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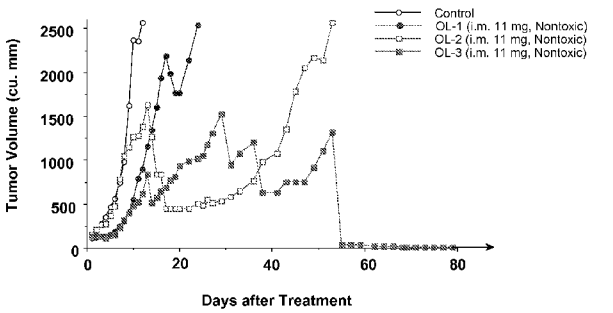
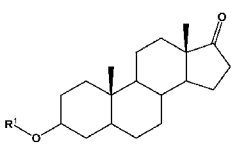


Fig. 9



(II)

(57) Abstract: Disclosed herein are epiandrosterone and androsterone derivatives of Formula (II), process of preparation thereof, pharmaceutical compositions thereof, and methods of use thereof.

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EPIANDROSTERONE AND/OR ANDROSTERONE DERIVATIVES AND METHOD OF USE THEREOF

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0001] The invention was supported by Grant No. DAMD17-99-1-9018 awarded by DOD. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] The disclosure relates to novel steroids and more particularly to androsterone and epiandrosterone derivatives useful as anti-cancer, anti-obesity, anti-diabetic and hypolipidemic agents.

BACKGROUND

[0003] Dehydroepiandorsterone (DHEA) and dehydroepiandrosterone-sulfate are major adrenal secretory products in many mammalian species. Although DHEA-sulfate is the main precursor of placental estrogen and is converted into active androgens in peripheral tissue, there is no strong biological role for either DHEA or DHEA-sulfate in the normal subject. Several studies suggest that these steroids are associated with cell proliferative disorders as well as other androgen-associated disorders.

[0004] Examples of androgen-associated disorders include, but are not limited to, prostate cancer, benign prostatic hyperplasia, acne, seborrhea, hirsutism, androgenic alopecia, precocious puberty, adrenal hyperplasia, and polycystic ovarian syndrome. Examples of estrogen-associated disorders include, but are not limited to, breast cancer, endometriosis, leiomyoma, and precocious puberty.

SUMMARY

[0005] The disclosure provides androsterone and epiandrosterone derivatives, methods of synthesis thereof, and methods of use thereof, for the treatment of various androgen- and estrogen-associated, androgen-sensitive, and estrogen-sensitive disorders.

[0006] In one embodiment, androsterone and/or epiandrosterone derivatives disclosed herein inhibit breast cancer cell growth via counteracting the effect of female hormones and/or inhibit cell

proliferation by binding to female hormone receptors (e.g., as antagonists), and/or induce apoptosis in abnormally dividing cells found with androgen and estrogen associated cell proliferative disorders.

[0007] In another embodiment, the disclosure provides epiandrosterone and/or androsterone ester compounds, pharmaceutical compositions thereof, and methods of use therof (e.g., for the treatment of cancer).

[0008] In yet another embodiment, the disclosure provides epiandrosterone and/or androsterone-camptothecin combination compounds, pharmaceutical compositions therof, methods of use thereof (e.g., for the treatment of cancer).

[0009] The details of one or more embodiments are set forth in the accompanying drawings and the description below. Other features, objects, and. advantages will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

[0010] **Figure 1** shows the effect of an androsteron derivative of the disclosure on cancer cells.

[0011] **Figure 2** shows that OL-1 is significantly more effective in killing DU-145 human prostate cancer cells than topotecan and irinotecan.

[0012] **Figure 3** shows that OL-2 is very effective in killing PC-3 human prostate cancer cells, with an IC50 of 131 nM.

[0013] **Figure 4** shows that OL-3 is very effective in killing PC-3 human prostate cancer cells, with an IC50 of 18 nM.

[0014] **Figure 5** shows that OL-2 is highly effective in killing human malignant peripheral nerve sheath tumor (MPNST) cells, with an IC50 of 76 nM.

[0015] **Figure 6** shows that OL-3 is extremely effective in killing human malignant peripheral nerve sheath tumor (MPNST) cells, with an IC50 of 4 nM.

[0016] **Figure 7** shows that OL-2 is effective in killing SF295 human glioblastoma cells, with an IC50 of 290 nM.

[0017] **Figure 8** shows that OL-3 is highly effective in killing SF295 human glioblastoma cells, with an IC50 of 31 nM.

[0018] **Figure 9** demonstrates that OL-1, OL-2, and OL-3 are all effective in inhibiting the growth of PC-3 prostate cancer xenografts in mice (tumor volume) as compared to the control group. OL-3 was the most effective compound in controlling the growth of PC-3 xenografts.

[0019] **Figure 10** shows that for the PC-3 tumor volume to reach 1000 cu.mm in size only takes around 7 days for the control, around 13 days for OL-1 treated mice, around 25 days for OL-2 treated mice, and around 38 days for OL-3 treated mice.

[0020] **Figure 11** shows that mice bearing PC-3 tumors lived for about 10 days for the control, around 18 days for OL-1 and OL-2 treated mice, and around 45 days for OL-3 treated mice.

[0021] **Figure 12** demonstrates that OL-1, OL-2, and OL-3 are all very effective in inhibiting the growth of DU-145 human prostate cancer xenografts in mice (tumor volume) as compared to the control group.

[0022] **Figure 13** shows that for the DU-145 tumor volume to reach 1000 cu.mm in size only takes around 16 days for the control, around 56 days for OL-1 and OL-2 treated mice, and around 62 days for OL-3 treated mice.

[0023] **Figure 14** shows that mice bearing DU-145 tumors lived for about 27 days for the control, around 60 days for OL-1 and OL-3 treated mice, and around 57 days for OL-2 treated mice.

DETAILED DESCRIPTION

[0024] As used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an antigen" includes a plurality of such, antigens and reference to "the immune cell" includes reference to one or more immune cells known to those skilled in the art, and so forth.

[0025] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure belongs.

Although similar or equivalent methods, devices, and materials to those described herein can be used to practice the invention disclosed herein, the exemplary methods, devices, and materials are described herein.

[0026] The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior disclosure. Furthermore, with respect to any similar or identical terms found in both in the incorporated publications or references and those terms expressly put forth or defined in this document, then those terms definitions or meanings expressly put forth in this document shall control in all respects.

[0027] The abbreviations used herein have their conventional meaning within the chemical and biological arts. For example: DCC, *N*,*N*'-dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; THF, tetrahydrofuran; BOC, *tert*-butyl carbamate; TFA, trifluoroacetic acid; NMR, nuclear magnetic resonance; MeOH, methanol; Ar, aryl, BCS, bovine calf serum; and HBSS, Hank's balanced salt solution.

[0028] "Aryl" refers to any functional group or substituent derived from an aromatic ring. For this invention, "aryl" can refer to a monocyclic ring or to an extended aryl ring system comprised of 2 to 6 aryl rings which are fused together, i.e. bi-, tri-, tetra-, penta-, or hexa- cyclic. Additionally, for purposes of this invention "aryl" will refer to both unsubstituted and substituted aromatic rings or a combination thereof for an extended aryl ring system, unless specifically stated otherwise. In one embodiment "aryl" refers to an unsubstituted aryl ring. In another embodiment "aryl" refers to a substituted aryl ring. In a preferred embodiment a substituted aryl has one or more electron withdrawing groups covalently bound to an aryl.

[0029] "Heterocycle" refers to a cyclic compound which has atoms of at least two different elements as members of its ring. For this invention, "heterocycle" can refer to a monocyclic ring or to an extended heterocyclic ring system comprised of 2 to 6

heterocyclic rings which are fused together, i.e. bi-, tri-, tetra-, penta-, or hexa- cyclic. Additionally, for purposes of this invention "heterocycle" will refer to both unsubstituted and substituted heterocyclic rings and a combination thereof for an extended heterocyclic ring system, unless specifically stated otherwise. In one embodiment "heterocycle" refers to an unsubstituted heterocyclic ring. In another embodiment "heterocycle" refers to a substituted heterocyclic ring. In a preferred embodiment a substituted heterocyclic has one or more electron withdrawing groups covalently bound to a heterocycle.

[0030] "Cycloalkyl" refers to a cyclic compound which has only carbons as members of its ring. For this invention, "cycloalkyl" can refer to a monocyclic ring or to an extended cycloalkyl ring system comprised of 2 to 6 cycloalkyl rings which are fused together, i.e. bi-, tri-, tetra-, penta-, or hexa- cyclic. Additionally, for purposes of this invention "cycloalkyl" will refer to both unsubstituted and substituted cycloalkyl rings or a combination thereof for an extended cycloalkyl ring system, unless specifically stated otherwise. In one embodiment "cycloalkyl" refers to an unsubstituted cycloalkyl ring. In another embodiment "cycloalkyl" refers to a substituted cycloalkyl ring. In a preferred embodiment a substituted cycloalkyl has one or more electron withdrawing groups covalently bound to a cycloalkyl.

[0031] "Fused ring system" refers to a ring system comprised of at least 2 fused rings and up to 10 fused rings that are comprised of a combination of cylcoalkyl, heterocycle, and aryl rings. For purposes of this invention, "fused ring system" will refer to both unsubstituted and substituted rings, and a combination thereof, unless specifically stated otherwise. In one embodiment "fused ring system" refers to only unsubstituted rings. In another embodiment "fused ring system" refers to only substituted rings. In a preferred embodiment substituted fused ring system refers to one or more electron withdrawing groups covalently bound to one or more aryl, cycloalkyl, or heterocycle rings that are part of the "fused ring system".

[0032] "Substituted" with respect to a ring structure, refers to one or more functional groups covalently bound to the core ring structure.

[0033] "Unsubstituted" with respect to a ring structure, refers to rings that have no functional groups covalently bound to the core ring structure.

[0034] "Electron withdrawing group" refers to a functional group attached to a ring or ring system, whether that ring is aryl, heterocycle, cycloalkyl, or a fused ring system, which draws electron density away from the ring (makes the rings more electrophilic). Examples of functional groups that withdraw electron density from rings, include, but are not limited to, nitros, trihalides, halogens, cyanos, sulfonates, carboxylic acids, esters, and carbonyls.

[0035] "(C_1 to C_6)" with respect to a chemical function group, such as (C_1 to C_6)alkyl, refers to a substituent that has one to six carbons.

[0036] Nonstereospecific covalent bonds are depicted by a line that has uniform thickness, while stereospecific bonds are represented by lines that are wider at one end than the other that have a wedge shape, which is either solid, indicating an element that is coming towards the viewer, or hashed, indicating an element that is going away from the viewer. For example, the single line connecting the O and steroid ring in Formula II would indicate that this bond is nonstereospecific, so that compounds of Formula II, for the purposes of this disclosure, include androsterone and/or epiandrosterone derivative compounds.

[0037] The term "disorder" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disease", "syndrome" and "condition" (as in medical condition), in that all reflect an abnormal condition of the body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms.

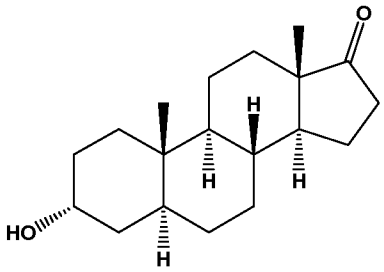
[0038] As used herein "carrier" or "excipient" means a pharmaceutically acceptable carrier or excipient and comprises any and all solvents, dispersive agents or media, coating(s),

antimicrobial agents, iso/hypo/hypertonic agents, absorption-modifying agents, and the like.

[0039] The term "protected" in respect to a functional group, refers to chemically modifying a functional group so that it is no longer reacts in a manner that would be expected if the functional group was not protected, allowing for chemoselectivity. A "protected" functional group can be subsequently deprotected in later steps to restore the functional group to its state prior to being protected.

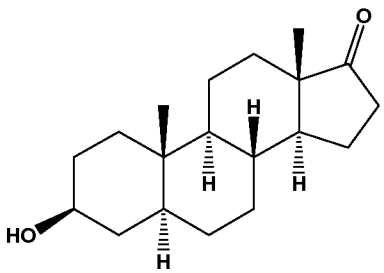
[0040] The term "linker portion" in respect to a reactant, refers to a covalently bonded organic compound containing at least 2 carbons where a carboxylic acid group is on one end, and the other end is covalently bonded to hydroxyl group of a camptothecin or camptothecin molecule, forming an ester bond.

[0041] Androstenone is a steroid hormone excreted in urine that reinforces masculine characteristics having the general formula as set forth in Formula I(a):



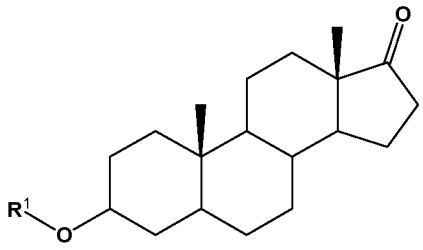
I(a)

[0042] Epiandrostenone is a steroid hormone excreted in urine that reinforces masculine characteristics having the general formula as set forth in Formula I(b):



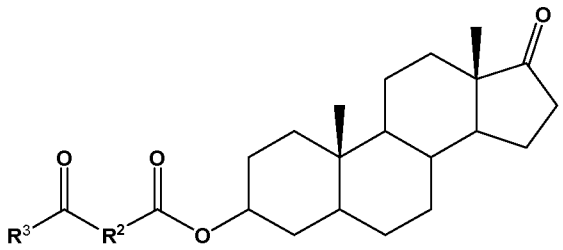
I(b)

[0043] In one exemplary embodiment, the present disclosure provides for androsterone and/or epiandrosterone derivative compounds having general Formula II:

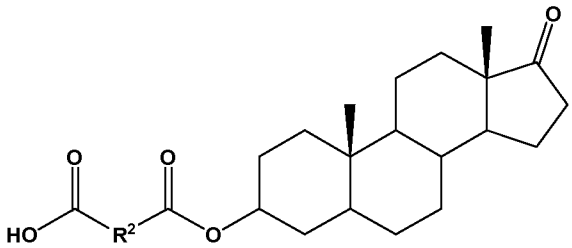


(II)

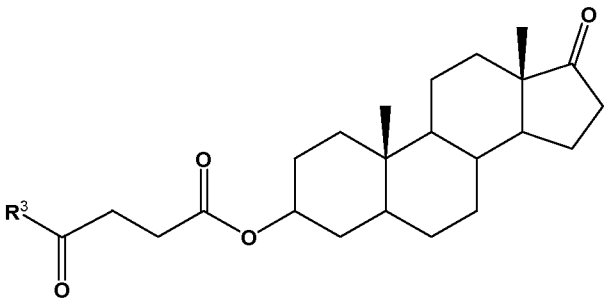
[0044] In another exemplary embodiment, a compound of Formula II, wherein R^1 is R^3-(C=O)-R^2-(C=O)- provides for androsterone and/or epiandrosterone derivative compounds having general Formulas III(a), III(b), III(c), and III(d):



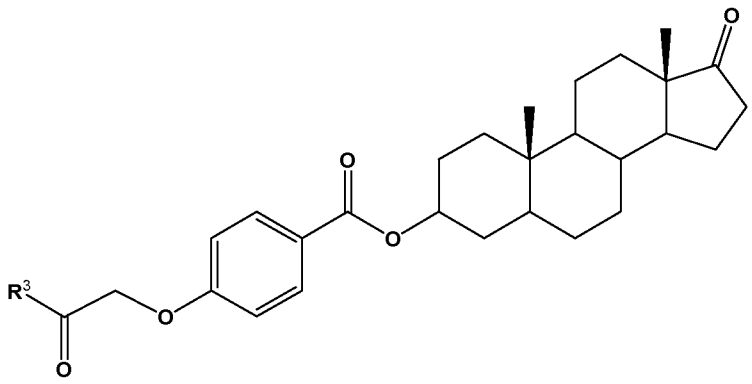
III(a)



III(b)



III(c)



III(d)

[0045] In yet another exemplary embodiment of the disclosure, R^1 is either an aryl, cycloalkyl, heterocycle, fused ring system, -$(CY_2)_w$-aryl, -$(CY_2)_w$-heterocycle, -$(CY_2)_w$-cycloalkyl, -$(CY_2)_w$-fused ring system, -(C=O)-heterocycle, -(C=O)-cycloalkyl, -(C=O)-aryl, -(C=O)-fused ring system, -(C=O)-$(CY_2)_w$-cycloalkyl, -(C=O)-$(CY_2)_w$-cycloalkyl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-heterocycle, -(C=O)-$(CY_2)_w$-heterocycle-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-aryl, -(C=O)-$(CY_2)_w$-aryl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-aryl, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-fused ring system, -(C=O)-$(CY_2)_w$-fused ring system-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-N=fused ring system, -(C=O)-$(CY_2)_w$-O-N=heterocycle, or R^3-(C=O)-R^2-(C=O)-.

[0046] In another exemplary embodiment of the disclosure, R^2 is either -$(CY_2)_w$-, -aryl-, -cycloalkyl-, -heterocycle-, -fused ring system-, -$(CY_2)_w$-heterocycle-, -$(CY_2)_w$-cycloalkyl-, -$(CY_2)_w$-aryl-, -$(CY_2)_w$-L-$(CY_2)_z$-, -$(CY_2)_w$-L-$(CY_2)_x$-aryl-, -$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-, -$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-, -$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-, -$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-, -$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-, -$(CY_2)_w$-L-cycloalkyl-, -$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-, -$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-, -$(CY_2)_w$-fused ring system-, -$(CY_2)_w$-fused ring system-$(CY_2)_z$-, -$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-, -$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-, or -

$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-. With respect to R^2, the left side of the formula is connected to R^3 (indicated by the dashed line) while the right side is connected to R^1 (indicated by a dashed line), e.g. -$(CY_2)_w$-aryl- should be interpreted as R^3-$(CY_2)_w$-aryl-R^1.

[0047] In a further exemplary embodiment of the disclosure, R^3 is either a hydroxyl, aryl, cycloalkyl, heterocycle, fused ring system, -O-aryl, -O-cycloalkyl, -O-heterocycle, -O-fused ring system, -O-$(CY_2)_w$-cycloalkyl, -O-$(CY_2)_w$-cycloalkyl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl, -O-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-heterocycle, -O-$(CY_2)_w$-heterocycle-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle, -O-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-aryl, -O-$(CY_2)_w$-aryl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-aryl, -O-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-fused ring system, -O-$(CY_2)_w$-fused ring system-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system, -O-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-O-N=fused ring system, or -O-$(CY_2)_w$-O-N=heterocycle.

[0048] In yet another exemplary embodiment of the disclosure, R^4 is independently either an alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aldehyde, carbonyl, alkoxycarbonyl, carboxyl, heterocycle, fused ring system, amino, imino, imido, azido, azo, alkylamine, arylamine, alkoxy, aryloxy, cyano, cyanato, hydroxyl, nitroso, or nitro.

[0049] In an additional exemplary embodiment of the disclosure, Y is either H, D, R^4, OR^4, $N(R^4)_2$, SR^4, cyano, CA_3, CA_2R^4, $CA(R^4)_2$, $C(R^4)_3$, or halogen.

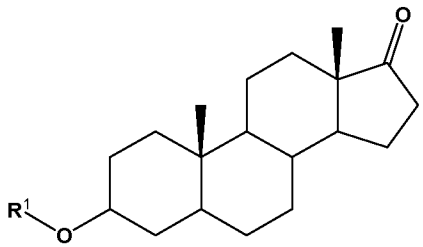
[0050] In a further exemplary embodiment of the disclosure, A is either H, D, or halogen.

[0051] In another exemplary embodiment of the disclosure, L is either O, C(=O)O, C(=O)N, C(A)=N(A), C(A)=C(A), C#C, N=N, O-N(A), N(Y), S, S(=O)(=O), or a covalent bond.

[0052] In yet another exemplary embodiment of the disclosure, w, x, y, and Z is either 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10,

wherein when w, x, y, or Z is 0 then the carbon containing group is absent and is replaced by a covalent bond to the next defined group. For example, when w is 0, CH_2-O-$(CH_2)_w$-aryl should be interpreted for the purposes of this disclosure as CH_2-O-aryl, wherein "-" indicates a single covalent bond. A double covalent bond is indicated by "=", for example (C=0), and a triple covalent bond is indicated by "#", for example (C#C).

[0053] In further exemplary embodiment of the disclosure, a compound has structural Formula II



(II)

wherein:

R^1 is either an aryl, cycloalkyl, heterocycle, fused ring system, -$(CY_2)_w$-aryl, -$(CY_2)_w$-heterocycle, -$(CY_2)_w$-cycloalkyl, -$(CY_2)_w$-fused ring system, -(C=O)-heterocycle, -(C=O)-cycloalkyl, -(C=O)-aryl, -(C=O)-fused ring system, -(C=O)-$(CY_2)_w$-cycloalkyl, -(C=O)-$(CY_2)_w$-cycloalkyl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-heterocycle, -(C=O)-$(CY_2)_w$-heterocycle-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-aryl, -(C=O)-$(CY_2)_w$-aryl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-aryl, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-fused ring system, -(C=O)-$(CY_2)_w$-fused ring system-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system, -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -(C=O)-$(CY_2)_w$-L-N=fused ring system, or -(C=O)-$(CY_2)_w$-O-N=heterocycle.

[0054] In another exemplary embodiment of the disclosure, the aryl, heterocycle, and fused ring system of R^1, R^2, R^3 and/or R^4 are substituted. In yet another exemplary embodiment, said substituted aryl, heterocycle, and fused ring system of R^1, R^2, R^3 and/or R^4 are

substituted with one or more electron withdrawing groups. In yet another exemplary embodiment, said substituted aryl, heterocycle, and fused ring system of R^1, R^2, R^3 and/or R^4 are substituted only with electron withdrawing groups.

[0055] In a further exemplary embodiment of the disclosure, R^1, R^2, R^3 and/or R^4 heterocycle is a nitrogen-containing heterocycle, and if the R^1, R^2, R^3 and/or R^4 fused ring system contains a heterocycle it is a nitrogen-containing heterocycle. In another exemplary embodiment, the nitrogen-containing heterocycle of R^1, R^2, R^3 and/or R^4 is aromatic.

[0056] Aromatic nitrogen-containing heterocycles, typically contain a 5- or 6-membered monocyclic substituent, or are bicyclic or tricyclic fused ring systems comprised of 4-, 5- or 6-membered monocyclic rings. In a further exemplary embodiment of the disclosure, a nitrogen containing heterocycle of R^1, R^2, R^3 and/or R^4 is aromatic and composed of 1 or more 4-, 5- or 6-membered rings.

[0057] In another exemplary embodiment of the disclosure, an aromatic nitrogen-containing heterocycle of R^1, R^2, R^3 and/or R^4 is selected from the group comprising: imidazole, imidazoline, pyrazole, pyrazoline, pyrazine, pyridazine, pyridine, pyrimidine, pyrrole, tetrazole, 1,2,3-triazole, 1,2,4-triazole, triazine, tetrazine, xanthine, oxazole, furazan, oxazine, purine, 2-amino-pyridine, benzimidazole, 2,5-diaminopyridine, 2,4-dimethylimidazole, 2,3-dimethylpyridine, 2,4-dimethylpyridine, 3,5-dimethylpryidine, methoxypyridine, γ-picoline, and 2,4,6-trimethylpyridine, and combinations thereof.

[0058] In a further exemplary embodiment of the disclosure, the R^1, R^2, R^3 and/or R^4 nitrogen containing heterocycle is not aromatic. Non-aromatic nitrogen-containing heterocycles, typically contain a 5- or 6-membered monocyclic substituent, or are bicyclic or tricyclic fused ring systems comprised of 4-, 5- or 6-membered monocyclic rings. In another exemplary embodiment of the disclosure, a nonaromatic nitrogen containing heterocycle of R^1, R^2, R^3 and/or R^4 is composed of 1 or more 4-, 5-, or 6-membered rings.

[0059] In yet another exemplary embodiment of the disclosure, a non-aromatic nitrogen containing heterocycles of R^1, R^2, R^3 and/or

R^4 is selected from the group comprising: azolidine, imidazolidine, pyrazolidine, morpholine, oxazolidine, lactam, maleimide, piperidine, piperazine, pyrrolidine, and succinimide, γ-butyrolactam, ε-caprolactam, *N*-phenyl-β-propiolactam, 1,2-dimethylpiperidine, 2,5-dimethylpiperazine, 1,2-dimethylpyrrolidine, 1-ethylpiperidine, n-methylpyrrolidine, morpholine, piperazine, piperidine, pyrrolidine, 2,2,6,6-tetramethylpiperidine, 2,2,4-trimethylpiperidine, and combinations thereof.

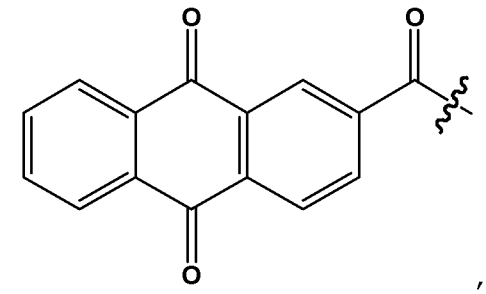
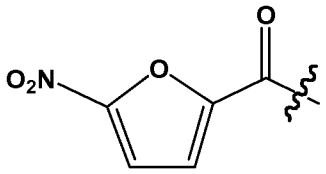
[0060] In another exemplary embodiment of the disclosure, a fused ring system of R^1, R^2, R^3 and/or R^4 is bicylic. In a further exemplary embodiment, a bicyclic ring of R^1, R^2, R^3 and/or R^4 is selected from the list consisting of: one $(C_3$-$C_7)$cycloalkyl and one phenyl ring, one heterocycle and one phenyl ring, and one $(C_3$-$C_7)$cycloalkyl ring and one heterocycle ring.

[0061] In yet a further exemplary embodiment of the disclosure, a bicylic fused ring system of R^1, R^2, R^3 and/or R^4 is selected from the list comprising: indole, quinoline, phthalimide, and 8-methyl-8-aza-bicyclo[3.2.1]octane.

[0062] In a certain exemplary embodiment of the disclosure, a fused ring system of R^1, R^2, R^3 and/or R^4 is tricylic. In a further exemplary embodiment, the tricyclic fused ring system of R^1, R^2, R^3 and/or R^4 is selected from the group consisting of: one phenyl, one heterocyle and one $(C_3$-$C_7)$cycloalkyl ring, one $(C_3$-$C_7)$cycloalkyl and two phenyl rings, one $(C_3$-$C_7)$cycloalkyl and two heterocycle rings, one heterocycle and two phenyl rings, one heterocycle and two $(C_3$-$C_7)$cycloalkyl rings, one phenyl and two $(C_3$-$C_7)$cycloalkyl rings, and one phenyl and two heterocycle rings.

