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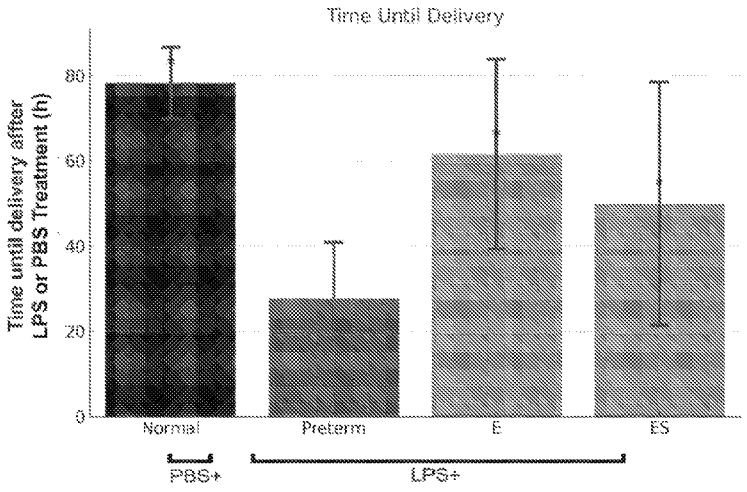
(54) Title: ESTROGENIC COMPOUNDS AND FORMULATIONS FOR GESTATION-RELATED COMPLICATIONS

Fig. 2B



(57) Abstract: Formulations, compounds, and methods to prolong gestation and for treatment of gestational complications are described. Treatments include administration of an estrogenic compound to mitigate uterine contractions.

WO 2024/259428 A2

ESTROGENIC COMPOUNDS AND FORMULATIONS FOR GESTATION-RELATED COMPLICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Ser. No. 63/508,763, entitled "Compounds and Formulations for Gestation-Related Complications," filed June 16, 2023, the disclosure of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The invention is generally directed toward compounds, formulations, and methods of treatment to prolong gestation and for treatment of gestational complications.

BACKGROUND

[0003] Various gestational complications include spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, and recurrent pregnancy loss. Each of these disorders is related to premature uterine contractions during pregnancy. Spontaneous preterm labor is the opening of the cervix after week 20 and before week 37 of gestation, and can result in a preterm birth that can dramatically hinder the health and may result in death of the newborn and/or mother. Spontaneous abortion (also referred to as miscarriage) is the spontaneous loss of a pregnancy before week 20 of gestation. Early term birth is the opening of the cervix after week 37 and before week 39 of gestation, and can result in a birth that less desirable than a full-term birth of greater than 39 weeks of gestation. Recurrent preterm birth is a condition in which a woman experiences two or more pregnancies that go into labor prior to week 37 of gestation. Recurrent early term birth is a condition in which a woman experiences two or more pregnancies that go into labor prior to week 39 of gestation. Recurrent pregnancy loss is a condition in which a woman experiences two or more spontaneous losses of pregnancy. Furthermore, individuals with a short cervix (e.g.,

cervix less than 30 mm, and especially less than 24 mm) have a higher risk of preterm labor.

SUMMARY

[0004] Various embodiments are directed towards formulations, compounds and methods to prolong gestation and for treating gestational complications, including recurrent preterm birth, recurrent early term birth, recurrent pregnancy loss, short cervix, early term birth, spontaneous preterm birth or spontaneous abortion.

[0005] In some aspects, the techniques described herein relate to a method of treating a pregnant individual for recurrent preterm birth, recurrent early term birth, recurrent pregnancy loss, or a short cervix, including: administering an estrogenic compound to an individual, wherein the individual is pregnant and has a medical history indicating recurrent preterm birth, recurrent early term birth, recurrent pregnancy loss, or a short cervix.

[0006] In some aspects, the techniques described herein relate to a method, wherein the estrogenic compound is administered in a therapeutically effective amount.

[0007] In some aspects, the techniques described herein relate to a method, wherein the administering step is to begin upon a determination that the individual is pregnant.

[0008] In some aspects, the techniques described herein relate to a method, wherein the administering step is to end by one of: week 40 of gestation, week 39 of gestation, week 38 of gestation, or week 37 of gestation.

[0009] In some aspects, the techniques described herein relate to a method of treating a pregnant individual for early term birth, spontaneous preterm birth or spontaneous abortion, including: determining that a pregnant individual is experiencing uterine contractions related to early term birth, spontaneous preterm birth or spontaneous abortion; and administering an estrogenic compound to an individual.

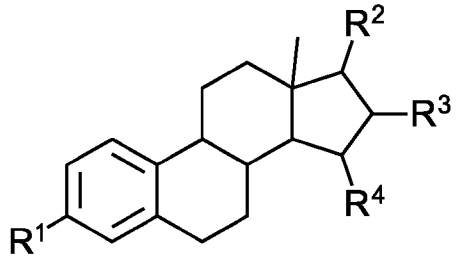
[0010] In some aspects, the techniques described herein relate to a method, wherein the estrogenic compound is administered in a therapeutically effective amount.

[0011] In some aspects, the techniques described herein relate to a method, wherein the administering step is to begin upon a determination that the uterine contractions are occurring prior to one of: week 39 of gestation or week 37 of gestation.

[0012] In some aspects, the techniques described herein relate to a method, wherein the administering step is to end by one of: week 40 of gestation, week 39 of gestation, week 38 of gestation, or week 37 of gestation.

[0013] In some aspects, the techniques described herein relate to a medicament for use in mitigating uterine contractions in an individual, the medicament including: an estrogenic compound.

[0014] In some aspects, the techniques described herein relate to a medicament, wherein the estrogenic compound is of formula:



wherein R1 is OH, phosphonic acid, sulfonic acid, or OR5; R2 is O, OH, phosphonic acid, sulfonic acid, or OR6; R3 is H, OH, phosphonic acid, sulfonic acid, or OR7; R4 is H, OH, phosphonic acid, sulfonic acid, or OR8; and OR5, OR6, OR7, and OR8 can each individually be galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate; wherein any acid can be an anionic formulation of that acid.

[0015] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is OH, R3 is OH and R4 is H, matching the formula for estriol.

[0016] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is OH, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is H.

[0017] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is OH, R3 is OH, and R4 is H.

[0018] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is phosphonic acid or sulfonic acid or OR6, R3 is OH, and R4 is H.

[0019] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is OH, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is H.

[0020] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is phosphonic acid or sulfonic acid or OR6, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is H.

[0021] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is phosphonic acid or sulfonic acid or OR6, R3 is OH, and R4 is H.

[0022] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is phosphonic acid or sulfonic acid or OR6, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is H.

[0023] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is OH, R3 is H, and R4 is H.

[0024] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is OH, R3 is H, and R4 is H.

[0025] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is phosphonic acid or sulfonic acid or OR6, R3 is H, and R4 is H.

[0026] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is phosphonic acid or sulfonic acid or OR6, R3 is H, and R4 is H.

[0027] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is O, R3 is H, and R4 is H.

[0028] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5 or, R2 is O, R3 is H, and R4 is H.

[0029] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is OH, R3 is OH and R4 is OH.

[0030] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is OH, R3 is OH, and R4 is OH.

[0031] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is phosphonic acid or sulfonic acid or OR6, R3 is OH, and R4 is OH.

[0032] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is OH, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is OH.

[0033] In some aspects, the techniques described herein relate to a medicament, wherein, R1 is OH, R2 is OH, R3 is OH, and R4 is phosphonic acid or sulfonic acid or OR8.

[0034] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is phosphonic acid or sulfonic acid or OR6, R3 is OH, and R4 is OH.

[0035] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is OH, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is OH.

[0036] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is phosphonic acid or sulfonic acid or OR6, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is OH.

[0037] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is OH, R3 is OH, and R4 is phosphonic acid or sulfonic acid or OR8.

[0038] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is phosphonic acid or sulfonic acid or OR6, R3 is OH, and R4 is phosphonic acid or sulfonic acid or OR8.

[0039] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is OH, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is phosphonic acid or sulfonic acid or OR8.

[0040] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is phosphonic acid or sulfonic acid or OR6, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is OH.

[0041] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is phosphonic acid or sulfonic acid or OR6, R3 is OH, and R4 is phosphonic acid or sulfonic acid or OR8.

[0042] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is OH, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is phosphonic acid or sulfonic acid or OR8.

[0043] In some aspects, the techniques described herein relate to a medicament, wherein R1 is OH, R2 is phosphonic acid or sulfonic acid or OR6, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is phosphonic acid or sulfonic acid or OR8.

[0044] In some aspects, the techniques described herein relate to a medicament, wherein R1 is phosphonic acid or sulfonic acid or OR5, R2 is phosphonic acid or sulfonic acid or OR6, R3 is phosphonic acid or sulfonic acid or OR7, and R4 is phosphonic acid or sulfonic acid or OR8.

[0045] In some aspects, the techniques described herein relate to a medicament, wherein the estrogenic compound is a synthetic estrogen selected from: dienestrol, dienstrol diacetate, dienestrol dipopropionate, dienestrol monobenzoate, hexestrol, hexestrol diacetate, hexestrol dipropionate, hexestrol monobenzoate, methallenestril, methallenestril acetate, methallenestril benzoate, methallenestril propionate, mestranol, 3-(2'.3'-epoxypropoxy)-1.3.5.(10)-estratrien-16.alpha, estriol-3-glycidyl ether, estriol-6-carboxymethyl oxime, or ethinylestradiol.

