(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 November 2014 (13.11.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/179867 A1

(51) International Patent Classification:
C07C 69/18 (2006.01) *A61P 35/00* (2006.01)
A61K 31/25 (2006.01) *C07C 69/16* (2006.01)

(21) International Application Number:
PCT/CA2014/000414

(22) International Filing Date:
9 May 2014 (09.05.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/822,186 10 May 2013 (10.05.2013) US

(71) Applicants: **BRITISH COLUMBIA CANCER AGENCY BRANCH** [CA/CA]; 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6 (CA). **THE UNIVERSITY OF BRITISH COLUMBIA UNIVERSITY-INDUSTRY LIAISON OFFICE** [CA/CA]; #103-6190 Agronomy Road, Vancouver, British Columbia V6T 1Z3 (CA).

(72) Inventors: **MAWJI, Nasrin R.**; c/o British Columbia Cancer Agency Branch, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6 (CA). **WANG, Jun**; c/o British Columbia Cancer Agency Branch, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6 (CA). **BANUELOS, Carmen Adriana**; c/o British Columbia Cancer Agency Branch, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6 (CA). **ANDERSEN, Raymond John**; c/o The University of British Columbia University-Industry Liaison Office, #103-6190 Agronomy Road, Vancouver, British Columbia V6T 1Z3 (CA). **FERNANDEZ, Javier Garcia**; c/o The University of British Columbia University-Industry Liaison Office, #103-6190 Agronomy Road, Vancouver, British Columbia V6T 1Z3 (CA). **SADAR, Marianne Dorothy**; c/o British Columbia Cancer Agency Branch, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6 (CA).

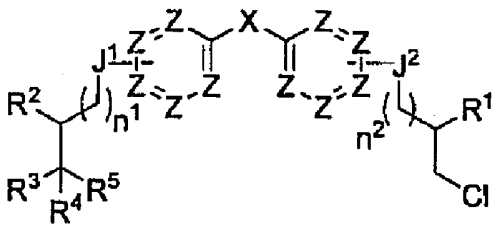
(74) Agent: **DEETH WILLIAMS WALL LLP**; 150 York Street, Suite 400, Toronto, Ontario M5H 3S5 (CA).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

[Continued on next page]

(54) Title: ESTER DERIVATIVES OF ANDROGEN RECEPTOR MODULATORS AND METHODS FOR THEIR USE



I

(57) Abstract: Compounds having a structure of Structure I or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof, wherein R^1, R^2, R^3, R^4, R^5, J^1, J^2, X, Z, $n^1$and n^2 are as defined herein, and wherein at least one of R^1, R^2 or R^3 is an alkyl, alkenyl, aryl or aralkyl ester, are provided. Uses of such compounds for treatment of various indications, including prostate cancer, as well as methods of treatment involving such compounds are also provided.

WO 2014/179867 A1

MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

ESTER DERIVATIVES OF ANDROGEN RECEPTOR MODULATORS AND METHODS FOR THEIR USE

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This Application claims the benefit of U.S. Provisional Application No. 61/822,186, filed on May 10, 2013, the entire contents of which are hereby incorporated by reference in their entirety for all purposes.

STATEMENT OF GOVERNMENT INTEREST

[002] This disclosure was made in part with government support under Grant No. 2R01 CA105304 awarded by the National Cancer Institute. The United States Government has certain rights in this disclosure.

BACKGROUND

Technical Field

[003] This disclosure generally relates to ester derivatives of bisphenol-related compounds and their use for treatment of various indications. In particular the disclosure relates to ester derivatives of bisphenol-related compounds and their use for treatment of various cancers, for example, all stages of prostate cancer, including androgen dependent, androgen-sensitive and castration-resistant prostate cancers.

Description of the Art

[004] Androgens mediate their effects through the androgen receptor (AR). Androgens play a role in a wide range of developmental and physiological responses and are involved in male sexual differentiation, maintenance of spermatogenesis, and male gonadotropin regulation (R. K. Ross, G. A. Coetzee, C. L. Pearce, J. K. Reichardt, P. Bretsky, L. N. Kolonel, B. E. Henderson, E. Lander, D. Altshuler & G. Daley, *Eur Urol* 35, 355-361 (1999); A. A. Thomson, *Reproduction* 121, 187-195 (2001); N. Tanji, K. Aoki & M. Yokoyama, *Arch Androl* 47, 1-7 (2001)). Several lines of evidence show that androgens are associated with the development of prostate carcinogenesis. Firstly, androgens induce prostatic carcinogenesis in rodent models (R. L. Noble, *Cancer Res* 37, 1929-1933 (1977); R. L. Noble, *Oncology* 34, 138-141 (1977)) and men receiving androgens in the form of anabolic steroids have a higher incidence of prostate cancer (J. T. Roberts & D. M. Essenhigh, *Lancet* 2, 742 (1986); J. A.

Jackson, J. Waxman & A. M. Spiekerman, *Arch Intern Med* 149, 2365-2366 (1989); P. D. Guinan, W. Sadoughi, H. Alsheik, R. J. Ablin, D. Alrenga & I. M. Bush, *Am J Surg* 131, 599-600 (1976)). Secondly, prostate cancer does not develop if humans or dogs are castrated before puberty (J. D. Wilson & C. Roehrborn, *J Clin Endocrinol Metab* 84, 4324-4331 (1999); G. Wilding, *Cancer Surv* 14, 113-130 (1992)). Castration of adult males causes involution of the prostate and apoptosis of prostatic epithelium while eliciting no effect on other male external genitalia (E. M. Bruckheimer & N. Kyprianou, *Cell Tissue Res* 301, 153-162 (2000); J. T. Isaacs, *Prostate* 5, 545-557 (1984)). This dependency on androgens provides the underlying rationale for treating prostate cancer with chemical or surgical castration (androgen ablation).

[005] Androgens also play a role in female cancers. One example is ovarian cancer where elevated levels of androgens are associated with an increased risk of developing ovarian cancer (K. J. Helzlsouer, A. J. Alberg, G. B. Gordon, C. Longcope, T. L. Bush, S. C. Hoffman & G. W. Comstock, *JAMA* 274, 1926-1930 (1995); R. J. Edmondson, J. M. Monaghan & B. R. Davies, *Br J Cancer* 86, 879-885 (2002)). The androgen receptor has been detected in a majority of ovarian cancers (H. A. Risch, *J Natl Cancer Inst* 90, 1774-1786 (1998); B. R. Rao & B. J. Slotman, *Endocr Rev* 12, 14-26 (1991); G. M. Clinton & W. Hua, *Crit Rev Oncol Hematol* 25, 1-9 (1997)), whereas estrogen receptor-alpha (ERa) and the progesterone receptor are detected in less than 50% of ovarian tumors.

[006] An effective treatment available for advanced prostate cancer is the withdrawal of androgens which are essential for the survival of prostate epithelial cells. Androgen ablation therapy causes a temporary reduction in tumor burden concomitant with a decrease in serum prostate-specific antigen (PSA). Unfortunately prostate cancer can eventually grow again in the absence of testicular androgens (castration-resistant disease) (Huber *et al* 1987 *Scand J. Urol Nephrol.* 104, 33-39). Castration-resistant prostate cancer is biochemically characterized before the onset of symptoms by a rising titre of serum PSA (Miller et al 1992 *J. Urol.* 147, 956-961). Once the disease becomes castration-resistant most patients succumb to their disease within two years.

[007] The androgen receptor has distinct functional domains that include the carboxy-terminal ligand-binding domain (LBD), a DNA-binding domain (DBD) comprising two zinc finger motifs, and an N-terminus domain (NTD) that contains one or more transcriptional activation domains. Binding of androgen (ligand) to the LBD of the androgen receptor results in its activation such that the receptor can effectively bind to its specific DNA

consensus site, termed the androgen response element (ARE), on the promoter and enhancer regions of "normally" androgen regulated genes, such as PSA, to initiate transcription. The androgen receptor can be activated in the absence of androgen by stimulation of the cAMP-dependent protein kinase (PKA) pathway, with interleukin-6 (IL-6) and by various growth factors (Culig *et al* 1994 *Cancer Res.* 54, 5474-5478; Nazareth *et al* 1996 *J. Biol. Chem.* 271, 19900-19907; Sadar 1999 *J. Biol. Chem.* 274, 7777-7783; Ueda *et al* 2002 A *J. Biol. Chem.* 277, 7076-7085; and Ueda *et al* 2002 B *J. Biol. Chem.* 277, 38087-38094). The mechanism of ligand-independent transformation of the androgen receptor AR has been shown to involve: 1) increased nuclear androgen receptor protein suggesting nuclear translocation; 2) increased androgen receptor /ARE complex formation; and 3) the AR-NTD (Sadar 1999 *J. Biol. Chem.* 274, 7777-7783; Ueda *et al* 2002 A *J. Biol. Chem.* 277, 7076-7085; and Ueda *et al* 2002 B *J. Biol. Chem.* 277, 38087-38094). The androgen receptor may be activated in the absence of testicular androgens by alternative signal transduction pathways in castration-resistant disease, which is consistent with the finding that nuclear androgen receptor protein is present in secondary prostate cancer tumors (Kim *et al* 2002 *Am. J. Pathol.* 160, 219-226; and van der Kwast *et al* 1991 *Inter. J. Cancer* 48, 189-193).

[008] Available inhibitors of the androgen receptor include nonsteroidal antiandrogens such as bicalutamide, nilutamide, flutamide, enzalutamide, and investigational drug ARN-509, and the steroidal antiandrogen, cyproterone acetate. These antiandrogens target the LBD of the androgen receptor and predominantly fail presumably due to poor affinity and mutations that lead to activation of the androgen receptor by these same antiandrogens (Taplin, M.E., Bubley, G.J., Kom Y.J., Small E.J., Uptonm M., Rajeshkumarm B., Balkm S.P., *Cancer Res.*, 59, 2511-2515 (1999)). These antiandrogens would also have no effect on the recently discovered androgen receptor splice variants that lack the ligand-binding domain (LBD) to result in a constitutively active receptor which promotes progression of androgen-independent prostate cancer (Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ., *Cancer Res* 68, 5469-77, 2008; Guo Z, Yang X, Sun F, Jiang R, Linn DE, Chen H, Chen H, Kong X, Melamed J, Tepper CG, Kung HJ, Brodie AM, Edwards J, Qiu Y., *Cancer Res.* 69, 2305-13, 2009; Hu et al 2009 Cancer Res. 69, 16-22; Sun et al 2010 J Clin Invest. 2010 120, 2715-30).

[009] Conventional therapy has concentrated on androgen-dependent activation of the androgen receptor through its C-terminal domain. Recent studies developing antagonists to the androgen receptor have concentrated on the C-terminus and specifically: 1) the allosteric

pocket and AF-2 activity (Estébanez-Perpiñá *et al* 2007, *PNAS* 104, 16074-16079); 2) *in silico* "drug repurposing" procedure for identification of nonsteroidal antagonists (Bisson *et al* 2007, *PNAS* 104, 11927 – 11932); and coactivator or corepressor interactions (Chang *et al* 2005, *Mol Endocrinology* 19, 2478-2490; Hur *et al* 2004, *PLoS Biol* 2, E274; Estébanez-Perpiñá *et al* 2005, *JBC* 280, 8060-8068; He *et al* 2004, *Mol Cell* 16, 425-438).

[010] The AR-NTD is also a target for drug development (e.g. WO 2000/001813), since the NTD contains Activation-Function-1 (AF-1) which is the essential region required for androgen receptor transcriptional activity (Jenster et al 1991. Mol Endocrinol. 5, 1396-404). The AR-NTD importantly plays a role in activation of the androgen receptor in the absence of androgens (Sadar, M.D. 1999 *J. Biol. Chem.* 274, 7777-7783; Sadar MD *et al* 1999 *Endocr Relat Cancer.* 6, 487-502; Ueda *et al* 2002 *J. Biol. Chem.* 277, 7076-7085; Ueda 2002 *J. Biol. Chem.* 277, 38087-38094; Blaszczyk *et al* 2004 *Clin Cancer Res.* 10, 1860-9; Dehm *et al* 2006 *J Biol Chem.* 28, 27882-93; Gregory *et al* 2004 *J Biol Chem.* 279, 7119-30). The AR-NTD is important in hormonal progression of prostate cancer as shown by application of decoy molecules (Quayle *et al* 2007, *Proc Natl Acad Sci U S A.* 104,1331-1336).

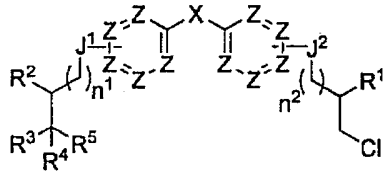
[011] While the crystal structure has been resolved for the androgen receptor C-terminus LBD, this has not been the case for the NTD due to its high flexibility and intrinisic disorder in solution (Reid *et al* 2002 *J. Biol. Chem.* 277, 20079-20086) thereby hampering virtual docking drug discovery approaches.

[012] Although progress has been made, there remains a need in the art for additional and/or improved compounds that modulate the androgen receptor. The present disclosure provides these and related advantages.

BRIEF SUMMARY

[013] This disclosure is based in part on the unexpected discovery that certain esters of bisphenol-related compounds have desirable properties for use as modulators of androgen receptor. In particular, the esters described herein are potent modulators of androgen receptor. Further advantages related to use of the described esters for modulation of androgen receptor (in vitro or in vivo) are also expected.

[014] In accordance with one embodiment, there is provided a compound having a structure of Structure I:



I

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein R^1, R^2, R^3, R^4, R^5, J^1, J^2, X, Z, n^1 and n^2 are as defined herein, and wherein at least one of R^1, R^2 or R^3 is an alkyl, alkenyl, aryl or aralkyl ester. Pharmaceutical compositions comprising a compound of Structure I, a pharmaceutically acceptable carrier and an optional additional therapeutic agent are also provided.

[015] In other embodiments, the present disclosure provides the use of a compound of Structure I or a composition comprising the same, for modulating androgen receptor (AR) activity. Related methods for modulating androgen receptor are also provided.

[016] These and other aspects of the disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

[017] **FIG. 1A** is a ^{1}H NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate.

[018] **FIG. 1B** is a ^{13}C NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate.

[019] **FIG. 1C** is a ^{13}C APT NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate.

[020] **FIG. 2A** is a ^{1}H NMR spectrum for the compound (S)-1-chloro-3-(4-(2-(4-((R)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate.

[021] **FIG. 2B** is a ^{13}C NMR spectrum for the compound (S)-1-chloro-3-(4-(2-(4-((R)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate.

[022] **FIG. 2C** is a ^{13}C APT NMR spectrum for the compound (S)-1-chloro-3-(4-(2-(4-((R)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate.

[023] **FIG. 3A** is a ^{1}H NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[024] **FIG. 3B** is a ^{13}C NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[025] **FIG. 4A** is a ^{1}H NMR spectrum for the compound (S)-3-(4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[026] **FIG. 4B** is a ^{13}C NMR spectrum for the compound (S)-3-(4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[027] **FIG. 4C** is a ^{13}C APT NMR spectrum for the compound (S)-3-(4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[028] **FIG. 5A** is a ^{1}H NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[029] **FIG. 5B** is a ^{13}C NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[030] **FIG. 5C** is a ^{13}C APT NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

[031] **FIG. 6A** is a ^{1}H NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate.

[032] **FIG. 6B** is a ^{13}C NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate.

[033] **FIG. 6C** a ^{13}C APT NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate.

[034] **FIG. 6D** illustrates electrospray ionization mass spectrometry data for (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate with positive ion polarity.

[035] **FIG. 6E** illustrates electrospray ionization mass spectrometry data for (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate with negative ion polarity.

[036] **FIG. 7A** is a ^{1}H NMR spectrum for the compound (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate.

[037] **FIG. 7B** is a ^{13}C NMR spectrum for the compound (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate.

[038] **FIG. 7C** is a ^{13}C APT NMR spectrum for the compound (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate

[039] **FIG. 7D** illustrates electrospray ionization mass spectrometry data for (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate with positive ion polarity.

[040] **FIG. 7E** illustrates electrospray ionization mass spectrometry data for (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate with negative ion polarity.

[041] **FIG. 8** illustrates dose response data for various compounds of the disclosure (3c, 7c, and 13b) and comparative compounds.

[042] **FIG. 9** illustrates dose response data for various compounds of the disclosure (1c, 3c, 7c, (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Example 21)) and comparative compounds.

[043] **FIG. 10** depicts cell proliferation assays, which demonstrate that a compound (7c) of the disclosure is twice as potent as its active compound (compound A).

[044] **FIG. 11** illustrates that a compound of the disclosure (7c) is effective at reducing tumor volume in a xenograft model.

[045] **FIG. 12** illustrates that a compound of the disclosure (7c) is effective at inhibiting the growth of LNCaP xenograft tumors.

[046] **FIG. 13** illustrates the IC50's of various compounds of the disclosure.

[047] **FIG. 14A** is a ^{1}H NMR spectrum for the compound 1-chloro-3-(4-(2-(4-(2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol bispropionate.

[048] **FIG. 14B** is a ^{13}C NMR spectrum for the compound 1-chloro-3-(4-(2-(4-(2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol bispropionate.

[049] **FIG. 15A** is a ^{1}H NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-(propionyloxy)propoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl dipropionate.

[050] **FIG. 15B** is a ^{13}C NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-3-chloro-2-(propionyloxy)propoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl dipropionate.

[051] **FIG. 16A** is a ^{1}H NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-2-(butyryloxy)-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl dibutyrate.

[052] **FIG. 16B** is a ^{13}C NMR spectrum for the compound (S)-3-(4-(2-(4-((S)-2-(butyryloxy)-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl dibutyrate.

DETAILED DESCRIPTION

I. Definitions

[053] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the disclosure may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed disclosure.

[054] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[055] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[056] "Amino" refers to the $-NH_2$ radical.

[057] "Cyano" refers to the -CN radical.

[058] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[059] "Imino" refers to the =NH substituent.

[060] "Nitro" refers to the $-NO_2$ radical.

[061] "Oxo" refers to the =O substituent.

[062] "Thioxo" refers to the =S substituent.

[063] "Alkyl" refers to a straight, branched or non-aromatic cyclic hydrocarbon ("cycloalkyl") chain radical which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), having from one to twenty carbon atoms (e.g., one to ten, or one to six carbon atoms), and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 20 are included. An alkyl comprising up to 10 carbon atoms is a C_1-C_{10} alkyl. A C_1-C_{10} alkyl includes C_{10} alkyls, C_9 alkyls, C_8 alkyls, C_7 alkyls, C_6 alkyls, C_5 alkyls, C_4 alkyls, C_3 alkyls, C_2 alkyls and C_1 alkyl (*i.e.*, methyl) and includes, for example, and without limitation, saturated C_1-C_{10} alkyl, C_2-C_{10} alkenyl and C_2-C_{10} alkynyl. Non-limiting examples of saturated C_1-C_{10} alkyl include methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i-butyl, sec-butyl, t-butyl and n-penty, n-hexyl, n-heptane, and the like. Non-limiting examples of C_2-C_{10} alkenyl include vinyl, allyl, isopropenyl, 1-propene-2-yl, 1-butene-1-yl, 1-butene-2-yl, 1-butene-3-yl, 2-butene-1-yl, 2-butene-2-yl, penteneyl , hexeneyl, and the like. Non-limiting examples of C_2-C_{10} alkynyl include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted (*i.e.*, a hydrogen atom in the alkyl group may be replaced with an optional substituent). Alkyls include cycloalkyls as defined below.

[064] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), and having from one to twenty carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, ethenylene, propenylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single or double bond and to the radical group through a single or double bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain may be optionally substituted.

[065] "Aliphatic carbon" refers to a carbon atom which is not aromatic.

[066] "Alkylaminocarbonyl" refers to a radical of the formula –C(=O)NR_aR_b where R_a and R_b are each independently an alkyl radical as defined above containing one to twenty carbon atoms. Unless stated otherwise specifically in the specification, an alkylaminocarbonyl group may be optionally substituted.

[067] "Alkylcarbonyl" refers to a radical of the formula –C(=O)R_a where R_a is an alkyl radical as defined above containing one to twenty carbon atoms. Unless stated otherwise specifically in the specification, an alkylcarbonyl group may be optionally substituted.

[068] "Alkoxy" refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined above containing one to twenty carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted.

[069] "Alkylamino" refers to a radical of the formula -NHR_a or -NR_aR_a where each R_a is, independently, an alkyl radical as defined above containing one to twenty carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted.

[070] "Aminocarbonyl" refers to a radical of the formula –C(=O)NH_2. Unless stated otherwise specifically in the specification, an alkylcarbonyl group may be optionally substituted.

[071] "Aromatic carbon" refers to a carbon atom which is part of an aromatic ring. Aromatic carbons are SP^2 hybridzed and from part of a conjugated, unsaturated ring system having 4n+2 electrons in pi orbitals. For example, aromatic carbons may be members on an aryl or heteroaryl ring as defined herein.

[072] "Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this disclosure, the aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

[073] "Aralkyl" refers to a radical of the formula -R_b-R_c where R_b is an alkylene chain as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl,

diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group may be optionally substituted.

