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In some embodiments, the estrogen receptor modulator is 4-23.

In some embodiments, the estrogen receptor modulator is 1-3 or 4-23.

In some embodiments, the estrogen receptor modulator is (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid or (S)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

In some embodiments, the estrogen receptor modulator is (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid.

In some embodiments, the estrogen receptor modulator is (S)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

In one aspect, there is provided an estrogen receptor modulator compound of Formula (D) for use in the treatment of an ER-related disease or condition in a patient

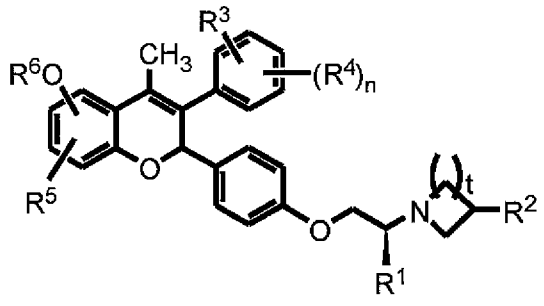
wherein the ER-related disease or condition is cancer;

wherein the patient has a mutation in the *ESR1* gene;

wherein the *ESR1* mutation results in a substitution of one or more amino acids in the ligand binding domain of the estrogen receptor;

wherein the amino acid substitution is at amino acid position 6, 118, 269, 311, 341, 350, 380, 392, 394, 433, 463, 503, 534, 535, 536, 537, 538 or 555 of SEQ ID NO: 2; and

wherein the compound of Formula (D) has the structure:



Formula (D)

where,

R^1 is H, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^2 is H, F, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

R^3 is H, halogen, -CN, -OR^6, -NHR^6, -NR^6R^7, -SR^6, -S(=O)R^7, -$S(=O)_2R^7$, C_1-C_4alkyl, or C_1-C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, and C_1-C_4 alkoxy;

each R^5 is H, F, Cl, -OH, -CH_3, -CF_3, or –OCH_3;

each R^6 is independently selected from H, -C(=O)R^7, -C(=O)OR^7, -C(=O)NHR^7, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2; and

t is 1 or 2,

or a pharmaceutically acceptable salt, or solvate thereof.

In some embodiments, the ER-related disease or condition is cancer. In some embodiments, the cancer is a breast cancer. In some embodiments, the breast cancer is a metastatic breast cancer. In some embodiments, the breast cancer is a hormone resistant breast cancer. In some embodiments, the breast cancer is an estrogen receptor positive breast cancer. In some embodiments, the breast cancer is a HER2 positive breast cancer. In some embodiments, the breast cancer is a HER2 negative breast cancer. In some embodiments, the breast cancer is resistant to treatment with an aromatase inhibitor. In some embodiments, the mutation in the *ESR1* gene is a somatic mutation. In some embodiments, the patient expresses a wild-type ER and a mutant ER. In some embodiments, the patient expresses a homodimer of two mutant ER-α polypeptides. In some embodiments, the patient expresses a heterodimer of one wild-type ER-α polypeptide and one mutant ER-α polypeptide or a heterodimer of one

wild-type ER-β polypeptide and one mutant ER-α polypeptide. In some embodiments, the patient has a tumor. In some embodiments, a plurality of cells of the tumor express the mutant ER. In some embodiments, the patient is pre-menopausal or post-menopausal. In some embodiments, the patient has failed one or more anti-cancer therapies. In some embodiments, the patient has received a chemotherapeutic agent, a biological therapy, a cancer vaccine, an angiogenesis inhibitor, hormone therapy, radiation therapy, surgery, or any combination thereof. In some embodiments, the biological therapy is a peptide, a cytokine, an antibody, a therapeutic virus, a therapeutic bacterium, gene therapy, siRNA, adoptive T-cell transfer, or any combination thereof. In some embodiments, the patient has received an aromatase inhibitor, a selective estrogen receptor modulator (SERM), a selective estrogen degrader (SERD), a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a

