ESTROGEN RECEPTOR MODULATOR AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/836,901 entitled "ESTROGEN RECEPTOR MODULATOR AND USES THEREOF" filed on June 19, 2013; and U.S provisional patent application no. 61/952,430 entitled "ESTROGEN RECEPTOR MODULATOR AND USES THEREOF" filed on March 13, 2014; all of which are incorporated by reference in their 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.

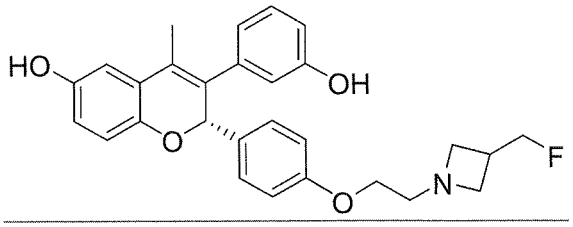
BACKGROUND OF THE INVENTION

[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~~

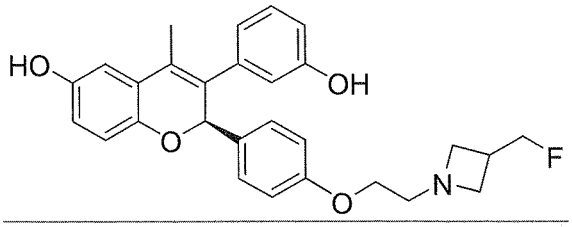
[0004a] In one aspect, there is provided a compound that has the following structure of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

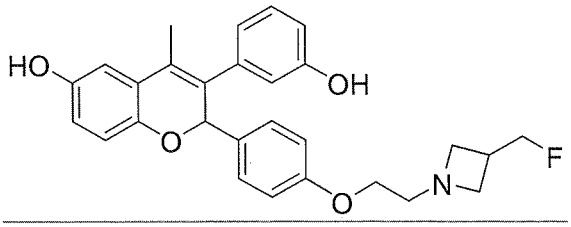
[0004b] In another aspect, there is provided a compound that has the following structure of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0004c] In another aspect, there is provided a compound that has the following structure of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0004d] In another aspect, there is provided a pharmaceutically acceptable salt of the compound as described herein.

[0004e] In another aspect, there is provided a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt, solvate or prodrug as described herein.

[0004f] In another aspect, there is provided a compound, or a pharmaceutically acceptable salt, solvate or prodrug thereof, as described herein for use as a medicament.

[0004g] In another aspect, there is provided use of a compound, or a pharmaceutically acceptable salt, solvate or prodrug thereof, as described herein in the manufacture of a medicament for the treatment of cancer in a mammal.

[0005] ~~In one aspect, p~~Presented herein are compounds of Formula (I), (II), and (III), or a pharmaceutically acceptable salt, solvate or prodrug thereof, 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, c~~Compounds of Formula (I), (II), and (III), or a pharmaceutically acceptable salt, solvate or prodrug thereof, are 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 sclerosis, cirrhosis), susceptibility to infection (hepatitis B, chronic liver disease), metabolic defects (bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis), neurological defects (Alzheimer's disease, Parkinson's disease, migraine, vertigo), psychiatric defects (anorexia nervosa, attention deficity hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis), uterine diseases (e.g. leiomyoma, uterine leiomyoma, endometrial hyperplasia, endometriosis), and reproductive defects (age of menarche, endometriosis, infertility).

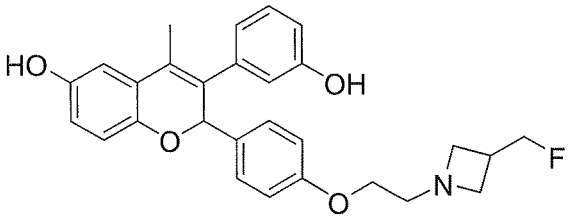
[0007] ~~In one aspect, d~~Described herein are compounds of Formula (I), (II), and (III), pharmaceutically acceptable salts, solvates, metabolites and prodrugs thereof. Compounds described herein are estrogen receptor modulators. In some embodiments, the compound of Formula (I), (II), or (III) is an estrogen receptor antagonist. In some embodiments, the compound of Formula (I), (II), or (III) is an estrogen receptor degrader. In some embodiments, the compound of Formula (I), (II), or (III) is an estrogen receptor antagonist as well as an estrogen receptor degrader. In some embodiments, the compound of Formula (I), (II), or (III) displays miminal or no estrogen receptor agonist activity. In some embodiments, in the context of treating cancers, the compound of Formula (I), (II), or (III) may offer improved therapeutic activity characterized by complete or longer-lasting tumor regression, a lower incidence or rate of development of resistance to treatment, and/or a reduction in tumor invasiveness.