[0046] In some aspects, the techniques described herein relate to a medicament, wherein the estrogenic compound is an estriol ester or estriol amino ester selected from: 3,17.beta.-Diisobutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Divaleryloxy-1,3,5(10)- estratrien-16.alpha.-ol, 3,17.beta.-Dihexanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dipivaloyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Didecanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibenzoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 6-alpha.-aminoestriol-16,17-diaceteate, 6.alpha.(N-diglycolylamido) estriol, 6.alpha.-aminoestriol, 6.alpha.-(N-diglycoylamido)estriol NHS-ester, estriol-N-hydroxysuccinimide (NHS) ester, estriol-aminooxy, or estriol-carboxylic acid hydrazide.

[0047] In some aspects, the techniques described herein relate to a medicament, wherein the estrogenic compound is a metabolite of estriol, estradiol, estrone, or estetrol selected from: 16α-hydroxyestrone, 2-methoxyestrone, 2-hydroxyestrone, 4-hydroxyestrone, 2-hydroxyestradiol, 2-hydroxyestradiol, or 16-ketoestradiol.

[0048] In some aspects, the techniques described herein relate to a medicament, wherein the medicament is for recurrent preterm birth, recurrent early term birth, recurrent pregnancy loss, or a short cervix.

[0049] In some aspects, the techniques described herein relate to a medicament, wherein the medicament is for early term birth, spontaneous preterm birth or spontaneous abortion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] The description and claims will be more fully understood with reference to the following figures and data graphs, which are presented as exemplary embodiments of the invention and should not be construed as a complete recitation of the scope of the invention.

[0051] Figure 1 provides examples of chemical structures in accordance with various embodiments.

[0052] Figure 2A provides a schematic of an experiment performed on a mouse model of preterm birth.

[0053] Figures 2B and 2C provide data results of an experiment performed on a mouse model of preterm birth.

[0054] Figures 3A and 3B provide data results of an experiment performed on mice to mitigate uterine contraction.

[0055] Figure 4 provides a data chart of the concentration of circulating estrone-3-sulfate in pregnant women over the period of gestation.

DETAILED DESCRIPTION

[0056] Turning now to the drawings and data, compounds, formulations and methods for treatment of an individual experiencing a gestational complication or to prolong gestation of an individual in accordance with various embodiments are described. In some embodiments, an individual is administered a compound that modulates uterine contraction. In some embodiments, an individual having a gestational complication, such as (for example) spontaneous preterm labor, spontaneous abortion, recurrent preterm birth, early term birth, or recurrent pregnancy loss is administered a compound described herein to treat the gestational complication. In some embodiments, the compound to treat the gestational complication is an estrogen steroid or a derivative thereof. Four naturally occurring estrogen steroids are estrone, estradiol, estriol, and estetrol.

[0057] Preterm birth, or birth before 37 weeks of gestation, is the leading cause of infant mortality and morbidity, associated with 70% of neonatal deaths. The incidence of preterm birth is rising in many countries, including the United States, where the frequency increased from 10.7% of all births in 1992 to 12.3% of all births 11 years later. Between 70-80% of these preterm births resulted from preterm labor. Current methods for the intervention of preterm labor include the acute treatment with tocolytic agents such as magnesium sulfate, nifedipine, beta-adrenoceptor agonists, and prostaglandin synthase inhibitors in order to delay delivery by 48-72 hours. This short delay allows enough time for the expectant mothers to be transported to hospitals with specialized care if necessary, as well as time for physicians to administer a full course of glucocorticoids to the expectant mother, which can reduce the incidence of respiratory distress syndrome in the preterm neonate. While the available treatments have shown some efficacy in

prolonging labor, they are often prematurely discontinued due to maternal and fetal side effects. Furthermore, there is a need for agents that can prolong gestation for longer periods of time and allow the pregnancy to progress closer to term.

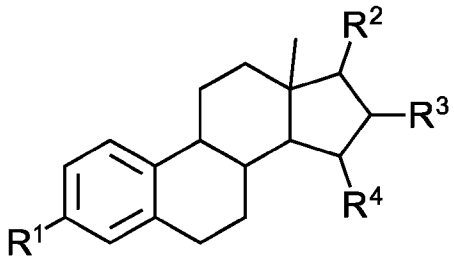
[0058] Many of the various embodiments described herein are based on experimentation on several estrogenic compounds. It was discovered that estriol, and estriol-related compounds, are able to prolong pregnancy and/or prevent preterm labor. In accordance with several embodiments, a formulation comprises an estrogenic compound for the treatment of spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, and recurrent pregnancy loss. In many embodiments, an individual experiencing spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss is administered an estrogenic compound. In some embodiments, a formulation comprises estriol or an estrogenic compound for prolonging gestation. In some embodiments, an individual is administered an estrogenic compound to prolong their pregnancy. Estrogenic compounds include estrone and estrone-related compounds, estradiol and estradiol-related compounds, estriol and estriol-related compounds, and estetrol and estetrol related compounds.

Compounds

[0059] Several embodiments are directed towards formulations and compounds and their use as therapeutics and/or supplements to treat an individual experiencing a gestational complication or to prolong gestation of the individual. A number of compounds have been identified that that reduce uterine cell contractions and thus can be utilized to mitigate complications that arise from premature and/or abnormal uterine contractions. In some embodiments, the compounds is an estrogenic compound. In some embodiments, a compound is estrone or estrone-related. An estrone-related compound that has a structural derivative of estrone or a metabolite of estrone. In some embodiments, a compound is estriol. In some embodiments, a compound is estriol-related. An estriol-related compound that has a structural derivative of estriol or a metabolite of estriol. In some embodiments, a compound is estradiol or estradiol-related. An estradiol-related

compound that has a structural derivative of estradiol or a metabolite of estradiol. In some embodiments, a compound is estetrol or estetrol-related. An estetrol-related compound that has a structural derivative of estetrol or a metabolite of estetrol.

[0060] In some embodiments, a formula to prolong gestation or for the treatment of spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss comprises a compound having the structure:



wherein R^1 is OH, phosphonic acid, sulfonic acid, or OR^5;

R^2 is O, OH, phosphonic acid, sulfonic acid, or OR^6;

R^3 is H, OH, phosphonic acid, sulfonic acid, or OR^7; and

R^4 is H, OH, phosphonic acid, sulfonic acid, or OR^8

OR^5, OR^6, OR^7, and OR^8 can each individually be galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). The formula can be 16α, 16β, 16α and 17β, 16β and 17α, 16α and 17α , 16β and 17β, 16α 17β and 18β, 16α 17β and 18 α, 16α 17α and 18β, 16α 17α and 18α, 16β 17β and 18β, 16β 17β and 18 α, 16β 17α and 18β, or 16β 17α and 18α. The formulae can further be provided as a therapeutically acceptable salt or a hydrate (e.g., hemihydrate).

[0061] In some embodiments, R^1 is OH, R^2 is OH, R^3 is OH and R^4 is H, matching the formula for estriol.

[0062] In some embodiments, R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H. OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0063] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is H. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0064] In some embodiments, R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H. OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid,

methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0065] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0066] In some embodiments, R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H. OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any

acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0067] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0068] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0069] In some embodiments, R^1 is OH, R^2 is OH, R^3 is H, and R^4 is H, matching the formula for estradiol.

[0070] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is H, and R^4 is H. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0071] In some embodiments, R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H. OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0072] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H. R^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^6 is

galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0073] In some embodiments, R^1 is OH, R^2 is O, R^3 is H, and R^4 is H, matching the formula for estrone.

[0074] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5 or, R^2 is O, R^3 is H, and R^4 is H. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0075] In some embodiments, R^1 is OH, R^2 is OH, R^3 is OH and R^4 is OH, matching the formula for estetrol.

[0076] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is OH. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric

acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0077] In some embodiments, R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH. OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0078] In some embodiments, R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH. OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0079] In some embodiments, R^1 is OH, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric

acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0080] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0081] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid,

sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0082] In some embodiments, R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH. OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0083] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0084] In some embodiments, R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid,

succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0085] In some embodiments, R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0086] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic

acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0087] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid,

dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0088] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid,

mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0089] In some embodiments, R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^6 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid,

methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0090] In some embodiments, R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8. OR^5 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^6 is

galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^7 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate). OR^8 is galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0091] Provided in Fig. 1 are examples of chemical structures of compounds that can be utilized in accordance with the various embodiments of the disclosure. The structures are derivatives of estriol. Notably, any of the ester functional groups (-O-R) extending

from the C17 within the structures of Fig. 1 can be utilized at any alcohol group (OH) in: estrone, estradiol, estriol, or estetrol.

[0092] In some embodiments, a formula to prolong gestation or for the treatment of spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss comprises a synthetic form of estrogen. Examples of synthetic estrogens include (but are not limited to) dienestrol, dienstrol diacetate, dienestrol dipopropionate, dienestrol monobenzoate, hexestrol, hexestrol diacetate, hexestrol dipropionate, hexestrol monobenzoate, methallenestril, methallenestril acetate, methallenestril benzoate, methallenestril propionate, mestranol, 3-(2'.3'-epoxypropoxy)-1.3.5.(10)-estratrien-16.alpha, estriol-3-glycidyl ether, estriol-6-carboxymethyl oxime, and ethinylestradiol.