nucleic acid sample. In some embodiments, the method further comprises amplifying a nucleic molecule comprising the mutation from the nucleic acid sample. In some embodiments, amplification is by polymerase chain reaction (PCR) or digital PCR. In some embodiments, PCR amplification comprises using a pair of oligonucleotide primers that flank the region comprising the mutation. In some embodiments, the methods comprise contacting the nucleic acid with a sequence specific nucleic acid probe, wherein the sequence specific nucleic acid probe that binds to the nucleic acid having the mutation and does not bind to the wild-type nucleic acid. In some embodiments, the sample comprises nucleic acid from one or more tumor cells. In some embodiments, the tumor cell is taken from a tumor biopsy sample, a blood sample, a serum sample, a lymph sample, or a bone marrow aspirate. In some embodiments, the tumor cell is a circulating tumor cell. In some embodiments, the sample comprises circulating tumor DNA (ctDNA).

Described herein, are kits comprising one or more reagents for the detection of a mutation in *ESR1* and an estrogen receptor modulator compound of Formula (A), (B), (C), or (D) as defined herein. In some embodiments, the kits comprise one or more primers or probes for the detection of a mutation in *ESR1*. In some embodiments, the ESR1 mutation results in a substitution, insertion or deletion of one or more amino acids in the ER polypeptide. In some embodiments, the ESR1 mutation results in an amino acid substitution the N-terminal domain, the DNA binding domain, the hinge region or the ligand binding domain of the estrogen receptor. In some embodiments, the ESR1 mutation results in an amino acid substitution in the ligand binding domain of the estrogen receptor. In some embodiments, the amino acid substitution is at amino acid position 6, 118, 269, 311, 341, 350, 380, 392, 394, 433, 463, 503, 534, 535, 536, 537, 538 and 555 of SEQ ID NO:2. In some embodiments, the amino acid substitution is selected from among H6Y, S118P, R269C, T311M, S341L, A350E, E380Q, V392I, R394H, S433P, S463P, R503W, V534E, P535H, L536R, L536P, L536Q, Y537N, Y537C, Y537S, D538G, and R555C. In some embodiments, the amino acid substitution is selected from among Y537N, Y537C, Y537S, and D538G.

In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered orally to a patient. In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered daily. In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered on a continuous daily dosing schedule.

In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered at about 5 mg per day to about 1000 mg per day. In some embodiments, the

therapeutically effective amount of an estrogen receptor modulator of Formula (A), (B), (C), (D) is about 10 mg per day to about 100 mg per day.

In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered once a day or multiple times a day. In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered once a day, twice a day, three times a day, or four times a day.

In another aspect, there is provided a pharmaceutical composition comprising an estrogen receptor modulator compound as defined herein and one or more pharmaceutically acceptable excipients, for use in the treatment of an ER-related disease or condition as defined herein.

Other objects, features and advantages of the methods, uses and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Breast cancer is the most common form of cancer and the leading cause of cancer death in women worldwide. Approximately 80% of all breast cancers express and are dependent on the estrogen receptor (ER) for tumor growth and progression. Other cancers also are thought to be dependent on ER-α signaling for growth and survival, such as, for example, ovarian and endometrial cancers.

Estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β) are steroid hormone receptors, which are members of the large nuclear receptor superfamily. Nuclear receptors share a common modular structure, which minimally includes a DNA binding domain (DBD) and a ligand binding domain (LBD). Steroid hormone receptors are soluble, intracellular proteins that act as ligand-regulated transcription factors. Vertebrates contain five closely related steroid hormone receptors (estrogen receptor, androgen receptor, progesterone receptor, glucocorticoid receptor, mineralcorticoid receptor), which regulate a wide spectrum of

WHAT IS CLAIMED IS:

1. An estrogen receptor modulator compound of Formula (D) for use in the treatment of an ER-related disease or condition in a patient