[0063] In an exemplary embodiment of the disclosure, R^1 and/or R^3 are selected from the group consisting of atropine, atropine derivative, scopolamine, or scopolamine derivative.

[0064] In an exemplary embodiment of the disclosure, R^1 is selected from the group consisting of: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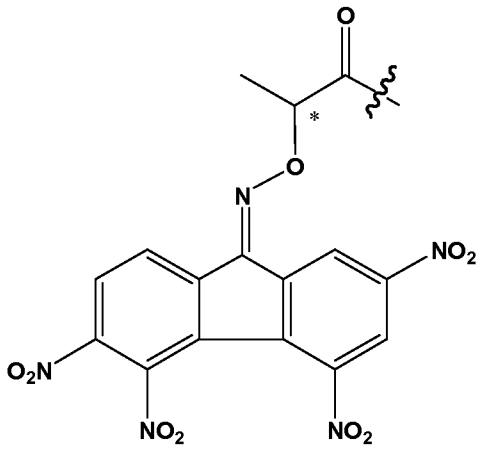


wherein * indicates the (+) chiral center in the original molecule.

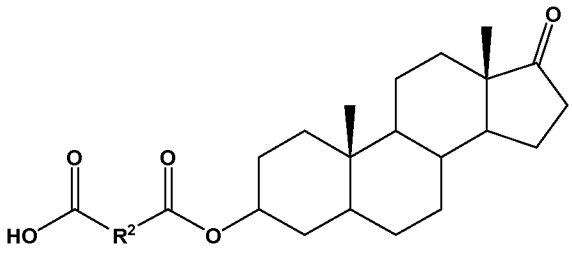
[0065] In a further exemplary embodiment of the disclosure, R^1 and/or R^3 are a camptothecin analog.

[0066] Many camptothecin(CPT)-based analogs are generally available in the art and would be known to one of ordinary skill in the art. These compounds are within the scope of invention and can be used to make CPT linked androsterone and epiandrosterone derivatives by using the methods disclosed herein or obvious variants thereof. Some examples of such CPT analogs include, but are not limited to, (20S)-9-nitro CPT, (20S)-7-chloro-n-propyldimethylsilyl CPT, (20S)-10-hydroxy-7-chloro-n-propyldimethylsilyl CPT, (20S)-10-acetoxy-7-chloro-n-propyldimethylsilyl CPT, (20s)-7-*tert*-butyldimethylsilyl CPT, (20S)-10-hydroxy-7-*tert*-butyldimethylsilyl CPT, (20S)-10-acetoxy-7-*tert*-butyldimethylsilyl CPT, (20S)-9-hydroxy CPT, (20S)-9-amino CPT, (20S)-10-amino CPT, (20S)-9-amino-10-hydroxy CPT, (20S)-9-methylamino CPT, (20S)-9-chloro CPT, (20S)-9-fluoro CPT, (20S)-9-piperidino CPT, (20S)-morpholinomethyl CPT, (20S)-9,10-dichloro CPT, (20S)-10-bromo CPT, (20S)-10-chloro-CPT, (20S)-10-methyl CPT, (20S)-10-fluoro CPT, (20S)-10-nitro CPT, (20S)-10,11-methylenedioxy

CPT, (20S)-10-formyl-CPT, (20S)-10-nonylcarbonyloxy CPT, (20S)-10-undecylcarbonyloxy CPT, (20S)-10-heptadecylcarbonyloxy CPT, (20S)-10-nonadecylcarbonyloxy CPT, (20S)-9-nitro-10,11-methylenedioxy CPT, (20S)-9-(4-methylpiperazinylmethyl)-10-hydroxy CPT, (20S)-9-[4-(1-piperidino)-1-piperidinomethyl]-10-hydroxy CPT, (20S)-9-methyl-10,11-methylenedioxy CPT, (20S)-9-chloro-10,11-methylenedioxy CPT, (20S)-9-cyano-10,11-methylenedioxy CPT, (20S)-9-acetoxy-10,11-methylenedioxy CPT, (20S)-9-acetylamino-10,11-methylenedioxy CPT, (20S)-9-aminomethyl-10-hydroxy CPT, (20S)-9-ethoxymethyl-10-hydroxy CPT, (20S)-methylaminomethyl-10-hydroxy CPT, (20S)-9-ethoxymethyl-10-hydroxy CPT, (20S)-9-methylaminomethyl-10-hydroxy CPT, (20S)-9-n-propylaminomethyl-10-hydroxy CPT, (20S)-9-dimethylaminomethyl-10-hydroxy CPT, (20S)-9-cylohexylaminomethyl-10-hydroxy CPT, (20S)-9-(2-hydroxyethyl)aminomethyl-10-hydroxy CPT, (20S)-9-(trimethylammonio)methyl-10-hydroxy CPT methansulfonate, (20S)-9-morpholinomethyl-10-hydroxy CPT, (20S)-9-cyanomethyl-10-hydroxy CPT, (20S)-CPT-7-aldehyde, (20S)-10-methoxy CPT-7-aldehyde, (20S)-7-acetxoymethyl CPT, (20S)-7-acetoxymethyl-10-methyl CPT, (20S)-7-cyano-10-methoxy CPT, (20S)-7-cyano CPT, (20S)-7-formylethenyl CPT, (20S)-7-ethoxycarbonylethenyl CPT, (20S)-7-cyanoethenyl CPT, (20S)-7-(2,2-dicyanoethenyl) CPT, (20S)-7-(2-cyano-2-ethoxycarbonyl)ethenyl CPT, (20S)-7-ethoxycarbonylethyl CPT, (20S)-7-ethyl CPT, (20S)-7-n-propyl CPT, (20S)-7-acetoxymethyl CPT, (20S)-7-n-propylcarbonyloxymethyl CPT, (20S)-7-ethoxycarbonyl CPT, (20S)-7-ethyl-10-hydroxy CPT, (20S)-7-ethyl-10-acetyloxy CPT, (20S)-7-methyl-10-aminocarbonyloxy CPT, (20S)-7-n-propyl-10-piperidinocarbonyloxy CPT, (20S)-7-ethyl-10-(2-dimethylamino)ethyl CPT; (20S)-7-ethyl-10-carbamoyloxy derivatives of CPT, including, but not limited to, (20S)-7-ethyl-10-[4-(1-piperidino)-piperidino]carbonyloxy CPT, (20S)-7-ethyl-10-(4-*i*-propylaminocarbonylmethylpiperazine)carbonyloxy CPT, (20S)-7-ethyl-10-[4-(1-pyrrolidinyl)piperazine]carbonyloxy CPT, (20S)-7-ethyl-10-[4-(1-dimethylamino)-1-piperidino]carbonyloxy CPT, (20S)-7-ethyl-10-[4-(di-n-propylamino)-1-piperidino]carbonyloxy CPT, (20S)-7-ethyl-10-[4-(di-n-butylamino)-1-piperidino]carbonyloxy CPT, (20S)-7-ethyl-10-[4-(1-pyrrolidino)-1-piperidino)]carbonyloxy CPT, (20S)-

7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy CPT, (20S)-7-ethyl-10-[*N*-methyl-*N*-2(dimethylamino)ethylamino]carbonyloxy CPT, (20S)-7-(*tert*-butyldimethylsilyl) CPT, (20S)-7-(*tert*-butoxyiminomethyl) CPT (Gimatecan®), (20S)-7-butyl-10,11-methylenedioxy CPT, (20S)-7-bromomethyl-10-hydroxy CPT, (20S)-7-butyl-10-amino CPT, (20S)-7-(*tert*-butyldimethylsilyl)-10-hydroxy CPT, (20S)-7-[2-trimethylsilyl)ethyl)] CPT (Karentican®), (20S)-7-[(4-fluorophenoxy)acetyloxymethyl] CPT, (20S)-7-[(4-methoxyphenoxy)acetyloxymethyl] CPT, (20S)-7-[(4-cyano-3-fluorophenoxy)acetyloxymethyl] CPT, (20S)-7-[(3,4,5-trimethoxyphenyl)acetyloxymethyl] CPT, (20S)-10[(4-cyano-3-fluorophenoxy)acetyloxy] CPT, (20S)-10-[(3,4,5-trimethoxyphenyl)acetyloxy] CPT, (20S)-7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy CPT (Exatecan®), (20S)-7-[2-(*N*-isopropylamino)ethyl] CPT (Belotecan®), (20S)-[5(RS)-(2-hydroxyethoxy)] CPT; and any combinations thereof.

[0067] In another exemplary embodiment of the disclosure, a compound of Formula II wherein R^1 is R^3-(C=O)-R^2-(C=O)-; and R^3 is hydroxyl; so that the compound has the general Formula III(b):



III(b)

[0068] In yet another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is selected from the group consisting of -$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-, -$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-, -$(CY_2)_w$-L-$(CY_2)_x$-aryl-, -$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-, and -$(CY_2)_w$-;

R^4 is independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aldehyde, carbonyl, alkoxycarbonyl, carboxyl, heterocycle, fused ring system, amino, imino, imido, azido, azo, alkylamine, arylamine, alkoxy, aryloxy, cyano, cyanato, hydroxyl, nitroso, and nitro;

Y is independently selected from the group consisting of H, D, R^4, OR^4, $N(R^4)_2$, SR^4, cyano, CA_3, CA_2R^4, $CA(R^4)_2$, $C(R^4)_3$, and halogen;

A is independently selected from the group consisting of H, D, and halogen;

L is independently selected from the group consisting of O, N(Y), S, and covalent bond;

w and x are independently selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

including any tautomers, pharmaceutically acceptable salts, and sterioisomers thereof, including mixtures thereof in all possible ratios;

with the following provisos:

if R^2 is $-(CY_2)_w$-L-$(CY_2)_x$-aryl-, wherein aryl is a substituted or unsubstituted phenyl and L is a covalent bond, then w and x cannot be 0;

if R^2 is $-(CY_2)_w$- L-$(CY_2)_x$-aryl, wherein aryl is a substituted phenyl and L is a covalent bond, then w cannot be 2 and x be 0; and

if L is O, then w cannot be 1 and x be 0.

[0069] In a further exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is either $-(CH_2)_w$-L-cyclo$(C_3$-$C_7)$alkyl-, $-(CH_2)_w$-L-heterocycle- where heterocycle is a fused bicyclic, tricyclic or tetracylic heterocycle made of 5- or 6-membered rings, $-(CH_2)_w$-L-aryl-, $-(CH_2)_w$-L-anthraquinone-, or $-(CH_2)_w$-;

L is either an O, N(H), S, or covalent bond; and

w is either an 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[0070] In yet another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is $-(CH_2)_w$-L-aryl- where aryl is substituted with 1 to 5 substituents independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, hydroxyl, $(C_1$-$C_6)$alkoxy, cyano, nitro amino, $(C_1$-$C_6)$alkylamino, halo$(C_1$-$C_6)$alkylamino, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, carbonyl, hydroxycarbonyl, $(C_1$-$C_6)$alkylcarbonyloxy, benzyloxy, a 5 or 6 membered heterocyclic ring, imide ring, $(C_1$-$C_6)$alkoxycarbonyl, and $(C_1$-$C_6)$ alkylcarbonylamino;

L is either an O, N(H), S, or covalent bond; and

w is either 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[0071] In a certain exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is $-(CH_2)_w$-L-aryl- where aryl is substituted with 1 to 5 substituents independently selected from the group consisting of halogen, (C_1-C_6)alkyl, hydroxyl, (C_1-C_6)alkoxy, cyano, nitro amino, (C_1-C_6)alkylamino, halo(C_1-C_6)alkylamino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, carbonyl, hydroxycarbonyl, (C_1-C_6)alkylcarbonyloxy, benzyloxy, a 5 or 6 membered heterocyclic ring, imide ring, (C_1-C_6)alkoxycarbonyl, and (C_1-C_6) alkylcarbonylamino;

L is either an O or S; and

w is either 1, 2, or 3.

[0072] In another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein: R^2 is $-(CH_2)$-O-aryl- where aryl is a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halogen, methyl, methoxy, nitro, trifluoromethyl, and carbonyl.

[0073] In a further exemplary embodiment of the disclosure, a compound of Formula III(b), wherein: R^2 is $-(CH_2)$-O-aryl- where aryl is a phenyl substituted with 1 to 2 halogens.

[0074] In another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein: R^2 is $-(CH_2)$-O-aryl- where aryl is a phenyl substituted with a methyl substituent.

[0075] In yet another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is either $-(CH_2)$-L-cyclo(C_3-C_7)alkyl-, $-(CH_2)$-L-heterocycle- where heterocycle is a fused bicyclic, tricyclic or tetracylic heterocycle made of 5- or 6-membered rings, or $-(CH_2)$-L-anthraquinone-; and

L is either an O, N(Y), S, or covalent bond.

[0076] In a further exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is either $-(CH_2)$-O-cyclo(C_3-C_7)alkyl-, $-(CH_2)$-O-heterocycle- where heterocycle is a fused bicyclic, tricyclic or tetracylic heterocycle made of 5- or 6-membered rings, or $-(CH_2)_w$-O-anthraquinone-; and

w is either an 0, 1, 2, or 3.

[0077] In another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is either $-(CH_2)_w$-cyclo(C_3-C_7)alkyl-, $-(CH_2)_w$-heterocycle- where heterocycle is a fused bicyclic, tricyclic or tetracylic heterocycle made of 5- or 6-membered rings, or $-(CH_2)_w$-anthraquinone-; and

w is either an 0, 1, 2, or 3.

[0078] In yet another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is $-(CH_2)_w$-heterocycle- where heterocycle is a fused bicyclic, tricyclic or tetracylic heterocycle; and

w is either an 0, 1, 2, or 3.

[0079] In a certain exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is $-(CH_2)_w$-quinolin-4-yl- where quinolin-4-yl is optionally substituted; and

w is either an 0, 1, 2, or 3.

[0080] In another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is $-(CH_2)_w$-2-phenylquinolin-4-yl; and

w is either an 0, 1, 2, or 3.

[0081] In yet another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is $-(CH_2)_w$-chromon-2-yl; and

w is either an 0, 1, 2, or 3.

[0082] In a further exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is either $-(CH_2)_w$-cyclo(C_3-C_7)alkyl- or $-(CH_2)_w$-anthraquinone-; and

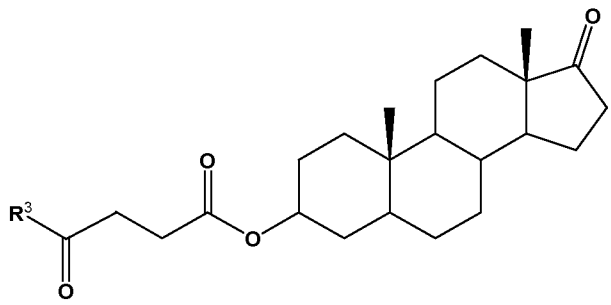
w is either an 0, 1, 2, or 3.

[0083] In another exemplary embodiment of the disclosure, a compound of Formula III(b), wherein:

R^2 is $-(CH_2)_w$-anthraquinon-1-yl-; and

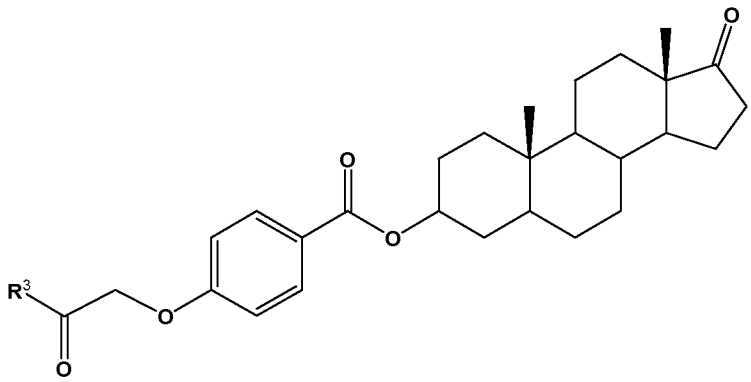
w is either an 0, 1, 2, or 3.

[0084] In another exemplary embodiment of the disclosure, a compound of Formula II, wherein R^1 is R^3-(C=O)-R^2-(C=O)-; R^2 is $-(CY_2)_w$-, Y is H, w is 2; so that the compound has the general Formula III(c):



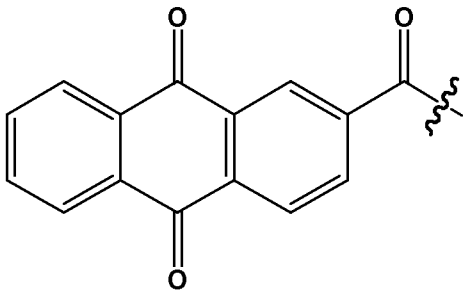
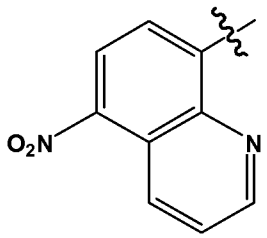
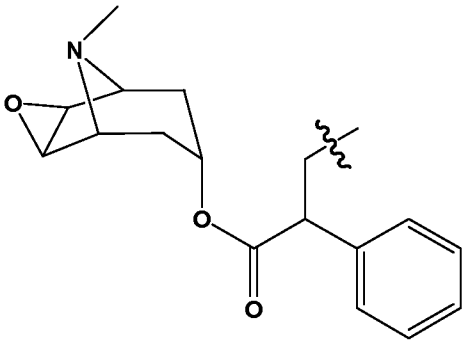
III(c)

[0085] In yet a further exemplary embodiment of the disclosure, a compound of Formula II wherein R^1 is R^3-(C=O)-R^2-(C=O)-; and R^2 is -$(CY_2)_w$-L-$(CY_2)_x$-aryl-; L is O; Y is H; w is 1; X is 0; and aryl is unsubstituted phenyl, so that the compound has the general Formula III(d):

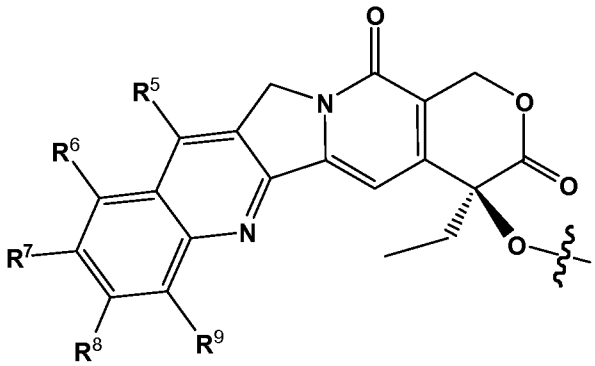


III(d)

[0086] In an exemplary embodiment of the disclosure, R^3 is a residue selected from the group consisting of:


, 
, and 
.

[0087] In an another exemplary embodiment of the disclosure, R^3 has the residue of:



[0088] In another exemplary embodiment of the disclosure, R^5 is either H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, tri(C_1-C_6)alkylsilyl, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonyloxymethyl, substituted vinyl, 1-hydroxy-2-nitroethyl, alkoxycarbonylethyl, aminocarbonyl, mono- or di-alkylcarbonyl, alkylcarbonylmethyl, benzoylmethyl, benzylcarbonyloxymethyl, $-(CH_2)_s-N(R^{12})R^{13}$, mono- or di (C_1-C_6)alkoxymethyl, or R^5 in combination with R^6 forms an amino substituted cyclo(C_1-C_6)alkyl.

[0089] In yet another exemplary embodiment of the disclosure, R^6 is either H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl,

$R^{10}C(=O)O$, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hyroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, -$CH_2NR^{12}R^{13}$, CH_2R^{14}, $NR^{15}R^{16}$, dialkylamino-alkyl, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamino, or R^6 in combination with R^5 forms an amino substituted cyclo(C_1-C_6)alkyl.

[0090] In a further exemplary embodiment of the disclosure, R^7 is either H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, amino(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, carbamoyloxy, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamino, or R^7 in combination with R^8 forms a [1,4]dioxino group.

[0091] In yet a further exemplary embodiment of the disclosure, R^8 is either H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamino, or R^8 in combination with R^7 form a [1,4]dioxino group.

[0092] In another exemplary embodiment of the disclosure, R^9 is either H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, or (C_1-C_6)akylcarbonylamino.

[0093] In yet another exemplary embodiment of the disclosure, R^{10} is R^{11}-O-$(CH_2)_s$-.

[0094] In an exemplary embodiment of the disclosure, R^{11} is either (C_1-C_6)alkyl, phenyl that is optionally substituted with one to five substituents that are either a halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, formyl, (C_1-C_6)alkylcarbonyl, hydroxycarbonyl, (C_1-C_6)alkylcarbonyloxy, benzyloxy, an optionally substituted piperazino, alkoxycarbonyl, and (C_1-C_6)alkylcarbonylamino, (C_3 to C_7)cycloalkyl that is optionally substituted with one to five substituents that are either a halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alky, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)alkylcarbonylamino, a fused 2-, 3-, or 4-ring heterocycle that is optionally substituted with one to five substituents

independently that are either a halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)alkylcarbonylamino, 1- or 2-naphthyl that is optionally substituted with one to four substituents that are either a halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)alkylcarbonylamino, and a 5 or 6 membered heterocycle containing one or two nitrogen atoms that is optionally substituted with one or two substituents that are either a halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, or (C_1-C_6)alkylcarbonylamino.

[0095] In yet another exemplary embodiment of the disclosure, R^{12} is either a H, D, (C_1 to C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino-(C_1-C_6)alkyl, R^{12} in combination with R^{13} forms an amino substituted cyclo(C_1-C_6)alkyl, R^{12} in combination with R^{13} forms an (C_1-C_6)alkyl substituted heterocycle containing 1 nitrogen, or R^{12} in combination with R^{13} forms a (C_1-C_6)alkyl substituted heterocycle containing 2 nitrogens.

[0096] In a further exemplary embodiment of the disclosure, R^{13} is either H, D, (C_1 to C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino-(C_1-C_6)alkyl, R^{13} in combination with R^{12} forms an amino substituted cyclo(C_1-C_6)alkyl, R^{13} in combination with R^{12} forms an (C_1-C_6)alkyl substituted heterocycle containing 1 nitrogen, or R^{13} in combination with R^{12} forms a (C_1-C_6)alkyl substituted heterocycle containing 2 nitrogens.

[0097] In yet a further exemplary embodiment of the disclosure, R^{14} is either (C_1-C_6)alkoxy, cyano, amino(C_1-C_6)alkoxy, mono- or di-(C_1-C_6)alkylamino-(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, amino (C_1-C_6)alklythio, or mono- or di- (C_1-C_6)alkylamino-(C_1-C_6)alkylthio.

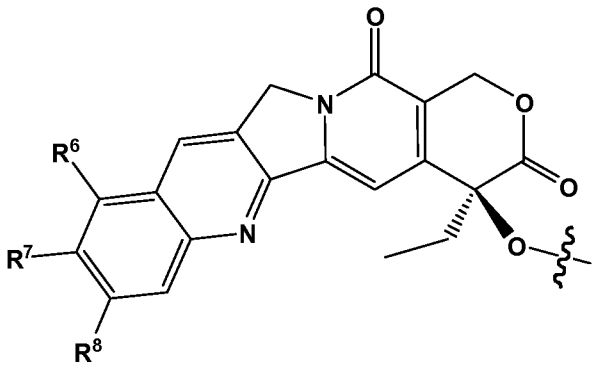
[0098] In another exemplary embodiment of the disclosure, R^{15} is either H, D, (C_1-C_6)alkyl, phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-

C_6)alkyl, or mono- or di- (C_1-C_6)alkyl, or R^{15} in combination with R^{16} forms a heterocycle.

[0099] In yet another exemplary embodiment of the disclosure, R^{16} is either H, D, (C_1-C_6)alkyl, phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or di- (C_1-C_6)alkyl, or R^{16} in combination with R^{15} forms a heterocycle.

[00100] In a further exemplary embodiment of disclosure, s is either 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

[00101] In an another exemplary embodiment of the disclosure, R^3 has the residue of:



wherein

R^6 is either a $CH_2NR^{12}R^{13}$, $NR^{15}R^{16}$, or a dialkylamino-alkyl;

R^7 is either (C_1-C_6)alkoxy, hydroxyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, carbamoyloxy, (C_1-C_6)alkylcarbonyloxy, or R^7 in combination with R^8 forms a [1,4]dioxino group;

R^8 is either H, or R^8 in combination with R^7 forms a [1,4]dioxino group;

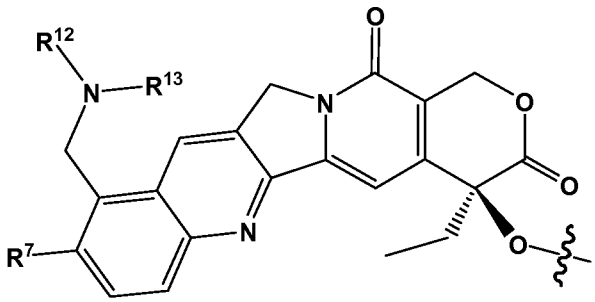
R^{12} is either H, (C_1-C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino-(C_1-C_6)alkyl, or R^{12} in combination with R^{13} forms an amino substituted cyclo(C_1-C_6)alkyl;

R^{13} is either H, (C_1 to C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino-(C_1-C_6)alkyl, or R^{12} in combination with R^{13} forms an amino substituted cyclo(C_1-C_6)alkyl;

R^{15} is either H, (C_1-C_6)alkyl, phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or di-(C_1-C_6)alkyl, or R^{15} in combination with R^{16} forms a heterocycle; and

R^{16} is either H, $(C_1\text{-}C_6)$alkyl, phenyl, hydroxy$(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_6)$alkyl, or mono- or di-$(C_1\text{-}C_6)$alkyl, or R^{16} in combination with R^{15} forms a heterocycle.

[00102] In a further exemplary embodiment of the disclosure, R^3 has the residue of:



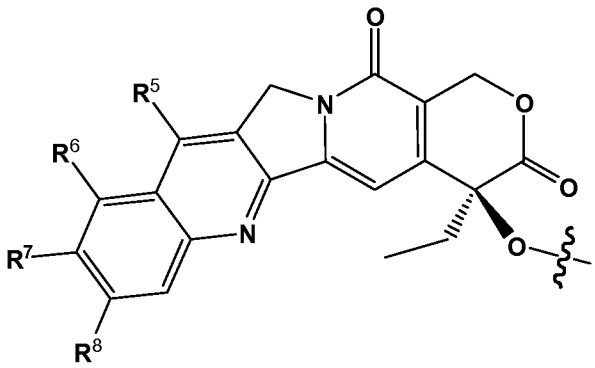
wherein:

R^7 is either a hydroxyl, alkoxy, or alkylcarbonyloxy;

R^{12} is $(C_1\text{-}C_6)$alkyl; and

R^{13} is $(C_1\text{-}C_6)$alkyl.

