FLUORINATED ESTROGEN RECEPTOR MODULATORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/570,756 entitled "ESTROGEN RECEPTOR MODULATORS AND USES THEREOF" filed on December 14, 2011, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, including pharmaceutically acceptable salts, solvates, metabolites, prodrugs thereof, methods of making such compounds, pharmaceutical compositions comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated.

BACKGROUND OF THE INVENTION

[0003] The estrogen receptor ("ER") is a ligand-activated transcriptional regulatory protein that mediates induction of a variety of biological effects through its interaction with endogenous estrogens. Endogenous estrogens include 17β-estradiol and estrones. ER has been found to have two isoforms, ER-α and ER-β.

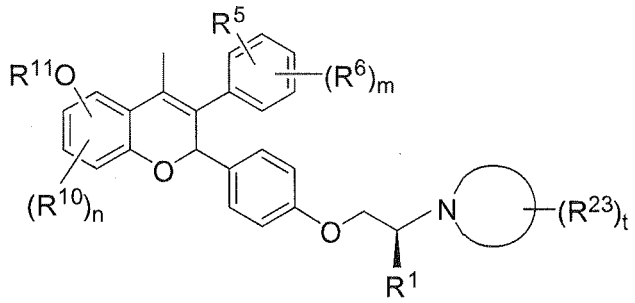
[0004] Estrogens and estrogen receptors are implicated in a number of diseases or conditions, such as breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, uterine cancer, as well as others diseases or conditions.

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[0005] In one aspect, presented herein are compounds of Formula (I), (II), (III), (IV), (V), and (VI) that diminish the effects of estrogens with estrogen receptors and/or lower the the concentrations of estrogen receptors, and therefore, are useful as agents for the treatment or prevention of diseases or conditions in which the actions of estrogens and/or estrogen receptors are involved in the etiology or pathology of the disease or condition or contribute to at least one symptom of the disease or condition and wherein such actions of estrogens and/or estrogen receptors are undesirable. In some embodiments, compounds disclosed herein are estrogen receptor degrader compounds.

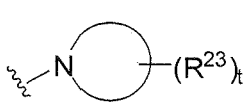
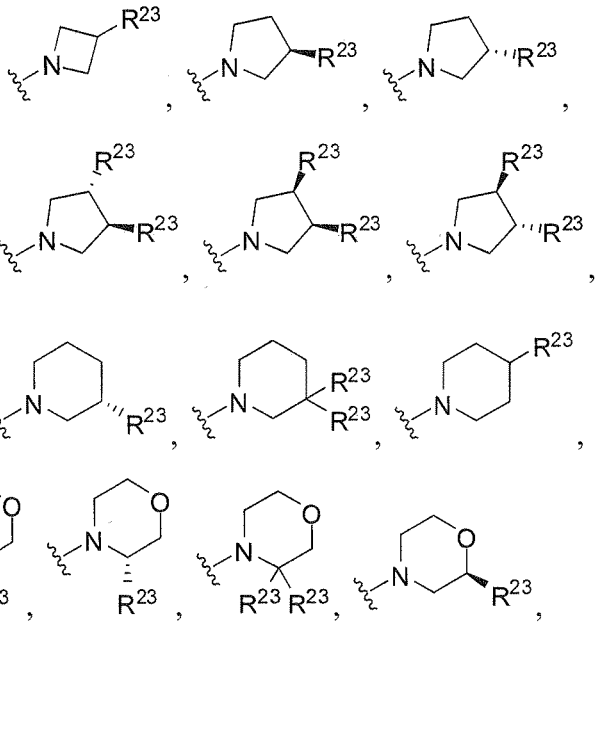
[0006] In one aspect, a compound of Formula (I), (II), (III), (IV), (V), or (VI) is useful for the treatment of ER-related diseases or conditions including, but not limited to, ER-α dysfunction associated with cancer (bone cancer, breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer), central nervous system (CNS) defects (alcoholism, migraine), cardiovascular system defects (aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension), hematological system defects (deep vein thrombosis), immune and inflammation diseases (Graves' Disease, arthritis, mulitple

[0014] In some embodiments, the compound of Formula (I) has the structure of Formula (II):



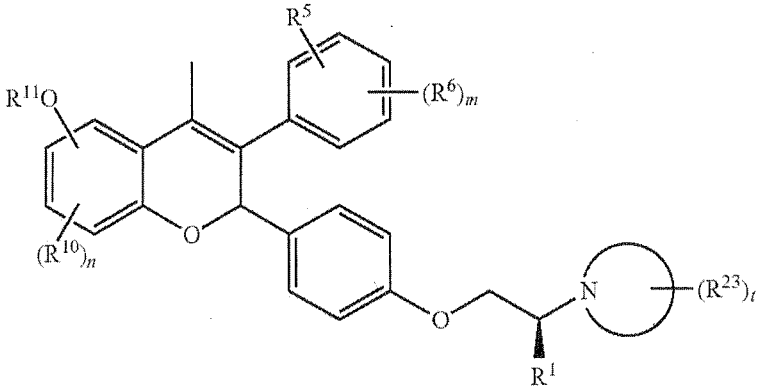
Formula (II)

or is a pharmaceutically acceptable salt, or solvate thereof.

[0015] In some embodiments,  is  .

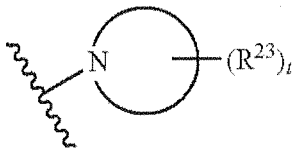
[0015a] In one aspect, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt, or solvate thereof:

Formula (II)

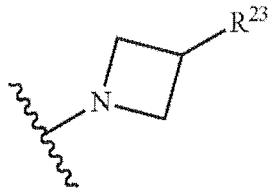


wherein,

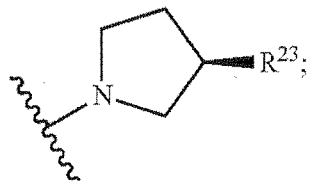
R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;



is



or



R^{23} is —CH_2F;

t is 1;

R^5 is H, halogen, —CN, —OH, —OR^{11}, —NHR^{11}, —$NR^{11}R^{12}$, SR^{11}, —S(=O)R^{12}, —S(O)$_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, —CN, —OH, —OR^{11}, —SR^{11}, —S(=O)R^{12}, —S(=O)$_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{10} is independently selected from H, halogen, —CN, —OH, —OR^{11}, —SR^{11}, —S(=O)R^{12}, —S(=O)$_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

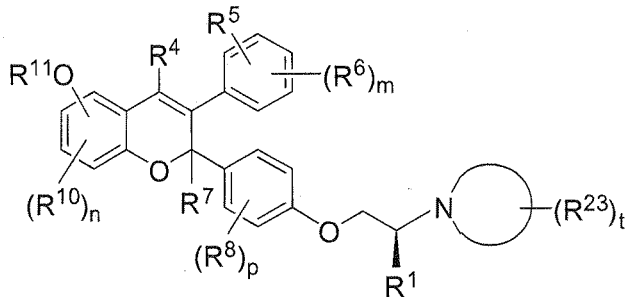
each R^{11} is independently selected from H, —C(=O)R^{12}, —C(=O)OR^{12}, —C(=O)NHR^{12}, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted aryl), and —C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted aryl), and —C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

m is 0, 1, 2, 3 or 4; and

n is 0, 1, or 2.

[0016] In another aspect, described herein is a compound of Formula (III), or a pharmaceutically acceptable salt, or solvate thereof:



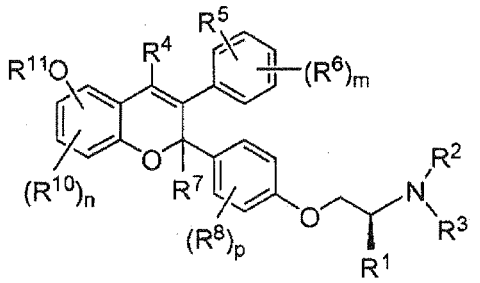
Formula (III)

wherein,

R^1 is C_1-C_6fluoroalkyl;

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

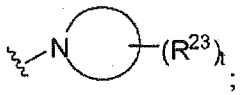
wherein,

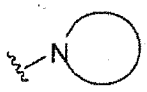
R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form

 ;

 is a monocyclic C_2-C_{10} heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

t is 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

R^7 is H or C_1-C_4alkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-

C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

m is 0, 1, 2, 3 or 4;

n is 0, 1, or 2;

p is 0, 1, or 2;

provided that the compound is not 2-(4-((S)-2-((R)-3-fluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

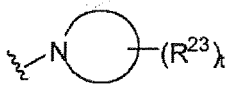
2. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is H or C_1-C_6alkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form



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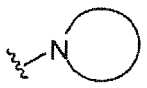


is a 4-, 5-, 6- or 7-membered monocyclic C_2-C_6heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

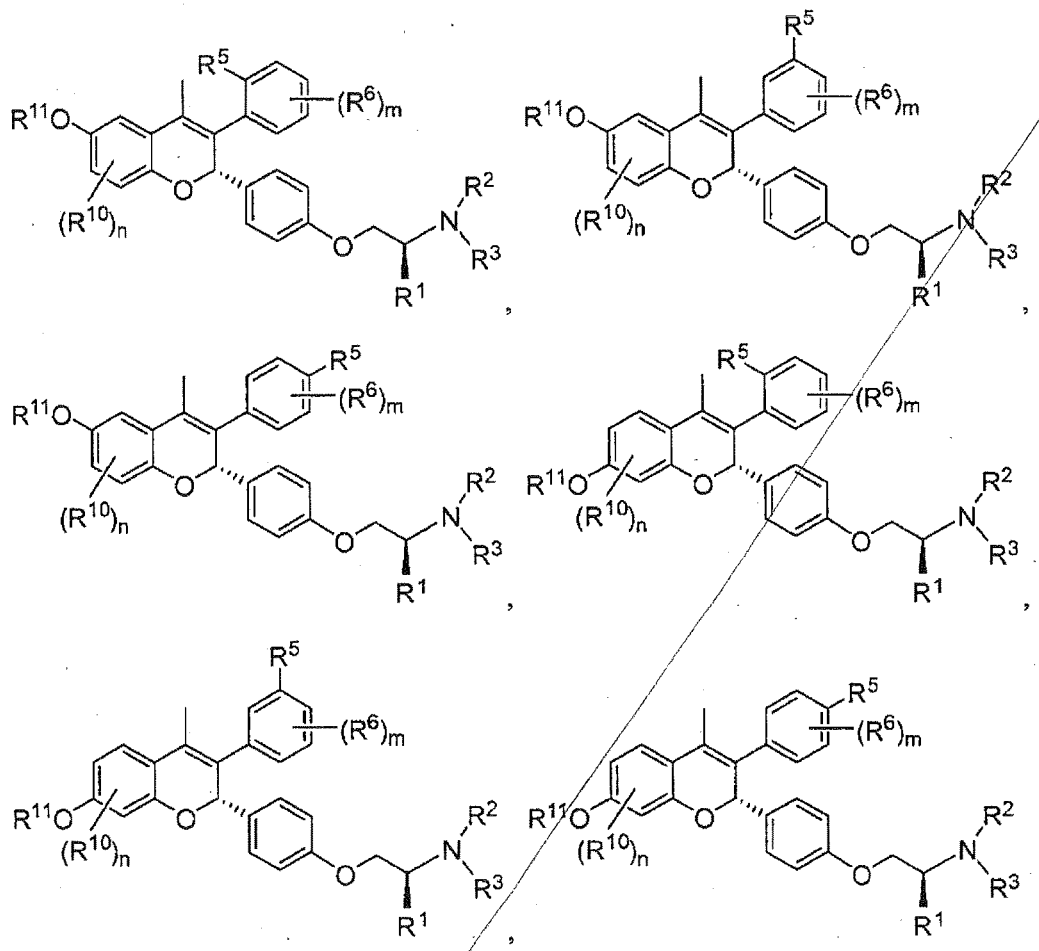
t is 1 or 2;

R^4 is -CH_3;

R^7 is H;

p is 0 or 1.

3. The compound of claim 1 or claim 2, wherein the compound has one of the following structures:



or is a pharmaceutically acceptable salt, or solvate thereof.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^5 is -OH;

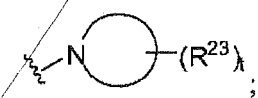
each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

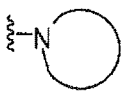
R^{11} is H.

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

R^1 is H, or $-CH_3$;

R^2 and R^3 are taken together with the N atom to which they are attached to form

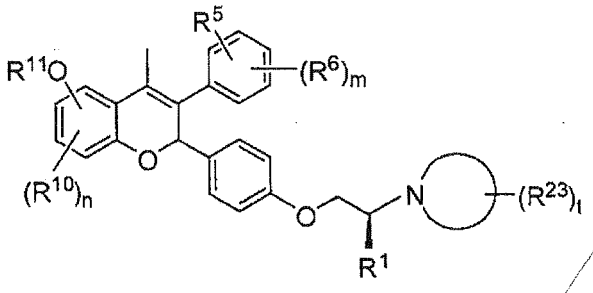
 ;



is azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, morpholinyl, or piperazinyl;

each R^{23} is independently F, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$.

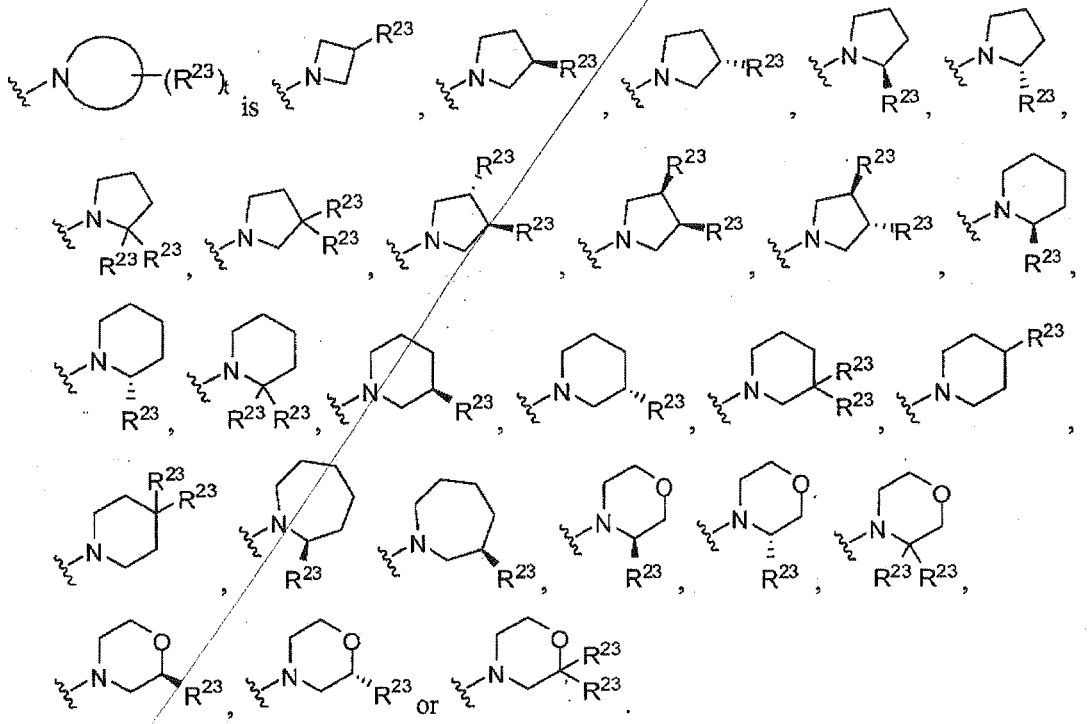
6. The compound of claim 1 or claim 2, wherein the compound of Formula (I) has the structure of Formula (II):



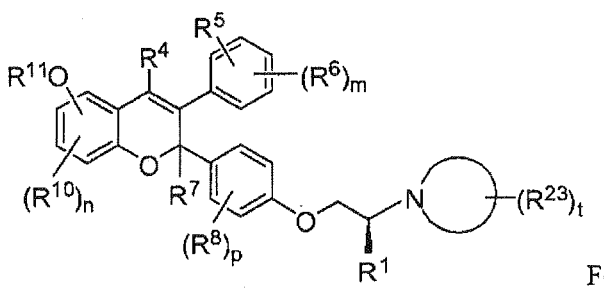
Formula (II)

or is a pharmaceutically acceptable salt, or solvate thereof.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



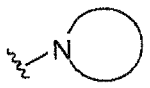
8. A compound of Formula (III), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (III)

wherein,

R^1 is C_1-C_6fluoroalkyl;

 is a monocyclic C_2-C_{10}heterocycloalkyl;

each R^{23} is independently F, C_1-C_6alkyl or C_1-C_6fluoroalkyl;

t is 0, 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, $-OR^{11}$, $-NHR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)NHR^{12}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

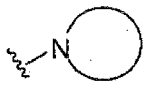
m is 0, 1, 2, 3 or 4;

n is 0, 1, or 2;

p is 0, 1, or 2.

9. The compound of claim 8, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is $-CH_2F$, $-CHF_2$, or $-CF_3$;

 is an azetidinyl, pyrrolidinyl, piperidinyl, or azepanyl;

each R^{23} is independently F, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$;

t is 0, 1 or 2;

R^4 is $-CH_3$;

R^7 is H;

p is 0 or 1.

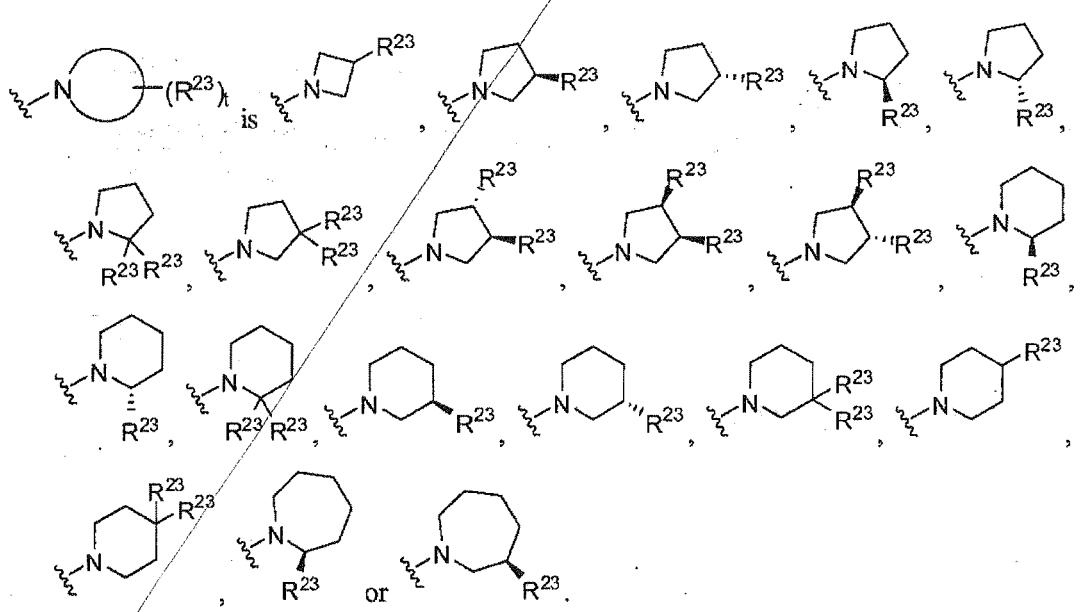
10. The compound of claim 8 or claim 9, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^5 is -OH;

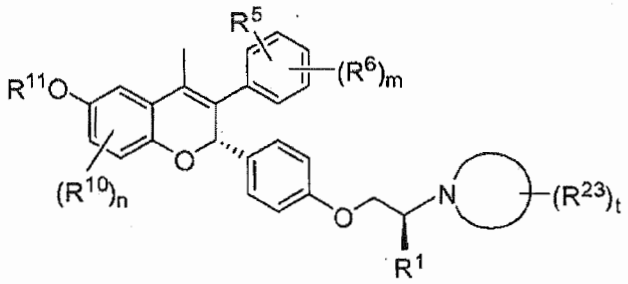
each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

R^{11} is H.

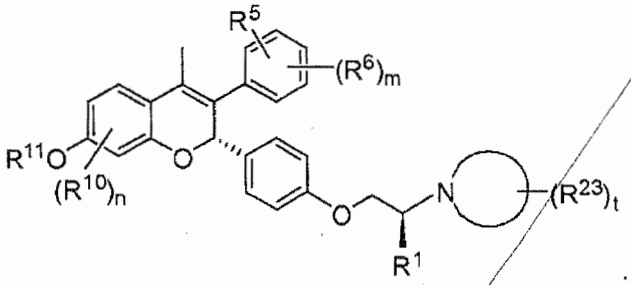
11. The compound of any one of claims 8-10, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



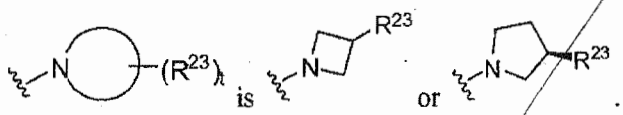
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has one of the following structures:



or



13. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



14. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof.

15. The pharmaceutical composition of claim 14, wherein the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration.

16. The pharmaceutical composition of claim 14, wherein the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

17. A compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, for use in the treatment of an estrogen receptor dependent or estrogen receptor mediated disease or condition in mammal, wherein the estrogen receptor dependent or estrogen receptor mediated disease or condition is selected from cancer, uterine disease, central nervous system (CNS) defects, cardiovascular system defects, hematological system defects, immune and inflammation diseases, susceptibility to infection, metabolic defects, neurological defects, psychiatric defects and reproductive defects

18. A compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, for use in the treatment of bone cancer, breast cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian cancer, uterine cancer, cervical cancer, lung cancer, leiomyoma,

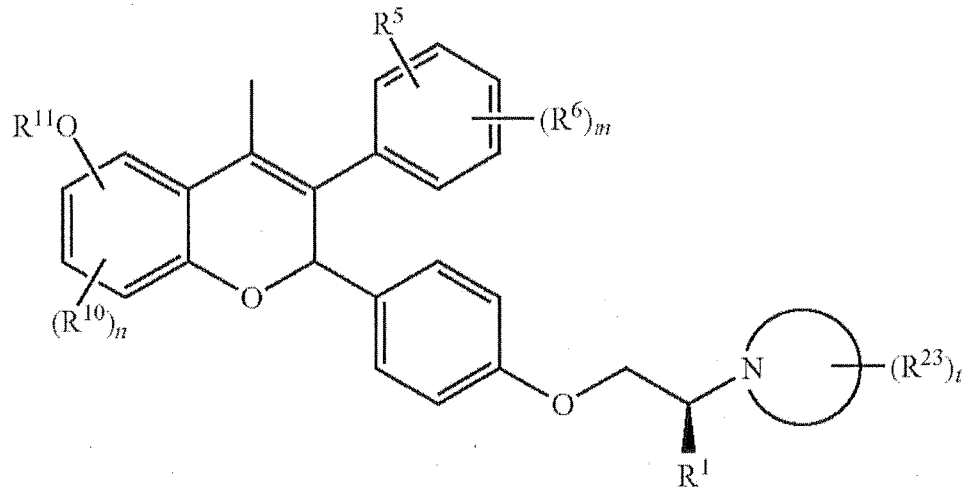
uterine leiomyoma, migraine, cardiovascular disease, hypertension, Graves' Disease, arthritis, multiple sclerosis, cirrhosis, hepatitis B, chronic liver disease, bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis, Alzheimer's disease, Parkinson's disease, dementia, major depressive disorder, psychosis, age of menarche, endometrial hyperplasia, or endometriosis in a mammal.