[074] "Carbocycle" refers to a cyclic structure, wherein the bonds that form the ring are each carbon-carbon bonds. Carbocycles generally contain from 3 to 20 carbon atoms within the ring and may be mon, bi or tri- cyclic. Bi and tricyclic carbocycles may be fused (*i.e.*, share two or more common carbon atoms), spiro (*i.e.*, share one common carbon atom) or linked via a linker atom or atoms. Carbocycles, include cycloalkyls and aryls as defined herein. Unless stated otherwise specifically in the specification, carbocycle group may be optionally substituted.

[075] "Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

[076] "Deuteroalkyl" refers to an alkyl radical as defined above, wherein at least one of the hydrogen atoms is replaced with a deuterium atom. Unless stated otherwise specifically in the specification, deuteroalkyl group may be optionally substituted.

[077] "Fused" refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the disclosure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with a nitrogen atom.

[078] "Halogen" or "halo" refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I) substituents. Halogen substitutents also include halogen radioisotopes.

[079] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

[080] "Heterocyclyl" or "heterocyclic ring" refers to a stable 3- to 18-membered ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group may be optionally substituted. Heterocycles include heteroaryls as defined below.

[081] "Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of this disclosure, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl,

pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group may be optionally substituted.

[082] The term "substituted" used herein means any of the above groups (*i.e.*, alkyl, alkylene, alkylaminocarbonyl, alkylcarbonyl, alkoxy, alkylamino, aminocarbonyl, cycloalkyl, aryl, aralkyl, carbocycle, deuteroalkyl, haloalkyl, heterocyclyl, and/or heteroaryl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, glycines, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo (i.e., C=O), carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles.

[083] For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$.

[084] "Substituted also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl.

[085] "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl,

heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents.

[086] "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the disclosure that is pharmaceutically acceptable. A prodrug may be active or inactive when administered to a subject in need thereof, but is converted *in vivo* to an active (or more active) compound. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam)). A discussion of prodrugs is provided in Higuchi, T., et al., A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, Ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987. The present disclosure is meant to ecompass all compounds of structure I, whether acting as a prodrug or the active compound itself, or both.

[087] The disclosure disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of Structure (I) being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabelled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labelled compounds of Structure (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[088] Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[089] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O, I^{123} and ^{13}N, can be useful in Positron Emission Topography (PET) or Single Photon Emission Computed Tomography (SPECT) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Structure (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[090] The disclosure disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the disclosure includes compounds produced by a process comprising administering a compound of this disclosure to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabelled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[091] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[092] "Mammal" includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[093] "Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[094] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer,

isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[095] "Pharmaceutically acceptable salt" includes both acid and base addition salts.

[096] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

[097] "Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine,

hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

[098] Often crystallizations produce a solvate of the compound of the disclosure. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the disclosure with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present disclosure may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compound of the disclosure may be true solvates, while in other cases, the compound of the disclosure may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

[099] A "pharmaceutical composition" refers to a formulation of a compound of the disclosure and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

[0100] An "effective amount" refers to a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result, such as reduced tumor size, increased life span or increased life expectancy. A therapeutically effective amount of a compound may vary according to factors such as the disease state, age, sex, and weight of the subject, and the ability of the compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the compound are outweighed by the therapeutically beneficial effects.
[0101] A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result, such as smaller tumors, increased life span, increased life expectancy or prevention of the progression of prostate cancer to an androgen-independent form. Typically, a prophylactic dose is used in subjects prior to or at an earlier stage of disease, so that a prophylactically effective amount may be less than a therapeutically effective amount.

[0102] "Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes:

(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, *i.e.*, arresting its development;

(iii) relieving the disease or condition, *i.e.*, causing regression of the disease or condition; or

(iv) relieving the symptoms resulting from the disease or condition, *i.e.*, relieving pain without addressing the underlying disease or condition. As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

[0103] The compounds of the disclosure, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms.

[0104] Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

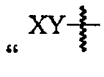
[0105] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable.

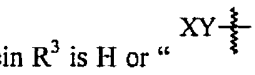
The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

[0106] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule accompanied by a switch of a single bond and adjacent double bond. The present disclosure includes tautomers of any said compounds.

[0107] The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program and/or ChemDraw Ultra Version 11.0.1 software naming program (CambridgeSoft), wherein the compounds of the disclosure are named herein as derivatives of the central core structure. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

[0108] As used herein, the symbol "  " (hereinafter may be referred to as "a point of attachment bond") denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond.

[0109] For example, "  " indicates that the chemical entity "XY" is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non-depicted chemical entity may be specified by inference.

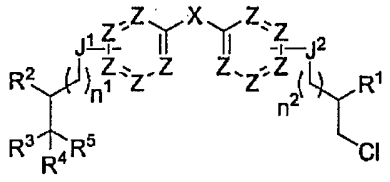
[0110] For example, the compound CH_3-R^3, wherein R^3 is H or "  " infers that when R^3 is "XY", the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3.

II. Compounds and Compositions

[0111] As noted above, certain embodiments of the present disclosure are directed to compounds useful for modulation of androgen receptor. As such, the compounds find utility

for treatment of various cancers, including various types of prostate cancers. The esters derivatives described herein are expected to have improved properties relative to other known androgen receptor modulators which do not contain the described ester moieties.

[0112] Accordingly, one embodiment of the present disclosure is directed to a compound having a structure of Structure I:



(I)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

[0113] J^1 and J^2 are each independently -O-, $-S(O)_m$-, $-NR^6$- or $-(CR^6R^7)$-;

[0114] X is a direct bond, $-C(R^8R^9)$-, $-C(=CR^8R^9)$-, $-C(R^8R^9)$-aryl-$C(R^8R^9)$-, $-C(=CR^8R^9)$-aryl-$C(=CR^8R^9)$-, $-C(=CR^8R^9)$-aryl-$C(R^8R^9)$-, $-C(R^8R^9)$-aryl-$C(=CR^8R^9)$-, -O-, $-S(O)_m$-, $-N(R^6)$-, $-CH(NR^6R^7)$-, $-C(=NOR^6)$-, $-C(=N\text{-}NHR^{10})$-, $-C(=NR^6)$- or -C(=O)-;

[0115] Z is, at each occurrence, independently $-C(R^{11})$- or –N-;

[0116] R^1 is hydroxyl, $-OR^{12}$ or $-OC(=O)R^{13}$;

[0117] R^2 and R^3 are each independently hydroxyl, halo, $-OR^{12}$ or $-OC(=O)R^{13}$;

[0118] R^4 and R^5 are each independently H or halo;

[0119] R^6 and R^7 are, at each occurrence, independently H or $C_{1\text{-}10}$ alkyl;

[0120] R^8 and R^9 are, at each occurrence, independently, H, hydroxyl, halo, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_1-C_{10} deuteroalkyl, C_1-C_{10} alkoxy, aryl, aralkyl, $-S(O)_mR^{14}$ or $-NR^6R^7$, or R^8 and R^9 may join to form a mono-, bi- or tri-cyclic carbocycle or heterocycle containing from 3 to 20 carbon atoms;

[0121] R^{10} is H, C_1-C_{10} alkyl, aryl, aminocarbonyl, C_1-C_{10} alkylcarbonyl or C_1-C_{10} alkylaminocarbonyl;

[0122] R^{11} is, at each occurrence, independently H, halo or C_1-C_{10} alkyl;

[0123] R^{12} is, at each occurrence, independently C_1-C_{20} alkyl or C_2-C_{20} alkenyl;

[0124] R^{13} is, at each occurrence, independently C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl or aralkyl, wherein the C_1-C_{20} alkyl does not include optional amino or alkylamino substituents and each aliphatic carbon of the C_1-C_{20} alkyl, C_2-C_{20} alkenyl or aralkyl groups may optionally be replaced with –O- or $-S(O)_m-$;

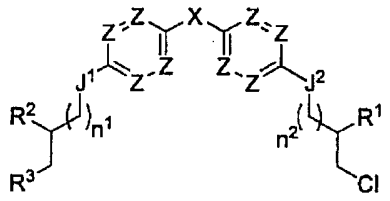
[0125] R^{14} is H, C_1-C_{10} alkyl or aryl;

[0126] m is, at each occurrence, independently 0, 1 or 2;

[0127] n^1 and n^2 are each independently 0, 1, 2, 3, 4 or 5,

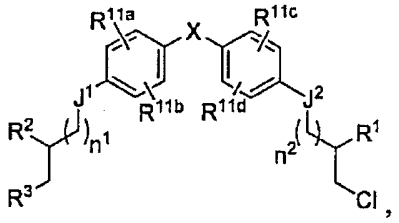
[0128] wherein at least one of R^1, R^2 or R^3 is $-OC(=O)R^{13}$.

[0129] In other embodiments, the compound has the following structure (Ia):



(Ia)

[0130] In still other embodiments, the compound has the following structure (Ib):



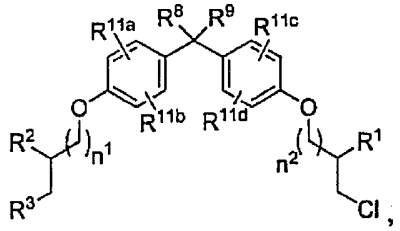
(Ib)

[0131] wherein R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, halo or C_1-C_{10} alkyl.

[0132] In any of the foregoing embodiments, J^1 and J^2 are each -O-.

[0133] In other of any of the foregoing embodiments, X is $-C(R^8R^9)-$.

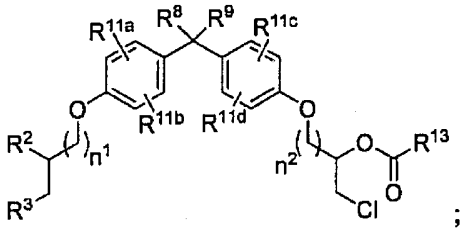
[0134] In still other of the foregoing embodiments, the compound has the following structure (Ic):



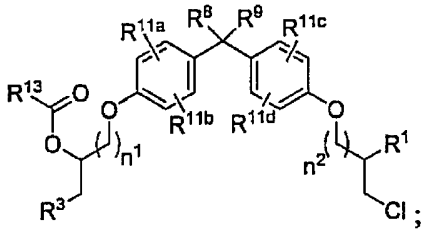
(Ic)

[0100] wherein R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, halo or C_1-C_{10} alkyl.

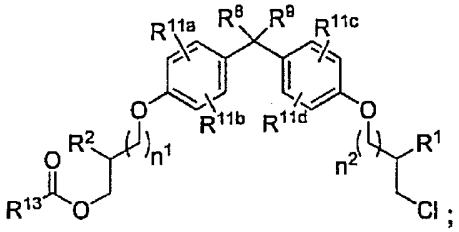
[0101] In yet other of the foregoing embodiments, the compound has one of the following structures (Id), (Ie), (If), (Ig), (Ih), (Ii) or (Ij):



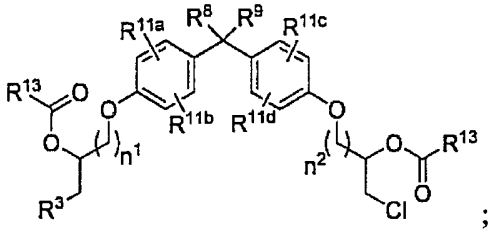
(Id)



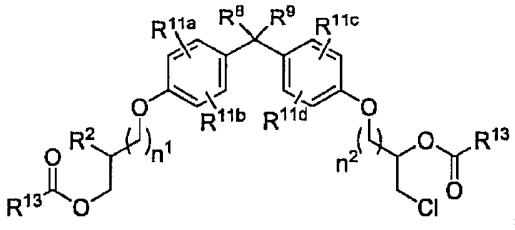
(Ie)



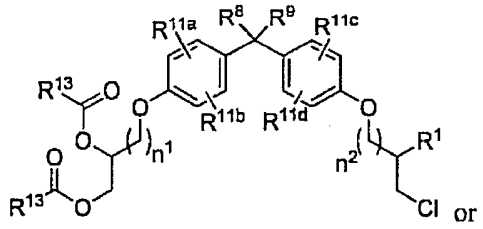
(If)



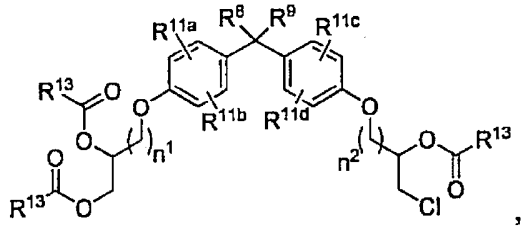
(Ig)



(Ih)



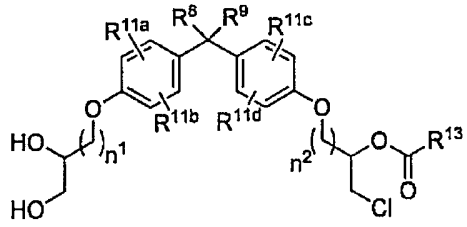
(Ii)



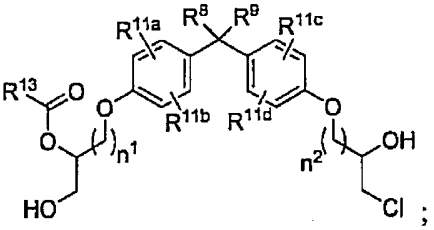
(Ij)

wherein R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, halo or C_1-C_{10} alkyl.

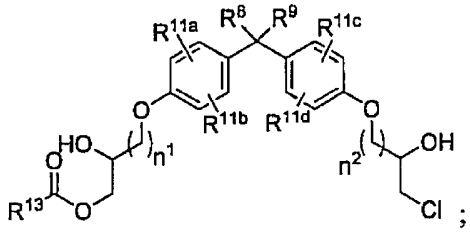
[0102] In still more of the foregoing embodiments, the compound has one of the following structures (Ik), (Il), (Im), (In), (Io) or (Ip):



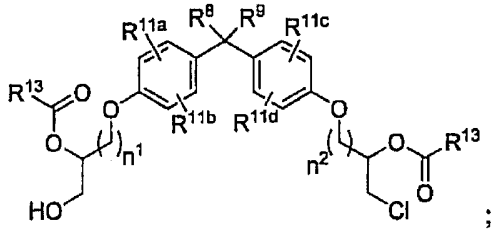
(Ik)



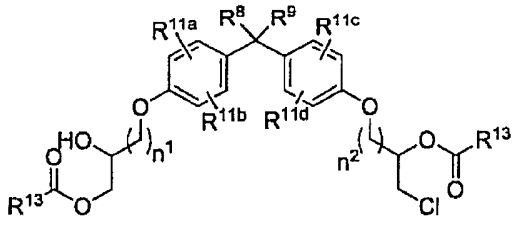
(Il)



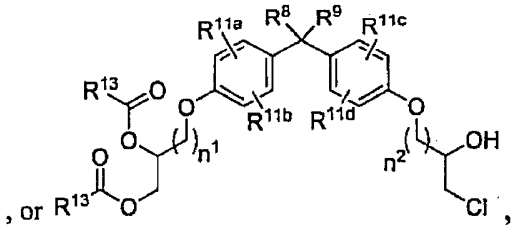
(Im)



(In)



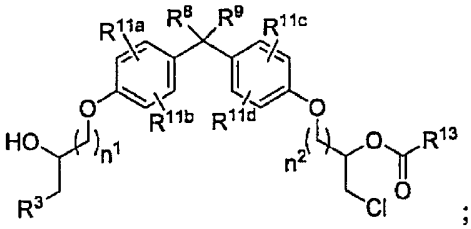
(Io)



(Ip)

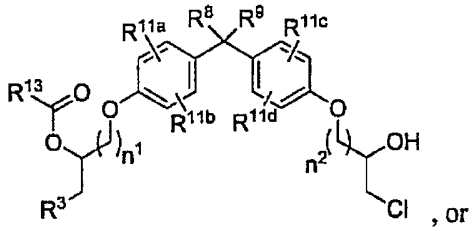
[0103] wherein R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, halo or C_1-C_{10} alkyl.

[0104] In other embodiments of any of the foregoing, the compound has one of the following structures (Iq), (Ir) or (Is):



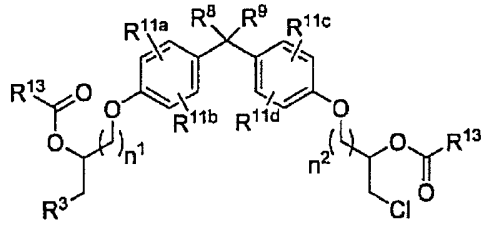
(Iq)

;



(Ir)

, or



(Is)

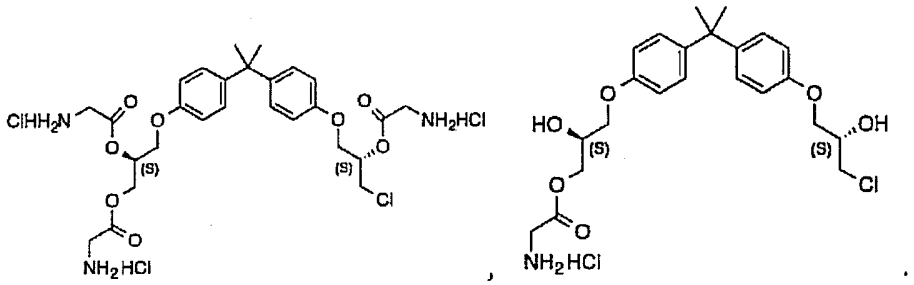
[0105] In some embodiments of the foregoing R^3 is $-OR^{12}$. For example, in some embodiments R^{12} is C_1-C_6 alkyl. In other embodiments, R^{12} is methyl, isopropyl or *n*-butyl.

[0106] In still other embodiments of any of the foregoing, R^3 is halo. For example, in some embodiments R^3 is fluoro.

[0107] In certain embodiments, the compounds include at least one alkyl ester. Accordingly, in some embodiments each R^{13} is independently C_1-C_{20} alkyl, for example C_1-C_6 alkyl. In some of these embodiments, the C_1-C_{20} or C_1-C_6 alkyl is unsubstituted. In some further embodiments, each R^{13} is independently methyl, ethyl or propyl. In even further embodiments, each R^{13} is methyl.

[0108] In yet other embodiments, the R^{13} is substituted. For example, in certain embodiments, the R^{13} is a substituted C_1-C_{20} alkyl or a substituted C_1-C_6 alkyl. In particular embodiments, the R^{13} subsituted alkyl comprises a Nitrogen substituent. In an aspect, the Nitrogen substituted R^{13} alkyl is methyl, which together with the adjacent carbonyl group forms a glycine substituent. In a particular aspect, the R^{13} substituted alkyl is a methyl with a Nitrogen and a terminal Chlorine, *i.e.* NH_2HCl.

[0109] In particular embodiments, the glycince substituted compounds with a terminal Chlorine are as follows:



[0110] In more embodiments of any of the foregoing compounds of Structure I, R^8 and R^9 are each independently C_1-C_6 alkyl. For example, in some embodiments R^8 and R^9 are each methyl.

[0111] In still other embodiments of any of the foregoing compounds of Structure I, at least one R^{11} is H or at least one of R^{11a}, R^{11b}, R^{11c} or R^{11d} is H. For example, in some embodiments each R^{11} is H or each of R^{11a}, R^{11b}, R^{11c} and R^{11d} is H..

[0112] In more embodiments of the foregoing, at least one of n^1 or n^2 is 1. In other embodiments of the foregoing, n^1 and n^2 are each 1. In some embodiments, n^1 is 2. In some embodiments, n^1 is 3. In some embodiments, n^1 is 4. In some embodiments, n^1 is 2. In some embodiments, n^2 is 2. In some embodiments, n^1 is 3. In some embodiments, n^1 is 4. In some embodiments, n^1 is 5.

[0113] In other embodiments, R^4 and R^5 are each H. In some different embodiments, at least one of R^4 or R^5 is halo. For example, in some embodiments R^4 and R^5 are each halo. In some of these foregoing embodiments, halo is fluoro.

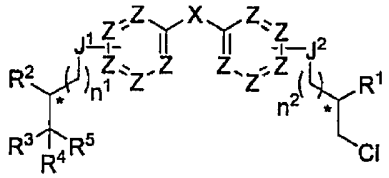
[0114] In some of the forgoing embodiments, R^{13} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl or aralkyl, and at least one of the aliphatic carbons of the C_1-C_{20} alkyl, C_2-C_{20} alkenyl or aralkyl group is substituted with a substituent. For example, the substituent may be selected from hydroxyl, halo, oxo and alkoxy. In other embodiments, the C_1-C_{20} alkyl, C_2-C_{20} alkenyl or aralkyl is unsubstituted.

[0115] In some other embodiments, R^{13} is aryl or aralkyl, and at least one of the aromatic carbons of the aryl or aralkyl group is substituted with a substituent For example, in some embodiments the substituent is selected from hydroxyl, halo and alkoxy. In other embodiments, the aryl or aralkyl is unsubstituted.

[0116] The compounds described herein are meant to include all racemic mixtures and all individual enantiomers or combinations thereof, whether or not they are specifically depicted herein. Accordingly, the compounds include racemic mixtures, enantiomers and diastereomers of any of the compounds described herein. Tautomers of any of the compounds of Structure I are also included within the scope of the disclosure.