[00103] In an another exemplary embodiment of the disclosure, R^3 has the residue of:



wherein:

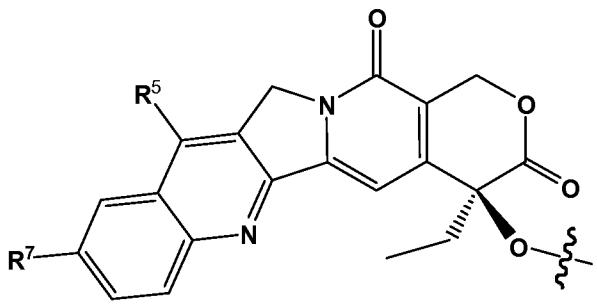
R^5 is either H, $(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkyl;

R^6 is either H or $(C_1\text{-}C_6)$alkyl;

R^7 is either $(C_1\text{-}C_6)$alkoxy, hydroxyl, halo$(C_1\text{-}C_6)$alkoxy, carbamoyloxy, $(C_1\text{-}C_6)$alkylcarbonyloxy, or R^7 in combination with R^8 forms a [1,4]dioxino group;

R^8 is either H, or R^8 in combination with R^7 forms a [1,4]dioxino group.

[00104] In an another exemplary embodiment of the disclosure, R^3 has the residue of:

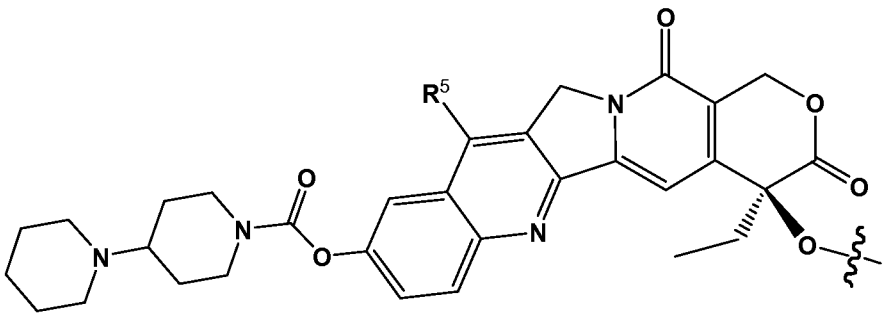


wherein:

R^5 is either H, $(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkyl;

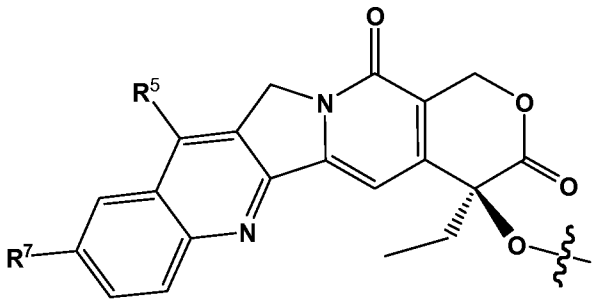
R^7 is a carbamoyloxy.

[00105] In yet another exemplary embodiment of the disclosure, R^3 has the residue of:



wherein: R^5 is a $(C_1\text{-}C_6)$alkyl.

[00106] In an another exemplary embodiment of the disclosure, R^3 has the residue of:

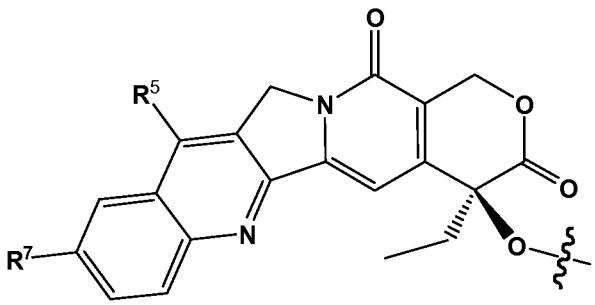


wherein:

R^5 is a $(C_1\text{-}C_6)$alkyl;

R^7 is selected either a hydroxyl, $(C_1\text{-}C_6)$alkoxy, halogenated$(C_1\text{-}C_6)$alkoxy, hydroxycarbonyl, formyl, $(C_1\text{-}C_6)$alkoxycarbonyl, carbamoyloxy, or $(C_1\text{-}C_6)$alkylcarbonyloxy.

[00107] In an another exemplary embodiment of the disclosure, R^3 has the residue of:

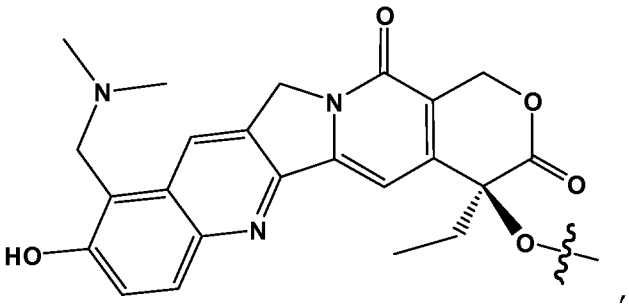


wherein:

R^5 is a tri-(C_1-C_6)alkylsilyl; and

R^7 is either a hydroxyl, (C_1-C_6)alkoxy, halogenated(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, carbamoyloxy, or (C_1-C_6)alkylcarbonyloxy.

[00108] In another exemplary embodiment of the disclosure, R^3 has the residue selected from the group consisting of:



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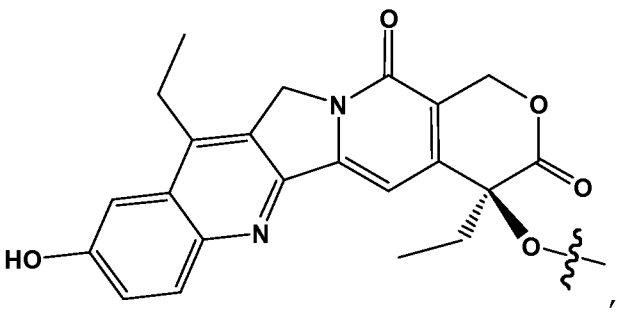

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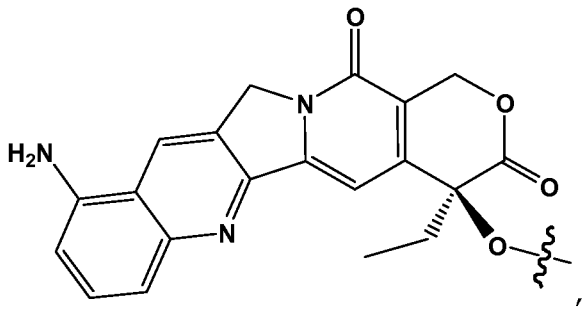

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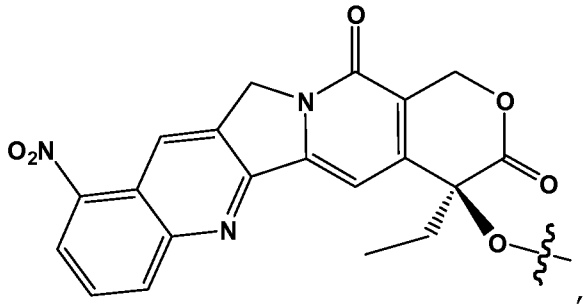

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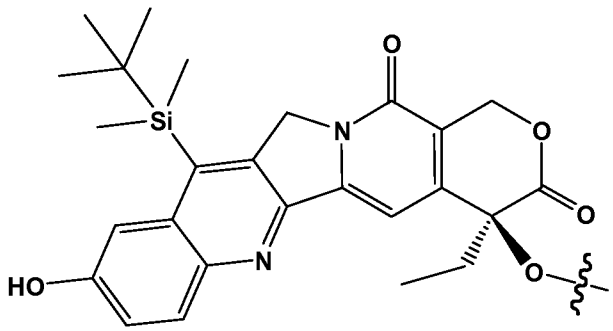
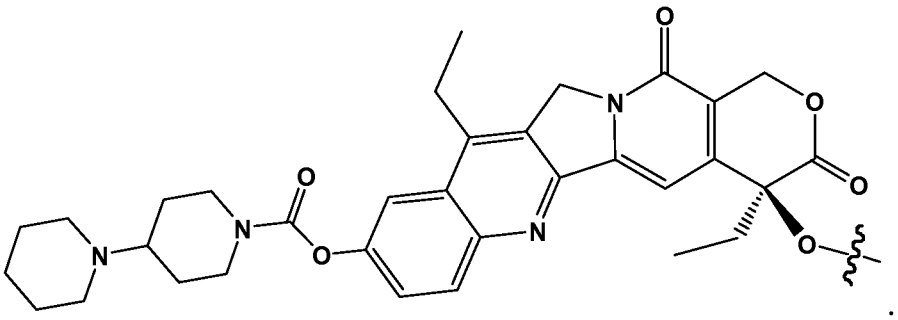


, and



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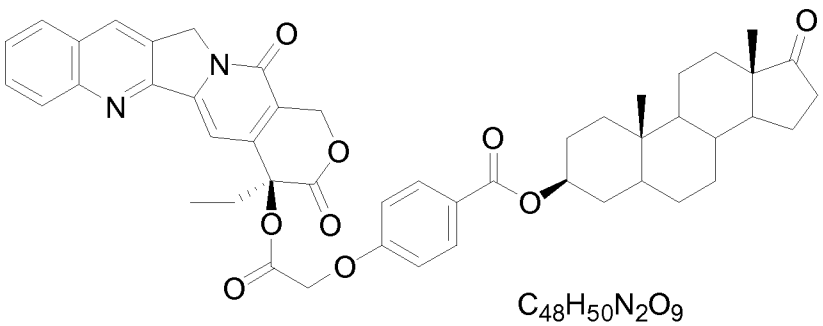
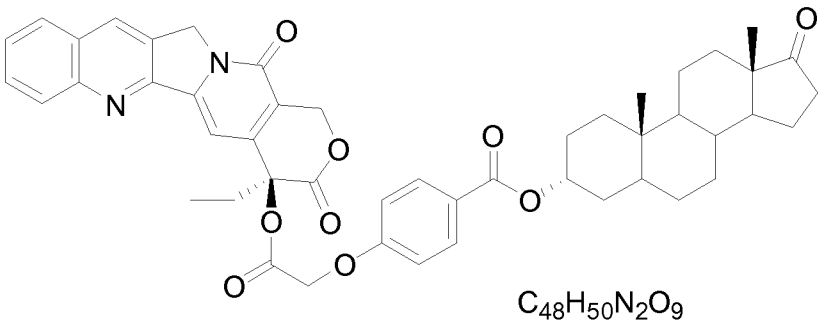
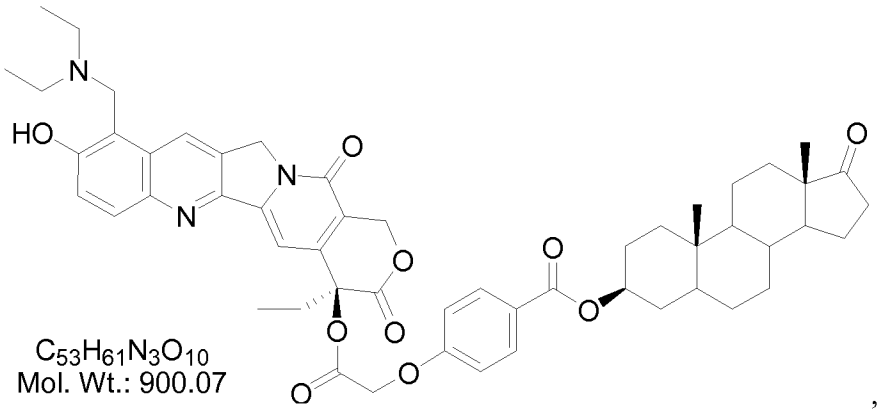
[00109] In yet another exemplary embodiment of the disclosure, the compound of Formula II is selected from the group consisting of:



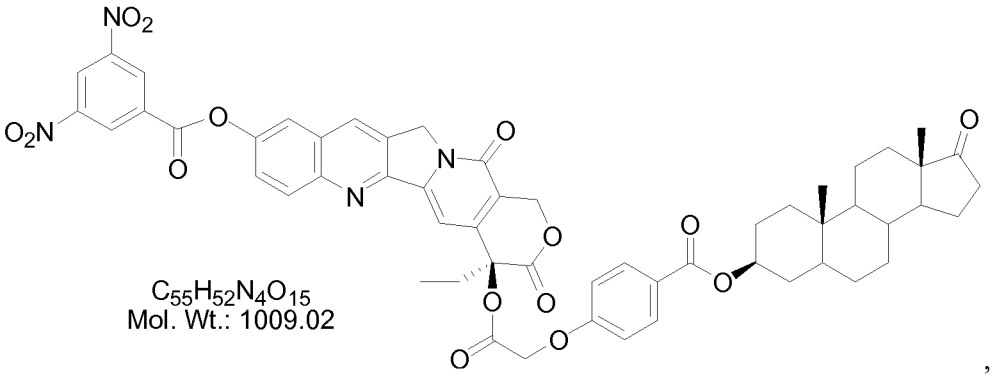
$C_{48}H_{50}N_2O_9$
Mol. Wt.: 798.92
,



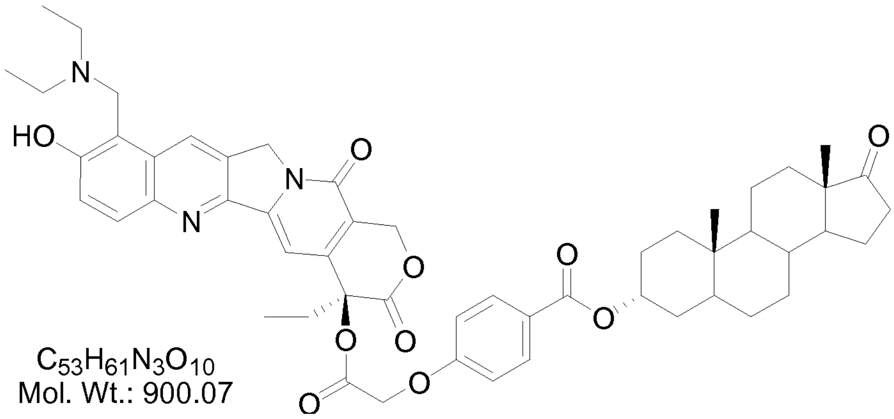
$C_{48}H_{50}N_2O_9$
Mol. Wt.: 798.92
,



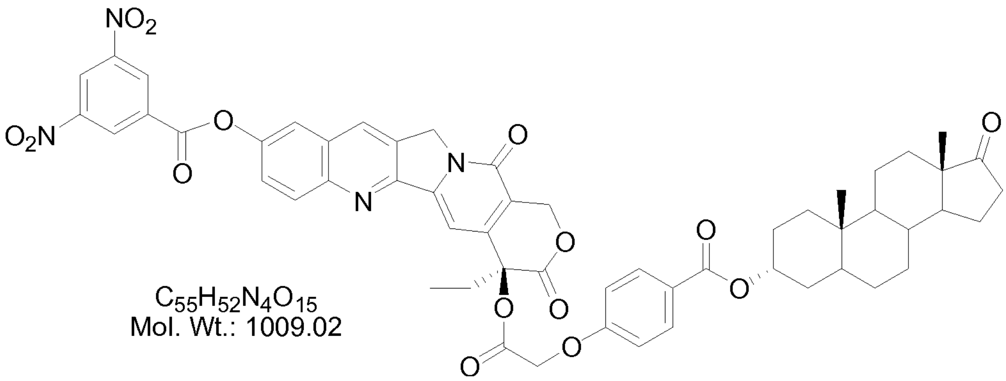
$C_{53}H_{61}N_3O_{10}$
Mol. Wt.: 900.07
,



$C_{55}H_{52}N_4O_{15}$
Mol. Wt.: 1009.02
,



, and



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[00110] In an exemplary embodiment of the disclosure, the methods of the disclosure utilize heterocyclic compounds in the synthesis of the androsterone and/or epiandrosterone derivatives of the disclosure.

[00111] In yet another exemplary embodiment of the disclosure, the methods of the disclosure utilize camptothecin compounds in the synthesis of the androsterone derivatives and/or epiandrosterone derivatives of the disclosure.

[00112] In a further exemplary embodiment of the disclosure is a pharmaceutical composition useful for treating an androgen-associated disorder in a warm-blooded animal, which composition comprises an epiandrosterone and/or androsterone derivative compound of the disclosure in combination with a pharmaceutically-acceptable excipient.

[00113] In an exemplary embodiment of the disclosure, a pharmaceutical composition containing an epiandrosterone and/or androsterone derivative compound of the disclosure and a pharmaceutically-acceptable excipient is in the form of a liposomal composition.

[00114] In yet another exemplary embodiment of the disclosure are methods to use an epiandrosterone and/or androsterone derivative compound described herein in the treatment of disorders, including, but not limited to, androgen-associated disorders, estrogen-associated, androgen-sensitive, and/or estrogen-sensitive disorders.

[00115] In a further exemplary embodiment of the disclosure, an epiandrosterone and/or androsterone derivative compound described herein can be used as a therapy to treat a patient that has cancer.

[00116] In an exemplary embodiment of the disclosure, an epiandrosterone and/or androsterone derivative compound disclosed herein can form a combination therapy with another therapeutic agent.

[00117] In a further exemplary embodiment of the disclosure, therapeutic agents that can be combined with epiandrosterone and/or androsterone derivative compounds of the disclosure include, but are not limited to, LHRH agonists, flutamide, nilutamide, bicalutamide, antiestrogenic agents, tamoxifen, ICT 182780, toremifene, LY 335563, LY 353381, lodoxifene, levormeloxifene, trilostane, inhibitors of testosterone 5-alpha-reductase, aromatase inhibitors, and androgenic compounds.

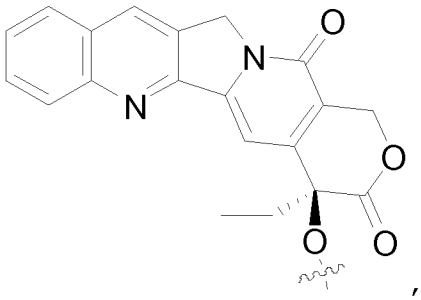
[00118] In another exemplary embodiment of the disclosure, a process for making a compound disclosed herein, by reacting androsterone or epiandrosterone with a reactant that is composed of two portions, a camptothecin or camptothecin analog portion, and a linker portion containing a nonprotected carboxyl group. In yet another embodiment, this reaction is carried out in the presence of a coupling agent and a solvent system. In a further exemplary embodiment, said reaction mixture further comprises a catalyst. In yet a further exemplary embodiment, the catalyst is a nucleophilic catalyst, such as DMAP. In another embodiment, the reaction mixture solvent system contains one or more aprotic solvents, preferably one or more polar aprotic solvents, such as dichloromethane.

[00119] In a further exemplary embodiment of the disclosure, the reaction mixture used to make a compound disclosed herein contains

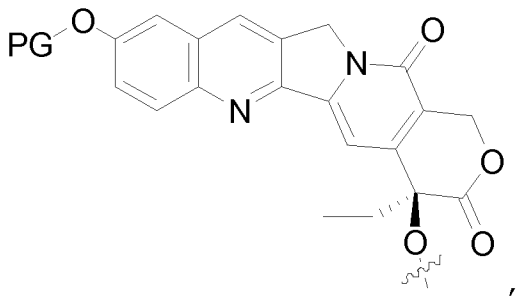
a carboiimide containing coupling agent, including, but not limited to, DCC, DIC and EDCI.

[00120] In another exemplary embodiment of the disclosure, the reactant can contain one or more protected functional groups, including, but not limited to, hydroxyl, carboxyl, and amino.

[00121] In another exemplary embodiment of the disclosure, the camptothecin or camptothecin analog portion of the reactant comprises:



, or



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wherein PG refers to a protecting group, such as BOC.

[00122] In yet a another embodiment of the disclosure, the linker portion of the reactant is either -C(=O)-(C_1-C_6)alkyl-oxy-aryl-C(=O)OH, or -C(=O)-(C_1-C_6)alkyl-C(=O)OH, wherein the "-"(C=O)-(C_1-C_6)alkyl… refers to where the linker portion and camptothecin or camptothecin analog portion are joined.

[00123] Pharmaceutical compositions containing epiandrosterone and/or androsterone derivative compounds are prepared in accordance with known formulation techniques to provide a composition suitable for oral, topical, transdermal, rectal, by inhalation, parenteral (intravenous, intramuscular, or intraperitoneal) administration, and the like. Detailed guidance for preparing compositions of the disclosure are found by reference to the 18.sup.th or 19.sup.th Edition of Remington's Pharmaceutical. Sciences, Published by the Mack Publishing Co., Easton, Pa. 18040.

[00124] Unit doses or multiple dose forms are contemplated, each offering advantages in certain clinical settings. The unit dose would contain a predetermined quantity of active epiandrosterone and/or androsterone derivative compound calculated to produce the desired effect(s) in the setting of treating disorder. The multiple dose form may be particularly useful when multiples of single doses, or fractional doses, are required to achieve the desired

effect. Either of these dosing forms may have specifications that are dictated by or directly dependent upon the unique characteristic of the particular compound, the particular therapeutic effect to be achieved, and any limitations inherent in the art of preparing the particular compound for treatment of a disorder.

[00125] An epiandrosterone and/or androsterone derivative compound may be administered orally in a suitable formulation as an ingestible tablet, including, but not limited to, a buccal tablet, capsule, caplet elixir, suspension, syrup, trouche, wafer, lozenge, and the like. Generally, the most convenient formulation is a tablet or capsule (individually or collectively designated as an "oral dosage unit"). Suitable formulations are prepared in accordance with standard formulating techniques available that match the characteristics of the compound to the excipients available for formulating an appropriate composition.

[00126] The form may deliver a compound rapidly or may be a sustained-release preparation. The epiandrosterone and/or androsterone derivative compound may be enclosed in a hard or soft capsule, may be compressed into tablets, or may be incorporated with beverages, food or otherwise into the diet.

[00127] The suitable formulation of an oral dosage unit may also comprise: a binder, such as gum tragacanth, acacia, com starch, and gelatin; sweetening agents such as lactose or sucrose; disintegrating agents such as com starch, alginic acid and the like; a lubricant such as magnesium stearate; or flavoring such a peppermint, oil of wintergreen or the like. Various other materials may be present as coating or to otherwise modify the physical form of the oral dosage unit. The oral dosage unit may be coated with shellac, a sugar or both. The pharmaceutical composition containing an epiandrosterone and/or androsterone derivative compound disclosed herein may be formulated as a syrup or elixir, and may contain sucrose as a sweetening agent, methyl and propylparabens as a preservative, a dye and a flavoring. Any material utilized should be pharmaceutically-acceptable and substantially non-toxic. Details of the types of excipients useful may be found in the nineteenth edition of "Remington: The Science and Practice of Pharmacy," Mack

Printing Company, Easton. Pa, See particularly chapters 91-93 for a fuller discussion.

[00128] An epiandrosterone and/or androsterone derivative compound disclosed herien, may be administered parenterally, e.g., intravenously, intramuscularly, intravenously, subcutaneously, or interperitonically. The carrier or excipient or excipient mixture can be a solvent or a dispersive medium containing, for example, various polar or non-polar solvents, suitable mixtures thereof, or oils. The use of such substances and the agents for pharmaceutically active substances is well known in the art, except insofar as any conventional media or agent is incompatible with the active ingredient, use in therapeutic compositions is contemplated. Moreover, other or supplementary active ingredients can also be incorporated into the final composition.

[00129] Solutions of the epiandrosterone and/or androsterone derivative compound may be prepared in suitable diluents such as water, ethanol, glycerol, liquid polyethylene glycol(s), various oils, and/or mixtures thereof, and others known to those skilled in the art.

[00130] The pharmaceutical forms suitable for injectable use include, but are not limited to, sterile solutions, dispersions, emulsions, and sterile powders. The final form must, be stable under conditions of manufacture and storage. Furthermore, the final pharmaceutical form must be protected against contamination and must, therefore, be able to inhibit the growth of microorganisms such as bacteria or fungi. A single intravenous or intraperitoneal dose can be administered. Alternatively, a slow long term infusion or multiple short term daily infusions may he utilized, typically lasting from 1 to 8 days. Alternate day or dosing once every several days may also be utilized.

[00131] Sterile, injectable solutions are prepared by incorporating an epiandrosterone and/or androsterone derivative compound in the required amount into one or more appropriate solvents to which other ingredients, listed above or known to those skilled in the art, may be added as required. Sterile injectable solutions are prepared by incorporating the epiandrosterone and/or androsterone derivative compound in the required amount in the

appropriate solvent with various other ingredients as required. Sterilizing procedures, such as filtration, would then follow. Typically, dispersions are made by incorporating the epiandrosterone and/or androsterone derivative compound into a sterile vehicle which also contains the dispersion medium and the required other ingredients as indicated above. In the case of a sterile powder, the preferred methods include vacuum drying or freeze drying to which any required ingredients are added.

[00132] In all cases the final form, as noted, must be sterile and must also be able to pass readily through an injection device such as a hollow needle. The proper viscosity may be achieved and maintained by the proper choice of solvents or excipients. Moreover, the use of molecular or particulate coatings such as lecithin, the proper selection of particle size in dispersions, or the use of materials with surfactant properties may be utilized.

[00133] Prevention or inhibition of growth of microorganisms may be achieved through the addition of one or more antimicrobial agents such as chlorobutanol, ascorbic acid, parabens, thermerosal, or the like. It may also be preferable to include agents that alter the tonicity such as sugars or salts.

[00134] In some cases, e.g., where an epiandrosterone and/or androsterone derivative compound of the disclosure is quite water insoluble, it may be useful to provide liposomal delivery. The system restrains the compound of the disclosure by incorporating, encapsulating, surrounding, or entrapping the compound of the disclosure in, on, or by lipid vesicles or liposomes, or by micelles.

[00135] Epiandrosterone and/or androsterone derivative compounds described herein can be used for the treatment of disorders, including, but not limited to, androgen-associated disorders, estrogen-associated disorders, androgen-sensitive disorders, and estrogen-sensitive disorders.