[0093] In some embodiments, a formula to prolong gestation or for the treatment of spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss comprises hydroxyestriol. Hydroxyestriol include (but are not limited to) 2-hydroxyestriol, 4-hydroxyestriol, and estetrol. Any alcohol group (OH) of the hydroxy estriol can be esterified with galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate. Any alcohol group (OH) of the hydroxy estriol can be substituted with phosphonic acid or sulfonic acid. Any acid can be an anionic formulation of that acid (e.g., oxalic acid can be oxalate).

[0094] In some embodiments, a formula to prolong gestation or for the treatment of spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss comprises an estriol ester. In some embodiments, a formula to prolong gestation or for the treatment of spontaneous

preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss comprises an estriol amino ester. In some embodiments, a formula to prolong gestation or for the treatment of spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss comprises an estriol ester or estriol amino ester selected from: 3,17.beta.-Diisobutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Divaleryloxy-1,3,5(10)- estratrien-16.alpha.-ol, 3,17.beta.-Dihexanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dipivaloyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Didecanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibenzoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 6-alpha.-aminoestriol-16,17-diaceteate, 6.alpha.(N-diglycolylamido) estriol, 6.alpha.-aminoestriol, 6.alpha.-(N-diglycoylamido)estriol NHS-ester, estriol-N-hydroxysuccinimide (NHS) ester, estriol-aminooxy, or estriol-carboxylic acid hydrazide.

[0095] In some embodiments, a formula to prolong gestation or for the treatment of spontaneous preterm labor, spontaneous abortion, early term birth, recurrent preterm birth, recurrent early term birth, or recurrent pregnancy loss comprises a metabolite of estriol, estradiol, estrone, or estetrol. Metabolites of estriol include (but are not limited to) 16α-hydroxyestrone, 2-methoxyestrone, 2-hydroxyestrone, 4-hydroxyestrone, 2-hydroxyestradiol, 2-hydroxyestradiol, and 16-ketoestradiol.

[0096] Any of the compounds listed herein can further be conjugated with an immunogen and/or any formula for treatment can comprise an immunogen. Immunogens include (but are not limited to) bovine serum albumin, pneumococcal polysaccharide serotype-14 (PPS-14), keyhole limpet hemocyanin, and ovalbumin.

Pharmaceutical Formulae

[0097] Provided herein are various embodiments of pharmaceuticals and/or supplements for use in a treatment and/or prophylaxis of menstrual complications, gestational complications, and/or to prolong gestation, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other active ingredients. Proper formulation is dependent upon the route of administration chosen. In

some embodiments, pharmaceutical formulae are utilized within a therapeutic and thus utilized to treat a condition. In some embodiments, pharmaceutical formulae are utilized within a supplement (e.g., prenatal supplement) as a prophylaxis. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. Pharmaceutical compositions may be formulated as a modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared utilizing the various method embodiments as described herein.

[0098] The term "active ingredient" refers to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients or carriers, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder. In various embodiments, active ingredients include any one of the compounds listed herein. In some embodiments, an active ingredient is estriol or an estriol-related compound. In some embodiments, an active ingredient is estradiol or an estradiol-related compound. In some embodiments, an active ingredient is estrone or an estrone-related compound. In some embodiments, an active ingredient is estetrol or an estetrol-related compound.

[0099] The compounds disclosed herein can exist as therapeutically acceptable salts. The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound with a suitable acid or base. Therapeutically acceptable salts include acid and basic addition salts. For a more complete discussion of the preparation and selection of salts, refer to "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed., (Wiley-VCH and VHCA, Zurich, 2002) or S. M. Berge, L. D. Bighley and D. C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19.

[0100] Numerous coating agents can be used in accordance with various embodiments of the invention. In some embodiments, the coating agent is one which acts as a coating agent in conventional delayed release oral formulations, including polymers

for enteric coating. Examples include hypromellose phthalate (hydroxy propyl methyl cellulose phthalate; HPMCP); hydroxypropylcellulose (HPC; such as KLUCEL®); ethylcellulose (such as ETHOCEL®); and methacrylic acid and methyl methacrylate (MAA/MMA; such as EUDRAGIT®).

[0101] Various embodiments of formulations also include at least one disintegrating agent. In some embodiments, a disintegrating agent is a super disintegrant agent. In many embodiments, disintegrants are combined with a resin. Additional disintegrating agents include, but are not limited to, agar, calcium carbonate, maize starch, potato starch, tapioca starch, alginic acid, alginates, certain silicates, and sodium carbonate. Suitable super disintegrating agents include, but are not limited to crospovidone, croscarmellose sodium, AMBERLITE (Rohm and Haas, Philadelphia, Pa.), and sodium starch glycolate.

[0102] Several embodiments of a formulation further utilize other components and excipients. For example, sweeteners, flavors, buffering agents, and flavor enhancers to make the dosage form more palatable. Sweeteners include, but are not limited to, fructose, sucrose, glucose, maltose, mannose, galactose, lactose, sucralose, saccharin, aspartame, acesulfame K, and neotame. Common flavoring agents and flavor enhancers that may be included in the formulation of the present invention include, but are not limited to, maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

[0103] Multiple embodiments of a formulation also include a surfactant. In certain embodiments, surfactants are selected from the group consisting of Tween 80, sodium lauryl sulfate, and docusate sodium.

[0104] Various embodiments of a formulation also include a lubricant. In certain embodiments, lubricants are selected from the group consisting of, but are not limited to, magnesium stearate, stearic acid, sodium stearyl fumarate, calcium stearate, hydrogenated vegetable oil, mineral oil, fish oil, castor oil, sesame oil, polyethylene glycol, polyethylene glycol 4000-6000, talc, and glyceryl behenate.

[0105] Modes of administration, in accordance with multiple embodiments, include, but are not limited to, oral, intravenous, subcutaneous, intramuscular, intrauterine (e.g.,

an implantable depot such as a hormone releasing intrauterine device), intraperitoneal, transdermal (e.g., patch), transmucosal (e.g., sublingual, nasal, vaginal or rectal) or a combination thereof. The actual amount of drug needed will depend on factors such as the size, age and severity of disease in the afflicted individual. The actual amount of drug needed will also depend on the effective concentration ranges of the various active ingredients. Vehicles of administration, in accordance with various embodiments, include ointments, solutions, gels, creams, suppositories, implants, tablets, or capsules, as appropriate.

[0106] In some embodiments, active ingredients are administered in a therapeutically effective amount as part of a course of treatment. As used in this context, to "treat" means to ameliorate at least one symptom of a disorder to be treated or to provide a beneficial physiological effect. For example, one such amelioration of a symptom could be reduction of risk of spontaneous preterm labor, spontaneous abortion, recurrent preterm birth, early term birth, or recurrent pregnancy loss.

[0107] A therapeutically effective amount can be an amount sufficient to prevent reduce, ameliorate or eliminate the symptoms of gestational complications susceptible to such treatment.

[0108] Dosage, toxicity and therapeutic efficacy of the compounds can be determined, *e.g.*, by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds that exhibit high therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to other tissue and organs and, thereby, reduce side effects.

[0109] Data obtained from cell culture assays or animal studies can be used in formulating a range of dosage for use in humans. If the pharmaceutical is provided systemically, the dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within

this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration or within the local environment to be treated in a range that includes the ED_{50} as determined in cell culture or animal models. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by mass spectrometry.

[0110] An "effective amount" is an amount sufficient to effect beneficial or desired results. For example, a therapeutic amount is one that achieves the desired therapeutic effect. This amount can be the same or different from a prophylactically effective amount, which is an amount necessary to prevent onset of disease or disease symptoms. An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a composition depends on the composition selected. The compositions can be administered from one or more times per day to one or more times per week; including once every other day, as determined to be beneficial. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of the compositions described herein can include a single treatment or a series of treatments. For example, several divided doses may be administered daily, one dose, or cyclic administration of the compounds to achieve the desired therapeutic result.

[0111] Preservatives and other additives, like antimicrobial, antioxidant, chelating agents, and inert gases, can also be present. One common preservative is benzyl alcohol. (See generally, Remington: The Science and Practice of Pharmacy, 21st Edition; Lippincott Williams & Wilkins: Philadelphia, PA, 2005.)

Methods of Treatment

[0112] Several embodiments are directed towards treatments of individuals with estriol, estradiol, estrone, estetrol, and related compounds thereof to prolong gestation or for gestational complications. In some embodiments, estriol, estradiol, estrone, estetrol, and related compounds thereof are administered to an individual experiencing spontaneous preterm labor, early term labor or spontaneous abortion. In some embodiments, estriol, estradiol, estrone, estetrol, and related compounds thereof are administered to an individual that have a medical history of recurrent preterm birth or recurrent pregnancy loss. In some embodiments, estriol, estradiol, estrone, estetrol, and related compounds thereof are administered to an individual having a short cervix. In some embodiments, estriol, estradiol, estrone, estetrol, and related compounds thereof are administered to an individual having a deficiency of the metabolic compound in relation to gestational progress. In some embodiments, estriol, estradiol, estrone, estetrol, and related compounds thereof are administered to an individual to prolong their gestation. In some embodiments, estriol, estradiol, estrone, estetrol, and related compounds thereof are administered to an individual as prophylaxis. In some embodiments, a prophylaxis is administered without knowing the individual's risk of gestational complications, and/or administered to a generally healthy pregnant individual. In some embodiments, compounds or derivatives thereof are utilized as a supplement, including (for example) a prenatal supplement for any individual.

