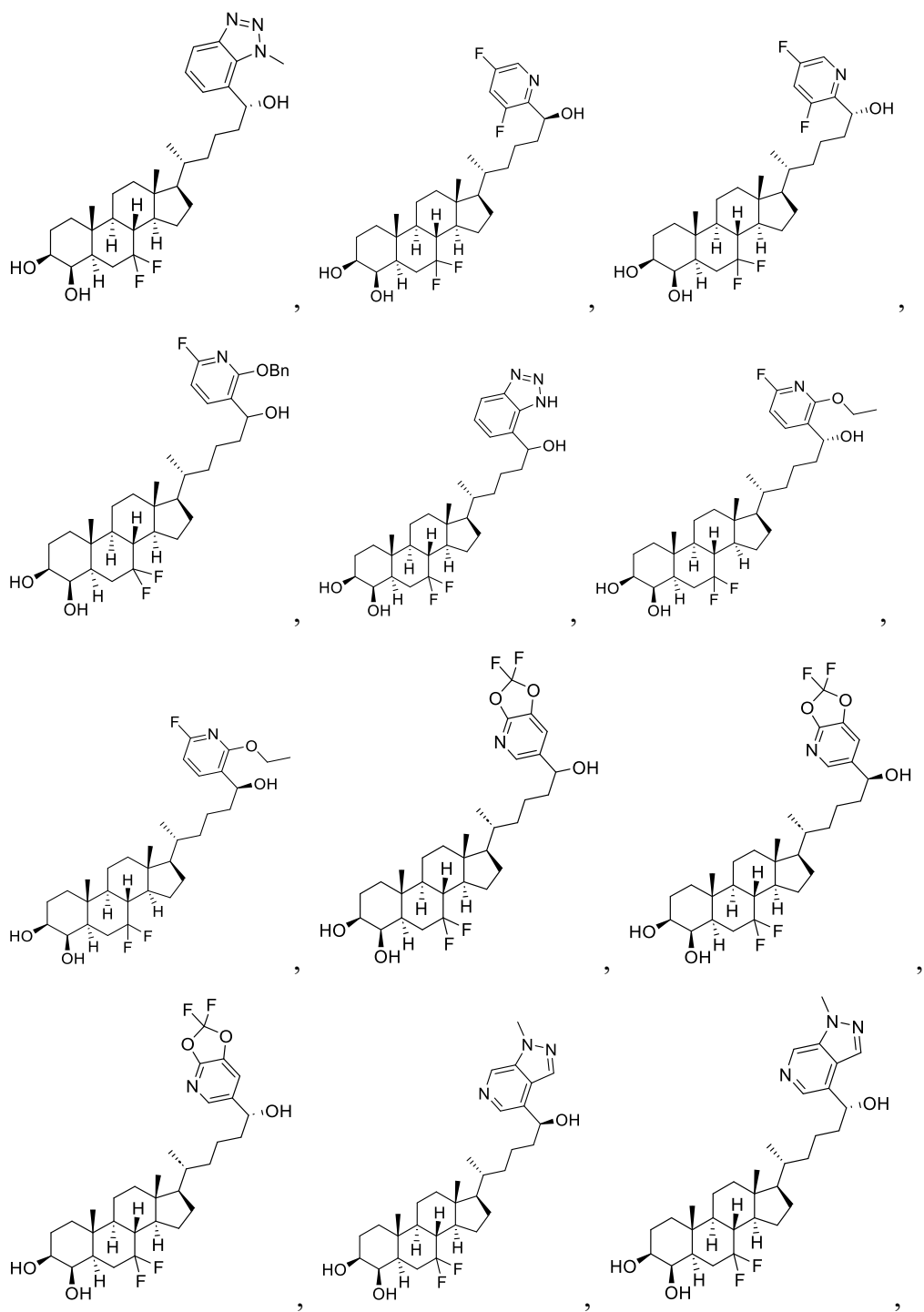


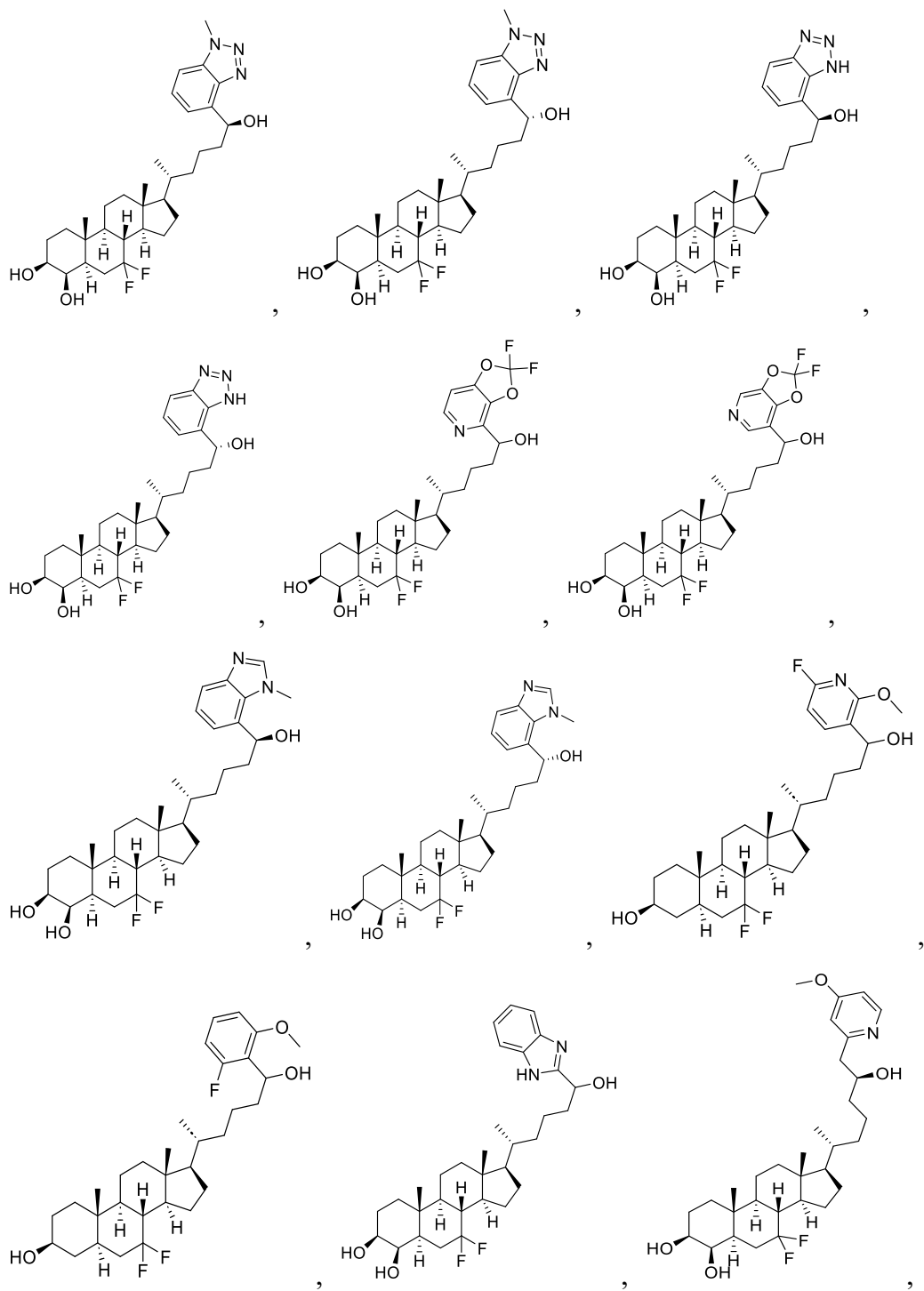


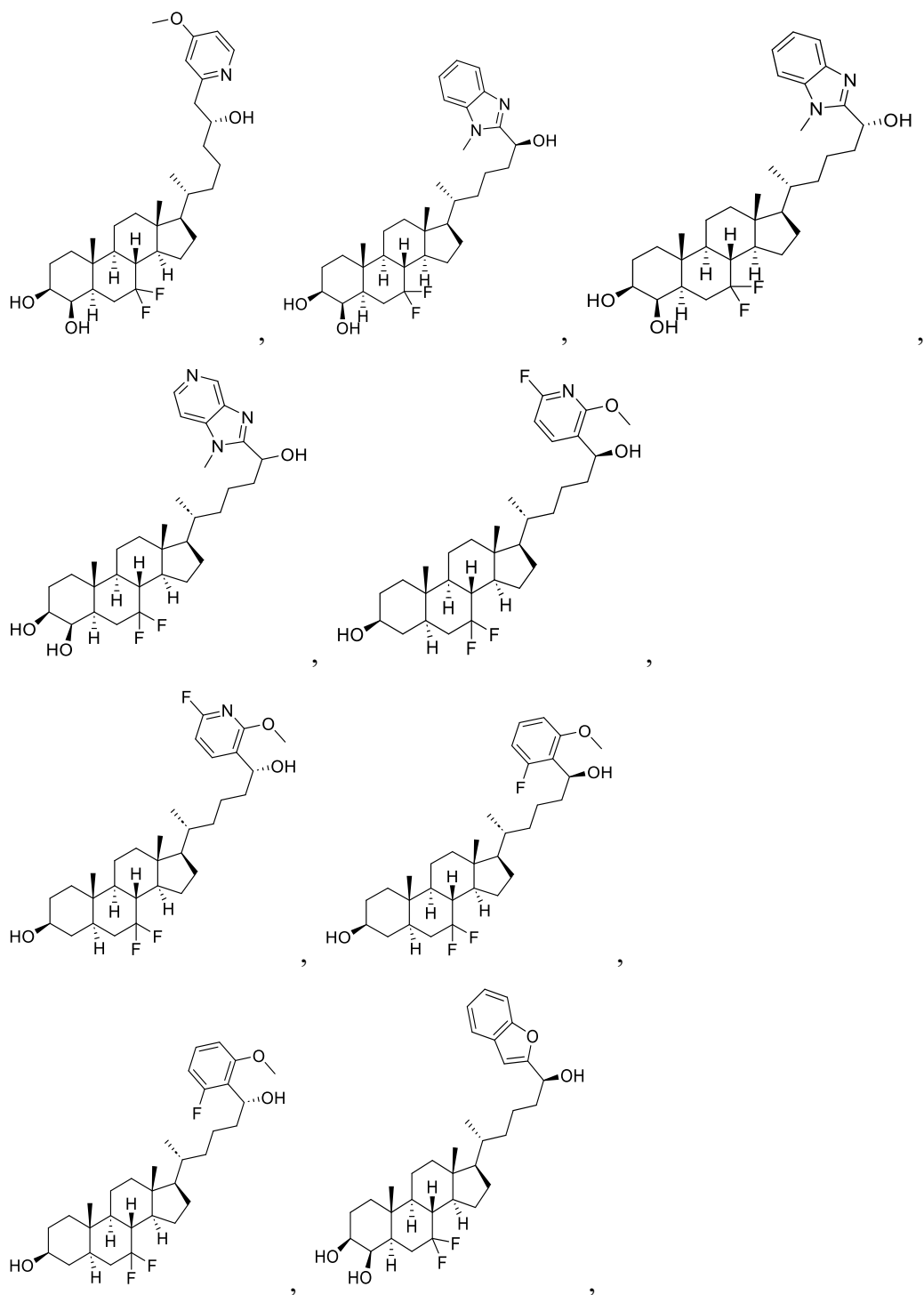


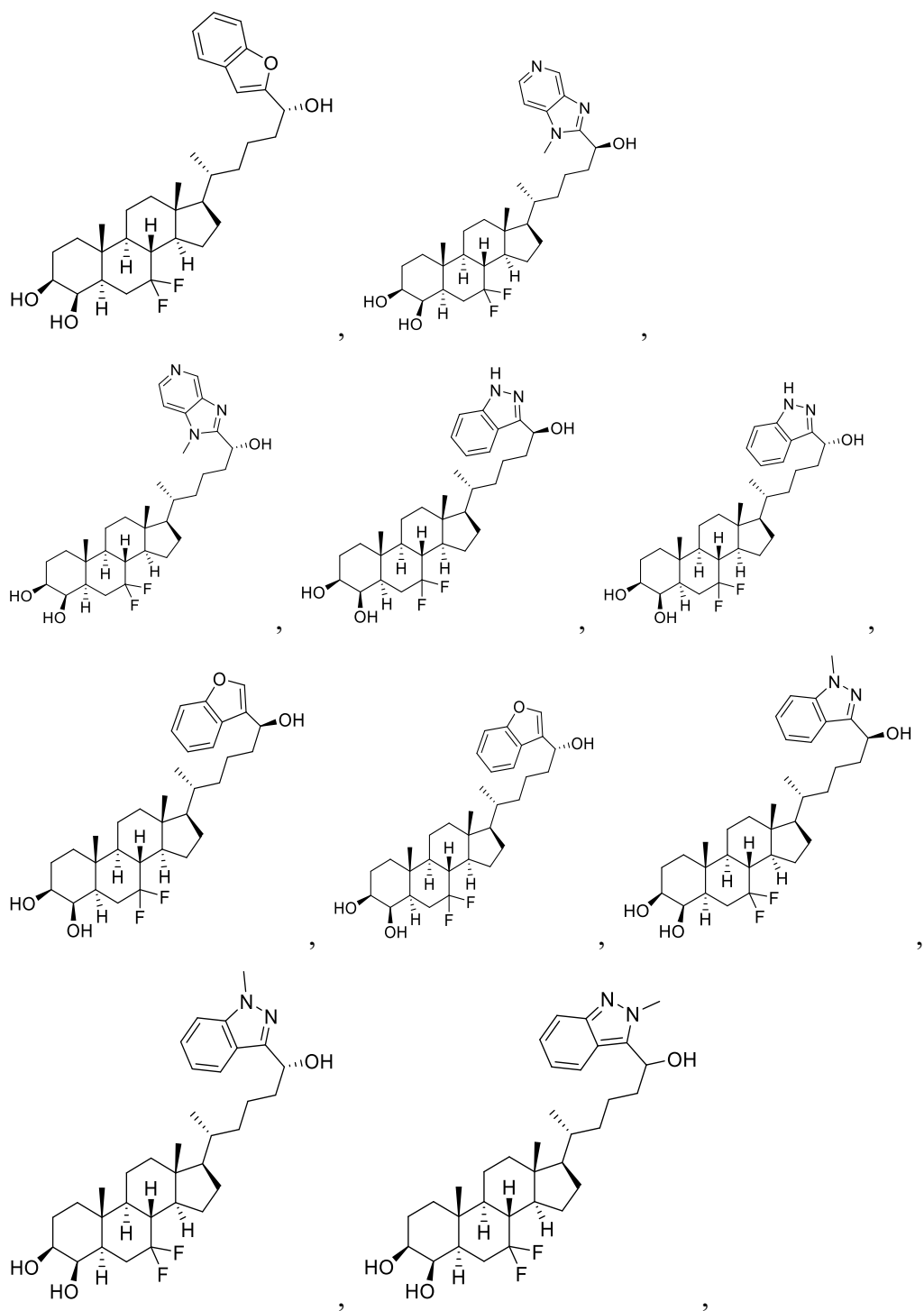