19. A compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, for use in medicine.

CLAIMS

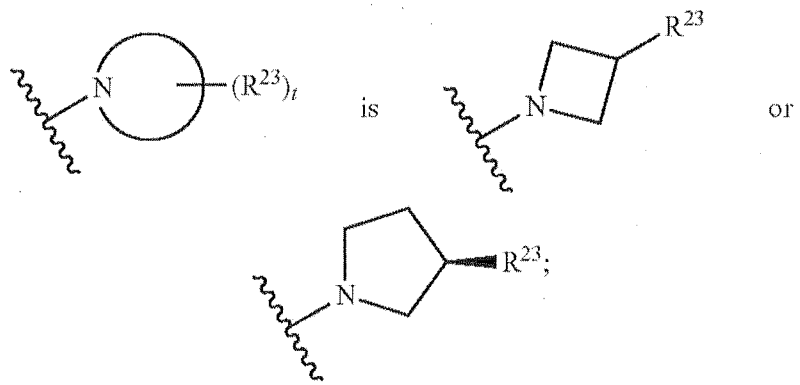
1. A compound of Formula (II), or a pharmaceutically acceptable salt, or solvate thereof:

Formula (II)



wherein,

R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;



R^{23} is —CH_2F;

t is 1;

R^5 is H, halogen, —CN, —OH, —OR^{11}, —NHR^{11}, —$NR^{11}R^{12}$, SR^{11}, —$S(=O)R^{12}$, —$S(O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, —CN, —OH, —OR^{11}, —SR^{11}, —$S(=O)R^{12}$, —$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{10} is independently selected from H, halogen, —CN, —OH, —OR^{11}, —SR^{11}, —$S(=O)R^{12}$, —$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, —$C(=O)R^{12}$, —$C(=O)OR^{12}$, —$C(=O)NHR^{12}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted aryl), and —C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), —C_1-C_2alkylene-(substituted or unsubstituted aryl), and —C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

m is 0, 1, 2, 3 or 4; and

n is 0, 1, or 2.

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

R^1 is H or C_1-C_6alkyl.

3. The compound of claim 2, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^5 is —OH;

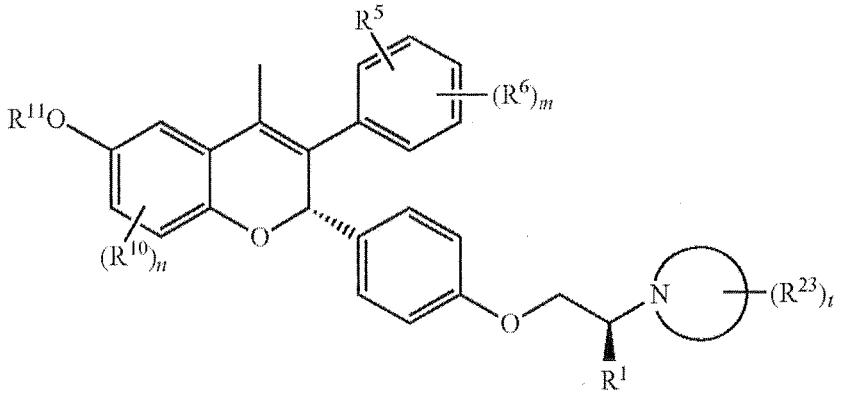
each R^{10} is independently selected from H, halogen, —CN, —OH, —$S(=O)R^{12}$, —$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; and

R^{11} is H.

4. The compound of claim 3, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is H, or —CH_3.

5. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has one of the following structures:



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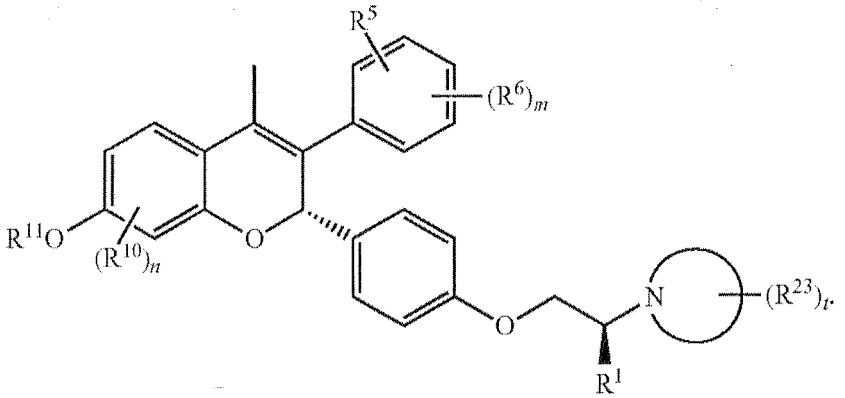


6. The compound of claim 5, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

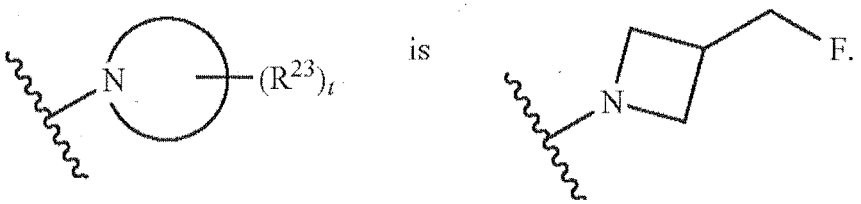
R^5 is —OH;

each R^6 is independently selected from H and halogen;

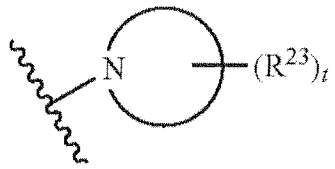
each R^{10} is independently selected from H and halogen; and

R^{11} is H.

7. The compound of claim 6, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



8. The compound of claim 6, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



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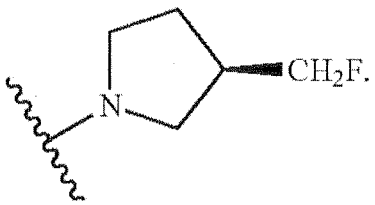
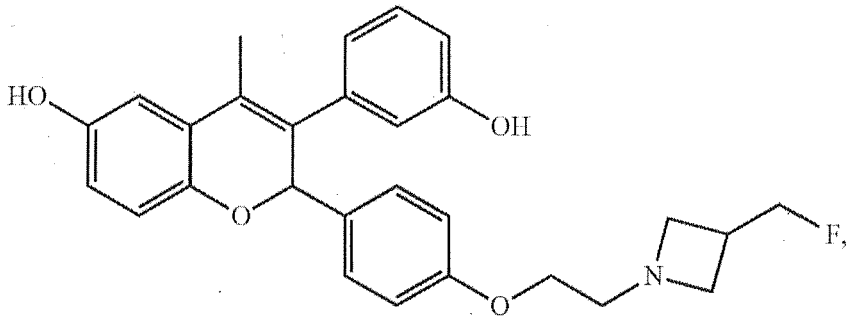
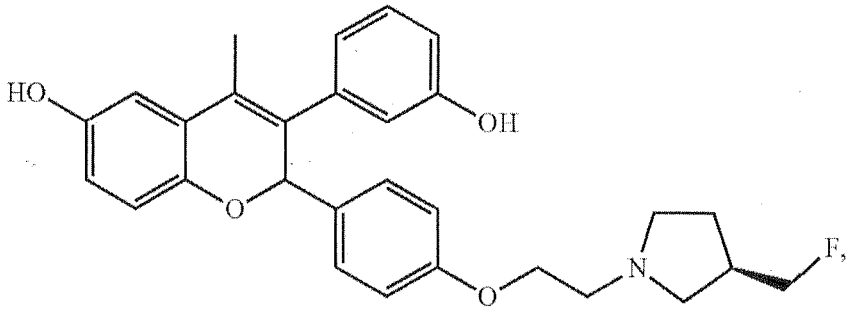
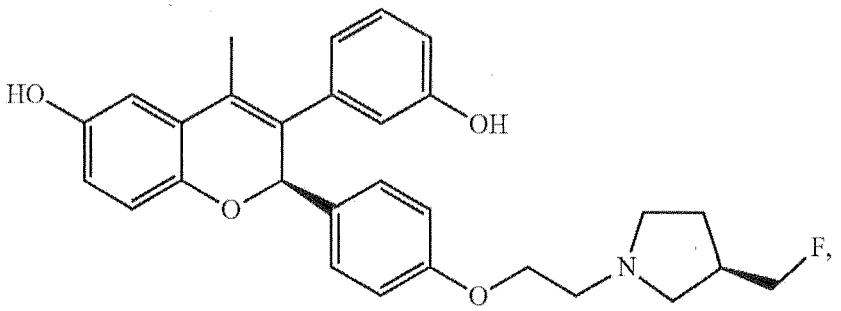
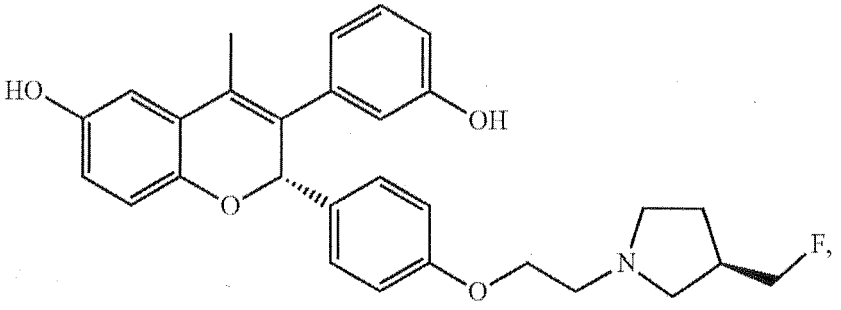


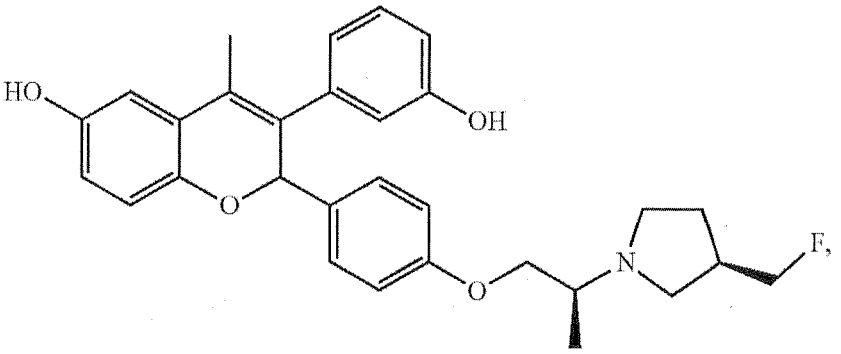
9. The compound of claim 1, wherein the compound has one of the following structures:

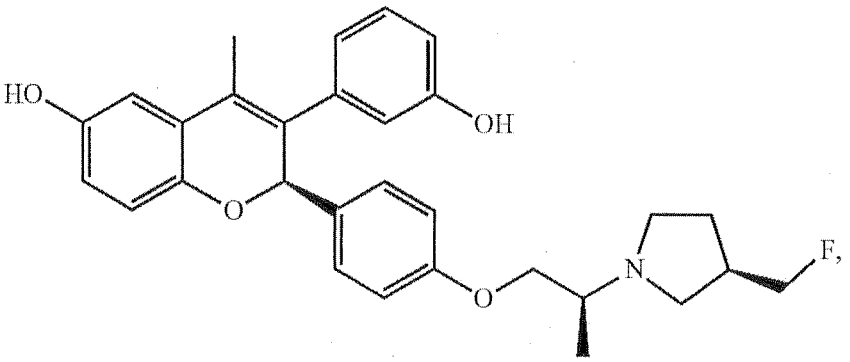


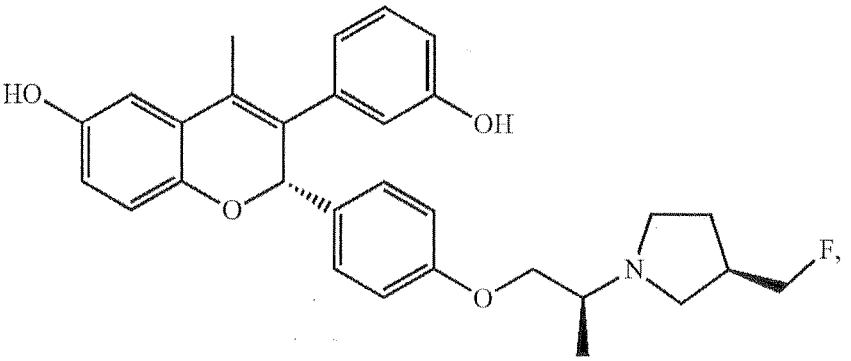


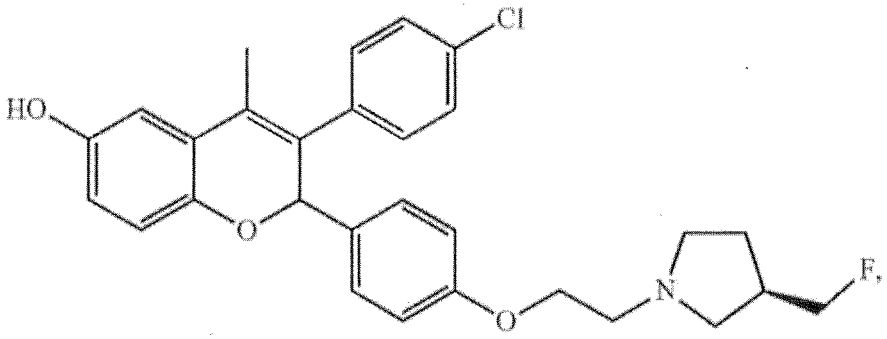


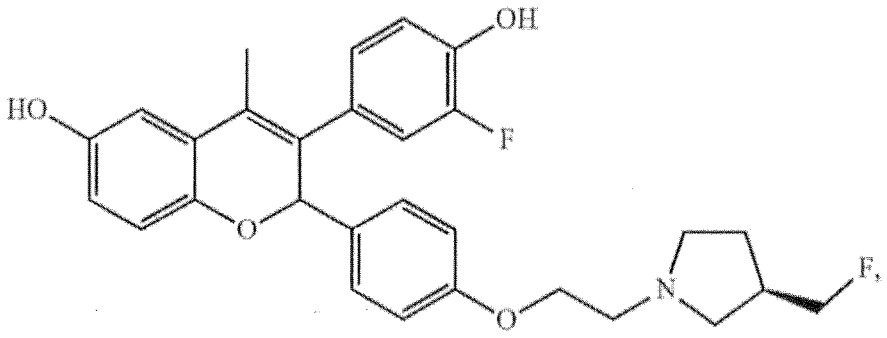


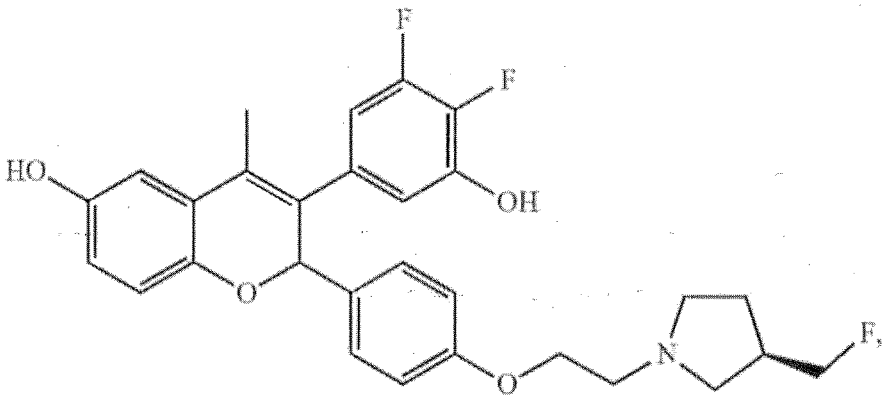


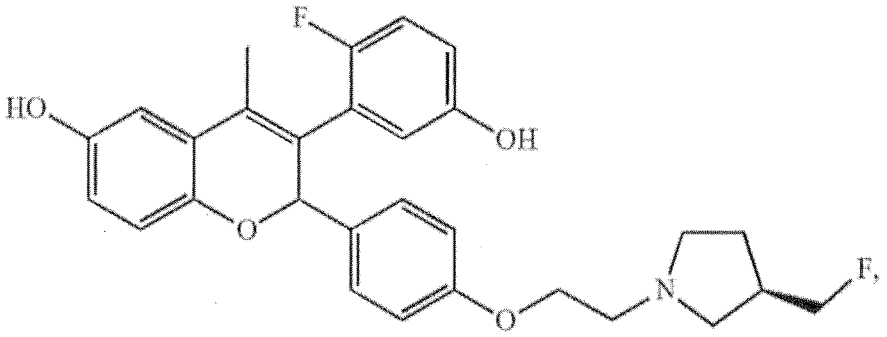


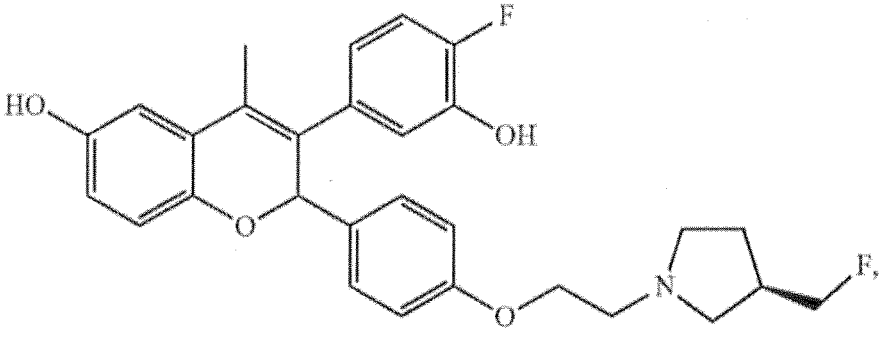


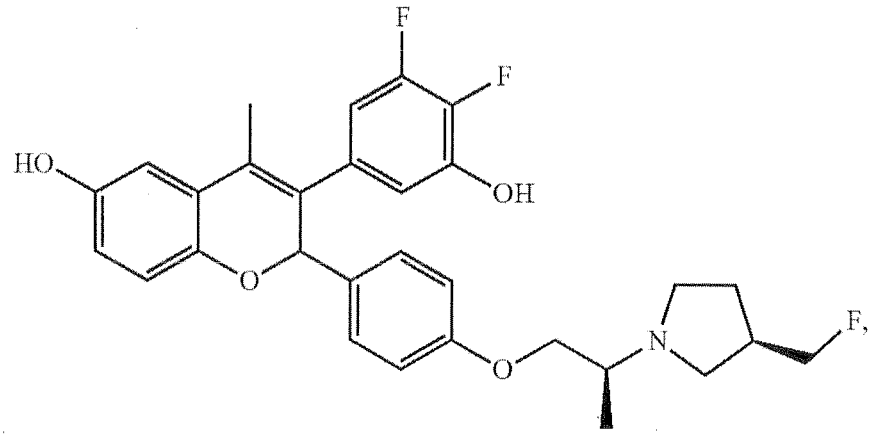








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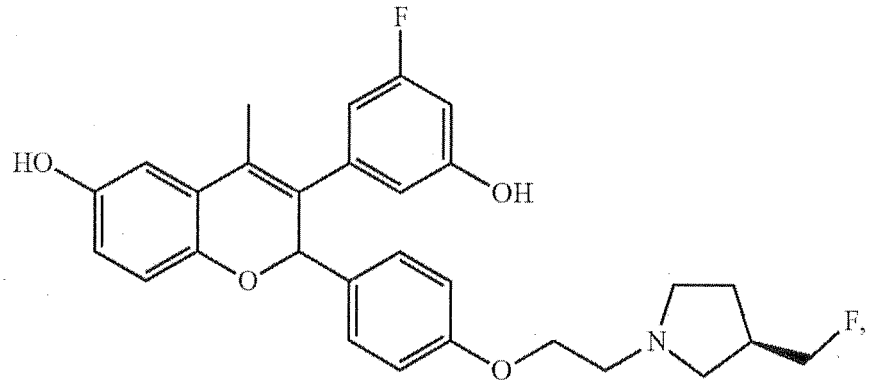
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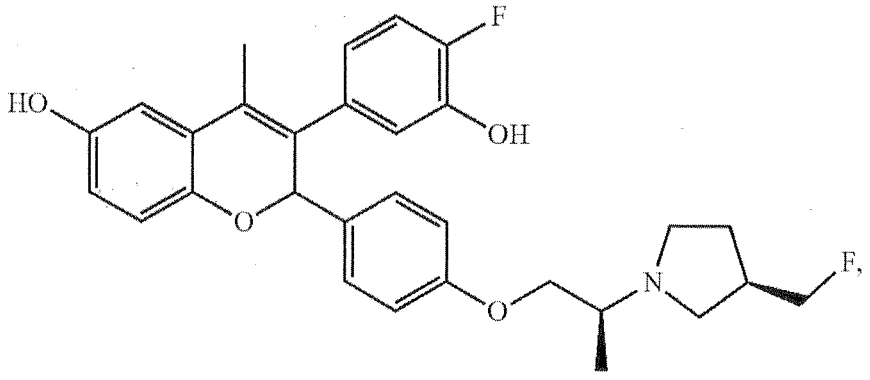
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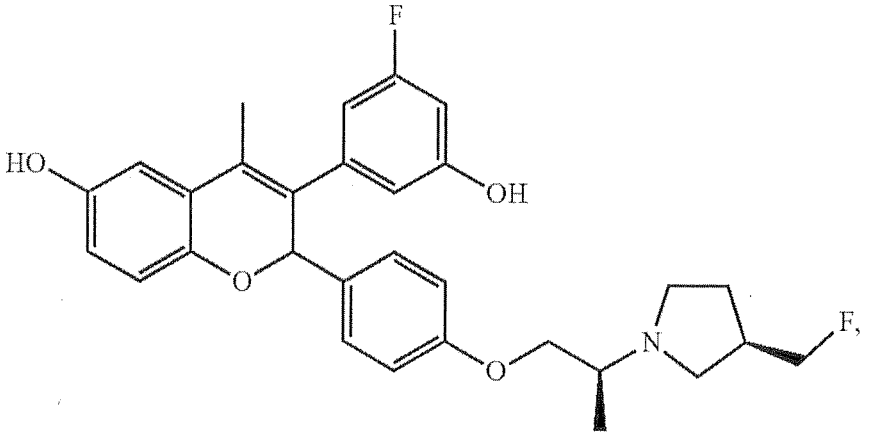
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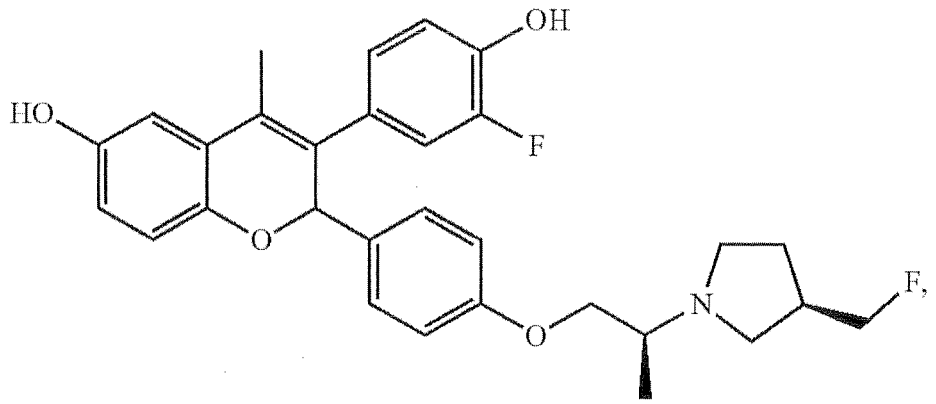
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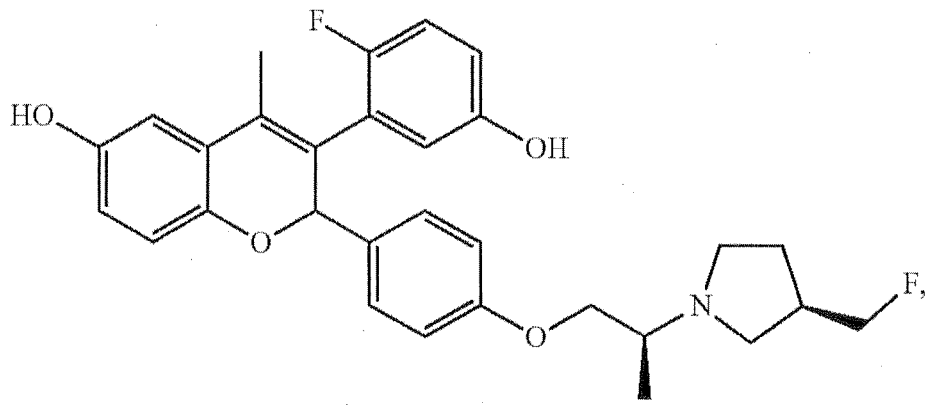
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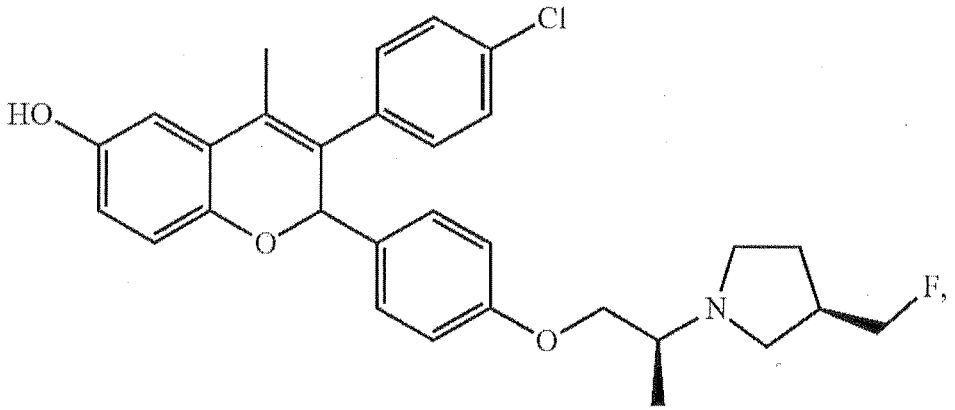
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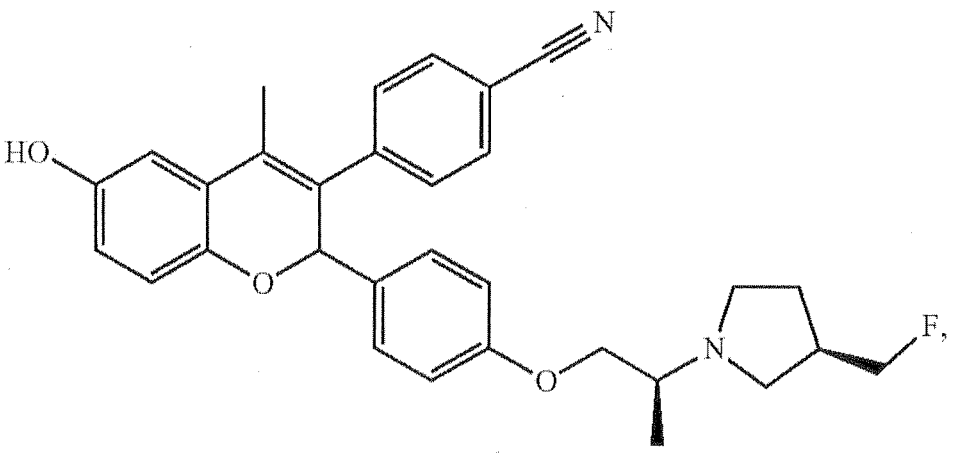
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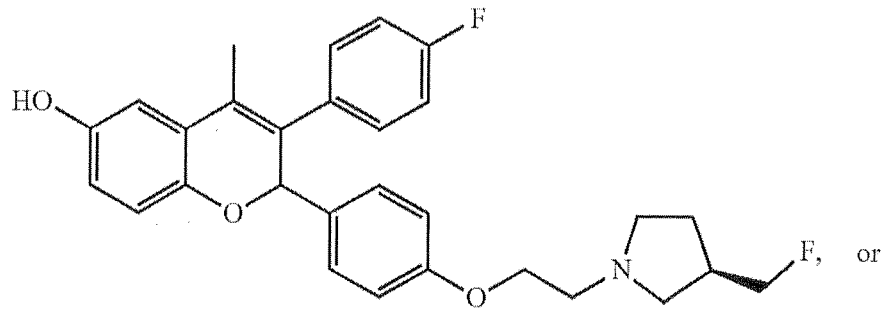