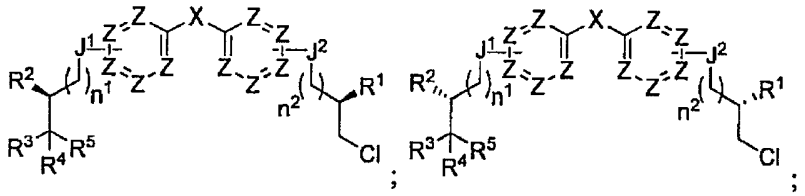
[0117] As noted above, the compounds of the present disclosure (*i.e.*, compounds of Structure 1) may contain one or more asymmetric centers. Accordingly, in some embodiments the compounds are mixtures of different enantiomers (*e.g.*, R and S) or different diastereomers. In other embodiments, the compounds are pure (or enriched) enantiomers or diastereomers. For purpose of clarity, the chiral carbons are not always depicted in the compounds; however, the present disclosure includes all stereoisomers (pure and mixtures) of all compounds of Structure I.

[0118] By way of example, compounds of Structure I contain at least two stereocenters marked with an * below:



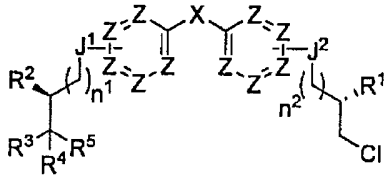
(I)

[0119] Although the compounds are generally depicted as above, the scope of the disclosure includes all possible stereoisomers. For example, with respect to Structure I, the disclosure also includes the following stereoisomers (I'), (I''), (I''') and (I''''):

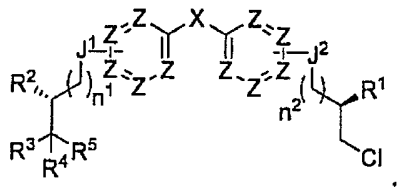


(I') ;

(I'') ;



(I''') , and



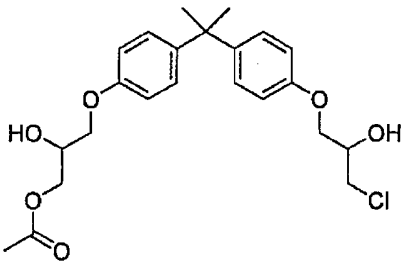
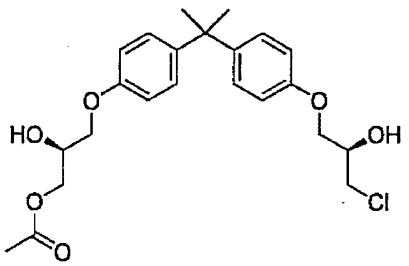
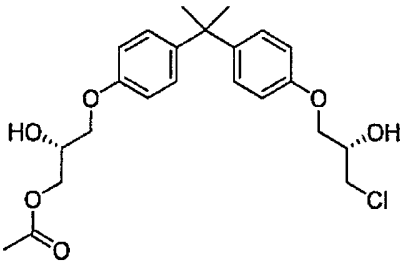
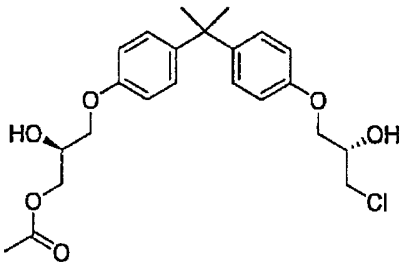
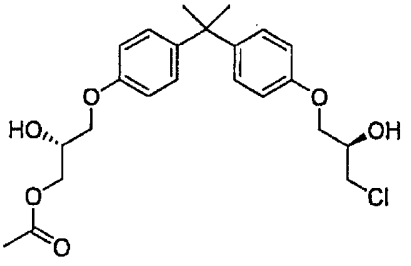
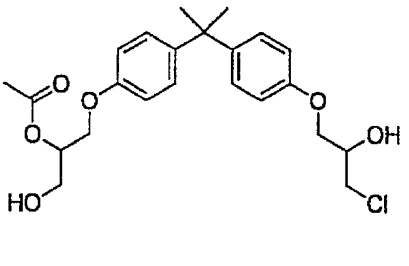
(I'''').

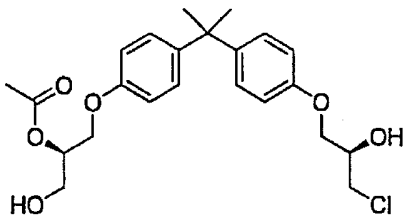
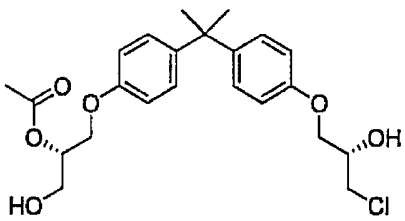
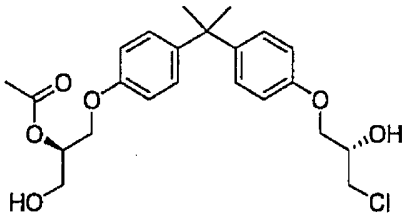
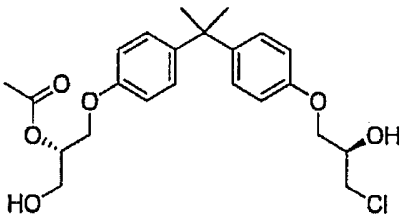
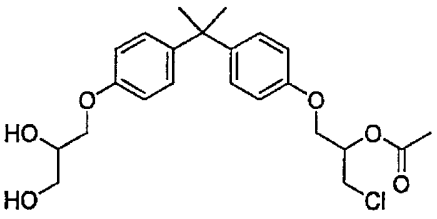
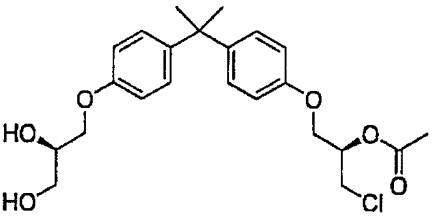
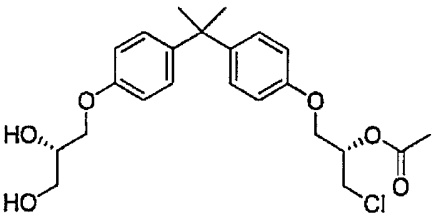
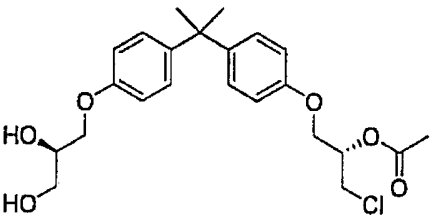
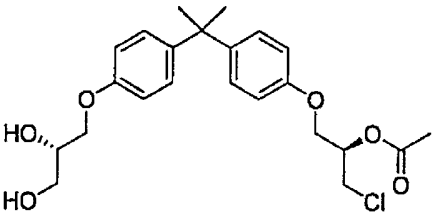
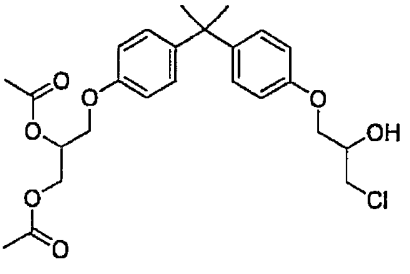
(I''') (I'''')

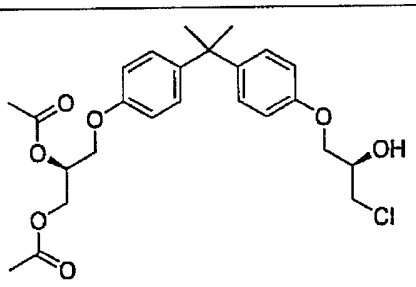
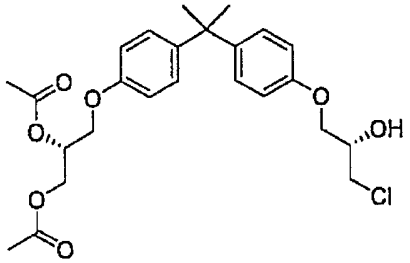
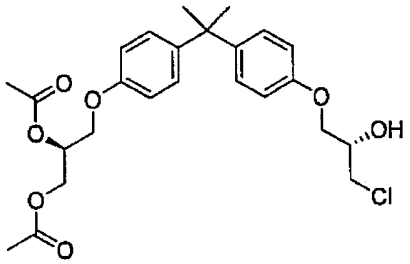
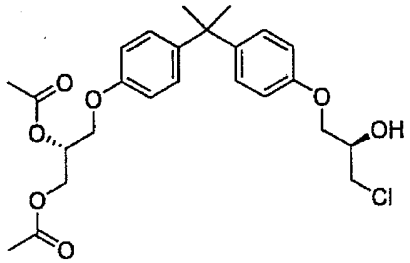
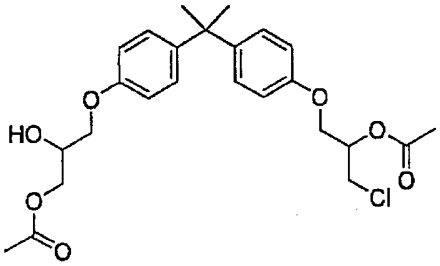
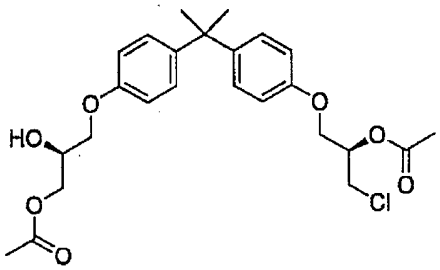
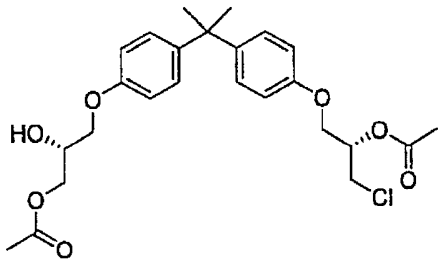
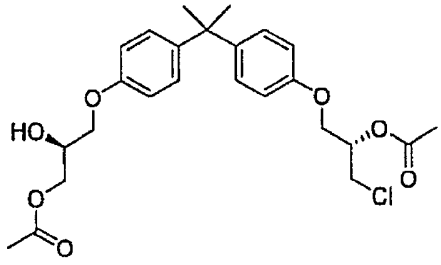
[0120] In an analogous fashion, the disclosure includes all possible stereoisomers of all compounds of Structure I (*e.g.*, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im, In, Io, Ip, Iq, Ir and Is), including the compounds provided in Table 1. One of ordinary skill in the art will readily understand how to derive all possible stereoisomers, especially in reference to the above example.

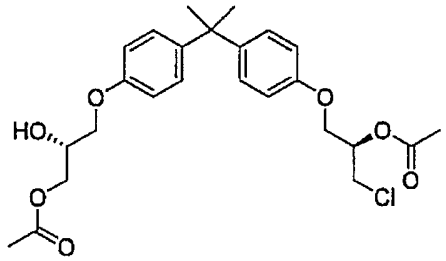
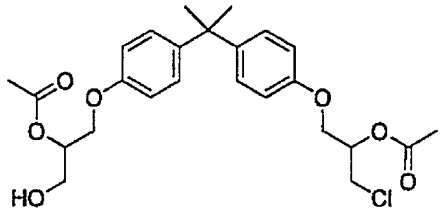
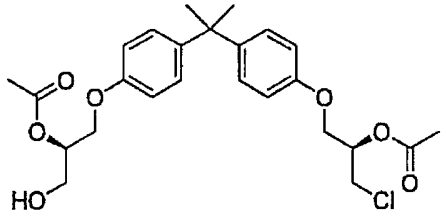
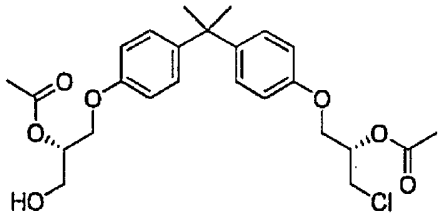
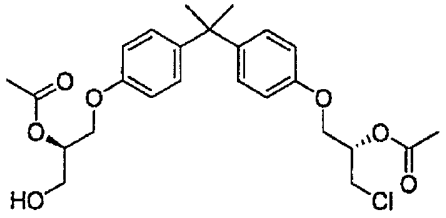
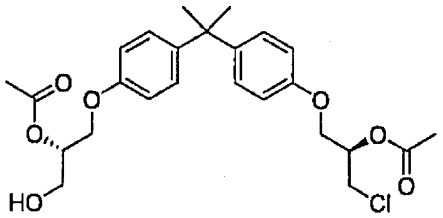
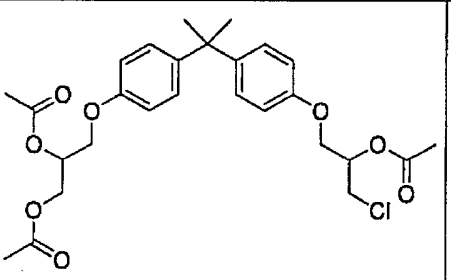
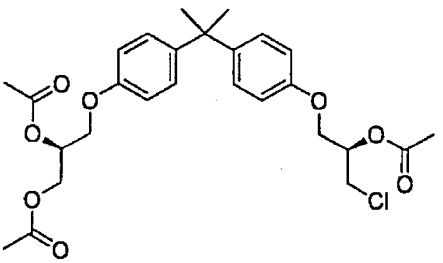
[0121] In other particular embodiments of the compounds, as described anywhere herein, the following compounds in Table 1 are provided.

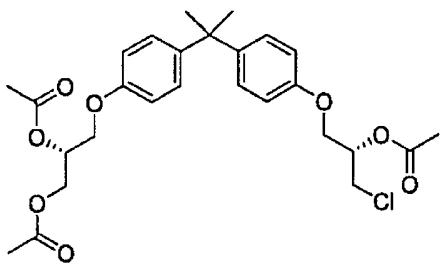
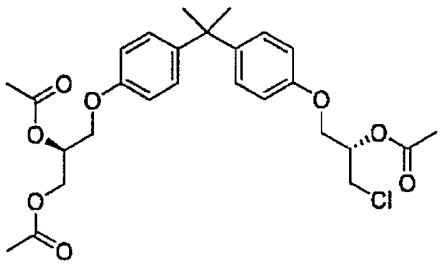
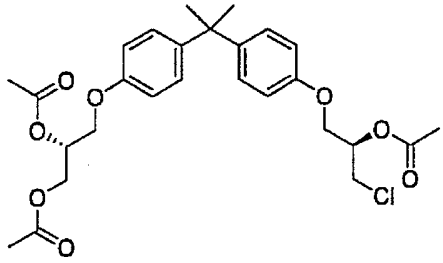
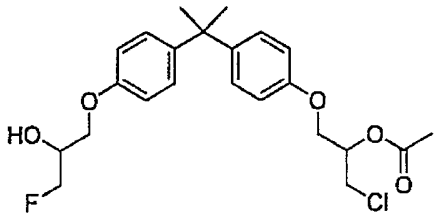
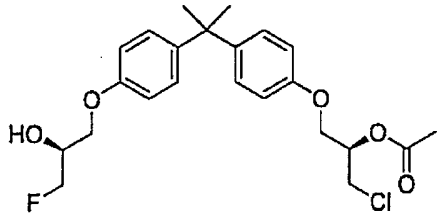
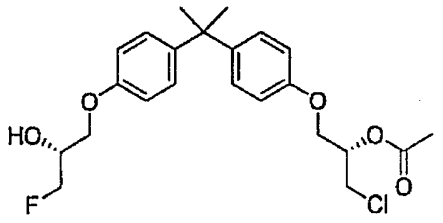
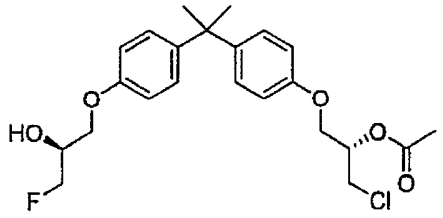
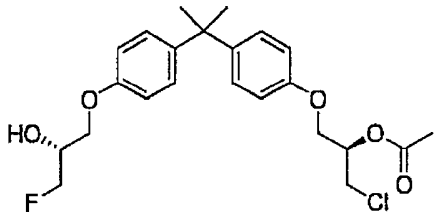
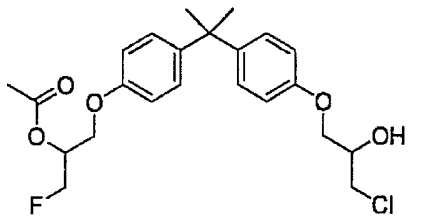
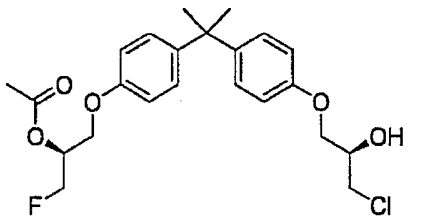
TABLE 1. Representative Compounds

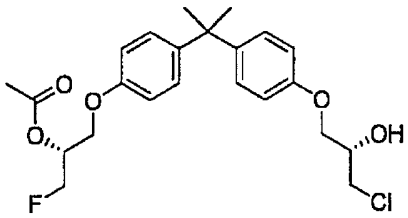
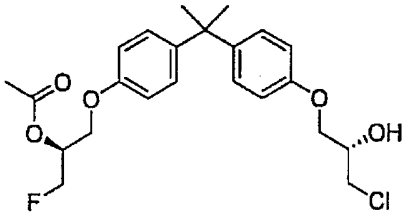
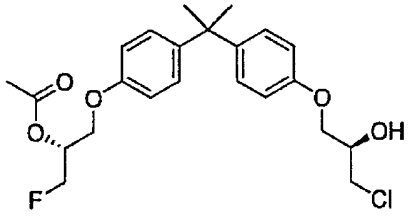
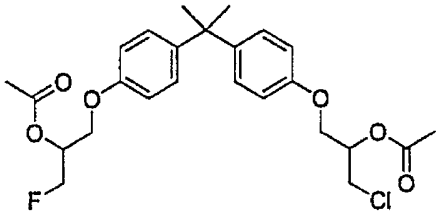
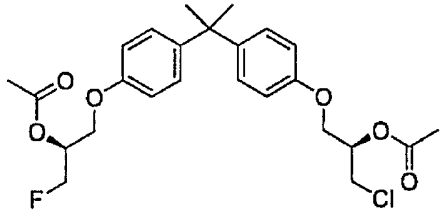
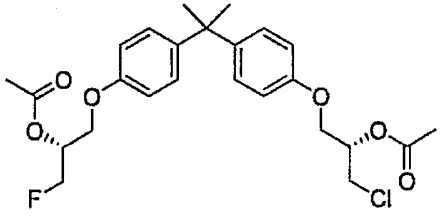
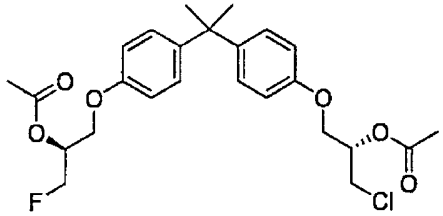
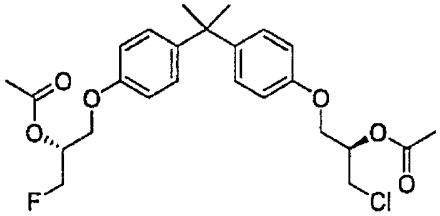
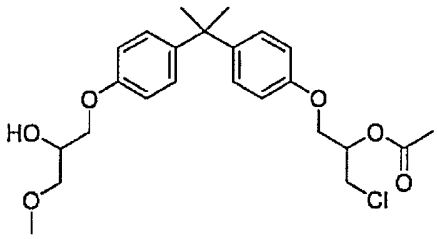
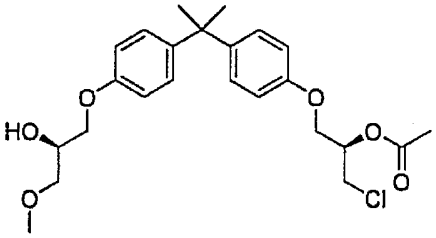
No.	Structure	No.	Structure
1		1a	
1b		1c	
1d		2	

