A61K 31/497 (2006.01)

57 (54) Title: COMPOUNDS AND TREATMENT METHODS

56 (57) Abstract: The disclosure describes compounds useful for treating disorders involving androgen, estrogen, and/or progesterone receptors.
COMPOUNDS AND TREATMENT METHODS

[01] This application claims the benefit of Serial No. 61/554,917 filed on November 2, 2011. Serial No. 61/554,917 and all other documents cited in this disclosure are incorporated herein by reference in their entireties.

TECHNICAL FIELD

[02] The technical field is treatment of disorders or conditions involving androgen, estrogen, and/or progesterone receptors.

DETAILED DESCRIPTION

[03] This disclosure describes the use of one or more compounds that fall within the scope of one or more of structural formulae I or II.

1. Definitions

[04] The term "alkyl" denotes branched or unbranched hydrocarbon chains. In some embodiments, having about 1 to about 8 carbons, such as, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, 2-methylpentyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl and the like. "Substituted alkyl" includes an alkyl group optionally substituted with one or more functional groups which can be attached to such chains, such as, hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, alkylthio, heterocyclyl, aryl, heteroaryl, carboxyl, carbalkyol, alkylenyl, nitro, amino, alkoxy, amido, and the like to form alkyl groups such as trifluoromethyl, 3-hydroxyhexyl, 2-carboxypropyl, 2-fluoroethyl, carboxymethyl, cyanobutyl and the like.

[05] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or more double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings. In some embodiments, 3 to 10 carbons, forming the ring and which can be fused to 1 or 2
aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl. "Substituted cycloalkyl" includes a cycloalkyl group optionally substituted with 1 or more substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents included in the definition of "substituted alkyl;" for example:

and the like.

[06] Unless otherwise indicated, the term "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, In some embodiments, 2 to 12 carbons, and in some embodiments, 2 to 8 carbons in the normal chain, which include one or more double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like. "Substituted alkenyl" includes an alkenyl group optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[07] Unless otherwise indicated, the term "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, In some
embodiments, 2 to 12 carbons and in some embodiments, 2 to 8 carbons in the normal chain, which include one or more triple bonds in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonylnyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like. "Substituted alkynyl" includes an alkynyl group optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[08] The terms "arylaikyl", "aryalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent. Representative examples of arylaikyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, phenethyl, benzhydryl and naphthylmethyl and the like. "Substituted arylaikyl" includes arylaikyl groups wherein the aryl portion is optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[09] The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine.

[10] The terms "halogenated alkyl", "halogenated alkenyl" and "alkynyl" as used herein alone or as part of another group refers to "alkyl", "alkenyl" and "alkynyl" which are substituted by one or more atoms selected from fluorine, chlorine, bromine, fluorine, and iodine.

[11] Unless otherwise indicated, the term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and polycyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and can optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings).

[12] "Substituted aryl" includes an aryl group optionally substituted with one or more functional groups, such as halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl,
cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxy carbonyl, arylcarbonyl, arylalkenyl,aminocarbonylaryl, arylthio, ary sulfanyl, a rylazo, heteroarylalkyl, heteroarylalkenyl, heteroaryllactone, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, alkylarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, ary sulfanyl, arylsulfanylalkyl, arylsulfonylamino or arylsul fonaminocarbonyl and/or any of the alkyl substituents set out herein.

[13] Unless otherwise indicated, the term "heterocyclic" or "heterocycle", as used herein, represents an unsubstituted or substituted stable 5- to 10-membered monocyclic ring system which can be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from N, O or S, and wherein the nitrogen and sulfur heteroatoms can optionally be oxidized, and the nitrogen heteroatom can optionally be quaternized. The heterocyclic ring can be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not limited to, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxopyrrolidinyl, o xoazepinyl, azepinyl, pyrrolyl, pyrrolidinyl, furanyl, thi enyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, thiadiazolyl, tetrahydropyranyl, thiamorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, and oxadiazolyl. The term "heterocyclic aromatic" as used here in alone or as part of another group refers to a 5- or 7-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur and such rings fused to an aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. "Substituted heteroaryl" includes a heteroaryl group optionally substituted with 1 to 4 substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl." Examples of heteroaryl groups include the following:
and the like.

2. Formula (I)

[14] In some embodiments, the compound is a compound of Formula I:
wherein W is selected from the group consisting of O and NR5, wherein R5 is selected from the group consisting of H, methyl, and

\[ \text{D} \]

wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

wherein R1 and R2 together comprise eight or fewer carbon atoms and are selected from the group consisting of alkyl, substituted alkyl including haloalkyl, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group,

wherein R3 is selected from the group consisting of hydrogen, halogen, methyl, Cl-C4 alkoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methoxycarbonyl, acetamido, methanesulfonamino, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, and C1-C6 alkyl or alkenyl optionally substituted with hydroxyl, methoxycarbonyl, cyano, amino, amido, nitro, carbamoyl, or substituted carbamoyl including methylcarbamoyl, dimethylcarbamoyl, and hydroxyethylcarbamoyl,

wherein R4 is selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl,

wherein R3 is not methylaminomethyl or dimethylaminomethyl; and

wherein Het is selected from the group consisting of
and wherein X is selected from the group consisting of trifluoromethyl and iodo.

In some embodiments, R5 is
In some embodiments, the compound is a compound of Formula I-A:

![Chemical Structure]

wherein R3 is selected from the group consisting of hydroxy, methylcarbamoyl, methylcarbamoylpropyl, methylcarbamoylthethyl, methylcarbamoylmethyl, methylsulfonecarbamoylpropyl, methylaminomethyl, dimethyaminomethyl, methylsulfonyloxymethyl, carbamoylmethyl, carboxamylethyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoylpropyl, carboxypropyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, hydroxyethylcarbamoylethyl, and hydroxyethoxycarbonylethyl,

wherein R10 and R11 are both H or, respectively, F and H, or H and F; and

wherein X is CF3. In some embodiments, R10 and R11 can both be H or, respectively, F and H, R3 can be methylcarbamoyl.

In some embodiments, R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, and R3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, and alkylcarbamoylalkyl, and R4 is H or F or R4 is 3-fluoro.

In some embodiments, R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, R3 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl,
dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl-1-piperazinyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, and 3-cyano-4-trifluoromethylphenylcarbamoyl, and R4 is F.