[0113] Spontaneous preterm labor is the opening of the cervix after week 20 and before week 37 of gestation. Early term birth is the opening of the cervix between 37 weeks, 0 days and 38 weeks, 6 days. Spontaneous abortion is the spontaneous loss of a pregnancy before week 20 of gestation. Each of these conditions are related to uterine wall contractions occurring prematurely during gestational progress before reaching full-term. Further, newly acquired data demonstrates that various metabolic compounds are involved in maintaining proper gestational time course and preventing uterine wall contractions and thus can be utilized in as part of treatment to mitigate spontaneous preterm and early term labor and/or spontaneous abortion. Accordingly, in some embodiments, when an individual is determined to be experiencing spontaneous preterm

labor or early term labor or spontaneous loss of pregnancy, the individual is administered a compound described herein, including estriol, estradiol, estrone, estetrol, or a related compound thereof.

[0114] Administration of compounds described herein can be combined with standards of care for the complication. When an individual is experiencing spontaneous preterm labor, in some embodiments, an individual is additionally administered betamethasone, progesterone, 17-α-hydroxyprogesterone, antibiotics, magnesium sulfate, or a combination thereof. When an individual is experiencing spontaneous preterm labor, in some embodiments, an individual is administered is additionally administered at least one other tocolytic drug. Tocolytic drugs include (but are not limited to) indomethacin, orciprenaline, ritodrine, terbutaline, salbutamol, nifedipine, fenoterol, nylidrin, or isoxsuprine.

[0115] Recurrent preterm birth is a condition in which a woman experiences two or more pregnancies that go into labor prior to week 37 of gestation. Recurrent pregnancy loss is a condition in which a woman experiences two or more spontaneous losses of pregnancy. In addition, individuals with a short cervix of less than 30 cm, and especially shorter than 25 cm have increased risk of preterm labor. Each of these conditions are related to repeatedly experiencing uterine wall contractions occurring prematurely during gestational progress. Further, newly acquired data demonstrates that various metabolic compounds are involved in maintaining proper gestational time course and preventing uterine wall contractions and thus can be utilized in as part of treatment to mitigate spontaneous preterm labor and/or spontaneous abortion. Accordingly, in some embodiments, when an individual is diagnosed with recurrent preterm birth, recurrent pregnancy loss, or a short cervix, the individual is administered a compound described herein, including estriol, estradiol, estrone, estetrol, or a related compound thereof. In some embodiments, a treatment plan is created prior to or early after conception to prepare for the potential of preterm labor or preterm abortion.

[0116] Administration of compounds described herein can be combined with standards of care for the complication. When an individual is diagnosed with recurrent preterm birth, in some embodiments, an individual is additionally administered

betamethasone, progesterone, 17-α-hydroxyprogesterone, antibiotics, magnesium sulfate, or a combination thereof. When an individual is diagnosed with recurrent pregnancy loss, in some embodiments, an individual is administered is additionally administered at least one other tocolytic drug. Tocolytic drugs include (but are not limited to) indomethacin, orciprenaline, ritodrine, terbutaline, salbutamol, nifedipine, fenoterol, nylidrin, or isoxsuprine. When an individual is experiencing recurrent pregnancy loss, in some embodiments, an individual is additionally administered a compound in combination with progesterone, 17-α-hydroxyprogesterone, human menopausal gonadotropin, a derivative thereof, or a combination thereof.

[0117] In various embodiments, an individual is administered a compound described herein, including estriol, estradiol, estrone, estetrol, or a related compound thereof, for a period of 1 to 24 hours, 24 to 48 hours, 48 to 96 hours, 96 to 168 hours, 1 to 2 weeks, 2 to 4 weeks, for a period of 4 to 6 weeks, for a period of 6 to 8 weeks, for a period of 8 to 10 weeks, for a period of 10 to 12 weeks, for a period of 12 to 14 weeks, for a period of 14 to 19 weeks, 20 to 25 weeks, 25 to 30 weeks, 30 to 35 weeks, or 35 to 39 weeks. In various embodiments, an individual is administered a compound described herein, including estriol, estradiol, estrone, estetrol, or a related compound thereof, upon a diagnosis of pregnancy, which may help in cases of recurrent pregnancy loss. In various embodiments, an individual is administered a compound described herein, including estriol, estradiol, estrone, estetrol, or a related compound thereof, upon beginning uterine contraction, especially when premature (e.g., before week 37 of gestation). In various embodiments, an individual is administered a compound described herein, including estriol, estradiol, estrone, estetrol, or a related compound thereof, up until the week 37 of gestation, up until week 38 of gestation, up until week 39 of gestation, or up to week 40 of gestation.

[0118] In various embodiments, the therapeutically effective amount of a compound described herein, including estriol, estradiol, estrone, estetrol, or a related compound thereof 1-10mcg/day, 10-20mcg/day, 20-30mcg/day, 30-40mcg/day, 40-50mcg/day, -60mcg/day, 60-70mcg/day, 70-80mcg/day, 80-90mcg/day, 90-100mcg/day, 100-200mcg/day, 200-300mcg/day, 300-400mcg/day, 400-500mcg/day, 500-600mcg/day,

600-700mcg/day, 700-800mcg/day, 800-900mcg/day, 900-1000mcg/day, 1-10mg/day, 10-20mg/day, 20-30mg/day, 30-40mg/day, 40-50mg/day, 50-60mg/day, 60-70mg/day, 70-80mg/day, 80-90mg/day, 90-100mg/day, 100-200mg/day, 200-300mg/day, 300-400mg/day, or 400-500mg/day. The dosage will depend on the formula and the route of delivery.

EXAMPLES

[0119] Biological data support the formulations, compounds, and methods to prolong gestation and treating gestational complications. In the ensuing sections, examples of formulations, compounds, and methods to prolong gestation and treating gestational complications (i.e., gestational age and/or time to delivery) are provided, indicating that the compounds described herein can be utilized to prolong gestation and/or treat an individual having a gestational complication.

Example 1: Compound Treatment in Mouse Models of Preterm Birth

[0120] Provided in Fig. 2A is an experimental schematic of compound treatment in mouse models of moderate preterm birth. Pregnant CD1 mice were intraperitoneally administered 2mg/kg LPS (*Escherichia coli* 0127:B8, chromatographically pure, Sigma-Aldrich) or PBS (as control) on E16. Mice were then treated with either intraperitoneal injections of vehicle (100 µl, 30% DMSO in pharmaceutical sesame oil), estriol-16-glucuronide (100 µl vehicle, 0.8mg/mouse first and second dose; 0.5 mg/mouse third and fourth dose), estriol (100 µl vehicle, 0.8mg/mouse first and second dose; 0.5 mg/mouse third and fourth dose), or estriol-3-sulfate (100 µl vehicle, 0.8mg/mouse first and second dose; 0.5 mg/mouse third and fourth dose). Compounds were administered via intraperitoneal injections after LPS: first dose at 6 hours, second dose at 12 hours, third dose at 24 hours, and fourth dose at 36 hours. Date and time of delivery was monitored 24 hours a day using infrared night-vision cameras. Results are provided in Figs. 2B and 2C.

[0121] Estriol and estriol-3-sulfate prolonged gestation and mitigated preterm delivery (Fig. 2B). Data are presented as mean ± standard deviation (SD). Statistical analysis was

conducted using one-way ANOVA followed by pairwise t-tests comparing each group with the Preterm group. Significant differences are indicated by asterisks (*) above the bars ($p < 0.05$).

[0122] Estriol and estriol-3-sulfate also increased survival rate of mouse pups (Fig. 2C). The survival rate is calculated as the percentage of 'Y' (Yes) responses for Birth Confirmation out of the total responses (Y + N). The data demonstrate the proportion of successful births for each group.

Example 2: Compound Treatment on Contractility in Mice

[0123] In another experiment, mice were treated with estriol or estriol-3-sulfate at three concentrations (1 μM, 1 mM, 10 mM). The contractility is measured and plotted as a relative force ratio compared to baseline for each treatment group. The relative contractile force is normalized to baseline values to show the effect of increasing concentrations of the compounds. The results indicates a dose-dependent response in uterine contractility upon treatment with estriol (Fig. 3A) or with estriol-3-sulfate (Fig. 3B). Error bars indicate the standard error of the mean (SEM).

Example 3: Estrone-3-sulfate Levels in Pregnant Women

[0124] The level of estrone-3-sulfate was tracked through gestation in 86 healthy, pregnant women (Fig. 4). Data points represent the mean levels of Estrone 3-sulfate across different gestational ages, rounded to the nearest whole number. The red vertical dashed line marks the mean birth age, providing a clear reference point for parturition. The x-axis denotes gestational age in weeks, while the y-axis represents the concentration of Estrone 3-sulfate.

WHAT IS CLAIMED IS:

1. A method of treating a pregnant individual for recurrent preterm birth, recurrent early term birth, recurrent pregnancy loss, or a short cervix, comprising:

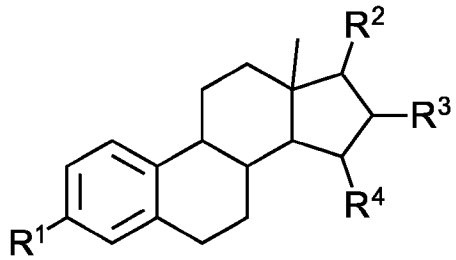
administering an estrogenic compound to an individual, wherein the individual is pregnant and has a medical history indicating recurrent preterm birth, recurrent early term birth, recurrent pregnancy loss, or a short cervix.