[0008] In some embodiments, compounds disclosed herein have high specificity for the estrogen receptor and have desirable, tissue-selective pharmacological activities. Desirable, tissue-selective pharmacological activities include, but are not limited to, ER antagonist activity in breast cells and no ER agonist activity in uterine cells. In some embodiments, compounds disclosed herein are estrogen receptor degraders that display full estrogen receptor antagonist activity with negligible or minimal estrogen receptor agonist activity.

[0009] In some embodiments, compounds disclosed herein are estrogen receptor degraders. In some embodiments, compounds disclosed herein are estrogen receptor antagonists. In some embodiments, compounds disclosed herein have minimal or negligible estrogen receptor agonist activity.

[0010] In some embodiments, presented herein are compounds selected from active metabolites, tautomers, pharmaceutically acceptable solvates, pharmaceutically acceptable salts or prodrugs of a compound of Formula (I), (II), or (III).

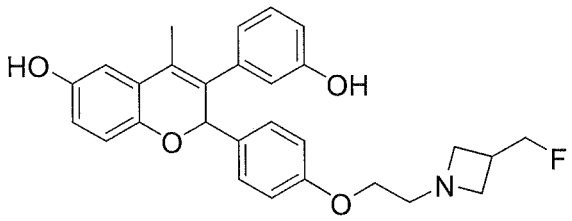
[0011] ~~In one aspect, d~~Described herein is a compound of Formula (I):



Formula (I)

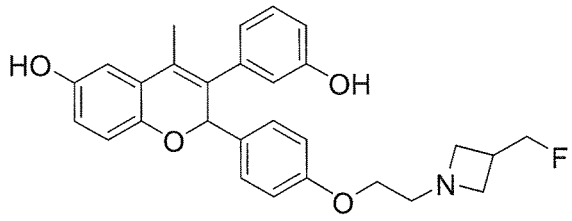
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0012] ~~In one aspect, d~~Described herein is a compound that has the following structure of Formula (I):



Formula (I).

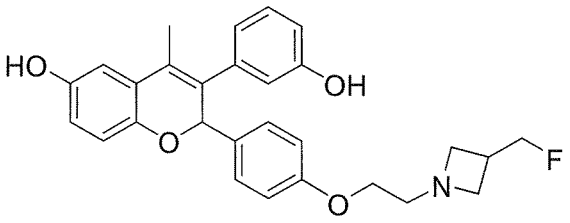
[0013] Also described is a pharmaceutically acceptable salt of a compound that has the following structure of Formula (I):



Formula (I).

[0014] In some embodiments, the pharmaceutically acceptable salt of the compound is an acid addition salt.

[0015] In some embodiments, the pharmaceutically acceptable salt of the compound is a hydrochloric acid salt, a hydrobromic acid salt, a sulfuric acid salt, a phosphoric acid salt, a metaphosphoric acid salt, an acetic acid salt, a propionic acid salt, a hexanoic acid salt, a cyclopentanepropionic acid salt, a glycolic acid salt, a pyruvic acid salt, a lactic acid salt, a malonic acid salt, a succinic acid salt, a malic acid salt, a L-malic acid salt, a maleic acid salt, an oxalic acid salt, a fumaric acid salt, a trifluoroacetic acid salt, a tartaric acid salt, a L-tartaric acid salt, a citric acid salt, a benzoic acid salt, a 3-(4-hydroxybenzoyl)benzoic acid salt, a cinnamic acid salt, a mandelic acid salt, a methanesulfonic acid salt, an ethanesulfonic acid salt, a 1,2-ethanedisulfonic acid salt, a 2-hydroxyethanesulfonic acid salt, a benzenesulfonic acid salt, a toluenesulfonic acid salt, a 2-naphthalenesulfonic acid salt, a 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid salt, a glucoheptonic acid salt, a 4,4'-methylenebis-(3-hydroxy-2-ene-1-

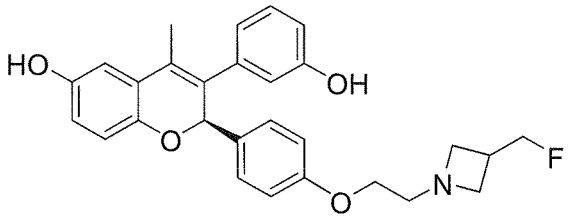


Formula (I).

[0018] In some embodiments, the pharmaceutically acceptable salt of the prodrug of a compound of Formula (I) is a hydrochloride salt.

[0019] In some embodiments, described is a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt or prodrug of a compound of Formula (I). In some embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some embodiments, 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.