[19] In some embodiments, the compound is a compound of Formula I-B:

![Formula I-B](image)

wherein R3 is selected from the group consisting of methylcarbonyl, methoxycarbonyl, acetamido, and methanesulfonamido, R4 is selected from the group consisting of F and H, and X is CF₃.

[20] In some embodiments, the compound is a compound of Formula I-C:

![Formula I-C](image)

wherein R4 is selected from the group consisting of F and H and wherein X is CF₃.
[21] In some embodiments, R1 and R2, together with the carbon to which they are linked, are

\[ \text{or} \]

[22] In some embodiments, the compound is a compound of Formula I-D:

\[ \text{(I-D)} \]

wherein \( R_1 \) and \( R_2 \) together include eight or fewer carbon atoms and are selected from the group consisting of alkyl, substituted alkyl, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group. \( R_3 \) is hydrogen, cyano, formyl,
$R_4$ is hydrogen, F, Cl, Br, or I. $R_1$ and $R_2$ can be the same or different and are hydrogen or methyl. $R_3$ is hydrogen or $-NR_{14}R_{15}$. $R_{14}$ and $R_{15}$ can be the same or different and are hydrogen or methyl.

In some embodiments, $R_1$ and $R_2$ can be independently methyl or, together with the carbon to which they are linked, cyclobutyl or cyclopentyl. In some embodiments, $R_{11}$ and $R_{12}$ can be both hydrogen or both methyl. In some embodiments, $R_{13}$ can be $-NH(CH_3)$ or $-N(CH_3)_2$. In some embodiments, when $R_4$, $R_{11}$ and $R_{12}$ are each hydrogen and when $R_1$ and $R_2$ together with the carbon to which they are linked are cyclobutyl, then $R_3$ can be other than cyano and

\[
\begin{array}{c}
\text{R}_{13} \\
\text{O}
\end{array}
\]

with $R_3$ hydrogen, $-NH_2$, $-NH(CH_3)$, or $-N(CH_3)_2$. 
In some embodiments, the compound is a compound disclosed in U.S. Patent 7,709,517, including those listed in the tables below except that, in for each individual compound,
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or
is either

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is either

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is either

or

and
is either

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3. Formula (II)

[24] In some embodiments, the compound is a compound of Formula II:

\[
\begin{align*}
&\text{Het-1} \\
&\text{N} \\
&\text{A} \\
&\text{X} \\
&\text{R}_3 \\
&\text{R}_4 \\
&\text{R}_5 \\
&\text{R}_6 \\
&\text{R}_7 \\
&\text{R}_8 \\
&\text{N} \\
&\text{B} \\
&\text{R}_1 \\
&\text{R}_2 \\
\end{align*}
\]

(II)

wherein Het-1 is selected from the group consisting of

\[
\begin{align*}
&\text{R}_5 \\
&\text{R}_6 \\
&\text{R}_7 \\
&\text{R}_8 \\
&\text{R}_9 \\
\end{align*}
\]

and

\[
\begin{align*}
&\text{R}_5 \\
&\text{R}_6 \\
\end{align*}
\]

wherein R5 is CN or N0 2 or S02R1 1, wherein R6 is CF3, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogen, wherein A is sulfur (S) or oxygen (O), wherein B is O or S or NR8, wherein R8 is selected from the group consisting of H, methyl, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted
alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, 
S02R1 1, NR1 1R1 2, (CO)OR 1 1, (CO)NR 1 1R1 2, (CO)R 1 1, (CS)R1 1, (CS)NR 1 1R1 2, (CS)OR 1 1,

wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C 1-C4 lower alkyl, wherein R1 and R2 are independently alkyl, haloalkyl, hydrogen, aryl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, or R1 and R2 are connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl,

wherein X is carbon or nitrogen and can be at any position in the ring, and wherein R3, R4, and R7 are independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methylcarbamoyl-substituted alkyl, dimethylcarbamoyl-
substituted alkyl, methoxy carbonyl, acetamido, methanesulfonamino, carbamoyl-
substituted alkyl, methanesulfonyl, 4-methanesulfonyl-piperazinyl, piperazinyl, 
hydroxyethylcarbamoyl-substituted alkyl, hydroxyl-substituted alkyl, hydroxyl-
substituted alkenyl, carbamoyl-substituted alkenyl, methoxycarbonyl-substituted alkyl, 
cyano-substituted alkyl,

\[ \text{OH} \quad \text{CH}_3, \]

aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, 
substituted alkynyl, halogenated alkenyl, halogenated alkynyl, S\(_2\)R \(_1\), NR\(_1\) \(_1\)R\(_2\), 
NR\(_1\)2(CO)OR \(_1\)2, NH(CO)NR \(_1\)I \(_2\), NR\(_1\)2(CO)R \(_1\)I, 0(CO)R \(_1\)I, 0(CO)OR \(_1\)I, 
0(CS)R \(_1\)I, NR\(_1\)2(CS)R \(_1\)I, NH(CS) NR\(_1\)I \(_2\), NR\(_1\)2(CS)OR \(_1\)I, aryl alkyl, arylalkenyl, 
arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or 
non-aromatic, cycloalkyl, substituted cycloalkyl, haloalkyl, methysulfonecarbamoyl-
substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxyethyl, 
methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, 
carboxymethyl, methoxycarbonylmethyl, methane sulfonyl, 4-cyano-3-
trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-
dimethylethoxy)carbonyl)-1-piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, 
hydroxyethoxycarbonyl-substituted alkyl, 3-cyano-4-trifluoromethylphenylcarbamoyl,

wherein R\(_1\) \(_1\) and R \(_2\) are independently hydrogen, aryl, aralkyl, substituted aralkyl, 
alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, 
halogenated alkyl, halogenated alkenyl, halogenated alkynyl, aryl alkyl, arylalkenyl, 
arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or 
non-aromatic, cycloalkyl, or substituted cycloalkyl, or R\(_1\) \(_1\) and R \(_2\) can be connected to 
form a cycle which can be heterocyclic aromatic or non-aromatic, substituted 
heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.
4. Formula (III)

In some embodiments, the compound is a compound of Formula III:

![Chemical Structure](image)

wherein:
X is S or O, and
when X is S, then R<sub>1</sub> is OH or NH<sub>2</sub>; and
when X is O then R<sub>1</sub> is OH, NH<sub>2</sub> or NHMe, and
Het is selected from the group consisting of
or a pharmaceutically acceptable salt or solvate thereof.
In some embodiments, a compound of Formula III is:
In some embodiments, a compound of Formula III is:
In some embodiments, a compound of Formula III is:
In some embodiments, a compound of Formula III is:
In some embodiments, a compound of Formula III is:
5. **Formula (IV)**

[31] In some embodiments, the compound is a hydantoin compound. Useful hydantoin compounds and their syntheses are disclosed, for example, in US 2011/0003839.