2. The method of claim 1, wherein the estrogenic compound is administered in a therapeutically effective amount.

3. The method of claim 1 or 2, wherein the administering step is to begin upon a determination that the individual is pregnant.

4. The method of any one of claims 1-3, wherein the administering step is to end by one of: week 40 of gestation, week 39 of gestation, week 38 of gestation, or week 37 of gestation.

5. The method of any one of claims 1-4, wherein the estrogenic compound is of formula:



wherein R^1 is OH, phosphonic acid, sulfonic acid, or OR^5;
R^2 is O, OH, phosphonic acid, sulfonic acid, or OR^6;
R^3 is H, OH, phosphonic acid, sulfonic acid, or OR^7;
R^4 is H, OH, phosphonic acid, sulfonic acid, or OR^8; and
OR^5, OR^6, OR^7, and OR^8 can each individually be galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic

acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate; wherein any acid can be an anionic formulation of that acid.

6. The method of claim 5, wherein R^1 is OH, R^2 is OH, R^3 is OH and R^4 is H, matching the formula for estriol.

7. The method of claim 5, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

8. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is H.

9. The method of claim 5, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H.

10. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

11. The method of claim 5, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

12. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H.

13. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

14. The method of claim 5, wherein R^1 is OH, R^2 is OH, R^3 is H, and R^4 is H.

15. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is H, and R^4 is H.

16. The method of claim 5, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H.

17. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H.

18. The method of claim 5, wherein R^1 is OH, R^2 is O, R^3 is H, and R^4 is H.

19. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5 or, R^2 is O, R^3 is H, and R^4 is H.

20. The method of claim 5, wherein R^1 is OH, R^2 is OH, R^3 is OH and R^4 is OH.

21. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is OH.

22. The method of claim 5, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH.

23. The method of claim 5, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

24. The method of claim 5, wherein, R^1 is OH, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

25. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH.

26. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

27. The method of claim 5, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

28. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

29. The method of claim 5, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

30. The method of claim 5, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

31. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

32. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

33. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

34. The method of claim 5, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

35. The method of claim 5, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

36. The method of any one of claims 1-4, wherein the estrogenic compound is a synthetic estrogen selected from: dienestrol, dienstrol diacetate, dienestrol dipopropionate, dienestrol monobenzoate, hexestrol, hexestrol diacetate, hexestrol dipropionate, hexestrol monobenzoate, methallenestril, methallenestril acetate, methallenestril benzoate, methallenestril propionate, mestranol, 3-(2'.3'-epoxypropoxy)-1.3.5.(10)-estratrien-16.alpha, estriol-3-glycidyl ether, estriol-6-carboxymethyl oxime, or ethinylestradiol.

37. The method of any one of claims 1-4, wherein the estrogenic compound is an estriol ester or estriol amino ester selected from: 3,17.beta.-Diisobutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Divaleryloxy-1,3,5(10)- estratrien-16.alpha.-ol, 3,17.beta.-Dihexanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dipivaloyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Didecanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibenzoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 6-alpha.-aminoestriol-16,17-diaceteate, 6.alpha.(N-diglycolylamido) estriol, 6.alpha.-aminoestriol, 6.alpha.-(N-diglycoylamido)estriol NHS-ester, estriol-N-hydroxysuccinimide (NHS) ester, estriol-aminooxy, or estriol-carboxylic acid hydrazide.

38. The method of any one of claims 1-4, wherein the estrogenic compound is a metabolite of estriol, estradiol, estrone, or estetrol selected from: 16α-hydroxyestrone, 2-methoxyestrone, 2-hydroxyestrone, 4-hydroxyestrone, 2-hydroxyestradiol, 2-hydroxyestradiol, or 16-ketoestradiol.

39. A method of treating a pregnant individual for early term birth, spontaneous preterm birth or spontaneous abortion, comprising:

determining that a pregnant individual is experiencing uterine contractions related to early term birth, spontaneous preterm birth or spontaneous abortion; and

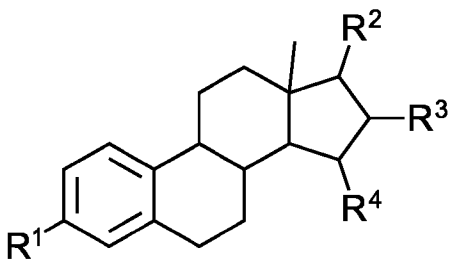
administering an estrogenic compound to an individual.

40. The method of claim 39, wherein the estrogenic compound is administered in a therapeutically effective amount.

41. The method of claim 39 or 40, wherein the administering step is to begin upon a determination that the uterine contractions are occurring prior to one of: week 39 of gestation or week 37 of gestation.

42. The method of any one of claims 39-41, wherein the administering step is to end by one of: week 40 of gestation, week 39 of gestation, week 38 of gestation, or week 37 of gestation.

43. The method of any one of claims 39-42, wherein the estrogenic compound is of formula:



wherein R^1 is OH, phosphonic acid, sulfonic acid, or OR^5;
R^2 is O, OH, phosphonic acid, sulfonic acid, or OR^6;
R^3 is H, OH, phosphonic acid, sulfonic acid, or OR^7;
R^4 is H, OH, phosphonic acid, sulfonic acid, or OR^8; and
OR^5, OR^6, OR^7, and OR^8 can each individually be galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate; wherein any acid can be an anionic formulation of that acid.

44. The method of claim 43, wherein R^1 is OH, R^2 is OH, R^3 is OH and R^4 is H, matching the formula for estriol.

45. The method of claim 43, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

46. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is H.

47. The method of claim 43, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H.

48. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

49. The method of claim 43, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

50. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H.

51. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

52. The method of claim 43, wherein R^1 is OH, R^2 is OH, R^3 is H, and R^4 is H.

53. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is H, and R^4 is H.

54. The method of claim 43, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H.

55. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H.

56. The method of claim 43, wherein R^1 is OH, R^2 is O, R^3 is H, and R^4 is H.

57. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5 or, R^2 is O, R^3 is H, and R^4 is H.

58. The method of claim 43, wherein R^1 is OH, R^2 is OH, R^3 is OH and R^4 is OH.

59. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is OH.

60. The method of claim 43, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH.

61. The method of claim 43, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

62. The method of claim 43, wherein, R^1 is OH, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

63. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH.

64. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

65. The method of claim 43, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

66. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

67. The method of claim 43, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

68. The method of claim 43, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

69. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

70. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

71. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

72. The method of claim 43, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

73. The method of claim 43, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

74. The method of any one of claims 39-42, wherein the estrogenic compound is a synthetic estrogen selected from: dienestrol, dienstrol diacetate, dienestrol dipopropionate, dienestrol monobenzoate, hexestrol, hexestrol diacetate, hexestrol dipropionate, hexestrol monobenzoate, methallenestril, methallenestril acetate, methallenestril benzoate, methallenestril propionate, mestranol, 3-(2'.3'-epoxypropoxy)-1.3.5.(10)-estratrien-16.alpha, estriol-3-glycidyl ether, estriol-6-carboxymethyl oxime, or ethinylestradiol.

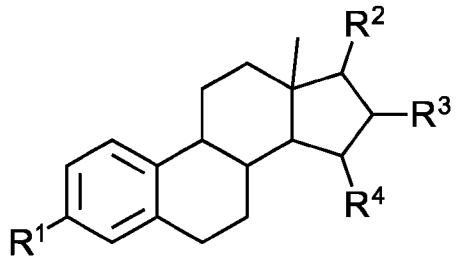
75. The method of any one of claims 39-42, wherein the estrogenic compound is an estriol ester or estriol amino ester selected from: 3,17.beta.-Diisobutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Divaleryloxy-1,3,5(10)- estratrien-16.alpha.-ol, 3,17.beta.-Dihexanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dipivaloyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Didecanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibenzoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 6-alpha.-aminoestriol-16,17-diaceteate, 6.alpha.(N-diglycolylamido) estriol, 6.alpha.-aminoestriol, 6.alpha.-(N-diglycoylamido)estriol NHS-ester, estriol-N-hydroxysuccinimide (NHS) ester, estriol-aminooxy, or estriol-carboxylic acid hydrazide.

76. The method of any one of claims 39-42, wherein the estrogenic compound is a metabolite of estriol, estradiol, estrone, or estetrol selected from: 16α-hydroxyestrone, 2-methoxyestrone, 2-hydroxyestrone, 4-hydroxyestrone, 2-hydroxyestradiol, 2-hydroxyestradiol, or 16-ketoestradiol.

77. A medicament for use in mitigating uterine contractions in an individual, the medicament comprising:

an estrogenic compound.

78. The medicament of claim 77, wherein the estrogenic compound is of formula:



wherein R^1 is OH, phosphonic acid, sulfonic acid, or OR^5;

R^2 is O, OH, phosphonic acid, sulfonic acid, or OR^6;

R^3 is H, OH, phosphonic acid, sulfonic acid, or OR^7;

R^4 is H, OH, phosphonic acid, sulfonic acid, or OR^8; and

OR^5, OR^6, OR^7, and OR^8 can each individually be galacturonic acid, glucoside, glucuronide, mannuronic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, 1,4-cyclohexanedicarboxylic acid, azelaic acid, sebacic acid, undecanedioic acid, dodecanedioic acid, maleic acid, fumaric acid, acetylenedicarboxylic acid, glutaconic acid, muconic acid, citraconic acid, mesaconic acid, itaconic acid, malic acid, tartaric acid, mucic acid, saccharic acid, formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, cypionic acid, sulfuric acid, phosphoric acid, methanolate, ethanolate, propanolate, or butanolate; wherein any acid can be an anionic formulation of that acid.