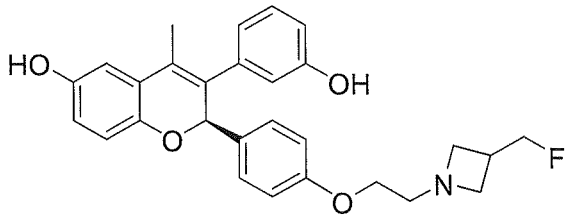
[0020] Also described herein is a compound that has the following structure of Formula (II):



Formula (II)

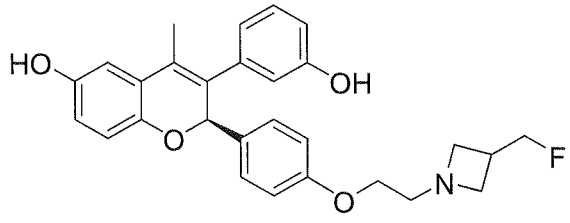
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0021] ~~In one aspect, d~~Described herein is a compound that has the following structure of Formula (II):



Formula (II).

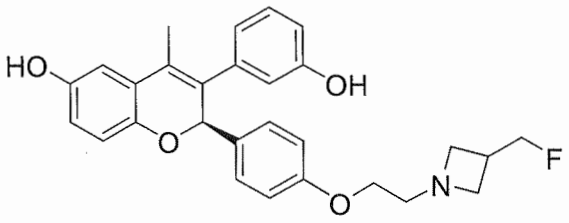
[0022] ~~In another aspect, d~~Described herein is a pharmaceutically acceptable salt of a compound that has the following structure of Formula (II):



Formula (II).

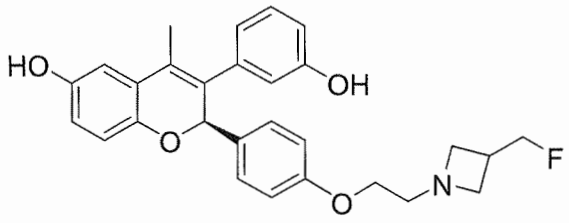
valproic acid. In some embodiments, described herein is a hydrochloride salt of a compound that has the structure of Formula (II).

[0024] ~~In another aspect, d~~Described herein is a prodrug of a compound that has the following structure of Formula (II):



Formula (II).

[0025] ~~In another aspect, d~~Described herein is a pharmaceutically acceptable salt of a prodrug of a compound that has the following structure of Formula (II):

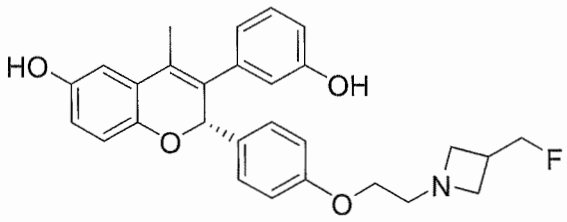


Formula (II).

[0026] In some embodiments, the pharmaceutically acceptable salt of the prodrug of a compound of Formula (II) is a hydrochloride salt.

[0027] In some embodiments, described herein is a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt or prodrug of a compound of Formula (II). In some embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some embodiments, 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. In some embodiments, the enantiomeric ratio of the compound is greater than 90:10. In some embodiments, the enantiomeric ratio of the compound is greater than 95:5. In some embodiments, the enantiomeric ratio of the compound is greater than 99:1.

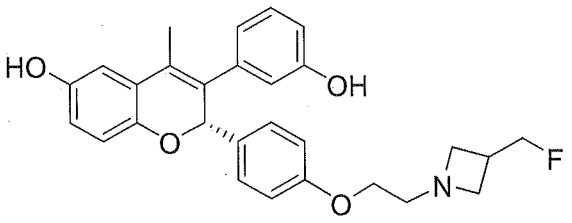
[0028] ~~In another aspect, d~~Described herein is a compound that has the following structure of Formula (III):



Formula (III)

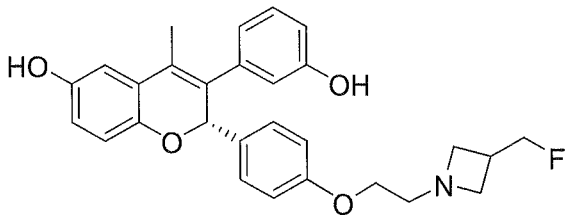
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0029] ~~In one aspect, d~~Described herein is a compound that has the following structure of Formula (III):



Formula (III).

[0030] ~~In another aspect, d~~Described herein is a pharmaceutically acceptable salt of a compound that has the following structure of Formula (III):



Formula (III).