[32] In some embodiments, a hydantoin compound is a compound of Formula IV:

![Formula IV](image)

[33] In Formula II, Het represents a heterocyclic unit of 5 or 6 atoms. A and B are independently selected from oxygen, sulfur, and \( \text{N} - R_9 \), with \( R_9 \) being selected from hydrogen, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, \( \text{SO}_2 R_1 \), \( \text{NR}_i . R_2 \), \( \text{NR}_2 \text{(CO)OR}_i \), \( \text{NH(CO)NR}_i . R_1 \), \( \text{NR}_2 \text{(CO)OR}_i \), \( 0(\text{CO})R_1 \), \( 0(\text{CO})OR_1 \), \( 0(\text{CS})R_1 \), \( \text{NH(CS)NR}_i . R_1 \), or \( \text{NR}_2 \text{(CS)OR}_i \), \( \text{NR}_1 \), \( \text{NR}_2 \text{(CO)R}_i \), \( 0(\text{CO})R_1 \), \( 0(\text{CO})OR_1 \), \( 0(\text{CS})R_1 \), or \( \text{NR}_1 \), \( \text{NR}_2 \text{(CS)OR}_i \), \( \text{NR}_1 \), \( \text{NR}_2 \text{(CO)R}_i \), \( 0(\text{CO})R_1 \), \( 0(\text{CO})OR_1 \), \( 0(\text{CS})R_1 \), \( \text{NH(CS)NR}_i . R_1 \), or
NRi₂(CS)OR₁₁. R₂ and R₃ are independently selected from hydrogen, aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, or, together with the carbon to which they are linked, form a cycle which can be cycloalkyl, substituted cycloalkyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic.

[34] R₂ and R₃ can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic. R₁₁ and R₁₂ can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.

[35] For example, the compound can be

![Chemical structure image]

[36] In some embodiments, heterocyclic units are selected from compounds represented by the structures

![Chemical structure image]
and the like. However, the hydantoins are not intended to be limited to compounds having these structures.

R₄, R₅, R₆, and R₇ are independently selected from the group consisting of hydrogen, alkyi, substituted alkyi, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryalkyl, arylalkenyl, arylalkynyl, halogenated alkyi, halogenated alkenyl, halogenated alkynyl, halogen, CN, N₀₂, OR₁₁, SR₁₁, NR₁₁R₁₂, NH(CO)OR₁₁, NH(CO)NR₁₁, R₁₂, NR₁₂(CO)R₁₁, .. 0(CO)R, .. 0(CO)OR₁₁, 0(CS)R, .. NR₁₂(CS)R₁₁, NH(CS)NRᵢᵢRᵢᵢ, NR₁₂(CS)ORᵢᵢ. In some embodiments, R₄ is CN or N₀₂. R₅ is trifluoromethyl, halogenated alkyi, halogenated alkenyl, halogenated alkynyl and halogen. R₆ and R₇ are hydrogen, alkyi or halogen. R₄, R₅, R₆, and R₇ can be independently connected to form a cycle which can be aromatic, substituted aromatic, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl. X is selected from sulfur (S), oxygen (O), NR₈ wherein N is nitrogen and is selected from the group consisting of hydrogen, alkyi, substituted alkyi, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryalkyl, arylalkenyl, arylalkynyl, halogenated alkyi, halogenated alkenyl, halogenated alkynyl, halogen, (CO)Rₙ, (CO)OR₁₁, (CS)R₁₁, (CS)OR₁₁.
[38] $R_i$ is selected from hydrogen, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aikynyl, substituted aikynyl, haintogenated alkyl, haintogenated alkenyl, haintogenated aikynyl, aylalkyl, aylalkenyl, aylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, $S_0$, $R_{11}, N_{R_{11}}$, $R_{12}, NR_{12}(CO)OR_{1}, NH(CO)NR_{1}, R_{12}, NR_{2}(CO)R_{1}, 0(CO)RI_{1}, 0(CO)OR_{1}, 0(CS)R_{1}, NR_{2}(CS)R_{1}, NH(CS)NR_{1}, R_{12}, NR_{12}(CS)OR_{1}$. In some embodiments, $R_i$ is aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl.

[39] $R_2$ and $R_3$ are independently selected from hydrogen, aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aikynyl, substituted aikynyl, haintogenated alkyl, haintogenated alkenyl, haintogenated aikynyl, aylalkyl, aylalkenyl, aylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl. $R_2$ and $R_3$ can be connected to form a cycle which can be heterocyclic aromatic or non aromatic, substituted heterocyclic aromatic or non aromatic, cycloalkyl, substituted cycloalkyl. $R_i$ and $R_2$ can be connected to form a cycle which can be heterocyclic aromatic or non aromatic, substituted heterocyclic aromatic or non aromatic.

[40] $A$ and $B$ are independently selected from oxygen (O), sulfur (S) and N--R9. $R_9$ is selected from hydrogen, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aikynyl, substituted aikynyl, haintogenated alkyl, haintogenated alkenyl, haintogenated aikynyl, aylalkyl, aylalkenyl, aylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, $S_0$, $R_{11}, NR_{11}, R_{12}, NR_{12}(CO)OR_{11}, NH(CO)NR_{11}, R_{12}, NR_{12}(CO)R_{11}, 0(CO)RI_{11}, 0(CO)OR_{11}, 0(CS)R_{11}, NR_{2}(CS)R_{11}, NH(CS)NR_{11}, R_{12}, NR_{12}(CS)OR_{11}, 0(CO)RI_{12}, 0(CO)OR_{12}, 0(CS)R_{12}, NR_{2}(CS)R_{12}, NH(CS)NR_{12}, R_{12}, NR_{12}(CS)OR_{12}, 0(CO)R_{12}, 0(CO)OR_{12}, 0(CS)R_{12}, NR_{2}(CS)R_{12}, NH(CS)NR_{12}, R_{12}, NR_{12}(CS)OR_{12}$.  