79. The medicament of claim 78, wherein R^1 is OH, R^2 is OH, R^3 is OH and R^4 is H, matching the formula for estriol.

80. The medicament of claim 78, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

81. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is H.

82. The medicament of claim 78, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H.

83. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

84. The medicament of claim 78, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

85. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is H.

86. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is H.

87. The medicament of claim 78, wherein R^1 is OH, R^2 is OH, R^3 is H, and R^4 is H.

88. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is H, and R^4 is H.

89. The medicament of claim 78, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H.

90. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is H, and R^4 is H.

91. The medicament of claim 78, wherein R^1 is OH, R^2 is O, R^3 is H, and R^4 is H.

92. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5 or, R^2 is O, R^3 is H, and R^4 is H.

93. The medicament of claim 78, wherein R^1 is OH, R^2 is OH, R^3 is OH and R^4 is OH.

94. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is OH.

95. The medicament of claim 78, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH.

96. The medicament of claim 78, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

97. The medicament of claim 78, wherein, R^1 is OH, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

98. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is OH.

99. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

100. The medicament of claim 78, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

101. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

102. The medicament of claim 78, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

103. The medicament of claim 78, wherein R^1 is OH, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

104. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is OH.

105. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is OH, and R^4 is phosphonic acid or sulfonic acid or OR^8.

106. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is OH, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

107. The medicament of claim 78, wherein R^1 is OH, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

108. The medicament of claim 78, wherein R^1 is phosphonic acid or sulfonic acid or OR^5, R^2 is phosphonic acid or sulfonic acid or OR^6, R^3 is phosphonic acid or sulfonic acid or OR^7, and R^4 is phosphonic acid or sulfonic acid or OR^8.

109. The medicament of claim 77, wherein the estrogenic compound is a synthetic estrogen selected from: dienestrol, dienstrol diacetate, dienestrol dipopropionate, dienestrol monobenzoate, hexestrol, hexestrol diacetate, hexestrol dipropionate, hexestrol monobenzoate, methallenestril, methallenestril acetate, methallenestril benzoate, methallenestril propionate, mestranol, 3-(2'.3'-epoxypropoxy)-1.3.5.(10)-estratrien-16.alpha, estriol-3-glycidyl ether, estriol-6-carboxymethyl oxime, or ethinylestradiol.

110. The medicament of any one of claims 77, wherein the estrogenic compound is an estriol ester or estriol amino ester selected from: 3,17.beta.-Diisobutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Divaleryloxy-1,3,5(10)- estratrien-16.alpha.-ol, 3,17.beta.-Dihexanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dipivaloyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Didecanoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-Dibenzoyloxy-1,3,5(10)-estratrien-16.alpha.-ol, 3,17.beta.-

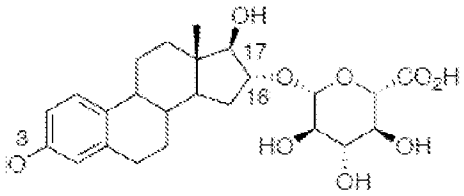
Dibutyryloxy-1,3,5(10)-estratrien-16.alpha.-ol, 6-alpha.-aminoestriol-16,17-diaceteate, 6.alpha.(N-diglycolylamido) estriol, 6.alpha.-aminoestriol, 6.alpha.-(N-diglycoylamido)estriol NHS-ester, estriol-N-hydroxysuccinimide (NHS) ester, estriol-aminooxy, or estriol-carboxylic acid hydrazide.

111. The medicament of any one of claims 77, wherein the estrogenic compound is a metabolite of estriol, estradiol, estrone, or estetrol selected from: 16α-hydroxyestrone, 2-methoxyestrone, 2-hydroxyestrone, 4-hydroxyestrone, 2-hydroxyestradiol, 2-hydroxyestradiol, or 16-ketoestradiol.

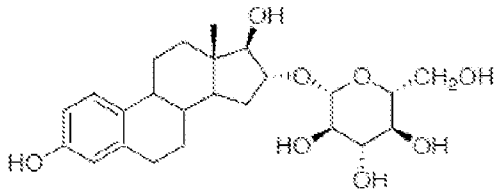
112. The medicament of any one of claims 77-111, wherein the medicament is for recurrent preterm birth, recurrent early term birth, recurrent pregnancy loss, or a short cervix.

113. The medicament of any one of claims 77-111, wherein the medicament is for early term birth, spontaneous preterm birth or spontaneous abortion.

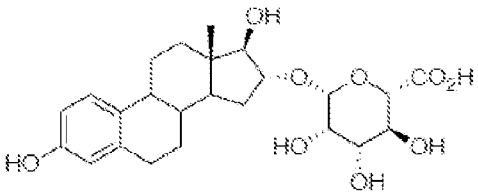
Fig. 1



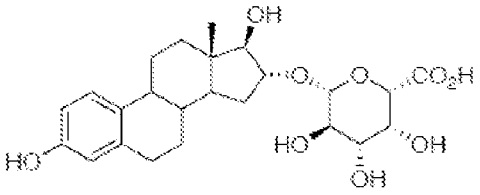
Estriol-16-glucuronide



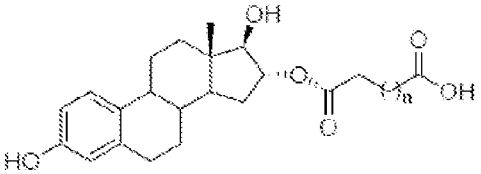
Glucoside



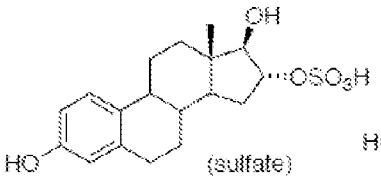
(mannuronic acid)



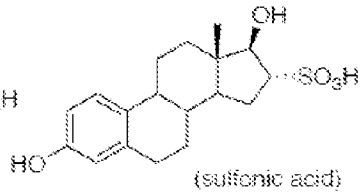
(galacturonic acid)



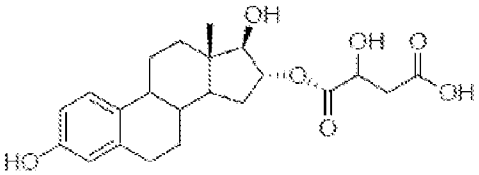
malonic thru suberic acids
n = 0 thru 9

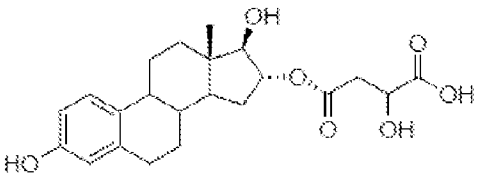


(sulfate)

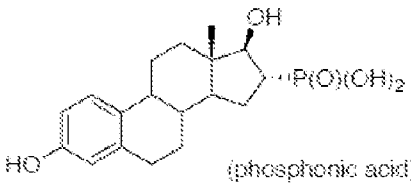


(sulfonic acid)

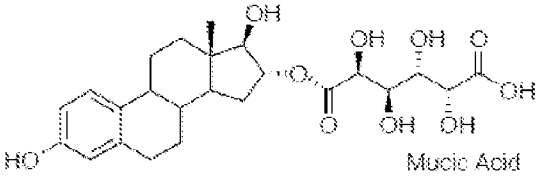




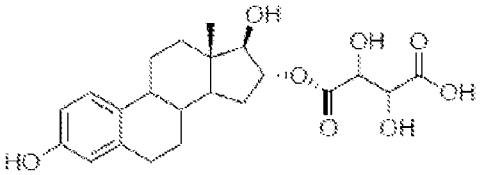
either enantiomer of malic for both regioisomers - four total



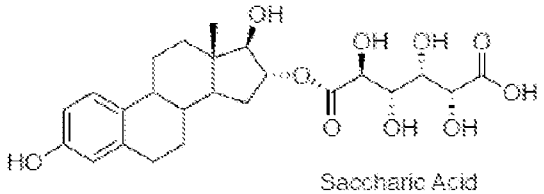
(phosphonic acid)