[0031] In some embodiments, the pharmaceutically acceptable salt of the compound is an acid addition salt. In some embodiments, the pharmaceutically acceptable salt of the compound is a hydrochloric acid salt, a hydrobromic acid salt, a sulfuric acid salt, a phosphoric acid salt, a metaphosphoric acid salt, an acetic acid salt, a propionic acid salt, a hexanoic acid salt, a cyclopentanepropionic acid salt, a glycolic acid salt, a pyruvic acid salt, a lactic acid salt, a malonic acid salt, a succinic acid salt, a malic acid salt, a L-malic acid salt, a maleic acid salt, an oxalic acid salt, a fumaric acid salt, a trifluoroacetic acid salt, a tartaric acid salt, a L-tartaric acid salt, a citric acid salt, a benzoic acid salt, a 3-(4-hydroxybenzoyl)benzoic acid salt, a cinnamic acid salt, a mandelic acid salt, a methanesulfonic acid salt, an ethanesulfonic acid salt, a 1,2-ethanedisulfonic acid salt, a 2-hydroxyethanesulfonic acid salt, a benzenesulfonic acid salt, a toluenesulfonic acid salt, a 2-naphthalenesulfonic acid salt, a 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid salt, a glucoheptonic acid salt, a 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid) salt, a 3-phenylpropionic acid salt, a trimethylacetic acid salt, a tertiary butylacetic acid salt, a lauryl sulfuric acid salt, a gluconic acid salt, a glutamic acid salt, a hydroxynaphthoic acid salt, a salicylic acid salt, a stearic acid salt, a muconic acid salt, a butyric acid salt, a phenylacetic acid salt, a phenylbutyric acid salt, or a valproic acid salt. In some embodiments, the pharmaceutically acceptable salt of the compound is a hydrochloric acid salt. In some embodiments, the pharmaceutically acceptable salt of the compound is formed by reacting the compound with an inorganic acid. In some embodiments, the pharmaceutically

capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[0040] In some embodiments, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, is administered orally.

[0041] In some embodiments, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, is administered systemically.

[0042] In some embodiments, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, is administered intravenously.

[0043] In some embodiments, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, is administered subcutaneously.

[0044] In some embodiments, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, is administered topically. In such embodiments, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, is formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. In some embodiments, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, is administered topically to the skin of mammal.

[0045] ~~In another aspect~~ There is provided the use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating a disease, disorder or conditions in which the activity of estrogen receptors contributes to the pathology and/or symptoms of the disease or condition. ~~In one aspect, t~~The disease or condition is any of the diseases or conditions specified herein.

[0046] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) adminstered non-systemically or locally to the mammal.

[0047] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[0048] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[0049] Also provided is a method of reducing ER activation in a mammal comprising administering to the mammal at least one compound having the structure of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof. In some embodiments, the method comprises reducing ER activation in breast cells, lung cells, ovarian cells, colon cells, prostate cells, endometrial cellls, or uterine cells in the mammal. In some embodiments, the method comprises reducing ER activation in breast cells, ovarian cells, colon cells, prostate cells, endometrial cellls, or uterine cells in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing the binding of estrogens to estrogen receptors in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing ER concentrations in the mammal.

[0050] ~~In one aspect~~ There is provided the use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of diseases or conditions of the uterus in a mammal. In some embodiments, the disease or condition of the uterus is leiomyoma, uterine leiomyoma, endometrial hyperplasia, or endometriosis. In some embodiments, the disease or condition of the uterus is a cancerous disease or condition of the uterus. In some other embodiments, the disease or condition of the uterus is a non-cancerous disease or condition of the uterus.

[0051] ~~In one aspect~~There is provided the use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of diseases or conditions that are estrogen sentitive, estrogen receptor dependent or estrogen receptor mediated. In some embodiments, the disease or condition is breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, or uterine cancer. In some embodiments, the disease or condition is described herein.

[0052] In some cases disclosed herein is the use of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of diseases or conditions

18. The pharmaceutical composition of claim 16, 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.

19. ~~Use of a~~ A compound, or a pharmaceutically acceptable salt, solvate or prodrug thereof, of any one of claims 1-15 for use ~~in the treatment of cancer in a mammal~~as a medicament.

20. Use of a compound, or a pharmaceutically acceptable salt, solvate or prodrug thereof, of any one of claims 1-15 in the manufacture of a medicament for the treatment of cancer in a mammal.

~~20.~~21. The use of claim ~~19~~20, wherein the cancer is amenable to treatment with an estrogen receptor modulator.

~~21.~~22. The use of claim ~~19~~20, wherein the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, lung cancer or uterine cancer.

~~22.~~23. The use of any one of claims ~~19~~20-~~21~~22 in combination with an analysis of CA-125 levels in a blood sample from the mammal.