[41] $R_{11}$ and $R_{12}$ are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl or substituted alkenyl, aikynyl or substituted aikynyl, aryl, substituted aryl, aylalkyl, aylalkenyl, aylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic. $R_{11}$ and $R_{12}$ can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, substituted cycloalkyl.
In some embodiments, R_i is alkyl, substituted alkyl, alkenyl, or substituted alkenyl. In some embodiments, R_i is selected from the group consisting of aryl and substituted aryl. In some embodiments, R_i is aryl substituted by at least one fluorine atom. In some embodiments, R_i is a 5- to 8-membered heterocyclic aromatic or non-aromatic ring. In some embodiments, R_2 and R_3 are independently methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, fluoromethyl, chloromethyl, or bromomethyl.

In some embodiments, A and B are independently oxygen or sulfur.

In some embodiments, Het comprises a heterocyclic unit of 6 atoms in which 1 or 2 heteroatoms independently are selected from nitrogen, oxygen, and sulfur. In some embodiments, Het comprises a 0 or 1 double-bonded substituent on the heterocyclic unit selected from the group consisting of oxygen and sulfur. In some embodiments, Het comprises from 3 to 4 single-bonded substituents on the heterocyclic unit selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, arylalkenyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogen, CN, NO_2, OR_n, SR_n, NR_1R_2, NH(CO)OR_1, NH(CO)NR_1R_2, NR_12(CO)R_1, 0(CO)R_1, 0(CO)OR_1, 0(CS)R_1, NR_1(CS)NR_1R_2, NR_1R(CS)OR_1, and NR_2(CS)OR_1. In some embodiments, a single-bonded substituent can be connected to another single-bonded substituent to form a cycle which is aromatic, substituted aromatic, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl.
In some embodiments, Het is
and R4, R5, R6, and R7 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, arylalkenyl, arylalkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogen, CN, NO2, OR11, S R11, NR11 R12, N H(CO)OR11, NH(CO)NR11 R12, NR12(CO)R11, O(CO)R11, O(CO)OR11, O(CS)R11, NR12(CSiRi.., NH(CS)NRi1 R12, NRi2(CS)ORi i, wherein any of R4, R5, R6, and R7 can be connected to any of R4, R5, R6, and R7 to form a cycle which can be aromatic, substituted aromatic, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl.

[46] In some embodiments, R6, and R7 are independently selected from the group consisting of hydrogen, alkyl, and or halogen. In some embodiments, R4 is selected from the group consisting of CN and NO2, wherein R5 is selected from the group consisting of trifluoromethyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, and halogen; in some of these embodiments R4 and R7 are independently selected from the group consisting of hydrogen, alkyl, and or halogen.

[47] In some embodiments, R4 is CN or NO2. In some embodiments, R5 is trifluoromethyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, or halogen. In some embodiments, R6, and R7 are independently hydrogen, alkyl, and or halogen.
In some embodiments, \( R_4 \) is CN or NO\(_2\) and \( R_5 \) is trifluoromethyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, or halogen.

In some embodiments, \( R_4 \) is CN or NO\(_2\) and \( R_6 \) and \( R_7 \) are independently hydrogen, alkyl, and or halogen.

In some embodiments, \( R_4 \) is CN or NO\(_2\), \( R_5 \) is trifluoromethyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, or halogen, and \( R_6 \), and \( R_7 \) are independently hydrogen, alkyl, and or halogen.

In some embodiments, \( R_5 \) is trifluoromethyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, or halogen and \( R_6 \), and \( R_7 \) are independently hydrogen, alkyl, and or halogen.

In some embodiments, \( R_5 \) is trifluoromethyl or iodide and \( R_6 \) and \( R_7 \) are independently hydrogen or halogen.

In some embodiments, Het is one of

![Diagram of heterocyclic units]

In some embodiments, Het comprises a heterocyclic unit of 5 atoms, wherein the heterocyclic unit comprises 1 or 2 heteroatoms independently selected from the group consisting of sulfur, oxygen, nitrogen, and NR\(_8\), wherein \( R_8 \) is selected from the group
consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, arylalkenyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogen, (CO)Ru, (CO)ORu, (CS)Rn, (CS)OR_{11}, wherein Het comprises from 2 to 3 single-bonded substituents on the heterocyclic unit selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, arylalkyl, arylalkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogen, CN, NO$_2$, OR$_{11}$, NR$_i$, NR$_{12}$, NH(CO)OR, N$_2$(CO)R$_i$, 0 (CO)R$_i$, 0 (CO)OR$_i$, 0 (CS)R$_i$, N$_2$(CS)R$_i$, NH(CS)NR$_i$R$_{12}$, N$_2$(CS)ORu,
wherein a single-bonded substituent can be connected to another single-bonded substituent to form a cycle which is aromatic, substituted aromatic, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl.

[55] In some embodiments, Het is selected from the group consisting of 5-membered rings of the compounds
and $R_4$, $R_5$, and $R_6$, are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, arylalkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkylene, halogen, CN, N0$_2$, OR$_{11}$, SR$_{11}$, NR$_1$R$_2$, NH(CO)OR$_{11}$, NH(CO)NR$_n$R$_{12}$, NR$_2$(CO)R$_i$, 0(CO)R$_{11}$, 0(CO)OR$_{11}$, 0(CS)R$_e$, 0(CS)OR$_{11}$, NH(CS)NR$_i$R$_{12}$, NR$_2$(CS)OR$_n$, wherein any of $R_4$, $R_5$, and $R_6$ can be connected to any of $R_4$, $R_5$, and $R_6$ to form a cycle which can be aromatic, substituted aromatic, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, wherein X is selected from sulfur, oxygen, and NRs, and wherein $R_8$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, arylalkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, halogen, (CO)R$_i$, (CO)OR$_{11}$, (CS)R$_{11}$, and (CS)OR$_{11}$.