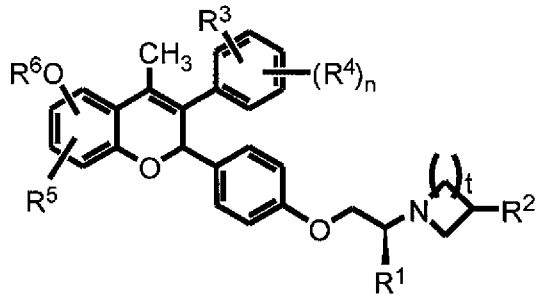
wherein the ER-related disease or condition is cancer;

wherein the patient has a mutation in the *ESR1* gene;

wherein the *ESR1* mutation results in a substitution of one or more amino acids in the ligand binding domain of the estrogen receptor;

wherein the amino acid substitution is at amino acid position 6, 118, 269, 311, 341, 350, 380, 392, 394, 433, 463, 503, 534, 535, 536, 537, 538 or 555 of SEQ ID NO: 2; and

wherein the compound of Formula (D) has the structure:



Formula (D)

where,

R^1 is H, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^2 is H, F, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

R^3 is H, halogen, -CN, -OR^6, -NHR^6, -NR^6R^7, -SR^6, -S(=O)R^7, -$S(=O)_2R^7$, C_1-C_4alkyl, or C_1-C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, and C_1-C_4 alkoxy;

each R^5 is H, F, Cl, -OH, -CH_3, -CF_3, or –OCH_3;

each R^6 is independently selected from H, -C(=O)R^7, -C(=O)OR^7, -C(=O)NHR^7, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

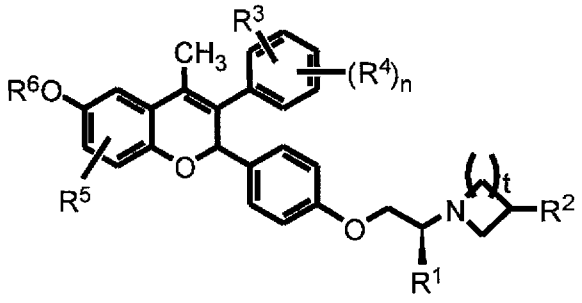
each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2; and

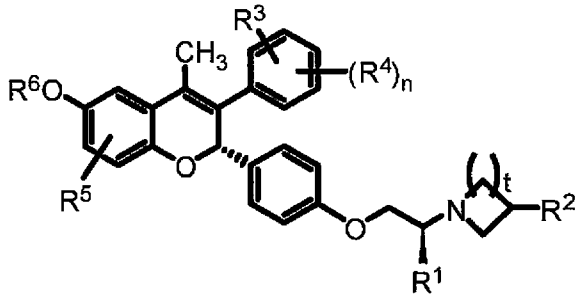
t is 1 or 2,

or a pharmaceutically acceptable salt, or solvate thereof.

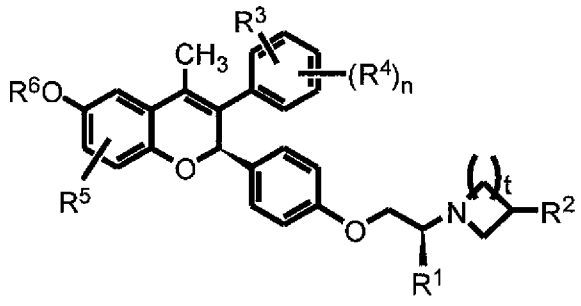
2. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1, wherein the estrogen receptor modulator is a compound selected from Formula (D-1), (D-2), (D-3), and (D-4), having the structures:



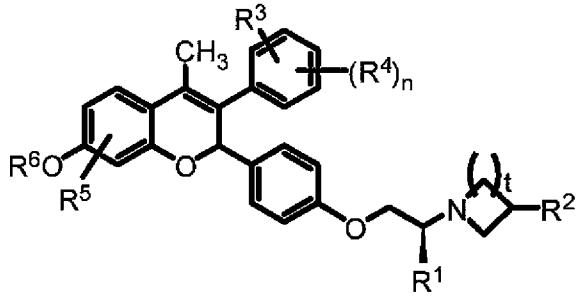
Formula (D-1)



Formula (D-2)