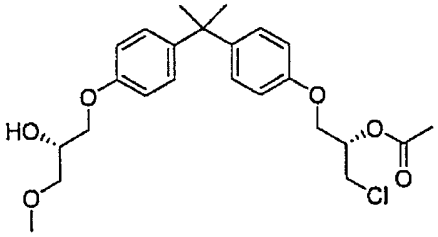
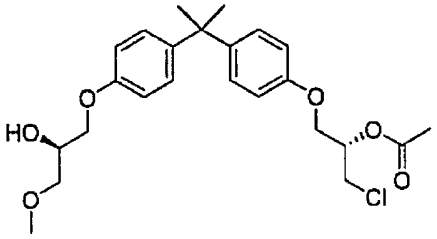
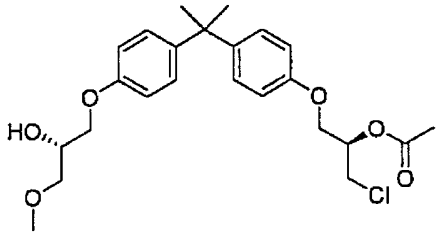
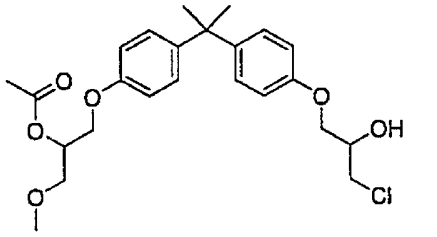
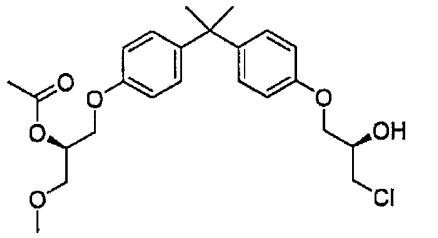
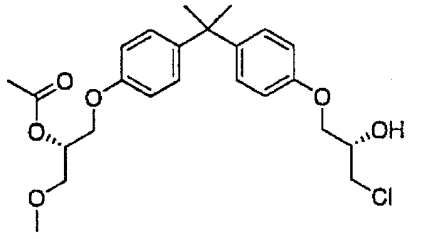
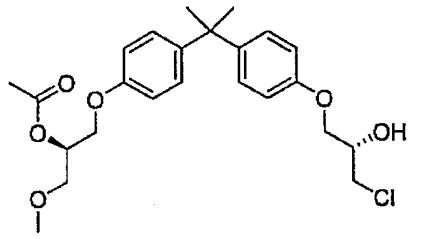
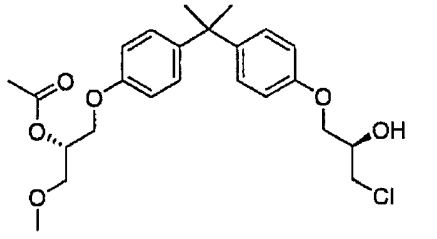
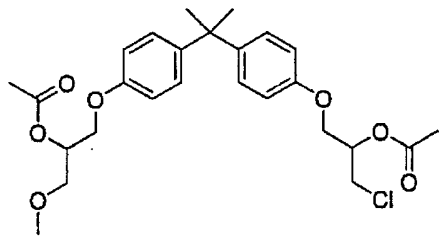
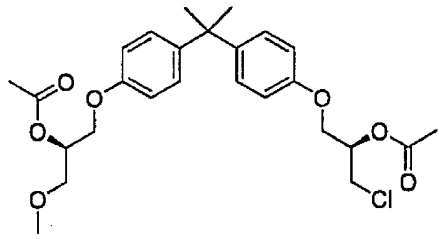
No.	Structure	No.	Structure
2a		2b	
2c		2d	
3		3a	
3b		3c	
3d		4	

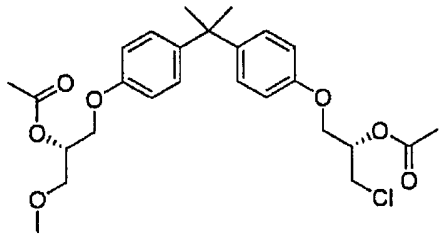
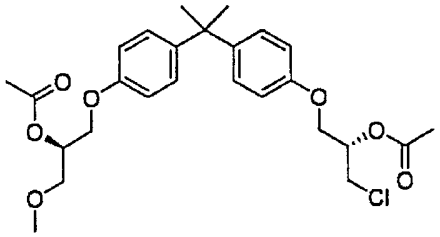
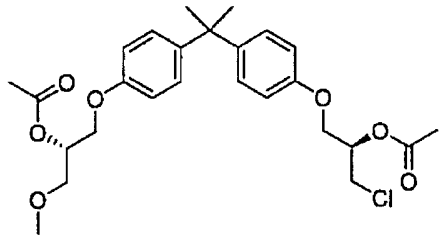
No.	Structure	No.	Structure
4a		4b	
4c		4d	
5		5a	
5b		5c	

No.	Structure	No.	Structure
5d		6	
6a		6b	
6c		6d	
7		7a	

No.	Structure	No.	Structure
7b		7c	
7d		8	
8a		8b	
8c		8d	
9		9a	

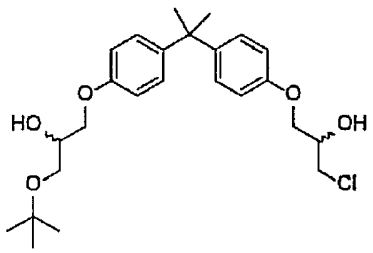
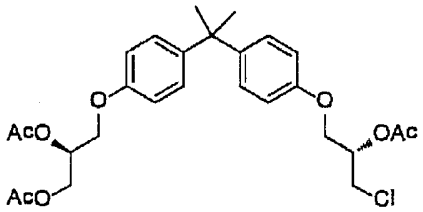
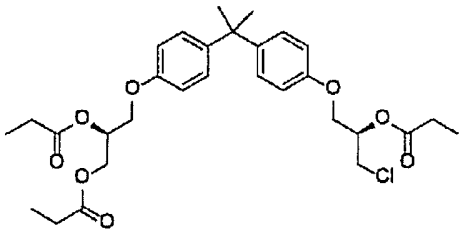
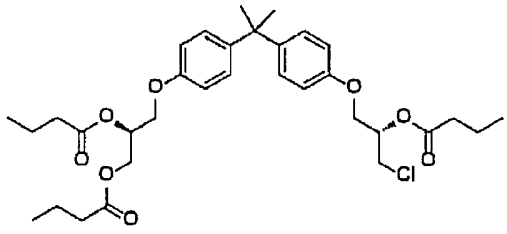
No.	Structure	No.	Structure
9b		9c	
9d		10	
10a		10b	
10c		10d	
11		11a	

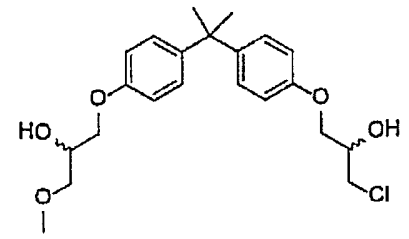
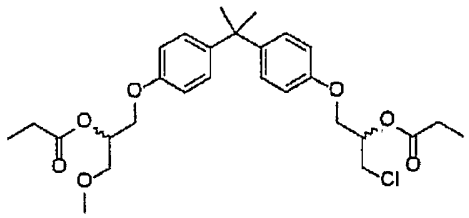
No.	Structure	No.	Structure
11b		11c	
11d		12	
12a		12b	
12c		12d	
13		13a	

No.	Structure	No.	Structure
13b		13c	
13d		N/A	N/A

[0122] In other particular embodiments of the compounds, as described anywhere herein, the following compounds in Table 2 are provided.

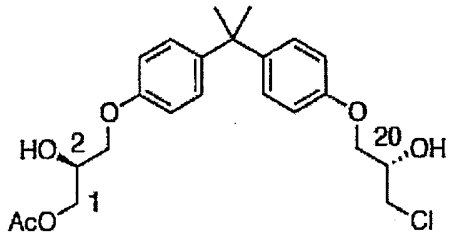
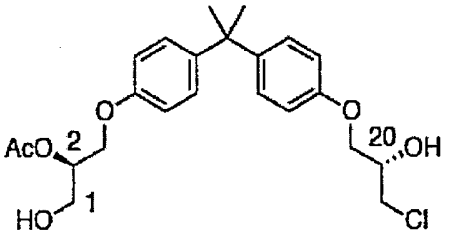
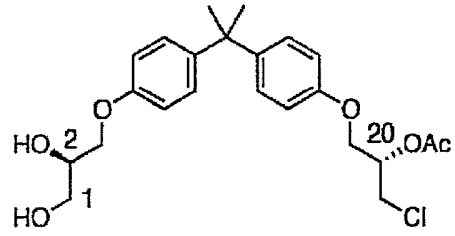
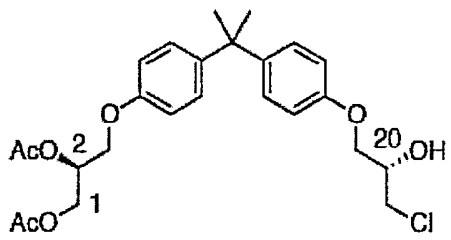
TABLE 2. Representative Compounds

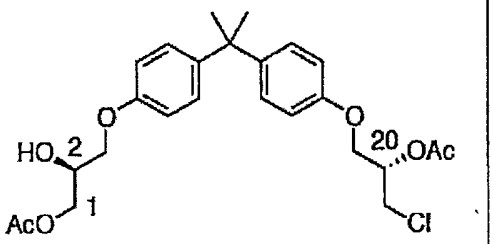
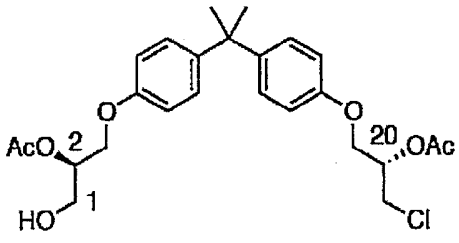
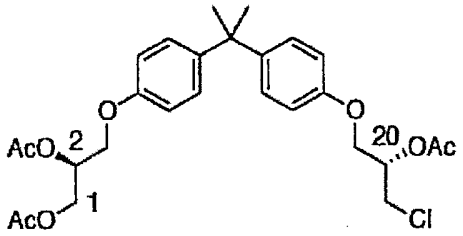
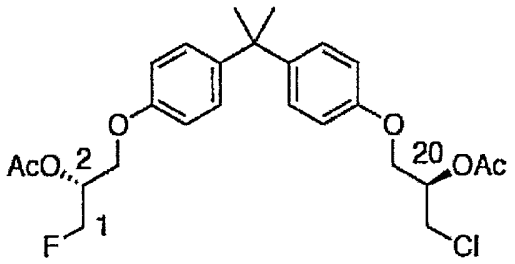
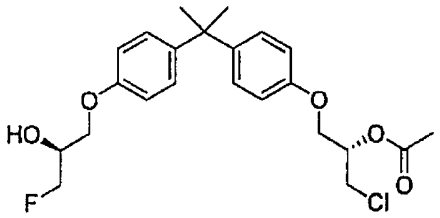
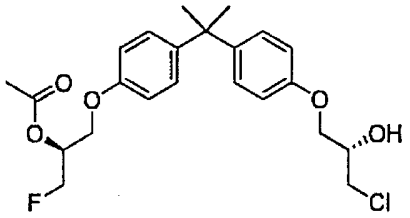
Structure	Structure
	
	

Structure	Structure
	

[0123] In other particular embodiments of the compounds, as described anywhere herein, the following compounds in Table 3 are provided, which have positions 1, 2, and 20 numbered for the majority of compounds.

TABLE 3. Representative Compounds

Structure	Structure
	
	

Structure	Structure
	
	
	

[0124] Compounds as described herein may be in the free form or in the form of a salt thereof. In some embodiments, compounds as described herein may be in the form of a pharmaceutically acceptable salt, which are known in the art (Berge et al., *J. Pharm. Sci.* 1977, 66, 1). Pharmaceutically acceptable salt as used herein includes, for example, salts that have the desired pharmacological activity of the parent compound (salts which retain the biological effectiveness and/or properties of the parent compound and which are not biologically and/or otherwise undesirable). Compounds as described herein having one or more functional groups capable of forming a salt may be, for example, formed as a pharmaceutically acceptable salt. Compounds containing one or more basic functional groups may be capable of forming a pharmaceutically acceptable salt with, for example, a pharmaceutically acceptable organic or inorganic acid. Pharmaceutically acceptable salts may be derived from, for example, and without limitation, acetic acid, adipic acid, alginic acid, aspartic acid, ascorbic acid, benzoic acid, benzenesulfonic acid, butyric acid, cinnamic acid,

citric acid, camphoric acid, camphorsulfonic acid, cyclopentanepropionic acid, diethylacetic acid, digluconic acid, dodecylsulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, glucoheptanoic acid, gluconic acid, glycerophosphoric acid, glycolic acid, hemisulfonic acid, heptanoic acid, hexanoic acid, hydrochloric acid, hydrobromic acid, hydriodic acid, 2-hydroxyethanesulfonic acid, isonicotinic acid, lactic acid, malic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-napthalenesulfonic acid, naphthalenedisulphonic acid, p-toluenesulfonic acid, nicotinic acid, nitric acid, oxalic acid, pamoic acid, pectinic acid, 3-phenylpropionic acid, phosphoric acid, picric acid, pimelic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, succinic acid, sulfuric acid, sulfamic acid, tartaric acid, thiocyanic acid or undecanoic acid. Compounds containing one or more acidic functional groups may be capable of forming pharmaceutically acceptable salts with a pharmaceutically acceptable base, for example, and without limitation, inorganic bases based on alkaline metals or alkaline earth metals or organic bases such as primary amine compounds, secondary amine compounds, tertiary amine compounds, quaternary amine compounds, substituted amines, naturally occurring substituted amines, cyclic amines or basic ion-exchange resins. Pharmaceutically acceptable salts may be derived from, for example, and without limitation, a hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation such as ammonium, sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese or aluminum, ammonia, benzathine, meglumine, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, glucamine, methylglucamine, theobromine, purines, piperazine, piperidine, procaine, N-ethylpiperidine, theobromine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, morpholine, N-methylmorpholine, N-ethylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine or polyamine resins. In some embodiments, compounds as described herein may contain both acidic and basic groups and may be in the form of inner salts or zwitterions, for example, and without limitation, betaines. Salts as described herein may be prepared by conventional processes known to a person skilled in the art, for example, and without limitation, by reacting the free form with an organic acid or inorganic acid or base, or by anion exchange or cation exchange from other salts. Those skilled in the art will appreciate that preparation of salts may occur *in situ* during isolation and purification of the

compounds or preparation of salts may occur by separately reacting an isolated and purified compound.

[0125] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, polymorphs, isomeric forms) as described herein may be in the solvent addition form, for example, solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent in physical association the compound or salt thereof. The solvent may be, for example, and without limitation, a pharmaceutically acceptable solvent. For example, hydrates are formed when the solvent is water or alcoholates are formed when the solvent is an alcohol.

[0126] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, solvates, isomeric forms) as described herein may include crystalline and amorphous forms, for example, polymorphs, pseudopolymorphs, conformational polymorphs, amorphous forms, or a combination thereof. Polymorphs include different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability and/or solubility. Those skilled in the art will appreciate that various factors including recrystallization solvent, rate of crystallization and storage temperature may cause a single crystal form to dominate.

[0127] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, solvates, polymorphs) as described herein include isomers such as geometrical isomers, optical isomers based on asymmetric carbon, stereoisomers, tautomers, individual enantiomers, individual diastereomers, racemates, diastereomeric mixtures and combinations thereof, and are not limited by the description of the Structure illustrated for the sake of convenience.

[0128] The present disclosure also provides a pharmaceutical composition comprising any one or more of the compounds (e.g., compounds of structure I) disclosed herein and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition may be for treating one or more of the following: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration.

[0129] In some embodiments, pharmaceutical compositions in accordance with this disclosure may comprise a compound of Structure I, or a salt of such a compound, preferably a pharmaceutically or physiologically acceptable salt and a pharmaceutically acceptable carrier. Pharmaceutical preparations will typically comprise one or more carriers, excipients or diluents acceptable for the mode of administration of the preparation, be it by injection, inhalation, topical administration, lavage, or other modes suitable for the selected treatment.
[0130] Suitable carriers, excipients or diluents are those known in the art for use in such modes of administration.

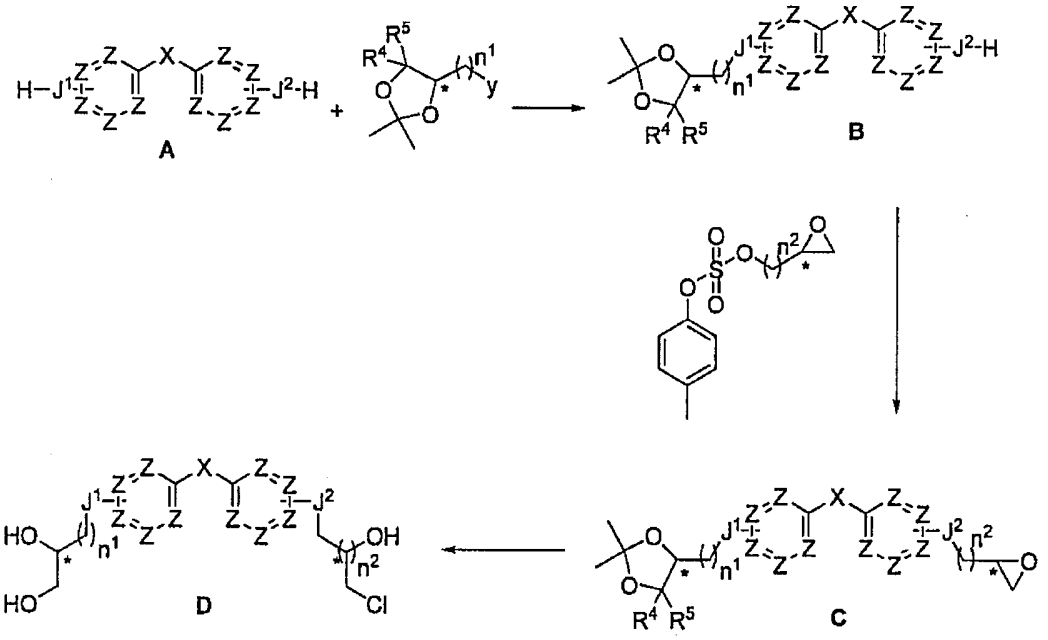
[0131] Suitable pharmaceutical compositions may be formulated by means known in the art and their mode of administration and dose determined by the skilled practitioner. For parenteral administration, a compound may be dissolved in sterile water or saline or a pharmaceutically acceptable vehicle used for administration of non-water soluble compounds such as those used for vitamin K. For enteral administration, the compound may be administered in a tablet, capsule or dissolved in liquid form. The tablet or capsule may be enteric coated, or in a formulation for sustained release. Many suitable formulations are known, including, polymeric or protein microparticles encapsulating a compound to be released, ointments, pastes, gels, hydrogels, or solutions which can be used topically or locally to administer a compound. A sustained release patch or implant may be employed to provide release over a prolonged period of time. Many techniques known to one of skill in the art are described in *Remington: the Science & Practice of Pharmacy* by Alfonso Gennaro, 20th ed., Lippencott Williams & Wilkins, (2000). Formulations for parenteral administration may, for example, contain excipients, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for modulatory compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

[0132] Compounds for use in the present disclosure may be obtained from medical sources or modified using known methodologies from naturally occurring compounds. In addition, methods of preparing or synthesizing compounds of the present disclosure will be understood

by a person of skill in the art having reference to known chemical synthesis principles, for example the synthetic procedures set forth in PCT Pub. Nos. WO 2010/000066; WO 2011/082487, WO 2011/082488, WO 2012/145330, WO 2012/139039, WO 2012/145328 in co-pending PCT Application No. US 2012/051481 and in co-pending U.S. Application Nos. 13/863,849 and 61/667,355, which applications are herby incorporated by reference in their entireties for all purposes.Auzou *et al* 1974 *European Journal of Medicinal Chemistry* 9(5), 548-554 also describes suitable synthetic procedures that may be considered and suitably adapted for preparing compounds of Structure I as set out above. Other references that may be helpful include: Debasish Das, Jyh-Fu Lee and Soofin Cheng "Sulfonic acid functionalized mesoporous MCM-41 silica as a convenient catalyst for Bisphenol-A synthesis" *Chemical Communications*, (2001) 2178–2179; US Patent 2571217 Davis, Orris L.; Knight, Horace S.; Skinner, John R. (Shell Development Co.) "Halohydrin ethers of phenols." (1951); and Rokicki, G.; Pawlicki, J.; Kuran, W. "Reactions of 4-chloromethyl-1,3-dioxolan-2-one with phenols as a new route to polyols and cyclic carbonates." Journal fuer Praktische Chemie (Leipzig) (1985) 327, 718-722. Each of the above references are hereby incorporated by reference in their entirety for all purposes.

[0133] For example, certain embodiments of the compounds of the present disclosure may be prepared with reference to the following General Reaction Scheme I:

General Reaction Scheme I



[0134] Compounds of structure I can be prepared in reference to General Reaction Scheme 1, wherein R^3, R^4, J^1, J^2, n^1, n^2 and x are as defined for structure I, y is a leaving group, such as chloro, and * indicates a stereocenter. Compounds of structure **A**, can be purchased from commercial sources or prepared according to methods known in the art. Reaction of **A** with an appropriately substituted 1,3-dioxolane yields compounds of structure **B**. Optically pure or racemic dioxolanes may be employed to yield the desired stereochemistry. Epoxidation of **B** with an appropriate reagent, for example an appropriately substituted glycidyl tosylate, results in compounds of structure **C**. Various epoxidation reagents may be employed, including optically pure reagents which yield optically pure epoxides (*e.g.*, + or - glycidyl tosylate). Treatment of **C** with an appropriate ring-opening reagent, for example $CeCl_3x7H_2O$, yields **D**.