In some embodiments, $R_4$ is selected from the group consisting of CN and N0$_2$, wherein $R_5$ is selected from the group consisting of trifluoromethyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, and halogen, and wherein $R_6$ is selected from the group consisting of hydrogen, alkyl, and halogen.

6. Salts

[56] Salts of compounds described above can be used in the disclosed methods. If a compound has, for example, at least one basic center, it can form an acid addition salt. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxyacarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C1-C4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example
by halogen, for example methyl- or p-toluene-sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center.

Compounds having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tert-butyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts can furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds or their pharmaceutically acceptable salts, are also included. In some embodiments, salts of compounds which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate. In some embodiments, salts of compounds which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

[57] In some embodiments, the salts are pharmaceutically acceptable (e.g., non-toxic, physiologically acceptable) salts. Pharmaceutically acceptable salts retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Further examples of pharmaceutically acceptable salts include those listed in Berge et al., Pharmaceutical Salts. J. Pharm. Sci. 1977
Pharmaceutically acceptable salts can be prepared in situ in the manufacturing process, or by separately reacting a purified compound in its free acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcohohlates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

**Therapeutic Methods**

Compounds disclosed herein can be used to treat disorders in which modulation of androgen, estrogen, and/or progesterone receptors would be beneficial. These disorders include indications discussed below and the therapeutic indications disclosed in U.S. Patent 7,709,517; US 201 1/0003839; WO 2010/1 18354; WO 201 1/044327; and WO 2010/099238. Compounds disclosed herein and related compounds may also be useful as modulators of other nuclear receptors, such as glucocorticoid receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, diabetes, cardiac diseases, and metabolism-related diseases.

"Treating" or "treatment" as used herein is an approach for obtaining a beneficial or desired result, including, but not limited to, relief from a symptom, lessening of a symptom, and preventing a worsening of a symptom associated with the disease being treated. With respect to cancer, treatment also includes, but is not limited to, any one or more of enhancing survival time, enhancing progression-free survival time, and reducing tumor size.
Disorders that can be treated include, but are not limited to:

1. neurodegenerative disorders, including, but not limited to, Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, prion disorders, multiple system atrophy, hereditary spastic paraparesis, spinocerebellar atrophies, Friedreich's ataxia, amyloidosis, metabolic disease-related neurodegeneration, toxin-related neurodegeneration, multiple sclerosis, Charcot Marie Tooth syndrome;

2. cancer, including, but not limited to, prostate cancer, bladder cancer, non-Hodgkin lymphoma, leukemia, thyroid cancer, breast cancer, ovarian cancer, glioblastoma, neuroblastoma, renal cancer, Wilms' tumor (nephroblastoma), retinoblastoma, pancreatic cancer, endometriosis cancer, hepatocellular carcinoma, desmoplastic small-round-cell tumor, colorectal cancer, esophageal cancer, head and neck cancer, lung cancer, melanoma; and

3. other disorders, such as polyglutamate disease, rheumatoid arthritis, systemic hyperandrogenism, seborrhea, hirsutism, precocious puberty; polycystic ovary syndrome, acne, alopecia, benign prostatic hyperplasia, intrauterine fibroids, endometriosis, glaucoma, meningiomas, Kennedy's disease (KD) or X-linked spinal and bulbar muscular atrophy.

In some embodiments, disclosed compounds can be used for medical termination of intrauterine pregnancies.

In some embodiments, disclosed compounds can be used as adjuvants to vaccines, including, but not limited to, vaccines for *N. meningitides, Streptococcus pneumoniae, Streptococcus agalacitae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Helicobacter pylori, Bordetella pertussis, Staphylococcus aureus, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus, Moraxella*
spp, Penicillium spp, Monolinia spp, Rhizoctonia spp, Paecilomyces spp, Pithomyces spp, Cladosporium spp, Neiserria gonorrhoeae, Chlamydia pneumoniae, Chlamydia trachomatis, Treponema pallidum, Haemophilus ducreyi, and Bacillus anthracis.

**Pharmaceutical Compositions**

[63] Compounds can be formulated in any type of pharmaceutical composition known in the art, including, but not limited to, tablets, troches, pills, capsules, syrups, elixirs, injectable solutions, and the like.

[64] A pharmaceutical composition typically includes a pharmaceutically or pharmacologically acceptable excipient or carrier. As used herein, by "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material that is not biologically or otherwise undesirable, e.g., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. In some embodiments, pharmaceutically acceptable carriers or excipients have met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[65] The term "excipient" as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, e.g., caromers, povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc (dc = "directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in
combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, *e.g.*, croscarmellose sodium, gelatin gum, sodium starch glycolate, etc.; creams or lotions include, *e.g.*, maltodextrin, carrageenans, etc.; lubricants include, *e.g.*, magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, *e.g.*, dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, *e.g.*, carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, *e.g.*, aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, *e.g.*, calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[66] Tablets, troches, pills, capsules, and the like can also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring can be added. When the unit dosage form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials can be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules can be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir can contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, a diarylhydantoin compound can be incorporated into sustained-release preparations and devices. For example, a compound can be incorporated into time release capsules, time release tablets, and time release pills.

[67] Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising a compound which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions,
optionally encapsulated in liposomes. The ultimate dosage form typically is sterile, fluid, and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, isotonic agents are included, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating a compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols or glycols or water/alcohol/glycol blends, in which a compound can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.
[70] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[71] Examples of useful dermatological compositions which can be used to deliver a compound to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortman (U.S. Pat. No. 4,820,508).

[72] In some embodiments, the pharmaceutical composition is a unit dosage form. As used herein, "unit dosage form" is a physically discrete unit containing a predetermined quantity of active.

Dosages

[73] As used herein, the term "effective amount" intends such amount of a compound which in combination with its parameters of efficacy and toxicity, as well as based on the knowledge of the practicing specialist should be effective in a given therapeutic form. As is understood in the art, an effective amount may be in one or more doses, i.e., a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any of the co-administered compounds may optionally be lowered due to the combined action (e.g., additive or synergistic effects) of the compounds.

[74] Useful dosages of compounds can be determined by comparing their in vitro activity and/or in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949. For example, the concentration of a compound in a liquid composition, such as a lotion, can be from about 0.1-25% by weight, or from about 0.5-
10% by weight. The concentration in a semi-solid or solid composition such as a gel or a powder can be about 0.1-5% by weight, or about 0.5-2.5% by weight.