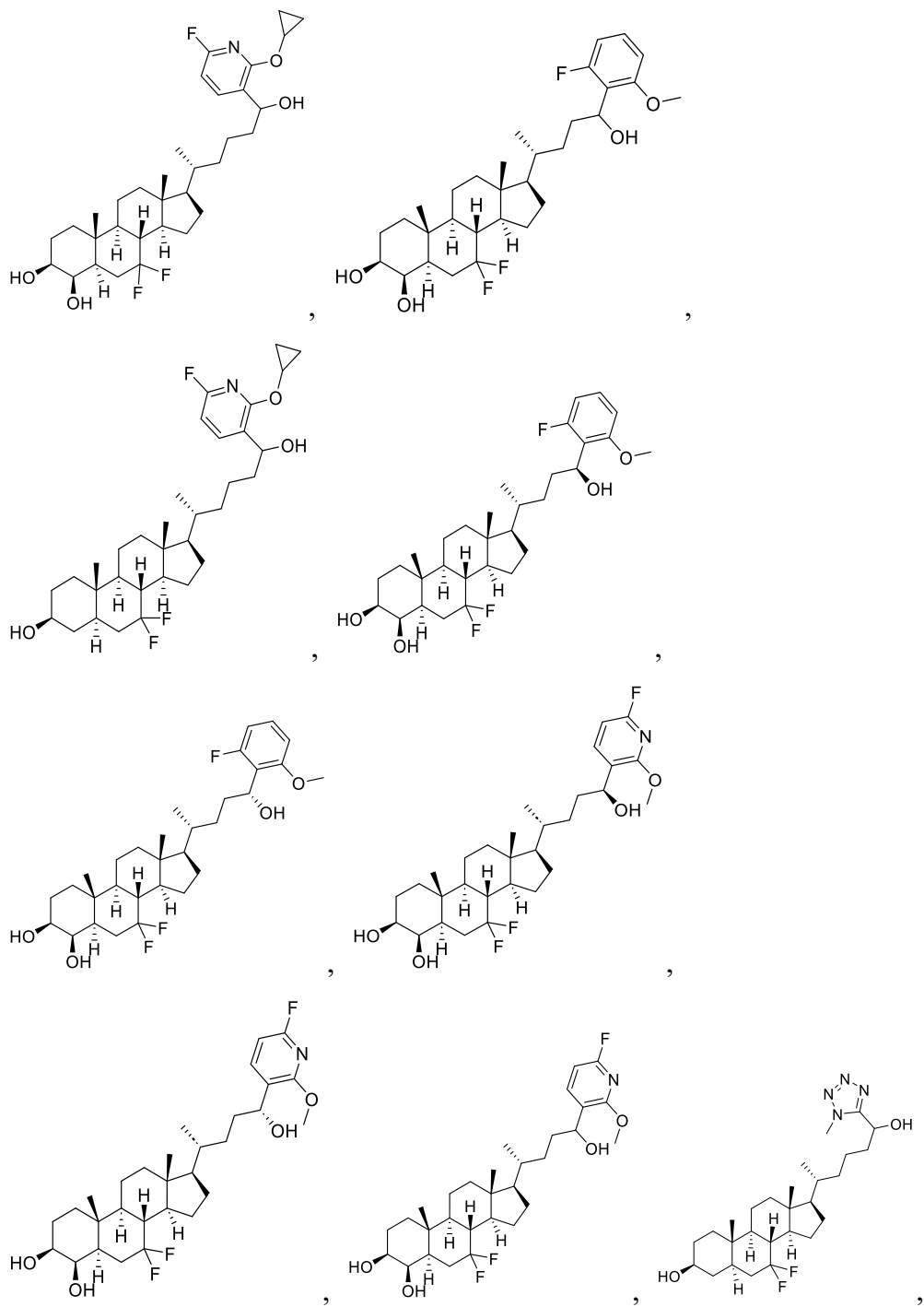


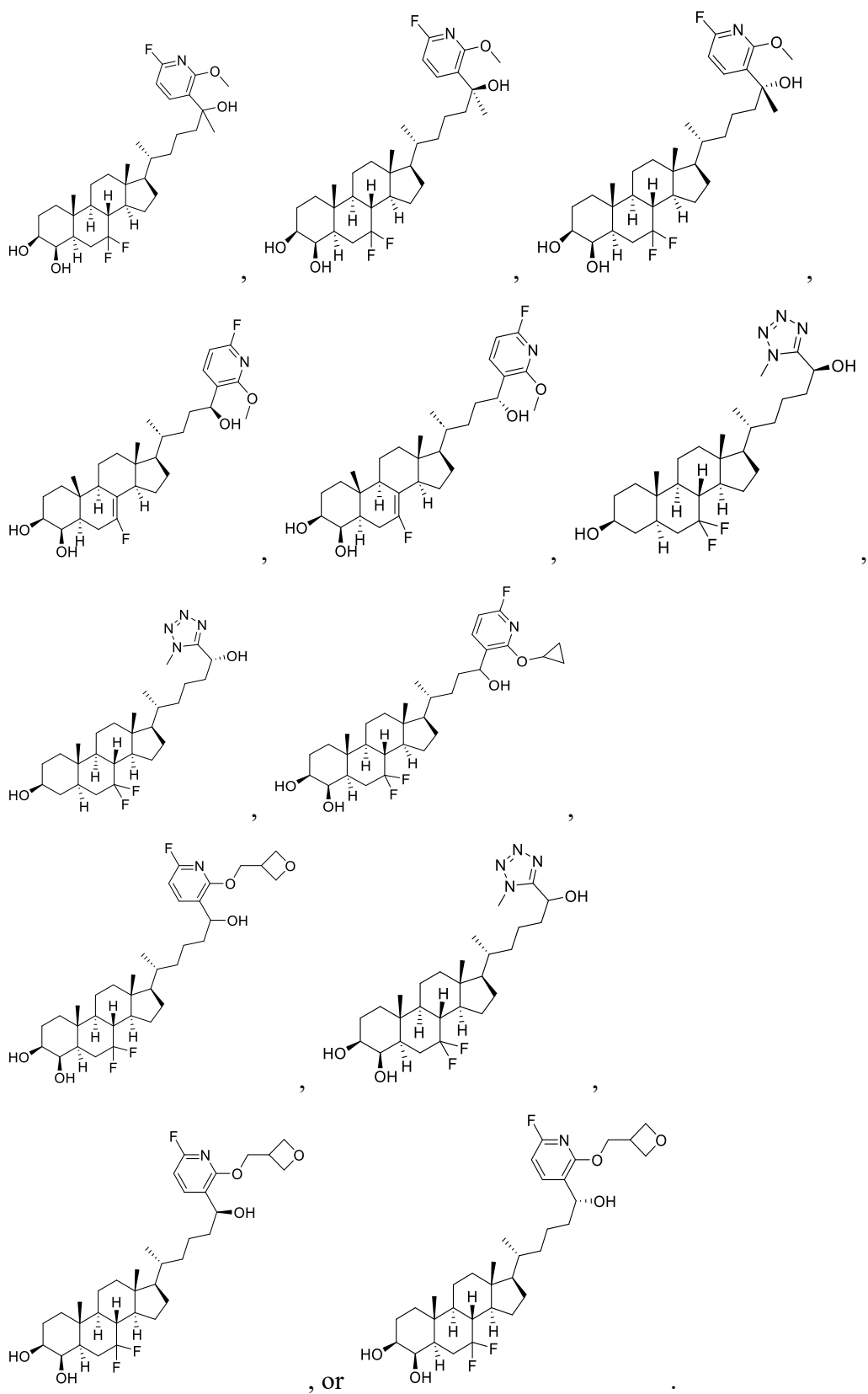












9. A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof as defined in any one of claims 1-8, and at least one pharmaceutical excipient.

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10. Use of the compound or the pharmaceutically acceptable salt thereof as defined in any one of claims 1-8, or the pharmaceutical composition as defined in claim 9 in the manufacture of a medicament for preventing and/or treating a disease, wherein the disease is obesity, hyperlipidemia, fatty liver, diabetes, atherosclerosis, cardiovascular and cerebrovascular diseases, liver cancer, or skin injury.

11. Use of the compound or the pharmaceutically acceptable salt thereof as defined in any one of claims 1-8, or the pharmaceutical composition as described above in the manufacture of a medicament for inhibiting the SREBP pathway.

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