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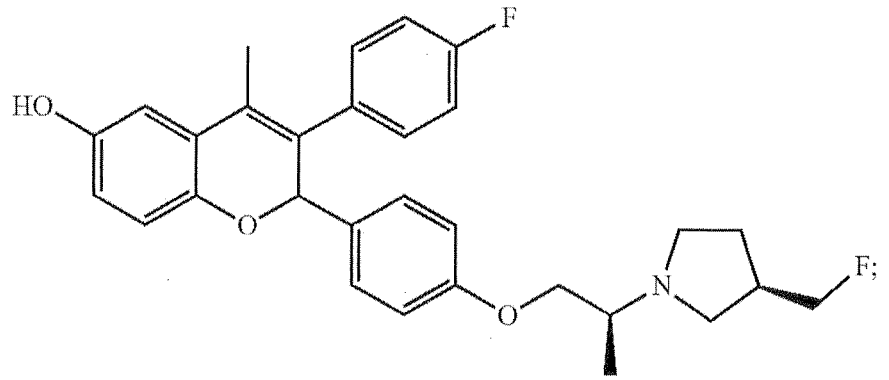
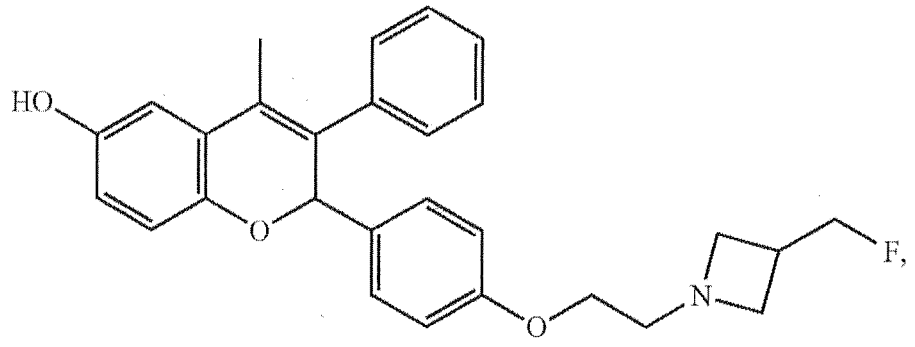
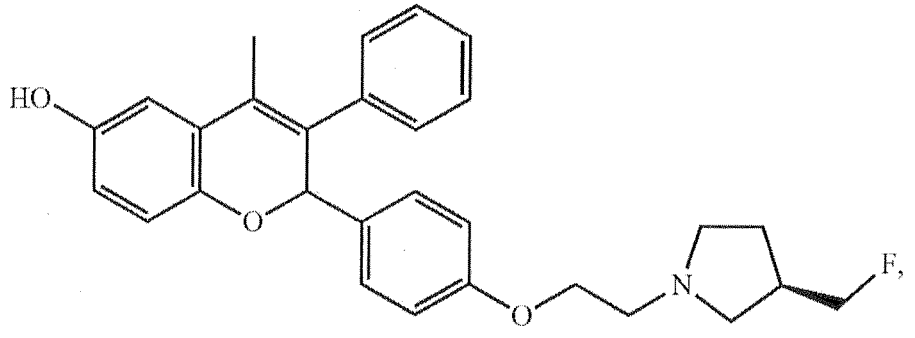
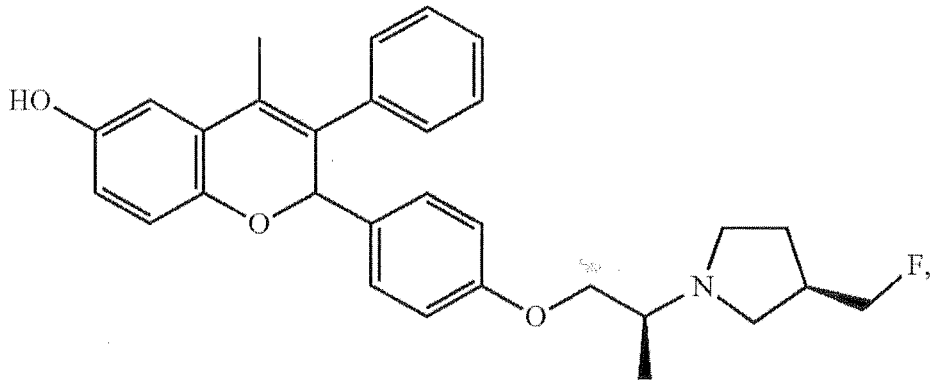


or a pharmaceutically acceptable salt, or solvate thereof.

10. The compound of claim 1, wherein the compound has one of the following structures:



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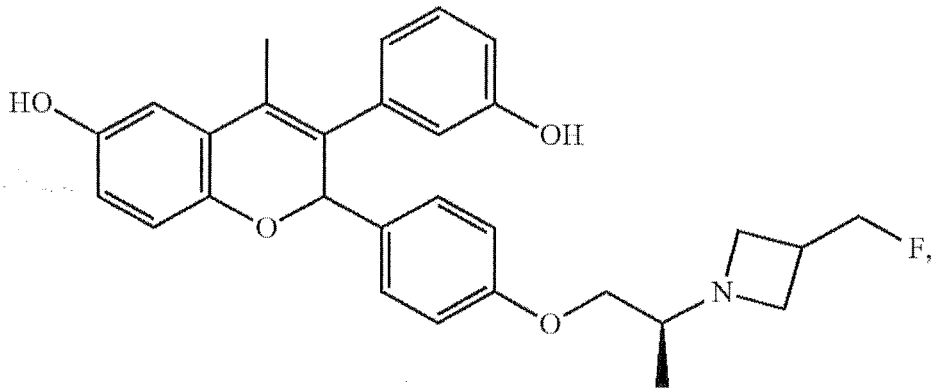
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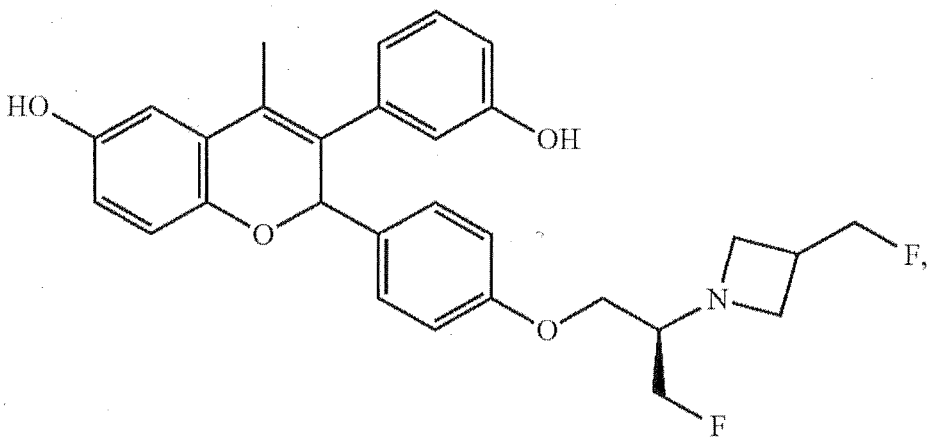
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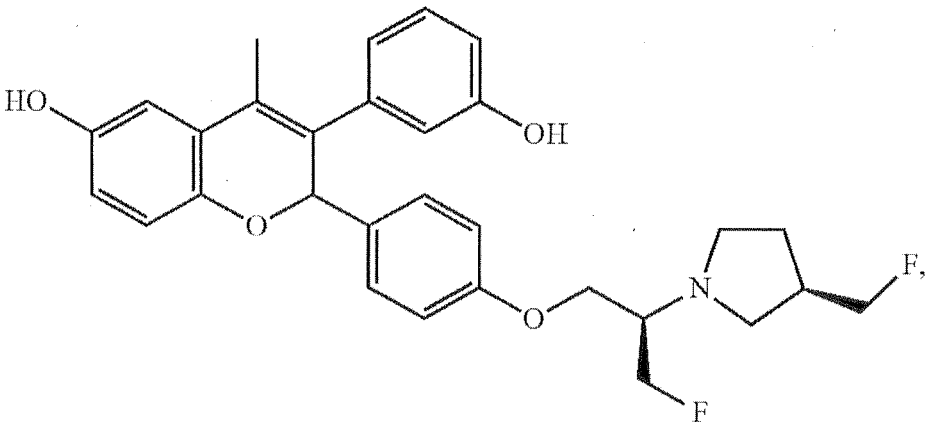
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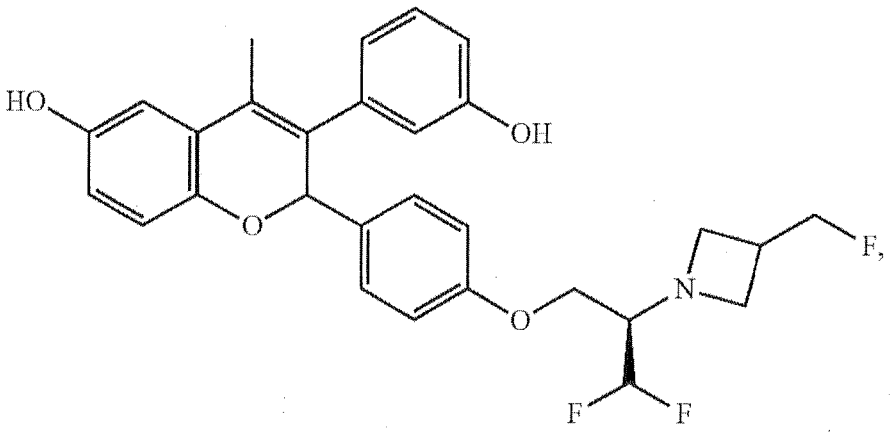