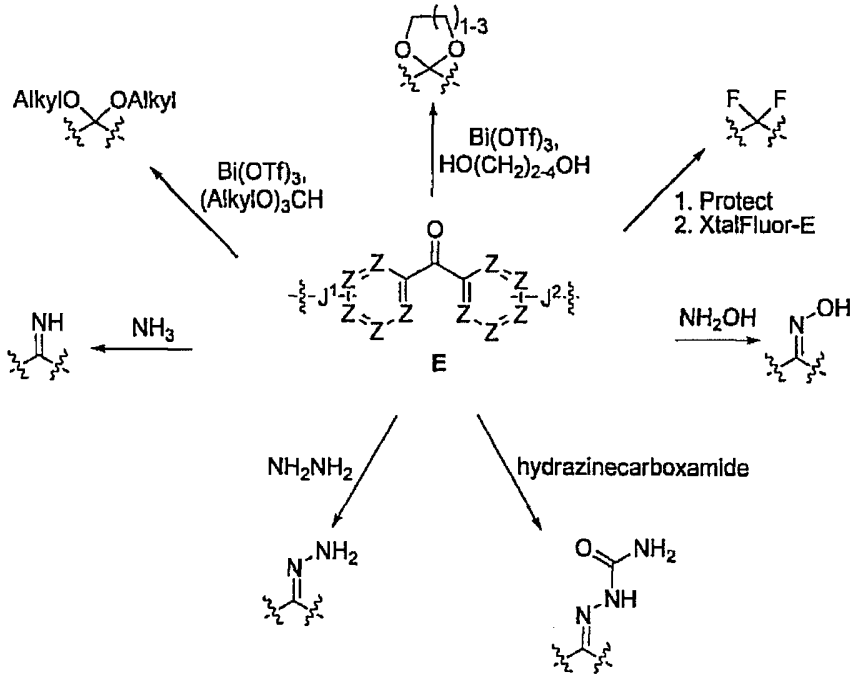
[0135] Compounds of structure **D**, can be used as intermediates for the preparation of various compounds of Structure I. For example, compound **D** can be modified to include an ester at the primary alcohol by treatment with the appropriate acid chloride (*e.g.*, acetyl chloride and the like). Alternatively, the 1,2-dihydroxyl moiety can be protected as a ketal by reaction with 2,2-dimethoxypropane, followed by conversion of the free secondary alcohol to an ester by treatment with the appropriate anhydride (e.g. acetic anhydride and the like) and deprotection of the ketal. Triester compounds of structure I can be prepared by treatment of compound **D** with an appropriate anhydride. Finally, the 1,2-dihydroxyls can both be converted to a desired ester group using a modification of the above scheme as demonstrated in Examples 9-11. Other compounds of structure I are easily prepared by one of ordinary skill in the art based on the above description.

[0136] Compounds of structure I, wherein R^3 is halo can be easily prepared by modifications to the above scheme. For example, treatment of D with an appropriate halogenating reagent, followed by esterification as described above, yields compounds of structure I wherein R^3 is halo (*e.g.*, fluoro). For example, in one embodiment a fluorine atom is introduced by treatment with diethylaminosulfurtrifluoride (DAST) or Xtalfluor-E or M (see *J. Org. Chem.* 2010, 75, 3401-3411, which is hereby incorporated by reference in its entirety). In other embodiments, the primary hydroxyl moiety in **D** may be converted to an appropriate leaving group, for example by reaction with tosyl chloride or mesyl anhydride, followed by reaction with $[K^+/2,2,2\text{-cryptand}]F^-$ or tetrabutylammonium fluoride. Other methods for fluorination of **D** are known to those of skill in the art. For descriptions of fluorination procedures see *J.*

Org. Chem. 2010, 75, 3401-3411, *Bioorg. Med. Chem.* 2009, 17, 7441-7448, and *J. Med. Chem.* 1990, 33, 2430-2437, each of which is hereby incorporated by reference in its entirety.

Compounds of structure I wherein R^3 is $-OR^{12}$ can be prepared by treating compounds of structure **A** with 2 equivalents of an appropriate epoxidation reagent, for example an appropriately substituted glycidyl tosylate, to yield a bis epoxide. One of these epoxides can be opened with an alcohol (*i.e.*, R^3OH), followed by opening of the remaining epoxide with $CeCl_3x7H_2O$ and esterification as described above to yield the compound of structure I.

General Reaction Scheme II



[0137] Compounds of structure I having various bridging groups (i.e., "X") can be prepared according to General Reaction Scheme II. Compounds of structure **E** can be used to prepare any number of various compounds of structure I. Methods for the reactions illustrated in General Reaction Scheme II are well known in the art. Any of the functional groups depicted in General Reaction Scheme II can be further functionalized using techniques and methods well-known to one of ordinary skill in the art.

[0138] One skilled in the art will recognize that variations to the order of the steps and reagents discussed in reference to the above synthetic schemes are possible. Furthermore, an appropriate protecting group strategy, such as those described in , *Greene's Protective Groups in Organic Synthesis*, 4th Ed., Peter G. M. Wuts and Theodora W. Greene, John

Wiley and Sons, Inc., 2007, which is hereby incorporated by reference in its entirety, may also be employed. In addition, compounds of structure I having various substitutions (e.g., different values for R^1, R^2, R^3, R^4, J^1, J^2, etc.) and different positional isomers can be prepared by modifications to the above starting materials and/or procedures. Such modifications are well within the ability of one of ordinary skill in the art.

III. Methods

[0139] The present compounds find use in any number of methods. For example, in some embodiments the compounds are useful in methods for modulating androgen receptors.

[0140] Accordingly, in one embodiment, the present disclosure provides the use of a composition comprising any one of the foregoing compounds of Structure (I) for modulating androgen receptor (AR) activity. For example in some embodiments, modulating androgen receptor (AR) activity is in a mammalian cell. Modulating androgen receptor may be in a subject in need thereof (e.g., a mammalian subject) and for treatment of any of the described conditions or diseases.

[0141] In other embodiments, modulating androgen receptor (AR) activity is for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. For example in some embodiments, the indication is prostate cancer. In other embodiments, the prostate cancer is castration resistant prostate cancer (also referred to as hormone refractory, androgen-independent, androgen deprivation resistant, androgen ablation resistant, androgen depletion-independent, castration-recurrent, anti-androgen-recurrent). While in other embodiments, the prostate cancer is androgen-dependent prostate cancer.

[0142] In other embodiments, the present disclosure provides a method of modulating androgen receptor (AR) activity, the method comprising administering a composition comprising any one of the foregoing compounds of Structure (I), or pharmaceutically acceptable salt, stereoisomer or tautomer thereof to a subject (e.g., mammal) in need thereof.

[0143] In other further embodiments of the foregoing method, modulating androgen receptor (AR) activity is for the treatment of one or more of the following: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar

muscular atrophy, and age-related macular degeneration. For example in some embodiments, the prostate cancer is castration resistant prostate cancer (also referred to as hormone refractory, androgen-independent, androgen deprivation resistant, androgen ablation resistant, androgen depletion-independent, castration-recurrent, anti-androgen-recurrent). In other embodiments, the prostate cancer is androgen-dependent prostate cancer.

[0144] In accordance with another embodiment, there is provided a use of the compounds of Structure (I) as described anywhere herein for preparation of a medicament for modulating androgen receptor (AR).

[0145] In other embodiments, the present disclosure provides a method for increasing the bioavailability (*e.g.*, oral bioavailability) of a hydroxyl-containing androgen receptor modulator, the method comprising replacing at least one hydroxyl moiety with an alkyl (*e.g.*, methyl), alkenyl, aryl or aralkyl ester.

[0146] In accordance with a further embodiment, there is provided a method of screening for androgen receptor modulating compounds, wherein the compounds screened are selected from the compounds as described anywhere herein.

[0147] The modulating of the androgen receptor (AR) activity may be in a mammalian cell. The modulating of the androgen receptor (AR) activity may be in a mammal. The mammal may be a human.

[0148] Alternatively, the administering may be to a mammal. The administering may be to a mammal in need thereof and in an effective amount for the treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy (*e.g.*, Kennedy's disease), and age-related macular degeneration.

[0149] The mammalian cell may be a human cell. The modulating androgen receptor activity may be for inhibiting androgen receptor N-terminal domain activity. The modulating androgen receptor activity may be for inhibiting androgen receptor activity. The modulating may be in vivo. The modulating androgen receptor activity may be for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy (*e.g.*, Kennedy's disease), and age-related macular degeneration. The indication may be prostate

cancer. The prostate cancer may be castration-resistant prostate cancer. The prostate cancer may be androgen-dependent prostate cancer.

[0150] In some embodiments, compounds and all different forms thereof as described herein may be used, for example, and without limitation, in combination with other treatment methods for at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. For example, compounds and all their different forms as described herein may be used as neoadjuvant (prior), adjunctive (during), and/or adjuvant (after) therapy with surgery, radiation (brachytherapy or external beam), or other therapies (*e.g.*, HIFU), and in combination with chemotherapies, androgen ablation, antiandrogens or any other therapeutic approach.

[0151] With respect to combination therapies, one embodiment of the present disclosure provides a combination of any one or more of a compound of Structure I with one or more currently-used or experimental pharmacological therapies which are or may be utilized to treat any of the above disease states (e.g., androgen-independent prostate cancer or Kennedy's disease). Methods, uses and pharmaceutical compositions comprising the above combination are also provided.

[0152] In some embodiments, the present disclosure is directed to a method for modulating androgen receptor (e.g., for treatment of any of the above conditions) by administering to a subject in need thereof a pharmaceutical composition comprising a compound of structure I and an additional therapeutic agent. Pharmaceutical compositions (and uses thereof) comprising any one of the foregoing compounds of Formula (I), an additional therapeutic agent and a pharmaceutically acceptable carrier are also provided. For example, in some embodiments, the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy or age-related macular degeneration.

[0153] The disclosed compounds, which are thought to interfere with the androgen receptor principally through binding to the N-terminus of the androgen receptor, are expected to demonstrate beneficial synergistic therapeutic effects when used in concert with existing approved and in-development agents. That is, the biological impact of using the agents in

concert with one another produces a biological and therapeutic effect which is greater than the simple additive effect of each of them separately.

[0154] Accordingly, one embodiment comprises the use of the disclosed compounds in combination therapy with one or more currently-used or experimental pharmacological therapies which are utilized for treating the above disease states irrespective of the biological mechanism of action of such pharmacological therapies, including without limitation pharmacological therapies which directly or indirectly inhibit the androgen receptor, pharmacological therapies which are cyto-toxic in nature, and pharmacological therapies which interfere with the biological production or function of androgen (hereinafter, the "Other Therapeutic Agents"). By "combination therapy" is meant the administration of any one or more of a compound of Structure I with one or more of another therapeutic agent to the same patient such that their pharmacological effects are contemporaneous with one another, or if not contemporaneous, that their effects are synergistic with one another even though dosed sequentially rather than contemporaneously.

[0155] Such administration includes without limitation dosing of one or more of a compound of Structure I and one or more of the Other Therapeutic Agent(s) as separate agents without any comingling prior to dosing, as well as formulations which include one or more Other Androgen-Blocking Therapeutic Agents mixed with one or more compound of Structure I as a pre-mixed formulation. Administration of the compound(s) of Structure I in combination with Other Therapeutic Agents for treatment of the above disease states also includes dosing by any dosing method including without limitation, intravenous delivery, oral delivery, intra-peritoneal delivery, intra-muscular delivery, or intra-tumoral delivery.

[0156] In another aspect of the present disclosure, the one or more of the Other Therapeutic Agent may be administered to the patient before administration of the compound(s) of Structure I. In another embodiment, the compound(s) of Structure I may be co-administered with one or more of the Other Therapeutic Agents. In yet another aspect, the one or more Other Therapeutic Agent may be administered to the patient after administration of the compound(s) of Structure I.

[0157] It is fully within the scope of the disclosure that the ratio of the doses of compound(s) of Structure I to that of the one or more Other Therapeutic Agents may or may not equal to one and may be varied accordingly to achieve the optimal therapeutic benefit.

For greater clarity the compound(s) of Structure I that are combined with the one or more Other Therapeutic Agents for improved treatment of the above disease states may comprise, but are not limited to any compound having a structure of Structure I, including those compounds shown in Table 2.

[0158] The Other Therapeutic Agents include without limitation any pharmacological agent which is currently approved by the FDA in the U.S. (or elsewhere by any other regulatory body) for use as pharmacological treatment of any of the above disease states, or which is currently being used experimentally as part of a clinical trial program that relates to the above disease states. Non-limiting examples of the Other Pharmacological Agents comprise, without limitation: the chemical entity known as **enzalutamide** (4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide) and related compounds, which appears to be a blocker of the androgen receptor LBD and is currently in development as a treatment for prostate cancer; the chemical entity known as **Galeterone** and related compounds which appears to be a blocker of the androgen receptor LBD, and a CYP17 lyase inhibitor, and also appears to decrease overall androgen receptor levels in prostate cancer cells. **Galeterone** is currently in development as a treatment for prostate cancer; the chemical entity known as **ARN-509** and related compounds which appears to be a blocker of the androgen receptor LBD and is currently in development as a treatment for prostate cancer; the chemical entity known as **abiraterone** (or CB-7630; (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol), and related molecules, which appears to block the production of androgen and is for the treatment of prostate cancer; the chemical entity known as **bicalutamide** (N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide) and related compounds, which appears to be a blocker of the androgen receptor LBD and which is currently used to treat prostate cancer, the chemical entity known as **nilutamide** (5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl] imidazolidine-2,4-dione) and related compounds, which appears to be a blocker of the AR LBD and which is currently used to treat prostate cancer, the chemical entity known as **flutamide** (2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-propanamide) and related compounds, which appears to be a blocker of the androgen receptor LBD and which is currently used to treat prostate cancer, the chemical entities know as **cyproterone acetate** (6-chloro-1β,2β-dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-4,6-diene-3,20-dione) and related compounds, which appears to be a

blocker of the androgen receptor LBD and which is currently used to treat prostate cancer, the chemical entity known as **docetaxel** (Taxotere; 1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}) and related compounds, which appears to be a cytotoxic antimicrotubule agent and is currently used in combination with prednisone to treat prostate cancer, the chemical entity known as **Bevacizumab** (Avastin), a monoclonal antibody that recognizes and blocks vascular endothelial growth factor A (VEGF-A) and may be used to treat prostate cancer, the chemical entity known as **OSU-HDAC42** ((S)-(+)-N-hydroxy-4-(3-methyl-2-phenylbutyrylamino)-benzamide), and related compounds, which appears to act as a histone deacetylase inhibitor, and is currently being developed as a treatment for prostate cancer, the chemical entity known as **VITAXIN** which appears to be a monoclonal antibody against the vascular integrin αvβ3 to prevent angiogenesis, and which may be used to treat prostate cancer, the chemical entity known as **sunitumib** (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide) and related compounds, which appears to inhibit multiple receptor tyrosine kinases (RTKs) and may be used for treatment of prostate cancer, the chemical entity known as **ZD-4054** (N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridin-3-sulfonamid) and related compounds, which appears to block the edta receptor and which may be used for treatment of prostate cancer; the chemical entity known as **Cabazitaxel (XRP-6258)**, and related compounds, which appears to be a cytotoxic microtubule inhibitor, and which is currently used to treat prostate cancer; the chemical entity known as **MDX-010 (Ipilimumab)**, a fully human monoclonal antibody that binds to and blocks the activity of CTLA-4 which is currently in development as an immunotherapeutic agent for treatment of prostate cancer; the chemical entity known as **OGX 427** which appears to target HSP27 as an antisense agent, and which is currently in development for treatment of prostate cancer; the chemical entity known as **OGX 011** which appears to target clusterin as an antisense agent; the chemical entity known as **finasteride** (Proscar, Propecia; N-(1,1-dimethylethyl)-3-oxo-(5α,17β)-4-azaandrost-1-ene-17-carboxamide), and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone, and may be used to treat prostate cancer; the chemical entity known as **dutasteride** (Avodart; 5α, 17β)-N-{2,5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide) and related molecules, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone, and may be used in the treatment of prostate cancer; the chemical entity known as **turosteride** ((4aR,4bS,6aS,7S,9aS,9bS,11aR)-1,4a,6a-trimethyl-2-oxo-N-(propan-

2-yl)-N-(propan-2ylcarbamoyl)hexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide), and related molecules, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used in the treatment of prostate cancer; the chemical entity known as **bexlosteride** (LY-191,704; (4aS,10bR)-8-chloro-4-methyl-1,2,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one), and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used in the treatment of prostate cancer; the chemical entity known as **izonsteride** (LY-320,236; (4aR,10bR)-8-[(4-ethyl-1,3-benzothiazol-2-yl)sulfanyl]-4,10b-dimethyl-1,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3(2H)-one) and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used for the treatment of prostate cancer; the chemical entity known as **FCE 28260** and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used for the treatment of prostate cancer; the chemical entity known as **SKF105,111**, and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used for treatment of prostate cancer.

[0159] Accordingly, in certain embodiments the additional therapeutic agent is enzalutamide, Galeterone; ARN-509; abiraterone, bicalutamide, nilutamide, flutamide, cyproterone acetate, docetaxel, Bevacizumab (Avastin), OSU-HDAC42, VITAXIN, sunitumib, ZD-4054, Cabazitaxel (XRP-6258), MDX-010 (Ipilimumab), OGX 427, OGX 011, finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111, Radium 233, or related compound(s) thereof.

[0160] In another embodiment, the present disclosure provides the use of any one of the foregoing pharmaceutical compositions (including compositions comprising a compound of Structure I and an additional therapeutic agent) for modulating androgen receptor (AR) activity. For example in some embodiments, modulating androgen receptor (AR) activity is in a mammalian cell.

[0161] In other embodiments, modulating androgen receptor (AR) activity is for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. For example in some embodiments, the indication is prostate cancer. For example, in some embodiments, the prostate cancer is

castration resistant prostate cancer, and in other embodiments the prostate cancer is androgen-dependent prostate cancer.

[0162] In yet another embodiment, the present disclosure provides a method of modulating androgen receptor (AR) activity, the method comprising administering any one of the foregoing pharmaceutical compositions (including compositions comprising a compound of Structure I and an additional therapeutic agent) to a subject in need thereof. For example in some embodiments, modulating androgen receptor (AR) activity is for the treatment of one or more of the following: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. In still other embodiments, the indication is prostate cancer. For example, in some embodiments, the prostate cancer is castration resistant prostate cancer, while in other embodiments, the prostate cancer is androgen-dependent prostate cancer.

[0163] In general, compounds of the disclosure should be used without causing substantial toxicity. Toxicity of the compounds of the disclosure can be determined using standard techniques, for example, by testing in cell cultures or experimental animals and determining the therapeutic index, *i.e.*,, the ratio between the LD50 (the dose lethal to 50% of the population) and the LD100 (the dose lethal to 100% of the population). In some circumstances however, such as in severe disease conditions, it may be necessary to administer substantial excesses of the compositions. Some compounds of this disclosure may be toxic at some concentrations. Titration studies may be used to determine toxic and non-toxic concentrations. Toxicity may be evaluated by examining a particular compound's or composition's specificity across cell lines using PC3 cells as a negative control that do not express functional AR. Animal studies may be used to provide an indication if the compound has any effects on other tissues. Systemic therapy that targets the AR will not likely cause major problems to other tissues since antiandrogens and androgen insensitivity syndrome are not fatal.

[0164] Compounds as described herein may be administered to a subject. As used herein, a "subject" may be a human, non-human primate, mammal, rat, mouse, cow, horse, pig, sheep, goat, dog, cat and the like. The subject may be suspected of having or at risk for having a cancer, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, or suspected of having or at risk for having acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty,

spinal and bulbar muscular atrophy, or age-related macular degeneration. Diagnostic methods for various cancers, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, and diagnostic methods for acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration and the clinical delineation of cancer, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, diagnoses and the clinical delineation of acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration are known to those of ordinary skill in the art.