[75] The amount of a compound required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[76] Effective dosages and routes of administration of compounds are conventional. The exact amount (effective dose) of the agent will vary from subject to subject, depending on, for example, the species, age, weight and general or clinical condition of the subject, the severity or mechanism of any disorder being treated, the particular agent or vehicle used, the method and scheduling of administration, and the like. A therapeutically effective dose can be determined empirically, by conventional procedures known to those of skill in the art. See, e.g., The Pharmacological Basis of Therapeutics, Goodman and Gilman, eds., Macmillan Publishing Co., New York. For example, an effective dose can be estimated initially either in cell culture assays or in suitable animal models. The animal model can also be used to determine the appropriate concentration ranges and routes of administration. Such information can then be used to determine useful doses and routes for administration in humans. A therapeutic dose can also be selected by analogy to dosages for comparable therapeutic agents.

[77] The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (e.g., the subject, the disease, the disease state involved, and whether the treatment is prophylactic). Treatment can involve daily or multi-daily doses of compound(s) over a period of a few days to months, or even years.

[78] In general, however, a suitable dose will be in the range of from about 0.001 to about 100 mg/kg, e.g., from about 0.1 to about 100 mg/kg of body weight per day, such as above about 0.1 mg per kilogram, or in a range of from about 1 to about 10 mg per kilogram.
body weight of the recipient per day. For example, a suitable dose can be about 1 mg/kg, 10 mg/kg, or 50 mg/kg of body weight per day.

[79] A compound is conveniently administered in unit dosage form; for example, containing 0.05 to 10000 mg, 0.5 to 10000 mg, 5 to 1000 mg, or about 100 mg of active ingredient per unit dosage form.

[80] A compound can be administered to achieve peak plasma concentrations of, for example, from about 0.5 to about 75 \( \mu \text{M} \), about 1 to 50 \( \mu \text{M} \), about 2 to about 30 \( \mu \text{M} \), or about 5 to about 25 \( \mu \text{M} \). Exemplary desirable plasma concentrations include at least or no more than 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 or 200 \( \mu \text{M} \). For example, plasma levels can be from about 1 to 100 micromolar or from about 10 to about 25 micromolar. This can be achieved, for example, by the intravenous injection of a 0.05 to 5\% solution of a diarylhydantoin or hydantoin compound, optionally in saline, or orally administered as a bolus containing about 1-100 mg of a diarylhydantoin or hydantoin compound. Desirable blood levels can be maintained by continuous infusion to provide about 0.00005-5 mg per kg body weight per hour, for example at least or no more than 0.00005, 0.0005, 0.005, 0.05, 0.5, or 5 mg/kg/hr. Alternatively, such levels can be obtained by intermittent infusions containing about 0.0002-20 mg per kg body weight, for example, at least or no more than 0.0002, 0.002, 0.02, 0.2, 2, 20, or 50 mg of a compound per kg of body weight.

[81] A compound can conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself can be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator.

Methods of Administration

[82] A compound can be administered using pharmaceutical compositions comprising a therapeutically effective amount of the compound and a pharmaceutically acceptable carrier or diluent, in a variety of forms adapted to the chosen route of administration, for
example, orally, nasally, intraperitoneally, or parenterally, by intravenous, intramuscular, topical or subcutaneous routes, or by injection into tissue.

A compound can be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier; or by inhalation or insufflation. It can be enclosed in hard or soft shell gelatin capsule, can be compressed into a tablet, or can be incorporated directly with the food of a patient's diet. For oral therapeutic administration, a compound can be combined with one or more excipients and used in the form of an ingestible tablet, a buccal tablet, troche, capsule, elixir, suspension, syrup, wafer, and the like. A compound can be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. In some embodiments, such compositions and preparations contain at least 0.1% diarylhydantoin or hydantoin compound. The percentage of the compositions and preparations can, of course, be varied and can conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of diarylhydantoin or hydantoin compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

A compound can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of a compound can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

Combination Therapies

In some embodiments, combinations of one or more compounds are used. A "combination" compounds includes one or more compounds administered substantially simultaneously, whether or not in the same pharmaceutical composition, or sequentially, compounds can, but need not be, chemically similar (i.e., two compounds of Formula I, one compound of Formula I and one compound of Formula II, etc.).
In some embodiments, one or more androgen, estrogen, and/or progesterone receptor antagonists is used in combination with one or more compounds of Formula I and/or II. Such antagonists include, but are not limited to, Bicalutamide (e.g., CASODEX®), Cyproterone Acetate (e.g., ANDROCUR®, CYPROSTAT®, CYPROTERON®, PROCUR®, CYPRONE®, CYPROHEXAL®, CIPROTERONA®, CYPROTERONUM®, NEOPROXIL®, SITERONE®), Dienogest (e.g., VISANNE®), Flutamide (e.g., EULEXIN®), Galeterone (TOK-001), Nilutamide (e.g., NILANDRON®), Spironolactone (e.g., ALDACTONE®), Abiraterone (e.g., ZYTIGA®), radium-223 chloride (e.g., ALPHARADIN®), TAX 700, OGX 111, Cabozantinib (XL 184), Dasatinib (e.g., SPRYCEL®), an mTOR inhibitor (e.g., Everolimus, Ridaforolimus, Rapamycin, Temsirolimus), an HDAC inhibitor (e.g., Vorinostat, CI-994, MS-275, BML-210, M344, NVP-LAQ824, Panobinostat, Mocetinostat, PXD101), Sipuleucel-T (e.g., PROVENGE®), Fulvestrant (e.g., FASLODEX®), Tamoxifen, Raloxifene, and Toremifene.