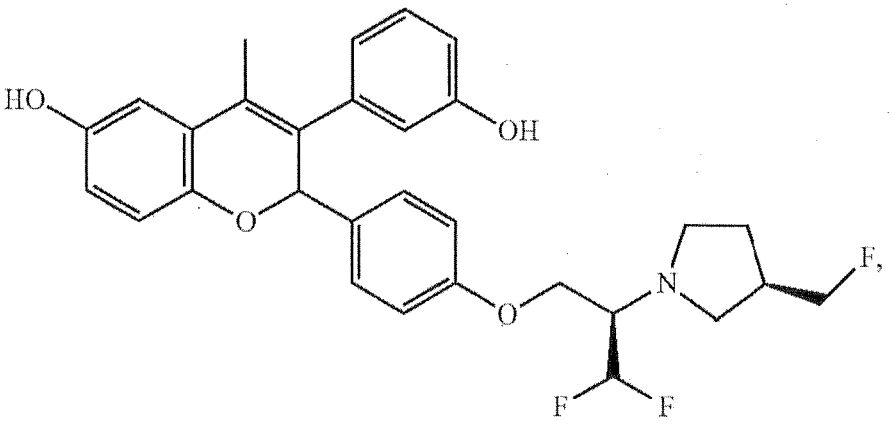

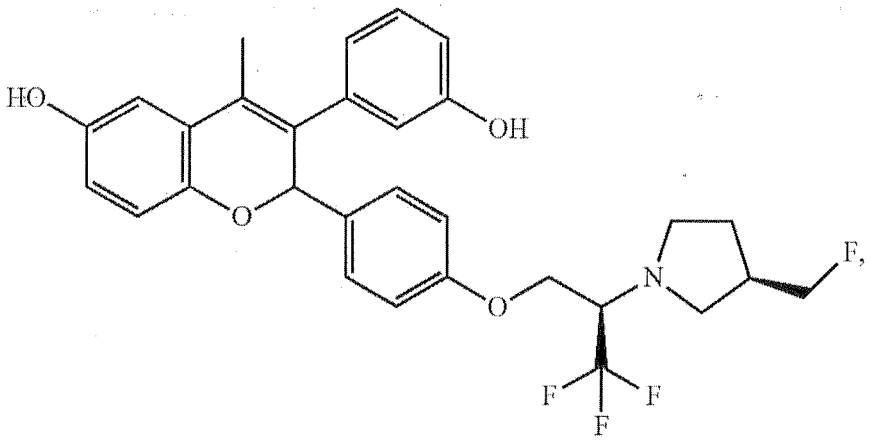

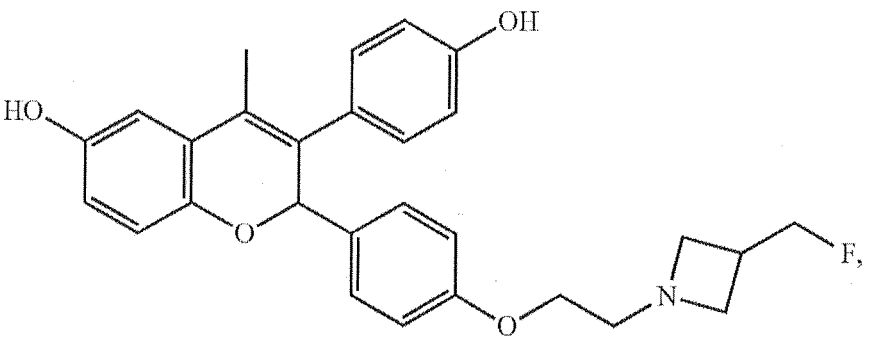

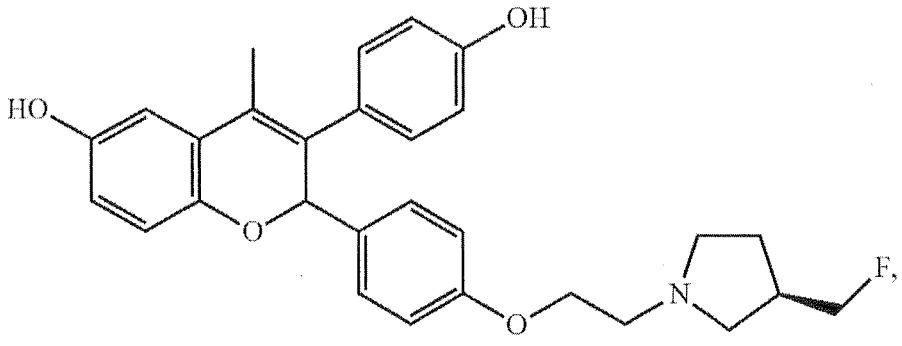
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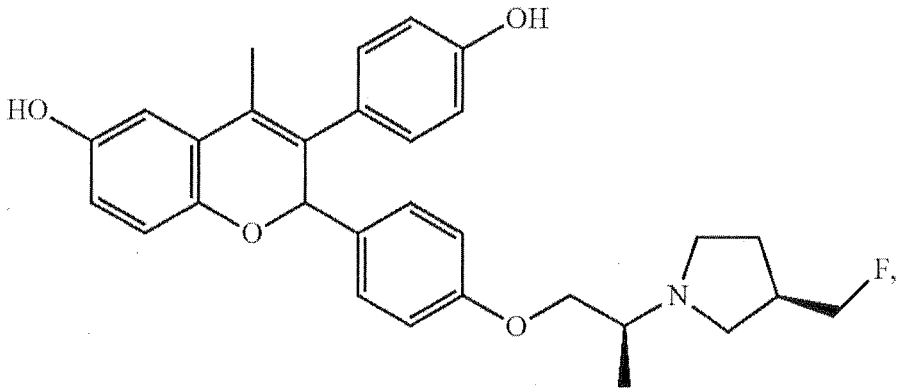
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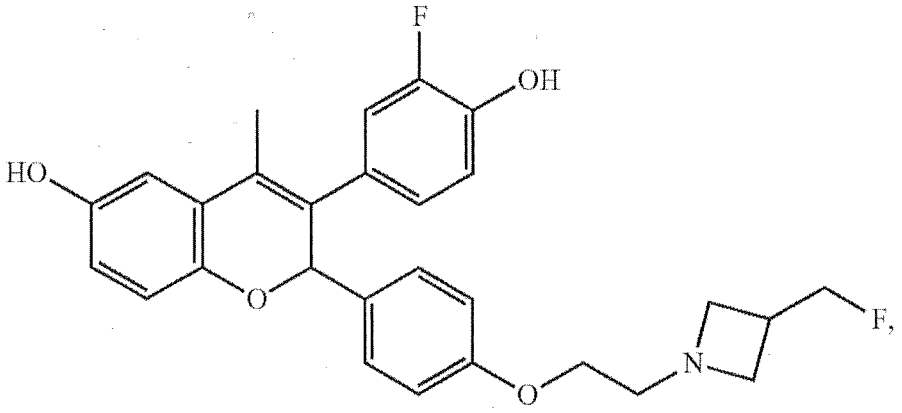
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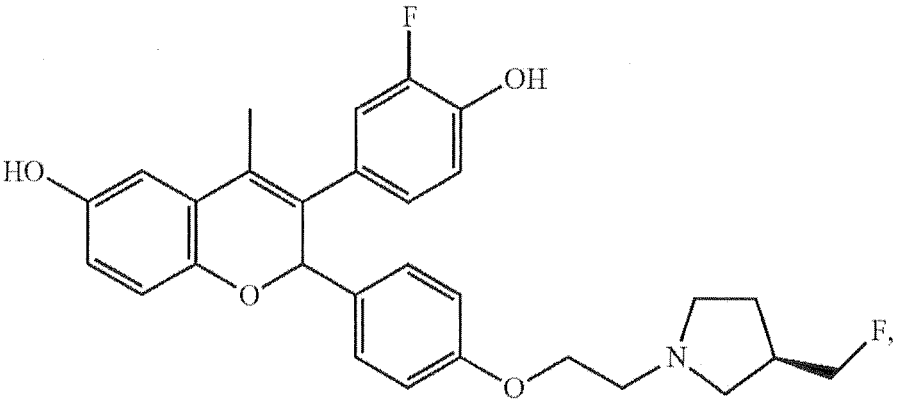
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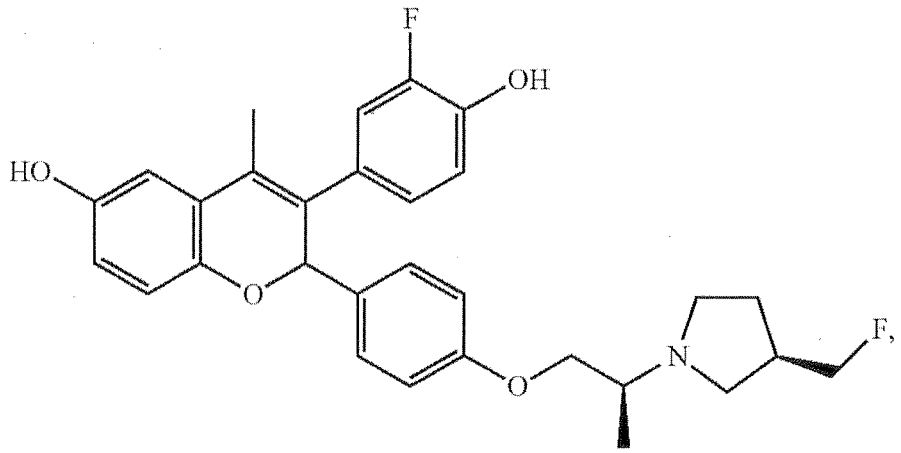
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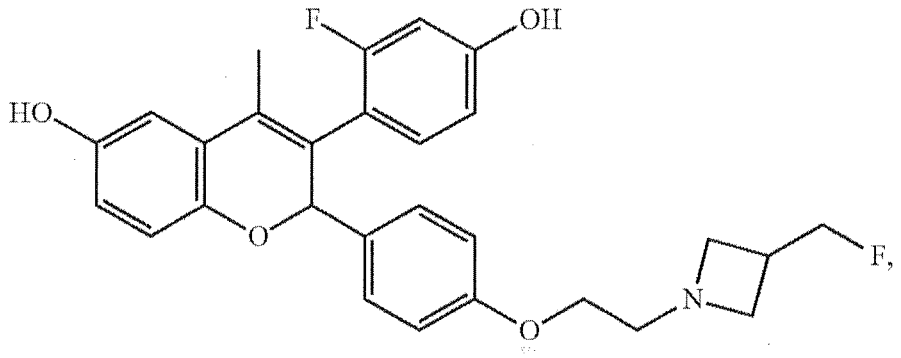
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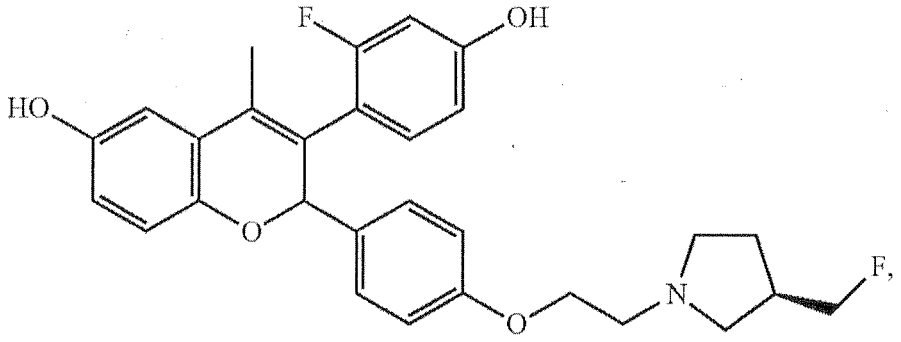
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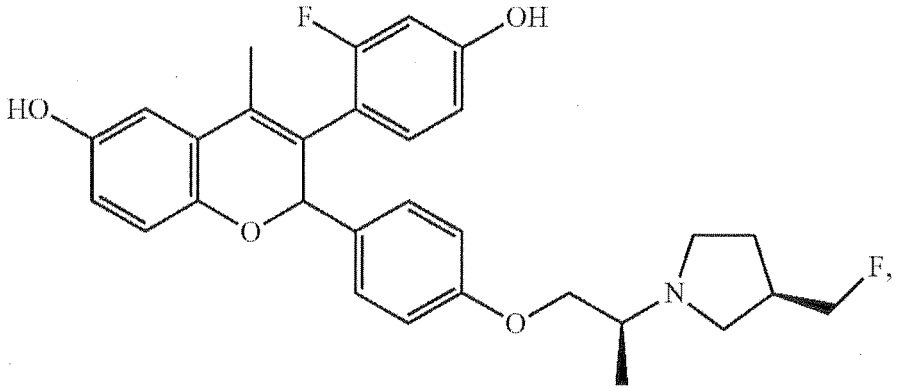
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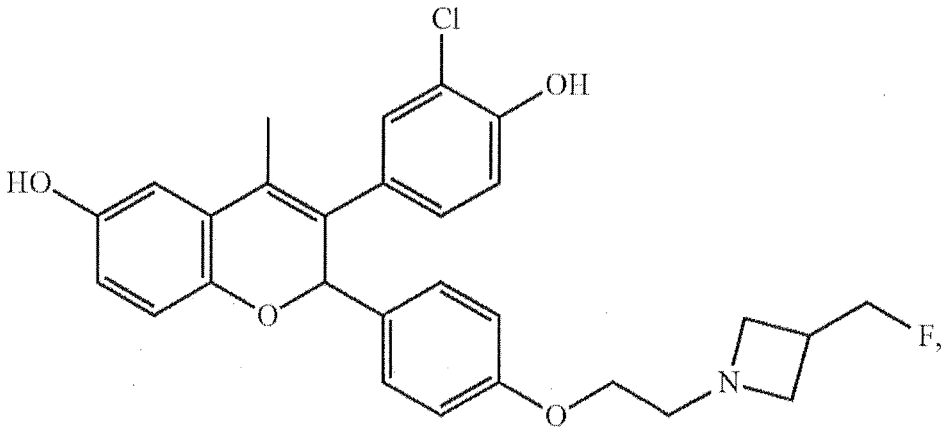
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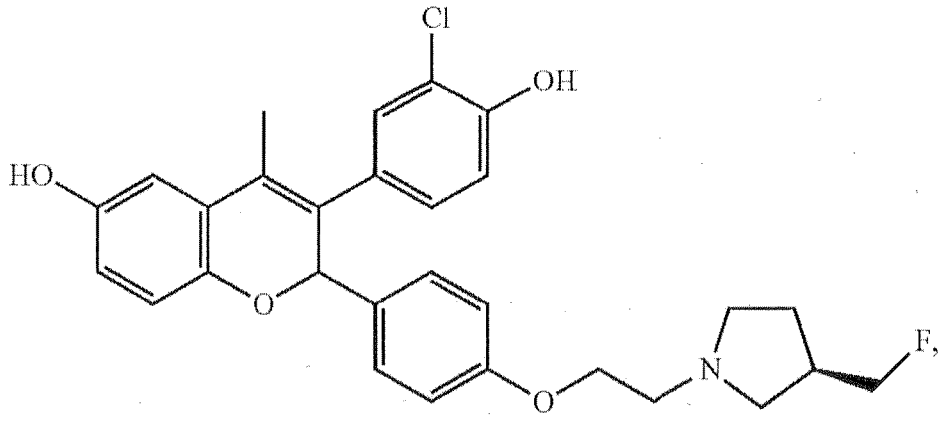
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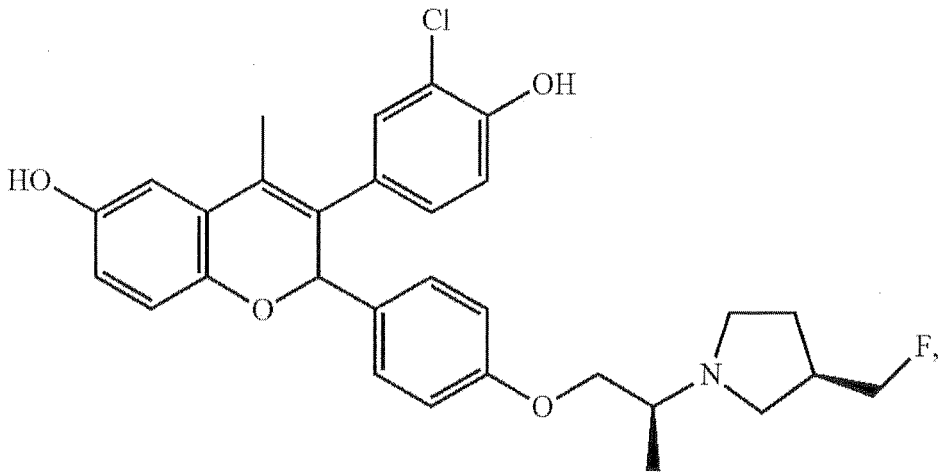
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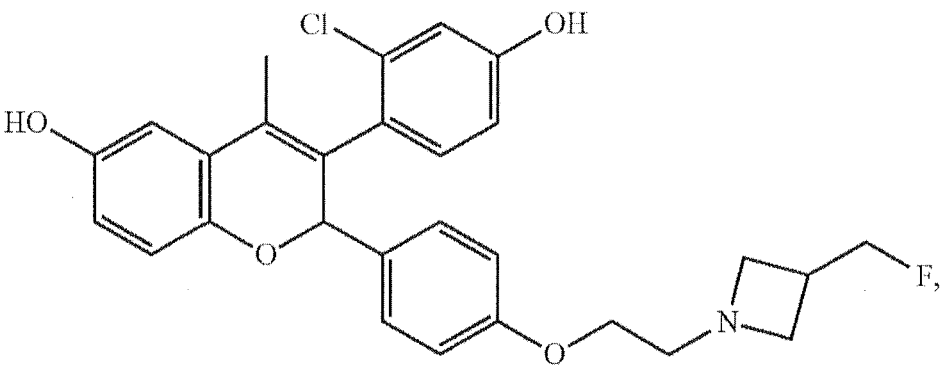
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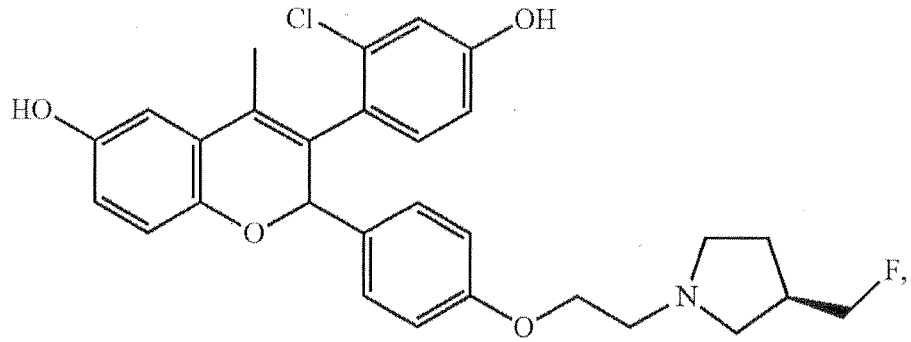
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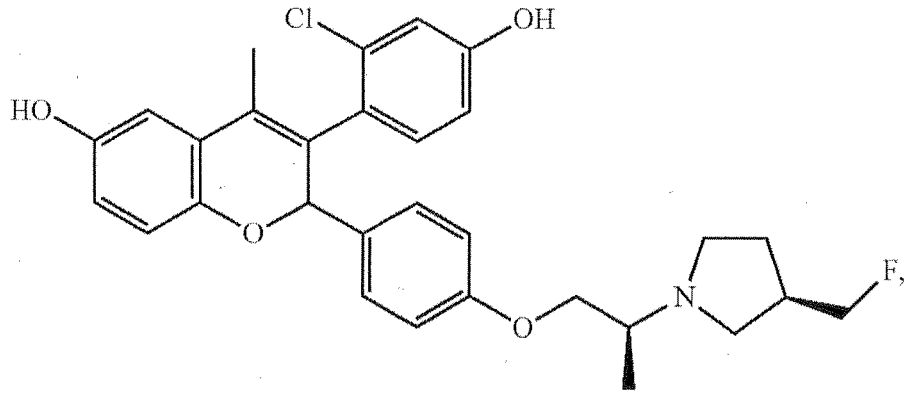
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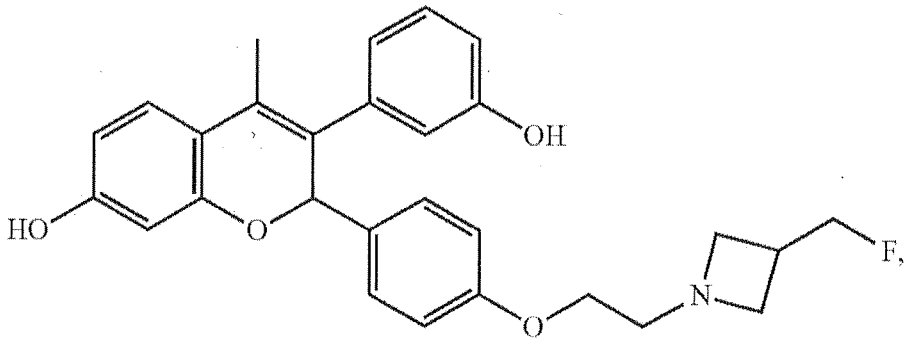
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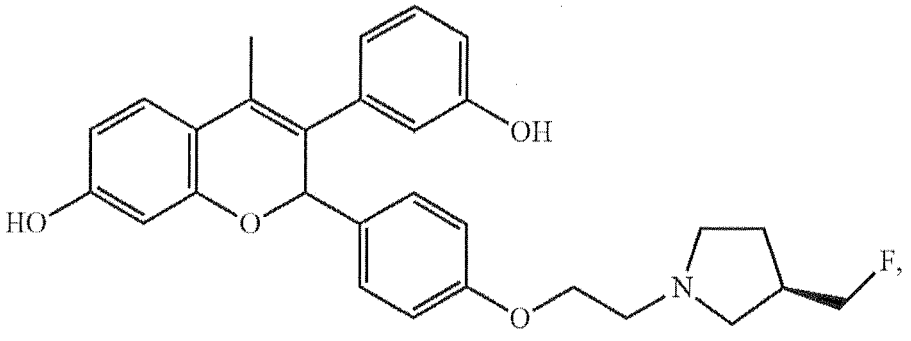
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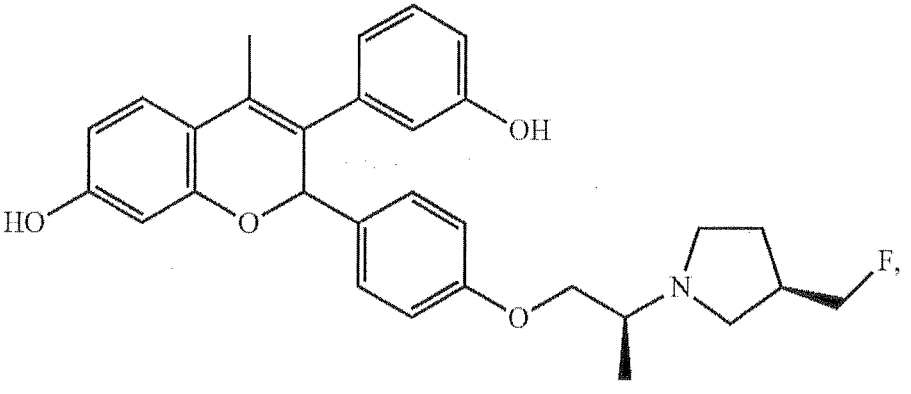
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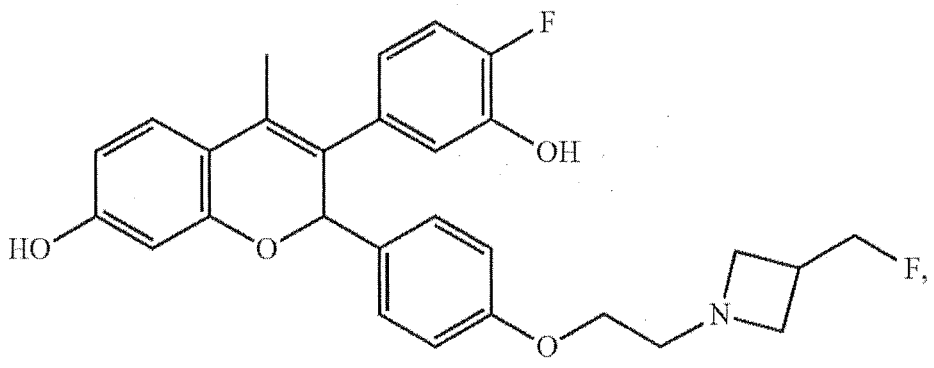

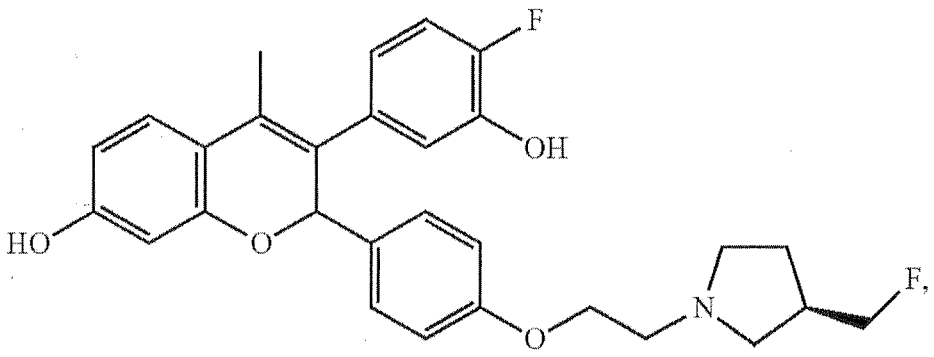

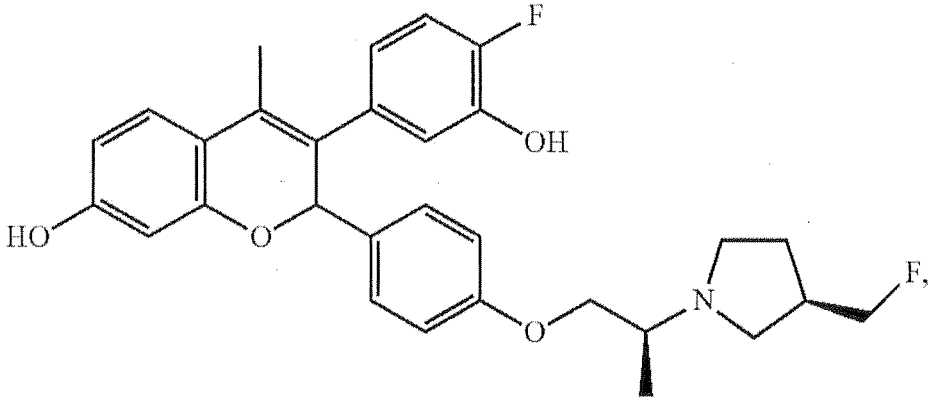

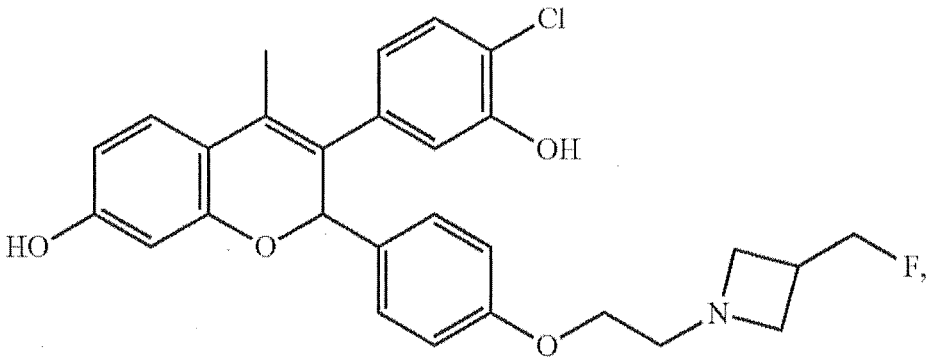

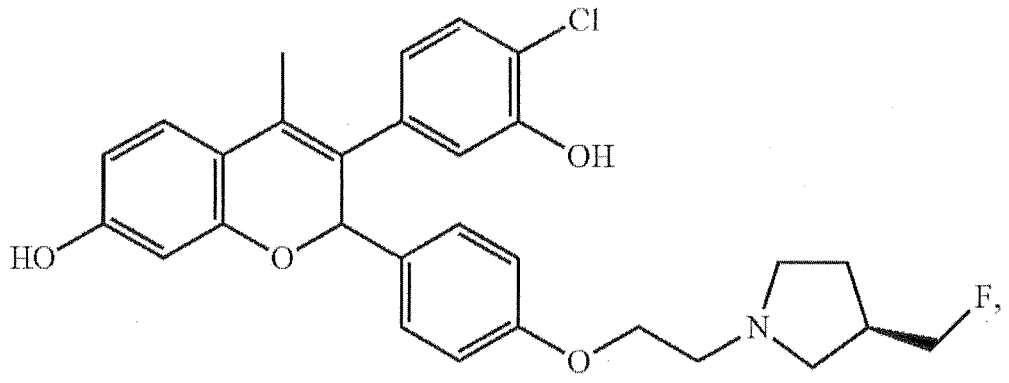
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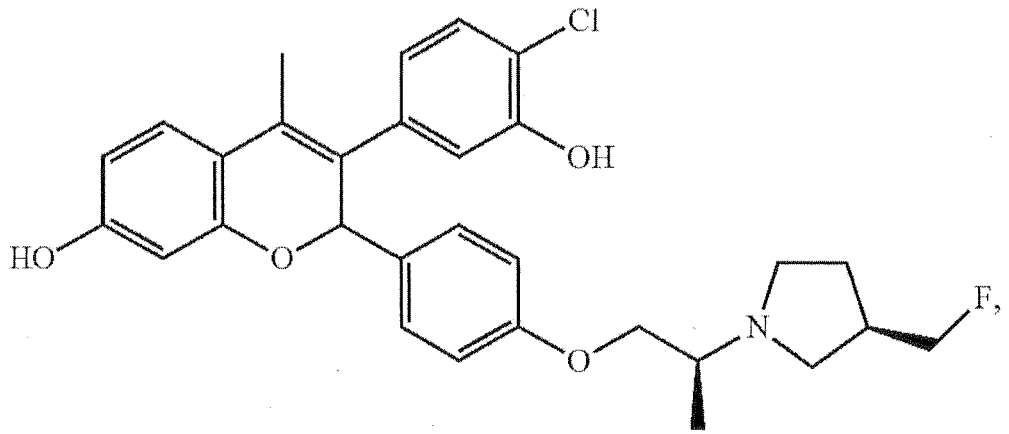
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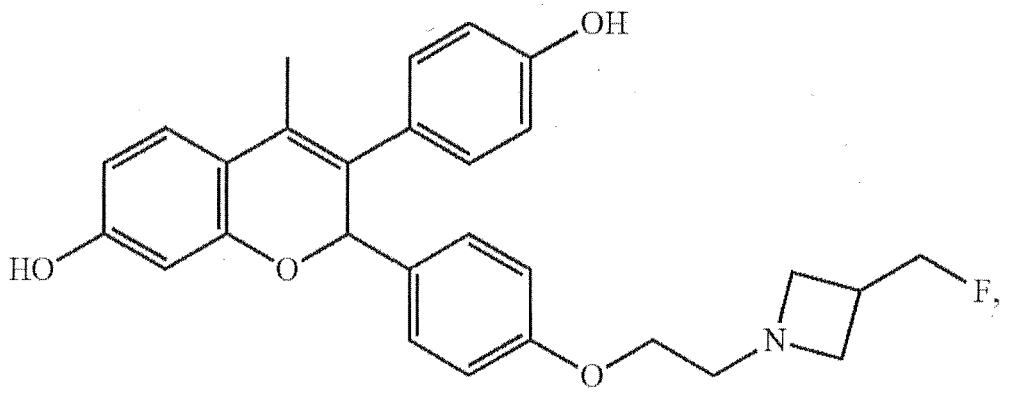
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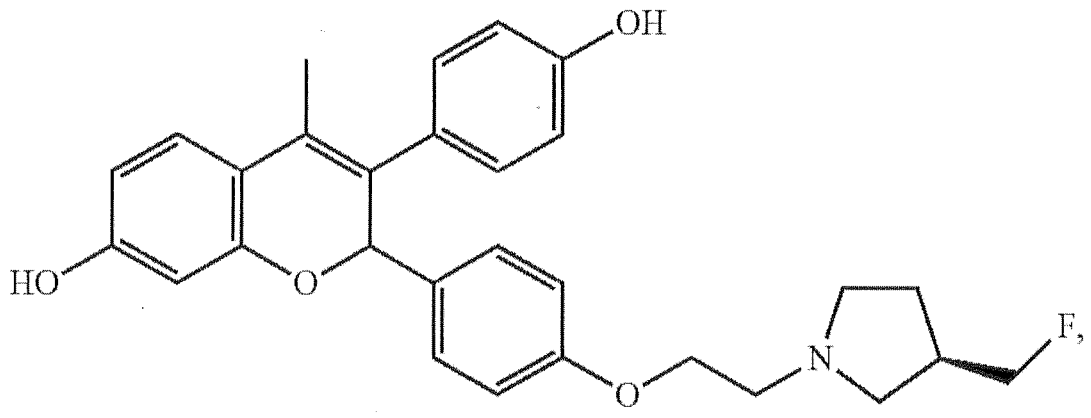
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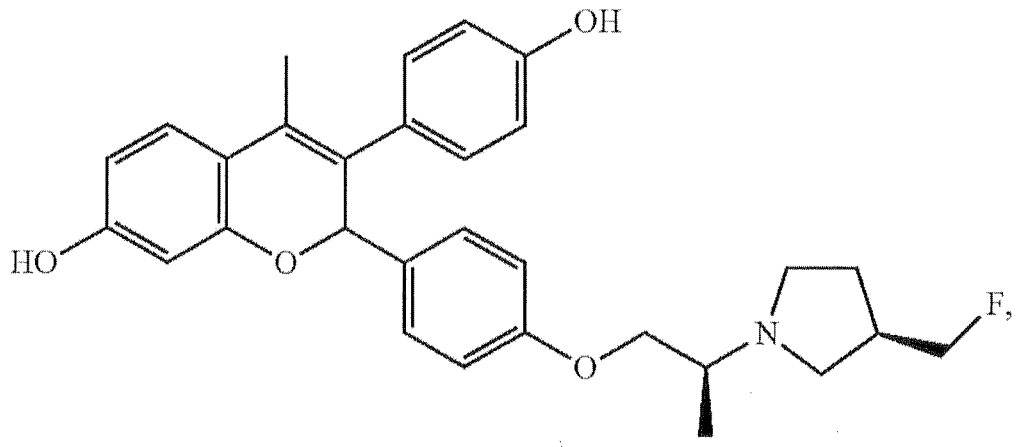