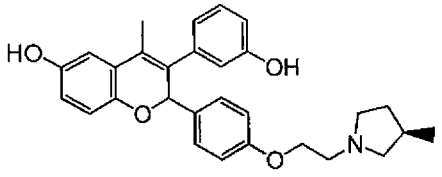
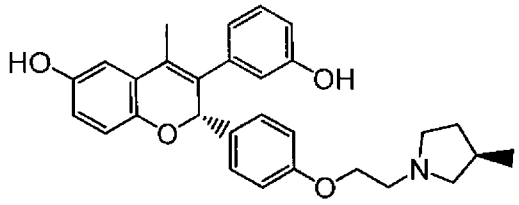
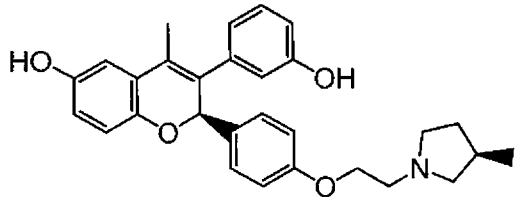
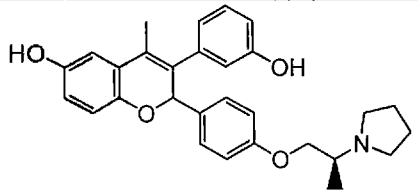
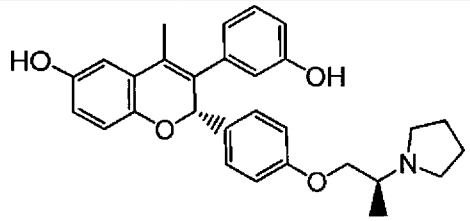
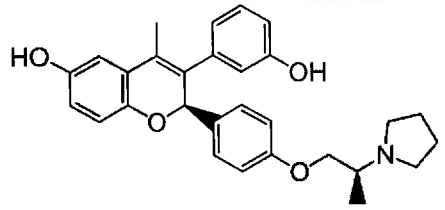
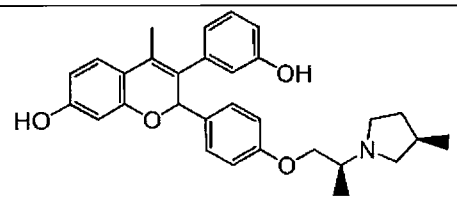


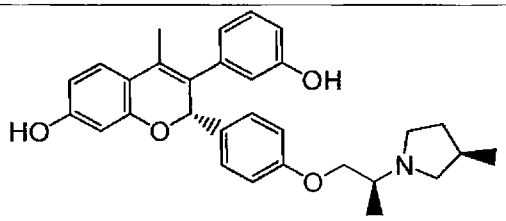
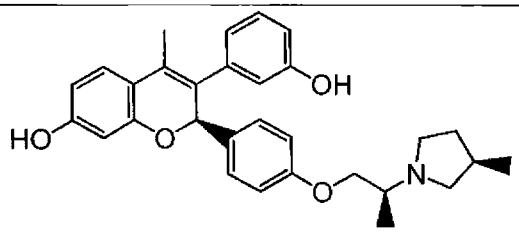
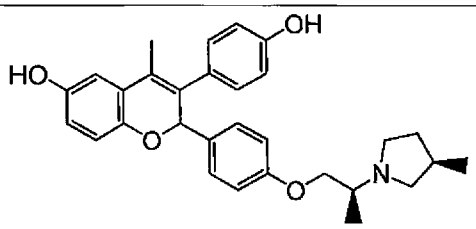
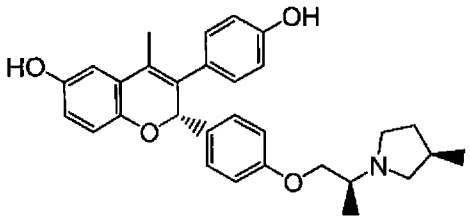
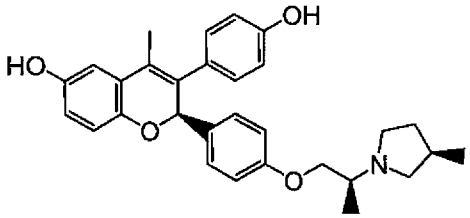
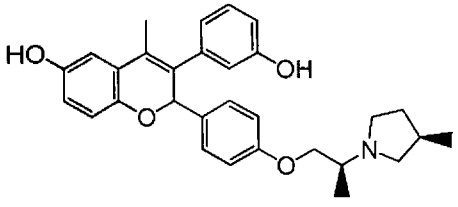
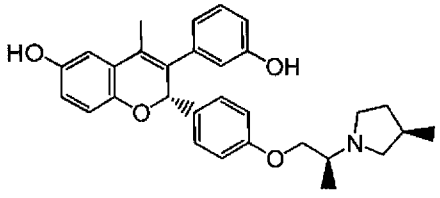
Formula (D-3)