[00136] Androgen-associated disorders include, but are not limited to, prostate cancer, benign prostatic hyperplasia, acne, seborrhea, hirsutism, androgenic alopecia, precocious puberty, adrenal hyperplasia, and polycystic ovarian syndrome. Estrogen-

associated disorders include, but are not limited to, breast cancer, endometriosis, leiomyoma, and precocious puberty.

[00137] Precocious puberty is usually associated with an excess of androgen secretion, usually of adrenal origin. Current treatments include a blockade of adrenal secretion by glucocorticoids. Another treatment is the use of LHRH agonists to cause medical castration.

[00138] Polycystic ovarian syndrome is associated with an excess of androgen secretion by the ovaries. LHRH agonists are used among other, as treatment to cause medical castration.

[00139] Androgenic and estrogenic activity may be suppressed by administering androgen receptor antagonists ("antiandrogens") or estrogen receptor antagonists ("antiestrogens"), respectively. See e.g. WO 94/26767 and WO 96/26201. Androgenic and estrogenic activity may also he reduced by inhibiting receptor activation using receptor antagonists, suppressing androgen or estrogen biosynthesis using inhibitors of engines that catalyze one or more steps of such biosynthesis or by-suppressing ovarian or testicular secretions by known methods.

[00140] Both androgen-sensitive and estrogen-sensitive disorders may be treated with an epiandrosterone and/or androsterone derivative compound of the disclosure. Androgen-sensitive disorders are those whose onset or progress is aided by androgen activation of androgen receptors, and should, therefore, respond favorably to treatment with an epiandrosterone and/or androsterone derivative compound of the disclosure. In would be expected that an epiandrosterone and/or androsterone derivative compound of the disclosure would suppress androgen biosynthesis. Estrogen-sensitive disorders are those disorders whose onset or progress is aided by activation of the estrogen receptor. In would be expected that an epiandrosterone and/or androsterone derivative compound of the disclosure would reduce estrogen biosynthesis by suppressing the formation of the androgen precursors required for estrogen biosynthesis. Androgen-sensitive disorders include, but are not limited to, prostatic cancer, benign prostatic hyperplasia, acne, seborrhea, hirsutism, androgenic alopecia and polycystic ovarian syndrome. Estrogen-sensitive disorders include, but are not limited

to, breast cancer, endometrial cancer, endometriosis, and endometrial leiomyoma.

[00141] Epiandrosterone and/or androsterone derivative compounds disclosed herein can inhibit estrogen activity while maintaining or increasing androgen activity. Conditions, such as breast cancer, ovarian cancer, uterine cancer, endometrial cancer and other estrogen-sensitive disorders, benefit by inhibiting estrogen related activity while maintaining or increasing androgen activity. Epiandrosterone and/or androsterone derivative compounds disclosed herein, therefore, can be effective treatments for disorders which respond negatively to estrogen and positively to androgen.

[00142] Androgen-camptothecin combination compounds disclosed herein can be effective anti-neoplastic agents. Camptothecin inhibits topoisomerase, an enzyme that is required for unwiding and relaxing DNA during molecular events, such as replication and transcription. Epiandrosterone and/or androsterone derivative compounds of the disclosure that contain a camptothecin or camptothecin component, would have an additive anti-neoplastic effect. Furthermore, an androsterone and/or epiandrosterone derivative of the disclosure can be utilized as part of a combination therapy with other anticancer therapeutics to provide greater and possibly better treatment options for patients with cancer. For example, a combination therapy can include an androsterone and/or epiandrosterone derivative of the disclosure with an anti-cancer agent selected from the group including, but not limited to, alkylating agents, anti-metabolite agents, mitotic inhibitors, tyrosine kinase inhibitors, topoisomerase inhibitors, cancer immunotherapy monoclonal antibodies, and anti-tumor antibiotic agents.

[00143] Epiandrosterone and/or androsterone derivative compounds of the disclosure can be utilized as part of a combination therapy with other strategies, which modulate androgen- or estrogen-associated disorders through other mechanisms, thus providing for synergistic combinations.

[00144] An androsterone and/or epiandrosterone derivatives of the disclosure can be utilized as part of a combination therapy with other strategies, which modulate androgen- or estrogen-

associated disorders and disorders through other mechanisms, thus providing synergistic combinations. For example, a combination therapy can include an androsterone and/or epiandrosterone derivative of the disclosure with an agent selected from the group including, but not limited to, LHRH agonists (see, e.g., U.S. Pat. No. 4,659,695 and 4,666,883); flutamide(*N*-[4-nitro-3-(trifluoromethyl)phenyl)3-2-methyl propanamide), nilutamide , or bicalutamide; antiestrogenic (e.g., EM-800 reported in PCT/CA96/00097; tamoxifen ((Z)-2-[4-(1,2-diphenyl-1-butenyl)}-*N*,*N*-dimethylethanamine) and ICT 182780 (available from AstraZeneca, UK), toremifene (available from Orion-Farmos Pharmaceutical, Finland), raloxifene (Pfizer Inc., USA), raloxifene (Eli Lilly and Co., USA), LY 335563 and LY 353381 (Eli Lilly and Co., USA), lodoxifene, (SmithKline Beecham, USA), levormeloxifene (Novo Nordisk- A/S, Denmark); trilostane (2α-cyano-4α,5α-epoxy-17β-hydroxyandrostan-3-one); inhibitors of testosterone 5-alpha-reductase (e.g., PROSCAR); an aromatase inhibitor (e.g., ARlMIDEX); and androgenic compounds (e.g., medroxyprogesterone acetate, and megestrol acetate).

[00145] In general, for both androgen-associated disorders and estrogen-associated disorders, simultaneous treatment with inhibitors of sex steroid biosynthesis (inhibitors of enzymes which catalyze one or more steps of estrogen or androgen biosynthesis) with estrogen receptor antagonists and/or androgen receptor antagonists, are believed to have additive, rather than redundant effects, because the mechanism of action for each drug is different.

[00146] Different sex steroid-dependent disorders respond differently to both androgen receptor activation and estrogen receptor activation. For example, breast cancer responds unfavorably to estrogen receptor activation, but favorably to androgen receptor activation. On the other hand, benign prostatic hyperplasia responds unfavorably to activation of either the estrogen or androgen receptor.

[00147] When an epiandrosterone and/or androsterone derivative compound of the disclosure is used, either alone or as part of one of the combination therapies described herein, the attending

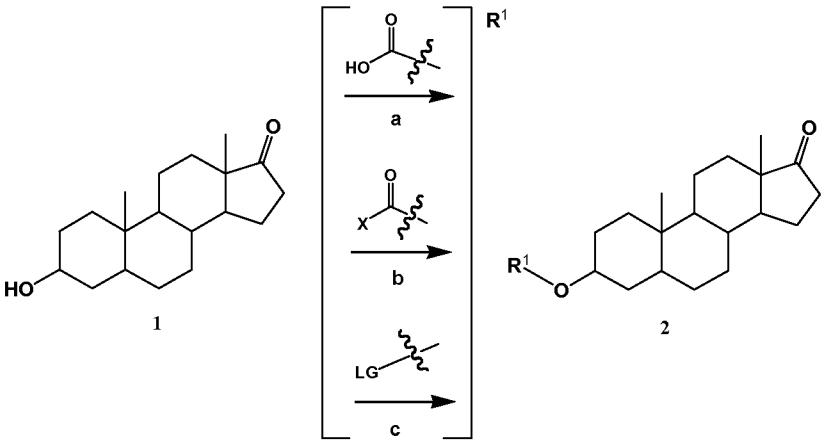
clinician will typically target the subject's serum concentration between 0.5 ng/rnl and 100 ng/ml, more typically between 1 ng/ml and 20 ng/ml, and more commonly between 1 ng/ml and 10 ng/ml. Serum concentration may be measured by various techniques known in the art (e.g.. LC/MS). When administered orally, the dosage which is usually effective to provide the desired serum levels is between 1.0.mg and 1.000 mg of active ingredient per day per 50 kg of body weight, typically between 10 mg and 500 mg and more commonly between 10 mg and 100 mg. However, dosage will vary with the bioavailability of the chosen inhibitor and with individual subject's response. The attending clinician will typically monitor aa individual subject's response and metabolism and adjust the subject's dosage accordingly. When administered by injection, a lower dosage is typically used, e.g. 10 mg to 100 mg per day per 50 kg of body weight.

[00148] All of the active ingredients (including an epiandrosterone and/or androsterone derivative compound of the disclosure) can be used in any of the therapies discussed herein, and may be formulated in pharmaceutical compositions which may include one or more additional active ingredients as discussed above. Alternatively, they may each be administered individually separately or simultaneously. In some embodiments of the disclosure, one or more active ingredients are formulated in a single pharmaceutical composition.

[00149] The compounds disclosed herein can be prepared by methods known to one of the skill in the art, and/or following procedures similar to those described in the Examples section herein and obvious modifications thereof. Compounds as disclosed herein can also be prepared as shown in any of the following schemes and obvious modifications thereof.

[00150] The following schemes can be used to practice embodiments of the disclosure.

Scheme I



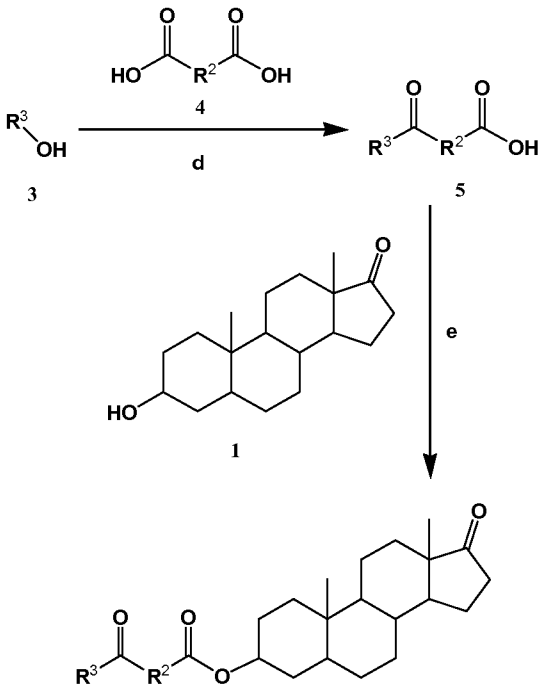
[00151] Reactions **a**, **b** and **c** are provided as representative methods to make androsterone or epiandrosterone derivative compounds of the disclosure and should not be interpreted as the definitive methods to make the androsterone or epiandrosterone derivative compounds as disclosed herein. It can be expected that there may additional steps for protecting and deprotecting functional groups that may be involved in competing reactions.

Reaction **a**: compound **1** can coupled to a R^1 compound containing a carboxylic acid group in presence of an appropriate coupling reagent, such as *N,N'*-dicyclohexylcarbodiimide (DCC), in an appropriate solvent, such as dichloromethane, to afford compound **2**. The rate of reaction **a** can be increased by adding an appropriate catalyst, such as 4-dimethylaminopyridine(DMAP).

Reaction **b**: compound **1** can be coupled to a R^1 compound containing an activated carboxylic acid derivative group, such as an acyl halide, in the presence of an appropriate base, such as triethylamine, in an appropriate solvent, such as dichloromethane, to give compound **2**.

Reaction **c**: compound **1** can be linked to a R^1 compound containing an appropriate leaving group (LG) through a SN^2 mechanism, in the presence of an appropriate base, such as triethylamine, in an appropriate solvent, such as dichloromethane, to afford compound **2**.

Scheme II



[00152] Reactions **d** and **e** are provided as representative methods to make androsterone or epiandrosterone derivative compounds of the disclosure and should not be interpreted as the definitive methods to make the androsterone or epiandrosterone derivative compounds as disclosed herein. It can be expected that there may additional steps for protecting and deprotecting functional groups that may be involved in competing reactions.

Reaction **d**: compound **3** can coupled to compound **4** in presence of an appropriate coupling reagent, such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) (EDCI), in an appropriate solvent, such as dichloromethane, to afford compound **5**. The rate of reaction **d** can be increased by adding an appropriate catalyst, such as 4-dimethylaminopyridine(DMAP).

Reaction **e**: compound **5** can be coupled to compound **1** in presence of an appropriate coupling reagent, such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) (EDCI), in an appropriate solvent, such as dichloromethane, to afford compound **6**. The rate of reaction **e** can be increased by adding an appropriate catalyst, such as 4-dimethylaminopyridine(DMAP).

[00153] The working examples below are provided to illustrate, not limit the disclosure. Various parameters of the scientific

methods employed in these Examples are described in detail below and provide guidance for practicing the disclosure in general.

EXAMPLES

[00154] The following examples are given to provide representative compounds included as part of this disclosure. The examples also provide descriptions of *in vitro* and *in vivo* assays to aid in determining the utility of the compounds. Throughout the examples chemical formulas will be used to name compounds as appropriate.

[00155] 1. (3β, 5a)-3-Hydroxyandrotan-17-one-9,10-dihydro-9-10-dioxo-2-anthracenecarboxylate (990624). A mixture of epiandrosterone (1.30 mg, 0.45 mmol), anthraquinone-2-carbonyl chloride (135 mg, 0.5 mmol), triethylamine (100 mg, 1.0 mmol) and dichloromethane (6.0 mL) was stirred at ambient temperature for 20 h. The mixture was then diluted by adding dichloromethane (20 mL). The dichloromethane containing organic layer was sequentially washed with water (20 mL), a saturated $NaHCO_3$ solution (15 mL), and brine (20 mL). After drying over $MgSO_4$, the solvent was removed *in vacuo*. The resulting solid was recrystallized from ethyl alcohol and ethyl acetate to give (3β, 5α)-3-hydroxyandrostan-17-one-9,10-dihydro-9,10-dioxo-2-anthracenecarboxylate (46 mg). ^{1}HNMR ($CDCl_3$, 600 MHz); δ 8.93 (s, 1H, Ar-H), 8.39-8.43 (m, 4H, Ar-H), 7.84 (s, 2H, Ar-H), 5.05 (s, 1H, H-3) 2.45 (t, 1H, H-16), 2.20-0.70 (m, 21H), 0.94 (s, 3H, CH3-19), 0.88 (s, 3H, CH_3).

[00156] 2. (3β,5α)-3-Hydroxyandrostan-17-one-5-nitro-2-furoate (991027). A mixture of 5-nitro-2-furoic acid (157 mg, 1.0 mmol), epiandrosterone (163 mg , 0.60 mmol), EDCI (200 mg, 1.05 mmol), DMAP (20 mg 0.2 mmol) and THF (4 mL) was stirred at ambient temperature for 6.5 h. After removing the solvent *in vacuo*, the resulting residue was dissolved in dichloromethane (20 mL). The dichloromethane containing organic layer was washed sequentially with water, a 5% Na_2CO_3 solution, and brine (20 mL). After drying over $MgSO_4$, the solvent was removed *in vacuo*. The resulting solid was recrystallized from ethanol to give (3β,5α)-3-hydroxyandrostan-17-one-5-nitro-2-furoate (180 mg; yield = 73.2 %). ^{1}HNMR ($CDCl_3$, 600 MHz): δ 7.35 (s, 1H, Ar-H), 7.28(s, 1H Ar-H), 4.99 (s, 1H, H-3),

2.45 (t, 1H, H-16), 2.20-0.70 (m, 21H), 0.90 (s, 3H, CH_3-19), 0.87 (s, 3H, CH_3).

[00157] 3. (3β,5α)-3-Hydroxyandrostan-17-one(+)-2-(2,4,5,6-tetranitro-9-flourenylidene-aminooxy)proprionate (991022). A mixture of (+)-2-(2,4,5,6-tetranitro-9-flourenylidene-aminooxy)-proprionic acid (224 mg, 0.5 mmol), epiandrosterone (122 mg, 0.45 mmol), DCC (123 mg, 0.6 mmol), DMAP (10 mg, 0.1 mmol) and THF (6 mL) was stirred at ambient temperature for 6 h. After adding 4 drops of water to the mixture, the mixture was stirred for 10 min at ambient temperature. The resulting solids were collected by filtration, washed with THF, and then the THF was removed *in vacuo*. The resulting residue was dissolved in dichloromethane (20 ml). The dichloromethane containing organic layer was then then washed sequentially with H_2O, a 5% Na_2CO_3, H_2O, and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. The resulting solid was recrystallized from ethyl acetate and petroleum ether to give(3β,5α)-3-hydroxyandrostan-17-one(+)-2-(2,4,5,6-tetranitro-9-flourenylidene-aminooxy)-proprionate (149 mg; yield = 47.3 %). ^{1}HNMR ($CDCl_3$, 600 MHz): δ 9.59 (s, 1H, Ar-H), 8.97 (d, 2H, Ar-H), 8.90 (s, 1H, Ar-H), 5.22 (q, 1H, CHCO), 4.88 (m, 1H, CHO), 2.45 (t, 1H, H-16), 2.20-0.70 (m, 21H), 1.83 (d, 3H, CH_3), 0.88 (s, 3H, CH_3-19), 0.86 (s, 3H, CH_3).

[00158] 4. 1-(3β,5α)-3-Hydroxyandrostan-17-one)-4-(2-(hydroxymethyl)anthraquinone)-succinate (991120). A mixture of (3β,5α)-3-hydroxyandrostan-17-one monosuccinate (25 mg, 0.064 mmol), 2-(hydroxymethyl)anthraquinone (16 mg, 0.067 mmol), EDCI (20 mg, 0.11 mmol), DMAP (2 mg, 0.02 mmol) and dichloromethane (4 mL) was stirred at ambient temperature for 6 h. The mixture was then diluted by adding dichloromethane (20 mL). The dichloromethane organic layer was washed sequentially with H_2O, a 5% Na_2CO_3 solution, H_2O, and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo* to give 1-(3β,5α)-3-hydroxyandrostan-17-one)-4-(2-(hydroxymethyl)anthraquinone)-succinate (37 mg) as a yellow solid. ^{1}HNMR ($CDCl_3$, 600 MHz): δ 8.30 (m, 4H, Ar-H), 7.80 (m, 3H, Ar-H), 5.30 (s, 2H, $ArCH_2O$), 4.69 (m, 1H, CHO), 2.74 (t, 2H, CH_2), 2.64 (t, 2H, CH_2), 2.41 (m, 1H, H-16), 2.20-0.67 (m, 21H), 1.83 (d, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.80 (s, 3H, CH_3).

[00159] 5. 1-(3β,5α)-3-Hydroxyandrostan-17-one)-4-(8-hydroxy-5-nitroquinoline)succinate (991123). A mixture of (3β,5α)-3-hydroxyandrostan-17-one monosuccinate (25 mg, 0.064 mmol), 8-hydroxy-5-nitroquinoline (13 mg, 0.070 mmol), EDCI (20 mg, 0.11 mmol), DMAP (2 mg, 0.02 mmol) and dichloromethane (4 mL) was stirred at ambient temperature for 6 h. The mixture was then diluted by adding dichloromethane (20 mL). The dichloromethane containing layer was washed sequentially with H_2O, a 5% Na_2CO_3 solution, H_2O, and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo* to give a crude residue that was then purified by column chromatography to give 1-(3β,5α)-3-hydroxyandrostan-17-one)-4-(8-hydroxy-5-nitroquinoline)succinate (24 mg) as a yellow solid. ^{1}HNMR ($CDCl_3$, 600 MHz): δ 9.09 (d, 1H, Ar-H), 9.01 (d, 1H, Ar-H), 845 (d, 1H, Ar-H), 7.68 (q, 1H, Ar-H), 7.57 (d, 1H, AR-H), 4.76 (m, 1H, CHO), 3.16 (1, 2H, CH_2), 2.81 (t, 2H, CH_2), 2.43 (m, 1H, H-16), 2.20-0.72 (m, 21H), 1.83 (d, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.88 (s, 3H, CH_3).

[00160] 6. 1-(3β,5α)-3-Hydroxyandrostan-17-one)-4-[(-)-scopolamine]succinate (991228). A mixture of (3β,5α)-3-hydroxyandrostan-17-one monosuccinate (39 mg, 0.10 mmol), (-)-scopolamine (30 mg, 0.10 mmol), EDCI (30 mg, 0.25 mmol), DMAP (3 mg, 0.028 mmol) and dichloromethane (4 mL) was stirred at ambient temperature for 20 h. The mixture was then diluted by adding dichloromethane (20 mL). The dichloromethane containing layer was washed sequentially with H_2O, a 5% Na_2CO_3 solution, H_2O, and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo* to give a crude residue that was then purified by column chromatography to give 1-(3β,5α)-3-Hydroxyandrostan-17-one)-4-[(-)-scopolamine]succinate. ^{1}HNMR ($CDCl_3$, 600 MHz): δ 6.81 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H), 6.39 (s, 2H, Ar-H), 5.98 (d, 2H, Ar-H), 5.92 (d, 1H, Ar-H), 4.72 (m, 1H, OCH), 4.61 (d, 1H), 4.40 (t, 1H), 4.19 (t, 1H), 3.82 (s, 3H, OCH_3), 3.76 (s, 6H, OCH_3), 3.00-0.60 (m, H).

[00161] The compounds of Examples 7-11 are prepared by coupling camptothecin to a linker (**intermediate 1**) and then coupling **intermediate 1** with androsterone or epiandrosterone.

[00162] Camptothecin-20*S*-O-ester of 4-carboxyphenoxyacetate (intermediate 1). A mixture of camptothecin (100 mg, 0.287 mmol), 4-carboxyphenoxyacetic acid (112 mg, 0.57 mmol), EDCI (82 mg, 0.43 mmol), DMAP (10 mg, 0.1 mmol), *N*,*N*'-dimethylformamide (4 mL), and dichloromethane (4 mL) was stirred at ambient temperature for 48 h. The mixture was diluted by adding dichloromethane (50 mL). The dichloromethane containing layer was washed sequentially with H_2O (20 mL), a saturated $NaHCO_3$ aqueous solution (20 mL), and brine (20 mL). After drying over $MgSO_4$, the solvent was removed *in vacuo* to give a crude residue that was then purified by column chromatography (eluent: $CHCl_3$/ ethanol (5:1))to give camptothecin-20*S*-O-4-**c**arboxyphenoxyacetate (80 mg; yield = 67%). ^{1}HNMR ($CDCl_3$, 600MHz); δ 8.40 (s, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 8.07 (m, 2H, Ar-H), 7.95 (cl 1H, Ar-H), 7.86 (t, 1H, Ar-H), 7.67 (t, 1H, Ar-H), 7.25 (s, 1H, Ar-H), 6.96 (m, 2H, Ar-H), 5.68 (d, 1H, Hl7), 5.43 (d, 1H, H17), 5.29 s, 2H, H5), 4.91 (q, 2H, OCH_2CO), 2.25 (dm, 2H, CH_2), 0.97 (t, 3H CH_3).

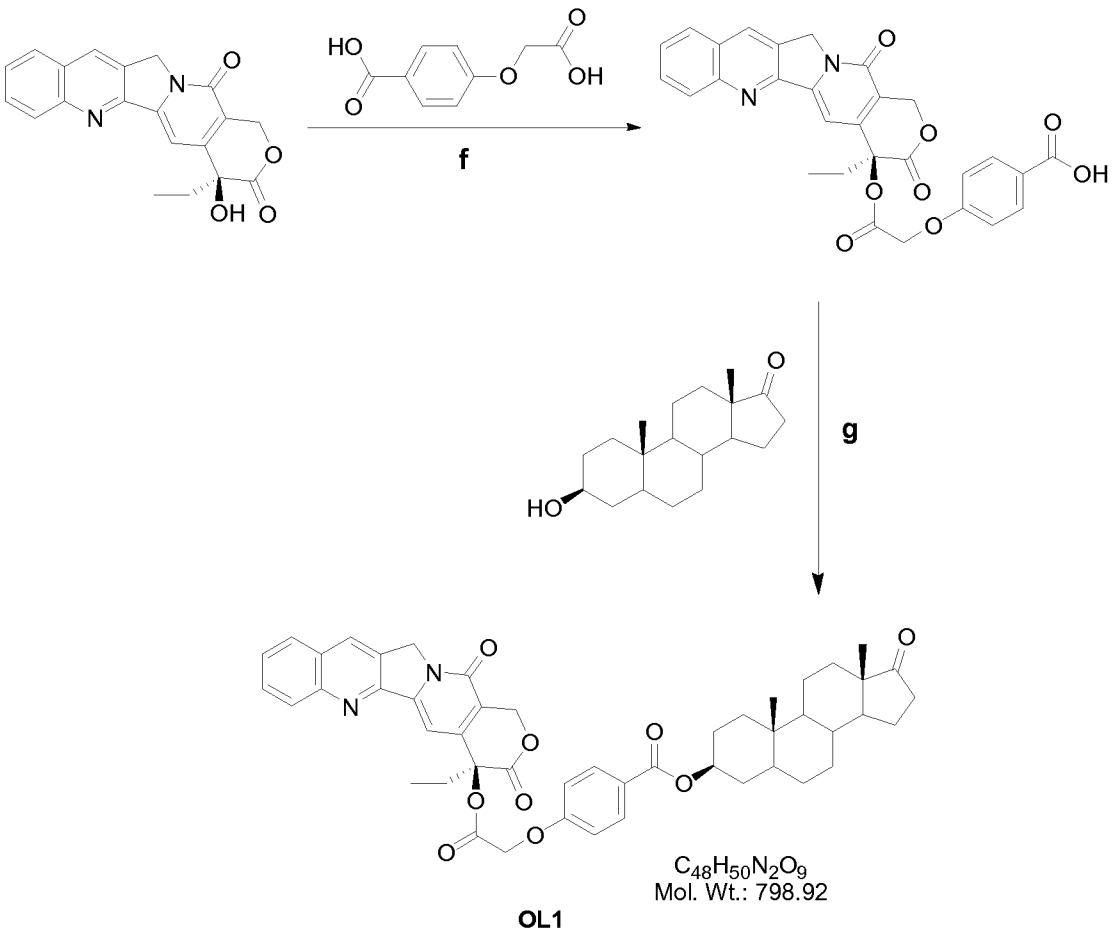
[00163] 7. Camptothecin-20*S*-O-(4-carboxyphenoxyacetate) linked with epiandrosterone (0103021). A mixture of intermediate 1 (10 mg, 0.019 mmol), epiandrosterone (11 mg, 0.038 mmol), EDCI (25 mg, 0.13 mmol), DMAP (2 mg, 0.02 mmol), and dichloromethane (3 mL) was stirred at ambient temperature for 24 h. The mixture was then diluted by adding dichloromethane (20 mL). The dichloromethane containing layer was washed sequentially with H_2O (20 mL), a saturated $NaHCO_3$ aqueous solution (10 mL), and brine (20 mL). After drying over $MgSO_4$, the solvent was removed *in vacuo* to give a crude residue that was then purified by column chromatography (eluent: ethyl acetate/ethanol (9:1))to give the title product (2.0 mg). ^{1}HNMR ($CDCl_3$, 600 MHz): δ 8.41 (s, 1H, Ar-H), 8.27 (d, 1H, Ar-H), 7.98 (m, 2H, Ar-H), 7.86 (t, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.24 (s, 1H, Ar-H), 7.21 (s, 1H, Ar-H), 6.95 (d, 1H, Ar-H), 5.68 (d, lH, CPT-Hl7), 5.42 (d, 1H, CPT-H17), 5.29 (s, 2H, CPT-H5), 4.89 (q, 2H, OCH_2CO), 4.23 (m, 1H, epiandrosterone-H3), 2.60-1.OO (m, 3OH, CPT-Hl8 and epiandrosterone-H).