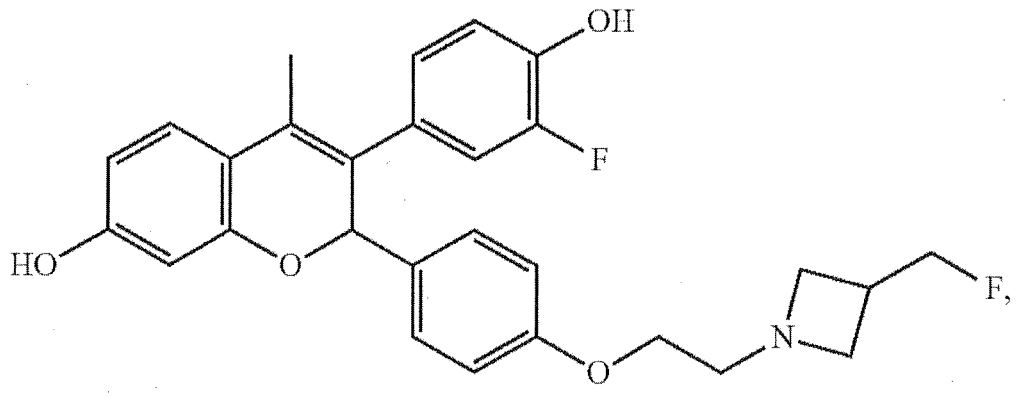

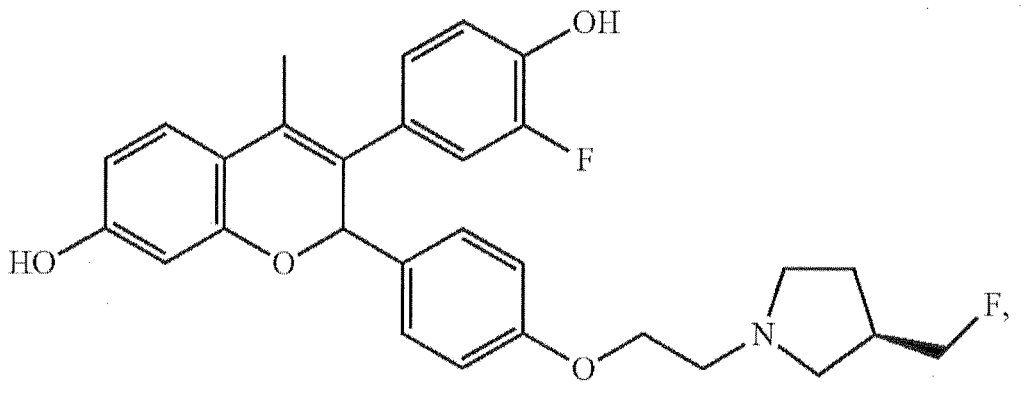

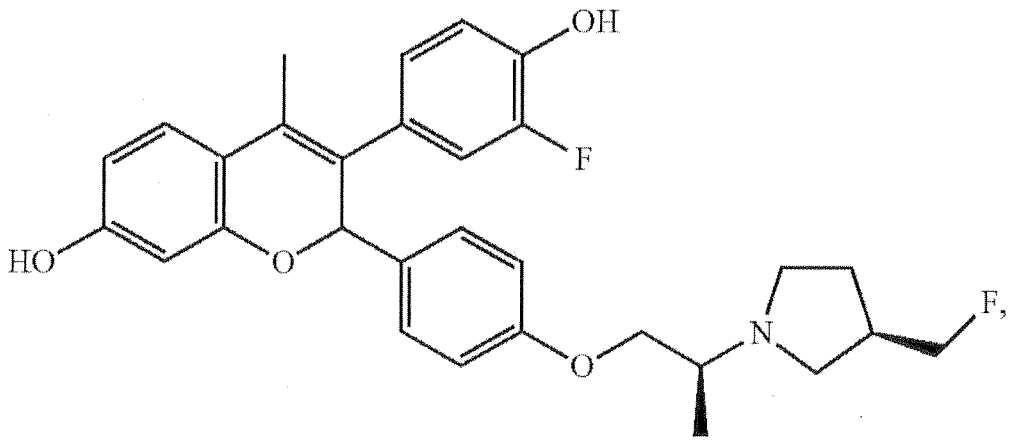

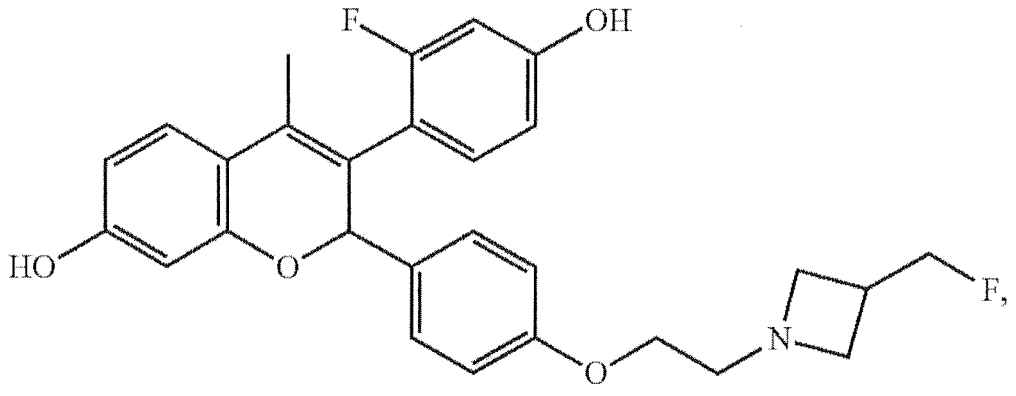
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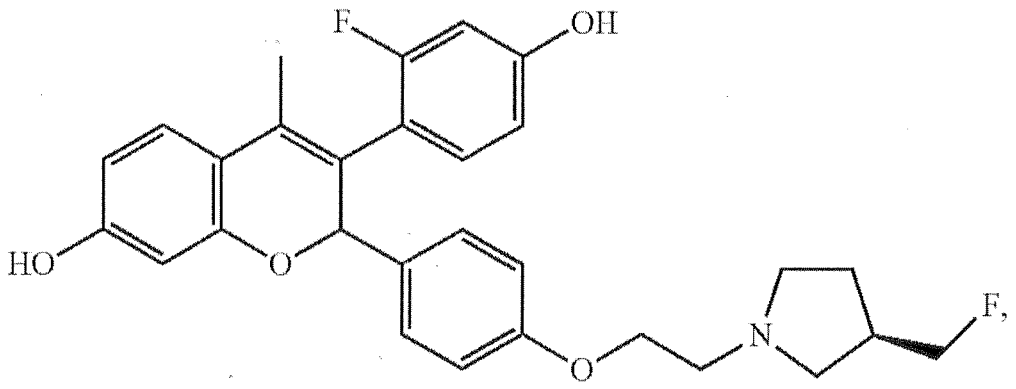
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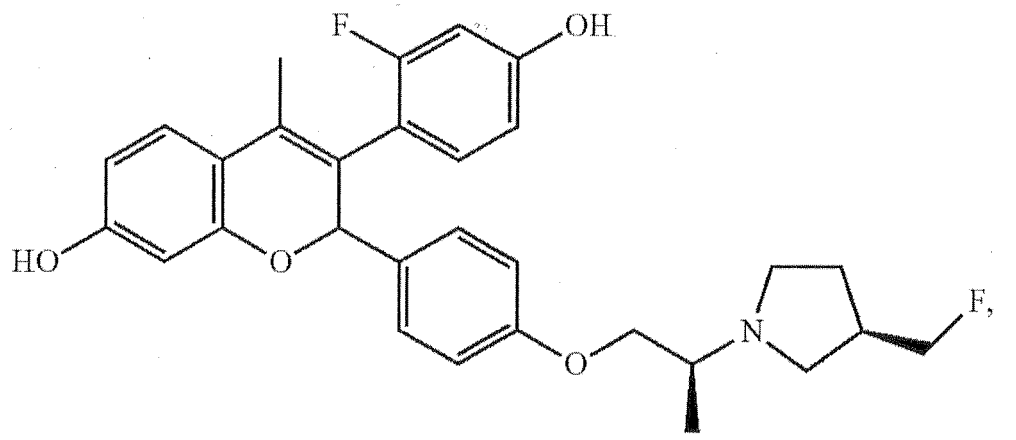
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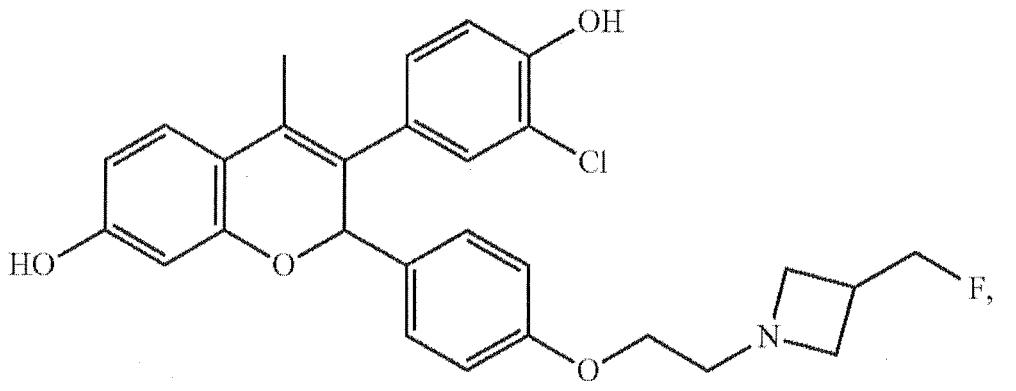
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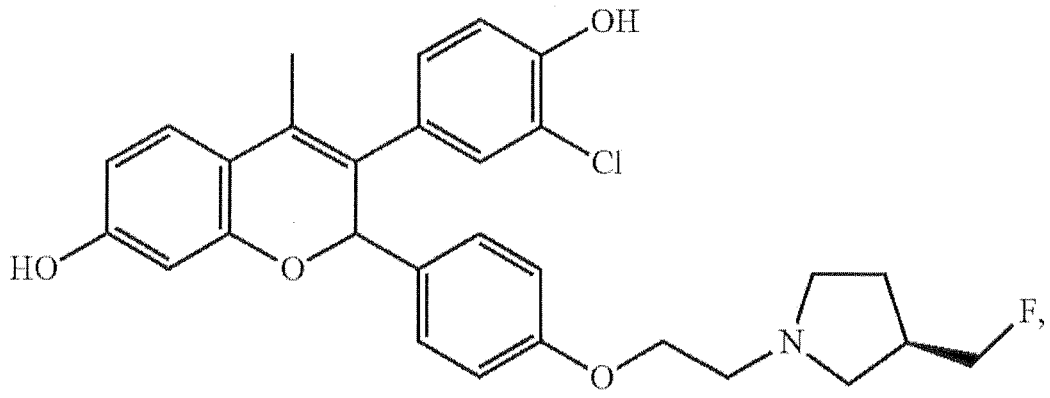
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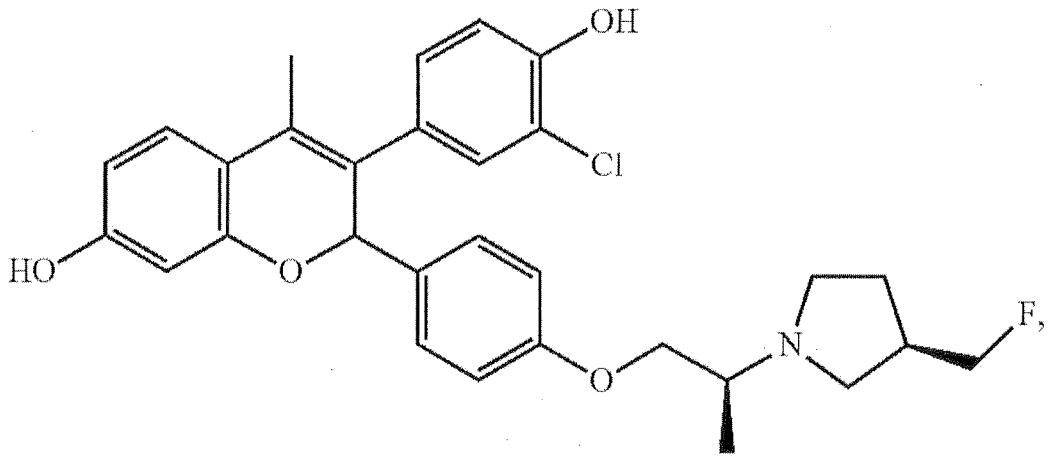
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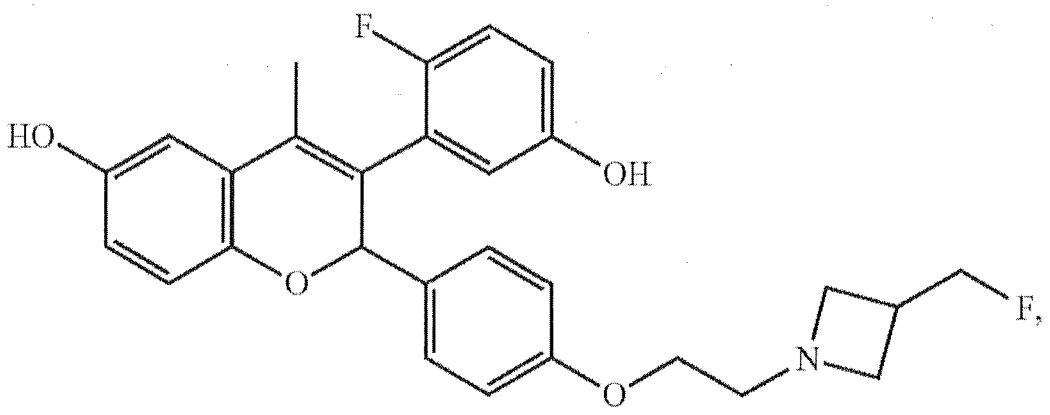
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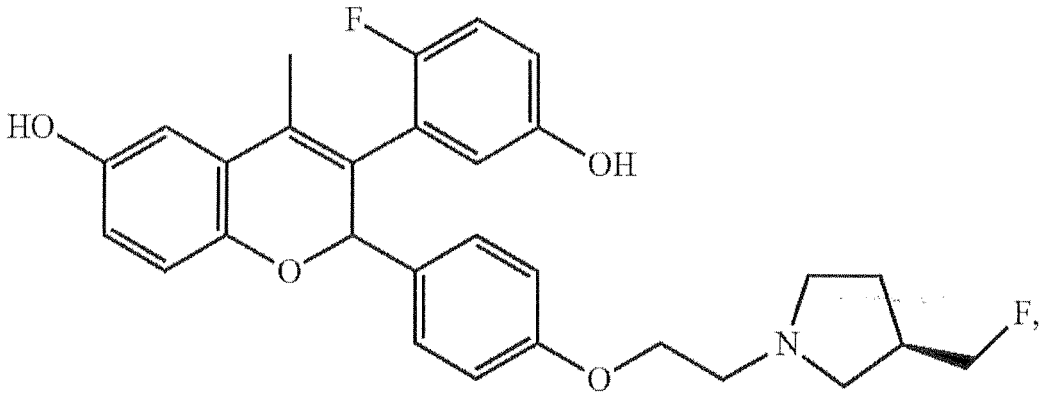
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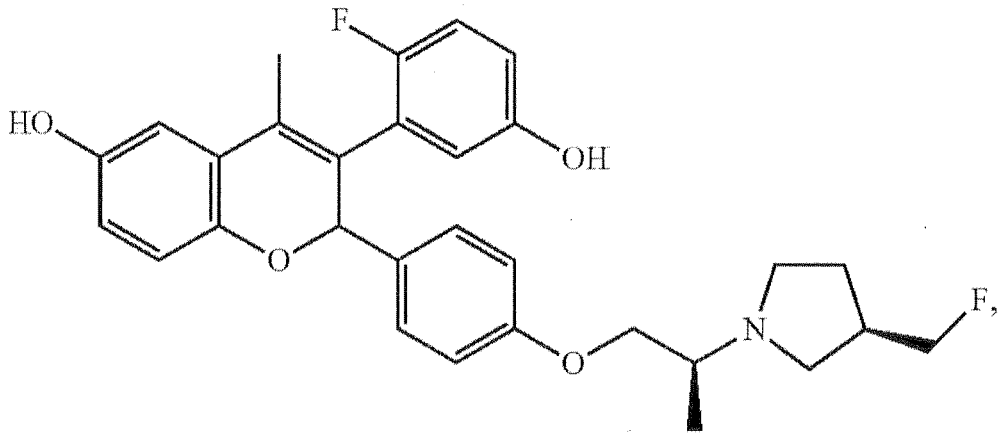
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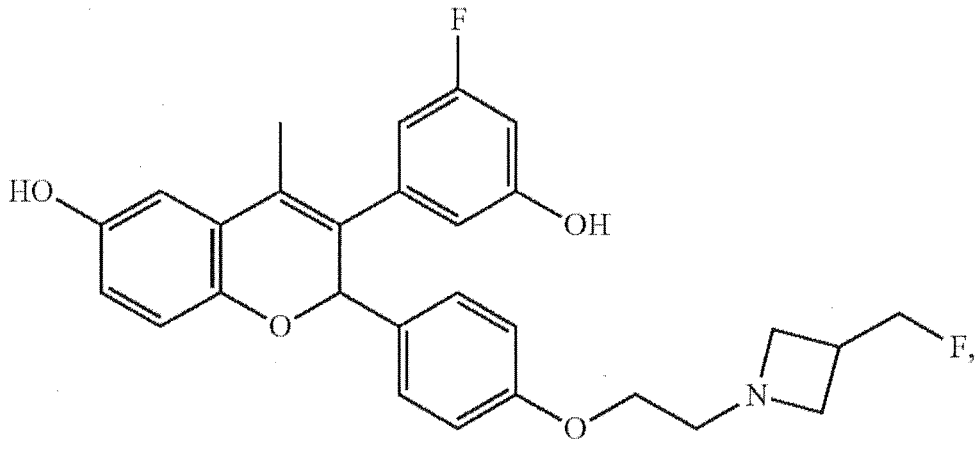
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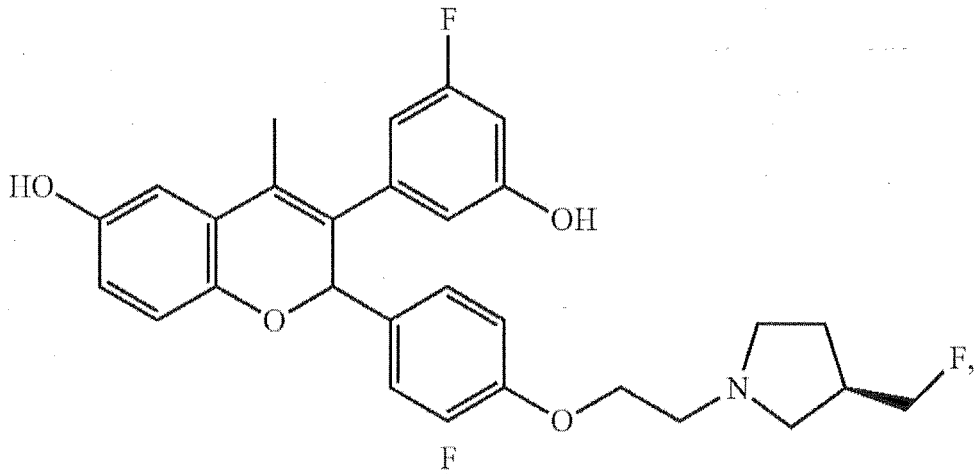
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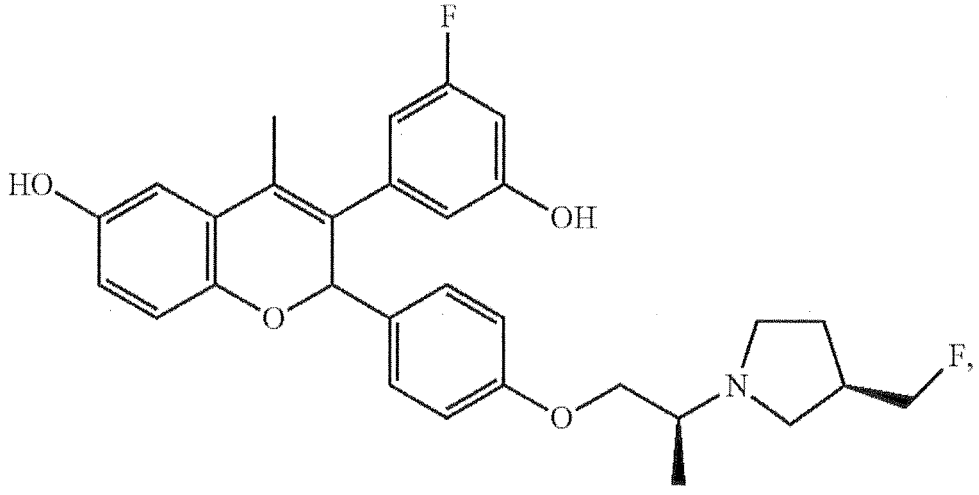
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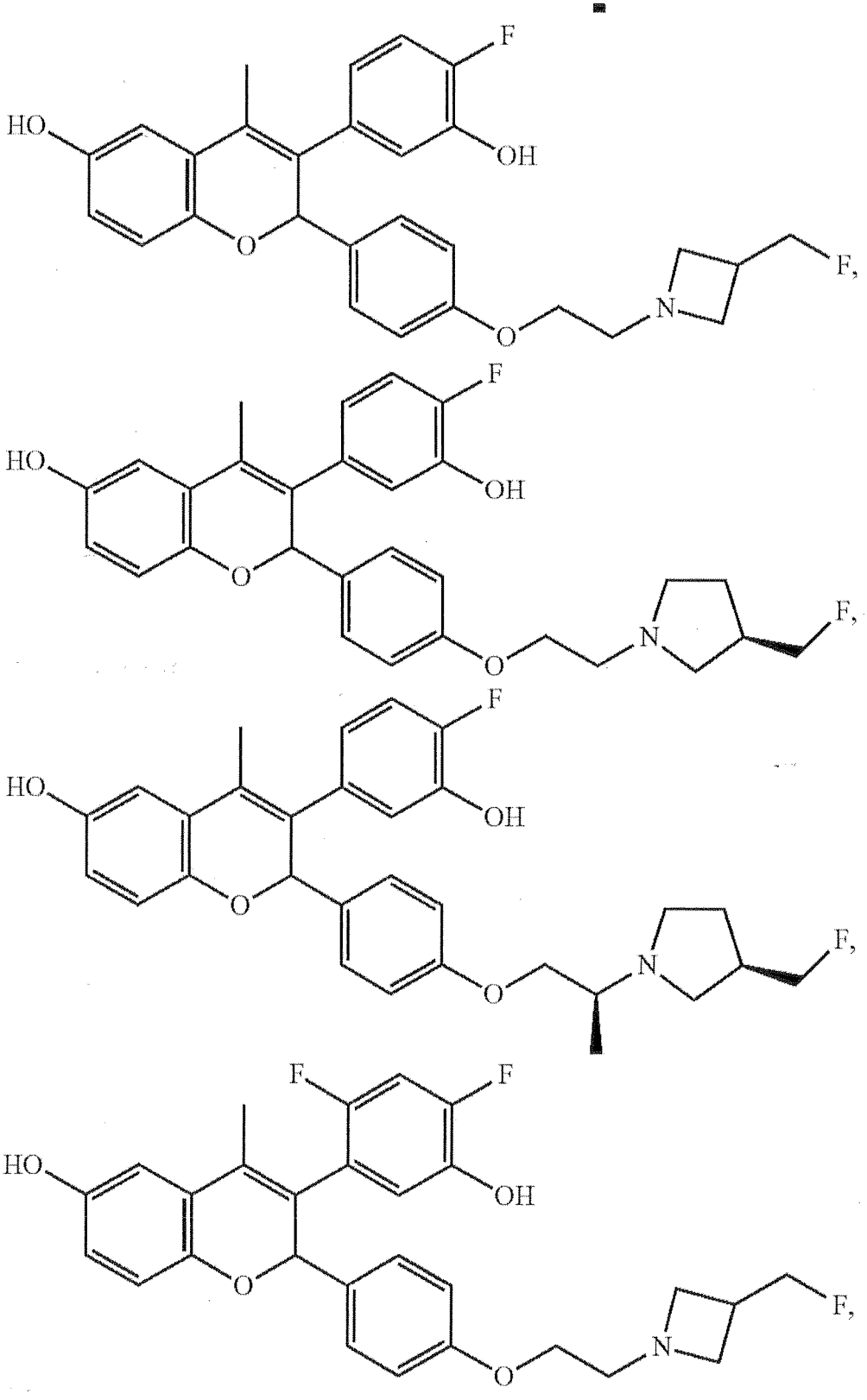