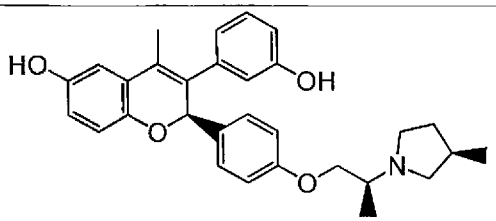
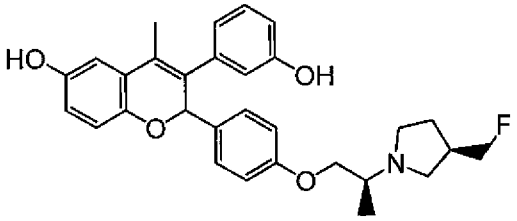
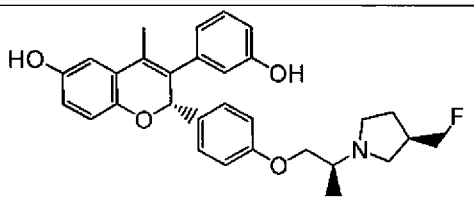
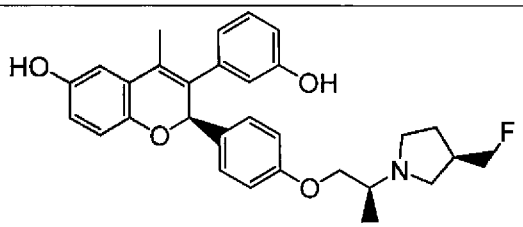
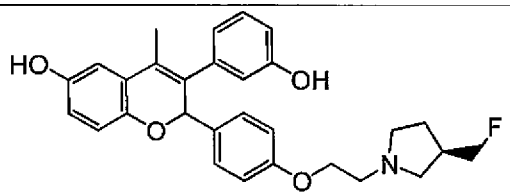
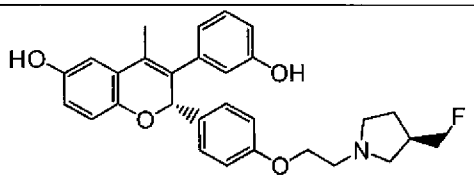
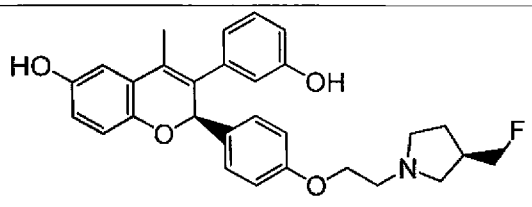