[00164] 8. Camptothecin-20*S*-O-(4-carboxyphenoxyacetate) linked with androsterone (010216). A mixture of intermediate 1 (10 mg,

0.019 mmol), androsterone (11 mg, 0.038 mmol), EDCI (25 mg, 0.13 mmol), DMAP (2 mg, 0.02 mmol)was stirred at ambient temperature for about 24 h. The mixture was then diluted by adding dichloromethane (20 mL). The dichloromethane containing layer was washed sequentially with H_2O (20 mL), a saturated $NaHCO_3$ aqueous solution (10 mL), and brine (20 mL). After drying over $MgSO_4$, the solvent was removed *in vacuo* to give a crude residue that was then purified by column chromatography (eluent: ethyl acetate/ethanol (9:1)) to give the title product as a solid (4.3 mg). ^{1}HNMR ($CDCl_3$, 600MHz): δ 8.41 (s, 1H, Ar-H), 8.28 (d, 1H, Ar-H), 7.99 (m, 3H, Ar-H), 7.87 (t, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 7.21 (s, 1H, Ar-H), 6.96 (d, 2H, Ar-H), 5.71 (d, 1H, CPT-H17), 5.43 (d, 1H, CPT-H17), 5.29 (S, 2H, CPT-H5), 4.90 (q, 2H, OCH_2CO), 4.13 (m, 1H, androsterone-H3), 3.00-2.00 (m, 21H, CPT-Hl8 and androsterone-H), 1.28 (s, 6H, CH_3), 0.97 (t, 3H, CPT-Hl9).

[00165] Scheme III is illustrative of the synthesis route to make 4-(4-Ethyl-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-4-yloxycarbonylmethoxy)-benzoic acid 10,13-dimethyl-17-oxo-hexadecahydro-cyclopenta[*a*]phenanthren-3-yl ester (OL-1).

Scheme III



OL1

[00166] 9. 4-(4-Ethyl-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-4-yloxycarbonylmethoxy)-benzoic acid-10,13-dimethyl-17-oxo-hexadecahydro-cyclopenta[*a*]phenanthren-3-yl ester (OL1).

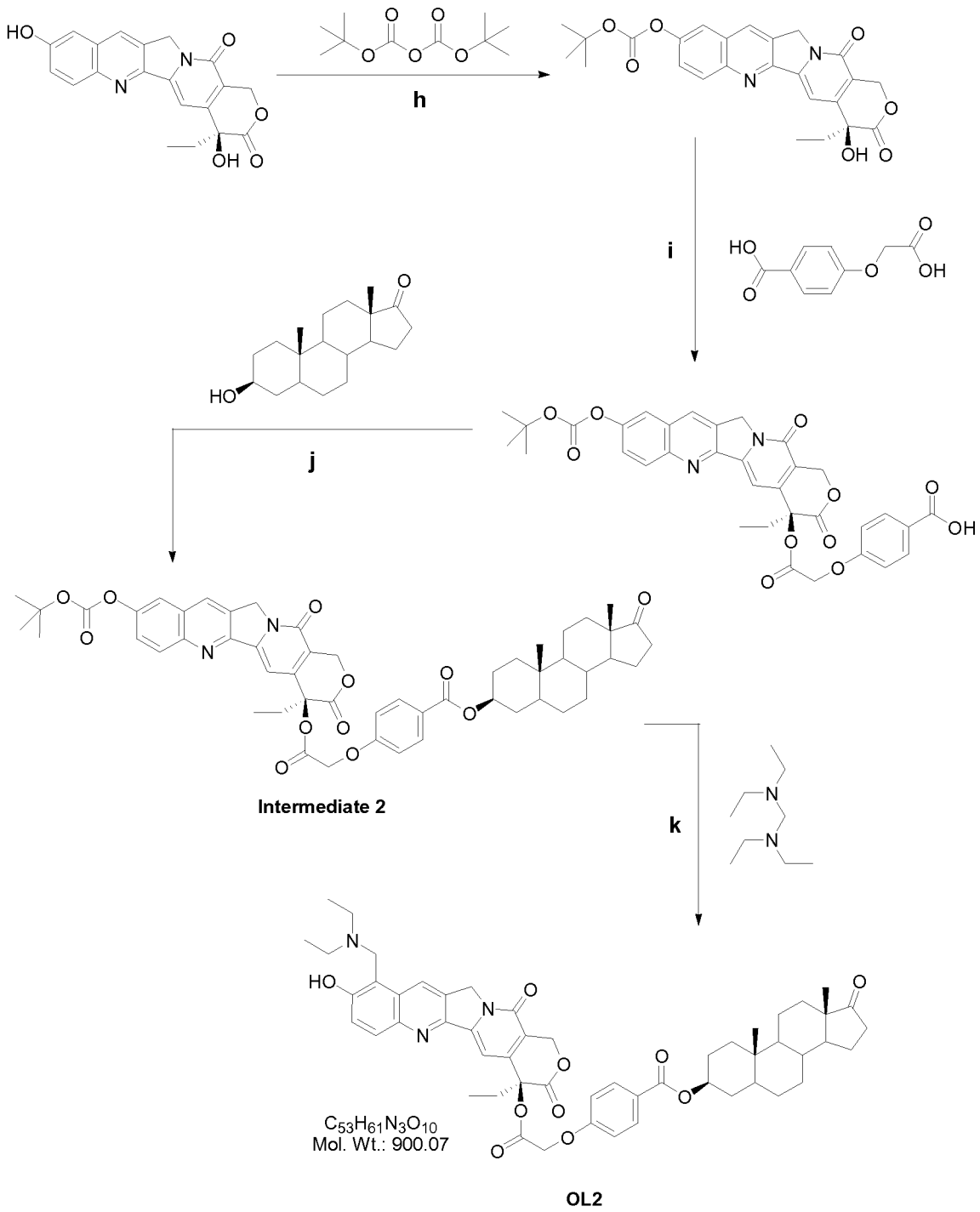
Reactions:

(f) CPT-phenoxyacetic acid: A mixture of camptothecin (100 mg, 0.29 mmol), 4-carboxyphenoxyacetic acid (112 mg, 0.57 mmol), EDCI (82 mg, 0.43 mmol), DMAP (10 mg, 0.10 mmol), and DMF/DCM (4 mL/4 mL) was stirred at ambient temperature for 48 hr. The resulting solution was then diluted by adding dichloromethane (50 mL). The dichloromethane containing organic layer was washed sequentially with a saturated NH_4Cl solution (20 mL), water (20 mL), and brine (20 mL). After drying over $MgSO_4$, the solvent was removed under *in vacuo*. The resulting residue was then purified by flash column chromatography (chloroform/methanol (20:1) to afford CPT-phenoxyacetic acid as a light yellow solid (129 mg; yield = 90%).

(g) OL-1: A mixture of CPT-phenoxyacetic acid (0.113g, 0.21 mmol), epiandrosterone (0.12g, 0.42 mmol), EDCI (0.28g, 1.46 mmol) and DMAP (0.03g, 0.24 mmol) and dichloromethane (5 mL) was stirred at ambient temperature for 24 h. The mixture was then diluted by adding dichloromethane (50 mL). The dichloromethane containing organic layer was washed sequentially with a saturated NH_4Cl solution (50 mL), water (50 mL), and brine (50 mL). After drying over Na_2SO_4, the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography (chloroform: methanol (50:1))to give the title product as an off-white solid (0.12g; yield = 70%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (s, 1H, Ar), 8.23 (d, *J* = 8.51 Hz, 1H, Ar), 7.97-7.91 (m, 3H, Ar), 7.83 (ddd, *J* = 8.37, 6.99, 1.20 Hz, 1H, Ar), 7.66 (t, *J* = 7.52, 7.52 Hz, 1H, Ar), 7.19 (s, 1H, Ar), 6.92 (d, *J* = 8.88 Hz, 2H, Ar), 5.66 (d, *J* = 17.27 Hz, 1H, C-CH_2-O-C(O)), 5.38 (d, *J* = 17.27 Hz, 1H, C-CH_2-O-C(O)), 5.27 (s, 2H, C-CH_2-N), 4.87 (d, *J* = 1.70 Hz, 2H, O-CH_2-C(O)-O), 3.57 (ddd, *J* = 15.90, 9.95, 4.64 Hz, 1H), 2.41 (dd, *J* = 19.35, 9.03 Hz, 2H), 2.27 (dt, *J* = 14.95, 14.88, 7.44 Hz, 1H), 2.19-1.98 (m, 3H), 1.96-1.85 (m, 3H), 1.81-1.59 (m, 8H), 1.27-1.18 (m, 5H), 0.94 (t, *J* = 7.51, 7.51 Hz, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.75-0.62 (m, 1H).

[00167] Scheme IV is illustrative of the synthesis route to make 4-(10-diethylaminomethyl-4-ethyl-9-hydroxy-3, 13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-4yl-oxycarbonylmethoxy)-benzoic acid 10,13-dimethyl-17-oxo-hexadecahydrocyclopenta[*a*]phenanthren-3yl-ester (OL-2).

Scheme IV



[00168] 10. 4-(10-Diethylaminomethyl-4-ethyl-9-hydroxy-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-4yl-oxycarbonylmethoxy)-benzoic acid 10,13-dimethyl-17-oxo-hexadecahydrocyclopenta[*a*]phenanthren-3yl-ester (OL-2).

Reactions:

(h) *BOC-CPT*: After 10-hydroxy-camptothecin (10-HO-CPT) (1 equiv.) and $(BOC)_2O$ (2 equiv.) were dissolved in *N,N'*-dimethylformamide, pyridine was added. The resulting mixture was stirred at ambient temperature for overnight. The mixture was then diluted by adding dichloromethane. The dichloromethane containing layer was washed sequentially with water, and 1N HCl. After drying over Na_2SO_4, the solvent was removed *in vacuo*. The resulting residue was then purified by flash column chromatography to give carbonic acid *tert*-butyl ester 4-ethyl-4-hydroxy-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-9-yl ester (BOC-CPT).

(i) *BOC-CPT-CPA*: A mixture of BOC-CPT, 4-carboxyphenoxyacetic acid (CPA), EDCI, DMAP, and dichloromethane was stirred at ambient temperature for 24 hr. The resulting solution was diluted with dichloromethane. The dichloromethane containing organic layer was washed sequentially with a saturated NH_4Cl solution, water, and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. The resulting residue was then purified by flash column chromatography to afford 4-(9-*tert*-butoxycarbonyloxy-4-ethyl-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-4-yloxycarbonylmethoxy)-benzoic acid (BOC-CPT-CPA).

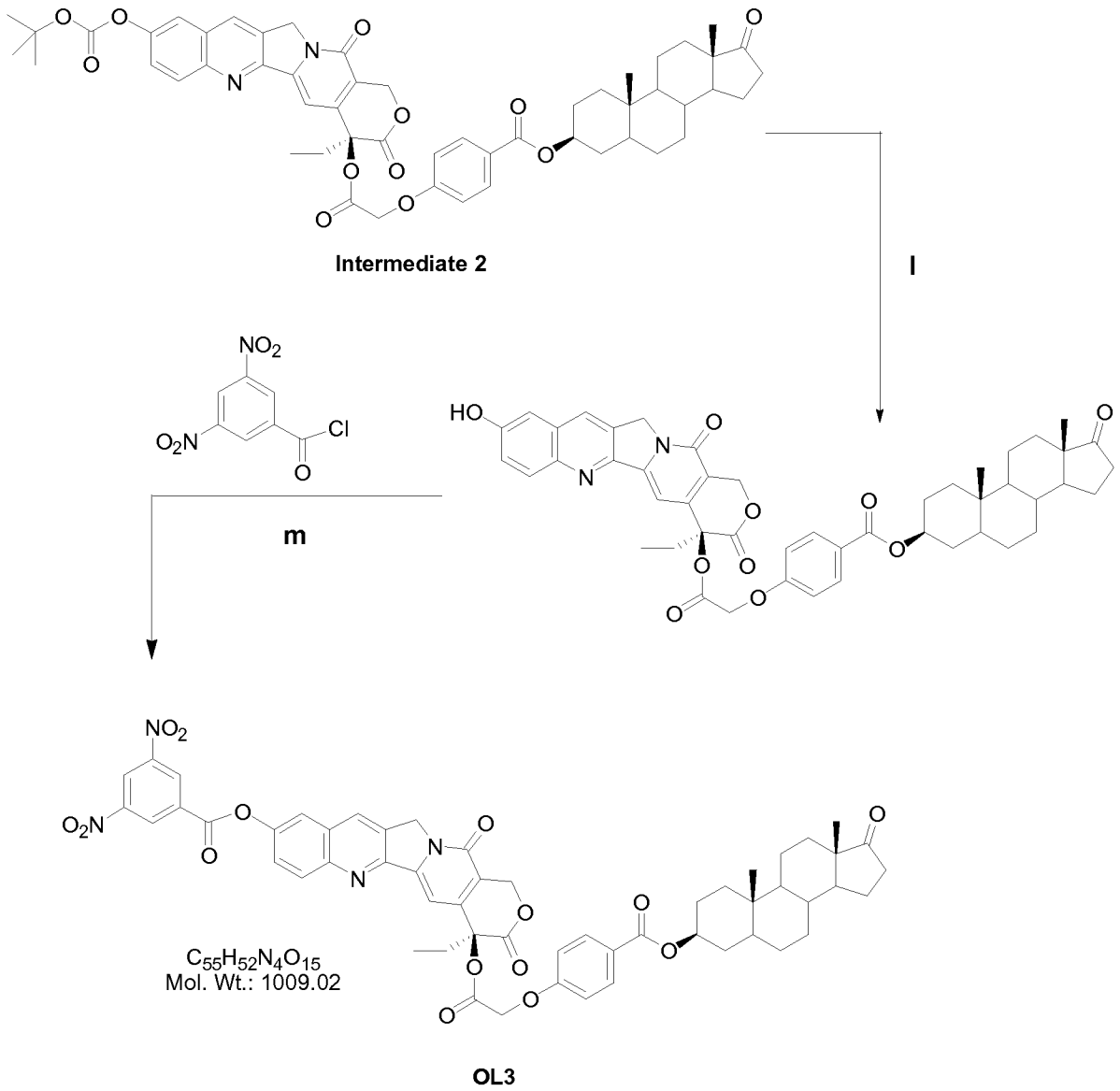
(j) *BOC-CPT-androgen* (**Intermediate 2**): A mixture of BOC-CPT-CPA, epiandrosterone, EDCI, DMAP, and dichloromethane was stirred at ambient temperature for 24 hr. The resulting solution was diluted with dichloromethane. The dichloromethane containing organic layer was washed sequentially with a 5% Na_2CO_3 solution, water, and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. The resulting residue was then purified by flash column to give 4-(9-*tert*-butoxycarbonyloxy-4-ethyl-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-4-yloxycarbonylmethoxy)-benzoic acid 10,13-dimethyl-17-oxo-hexadecahydro-cyclopenta[*a*]phenanthren-3-yl ester (BOC-CPT-androgen).

(k) *OL-2*: After BOC-CPT-androgen (0.191g, 0.21 mmol) was dissolved in dichloromethane (0.80 mL, 12.48 mmol), TFA (0.62 mL, 8.33 mmol) was added dropwise. The mixture was stirred at ambient

temperature for overnight. The mixture was cooled to 0 °C in an ice bath, and then *N*,*N*,*N*,*N*-tetraethylmethanediamine (0.98 mL, 5.02 mmol) was added dropwise. After stirring the mixture at ambient temperature for 2 h, the mixture was then diluted by adding dichlormethane/acetone (1:5). The organic layer was washed sequentially with water (50 mL), a saturated $NaHCO_3$ (50 mL) solution, and brine (50 mL). The aqueous layer was re-extracted with dichloromethane (3 x 25 mL). The organic layers were combined and dried over Na_2SO_4. After removing the solvents *in vacuo*, the resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH 50:1) to give the title product as a bright yellow solid (0.049 g; yield = 26%). ^{1}H NMR (400 MHz, $CDCl_3$), δ ppm 8.33 (s, 1H, Ar), 8.06 (d, *J* = 9.10 Hz, 1H, Ar), 7.98 (dd, *J* = 8.89, 2.39 Hz, 2H, Ar), 7.40 (d, *J* = 9.21 Hz, 1H, Ar), 7.13 (s, 1H, Ar), 6.95 (dd, *J* = 8.84, 3.56 Hz, 2H, Ar), 5.68 (d, *J* = 17.13 Hz, 1H, C-CH_2-O-C(O)), 5.39 (d, *J* = 17.16 Hz, 1H, C-CH_2-O-C(O)), 5.24 (s, 2H, C-CH_2-N), 4.89 (s, 2H, O-CH_2-C(O)-O), 4.25 (s, 2H, Ar-**CH_2**-N-(CH_2CH_3)$_2$), 3.66-3.55 (m, 1H), 2.77 (q, *J* = 7.21, 7.17, 7.17 Hz, 4H, C-N-(**CH_2**-CH_3)$_2$), 2.44 (dd, *J* = 19.12, 9.04 Hz, 2H), 2.34-2.22 (m, 1H), 2.22-2.00 (m, 3H), 1.99-1.88 (m, 2H), 1.85-1.76 (m, 5H), 1.76-1.63 (m, 4H), 1.62-1.46 (m, 5H), 1.22 (t, *J* = 7.10, 7.10 Hz, 6H, C-N-(CH_2-**CH_3**)$_2$), 0.96 (t, *J* = 7.42, 7.42 Hz, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.78-0.65 (m, 1H).

[00169] Scheme V is illustrative of the synthesis route to make 3,5-dinitro-benzoic acid 4-{2-[4-(10,13-dimethyl-17-oxo-hexadecahydro-cyclopent[*a*]phenanthren-3-yloxycarbonyl)-phenoxy]-acetoxy}-4-ethyl-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-9yl ester (OL-3).

Scheme V



OL3

[00170] 11. 3,5-Dinitro-benzoic acid 4-{2-[4-(10,13-dimethyl-17-oxo-hexadecahydro-cyclopent[*a*]phenanthren-3-yloxycarbonyl)-phenoxy]-acetoxy}-4-ethyl-3,13-dioxo-3,4,12,13-tetrahydro-1*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluoren-9yl ester (OL-3). **Intermediate 2** can me made by following reaction steps f, g, and h in Example 10. Reations:

(l) *10-OH-CPT-20-androgen*: After BOC-CPT-androgen (0.767 g, 0.84 mmol) was dissolved in dichloromethane (3.22 mL, 50.24 mmol), TFA (2.50 mL, 33.57 mmol) was added dropwise. The reaction was stirred at ambient temperature overnight. The mixture was diluted by adding dichloromethane/acetone (1:5). The organic layer was

then washed sequentially with water (150 mL), and a saturated $NaHCO_3$ solution (150 mL). After drying over over Na_2SO_4, the solvents were removed *in vacuo*. The resulting residue was purified by flash column chromatography (chloroform/methanol 50:1) to afford the product (10-OH-CPT-20-androgen) as a white solid.

(m) *OL-3*: A mixture of 10-OH-CPT-20-androgen (0.025 g, 0.031 mmol) and 3,5-dinitrobenzoyl chloride (0.035 g, 0.152 mmol) in neat pyridine (2 mL) was stirred at ambient temperature for 4 h. The mixture was poured onto ice and then extracted with dichloromethane (3 x 50 mL). The organic layers were combined, washed sequentially with water (50 mL), 1.0 N HCl (50 mL), and brine (50 mL), and then dried over Na_2SO_4. After the solvents were removed *in vacuo*, the resulting residue was purified by flash column chromatography (chloroform/methanol (100:1)) to give the title product as an off-white solid (0.029 g; yield = 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.38-9.34 (m, 2H, Ar), 9.32 (t, *J* = 2.09, 2.09 Hz, 1H, Ar), 8.40 (s, 1H, Ar), 8.37 (dd, *J* = 9.20, 3.88 Hz, 1H, Ar), 7.98 (dd, *J* = 11.68, 8.92 Hz, 2H, Ar), 7.89 (d, *J* = 2.25 Hz, 1H, Ar), 7.75 (td, *J* = 9.20, 2.55, 2.55 Hz, 1H, Ar), 7.17 (d, *J* = 6.67 Hz, 1H, Ar), 6.93 (dd, *J* = 8.95, 3.22 Hz, 2H, Ar), 5.66 (d, *J* = 17.33 Hz, 1H, C-CH_2-O-C(O)), 5.38 (d, *J* = 17.32 Hz, 1H, C-CH_2-O-C(O)), 5.29 (s, 2H, C-CH_2-N), 4.87 (d, *J* = 2.24 Hz, 2H, O-CH_2-C(O)-O), 3.52 (q, *J* = 7.01, 7.01, 7.01 Hz, 1H), 2.40 (dd, *J* = 19.02, 8.63 Hz, 1H), 2.26 (qd, *J* = 14.79, 7.35, 7.34, 7.34 Hz, 2H), 2.13 (td, *J* = 22.91, 8.09, 8.09 Hz, 2H), 2.07-1.98 (m, 1H), 1.95-1.83 (m, 2H), 1.81-1.56 (m, 5H), 1.48-1.40 (m, 1H), 1.36-1.15 (m, 8H), 1.07 (dd, *J* = 13.86, 3.79 Hz, 1H), 0.94 (t, *J* = 7.41, 7.41 Hz, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.70 (dt, *J* = 11.53, 11.39, 3.81 Hz, 1H).

[00171] A person with ordinary skill in the art would recognize that by simply substituting androsterone for epiandrosterone in the protocols for Examples 7-11, one can make androsterone derivatives of the disclosure.

[00172] One with skill in the art will recognize that various androsterone analogs and/or epiandrosterone analogs may be obtained from commercial sources or be prepared de-novo by procedures known in the art. These analogs can then be used by the methods disclosed herein to prepare compounds of this disclosure. By

reacting a compound with a camptothecin-based analog, including those camptothecin-based analogs disclosed herein, with an androsterone or epiandrosterone analog in accordance to the procedures disclosed herein or obvious variants thereof, compounds of the disclosure will be obtained. These compounds will exhibit the desired characteristics to a greater or lesser extent.

[00173] 12. *In vitro* Antitumor Assays in HCT116 Cells and MCF-7-ADR Cell Survival Studies with Epiandrosterone and/or Androsterone Derivative Compounds of the Disclosure. To test the biological effect of epiandrosterone and/or androsterone derivative compounds of the disclosure, HCT116 cells (colorectal carcinoma cells) were contacted with various concentrations of epiandrosterone and/or androsterone derivative compounds as disclosed herein. The results are presented in Table 1. Moreover, experiments with epiandrosterone and/or androsterone derivative compounds of the disclosure in MCF-7-ADR cells, breast cancer cells which have resistance to doxorubicin, increased the mortality rate of the MCF-7-ADR cells (see, e.g. Figure 1). Epiandrosterone and/or androsterone derivative compounds of the disclosure, however, were less toxic to normal cells while being effective at killing cancer cells (particularly breast cancer cells).

Table 1. *In vitro* antitumor activity of epiandrosterone and/or androsterone derivative compounds against HCT116 cells.

Epiandrosterone and/or Androsterone Derivative Cmpds.	10μM	1μM	100 nM	10 nM
990624	0	100		
991022	0	100		
991228	0	98.29		
991120	0	100		
991123	0	96.97		
991027	0	0	4.00	
5-FU	17.00			

[00174] 13. HCT116 Cell Survival Studies with Epiandrosterone and/or Androsterone Derivative Compounds of the Disclosure. To test the cytotoxicity of androsterone and/or epiandrosterone

derivatives of the disclosure on cancer cells, HCT116 cells (colorectal carcinoma cells) were plated in 60 mm Petri dishes containing 2.7 ml of medium (modified McCoy's 5a medium containing 10% fetal bovine serum and 100 units/ml penicillin and 100 µg/mL streptomycin). The cells were incubated in a CO_2 incubator at 37°C for 5 hours to allow for cell attachment to the bottom of the Petri dishes. A stock solution containing either the compound of Example 8 or 9 was made right before the experiment in fresh medium at ten times the final concentration. Then 0.3 ml of this stock solution was added to the 2.7 mL of medium containing 5% bovine calf serum (BCS) in the Petri dish. The cells were then incubated with the compounds for 72 hours at 37 °C. At the end of incubation, the drug-containing media was decanted off, the cells were washed with 4 ml of Hank's Balance Salt Solution (HBSS), and then 5 mL of fresh medium containing 15% BCS was added. The dishes were returned to the incubator to allow for colony formation. After 8 days, the cell colonies were stained with methylene blue (0.3% in ethanol) and then counted using a colony counter. Cell survival was calculated and the IC 50 values (the drug concentration producing 50% inhibition of colony formation) were determined for each compound tested. The IC50 values were 2.5 nM for Example 9 (010216) and 3.5 nM for Example 8 (0103021). The results are presented in Table 2.