In some embodiments, use of one or more compounds is combined other cancer therapies, such as internal or external radiation, surgery, and chemotherapies, including:

1. anthracyclines, such as doxorubicin (e.g., ADRIAMYCIN®, DOXIL®), including liposomal doxorubicin, epirubicin (e.g., ELLENCE®), and daunorubicin (e.g., CERUBIDINE®, DAUNOXOME®);

2. taxanes, such as tamoxifen (e.g., NOLVADEX®, SOLTAMOX®, ISTUBAL®, VALODEX®), docetaxel (e.g., TAXOTERE®), paclitaxel (e.g., TAXOL®, ABRAXANE®), and protein-bound paclitaxel (e.g., ABRAXANE®);

3. cyclophosphamide (e.g., CYTOXAN®);

4. capecitabine (e.g., XELODA®)

5. 5-fluorouracil or 5 FU (e.g., ADRUCIL®);

6. vinorelbine (e.g., NAVELBINE®);
7. gemcitabine (e.g., GEMZAR®);
8. trastuzumab (e.g., HERCEPTIN®);
9. carboplatin (e.g., PARAPLATIN®);
10. eribulin (e.g., HALAVEN®);
11. ixabepilone (e.g., IXEMPRA®);
12. methotrexate (e.g., AMETHOPTERIN®, MEXATE®, FOLEX®);
13. mutamycin (e.g., MITOMYCIN®);
14. mitoxantrone (e.g., NOVANTRONE®);
15. thiotepa (e.g., THIOPLEX®);
16. vincristine (e.g., ONCOVIN®, VINCASAR PES®, VINCREX®);
17. aromatase inhibitors such as anastrozole (e.g., ARIMIDEX), exemestane (AROMASIN), and letrozole (FEMARA);
18. raloxifene (e.g., EVISTA®);
19. toremifene (e.g., FARESTON®);
20. fulvestrant (e.g., FASLODEX®);
21. lapatinib (e.g., TYKERB®); and
22. metformin.

[88] Use of one or more compounds also can be used in conjunction with combinations of chemical therapies, such as:

1. doxorubicin and docetaxel (e.g., "AT," ADRIAMYCIN® and TAXOTERE®);
2. doxorubicin and cyclophosphamide, with or without paclitaxel or docetaxel (e.g. "AC ± T," ADRIAMYCIN® and CYTOXAN®, with or without TAXOL® or TAXOTERE®);

3. cyclophosphamide, methotrexate, and fluorouracil (e.g., "CMF," CYTOXAN®, methotrexate, and fluorouracil);

4. cyclophosphamide, epirubicin, and fluorouracil (e.g., "CEF," CYTOXAN®, ELLENCE®, and fluorouracil);

5. fluorouracil, doxorubicin, and cyclophosphamide (e.g., "FAC," fluorouracil, ADRIAMYCIN®, and CYTOXAN® or "CAF," CYTOXAN®, ADRIAMYCIN®, and fluorouracil);

6. docetaxel, doxorubicin, and cyclophosphamide (e.g., "TAC," TAXOTERE®, ADRIAMYCIN®, and CYTOXAN®); and

7. gemcitabine, epirubicin, and paclitaxel (e.g., "GET," GEMZAR®, ELLENCE®, and TAXOL®).

[89] Nothing in this specification should be considered as limiting the scope of this disclosure. All examples presented are representative and non-limiting. The above-described embodiments can be modified or varied, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the embodiments disclosed herein can be practiced otherwise than as specifically described.

**EXAMPLE 1**

[90] Androgen receptor-expressing human urothelial carcinoma UM-UC-3 cells are purchased from the American Type Culture Collection, Manassas, VA, USA) and maintained in MEM medium (Gibco, 51200) supplemented with glutamine, non-essential amino acids, and 10% fetal bovine serum (FBS) at 37°C in a humidified atmosphere of 5% CO2.
Cells are cultured in phenol red-free medium supplemented with 5% charcoal-stripped FBS (CSS) at least 24 h before experimental treatment with DHT (dihydrotestosterone) or a compound disclosed herein.

Cells (3x10^3) are seeded in 96-well tissue culture plates and incubated for 3 or 6 days with medium supplemented with 5% CSS containing different treatments: a compound disclosed herein at 0 (control), 1, 10, or 30µM or DHT at 0 (control), 0.1, 1 or 10nM. An MTS assay is used to determine cell viability.
CLAIMS

1. A compound of structural formula 1

wherein \( W \) is selected from the group consisting of \( O \) and \( NR_5 \), wherein \( R_5 \) is selected from the group consisting of \( H \), methyl, and

\[
\begin{align*}
\text{Het} & \\
\text{N} & \\
\text{S} & \\
\text{N} & \\
\text{W} & \\
\text{R}_1 & \\
\text{R}_2 & \\
\text{R}_3 & \\
\text{R}_4 & \\
\end{align*}
\]

wherein \( D \) is \( S \) or \( O \) and \( E \) is \( N \) or \( O \) and \( G \) is alkyi, aryl, substituted alkyi or substituted aryl; or \( D \) is \( S \) or \( O \) and \( E-G \) together are \( C_1-C_4 \) lower alkyi,

wherein \( R_1 \) and \( R_2 \) together comprise eight or fewer carbon atoms and are selected from the group consisting of alkyi, substituted alkyi including haloalkyi, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group,

wherein \( R_3 \) is selected from the group consisting of hydrogen, halogen, methyl, \( C_1-C_4 \) alkoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyi, methoxycarbonyl, acetamido, methanesulfonamino, methanesulfonyle, 4-methanesulfonyl-1-piperazinyl, piperazinyl, and \( C_1-C_6 \) alkyi or alkenyl optionally substituted with hydroxyl, methoxycarbonyl, cyano, amino, amido, nitro, carbamoyl, or substituted carbamoyl including methylcarbamoyi, dimethylcarbamoyi, and hydroxyethylcarbamoyl,
wherein $R_4$ is selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl,

wherein $R_3$ is not methyaminomethyl or dimethyaminomethyl; and

wherein $\text{Het}$ is selected from the group consisting of

and wherein $X$ is selected from the group consisting of trifluoromethyl and iodo, or a pharmaceutically acceptable salt thereof.
2. A compound of structural formula (11)

\[
\begin{align*}
\text{Het-1} & \quad \text{A} \quad \text{X} \quad \text{R}_3 \\
\text{B} & \quad \text{R}_1 \\
\text{R}_2 & \quad \text{R}_4 \\
\end{align*}
\]

wherein Het-1 is selected from the group consisting of

\[
\begin{align*}
R_5 & \quad N \quad R_6 \\
R_5 & \quad N \quad R_6 \\
R_5 & \quad N \quad R_6 \\
R_5 & \quad N \quad R_6 \\
R_5 & \quad N \quad R_6 \\
R_5 & \quad N \quad R_6 \\
\end{align*}
\]