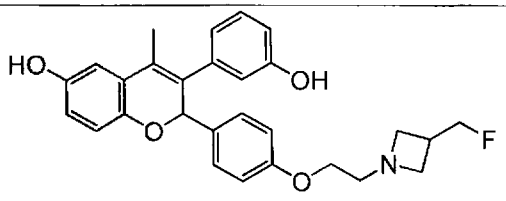
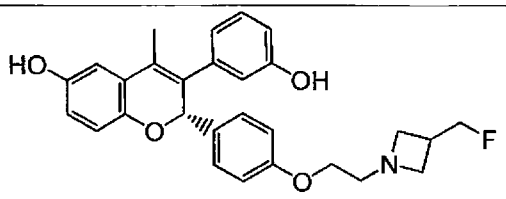
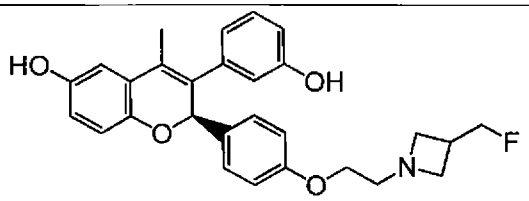
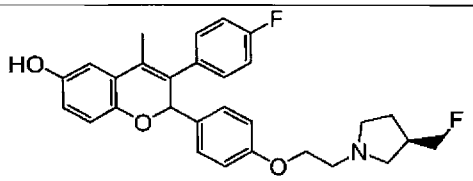
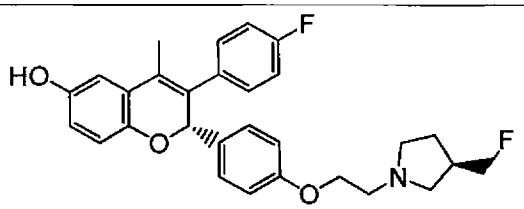
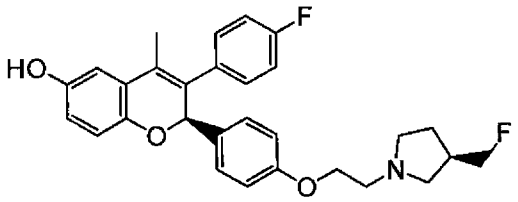
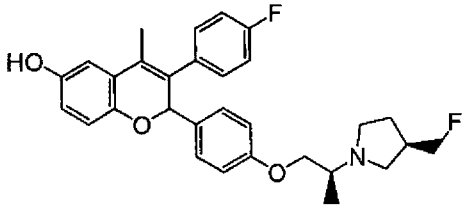
Formula (D-4).

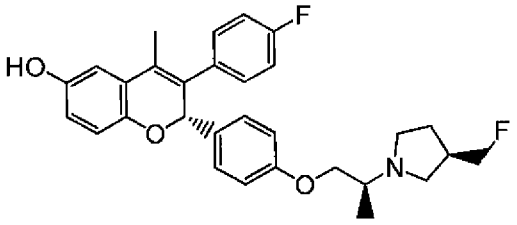
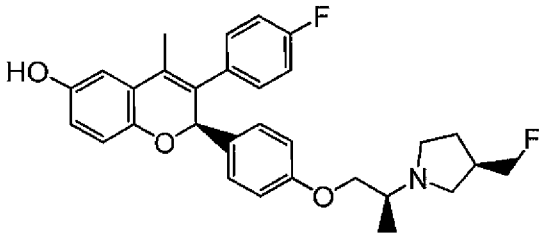
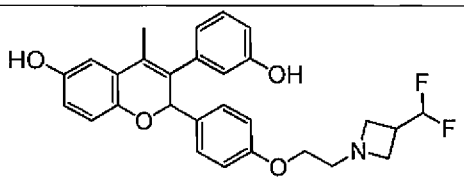
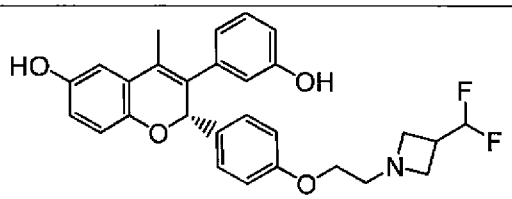
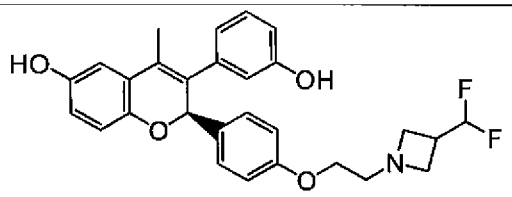
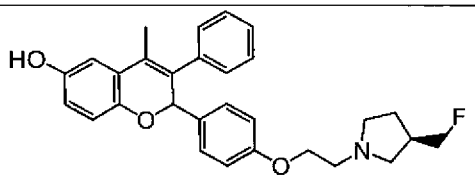
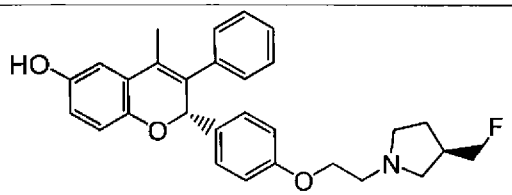
3. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1 wherein the estrogen receptor modulator is selected from among a compound 4-1, 4-2, 4-3, 4-4, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, 4-13, 4-14, 4-15, 4-16, 4-17, 4-18, 4-19, 4-20, 4-21, 4-22, 4-23, 4-24, 4-25, 4-26, 4-27, 4-28, 4-29, 4-30, 4-31, 4-32, 4-33, 4-34, 4-35, 4-36, 4-37, 4-38, 4-39, 4-40, 4-41, 4-42, 4-43, 4-44 and 4-45:

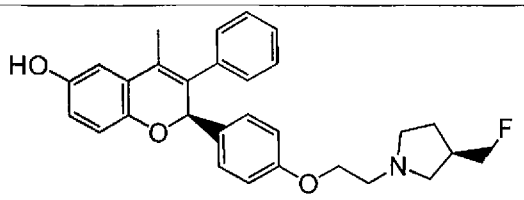
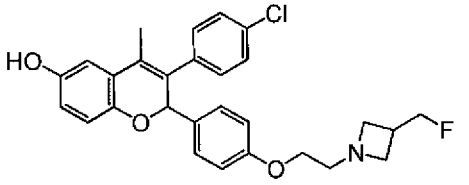
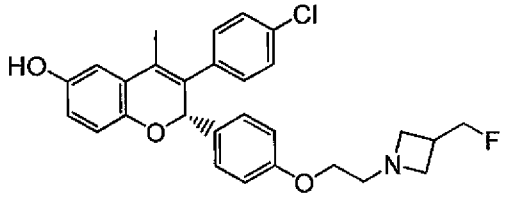
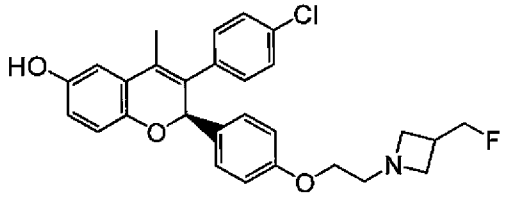
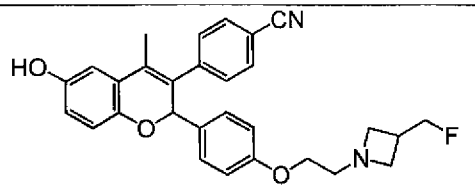
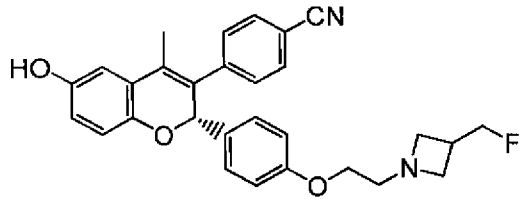
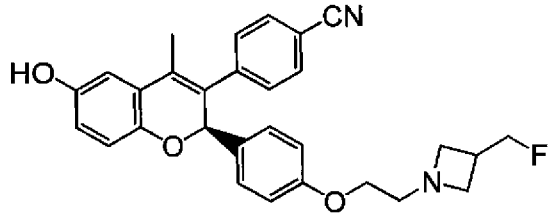
Compound	Name	Structure
4-1	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol	
4-2	(S)-3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol	
4-3	(R)-3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol	
4-4	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-(pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-5	(S)-3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-(pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-6	(R)-3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-(pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-7	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-7-ol	