TABLE 2: Cell survival of HCT116 cells treated with 010216 and 0103021

Drug conc (nM)	%Survival for 010216	%Survival for 0103021
0	100	100
1	91	100
5	2	24
10	0	0

[00175] **14. *In Vitro* DU-145, PC3, ST88-14, and SF295 Cell Based Assays to Determine the Cytotoxicity of Epiandrosterone and/or Androsterone Derivative Compounds of the Disclosure on Cancer Cells.** The cytotoxic effects of epiandrosterone and/or

androsterone derivatives of the disclosure on DU-145 human prostate cancer cells were evaluated *in vitro* on DU-145 human prostate cancer cells subjected to 72 h drug treatment at 37 ^{0}C. After treatment the dishes were rinsed, fresh medium was added, and then incubated for 8 days at 37^{0}C. Cell survival was determined by the colony formation assay. The values of IC50 (drug concentrations producing 50% inhibition of colony formation) were calculated. The results in **Fig. 2** showed that OL-1 (IC50 = 1.5 nM) was significantly more effective in killing DU-145 prostate cancer cells than topotecan (IC50 = 15 nM), and irinotecan (IC50 = 250 nM, due to its property of prodrug). As shown in **Figs. 3** and **4**, OL-2 and OL-3 proved to be very effective against PC-3 human prostate cancer cells. The IC50 values for OL-2 and OL-3 were 131 nM and 18 nM, respectively. Interestingly, OL-2 and OL-3 exhibited high effectiveness in killing on human malignant peripheral nerve sheath tumor (MPNST) cells (ST88-14) and SF295 human glioblastoma cells (**Figs. 5-8**). The IC50 values for OL-2 and OL-3 in killing ST88-14 cells were 76 nM and 4 nM, respectively. The IC50 values for OL-2 and OL-3 in killing SF295 cells were 290 nM and 31 nM, respectively. The data proved that OL-3 was significantly more effective in killing both ST88-14 and SF295 cells than OL-2. It indicated that epiandrosterone and/or androsterone derivative compounds of the disclosure would be effective in treatment of patients with glioblastoma and MPNST.

[00176] 15. *In Vivo* Asssys in Mice to Evaluate the Toxicity of Epiandrosterone and Androsterone Derivative Compounds of the Disclosure. The toxic effects of epiandrosterone and/or androsterone derivative compounds of the disclosure were evaluated in sustained release injectable formulations in normal mice. The acute toxicity of OL-1, OL-2 and OL-3 (i.m.) was evaluated on C3H/HeN mice (male, 8 week old). The OL-1, OL-2 and OL-3 solutions (sustained release injectable formulations) were administered to C3H/HeN mice by a single i.m injection of 0,5 ml/20 g mouse with a drug dose of 11 mg (500 mg/kg). Drug toxicity was evaluated on mice checked daily for 45 days. No toxicity was observed in mice treated with OL-1, OL-2, and OL-3. The toxicity parameters reported were the values of MTD_{40}. The MTD is defined as the

highest dose causing no severe irreversible toxicity in one treatment group, but at least one animal exhibiting severe and irreversible toxicity and being euthanized at next higher dose. Since no severe irreversible toxicity in any treatment group was observed, the MTD values of OL-1, OL-2 and OL-3 would be higher than 500 mg/kg. The toxicity data suggests that the toxicity of epiandrosterone and/or androsterone derivatives of the disclosure in normal mice is extremely low (for OL-1, OL-2, and OL-3) or predicted to be extremely low for other nontested epiandrosterone and/or androsterone derivatives disclosed herein.

[00177] 16. *In Vivo* Assays in Mice to Evaluate Epiandrosterone and/or Androsterone Compounds of the Disclosure on Tumor Suppression and Mouse Survivability. *In vivo* efficacy studies with epiandrosterone and/or androsterone derivative compounds of the disclosure on two human prostate cancer xenografts (PC-3 and DU-145) in male nude mice (8 week old, body weight 18 - 22 g, nu/nu genotype) were performed. The nude mice were given a s.c. implant of a tumor fragment with a 13-gauge trocar. These tumors grew exponentially following implantation into the backs of the mice and reach a tumor volume of about 100 cu. mm. Animals were evenly distributed to various treatment and control groups. Treatment was initiated at that time, with the first day of treatment designated as day 0 for all calculations and plots. Mice were injected i.m. with the drug solutions (sustained release injectable formulations) or vehicle alone. Treated animals were checked daily for treatment related toxicity/mortality. After treatment, tumor sizes were measured by caliper every other day. The measurement of the tumor diameters (d1, d2) in two orthogonal directions will be used to calculate the tumor volume (tumor volume = $\pi/6$ $\{(d1+d2)/2\}^3$) using the approximation that the tumors are spherical.

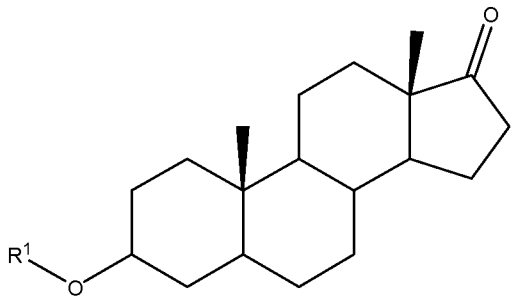
[00178] As can be seen from **Figs. 9-11**, three novel OL compounds were significantly effective in the inhibition of the growth of PC-3 prostate cancer xenografts, compared with the control group. Among three OL compounds, OL-3 was the most effective compound in controlling the growth of PC-3 xenografts. In OL-3 treated group, one mouse exhibited tumor-free. The survival time of the nude mice

treated with OL-3 was remarkably longer than that of the mice treated with OL-1 or OL-2. The results in **Figs. 12-14** showed that all three OL compounds were also markedly effective in inhibiting the growth of DU-145 prostate cancer xenografts, compared with the control group. The survival time of the mice treated with both OL-1 and OL-3 was longer than that of the mice treated with OL-2. The data in **Fig. 13** showed that the mean time for tumor volume reaching 1,000 cu. mm in the group treated with OL-3 was notably longer than that of the groups treated with OL-1 and OL-2. All the results demonstrate that OL-1, OL-2 and OL-3 were significantly effective and non-toxic compounds against both PC-3 and DU-145 human prostate cancer xenografts. Untested epiandrosterone and/or androsterone derivative compounds of the disclosure are likely to be effective anti-neoplastic agents.

[00179] A number of embodiments have been described herein. Nevertheless, it should be understood that various modifications may be made without departing from the spirit and scope of the description. Accordingly, other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. The compound comprising the general Formula II:



(II)

wherein:

R^1 is selected from the group consisting of aryl, cycloalkyl, heterocycle, fused ring system, $-(CY_2)_w$-aryl, $-(CY_2)_w$-heterocycle, $-(CY_2)_w$-cycloalkyl, $-(CY_2)_w$-fused ring system, -(C=O)-heterocycle, -(C=O)-cycloalkyl, -(C=O)-aryl, -(C=O)-fused ring system, $-(C=O)-(CY_2)_w$-cycloalkyl, $-(C=O)-(CY_2)_w$-cycloalkyl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-heterocycle, $-(C=O)-(CY_2)_w$-heterocycle-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-heterocycle, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-aryl, $-(C=O)-(CY_2)_w$-aryl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-aryl, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-fused ring system, $-(C=O)-(CY_2)_w$-fused ring system-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-fused ring system, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-N=fused ring system, $-(C=O)-(CY_2)_w$-O-N=heterocycle, and R^3-(C=O)-R^2-(C=O)-;

R^2 is selected from the group consisting of $-(CY_2)_w$-, -aryl-, -cycloalkyl-, -heterocycle-, -fused ring system-, $-(CY_2)_w$-heterocycle-, $-(CY_2)_w$-cycloalkyl-, $-(CY_2)_w$-aryl-, $-(CY_2)_w$-L-$(CY_2)_z$-, $-(CY_2)_w$-L-$(CY_2)_x$-aryl-, $-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-, $-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-, $-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-, $-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-, $-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-, $-(CY_2)_w$-L-cycloalkyl-, $-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-, $-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-, $-(CY_2)_w$-fused ring system-, -

$(CY_2)_w$-fused ring system-$(CY_2)_z$-, -$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-, -$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-, and -$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-.

R^3 is selected from the group consisting of hydroxyl, aryl, cycloalkyl, heterocycle, fused ring system, -O-aryl, -O-cycloalkyl, -O-heterocycle, -O-fused ring system, -O-$(CY_2)_w$-cycloalkyl, -O-$(CY_2)_w$-cycloalkyl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl, -O-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-heterocycle, -O-$(CY_2)_w$-heterocycle-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle, -O-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-aryl, -O-$(CY_2)_w$-aryl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-aryl, -O-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-fused ring system, -O-$(CY_2)_w$-fused ring system-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system, -O-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), -O-$(CY_2)_w$-O-N=fused ring system, and -O-$(CY_2)_w$-O-N=heterocycle;

R^4 is independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aldehyde, carbonyl, alkoxycarbonyl, carboxyl, heterocycle, fused ring system, amino, imino, imido, azido, azo, alkylamine, arylamine, alkoxy, aryloxy, cyano, cyanato, hydroxyl, nitroso, and nitro;

Y is independently selected from the group consisting of H, D, R^4, OR^4, $N(R^4)_2$, SR^4, cyano, CA_3, CA_2R^4, $CA(R^4)_2$, $C(R^4)_3$, and halogen;

A is independently selected from the group consisting of H, D, and halogen;

L is independently selected from the group consisting of O, C(=O)O, C(=O)N, C(A)=N(A), C(A)=C(A), C#C, N=N, O-N(A), N(Y), S, S(=O)(=O), and covalent bond;

w, x, y, and z are independently selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

including any tautomers, pharmaceutically acceptable salts, and sterioisomers thereof, including mixtures thereof in all possible ratios.

2. The compound of Claim 1, wherein:

R^1 is selected from the group consisting of aryl, cycloalkyl, heterocycle, fused ring system, $-(CY_2)_w$-aryl, $-(CY_2)_w$-heterocycle, $-(CY_2)_w$-cycloalkyl, $-(CY_2)_w$-fused ring system, -(C=O)-heterocycle, -(C=O)-cycloalkyl, -(C=O)-aryl, -(C=O)-fused ring system, $-(C=O)-(CY_2)_w$-cycloalkyl, $-(C=O)-(CY_2)_w$-cycloalkyl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-heterocycle, $-(C=O)-(CY_2)_w$-heterocycle-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-heterocycle, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-aryl, $-(C=O)-(CY_2)_w$-aryl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-aryl, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-fused ring system, $-(C=O)-(CY_2)_w$-fused ring system-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-fused ring system, $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-(C=O)-(CY_2)_w$-L-N=fused ring system, and $-(C=O)-(CY_2)_w$-O-N=heterocycle;

R^4 is independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aldehyde, carbonyl, alkoxycarbonyl, carboxyl, heterocycle, fused ring system, amino, imino, imido, azido, azo, alkylamine, arylamine, alkoxy, aryloxy, cyano, cyanato, hydroxyl, nitroso, and nitro;

Y is independently selected from the group consisting of H, D, R^4, OR^4, $N(R^4)_2$, SR^4, cyano, CA_3, CA_2R^4, $CA(R^4)_2$, $C(R^4)_3$, and halogen;

A is independently selected from the group consisting of H, D, and halogen;

L is independently selected from the group consisting of O, C(=O)O, C(=O)N, C(A)=N(A), C(A)=C(A), C#C, N=N, O-N(A), N(Y), S, S(=O)(=O), and covalent bond;

w, x, y, and z are independently selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

including any tautomers, pharmaceutically acceptable salts, and sterioisomers thereof, including mixtures thereof in all possible ratios.

3. The compound of Claim 2, wherein aryl, heterocyle, or fused ring system is substituted.

4. The compound of Claim 3, wherein the substituted aryl, heterocycle, or fused ring system contains at least one or more electron withdrawing group.

5. The compound of Claim 4, wherein the substituted aryl, heterocycle, or fused ring system contains only electron withdrawing groups.

6. The compound of Claim 2, wherein heterocycle is a nitrogen containing heterocycle, and wherein fused ring system which contains a heterocycle is a nitrogen containing heterocycle.

7. The compound of Claim 6, wherein the nitrogen containing heterocycle is aromatic.

8. The compound of Claim 7, wherein the aromatic nitrogen containing heterocycle is composed of one or more 4-, 5- or 6-membered rings.

9. The compound of Claim 7, wherein the aromatic nitrogen containing heterocycle is selected from the group consisting of imidazole, imidazoline, pyrazole, pyrazoline, pyrazine, pyridazine, pyridine, pyrimidine, pyrrole, tetrazole, 1,2,3-triazole, 1,2,4-triazole, triazine, tetrazine, xanthine, oxazole, furazan, oxazine, purine, 2-amino-pyridine, benzimidazole, 2,5-diaminopyridine, 2,4-dimethylimidazole, 2,3-dimethylpyridine,γ-picoline,and 2,4,6-trimethylpyridine.

10. The compound of Claim 6, wherein the nitrogen containing heterocycle is nonaromatic.

11. The compound of Claim 10, wherein the nonaromatic nitrogen containing heterocycle is composed of one or more 4-, 5-, or 6-membered rings.

12. The compound of Claim 11, wherein the nonaromatic nitrogen containing heterocycle is selected from the group consisting of azolidine, imidazolidine, pyrazolidine, morpholine, oxazolidine, lactam, maleimide, piperidine, piperazine, pyrrolidine, and succinimide, γ-butyrolactam, ε-caprolactam, *N*-phenyl-β-propiolactam, 1,2-dimethylpiperidine, 2,5-dimethylpiperazine, 1,2-dimethylpyrrolidine, 1-ethylpiperidine, n-methylpyrrolidine, morpholine, piperazine, piperidine, pyrrolidine, 2,2,6,6-tetramethylpiperidine, and 2,2,4-trimethylpiperidine.

13. The compound of Claim 2, wherein the fused ring system of R^1 is bicylic.

14. The compound of Claim 13, wherein the bicyclic fused ring system contains rings selected from the group consisting of, one (C_3-C_7)cycloalkyl and one phenyl ring, one heterocycle and one phenyl ring, and one (C_3-C_7)cycloalkyl ring and one heterocycle ring.

15. The compound of Claim 13, wherein the bicyclic ring is selected from the group consisting of indole, quinoline, phthalimide, and 8-methyl-8-aza-bicyclo[3.2.1]octane.

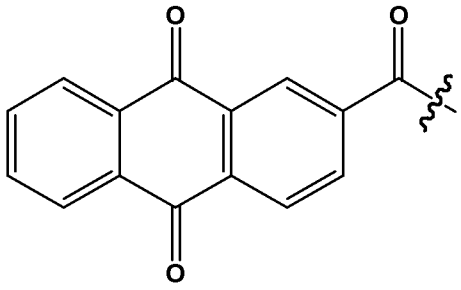
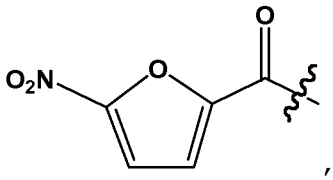
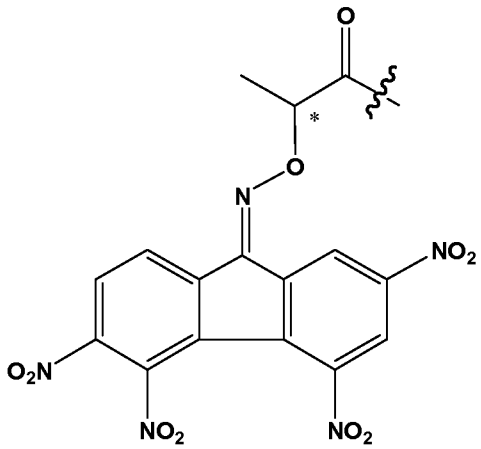
16. The compound of Claim 2, where the fused ring system of R^1 is tricylic.

17. The compound of Claim 16, wherein the tricyclic fused ring system contains rings selected from the group consisting of, one phenyl, one heterocyle and one (C_3-C_7)cycloalkyl ring, one (C_3-C_7)cycloalkyl and two phenyl rings, one (C_3-C_7)cycloalkyl and two heterocycle rings, one heterocycle and two phenyl rings, one heterocycle and two (C_3-C_7)cycloalkyl rings, one phenyl and two (C_3-C_7)cycloalkyl rings, and one phenyl and two heterocycle rings.

18. The compound of Claim 2, wherein R^1 is selected from the group consisting of atropine, atropine analog, scopolamine, or scopolamine analog.

19. The compound of Claim 2, wherein R^1 is a camptothecin analog.

20. The Compound of Claim 2, wherein R^1 is selected from the group consisting of:


,

, and


wherein * indicates the (+) chiral center in the original molecule.

21. A compound of Claim 1, wherein:

R^1 is R^3-(C=O)-R^2-(C=O)-

R^2 is selected from the group consisting of -$(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-, -$(CY_2)_w$-L-$(CY_2)_x$-heterocycle-, -$(CY_2)_w$-L-$(CY_2)_x$-aryl-, -$(CY_2)_w$-L-$(CY_2)_x$-fused ring system-, and -$(CY_2)_w$-;

R^4 is independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aldehyde, carbonyl, alkoxycarbonyl, carboxyl, heterocycle, fused ring system, amino, imino, imido, azido, azo, alkylamine, arylamine, alkoxy, aryloxy, cyano, cyanato, hydroxyl, nitroso, and nitro;

R^3 is a hydroxyl;

Y is independently selected from the group consisting of H, D, R^4, OR^4, $N(R^4)_2$, SR^4, cyano, CA_3, CA_2R^4, $CA(R^4)_2$, $C(R^4)_3$, and halogen;

A is independently selected from the group consisting of H, D, and halogen;

L is independently selected from the group consisting of O, N(Y), S, and covalent bond;

w and x are independently selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

including any tautomers, pharmaceutically acceptable salts, and sterioisomers thereof, including mixtures thereof in all possible ratios;

with the following provisos:

if R^2 is $-(CY_2)_w$-L-$(CY_2)_x$-aryl-, wherein aryl is a substituted or unsubstituted phenyl and L is a covalent bond, then w and x cannot be 0;

if R^2 is $-(CY_2)_w$- L-$(CY_2)_x$-aryl, wherein aryl is a substituted phenyl and L is a covalent bond, then w cannot be 2 and x be 0; and

if L is O, then w cannot be 1 and x be 0.

22. The compound of claim 21, wherein:

the heterocycle of R^2 is a fused bicyclic, tricyclic or tetracylic heterocycle made of 5- or 6-membered rings;

the aryl of R^2 is selected from the group consisting of phenyl, and 1- or 2- naphthyl;

the cycloalkyl of R^2 is a $(C_3$-$C_7)$cycloalkyl;

the fused ring system of R^2 is anthraquinone; and

x is 0; and

Y is H.

23. The compound of claim 22, wherein:

R^2 is a phenyl that is substituted with 1 to 5 substituents independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, hydroxyl, $(C_1$-$C_6)$alkoxy, cyano, nitro amino, $(C_1$-$C_6)$alkylamino, halo$(C_1$-$C_6)$alkylamino, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, carbonyl, hydroxycarbonyl, $(C_1$-$C_6)$alkylcarbonyloxy,

benzyloxy, a 5 or 6 membered heterocyclic ring, imide ring, (C_1-C_6)alkoxycarbonyl, and (C_1-C_6) alkylcarbonylamino; and

w is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

24. The compound of claim 23, wherein:

L is selected from the group consisting of S or O; and

w is selected from the group consisting of 1, 2, and 3.

25. The compound of claim 24, wherein:

R^2 is a phenyl that is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, methyl, methoxy, nitro, trifluoromethyl, and carbonyl;

L is O; and

w is 1.

26. The compound of claim 25, wherein: R^2 is a phenyl substituted with 1 to 2 halogens.

27. The compound of claim 25, wherein: R^2 is phenyl substituted with a methyl.

28. The compound of claim 22, wherein:

R^2 is either -$(CH_2)_w$-L-cyclo(C_3-C_7)alkyl-, -$(CH_2)_w$-L-heterocycle- where heterocycle is a fused bicyclic, tricyclic or tetracylic heterocycle made of 5- or 6-membered rings, or -$(CH_2)_w$-L-anthraquinone-; and

w is 1.

29. The compound of claim 22, wherein:

L is O; and

w is selected from the group consisting of 0, 1, 2, and 3.

30. The compound of claim 22, wherein:

L is a covalent bond; and

w is selected from the group consisting of 0, 1, 2, and 3.

31. The compound of claim 30, wherein:
R^2 is a fused bicyclic, tricyclic or tetracylic heterocycle.

32. The compound of Claim 31, wherein:
R^2 is an optionally substituted quinolin-4-yl.

33. The compound of Claim 32, wherein:
R^2 is 2-phenylquinolin-4-yl.

34. The compound of Claim 31, wherein:
R^2 is chrom-2-yl.

35. The compound of Claim 30, wherein:
R^2 is either $-(CH_2)_w$-cyclo(C_3-C_7)alkyl- or $-(CH_2)_w$-anthraquinone-.

36. The compound of Claim 35, wherein:
R^2 is anthraquinon-1-yl.

37. The compound of Claim 1, wherein
R^1 is R^3-(C=O)-R^2-(C=O)-;
R^2 is $-(CY_2)_w$- where Y is H, and w is 2;
R^3 is selected from the group consisting of hydroxyl, aryl, cycloalkyl, heterocycle, fused ring system, -O-aryl, -O-cycloalkyl, -O-heterocycle, -O-fused ring system, $-O-(CY_2)_w$-cycloalkyl, $-O-(CY_2)_w$-cycloalkyl-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl, $-O-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-cycloalkyl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-heterocycle, $-O-(CY_2)_w$-heterocycle-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-heterocycle, $-O-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-heterocycle-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-aryl, $-O-(CY_2)_w$-aryl-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-aryl, $-O-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-aryl-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-fused ring system, $-O-(CY_2)_w$-fused ring system-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-fused ring system, $-O-(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-L-$(CY_2)_x$-fused ring system-$(CY_2)_y$-L-$(CY_2)_z$-(CY_3), $-O-(CY_2)_w$-O-N=fused ring system, and $-O-(CY_2)_w$-O-N=heterocycle;

R^4 is independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aldehyde, carbonyl, alkoxycarbonyl, carboxyl, heterocycle, fused ring system, amino, imino, imido, azido, azo, alkylamine, arylamine, alkoxy, aryloxy, cyano, cyanato, hydroxyl, nitroso, and nitro;

Y is independently selected from the group consisting of H, D, R^4, OR^4, $N(R^4)_2$, SR^4, cyano, CA_3, CA_2R^4, $CA(R^4)_2$, $C(R^4)_3$, and halogen;

A is independently selected from the group consisting of H, D, and halogen;

L is independently selected from the group consisting of O, C(=O)O, C(=O)N, C(A)=N(A), C(A)=C(A), C#C, N=N, O-N(A), N(Y), S, and S(=O)(=O);

w, x, y and z are independently selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

including any tautomers, pharmaceutically acceptable salts, and sterioisomers thereof, including mixtures thereof in all possible ratios.

38. The compound of Claim 37, wherein aryl, heterocyle, or fused ring system is substituted.

39. The compound of Claim 38, wherein the substituted aryl, heterocycle, or fused ring system contains at least one or more electron withdrawing group.

40. The compound of Claim 39, wherein the substituted aryl, heterocycle, or fused ring system contains only electron withdrawing groups.

41. The compound of Claim 40, wherein heterocycle is a nitrogen containing heterocycle, and wherein fused ring system which contains a heterocycle is a nitrogen containing heterocycle.

42. The compound of Claim 41, wherein the nitrogen containing heterocycle is aromatic.

43. The compound of Claim 42, wherein the aromatic nitrogen containing heterocycle is composed of one or more 4-, 5- or 6-membered rings.

44. The compound of Claim 42, wherein the aromatic nitrogen containing heterocycle is selected from the group consisting of imidazole, imidazoline, pyrazole, pyrazoline, pyrazine, pyridazine, pyridine, pyrimidine, pyrrole, tetrazole, 1,2,3-triazole, 1,2,4-triazole, triazine, tetrazine, xanthine, oxazole, furazan, oxazine, purine, 2-amino-pyridine, benzimidazole, 2,5-diaminopyridine, 2,4-dimethylimidazole, 2,3-dimethylpyridine, 2,4-dimethylpyridine, 3,5-dimethylpryidine, methoxypyridine, γ-picoline,and 2,4,6-trimethylpyridine.

45. The compound of Claim 41, wherein the nitrogen containing heterocycle is nonaromatic.

46. The compound of Claim 45, wherein the nonaromatic nitrogen containing heterocycle is composed of one or more 4-, 5-, or 6-membered rings.

47. The compound of Claim 45, wherein the nonaromatic nitrogen containing heterocycle is selected from the group consisting of azolidine, imidazolidine, pyrazolidine, morpholine, oxazolidine, lactam, maleimide, piperidine, piperazine, pyrrolidine, and succinimide, γ-butyrolactam, ε-caprolactam, *N*-phenyl-β-propiolactam, 1,2-dimethylpiperidine, 2,5-dimethylpiperazine, 1,2-dimethylpyrrolidine, 1-ethylpiperidine, n-methylpyrrolidine, morpholine, piperazine, piperidine, pyrrolidine, 2,2,6,6-tetramethylpiperidine, and 2,2,4-trimethylpiperidine.

48. The compound of Claim 37, wherein the fused ring system of R^1 is bicylic.

49. The compound of Claim 48, wherein the bicyclic fused ring system contains rings selected from the group consisting of, one $(C_3\text{-}C_7)$cycloalkyl and one phenyl ring, one heterocycle and one

phenyl ring, and one (C_3-C_7)cycloalkyl ring and one heterocycle ring.

50. The compound of Claim 48, wherein the bicyclic ring is selected from the group consisting of indole, quinoline, phthalimide, and 8-methyl-8-aza-bicyclo[3.2.1]octane.

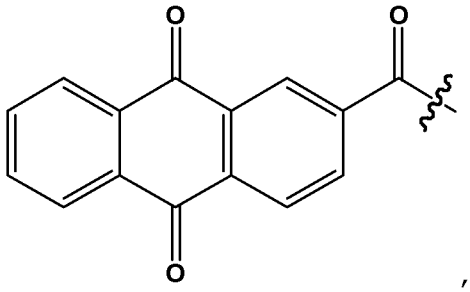
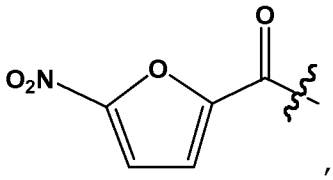
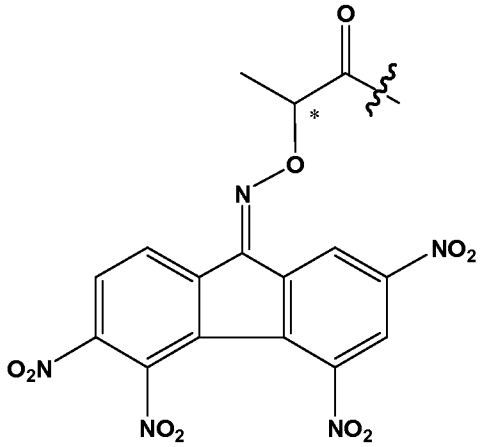
51. The compound of Claim 37, where the fused ring system of R^1 is tricylic.