[0165] Compounds described herein may also be used in assays and for research purposes. Definitions used include ligand-dependent activation of the androgen receptor (AR) by androgens such as dihydrotestosterone (DHT) or the synthetic androgen (R1881) used for research purposes. Ligand-independent activation of the AR refers to transactivation of the AR in the absence of androgen (ligand) by, for example, stimulation of the cAMP-dependent protein kinase (PKA) pathway with forskolin (FSK). Some compounds and compositions of this disclosure may inhibit both FSK and androgen (e.g. R1881, a synthetic androgen) induction of ARE-luciferase (ARE-luc). Constitutive activity of the AR refers to splice variants lacking the AR ligand-binding domain. Such compounds may block a mechanism that is common to both ligand-dependent and ligand-independent activation of the AR, as well as constitutively active splice variants of the AR that lack ligand-binding domain. This could involve any step in activation of the AR including dissociation of heatshock proteins, essential posttranslational modifications (e.g., acetylation, phosphorylation), nuclear translocation, protein-protein interactions, formation of the transcriptional complex, release of co-repressors, and/or increased degradation. Some compounds and compositions of this disclosure may inhibit ligand-only activity and may interfere with a mechanism specific to ligand-dependent activation (e.g., accessibility of the ligand binding domain (LBD) to androgen). Numerous disorders in addition to prostate cancer involve the androgen axis (e.g., acne, hirsutism, alopecia, benign prostatic hyperplasia) and compounds interfering with this mechanism may be used to treat such conditions. Some compounds and compositions of this disclosure may only inhibit FSK induction and may be specific inhibitors to ligand-independent activation of the AR. These compounds and compositions may interfere with the cascade of events that normally occur with FSK and/or PKA activity or any

downstream effects that may play a role on the AR (e.g. FSK increases MAPK activity which has a potent effect on AR activity). Examples may include an inhibitor of cAMP and or PKA or other kinases. Some compounds and compositions of this disclosure may induce basal levels of activity of the AR (no androgen or stimulation of the PKA pathway). Some compounds and compositions of this disclosure may increase induction by R1881 or FSK. Such compounds and compositions may stimulate transcription or transactivation of the AR.

[0166] Some compounds and compositions of this disclosure may inhibit activity of the androgen receptor. Interleukin-6 (IL-6) also causes ligand-independent activation of the AR in LNCaP cells and can be used in addition to FSK.

[0167] Compounds or pharmaceutical compositions in accordance with this disclosure or for use in this disclosure may be administered by means of a medical device or appliance such as an implant, graft, prosthesis, stent, etc. Also, implants may be devised which are intended to contain and release such compounds or compositions. An example would be an implant made of a polymeric material adapted to release the compound over a period of time.

[0168] It is to be noted that dosage values may vary with the severity of the condition to be alleviated. For any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Dosage ranges set forth herein are exemplary only and do not limit the dosage ranges that may be selected by medical practitioners. The amount of active compound(s) in the composition may vary according to factors such as the disease state, age, sex, and weight of the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It may be advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage.

[0169] The compounds described herein may be used for *in vivo* or *in vitro* research uses (i.e. non-clinical) to investigate the mechanisms of orphan and nuclear receptors (including steroid receptors such as the androgen receptor). Furthermore, these compounds may be used individually or as part of a kit for *in vivo* or *in vitro* research to investigate signal transduction pathways and/or the activation of orphan and nuclear receptors using recombinant proteins, cells maintained in culture, and/or animal models.

[0170] Various alternative embodiments and examples of the disclosure are described herein. These embodiments and examples are illustrative and should not be construed as limiting the scope of the disclosure. The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

[0171] All non-aqueous reactions were performed in flame-dried round bottomed flasks. The flaks were fitted with rubber septa and reactions were conducted under a positive pressure of argon unless otherwise specified. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923) using 230-400 mesh silica gel. Thin-layer chromatography was performed using aluminium plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light and a "Seebach" staining solution (700 mL water, 10.5 g Cerium (IV) sulphate tetrahydrate, 15.0 g molybdato phosphoric acid, 17.5 g sulphuric acid) followed by heating (~1 min) with a heating gun (~250 °C). Organic solutions were concentrated on Büchi R-114 rotatory evaporators at reduced pressure (15-30 torr, house vacuum) at 25-40 °C.

[0172] Commercial regents and solvents were used as received. All solvents used for extraction and chromatography were HPLC grade. Normal-phase Si gel Sep paks™ were purchased from waters, Inc. Thin-layer chromatography plates were Kieselgel $60F_{254}$. All synthetic reagents were purchased from Sigma Aldrich and Fisher Scientific Canada.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 25 °C using a Bruker 400 with inverse probe and Bruker 400 spectrometers, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent ($CDCl_3$: δ 7.24 ($CHCl_3$)). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker 400 spectrometer, are reported in parts per million on the δ scale, and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.23). Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad); coupling constant (*J*, Hz, number of protons).

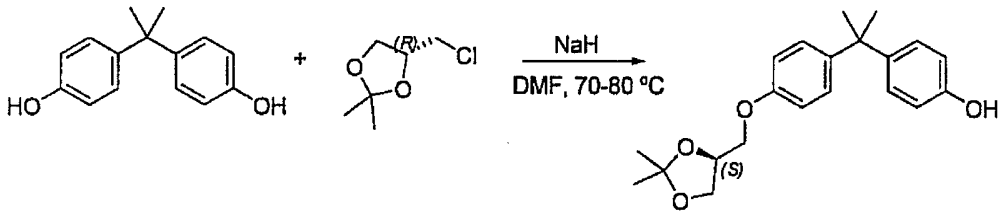
[0173] LNCaP cells were employed for experiments because they are well-differentiated human prostate cancer cells in which ligand-dependent and ligand-independent activation of AR by FSK has been characterized (Nazareth *et al* 1996 *J. Biol. Chem.* 271, 19900-19907; and Sadar 1999 *J. Biol. Chem.* 274, 7777-7783). LNCaP cells express endogenous AR and secrete prostate-specific antigen (PSA) (Horoszewicz *et al* 1983 *Cancer Res.* 43, 1809-1818). LNCaP cells can be grown either as monolayers in cell culture or as tumors in the well-characterized xenograft model that progresses to castration-resistant prostate cancer

(CRPC) in castrated hosts (Sato *et al* 1996 *J. Steroid Biochem. Mol. Biol.* 58, 139-146; Gleave *et al* 1991 *Cancer Res.* 51, 3753-3761; Sato *et al* 1997 *Cancer Res.* 57, 1584-1589; and Sadar *et al* 2002 *Mol. Cancer Ther.* 1(8), 629-637). R1881 (a synthetic androgen) is employed since it is stable and avoids problems associated with the labile physiological ligand dihydrotestosterone (DHT).

[0174] One well characterized ARE-driven reporter gene construct that has been used extensively is the PSA (6.1 kb) enhance/promoter which contains several AREs and is highly inducible by androgens as well as by FSK (Ueda *et al* 2002 A *J. Biol. Chem.* 277, 7076-7085).

EXAMPLE 1

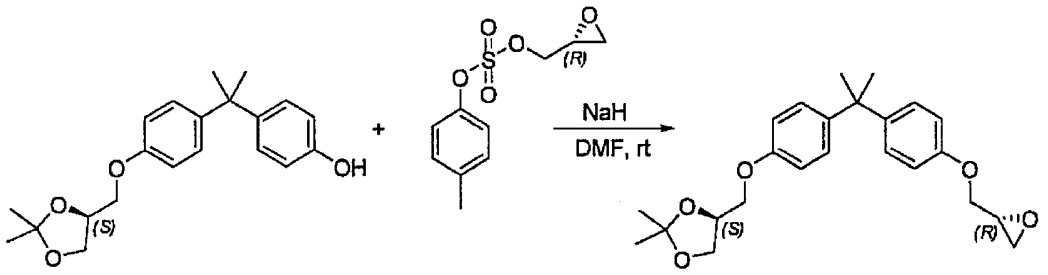
SYNTHESIS OF (S)-4-(2-(4-((2,2-DIMETHYL-1,3-DIOXOLAN-4-YL)METHOXY)PHENYL)PROPAN-2-YL)PHENOL



[0175] Sodium hydride (60% dispersion in mineral oil, 1750 mg, 43.80 mmol, 1.0 equiv) was added slowly to a stirred solution of Bisphenol A (10000 mg, 43.80 mmol, 1 equiv) in anhydrous dimethyl formamide (30 mL), at room temperature, and the contents were stirred under an atmosphere of argon for 20 min. (*R*)-(+)-4-chloromethyl-2,2-dimethyl-1,3-dioxolane 98% (7.10 mL, 52.56 mmol, 1.2 equiv) was added via syringe and the mixture was allowed to react at 70-80 °C for 40 h. Then, the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL), and the mixture was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with deionized water (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 10% ethyl acetate in hexane) to provide the title compound (3560 mg, 24%, 25-30% conversion) as a foam.

EXAMPLE 2

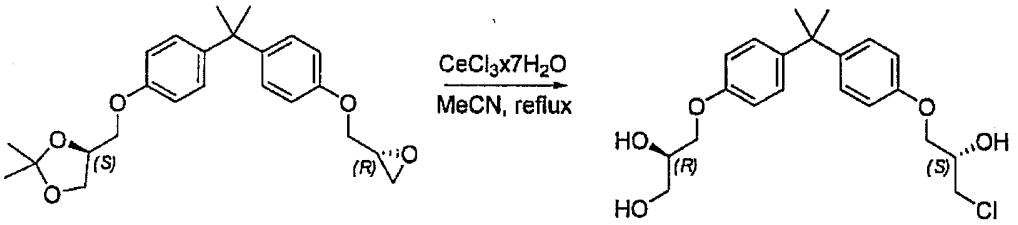
SYNTHESIS OF (S)-2,2-DIMETHYL-4-((4-(2-(4-((R)-OXIRAN-2-YLMETHOXY)PHENYL)PROPAN-2-YL)PHENOXY)METHYL)-1,3-DIOXOLANE



[0176] Sodium hydride (60% dispersion in mineral oil, 391 mg, 9.78 mmol, 1.5 equiv) was added slowly to a stirred solution of (S)-4-(2-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)propan-2-yl)phenol (2230 mg, 6.52 mmol, 1 equiv) in anhydrous dimethyl formamide (15 mL), at room temperature, and the contents were stirred under an atmosphere of argon for 30 min. A solution of (2*R*)-(-)-glycidyl tosylate 98% (2230 mg, 9.78 mmol, 1.5 equiv) in anhydrous dimethyl formamide (5 mL) was added via syringe and the mixture was allowed to react at room temperature for 16 h. Then, the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL), and the mixture was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with deionized water (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 20% to 40% ethyl acetate in hexane) to provide the title compound (2.53 g, 94%) as a clear foam.

EXAMPLE 3

SYNTHESIS OF (R)-3-(4-(2-(4-((S)-3-CHLORO-2-HYDROXYPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIOL

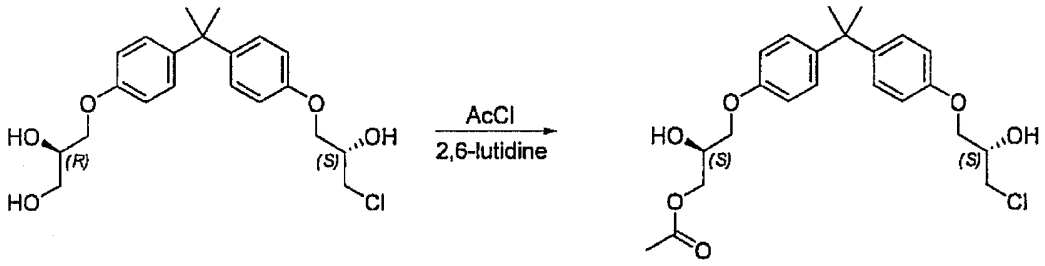


[0177] To a solution of (S)-2,2-dimethyl-4-((4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)methyl)-1,3-dioxolane (2530 mg, 6.34 mmol, 1

equiv) in acetonitrile (25 mL) was added $CeCl_3 \cdot 7H_2O$ (5910 mg, 15.87 mmol, 2.5 equiv) and the mixture was refluxed for 20 h. The resulting white paste was filtered and washed with ethyl acetate, and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 20% hexane in ethyl acetate to 100% ethylacetate) and Si gel Sep pak (10g, eluent: 50% hexane in ethyl acetate to 80% ethylacetate) to provide the title compound (2250 mg, 90%) as a transparent foam.

EXAMPLE 4

SYNTHESIS OF (S)-3-(4-(2-(4-((S)-3-CHLORO-2-HYDROXYPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)-2-HYDROXYPROPYL ACETATE

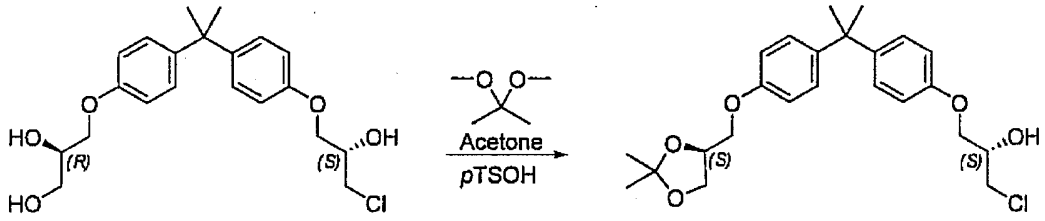


[0178] To a solution of (R)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (1000 mg, 2.53 mmol) in anhydrous dichloromethane (8.0 mL) at – 78 °C were successively added 2,6-lutidine (590 µL, 5.06 mmol) and acetic chloride (144 µL, 2.02 mmol) dropwise. After 1 h, the reaction mixture was quenched with an aqueous solution of sodium chloride and stirred for 15 min, and the resulting mixture was extracted twice with dichloromethane. The organic phases were combined, dried over anhydrous magnesium sulfate and filtered. Solvents were evaporated, and the resulting crude material was purified by silica gel flash chromatography (eluent: 2% methanol in dichloromethane) to provide the title compound (300 mg, 27%) as a sticky solid.

[0179] FIGS. 1(A)-(C) illustrates ^1H and ^{13}C-NMR data for the title compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate.

EXAMPLE 5

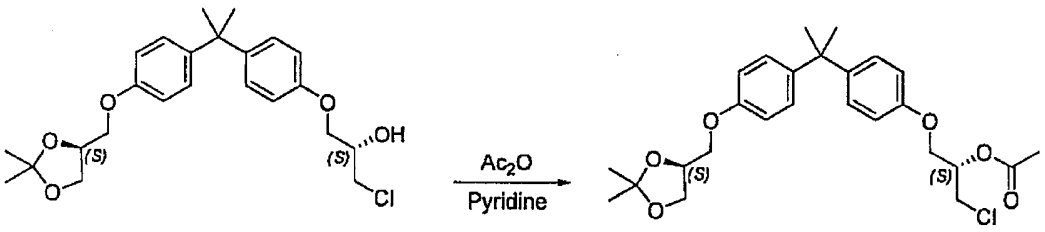
SYNTHESIS OF (S)-1-CHLORO-3-(4-(2-(4-(((S)-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL)METHOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-OL



[0180] To a solution of (R)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (1000 mg, 2.53 mmol) in acetone (8.0 mL) was added 2,2-dimethoxypropane (630 μL, 5.06 mmol) and catalytic amounts of p-toluenesulfonic acid. After 14 h, the reaction mixture was quenched with an aqueous solution of sodium chloride and stirred for 15 min, and the resulting mixture was extracted twice with ethyl acetate. The organic phases were combined, dried over anhydrous magnesium sulfate and filtered. Solvents were evaporated, and the resulting crude material was purified by silica gel flash chromatography (eluent: 2% methanol in dichloromethane) to provide the title compound.

EXAMPLE 6

SYNTHESIS OF (S)-1-CHLORO-3-(4-(2-(4-(((S)-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL)METHOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-YL ACETATE

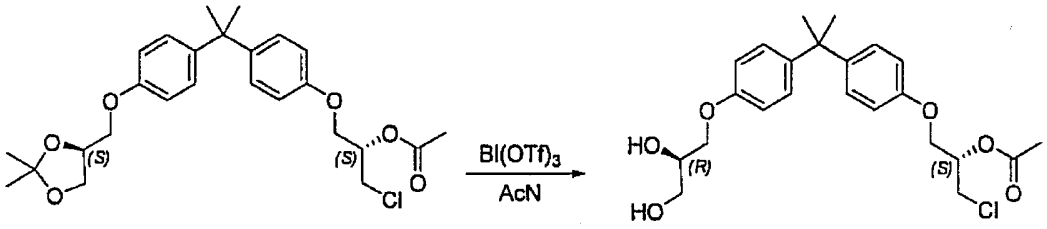


[0181] To a solution of (S)-1-chloro-3-(4-(2-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (850 mg, 1.95 mmol) in anhydrous pyridine (6.0 mL) were successively added acetic anhydride (280 μL, 2.93 mmol) and catalytic amount of DMAP. After 3 h, the reaction mixture was quenched with an aqueous solution of sodium chloride and stirred for 15 min, and the resulting mixture was extracted twice with ethyl acetate. The organic phases were combined, dried over anhydrous

magnesium sulfate and filtered. Solvents were evaporated, and the resulting crude material was used without further purification.

EXAMPLE 7

SYNTHESIS OF (S)-1-CHLORO-3-(4-(2-(4-((R)-2,3-DIHYDROXYPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-YL ACETATE

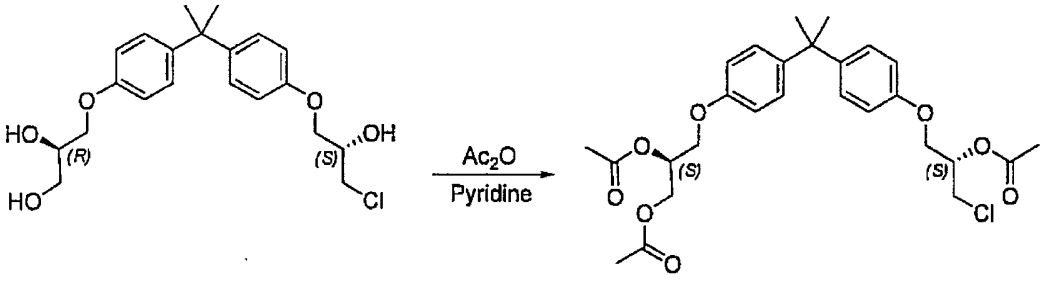


[0182] To a solution of crude (S)-1-chloro-3-(4-(2-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate in anhydrous acetonitrile (8.0 mL) was added bismuth triflate (300 mg, 0.46 mmol) in one portion. After 0.5 h, the reaction mixture was partitioned twice with sodium bicarbonate and ethyl acetate. The organic phased were combined, dried over anhydrous magnesium sulfate, and filtered. Solvents were evaporated, and the resulting crude material was purified by silica gel flash chromatography (eluent: 2% to 5% methanol in dichloromethane) to provide the title compound (734 mg, 86%) as a sticky solid.

[0183] **FIGS. 2(A)-(C)** illustrates ^{1}H and ^{13}C-NMR data for the title compound (S)-1-chloro-3-(4-(2-(4-((R)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate.

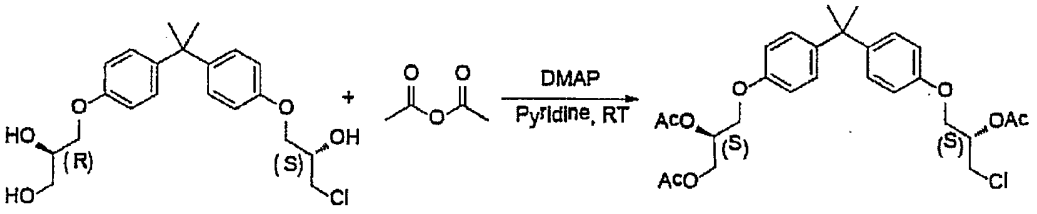
EXAMPLE 8

SYNTHESIS OF (S)-3-(4-(2-(4-((S)-2-ACETOXY-3-CHLOROPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIYL DIACETATE



[0184] To a solution of (R)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (500 mg, 1.27 mmol) in anhydrous pyridine (6.0 mL) were successively added acetic anhydride (605 µL, 6.35 mmol) and a catalytic amount of DMAP. After 14 h, the reaction mixture was quenched with an aqueous solution of sodium chloride and stirred for 15 min, and the resulting mixture was extracted twice with dichloromethane. The organic phases were combined, dried over anhydrous magnesium sulfate, and filtered. Solvents were evaporated, and the resulting crude material was purified by silica gel flash chromatography (eluent: 2% methanol in dichloromethane) to provide the title compound (621 mg, 94%) as a sticky solid.

[0185] In a further embodiment, the title compound (S)-3-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate can be synthesized *via* the following reaction scheme.

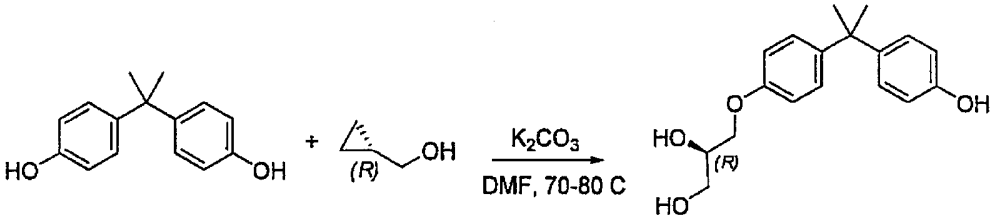


[0186] Acetic Anhydride (4.3 g, 41.7 mmol) was added to a solution of (R)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (2.8 g, 6.95 mmol) and DMAP (30mg, 0.25mmol) in anhydrous pyridine (24 mL) in a water bath. The resulting solution was stirred overnight. The pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate (50 mL), washed subsequently with water (2 x 40mL), then cold aqueous 1M HCl (40 mL), saturated $NaHCO_3$ (40 mL) and water (40 mL). The organic layer was dried over Mg_2SO_4, filtered and concentrated to give light yellow oil. The crude product was purified by column chromatography (eluent: 5% ethyl acetate in hexane to 20% ethyl acetate in hexane) to afford the title compound (3.30 g, 91.5% yield) as a colorless viscous oil.