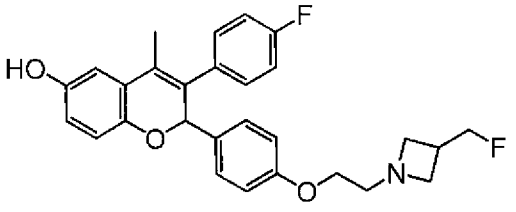
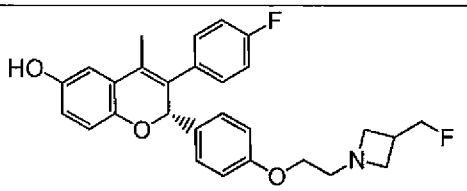
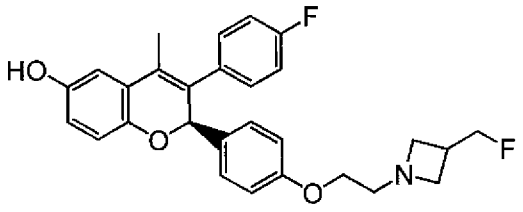
Compound	Name	Structure
4-8	(S)-3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-7-ol	
4-9	(R)-3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-7-ol	
4-10	3-(4-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-11	(S)-3-(4-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-12	(R)-3-(4-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-13	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-14	(S)-3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	

Compound	Name	Structure
4-15	(R)-3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol	
4-16	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-17	(S)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-18	(R)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-19	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-20	(S)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-21	(R)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	

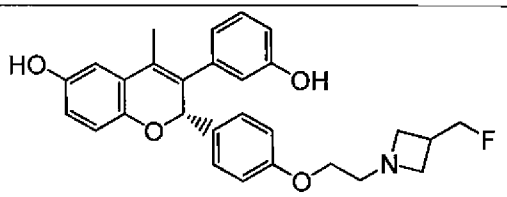
Compound	Name	Structure
4-22	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-23	(S)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-24	(R)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-25	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	
4-26	(S)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	
4-27	(R)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	
4-28	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	

Compound	Name	Structure
4-29	(S)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	
4-30	(R)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	
4-31	2-(4-(2-(3-(difluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-32	(S)-2-(4-(2-(3-(difluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-33	(R)-2-(4-(2-(3-(difluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	
4-34	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-3-phenyl-2H-chromen-6-ol	
4-35	(S)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-3-phenyl-2H-chromen-6-ol	

Compound	Name	Structure
4-36	(R)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-3-phenyl-2H-chromen-6-ol	
4-37	3-(4-chlorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol	
4-38	(S)-3-(4-chlorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol	
4-39	(R)-3-(4-chlorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol	
4-40	4-(2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)benzonitrile	
4-41	(S)-4-(2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)benzonitrile	
4-42	(R)-4-(2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)benzonitrile	

Compound	Name	Structure
4-43	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	
4-44	(S)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	
4-45	(R)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol	

4. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1 wherein the estrogen receptor modulator is 4-23:

Compound	Name	Structure
4-23	(S)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol	

5. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1 wherein the cancer is selected from breast, cervical, colon, endometrial, glioma, lung, melanoma, ovarian, pancreatic, and prostate.

6. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 5 wherein the cancer is breast cancer.

7. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1 wherein the patient has received an aromatase inhibitor, a selective estrogen receptor modulator (SERM), a selective estrogen degrader (SERD), a PI3 kinase/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

8. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1 wherein the patient has received fulvestrant,

tamoxifen, anastrozole, letrozole, exemestane, goserelin, leuprolide, raloxifene, toremifene, megestrol acetate, bazedoxifene, or any combination thereof.

9. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1 wherein the amino acid substitution is selected from among H6Y, S118P, R269C, T311M, S341L, A350E, E380Q, V392I, R394H, S433P, S463P, R503W, V534E, P535H, L536R, L536P, L536Q, Y537N, Y537C, Y537S, D538G, and R555C.

10. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 9 wherein the amino acid substitution is selected from among L536R, Y537N, Y537C, Y537S, and D538G.

11. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 1 wherein the patient is selected for treatment with the estrogen receptor modulator compound by the steps of:

    a) detecting a mutation in the *ESR1* gene in a sample comprising nucleic acid from the patient; and

    b) selecting the patient for treatment with the estrogen receptor modulator compound if the patient has the *ESR1* mutation.

12. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 11 wherein the nucleic acid is RNA or DNA.

13. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 12 wherein the DNA is genomic DNA.

14. A pharmaceutical composition comprising an estrogen receptor modulator compound as defined in any of claims 1 to 13 and one or more pharmaceutically acceptable excipients, for use in the treatment of an ER-related disease or condition as defined in any of claims 1 to 13.

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