52. The compound of Claim 51, wherein the tricyclic fused ring system contains rings selected from the group consisting of, one phenyl, one heterocyle and one (C_3-C_7)cycloalkyl ring, one (C_3-C_7)cycloalkyl and two phenyl rings, one (C_3-C_7)cycloalkyl and two heterocycle rings, one heterocycle and two phenyl rings, one heterocycle and two (C_3-C_7)cycloalkyl rings, one phenyl and two (C_3-C_7)cycloalkyl rings, and one phenyl and two heterocycle rings.

53. The compound of Claim 37, wherein R^3 is selected from the group consisting of atropine, atropine analog, scopolamine, or scopolamine analog.

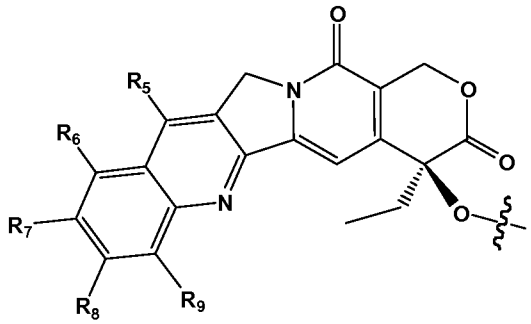
54. The compound of Claim 53, wherein R^3 is a camptothecin analog.

55. The Compound of Claim 37, wherein R^3 is a residue selected from the group consisting of:



, , and


wherein * indicates the (+) chiral center in the original molecule.

56. The Compound of Claim 1, wherein R^3 has the residue



wherein:

R^5 is selected from the group consisting H, D, halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, hydroxycarbonyl, formyl, $(C_1$-$C_6)$alkoxycarbonyl, tri$(C_1$-$C_6)$alkylsilyl, $(C_1$-$C_6)$alkylcarbonyloxy, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonyloxymethyl, substituted vinyl, 1-hydroxy-2-nitroethyl, alkoxycarbonylethyl, aminocarbonyl, mono- or di-alkylcarbonyl, alkylcarbonylmethyl, benzoylmethyl, benzylcarbonyloxymethyl, $-(CH_2)_s-N(R^{12})R^{13}$, mono- or di $(C_1$-$C_6)$alkoxymethyl, and R^5 in combination with R^6 forms an amino substituted cyclo$(C_1$-$C_6)$alkyl;

R^6 is selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hyroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, $-CH_2NR^{12}R^{13}$, CH_2R^{14}, $NR^{15}R^{16}$, dialkylamino-alkyl, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamino, and R^6 in combination with R^5 forms an amino substituted cyclo(C_1-C_6)alkyl;

R^7 is selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, amino(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, carbamoyloxy, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamino, and R^7 in combination with R^8 forms a [1,4]dioxino group.

R^8 is selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, $R^{10}C(=O)O$, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, (C_1-C_6)alkylcarbonylamino, and R^8 in combination with R^7 form a [1,4]dioxino group;

R^9 is selected from the group consisting of H, D, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, $R^{10}C(=O)O$, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)akylcarbonylamino;

R^{10} is $R^{11}-O-(CH_2)_s-$;

R^{11} is selected from the group consisting of (C_1-C_6)alkyl, phenyl that is optionally substituted with one to five substituents that are independently selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, formyl, (C_1-C_6)alkylcarbonyl, hydroxycarbonyl, (C_1-C_6)alkylcarbonyloxy, benzyloxy, an optionally substituted piperazino, alkoxycarbonyl, and (C_1-C_6)alkylcarbonylamino, $(C_3$ to $C_7)$cycloalkyl that is optionally substituted with one to five substituents independently selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alky, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)alkylcarbonylamino, a fused 2-, 3-, or 4-ring heterocycle

that is optionally substituted with one to five substituents independently selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)alkylcarbonylamino, 1- or 2-naphthyl that is optionally substituted with one to four substituents independently selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)alkylcarbonylamino, and a 5 or 6 membered heterocycle containing one or two nitrogen atoms that is optionally substituted with one or two substituents selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxyl, cyano, nitro, amino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyloxy, and (C_1-C_6)alkylcarbonylamino;

R^{12} is independently selected from the group consisting of H, D, (C_1 to C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino-(C_1-C_6)alkyl, R^{12} in combination with R^{13} forms an amino substituted cyclo(C_1-C_6)alkyl, R^{12} in combination with R^{13} forms an (C_1-C_6)alkyl substituted heterocycle containing 1 nitrogen, and R^{12} in combination with R^{13} forms a (C_1-C_6)alkyl substituted heterocycle containing 2 nitrogens;

R^{13} is independently selected from the group consisting of H, D, (C_1 to C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino-(C_1-C_6)alkyl, R^{13} in combination with R^{12} forms an amino substituted cyclo(C_1-C_6)alkyl, R^{13} in combination with R^{12} forms an (C_1-C_6)alkyl substituted heterocycle containing 1 nitrogen, and R^{13} in combination with R^{12} forms a (C_1-C_6)alkyl substituted heterocycle containing 2 nitrogens;

R^{14} is selected from the group consisting of (C_1-C_6)alkoxy, cyano, amino(C_1-C_6)alkoxy, mono- or di-(C_1-C_6)alkylamino-(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, amino (C_1-C_6)alklythio, and mono- or di-(C_1-C_6)alkylamino-(C_1-C_6)alkylthio;

R^{15} is selected from the group consisting of H, D, (C_1-C_6)alkyl, phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or di- (C_1-C_6)alkyl, and R^{15} in combination with R^{16} forms a heterocycle;

R^{16} is selected from the group consisting of H, D, (C_1-C_6)alkyl, phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or di- (C_1-C_6)alkyl, and R^{16} in combination with R^{15} forms a heterocycle;

w, x, y and z are selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; and

including any tautomers, pharmaceutically acceptable salts, and sterioisomers thereof, including mixtures thereof in all possible ratios.

57. The Compound of Claim 56, wherein

R^5 is hydrogen;

R^6 is selected from the group consisting of $CH_2NR^{12}R^{13}$, $NR^{15}R^{16}$, and dialkylamino-alkyl;

R^7 is selected from the group consisting of (C_1-C_6)alkoxy, hydroxyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, carbamoyloxy, (C_1-C_6)alkylcarbonyloxy, and R^7 in combination with R^8 forms a [1,4]dioxino group;

R^8 is selected from the group consisting of H, and R^8 in combination with R^7 forms a [1,4]dioxino group;

R^9 is H;

R^{12} is selected from the group consisting of H, (C_1-C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino- (C_1-C_6)alkyl, and R^{12} in combination with R^{13} forms an amino substituted cyclo(C_1-C_6)alkyl;

R^{13} is selected from the group consisting of H, (C_1 to C_6)alkyl, optionally substituted phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or dialkylamino-(C_1-C_6)alkyl, and R^{12} in combination with R^{13} forms an amino substituted cyclo(C_1-C_6)alkyl;

R^{15} is selected from the group consisting of H, (C_1-C_6)alkyl, phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or di-(C_1-C_6)alkyl, and R^{15} in combination with R^{16} forms a heterocycle; and

R^{16} is selected from the group consisting of H, (C_1-C_6)alkyl, phenyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, or mono- or di-(C_1-C_6)alkyl, and R^{16} in combination with R^{15} forms a heterocycle.

58. The Compound of Claim 57, wherein

R^6 is $CH_2NR^{12}R^{13}$;

R^7 is selected from the group consisting of hydroxy, alkoxy, and alkylcarbonyloxy;

R^8 is H;

R^{12} is (C_1-C_6)alkyl; and

R^{13} is (C_1-C_6)alkyl.

59. The compound of Claim 58, wherein

R^6 is $CH_2N(CH_3)_2$; and

R^7 is hydroxyl.

60. The compound of Claim 59, wherein

R^5 is selected from the group consisting of H, (C_1-C_6)alkyl, and halo(C_1-C_6)alkyl;

R^6 is selected from the group consisting of H, and (C_1-C_6)alkyl;

R^7 is selected from the group consisting of (C_1-C_6)alkoxy, hydroxyl, halo(C_1-C_6)alkoxy, carbamoyloxy, (C_1-C_6)alkylcarbonyloxy, and R^7 in combination with R^8 forms a [1,4]dioxino group;

R^8 is selected from the group consisting of H, and R^8 in combination with R^7 forms a [1,4]dioxino group; and

R^9 is hydrogen.

61. The compound of Claim 60, wherein

R^6 is H;

R^7 is carbamoyloxy; and

R^8 is H.

62. The compound of Claim 61, wherein

R^5 is a (C_1-C_6)alkyl; and

R^7 is 4-(1-piperidino)-1-piperidinocarbonyloxy.

63. The compound of Claim 63, wherein
R^5 is ethyl.

64. The compound of Claim 56, wherein
R^5 is a (C_1-C_6)alkyl;
R^6 is H;
R^7 is selected from the group consisting of hydroxyl, (C_1-C_6)alkoxy, halogenated(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, carbamoyloxy, and (C_1-C_6)alkylcarbonyloxy;
R^8 is H; and
R^9 is H.

65. The compound of Claim 64, wherein
R^5 is ethyl; and
R^7 is hydroxyl.

66. The compound of Claim 56, wherein
R^5, R^7, R^8, and R^9 are hydrogen; and
R^6 is selected from the group consisting of amino and nitro.

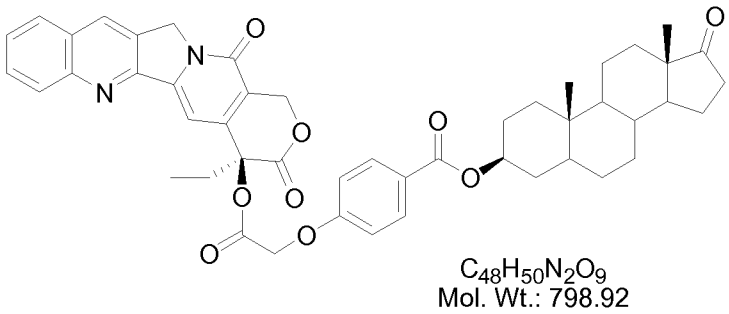
67. The compound of Claim 66, wherein R^6 is amino.

68. The compound of Claim 66, wherein R^6 is nitro.

69. The compound of Claim 56, wherein
R^5 is tri-(C_1-C_6)alkylsilyl;
R^6 is hydrogen;
R^7 is selected from the group consisting of hydroxyl, (C_1-C_6)alkoxy, halogenated(C_1-C_6)alkoxy, hydroxycarbonyl, formyl, (C_1-C_6)alkoxycarbonyl, carbamoyloxy, and (C_1-C_6)alkylcarbonyloxy;
R^8 is H; and
R^9 is H.

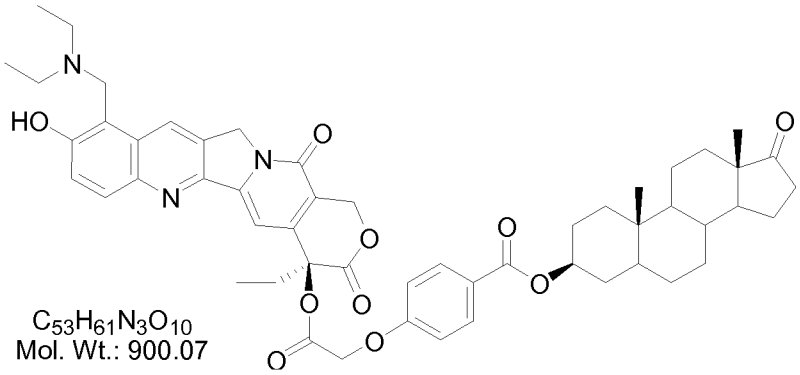
70. The compound of Claim 69, wherein
R^5 is *t*-butyldimethylsilyl; and
R^7 is hydroxyl.

71. A compound of Claim 56, with the structural formula:



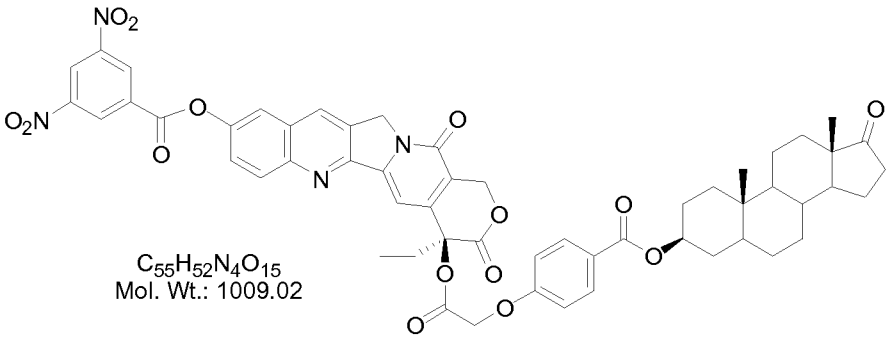
or a pharmaceutically acceptable salt thereof.

72. A compound of Claim 56, with the structural formula:



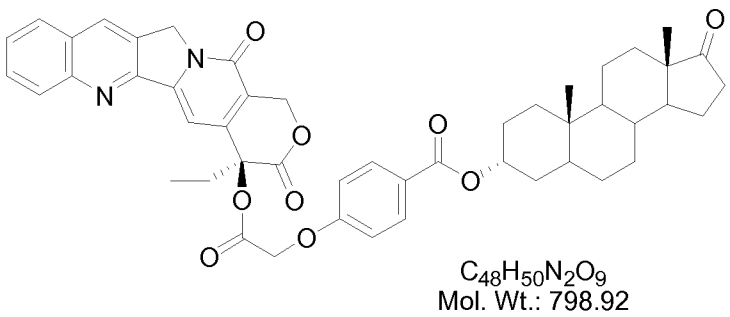
or a pharmaceutically acceptable salt thereof.

73. A compound of Claim 56, with the structural formula:



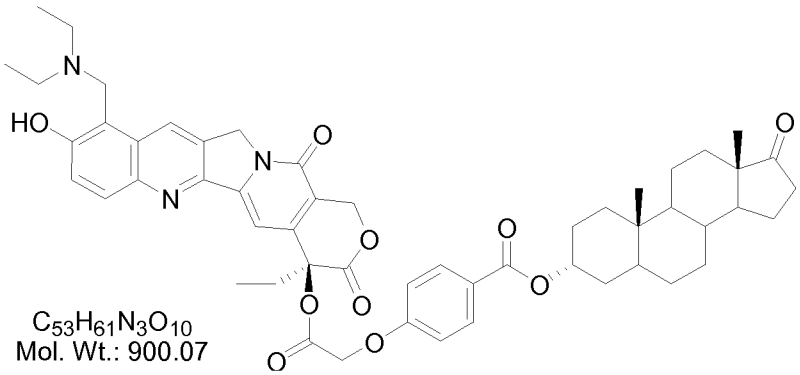
or a pharmaceutically acceptable salt thereof.

74. A compound of Claim 56, with the structural formula:



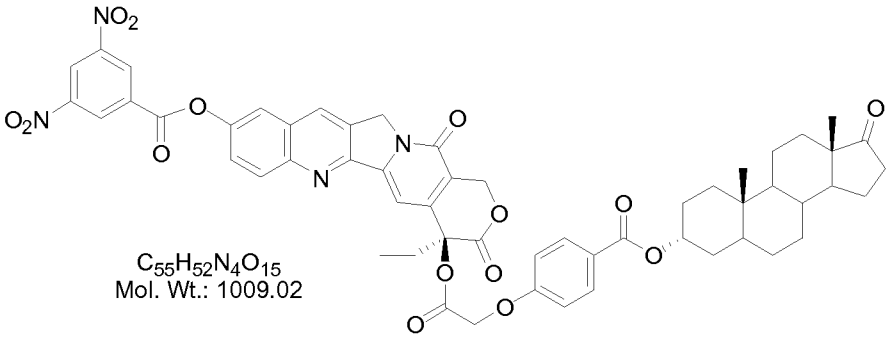
or a pharmaceutically acceptable salt thereof.

75. A compound of Claim 56, with the structural formula:



or a pharmaceutically acceptable salt thereof.

76. A compound of Claim 56, with the structural formula:



or a pharmaceutically acceptable salt thereof.

77. A pharmaceutical composition comprising a compound according to Claim 1, 56, 71, 72, 73, 74, 75, or 76 and at least one pharmaceutically-acceptable excipient.

78. The pharmaceutical composition as recited in claim 77, which is in the form of a liposomal composition.

79. The pharmaceutical composition as recited in Claim 77, further comprising another therapeutic agent.

80. The pharmaceutical composition as recited in Claim 77, wherein the therapeutic agent is selected from the group consisting of LHRH agonist, flutamide, nilutamide, bicalutamide, antiestrogenic agent, tamoxifen, ICT 182780, toremifene, LY 335563, LY 353381, lodoxifene, levormeloxifene, trilostane, inhibitor of testosterone 5-alpha-reductase, aromatase inhibitor, and androgenic compound.

81. The pharmaceutical composition as recited in Claim 79, wherein the therapeutic agent is an agent to treat cancer.

82. A method for the treatment of one of more symptoms of an androgen-associated disorder, estrogen-associated disorder, androgen-sensitive disorder or estrogen-sensitive disorder, in a subject, comprising administering a therapeutically effective amount of the compound of Claim 1.

83. A method for treating cancer in a patient, which method comprises administering a therapeutically effective amount of a compound of Claim 1, 56, 71, 72, 73, 74, 75, or 76 to the patient.

84. A process of making a compound of Claim 56, comprising reacting androsterone or epiandrosterone with a reactant that is composed of two portions, a camptothecin or camptothecin analog portion, and a linker portion containing a nonprotected carboxyl group.

85. The process as recited in Claim 84, wherein the reaction is carried in the presence of a coupling agent and a solvent system.

86. The process as recited in Claim 85, further comprising a catalyst.

87. The process as recited in Claim 86, wherein the catalyst is a nucleophilic catalyst.

88. The process as recited it Claim 87, wherein the nucleophilic catalyst is DMAP.

89. The process as recited in Claim 85, wherein, the solvent system contains one or more aprotic solvents.

90. The process as recited in Claim 89, wherein, the aprotic solvent is polar.

91. The process as recited in Claim 85, wherein, the coupling agent contains a carboiimide functional group.

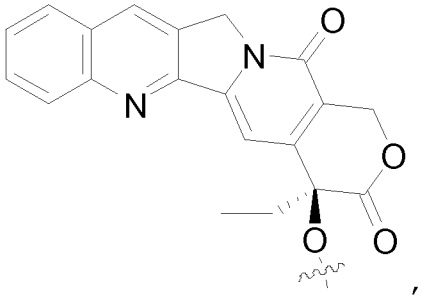
92. The process as recited in Claim 91, wherein, the carboiimide containing coupling agent is selected from the group consisting of DCC, DIC, and EDCI.

93. The process as recited in Claim 92, wherein, the carboiimide coupling agent is EDCI.

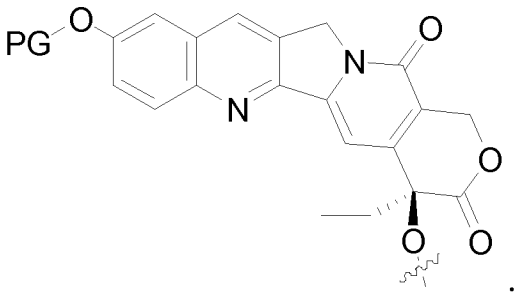
94. The process as recited in Claim 84, wherein, the reactant contains one or more protected functional groups.

95. The process as recited in Claim 94, wherein, the protected functional group is selected from the group consisting of hydroxyl, amino, and carboxyl.

96. The process as recited in Claim 84, wherein, the camptothecin or camptothecin analog portion of the reactant is selected from the group consisting of:



, and



.

97. The process as recited in Claim 84, wherein, the linker portion of the reactant is -(C=O)-(C_1-C_6)alkyl-oxy-aryl-C(=O)OH.

98. The process as recited in Claim 84, wherein, the linker portion of the reactant is -(C=O)-(C_1-C_6)alkyl-C(=O)OH.

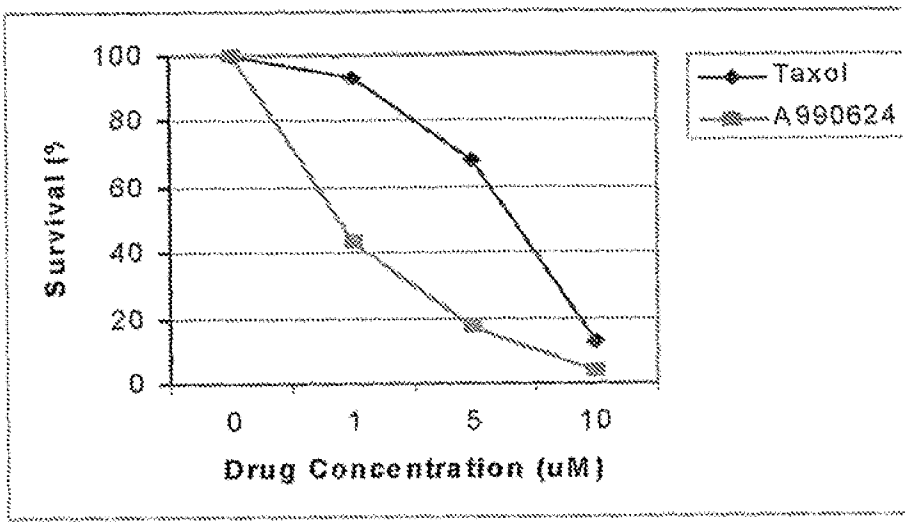

100
80
60
40
20
0
Survival (%
0
1
5
10
Drug Concentration (uM)
Taxol
A990624

Fig. 1

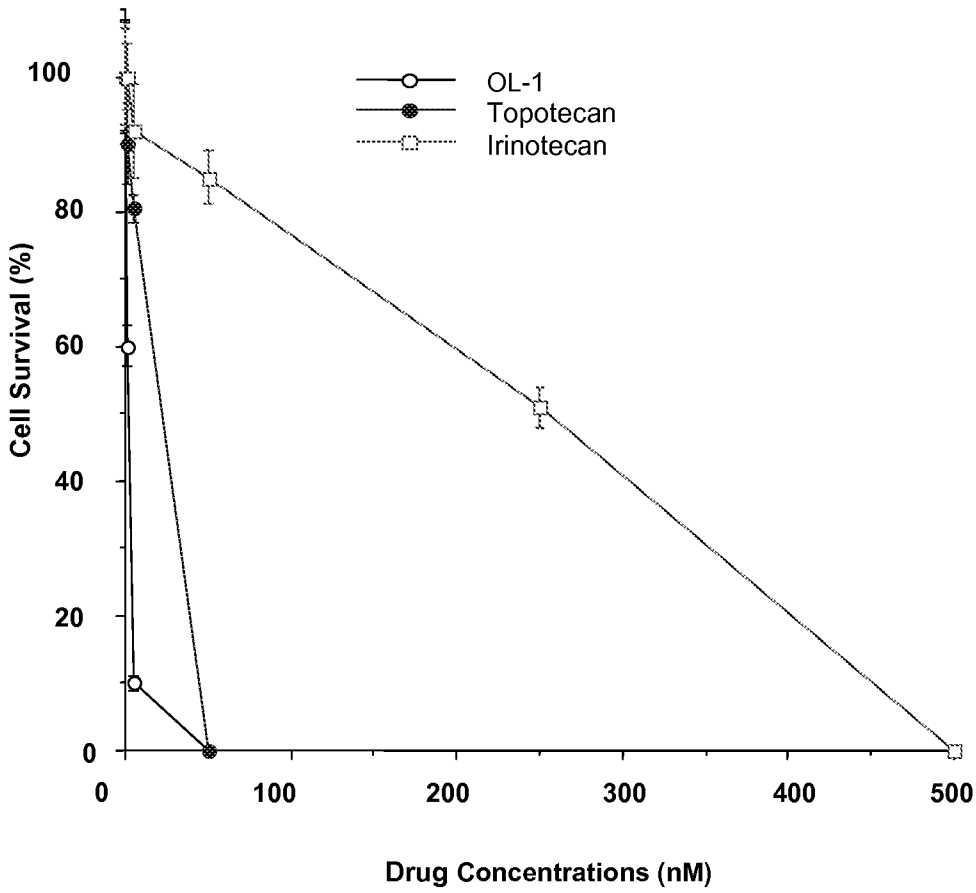

100
80
60
40
20
0
Cell Survival (%)
0
100
200
300
400
500
Drug Concentrations (nM)
OL-1
Topotecan
Irinotecan

Fig. 2

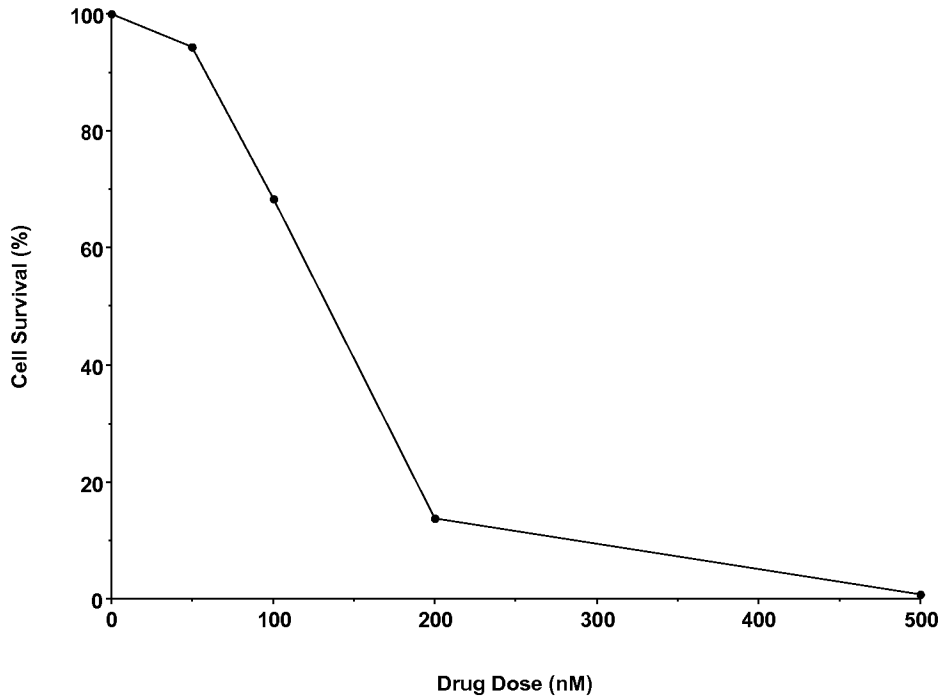

100
80
60
40
20
0
Cell Survival (%)
0
100
200
300
400
500
Drug Dose (nM)