[0187] **FIGS. 3(A)-(B)** illustrates ^{1}H and ^{13}C-NMR data for the title compound (S)-3-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

EXAMPLE 9

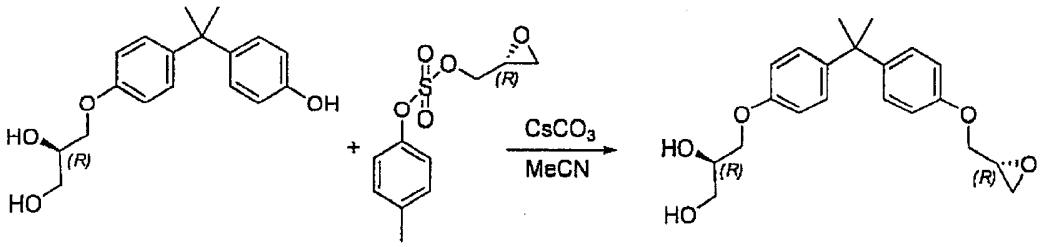
SYNTHESIS OF (R)-3-(4-(2-(4-HYDROXYPHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIOL



[0188] To a stirred solution of bisphenol A (10 g, 43.84 mmol, 1.0 equiv) in anhydrous dimethyl formamide (35 mL) at rt was added K_2CO_3 (9.1 g, 65.76 mmol, 1.5 equiv), and the mixture was stirred for 20 min under argon atmosphere. R (+) glycidol (3.8 mL, 56.99 mmol, 1.3 equiv) was added and the mixture was stirred for 5 h at 70-80 °C. A saturated solution of ammonium chloride (10 mL) was added to the resulting orange-brown solution at room temperature. The mixture was extracted with ethyl acetate (3 x 15 mL). The organic layer was washed with deionized water (10 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 40% to 90% ethyl acetate in hexane) to provide the title compound (3.77 g, 28%) as a clear foam.

EXAMPLE 10

SYNTHESIS OF (R)-3-(4-(2-(4-((R)-OXIRAN-2-YLMETHOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIOL

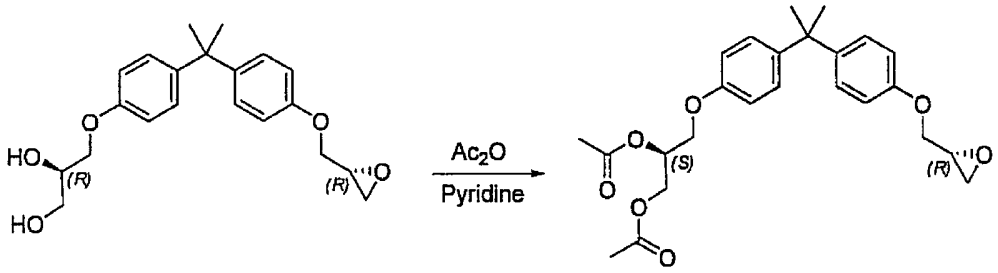


[0189] To a stirred solution of (R)-3-(4-(2-(4-hydroxyphenyl)propan-2-yl)phenoxy)propane-1,2-diol (3.77 g, 12.49 mmol, 1.0 equiv) in anhydrous acetonitrile (35 mL) at rt was added cesium carbonate (6.1 g, 18.73 mmol, 1.5 equiv), and the mixture was stirred for 20 min under argon atmosphere. A solution of (2*R*)-(-)-glycidyl tosylate 98% (4.3 g, 18.73 mmol, 1.5 equiv) in anhydrous acetonitrile (8 mL) was added slowly via syringe, and the mixture was allowed to react at 30 °C for 120 h. The reaction mixture was quenched at room

temperature with a saturated solution of ammonium chloride (5 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with deionized water (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 5% to 10% methanol in dichloromethane) to provide the title compound (4.1 g, 91%) as a transparent foam.

EXAMPLE 11

SYNTHESIS OF (S)-3-(4-(2-(4-((R)-OXIRAN-2-YLMETHOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIYL DIACETATE

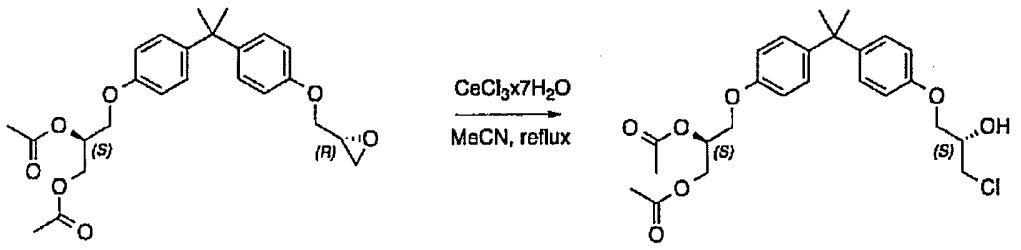


[0190] To a solution of (R)-3-(4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (3000 mg, 8.37 mmol) in anhydrous pyridine (15.0 mL) were successively added acetic anhydride (1.97 mL, 20.92 mmol) and a catalytic amount of DMAP. After 14 h, the reaction mixture was quenched with an aqueous solution of sodium chloride and stirred for 15 min, and the resulting mixture was extracted twice with dichloromethane. The organic phases were combined, dried over anhydrous magnesium sulfate and filtered. Solvents were evaporated, and the resulting crude material was purified by silica gel flash chromatography (eluent: 2% methanol in dichloromethane) to provide the title compound (3.3 g, 89%) as a sticky solid.

[0191] FIGS. 4(A)-(C) illustrates ^{1}H and ^{13}C-NMR data for the title compound (S)-3-(4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

EXAMPLE 12

SYNTHESIS OF (S)-3-(4-(2-(4-((S)-3-CHLORO-2-HYDROXYPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIYL DIACETATE

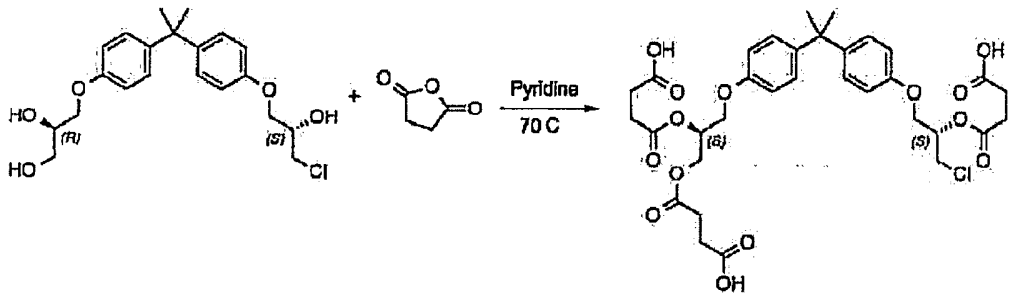


[0192] To a solution of (S)-3-(4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate (180 mg, 0.41 mmol, 1 equiv) in acetonitrile (6 mL) was added $CeCl_3 \cdot 7H_2O$ (227 mg, 0.61 mmol, 1.5 equiv) and the mixture was refluxed for 6 h. The resulting white paste was filtered and washed with ethyl acetate and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 20% hexane in ethyl acetate to 60% ethylacetate) to provide the title compound (172 mg, 88%) as a sticky mass.

[0193] FIGS. 5(A)-(C) are ^{1}H, ^{13}C and ^{13}C APT NMR spectra for the title compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate.

EXAMPLE 13

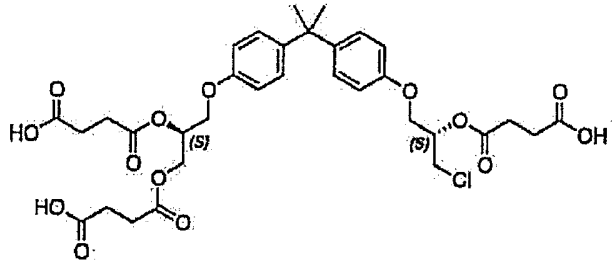
(S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate:



[0194] To a solution of (R)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (700 mg, 1.77 mmol) in anhydrous pyridine (6.0 ml) were added succinic anhydride (710 mg, 7.10 mmol) and the mixture was heated at 70°C. After 3 h, the reaction mixture was quenched with an aqueous solution of sodium chloride and stirred for 15 min, and the resulting mixture was extracted twice with ethyl acetate. The organic

phases were combined, dried over anhydrous magnesium sulfate, and filtered. Solvents were evaporated, and the resulting crude material was purified by silica gel flash chromatography (eluent: 5% to 30% methanol in dichloromethane) to provide the title compound.

[0195] The molecular formula of the title compound may also be illustrated as follows:

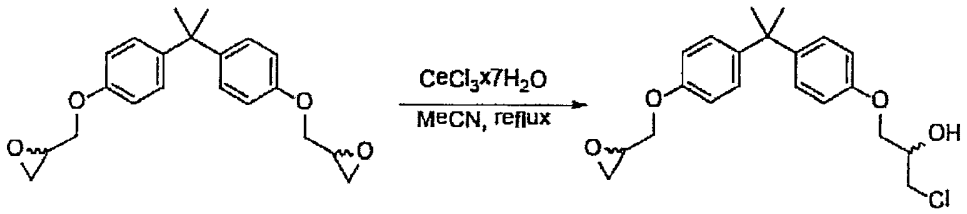


[0196] **FIGS. 6(A)-(C)** are ^{1}H and ^{13}C and ^{13}C APT NMR spectra for the title compound (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate.

[0197] **FIGS. 6(D) and (E)** are ESI MS spectrographs for (S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate.

EXAMPLE 14

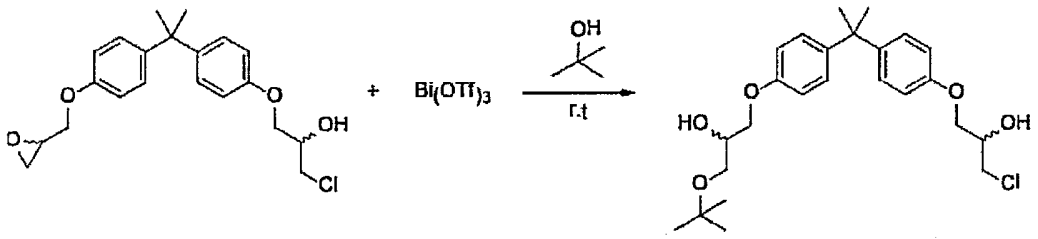
SYNTHESIS OF (2S)-1-CHLORO-3-(4-(2-(4-(OXIRAN-2-YLMETHOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-OL



[0198] To a solution of racemic derivative Bisphenol A diglycidyl ether (13.30 g, 39.27 mmol, 1 equiv) in acetonitrile (30 mL) was added $CeCl_3 \cdot 7H_2O$ (7.30 g, 19.63 mmol, 1/2 equiv) and the mixture was refluxed for 3.5 h. The resulting white paste was filtered and washed with ethyl acetate and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 10% ethyl acetate in hexane) to provide (2S)-1-chloro-3-(4-(2-(4-(oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (2.12 g, 14%) as a pale liquid.

EXAMPLE 15

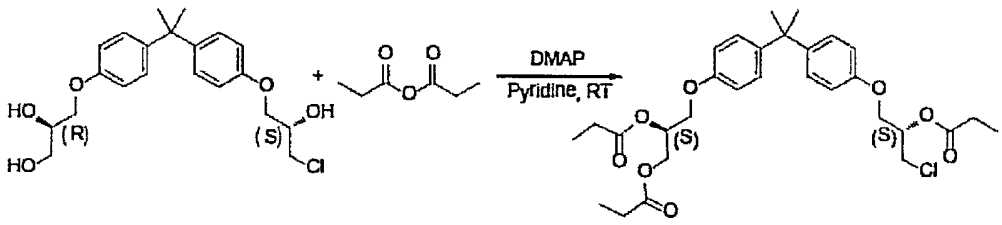
SYNTHESIS OF 1-(TERT-BUTOXY)-3-(4-(2-(4-(3-CHLORO-2-HYDROXYPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-OL



[0199] To a solution of racemic 1-chloro-3-(4-(2-(4-(oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (300 mg, 0.8 mmol, 1 equiv) in t-Butanol (5 mL) was added solid Bismuth (III) trifluoromethanesulfonate (10 mg, 0.015 mmol, 1/50 equiv) in one portion and the mixture was stirred at room temperature for 12 h. Sodium bicarbonate was added (0.5 mL), the organic solvent was evaporated under reduced pressure, and the residue was extracted with dichloromethane (3 x 10 mL). The organic layer was washed with deionized water (2 x 10 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 40% to 80% ethyl acetate in hexane) to provide 1-(tert-butoxy)-3-(4-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (100 mg, 28%) as a foam.

EXAMPLE 16

SYNTHESIS OF (S)-3-(4-(2-(4-((S)-3-CHLORO-2-(PROPIONYLOXY)PROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIYL DIPROPIONATE



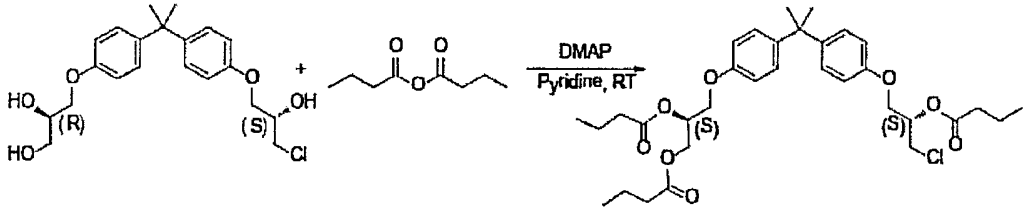
[0200] Propanoic Anhydride (4.3 g, 41.7 mmol) was added to a solution of (R)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (2.8 g, 6.95 mmol) and DMAP (30mg, 0.25mmol) in anhydrous pyridine (24 mL) in a water bath. The

resulting solution was stirred overnight. The pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate (50 mL), washed subsequently with water (2 x 40mL), then cold aqueous 1M HCl (40 mL), saturated $NaHCO_3$ (40 mL) and water (40 mL). The organic layer was dried over Mg_2SO_4, filtered and concentrated to give light yellow oil. The crude product was purified by column chromatography (eluent: 5% ethyl acetate in hexane to 20% ethyl acetate in hexane) to afford the title compound (3.30 g, 91.5% yield) as a colorless viscous oil.

[0201] FIGS. 15A and **15B** are ^1H and ^{13}C NMR spectra of (S)-3-(4-(2-(4-((S)-3-chloro-2-(propionyloxy)propoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl dipropionate.

EXAMPLE 17

SYNTHESIS OF (S)-3-(4-(2-(4-((S)-2-(BUTYRYLOXY)-3-CHLOROPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIYL DIBUTYRATE

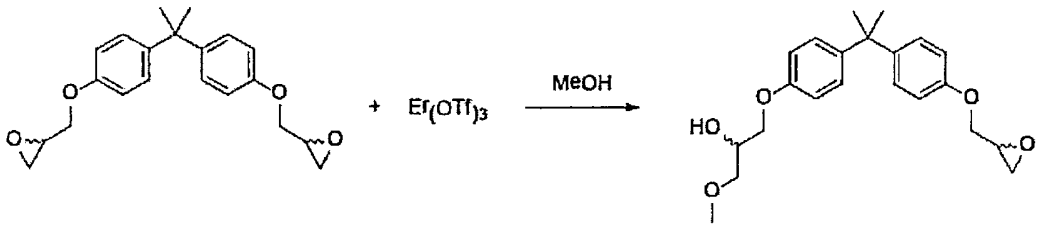


[0202] Butanoic Anhydride (4.3 g, 41.7 mmol) was added to a solution of (R)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (2.8 g, 6.95 mmol) and DMAP (30mg, 0.25mmol) in anhydrous pyridine (24 mL) in a water bath. The resulting solution was stirred overnight. The pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate (50 mL), washed subsequently with water (2 x 40mL), then cold aqueous 1M HCl (40 mL), saturated $NaHCO_3$ (40 mL) and water (40 mL). The organic layer was dried over Mg_2SO_4, filtered and concentrated to give light yellow oil. The crude product was purified by column chromatography (eluent: 5% ethyl acetate in hexane to 20% ethyl acetate in hexane) to afford the title compound (3.30 g, 91.5% yield) as a colorless viscous oil.

[0203] FIGS. 16A and **16B** are ^1H and ^{13}C NMR spectra of (S)-3-(4-(2-(4-((S)-2-(butyryloxy)-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl dibutyrate.

EXAMPLE 18

SYNTHESIS OF 1-METHOXY-3-(4-(2-(4-(OXIRAN-2-YLMETHOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-OL



[0204] To a solution of racemic derivative Bisphenol A diglycidyl ether (500 mg, 1.46 mmol, 1 equiv) in methanol (5 mL) was added solid Erbium(III) trifluoromethanesulfonate (90 mg, 0.146 mmol, 1/10 equiv) in one portion and the mixture was stirred at room temperature for 1 h. Sodium bicarbonate was added (1 mL), the organic solvent was evaporated under reduced pressure and the residue was extracted with dichloromethane (3 x 5 mL). The organic layer was washed with deionized water (2 x 5 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 10% to 40% ethyl acetate in hexane) to provide the title compound (128 mg, 23%) as a pale foam.

EXAMPLE 19

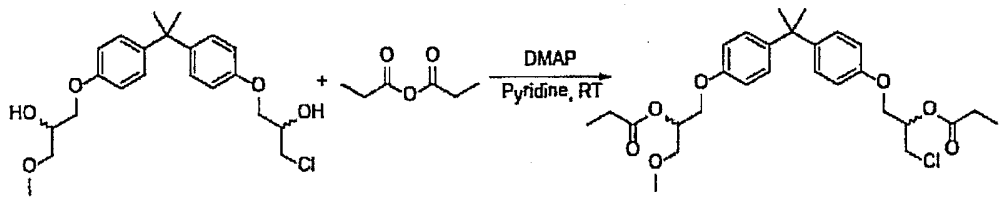
SYNTHESIS OF 1-CHLORO-3-(4-(2-(4-(2-HYDROXY-3-METHOXYPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-OL

[0205] To a solution of racemic derivative 1-methoxy-3-(4-(2-(4-(oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (64 mg, 0.17 mmol, 1 equiv) in acetonitrile (2 mL) was added $CeCl_3 \cdot 7H_2O$ (96 mg, 0.25 mmol, 1.5 equiv) and the mixture was refluxed for 17 h. The resulting white paste was filtered and washed with ethyl acetate and the clear suspension was concentrated under reduced pressure. The resulting residue was

purified by flash column chromatography on silica gel (eluent: 40% ethyl acetate in hexane) to provide the title compound (70 mg, 99%) as a pale foam.

EXAMPLE 20

SYNTHESIS OF 1-CHLORO-3-(4-(2-(4-(2-HYDROXY-3-METHOXYPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)PROPAN-2-OL BISPROPIONATE

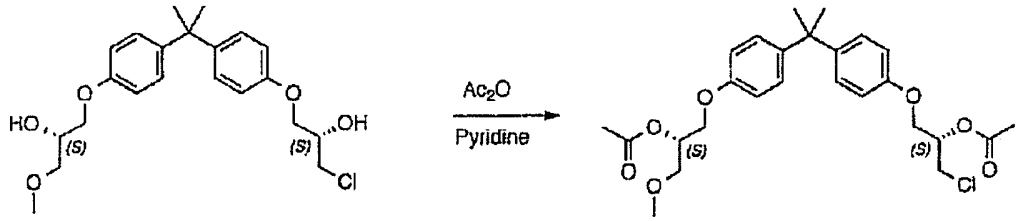


Prepared as described in Example 17 for (S)-3-(4-(2-(4-((S)-3-chloro-2-(propionyloxy)propoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl dipropionate.

[0206] FIGS. 14A and **14B** are ^{1}H and ^{13}C NMR spectra of 1-chloro-3-(4-(2-(4-(2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol bispropionate.

EXAMPLE 21

SYNTHESIS OF (S)-1-(4-(2-(4-((S)-2-ACETOXY-3-CHLOROPROPOXY)PHENYL)PROPAN-2-YL)PHENOXY)-3-METHOXYPROPAN-2-YL ACETATE



[0207] To a solution of (S)-1-chloro-3-(4-(2-(4-((S)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (15 mg, 0.036 mmol) in anhydrous pyridine (1.0 ml) were successively added acetic anhydride (9 µL, 0.091 mmol) and catalytic amount of DMAP. After 5 h, the reaction mixture was quenched with an aqueous solution of sodium chloride and stirred for 15 min, and the resulting mixture was extracted twice with dichloromethane. The organic phases were combined, dried over anhydrous magnesium sulfate, and filtered. Solvents were evaporated, and the resulting crude

material was purified by silica gel flash chromatography (eluent: 10 to 20% ethyl acetate in hexane) to provide the title compound as a sticky solid.

[0208] FIGS. 7(A)-(C) are ^{1}H, ^{13}C and ^{13}C APT NMR spectra for the title compound (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate.