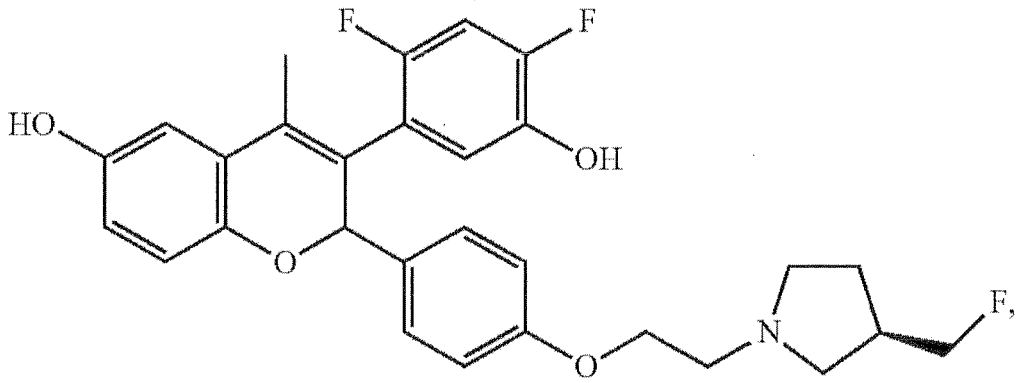

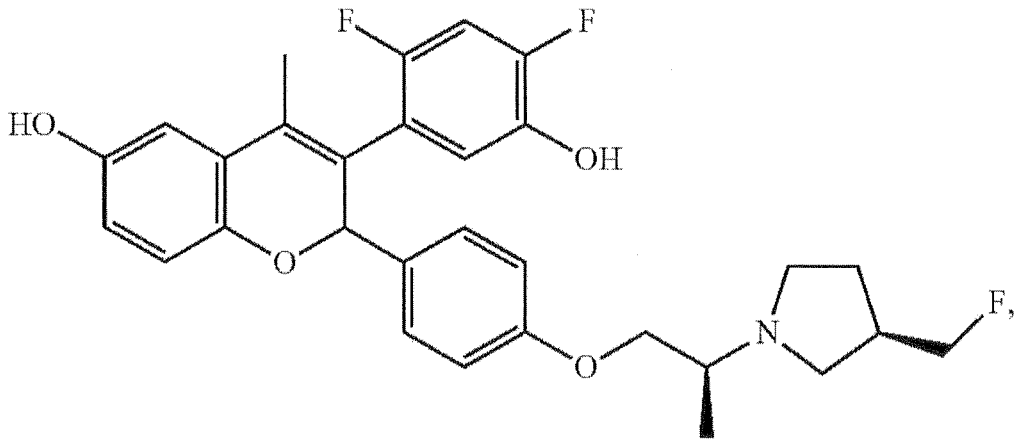

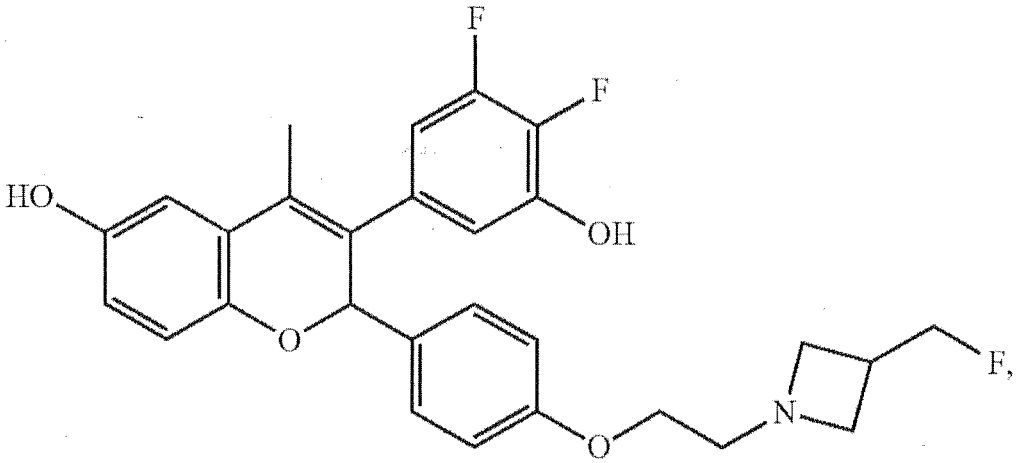

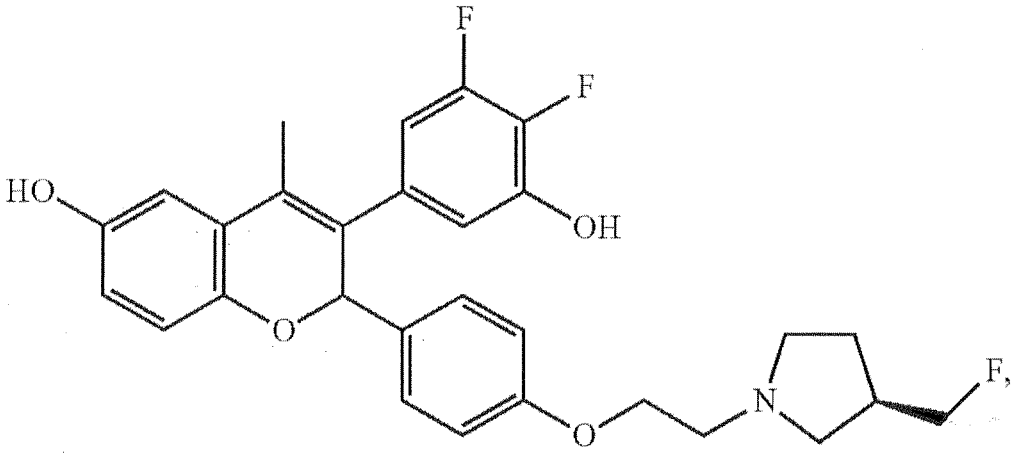

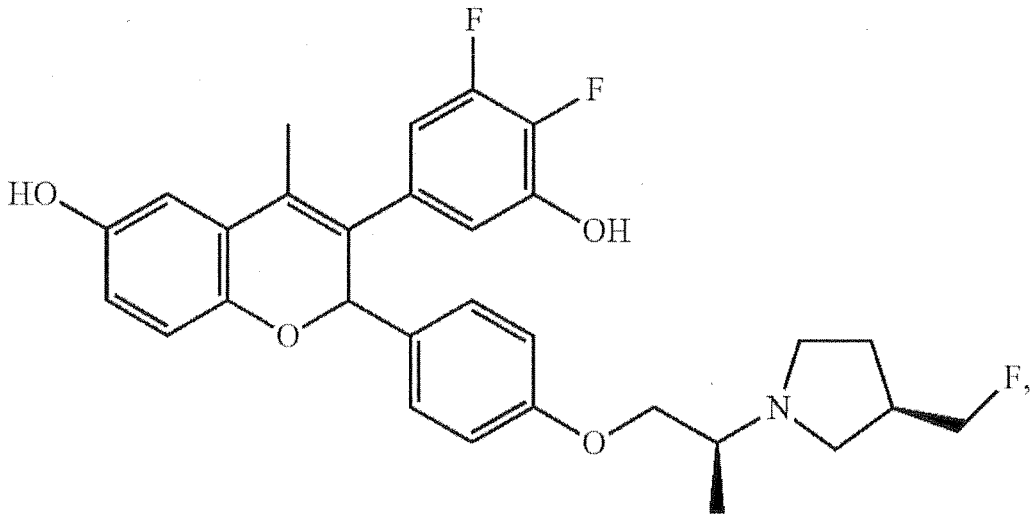

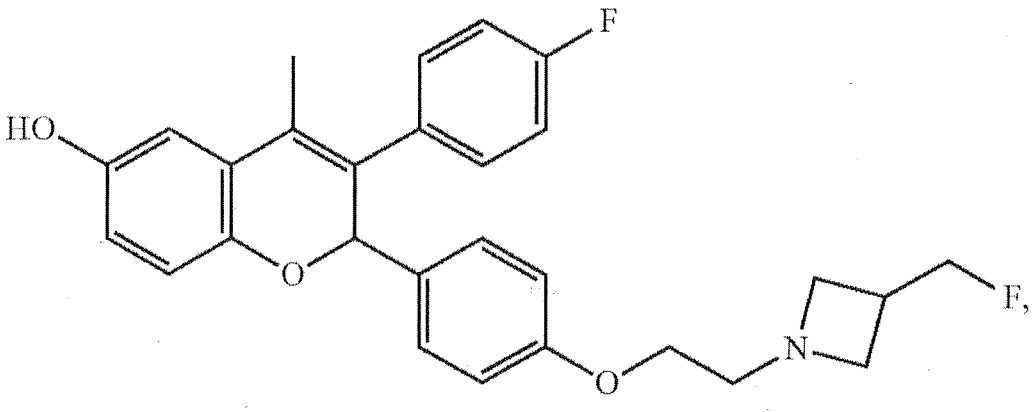

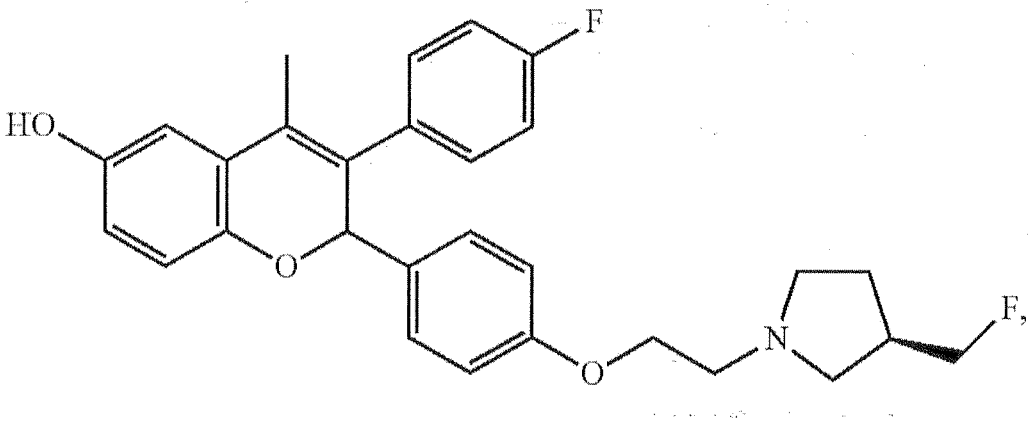

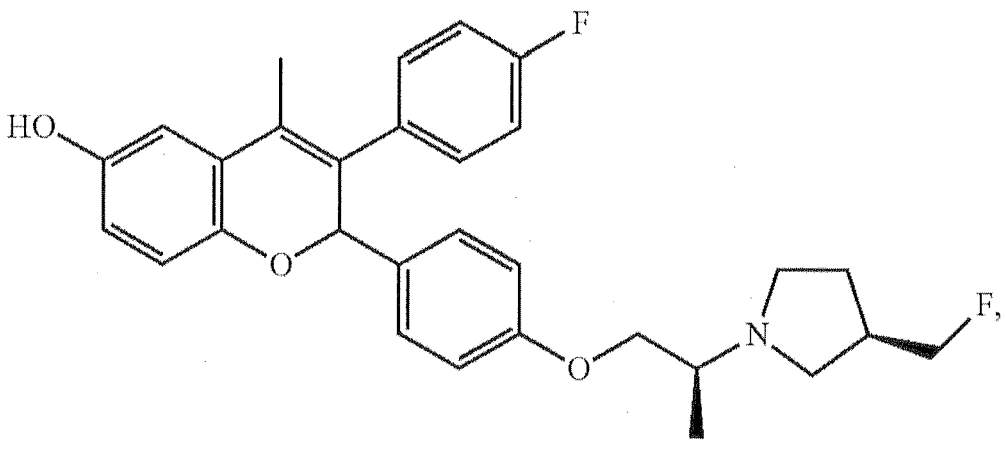

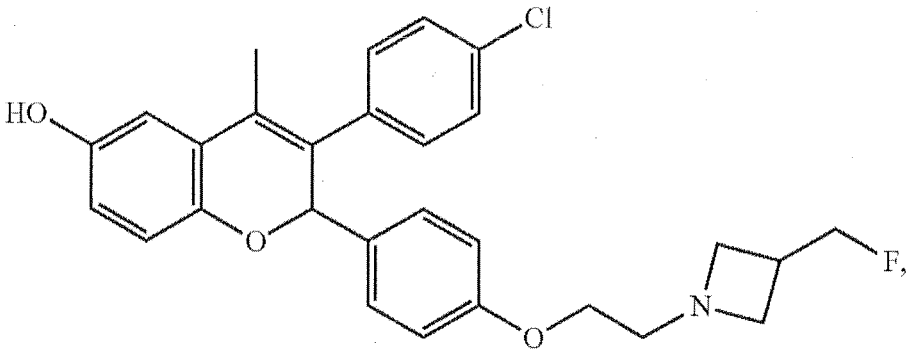
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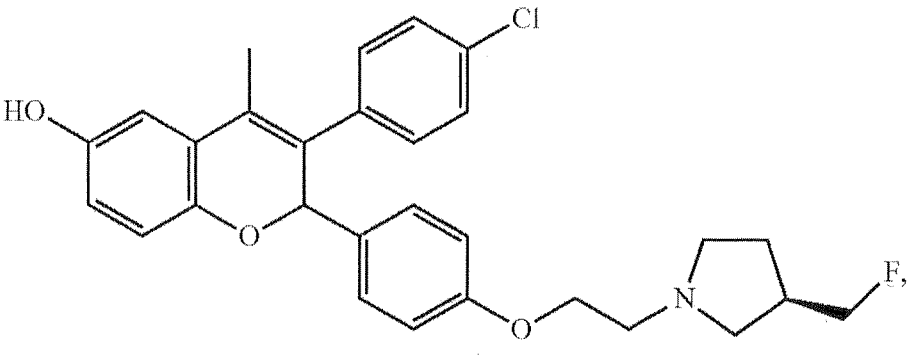
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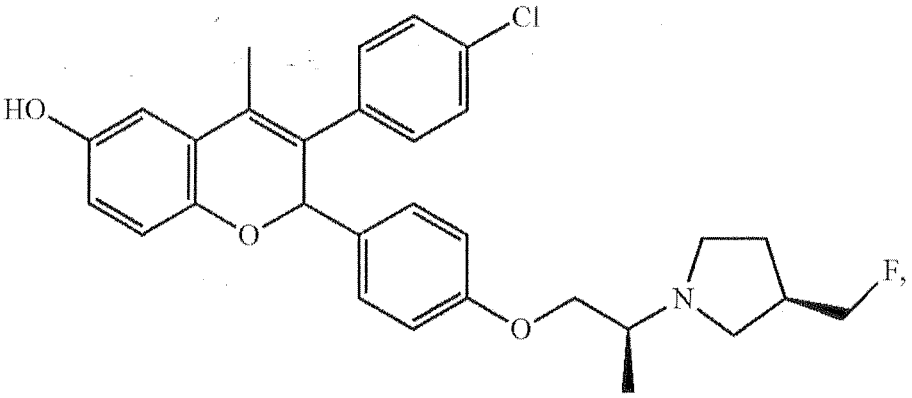
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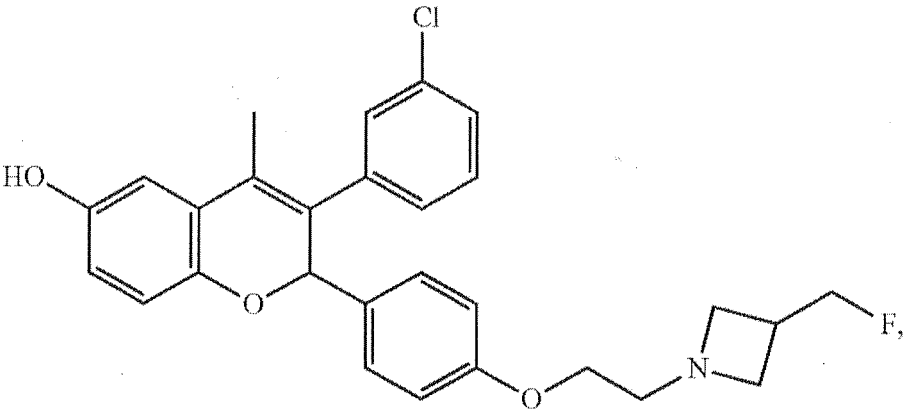
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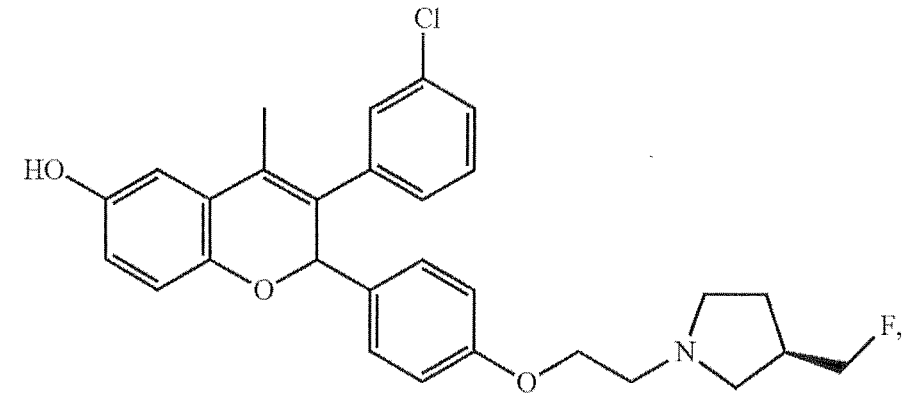
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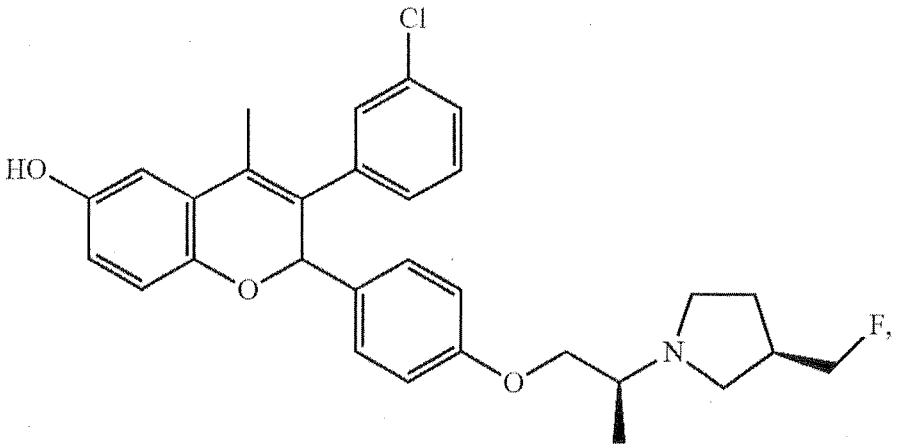
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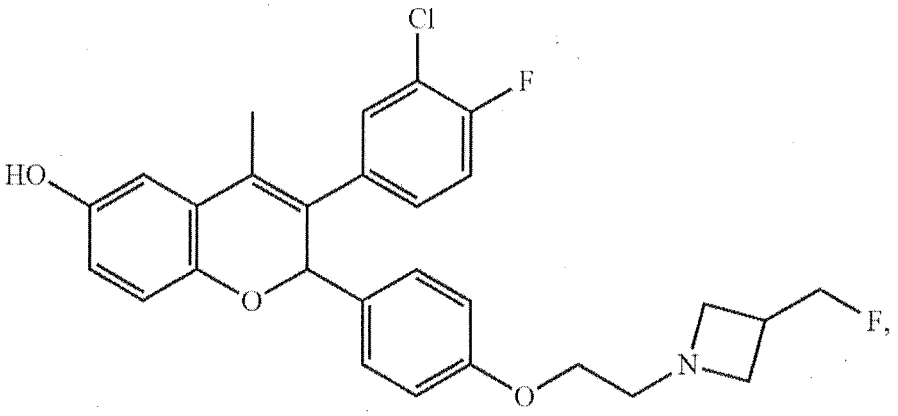
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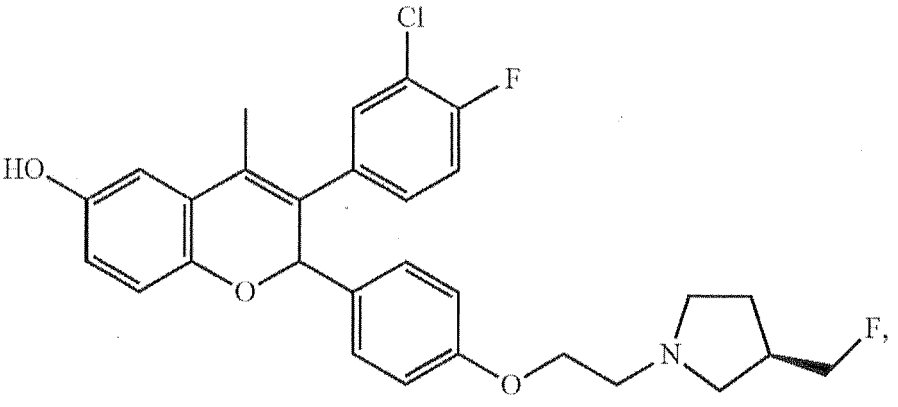
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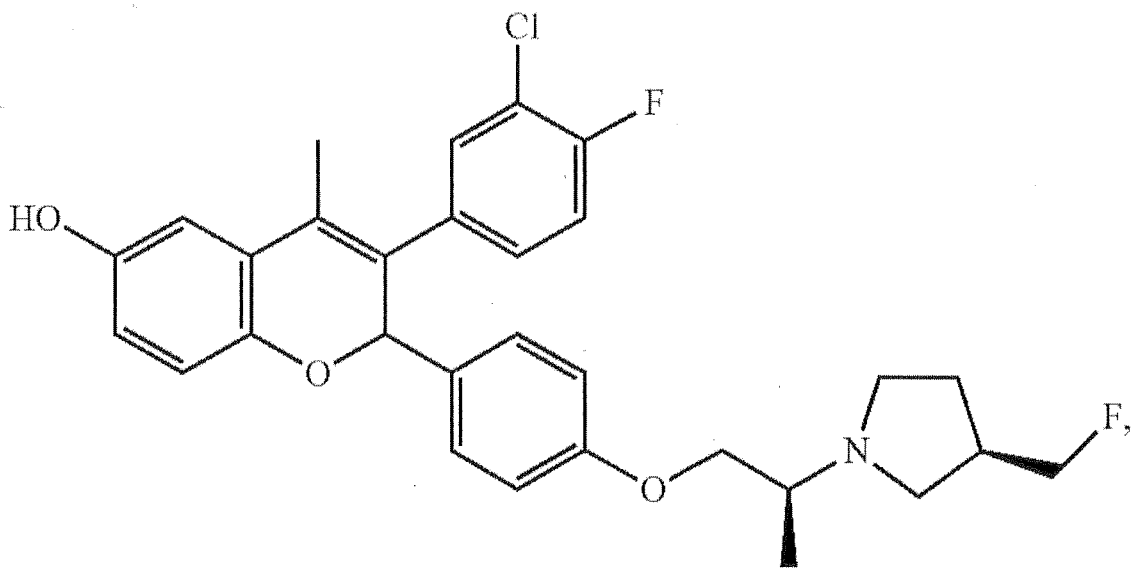
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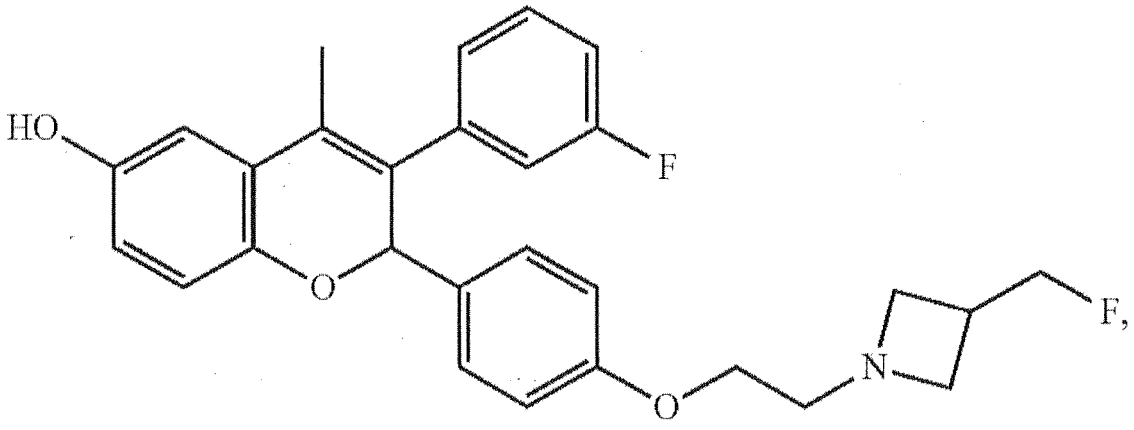
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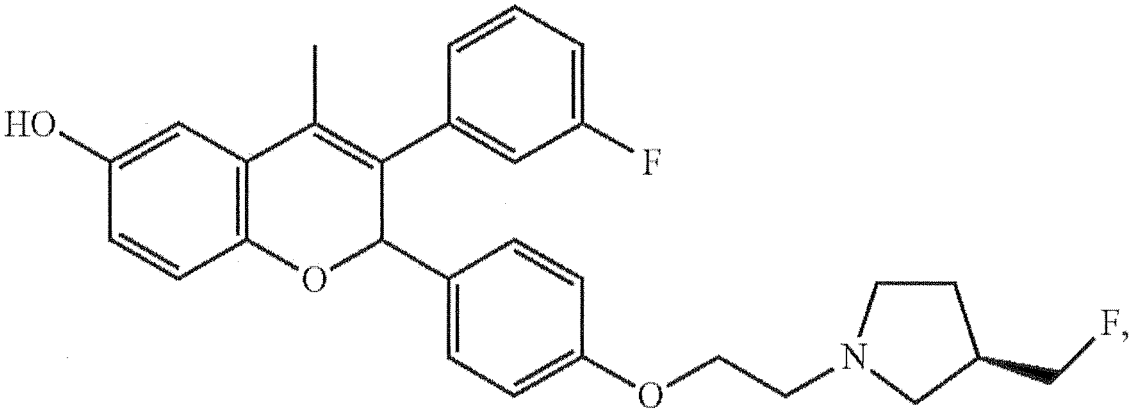
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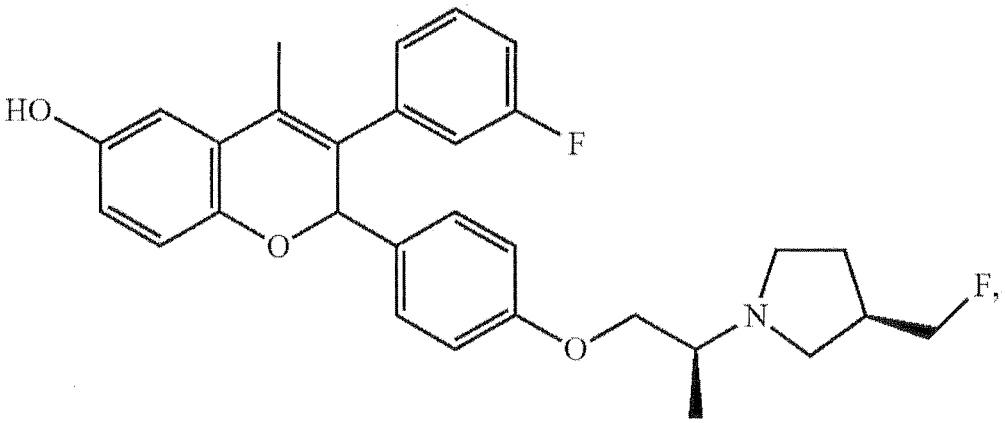
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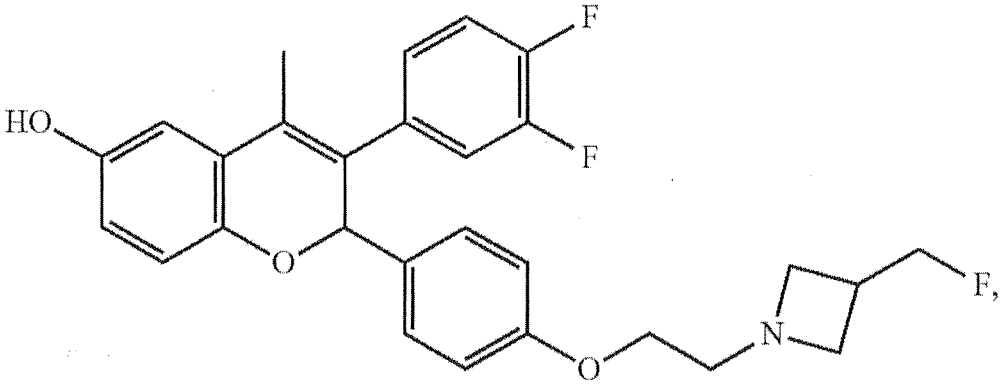
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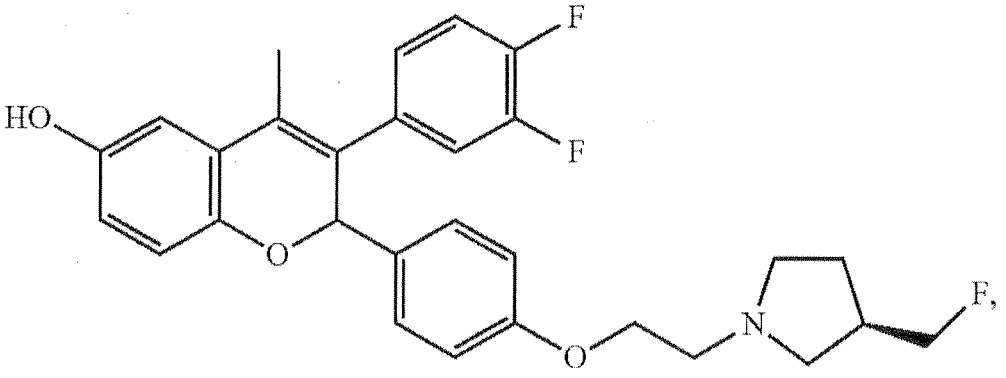
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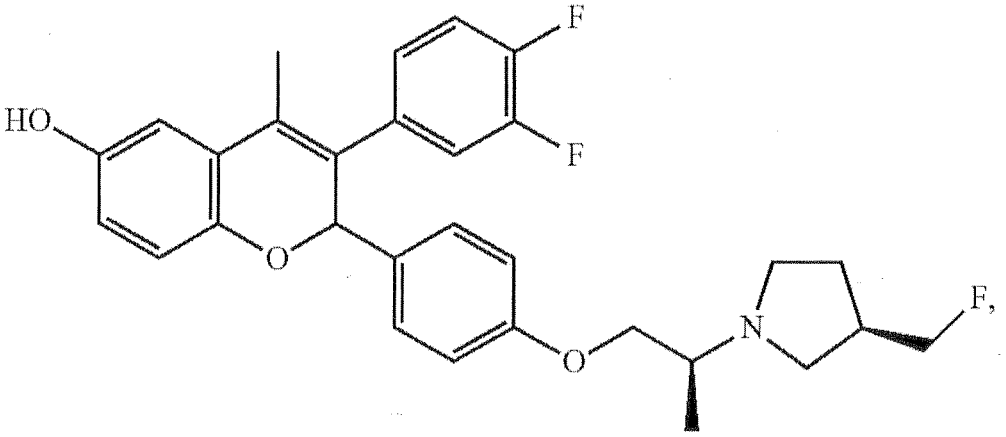
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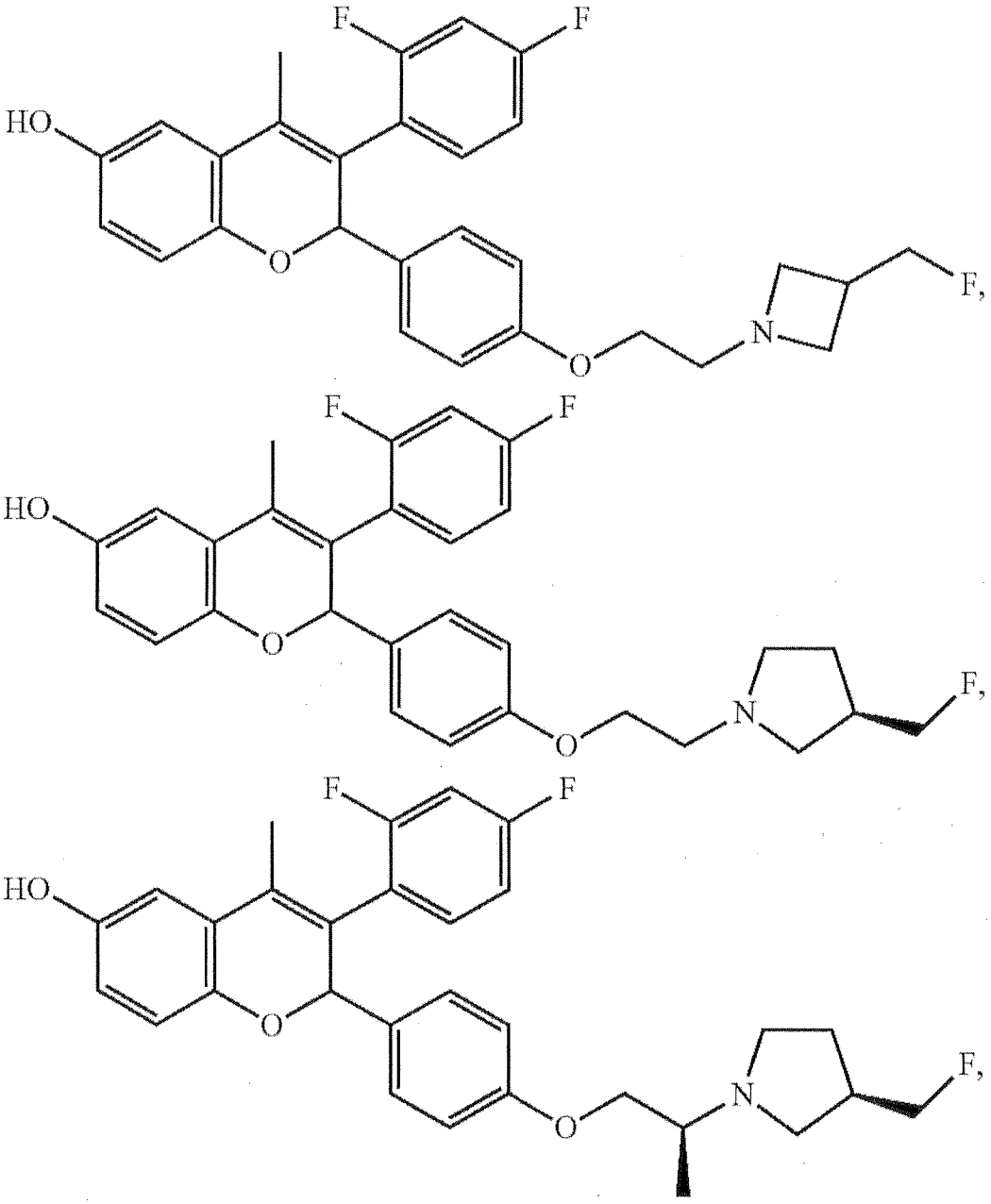