Fig. 3

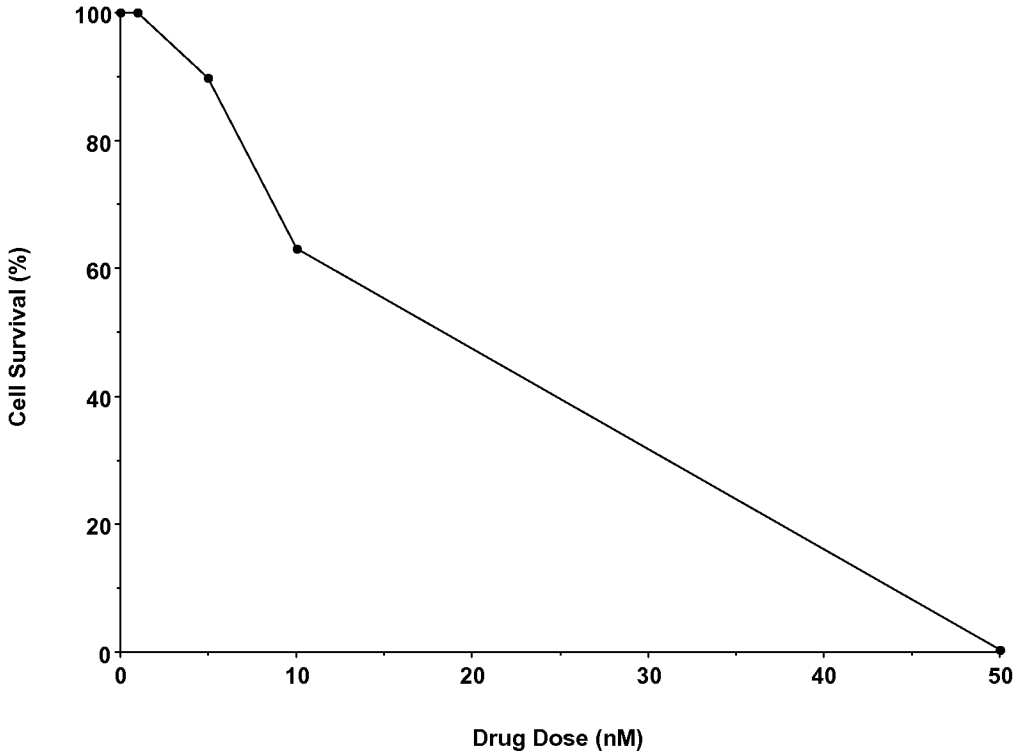

100
80
60
40
20
0
Cell Survival (%)
0
10
20
30
40
50
Drug Dose (nM)

Fig. 4

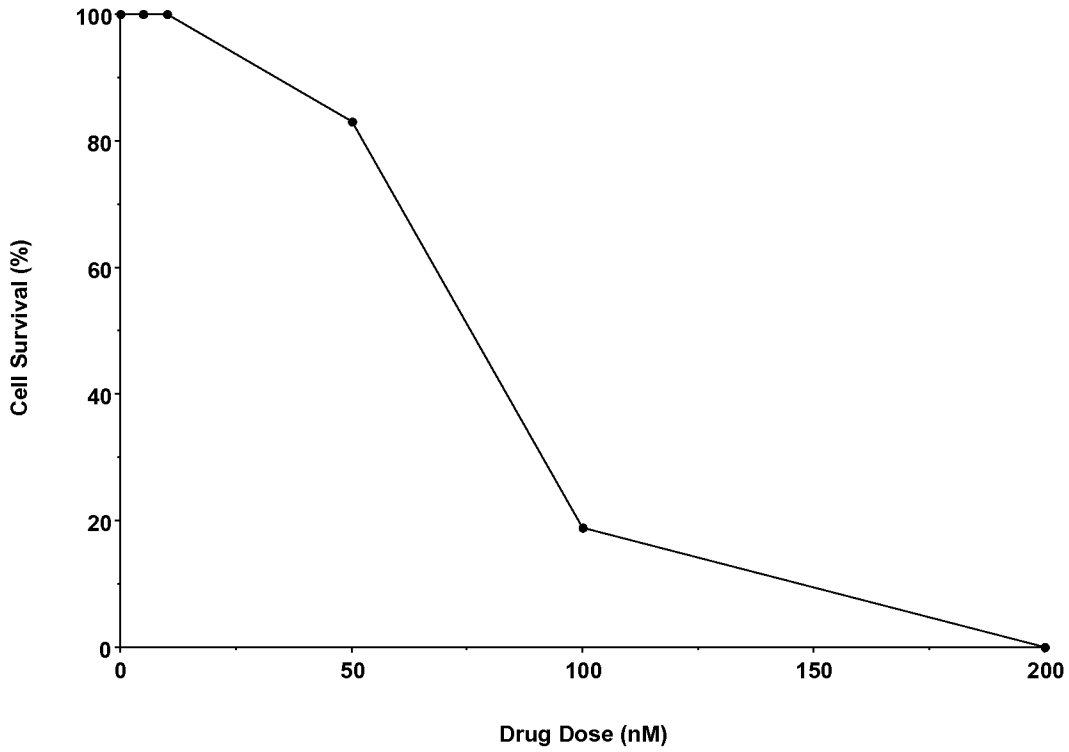

100
80
60
40
20
0
Cell Survival (%)
0
50
100
150
200
Drug Dose (nM)

Fig. 5

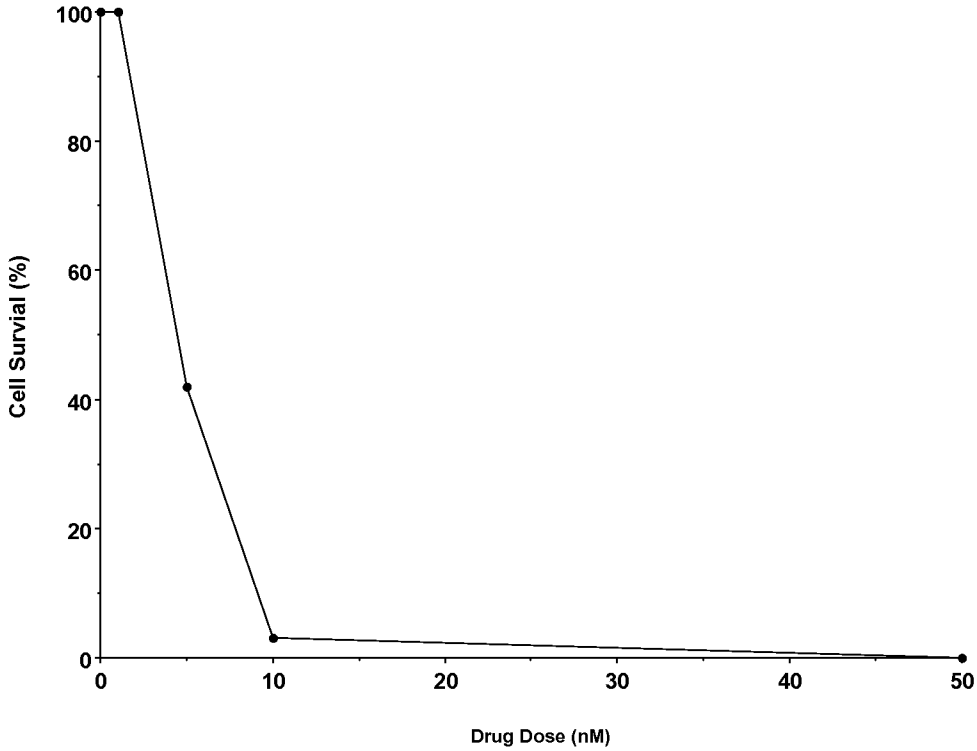

100
80
60
40
20
0
Cell Survial (%)
0
10
20
30
40
50
Drug Dose (nM)

Fig. 6

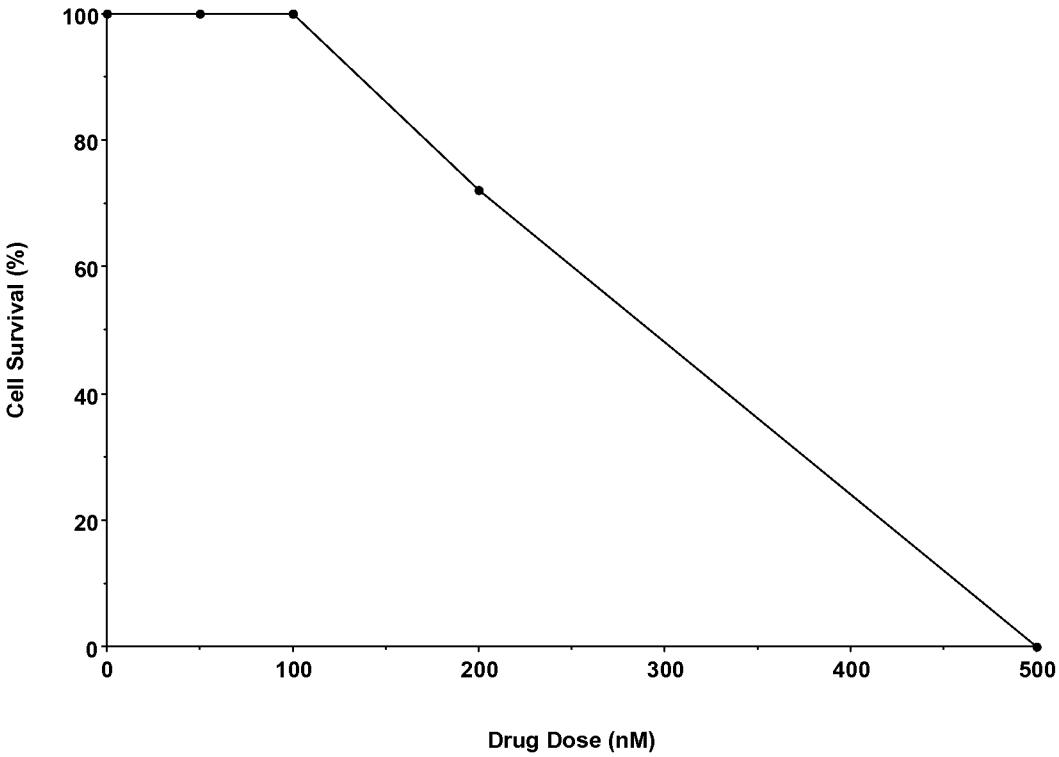

100
80
60
40
20
0
Cell Survival (%)
0
100
200
300
400
500
Drug Dose (nM)

Fig. 7

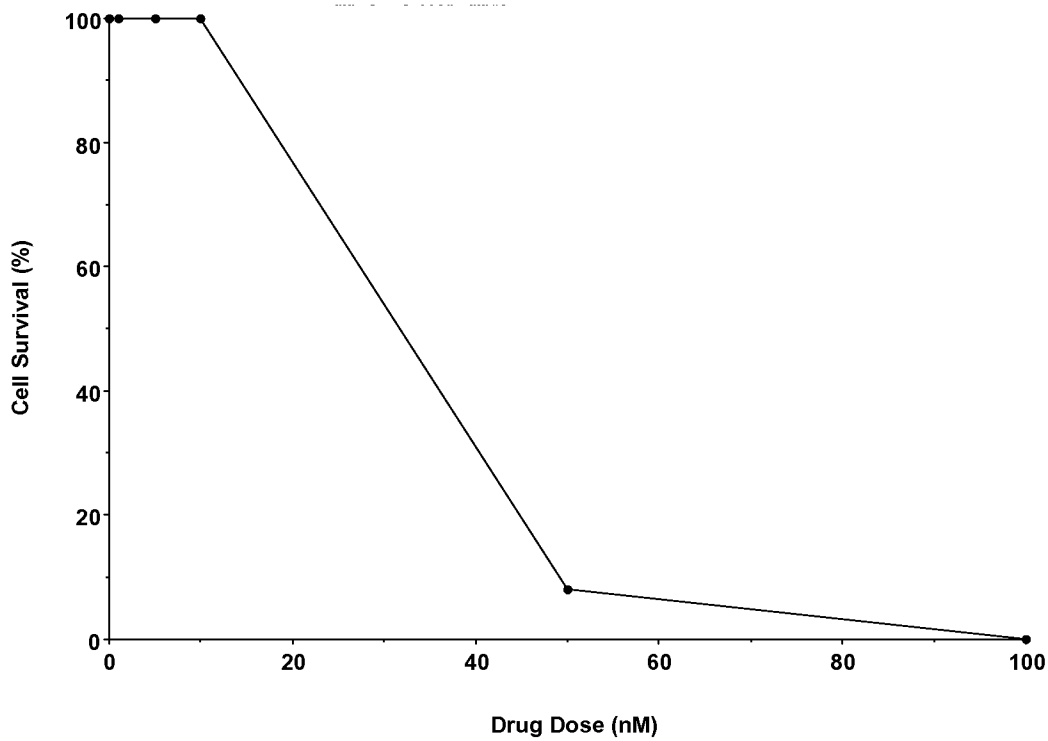

100
80
60
40
20
0
Cell Survival (%)
0
20
40
60
80
100
Drug Dose (nM)

Fig. 8

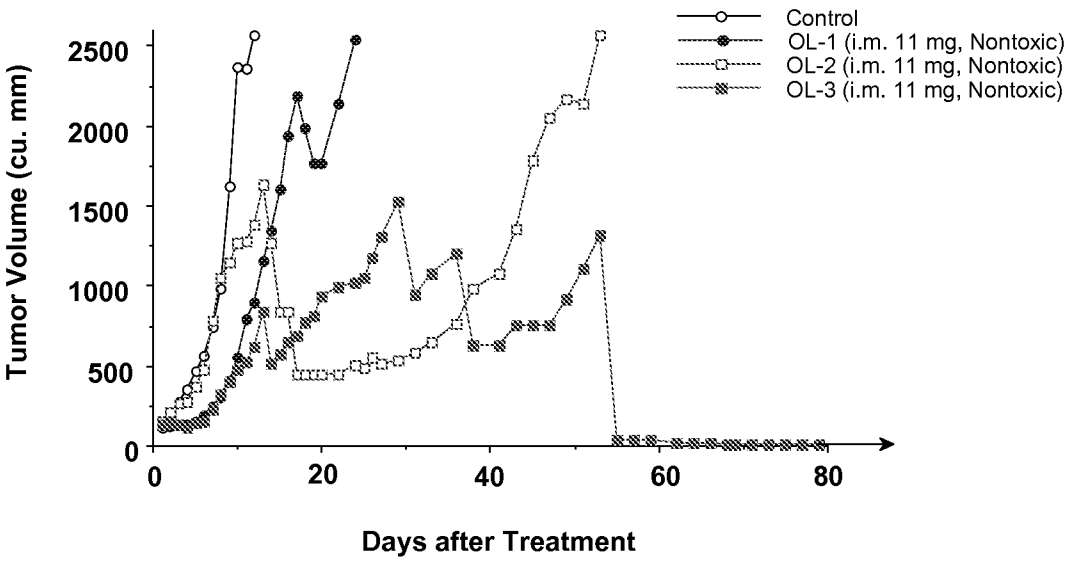

Control
OL-1 (i.m. 11 mg, Nontoxic)
OL-2 (i.m. 11 mg, Nontoxic)
OL-3 (i.m. 11 mg, Nontoxic)
Tumor Volume (cu. mm)
2500
2000
1500
1000
500
0
0
20
40
60
80
Days after Treatment

Fig. 9

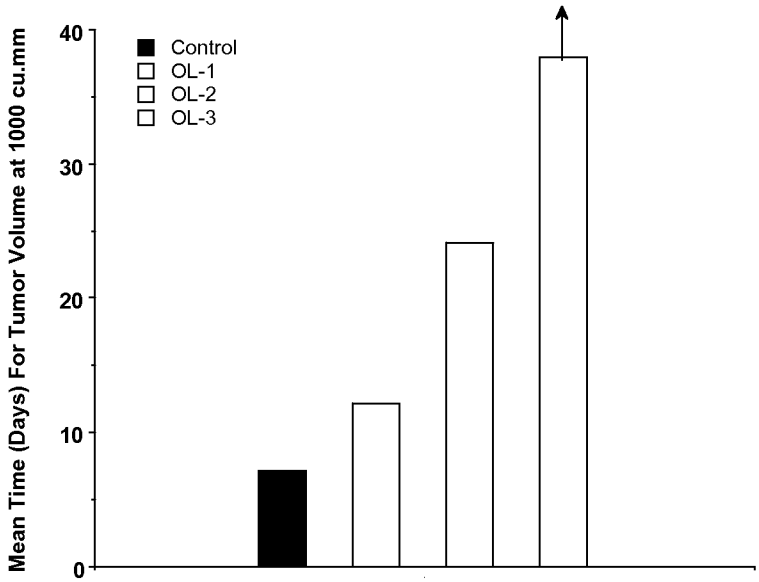

Control
OL-1
OL-2
OL-3
Mean Time (Days) For Tumor Volume at 1000 cu.mm
40
30
20
10
0

Fig. 10

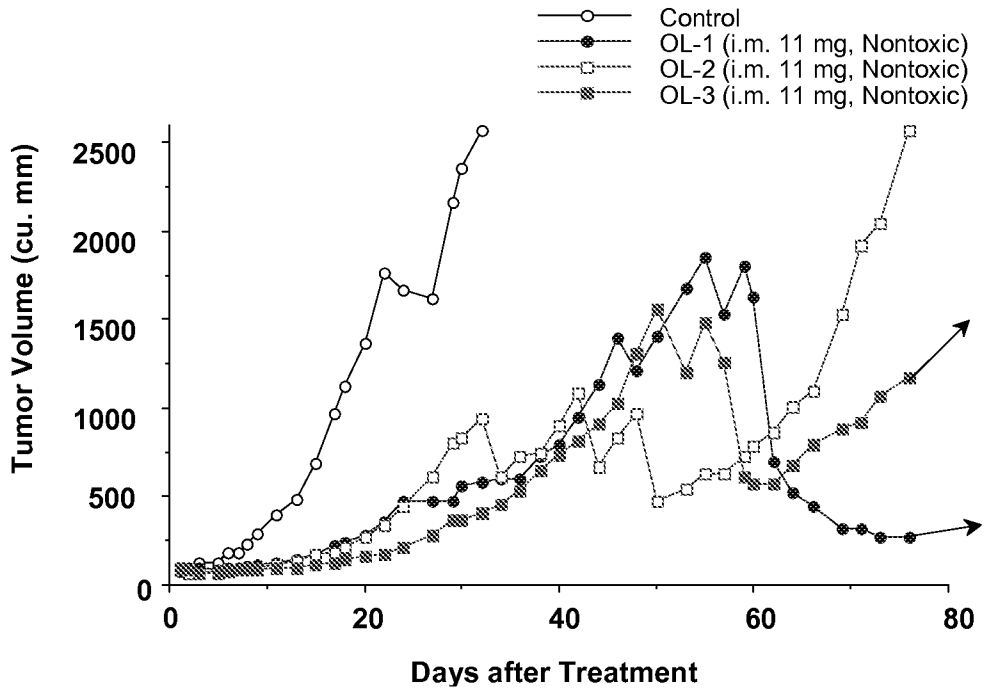

Control
OL-1 (i.m. 11 mg, Nontoxic)
OL-2 (i.m. 11 mg, Nontoxic)
OL-3 (i.m. 11 mg, Nontoxic)
Tumor Volume (cu. mm)
2500
2000
1500
1000
500
0
0
20
40
60
80
Days after Treatment

Fig. 11

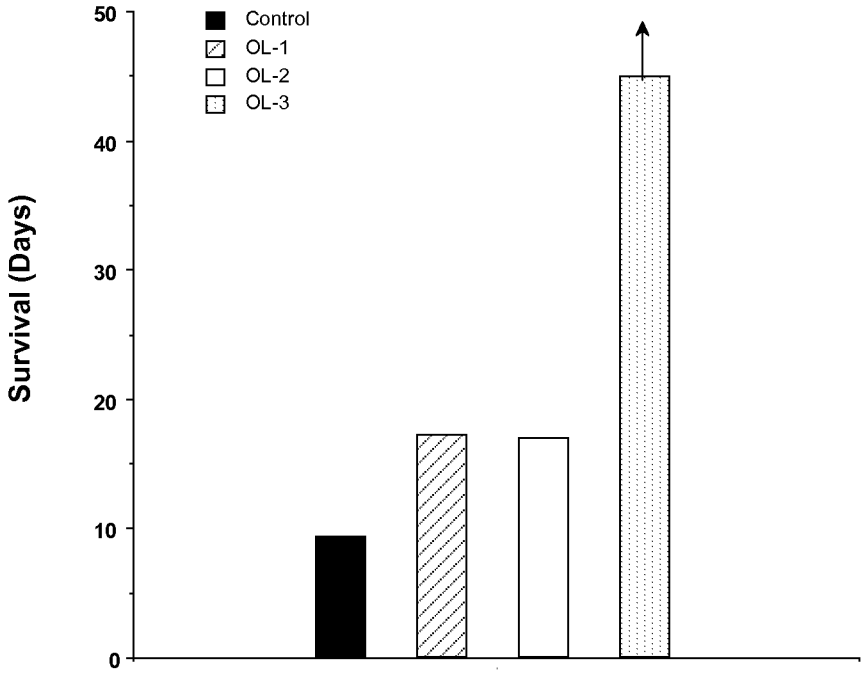

Survival (Days)
50
40
30
20
10
0
Control
OL-1
OL-2
OL-3

Fig. 12

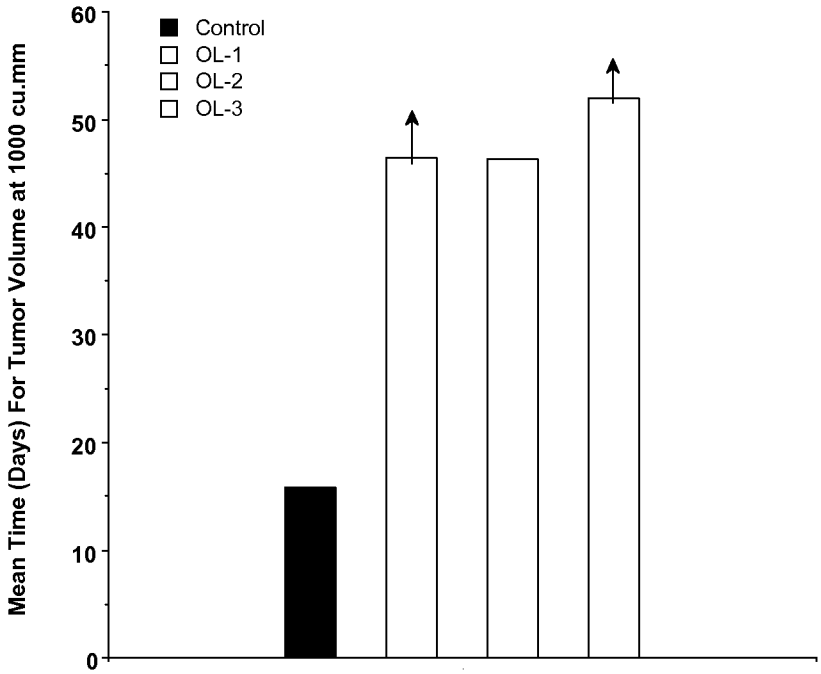

Mean Time (Days) For Tumor Volume at 1000 cu.mm
60
50
40
30
20
10
0
Control
OL-1
OL-2
OL-3

Fig. 13

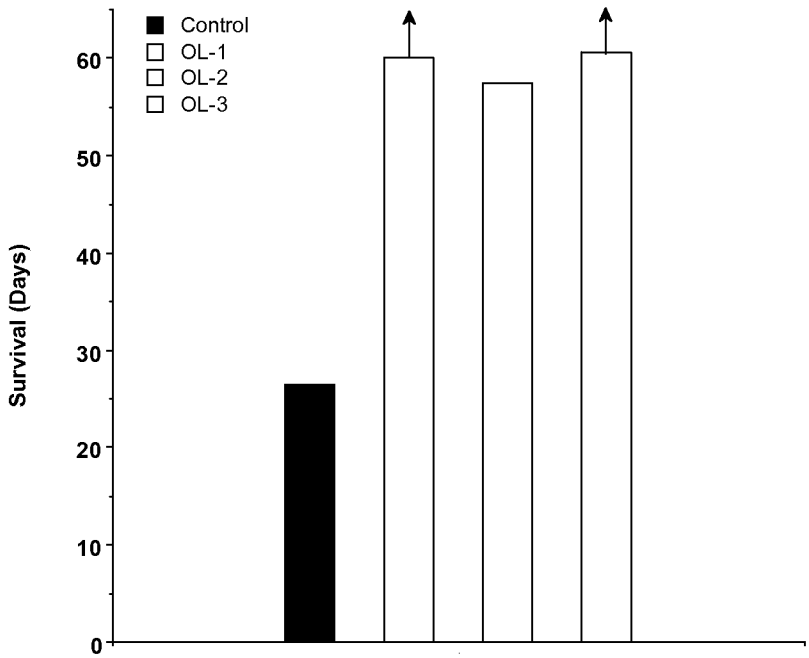


Fig. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/030306

A. CLASSIFICATION OF SUBJECT MATTER

C07J 1/00(2006.01)i, C07D 471/04(2006.01)i, A61K 31/565(2006.01)i, A61P 35/00(2006.01)i, A61P 5/00(2006.01)i

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)

C07J 1/00; C07J 43/00; C07D 491/22; A61K 31/58; A61K 31/56; A61K 31/704; A61K 31/435

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: epiandrosteron, androsteron, hydroxyandrotan, dehydroepiandrosterone, camptothecin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US20090105202 A1 (YANG, LI-XI) 23 April 2009 See claims 1-29; paragraphs [0034], [0044], [0051]-[0069]	1-55,77-81 56-76,84-98
A	US6350756 B1 (YANG, LI-XI) 26 February 2002 See claim 1; column 39, lines 20-46; example 17	1-81,84-98
A	US20050261208 A1 (ROBINSON, C. B. et al.) 24 November 2005 See claim 1; paragraphs [0103]-[0112]	1-81,84-98
A	US20020032160 A1 (NYCE, J. W.) 14 March 2002 See abstract; claim 1	1-81,84-98
A	US6025347 A (GUBERNICK, J. et al.) 15 February 2000 See abstract; claim 1	1-81,84-98

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 APRIL 2012 (25.04.2012)	**27 APRIL 2012 (27.04.2012)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 189 Cheongsa-ro,
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/030306

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 82,83
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 82, 83 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under PCT.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2011/030306

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2011/030306

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