Mucic Acid



any stereomer of tartaric acid - 3 total



Saccharic Acid

Fig. 2A

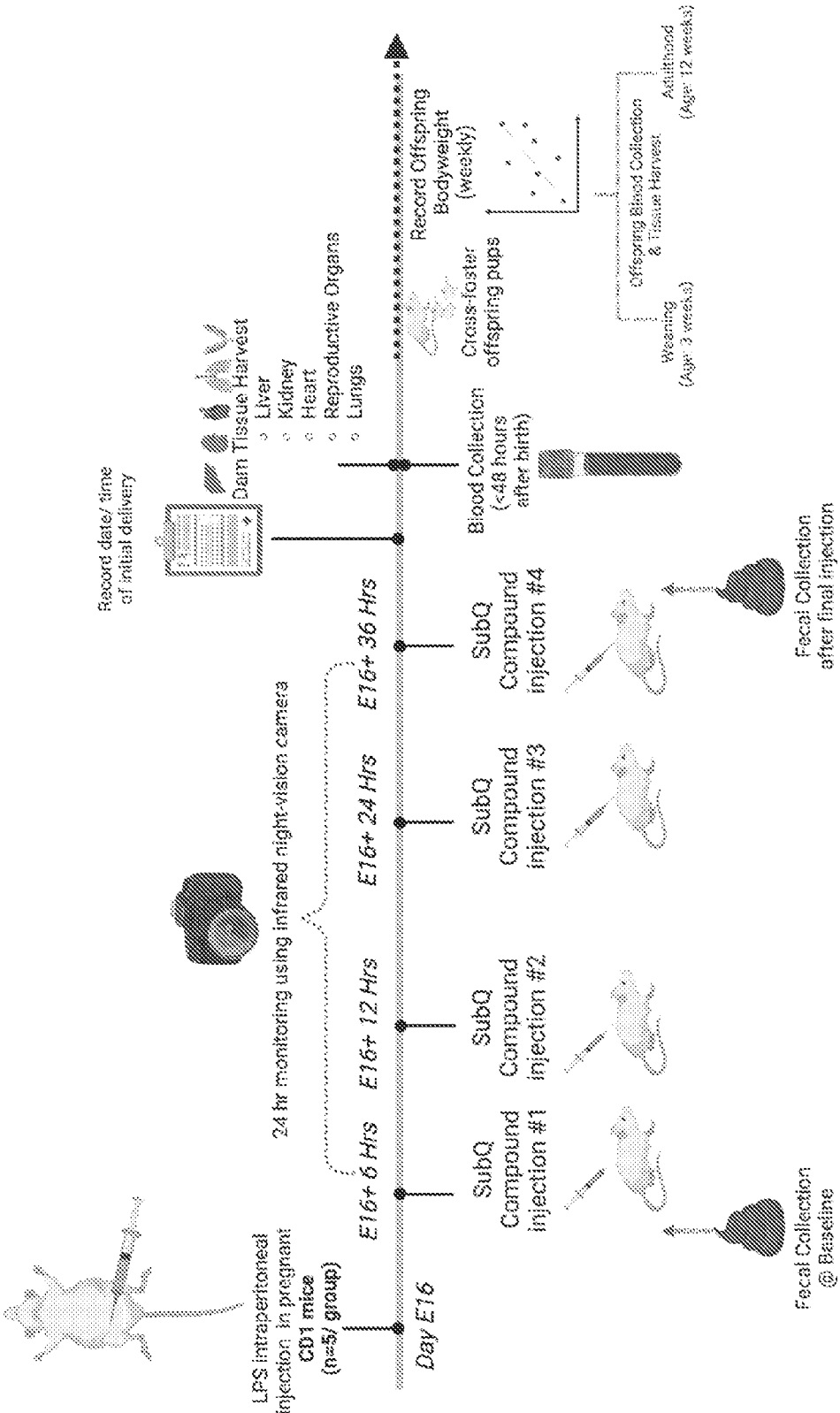

LPS intraperitoneal injection in pregnant CD1 mice (n=5/ group)
Day E16
E16+ 6 Hrs
E16+ 12 Hrs
E16+ 24 Hrs
E16+ 36 Hrs
24 hr monitoring using infrared night-vision camera
Record date/ time of initial delivery
SubQ Compound injection #1
SubQ Compound injection #2
SubQ Compound injection #3
SubQ Compound injection #4
Fecal Collection @ Baseline
Fecal Collection after final injection
Dam Tissue Harvest
Liver
Kidney
Heart
Reproductive Organs
Lungs
Blood Collection (<48 hours after birth)
Cross-foster offspring pups
Record Offspring Bodyweight (weekly)
Weaning (Age: 3 weeks)
Offspring Blood Collection & Tissue Harvest
Adulthood (Age: 12 weeks)

Fig. 2B

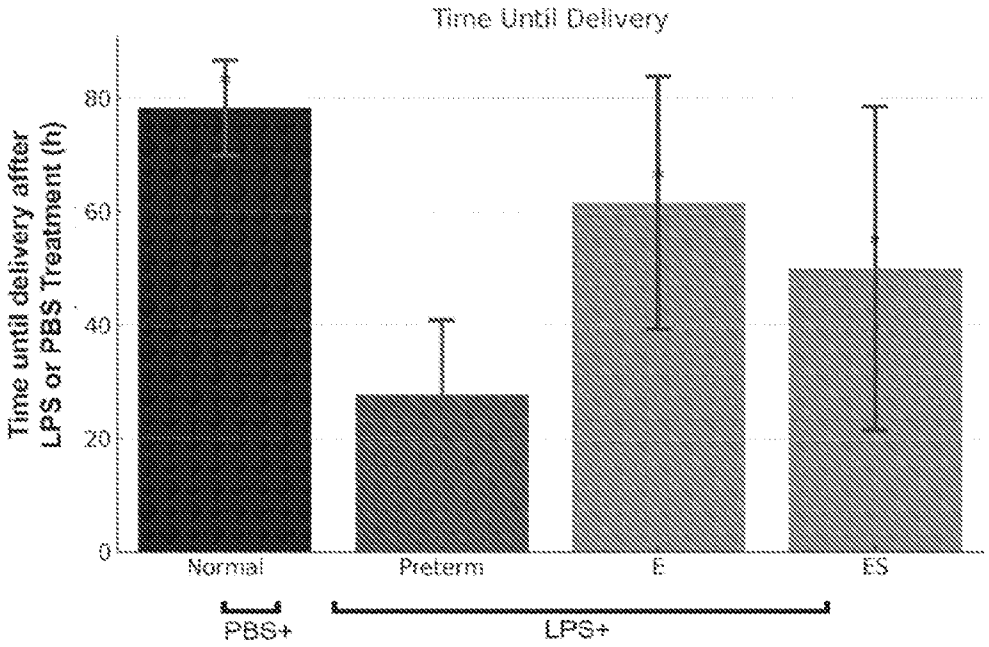
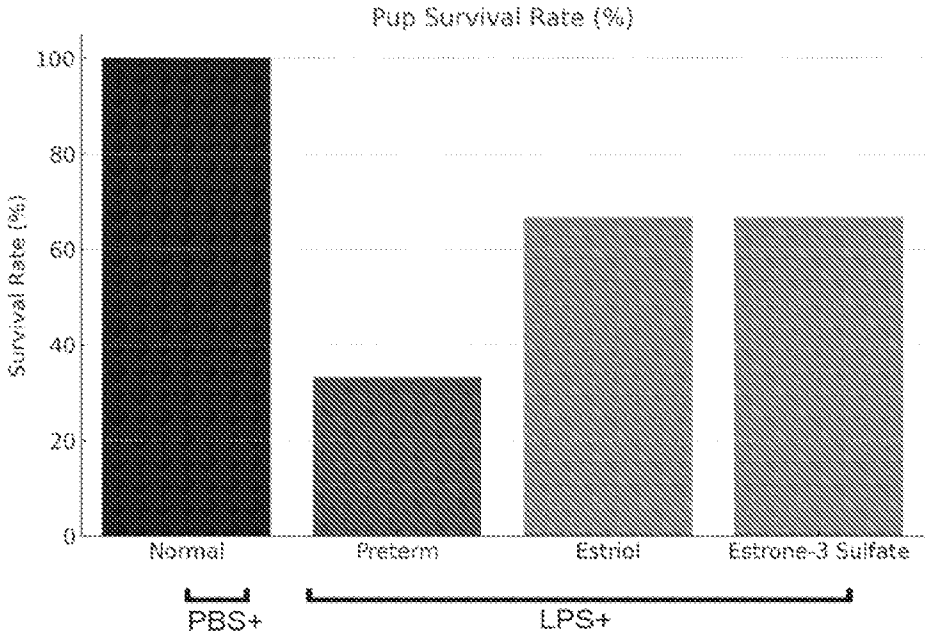

Time Until Delivery
Time until delivery after LPS or PBS Treatment (h)
0
20
40
60
80
Normal
Preterm
E
ES
PBS+
LPS+

Fig. 2C


Pup Survival Rate (%)
Survival Rate (%)
0
20
40
60
80
100
Normal
Preterm
Estriol
Estrone-3 Sulfate
PBS+
LPS+