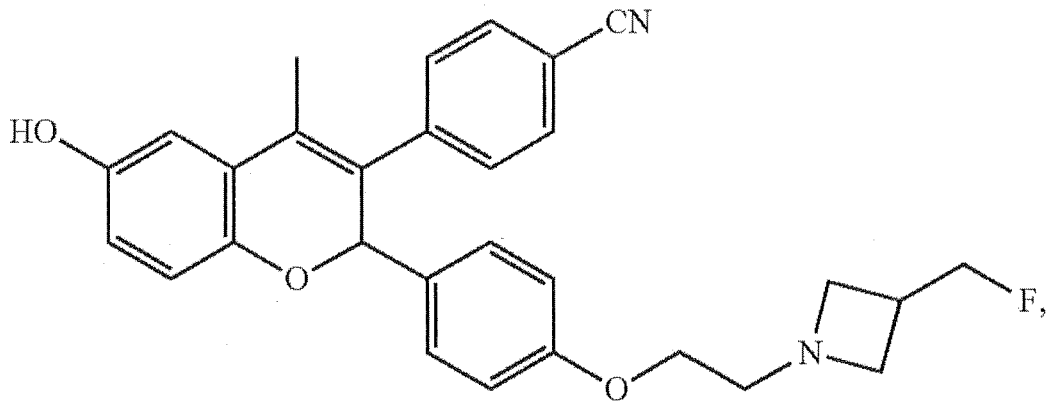
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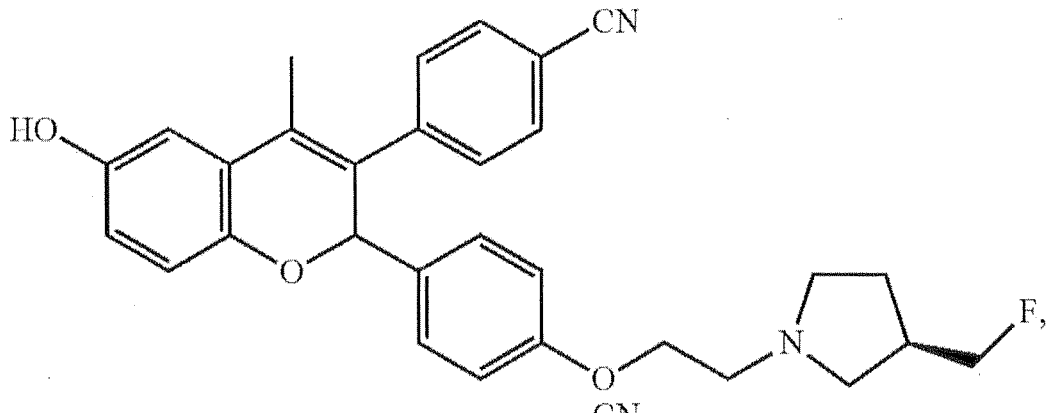
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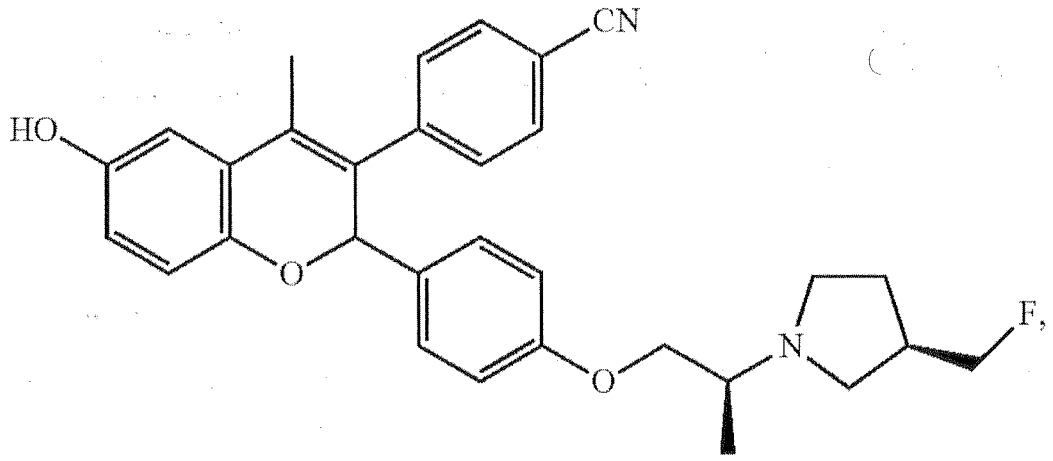
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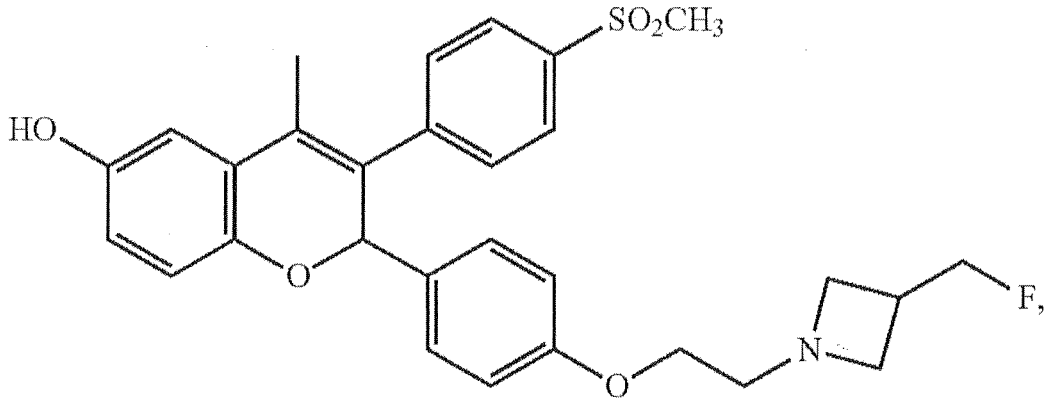
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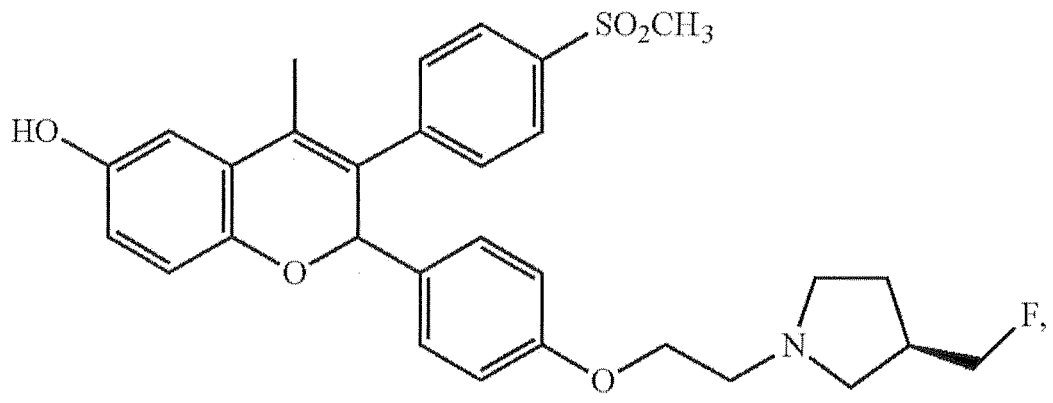
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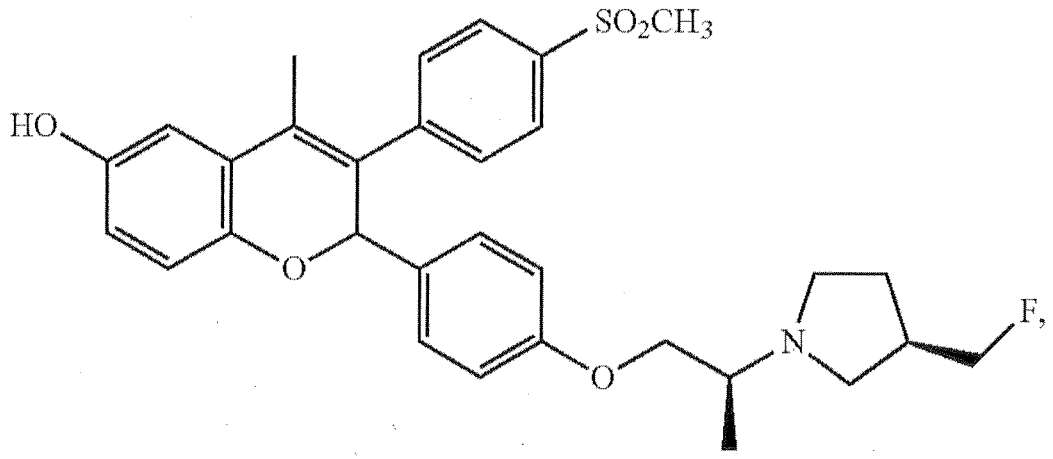
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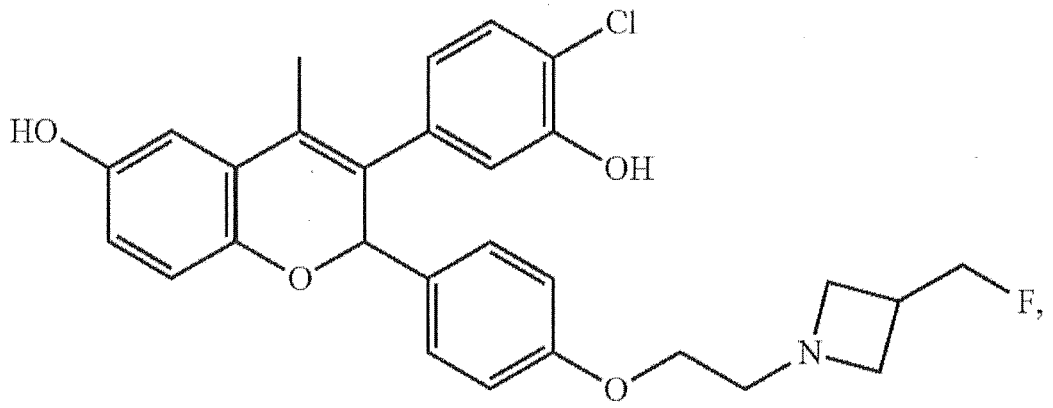
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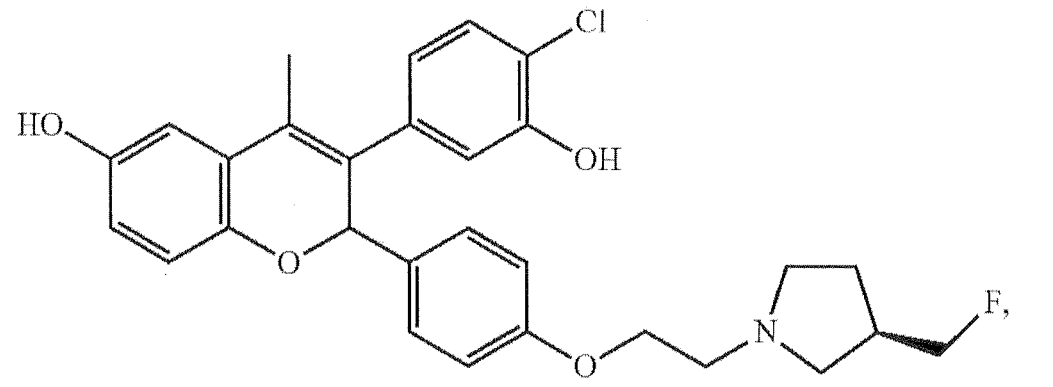
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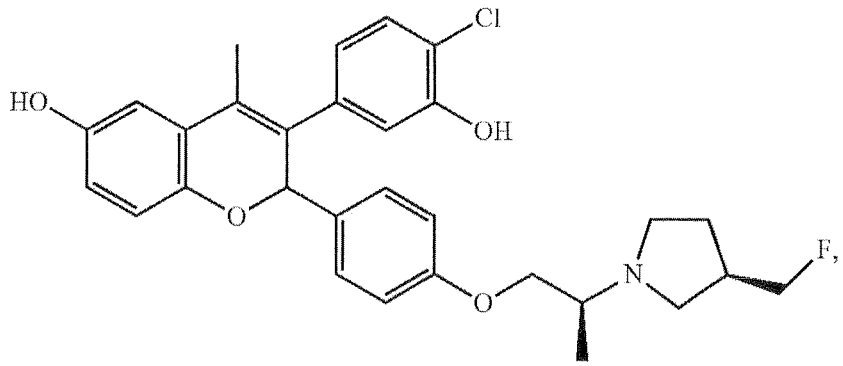
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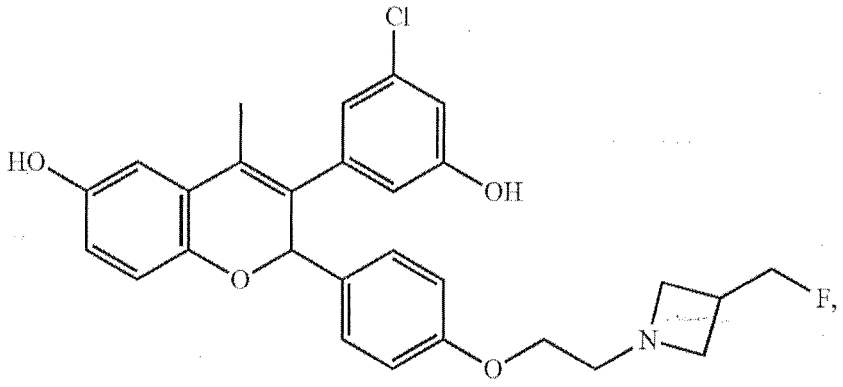
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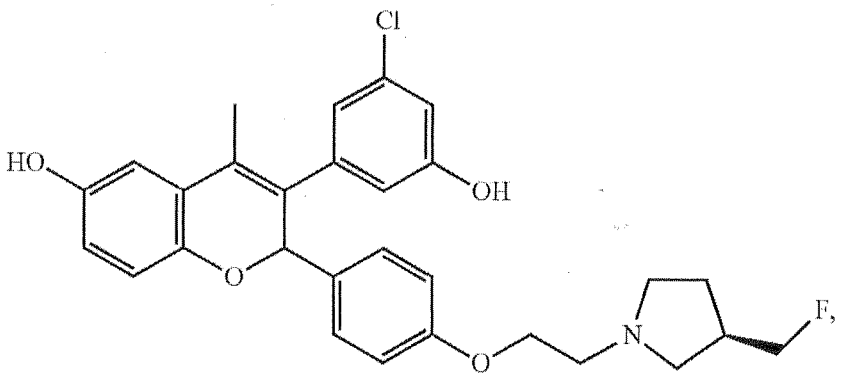
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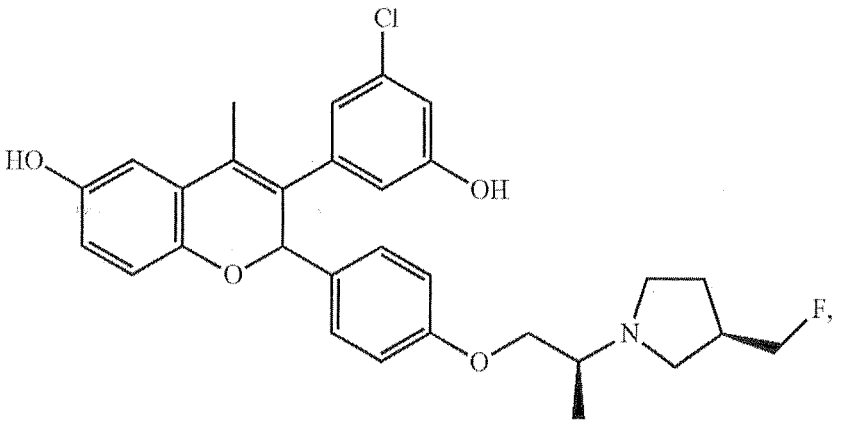
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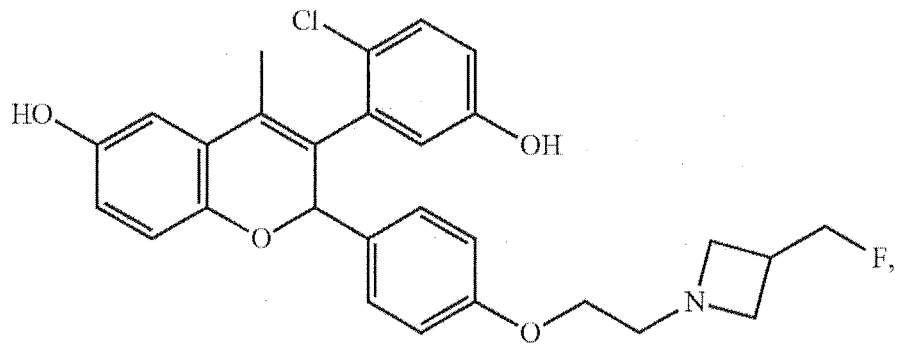
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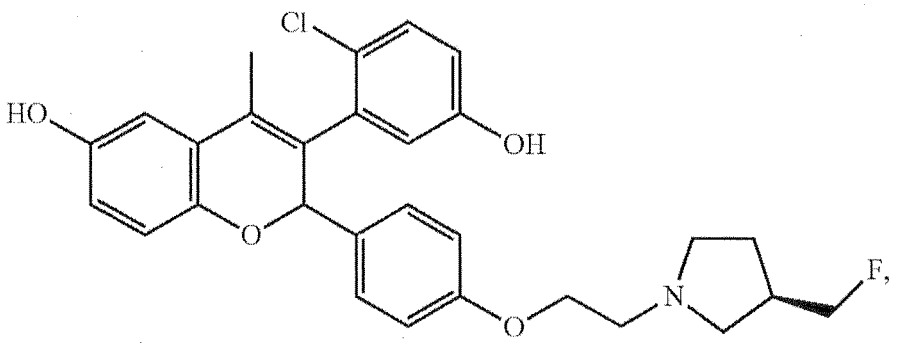
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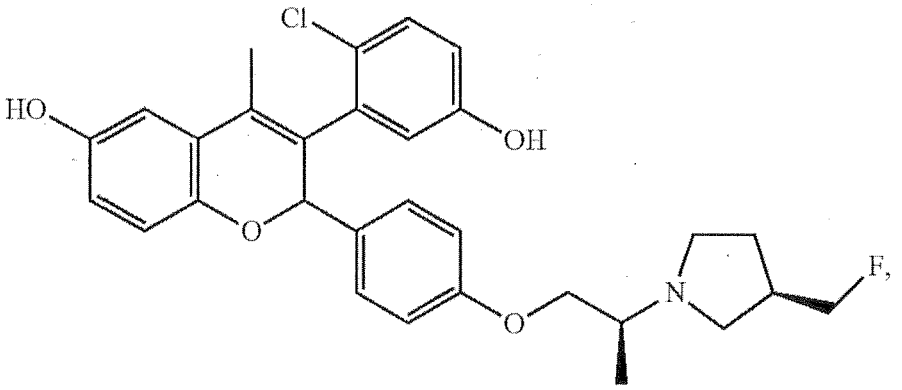