wherein R5 is CN or NO2 or SO2R11, wherein R6 is CF3, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aikynyl, substituted aikynyl, halogenated alkyl, halogenated alkenyl, halogenated aikynyl, halogen, wherein A is sulfur (S) or oxygen (O), wherein B is O or S or NR8, wherein R8 is selected from the group consisting of H, methyl, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aikynyl, substituted aikynyl, aroylalkyl, aryalkenyl, heterocyclic aromatic or non-aromatic.
substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, S02R, NR1R12, (CO)OR11, (CO)NR1R12, (CO)R11, (CS)R11, (CS)NR1R12, (CS)OR11,

wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl, wherein R1 and R2 are independently alkyl, haloalkyl, hydrogen, aryl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, or R1 and R2 are connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl,

wherein X is carbon or nitrogen and can be at any position in the ring, and wherein R3, R4, and R7 are independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methylcarbamoyl-substituted alkyl, dimethylcarbamoyl-substituted alkyl, methoxy carbonyl, acetamido, methanesulfonamino, carbamoyl-
substituted alkyl, methanesulfonyl, 4-methanesulfonyl-lpiperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyl-substituted alkyl, hydroxyl-substituted alkenyl, carbamoyl-substituted alkenyl, methoxycarbonyl-substituted alkyl, cyano-substituted alkyl, aryl, substituted aryl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated alkynyl, S02R1, NR1 1R12, NR1 (CO)OR1, NH(CO)NR1 1R12, NR12 (CO)R11, 0(CO)R1 11, 0(CO)OR1 11, 0(CS)R1 1, NR12(CS)R1 1, NH(CS) NR1 1R12, NR12(CS)OR1 1, aryl alkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, haloalkyl, methylsulfonylcarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methane sulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl-1-piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, wherein R1 and R12 are independently hydrogen, aryl, aralkyl, substituted aralkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, aryl alkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, or R1 and R12 can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.
3. A compound of structural formula III:

wherein:
X is S or O, and
when X is S, then R₁ is OH or NH₂; and
when X is O then R₁ is OH, NH₂ or NHMe, and
Het is selected from the group consisting of
or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound of structural formula 1, 11, or 111 and a pharmaceutically acceptable vehicle.

5. A method of treating a disorder involving an androgen, estrogen, and/or progesterone receptor, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of:

structural Formula 1:

structural formula 11:

structural formula III; or

structural formula IV:

\[
\text{(IV)}
\]

wherein Het represents a heterocyclic unit of 5 or 6 atoms; A and B are independently selected from oxygen, sulfur, and N—R9, with R9 being selected from hydrogen, aryl, substituted aryl, alkyl, substituted alkyi, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, aryalkenyl, aryalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl,
substituted cycloalkyl, $S_0^R_1^i NR, iR, _2 NR, _2 (CO)OR_1 NR, _1, 0 (CO)R, _1 0 (CO)OR, _1 0 (CS)R, R_1$ and $R_{i2}$ are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, aryl, substituted aryl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, or substituted heterocyclic aromatic or non-aromatic. $R_{i}$ is selected from hydrogen, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, $S_0^R_2 R_{11}, NR, R_{11}$. $NR, _2 (CO)OR, _1 0 (CO)NR, _1 0 (CO)R, _1 0 (CO)OR, _1 0 (CS)R, R_1$ and $R_{i2}$ or $NR, _2 (CS)OR, _1, R_2$, $R_3$ are independently selected from hydrogen, aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, or, together with the carbon to which they are linked, form a cycle which can be cycloalkyl, substituted cycloalkyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic; $R_2$ and $R_3$ can be connected to form a cycle which can be heterocyclic aromatic or non aromatic, substituted heterocyclic aromatic or non aromatic; and $R_{11}$ and $R_{12}$ can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.

6. The method of claim 5 wherein the disorder is selected from the group consisting of neurodegenerative disorders, cancer, polyglutamate disease, rheumatoid arthritis, systemic hyperandrogenism, seborrhea, hirsuitism, precocious puberty, polycystic ovary syndrome, acne,
alopecia, benign prostatic hyperplasia, intrauterine fibroids, endometriosis, glaucoma, meningiomas, Kennedy's disease (KD) or X-linked spinal and bulbar muscular atrophy.

7. The method of claim 6 wherein the disorder is a neurodegenerative disorder and the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, prion disorders, multiple system atrophy, hereditary spastic paraparesis, spinocerebellar atrophies, Friedreich's ataxia, amyloidosis, metabolic disease-related neurodegeneration, toxin-related neurodegeneration, multiple sclerosis, and Charcot Marie Tooth syndrome.

8. The method of claim 6 wherein the disorder is cancer and the cancer is selected from the group consisting of prostate cancer, bladder cancer, non-Hodgkin lymphoma, leukemia, thyroid cancer, breast cancer, ovarian cancer, glioblastoma, neuroblastoma, renal cancer, Wilms' tumor (nephroblastoma), retinoblastoma, pancreatic cancer, endometrial cancer, hepatocellular carcinoma, desmoplastic small-round-cell tumor, colorectal cancer, esophageal cancer, head and neck cancer, lung cancer, and melanoma.

9. A vaccine composition comprising an androgen, estrogen, and/or progesterone receptor antagonist.

10. The vaccine composition of claim 8 which comprises a compound of Formula I, a compound of Formula II, or a compound of Formula III.

11. A method of vaccinating an individual, comprising administering to an individual in need thereof the vaccine composition of claim 9.

12. A method of terminating an intrauterine pregnancy, comprising administering to an individual in need thereof a compound of structural formula I, II, or III.
## A. CLASSIFICATION OF SUBJECT MATTER

**IPCC(8)** - A61K 31/497 (201 2.01)

**USPC** - 514/254.05

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**USPC:** 514/254.05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

Electronic Database Searched: PUBWEST (PGPB,USPT,USOC,EPAB,JPAB), surechem, google. Search Terms Used Thiodyantoin, androgen, estrogen, progesterone receptor

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

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**T**- later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X**- document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**Y**- document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

**Z**- document member of the same patent family

Date of the actual completion of the international search


Date of mailing of the international search report

17 JAN 2013

Authorized officer: Lee W. Young

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PCT GIS: 971-272-7174

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