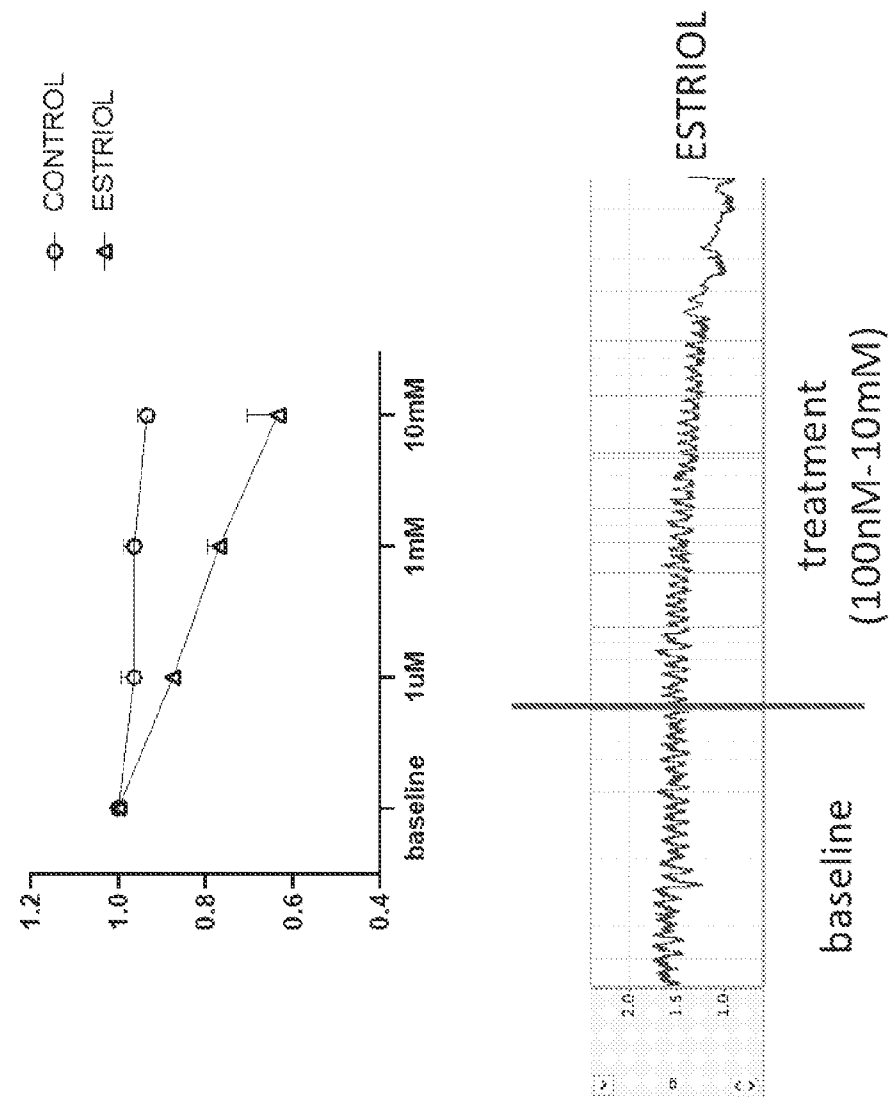

ESTRIOL
CONTROL
ESTRIOL
1.2
1.0
0.8
0.6
0.4
baseline
1uM
1mM
10mM
ESTRIOL
treatment
(100nM-10mM)
baseline

Fig. 3A

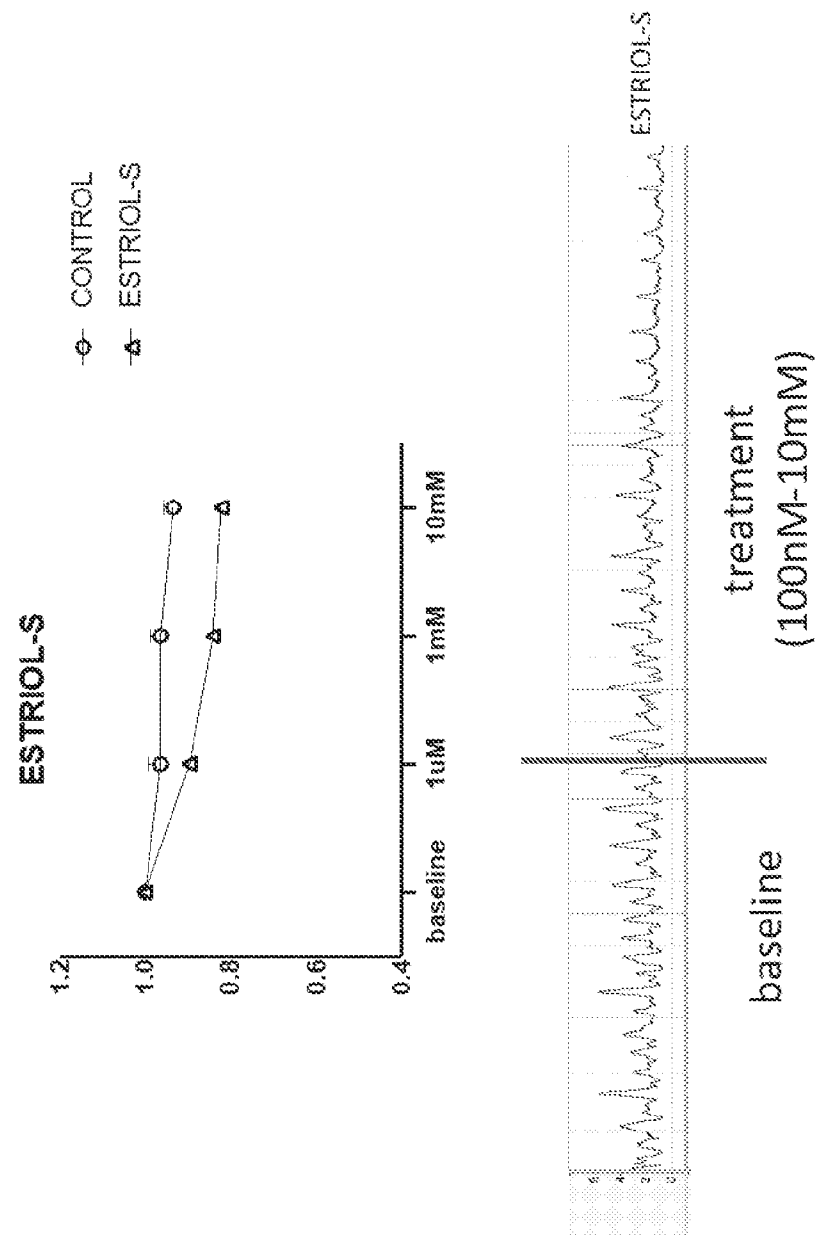

CONTROL
ESTRIOL-S
ESTRIOL-S
1.2
1.0
0.8
0.6
0.4
baseline
1uM
1mM
10mM
ESTRIOL-S
treatment
(100nM-10mM)
baseline

Fig. 3B

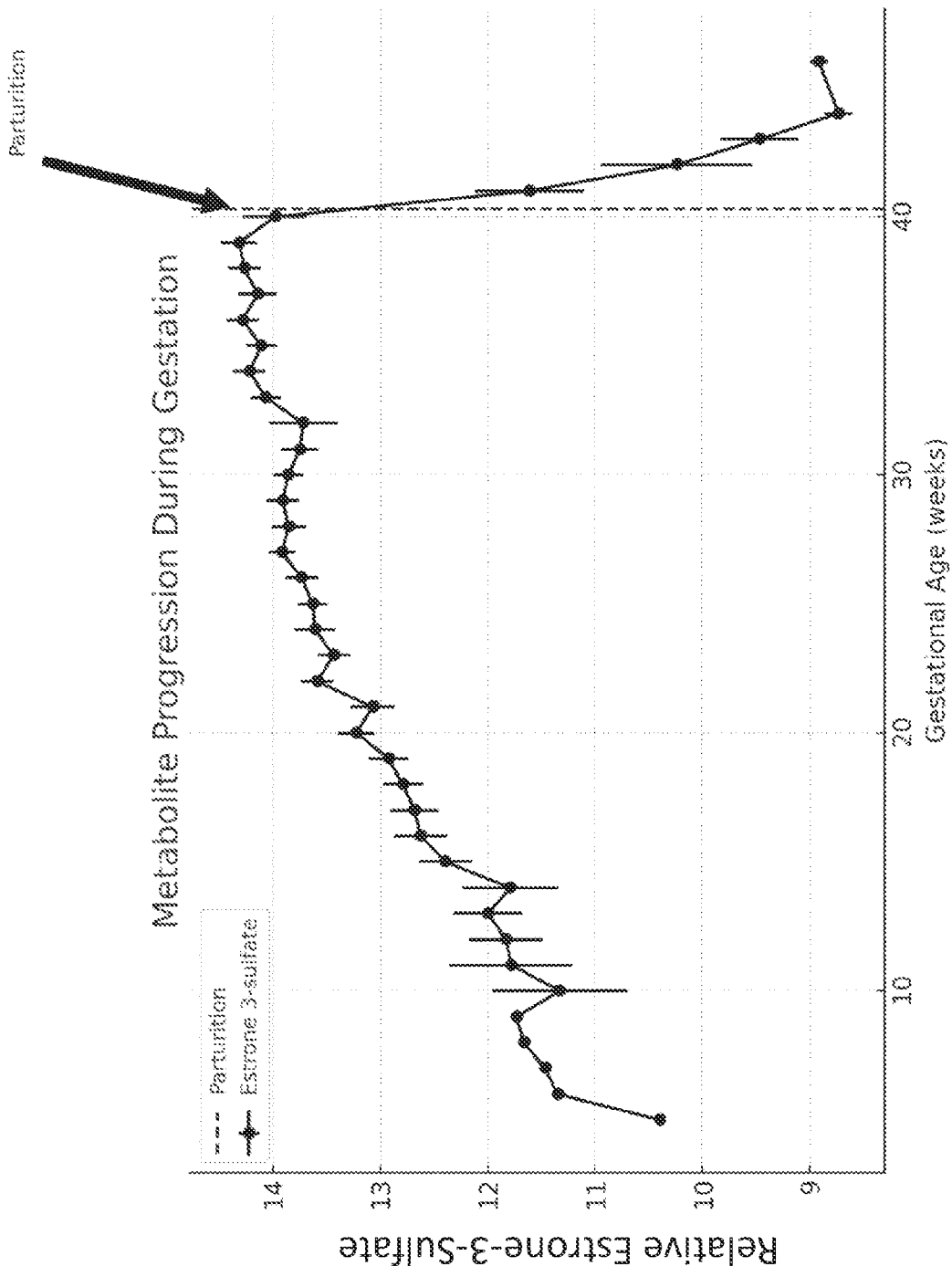

Metabolite Progression During Gestation
Parturition
Parturition
Estrone 3-sulfate
Relative Estrone-3-Sulfate
Gestational Age (weeks)
14
13
12
11
10
9
10
20
30
40

Fig. 4