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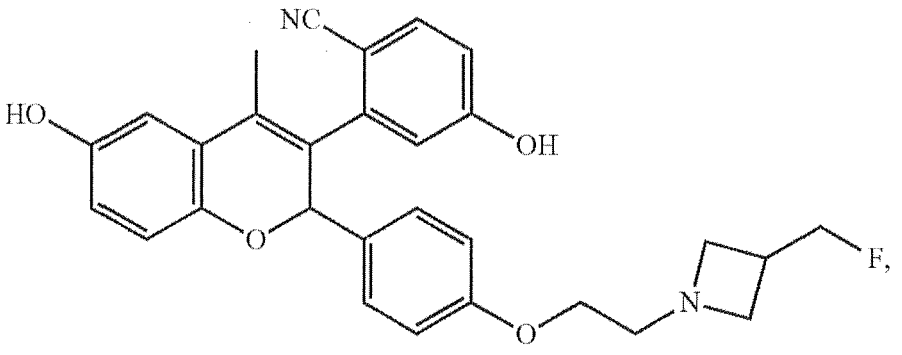
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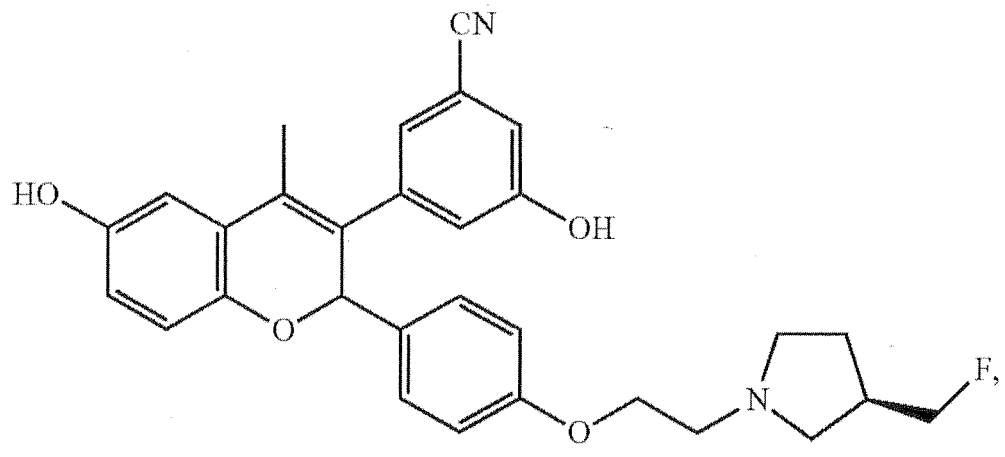
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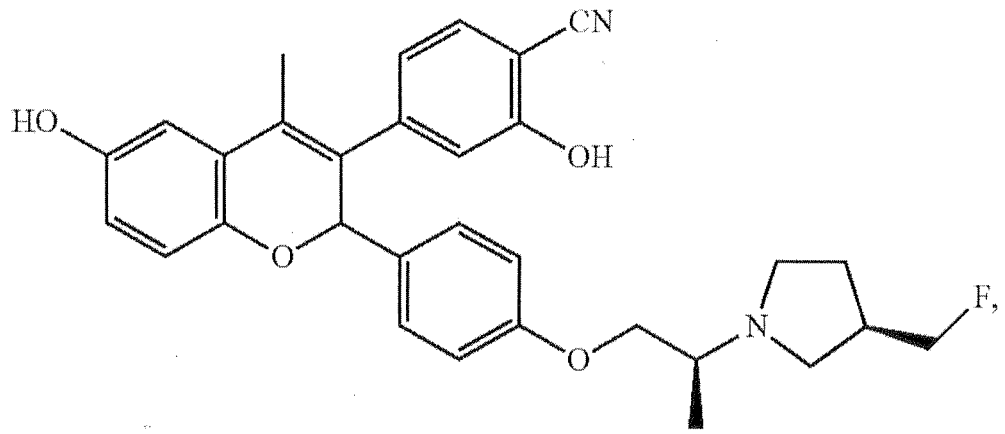
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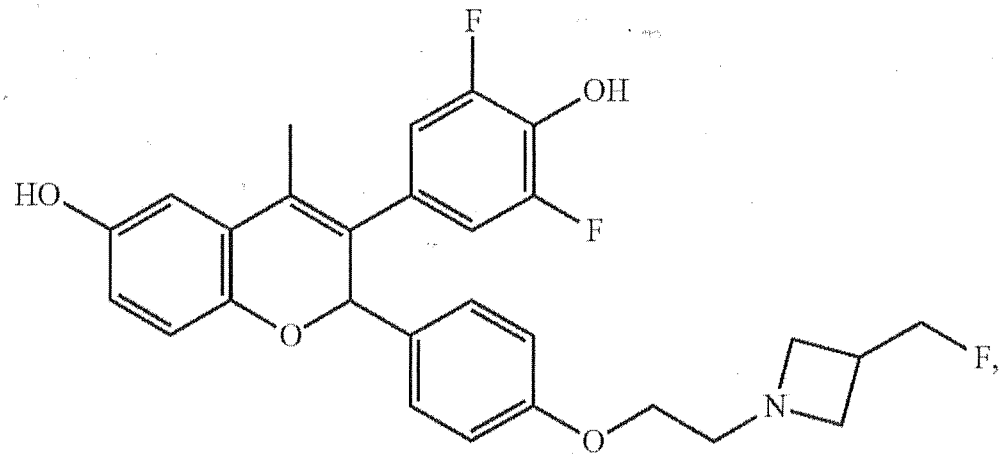
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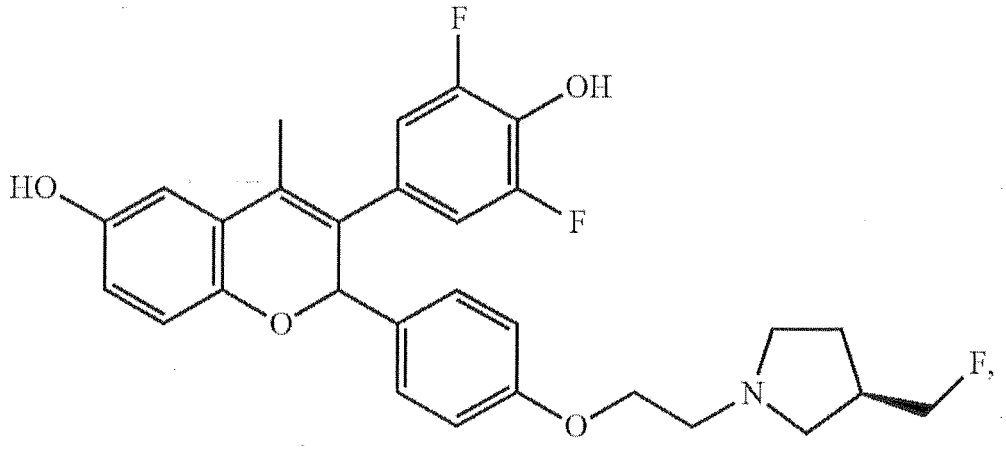
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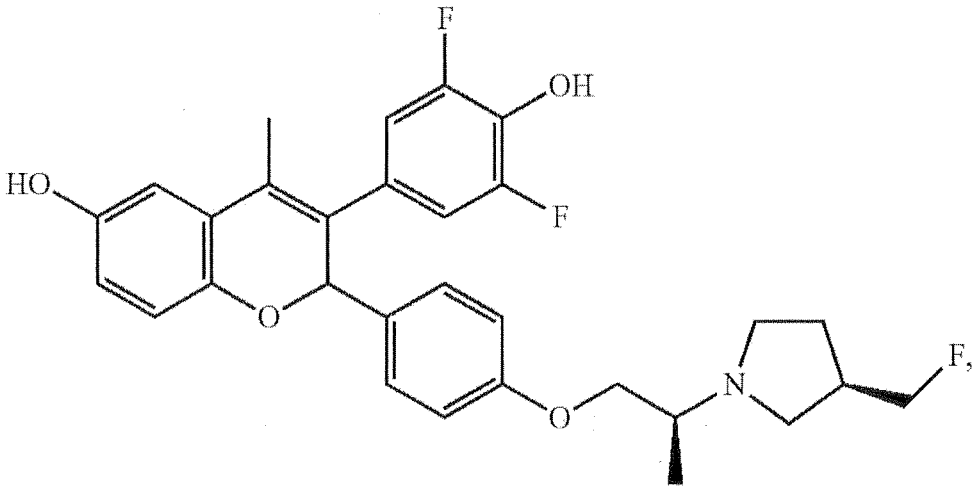
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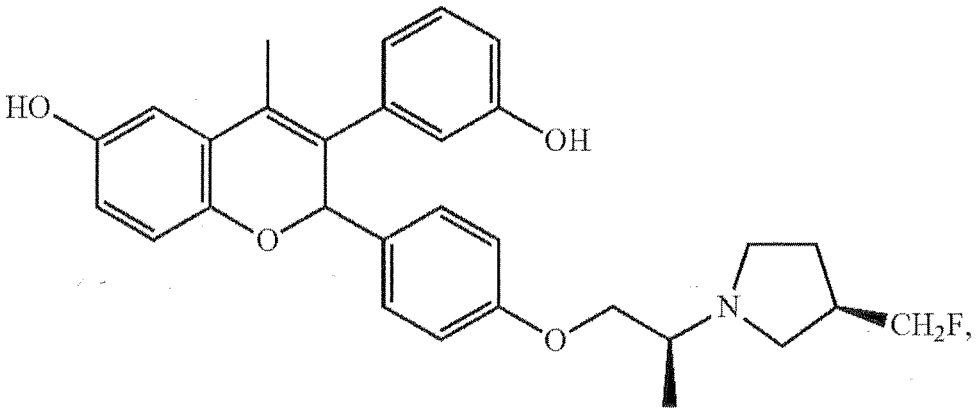
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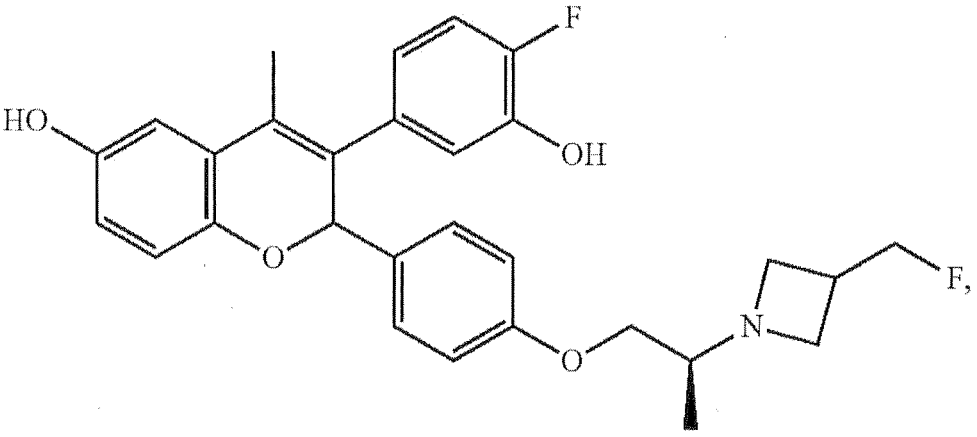
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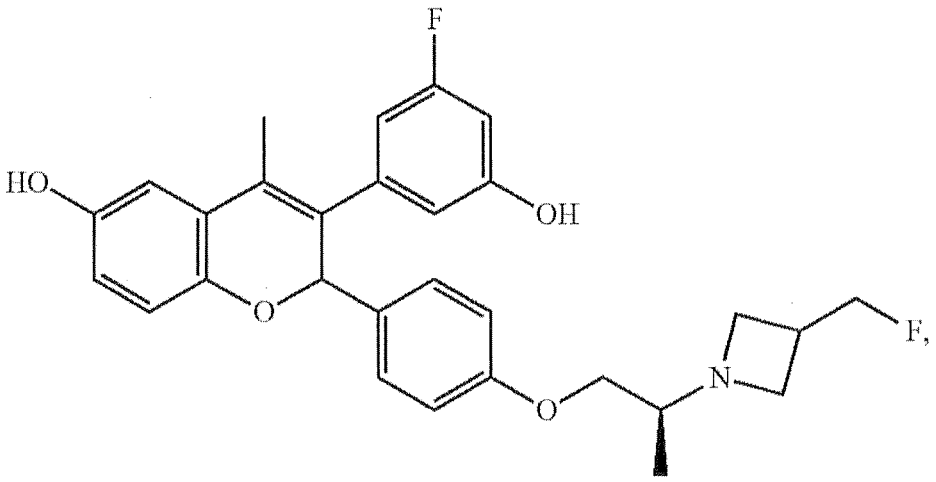

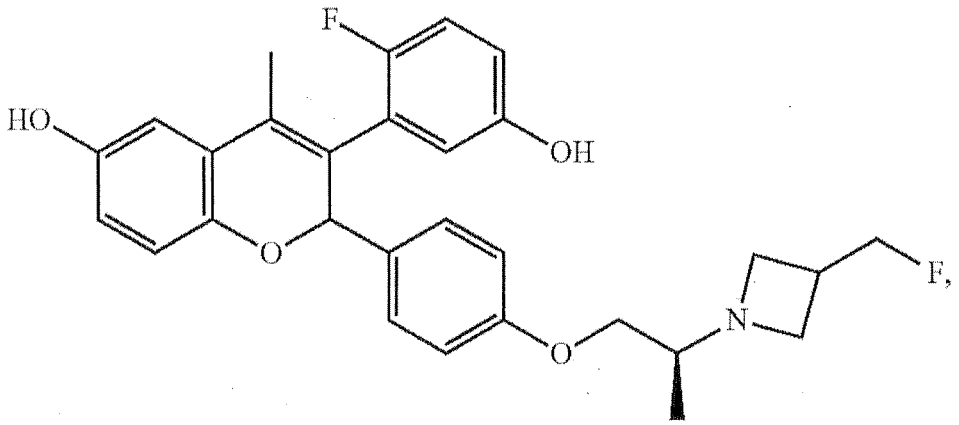

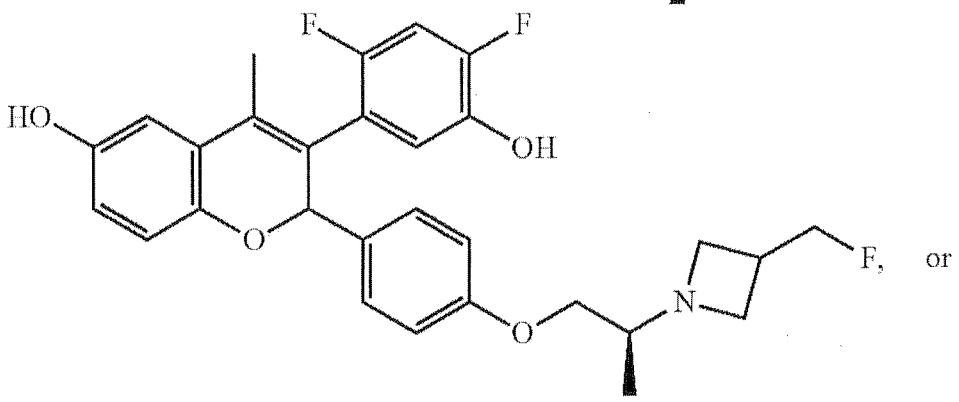

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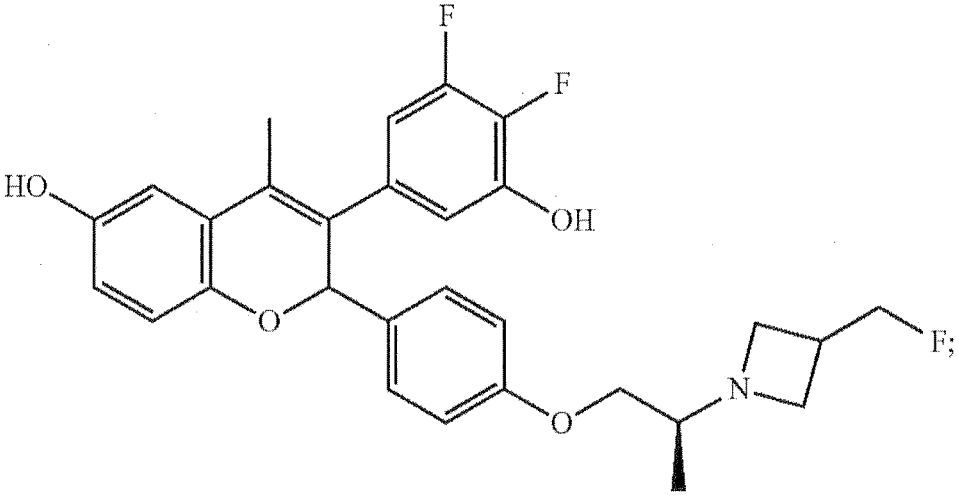

or a pharmaceutically acceptable salt, or solvate thereof.

11. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable inactive ingredient.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration.

13. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.