[0209] FIGS. 6(D) and (E) are ESI MS spectrographs for (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate.

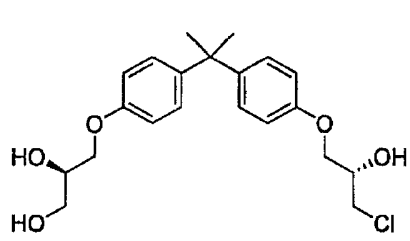
IN VITRO ACTIVITY OF COMPOUNDS

EXAMPLE 22

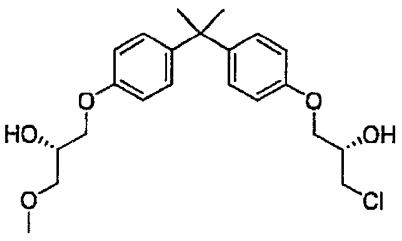
[0210] LNCaP ($2.4x10^4$ cell/well) cells were seeded on 24-well plates overnight before transfection with PSA(6.1kb)-luciferase plasmid (0.25 ug /well) in serum-free, red phenol-free media. The next day, cells were pre-treated with compounds of the disclosure for 1 hour before the addition of synthetic androgen, R1881 (1 nM) to transactivate the androgen receptor. After 48 h of incubation with R1881, the cells were harvested, and relative luciferase activity was determined as a read-out for androgen receptor transcriptional activity. Test compounds were added to the cells at various concentrations and activity for each treatment was normalized to the predicted maximal activity induction (in the absence of test compounds, vehicle only). Transfection experiments were performed using triplicate wells.

[0211] FIG. 8 presents in vitro dose response of various compounds of the disclosure (7c, 3c and 13b) relative to comparative compounds A and B.

[0212] As seen in **FIG. 8**, each of the tested compounds of the disclosure showed a dose response.



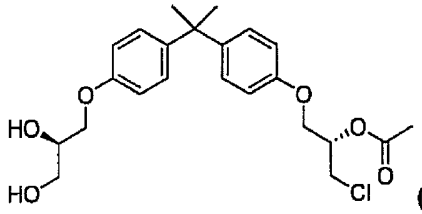
Compound A



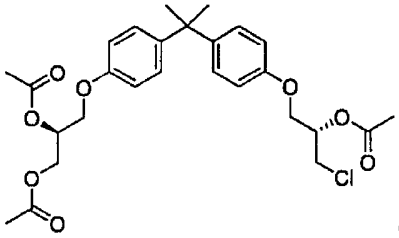
Compound B

[0213] Furthermore, toxicity was assessed by both microscopic examination and reduction of protein levels. Solubility was assessed both macroscopically (cloudy media) and microscopically (formation of granules or crystals).

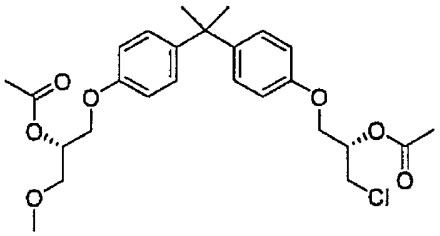
[0214] Thus, tested compounds



(3c),



(7c). and



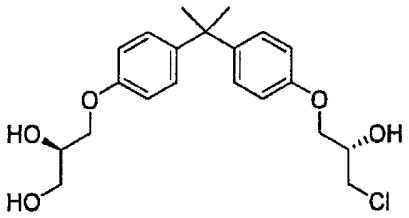
(13b)

are effective in the treatment methods disclosed herein and demonstrated a dose response at 5μM, 10 μM, and 20 μM.

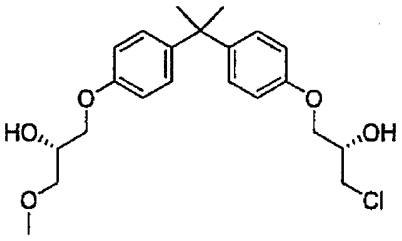
EXAMPLE 23

[0215] Further experiments, as outlined in Example 22, were conducted with LNCaP cells transfected with PSA-luciferase plasmid to evaluate the dose response of particular compounds of the disclosure.

The compounds of the disclosure were compared to compounds A and B, as in Example 22:

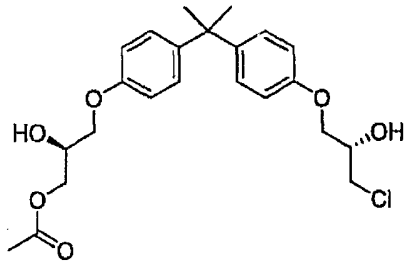


Compound A

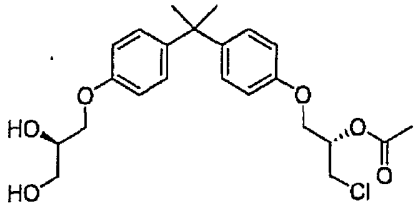


Compound B

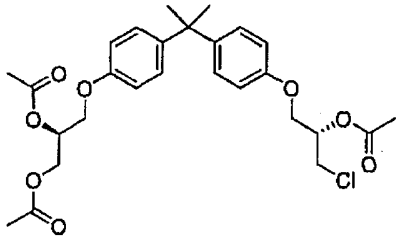
The compounds of the disclosure evaluated were as follows:



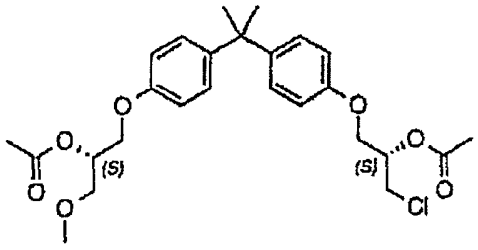
(1c),



(3c),



(7c), and



(S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Example 21)

[0216] **FIG. 9** presents in vitro dose response of various compounds of the disclosure (1c, 3c 7c, and (S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Example 21)) relative to comparative compounds A and B.

[0217] The following Table 4 also illustrates the data contained in **FIG. 9** and demonstrates that the compounds of the disclosure exhibit a dose response.

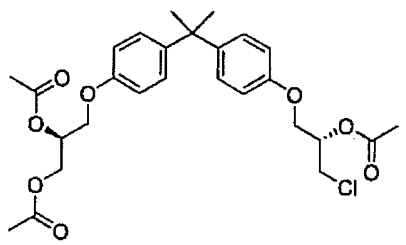
TABLE 4.

Analog	**IC50 (μM + Standard Deviation)**
Compound A	15.02 + 1.25
Compound 1C	25.58 + 6.89
Compound 3C	11.61 + 2.6
Compound 7C	8.81 + 0.93
Compound B	9.80 + 2.28
(S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Example 21)	8.07 + 1.48

EXAMPLE 24

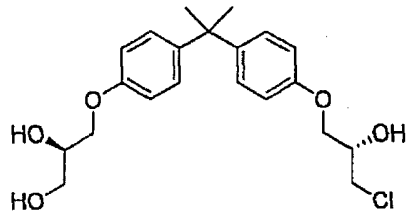
[0218] Viability and proliferation assays were conducted and demonstrate that a prodrug compound of the disclosure is twice as potent as its active compound.

A compound of the disclosure:



(7c),

was compared to compound A:



Compound A.

[0219] Protocol: Proliferation assays using AlamarBlue, wherein the % androgen-dependent proliferation represents proliferation of LNCaP cells in response to R1881 compared to basal levels. PC3 cells do not express functional androgen receptor and % viability provides an indication of cytotoxicity or off-target effects unrelated to the androgen receptor.

[0220] *Viability and proliferation assays.* PC3 and LNCaP cells were plated in 96-well plates in respective media plus 0.5% FBS. The next day, PC3 cells were treated with vehicle and increasing concentrations of Compound A or Compound 7c for 2 days, and LNCaP cells were pretreated with vehicle and Compound A for 1 hour before treating with 0.1 nM R1881 for 3 days. Cell viability was measured using alamarBlue Cell Viability Assay (Invitrogen) following the manufacturer's protocol.

[0221] The results are illustrated in **FIG. 10** and demonstrate that a prodrug compound of the disclosure (*i.e.* 7c) is twice as potent as its active compound (*i.e.* compound A).

EXAMPLE 25

[0222] *Xenograft Experiment*

[0223] Male NOD-SCID mice bearing subcutaneous tumors were castrated when tumor volume was approximately 100 mm3.

[0224] Animals bearing LNCaP xenografts were dosed daily by oral gavage with Compound 7c, Compound A, or 10%DMSO/corn oil vehicle control.

[0225] Tumors were measured using caliphers and the volume calculated by application of the formula (LxWxH)*0.5236.

[0226] As can be seen from **FIG. 11**, a compound of the disclosure (*i.e.* compound 7c) is effective at reducing tumor volume.

[0227] Further, **FIG. 11** demonstrates that a prodrug compound of the disclosure (*i.e.* compound 7c) is more effective than its active compound (*i.e.* compound A) at reducing tumor volume in the xenograft mouse model.

EXAMPLE 26

[0228] *Further Xenograft Experiment*

[0229] Male NOD-SCID mice bearing subcutaneous tumors were castrated when tumor volume was approximately 100 mm3.

[0230] Animals bearing LNCaP xenografts were dosed daily by oral gavage with 55.23 mg/kg body weight of Compound 7c or CMC/10%DMSO/Tween-20 vehicle control.

[0231] Tumors were measured using caliphers and the volume calculated by application of the formula (LxWxH)*0.5236Male

[0232] As can be seen from **FIG. 12**, a prodrug stereoisomer of a compound of the disclosure (*i.e.* compound 7c) is effective at reducing tumor volume.

EXAMPLE 27

[0233] *IC50's of Prodrugs of the Disclosure*

[0234] Table 5 illustrates the IC50's of various prodrugs of the disclosure, as compared to Compound A.

[0235] **FIG. 13** further illustrates the IC50's of various compounds of the disclosure.

TABLE 5

	PSA-luc IC50s (uM)		
COMPOUND	MEAN	SD	n
Compound A	14.0	0.8	5
Compound 4c	15.3	3.4	4

(S)-3-(4-(2-(4-((R)-oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate	26.0	4.1	4
(S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol trisuccinate	60.2	8.1	2
(S)-3-(4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl 2-aminoacetate	12.1	2.5	4

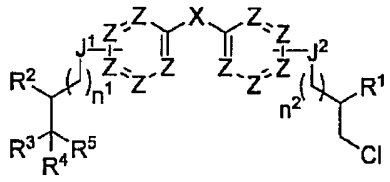
INCORPORATION BY REFERENCE

[0236] All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications, and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety for all purposes.

[0237] Aspects of the embodiments can be modified, if necessary, to employ concepts of the various patents, applications, and publications, incorporated by reference herein, to provide yet further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description.

CLAIMS

1. A compound having the following structure (I):



(I)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

J1 and J2 are each independently -O-, -S(O)m-, -NR6- or -(CR6R7)-;

X is a direct bond, –C(R8R9)-, –C(=CR8R9)-, -C(R8R9)-aryl-C(R8R9)-, -C(=CR8R9)-aryl-C(=CR8R9)-, -C(=CR8R9)-aryl-C(R8R9)-, -C(R8R9)-aryl-C(=CR8R9)-, -O-, -S(O)m-, -N(R6)-, –CH(NR6R7)-, -C(=NOR6)-, -C(=N-NHR10)-, -C(=NR6)- or -C(=O)-;

Z is, at each occurrence, independently –C(R11)- or –N-;

R1 is hydroxyl, -OR12 or –OC(=O)R13;

R2 and R3 are each independently hydroxyl, halo, -OR12 or -OC(=O)R13;

R4 and R5 are each independently H or halo;

R6 and R7 are, at each occurrence, independently H or C1-10 alkyl;

R8 and R9 are, at each occurrence, independently, H, hydroxyl, halo, C1-C10 alkyl, C1-C10 haloalkyl, C1-C10 deuteroalkyl, C1-C10 alkoxy, aryl, aralkyl, -S(O)mR14 or -NR6R7, or R8 and R9 may join to form a mono-, bi- or tri-cyclic carbocycle or heterocycle containing from 3 to 20 carbon atoms;

R10 is H, C1-C10 alkyl, aryl, aminocarbonyl, C1-C10 alkylcarbonyl or C1-C10 alkylaminocarbonyl;

R11 is, at each occurrence, independently H, halo or C1-C10 alkyl;

R12 is, at each occurrence, independently C1-C20 alkyl or C2-C20 alkenyl;

R13 is, at each occurrence, independently C1-C20 alkyl, C2-C20 alkenyl, aryl or aralkyl, wherein the C1-C20 alkyl does not include optional amino or alkylamino substituents and each aliphatic carbon of the C1-C20 alkyl, C2-C20 alkenyl or aralkyl groups may optionally be replaced with –O- or –S(O)m-;

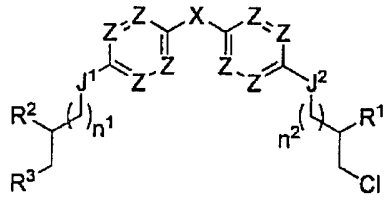
R14 is H, C1-C10 alkyl or aryl;

m is, at each occurrence, independently 0, 1 or 2;

n1 and n2 are each independently 0, 1, 2, 3, 4 or 5,

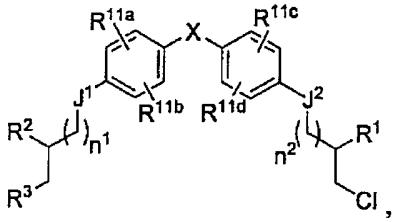
wherein at least one of R1, R2 or R3 is –OC(=O)R13.

2. The compound of claim 1, wherein the compound has the following structure (Ia):



(Ia)

3. The compound of any one of claims 1 or 2, wherein the compound has the following structure (Ib):



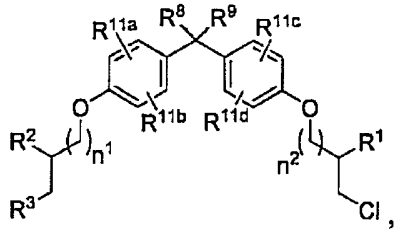
(Ib)

wherein R11a, R11b, R11c and R11d are each independently H, halo or C1-C10 alkyl.

4. The compound of any one of claims 1-3, wherein J1 and J2 are each -O-.

5. The compound of any one of claims 1-4, wherein X is –C(R8R9)-.

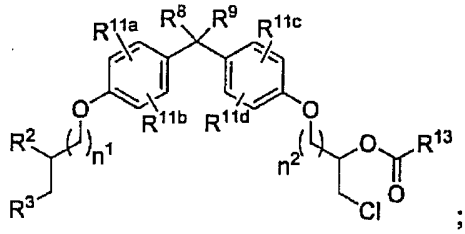
6. The compound of any one of claims 1-5, wherein the compound has the following structure (Ic):



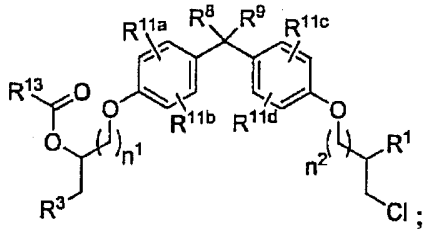
(Ic)

wherein R11a, R11b, R11c and R11d are each independently H, halo or C1-C10 alkyl.

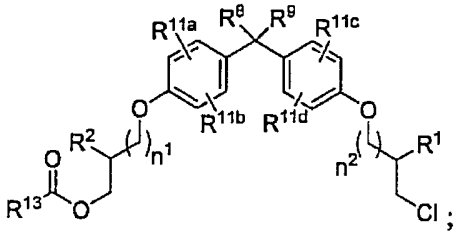
7. The compound of any one of claims 1-6, wherein the compound has one of the following structures (Id), (Ie), (If), (Ig), (Ih), (Ii) or (Ij):



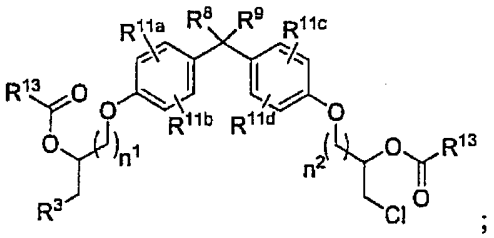
(Id)



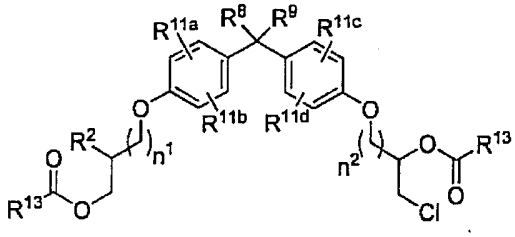
(Ie)



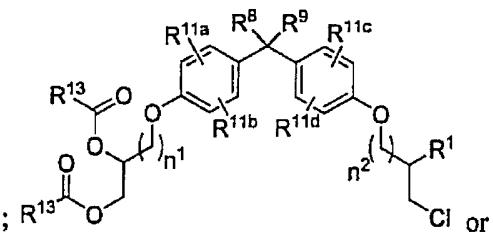
(If)



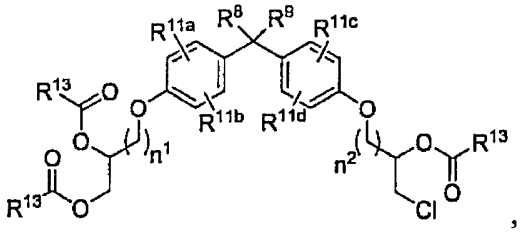
(Ig)



(Ih)



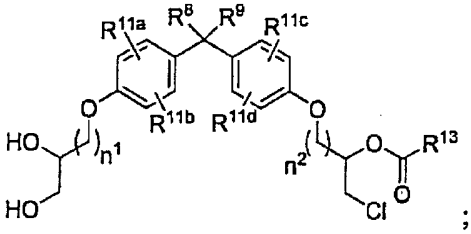
(Ii)



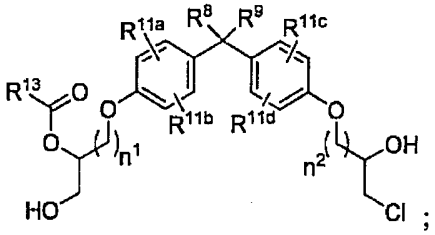
(Ij)

wherein R11a, R11b, R11c and R11d are each independently H, halo or C1-C10 alkyl.

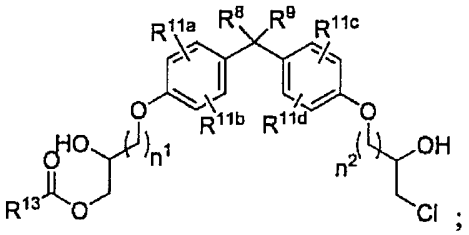
8. The compound of any one of claims 1-7, wherein the compound has one of the following structures (Ik), (Il), (Im), (In), (Io) or (Ip):



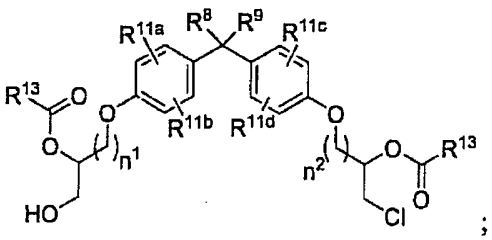
(Ik)



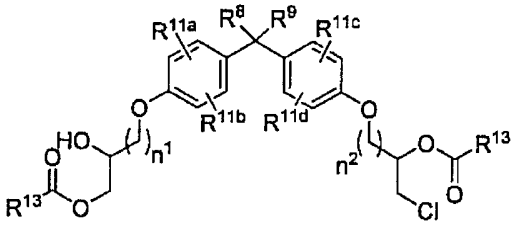
(Il)



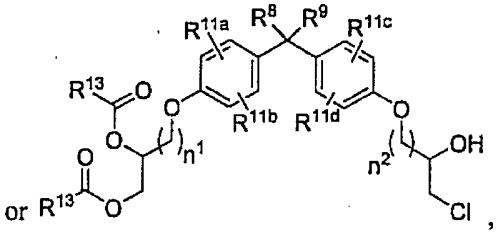
(Im)



(In)



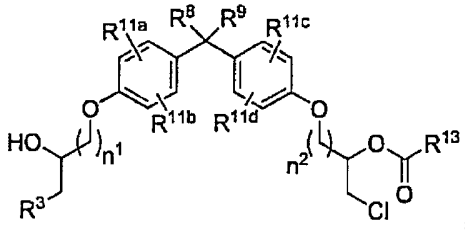
(Io)



(Ip)

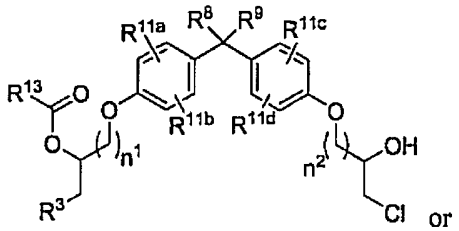
wherein R11a, R11b, R11c and R11d are each independently H, halo or C1-C10 alkyl.

9. The compound of any one of claims 1-7, wherein the compound has one of the following structures (Iq), (Ir) or (Is):



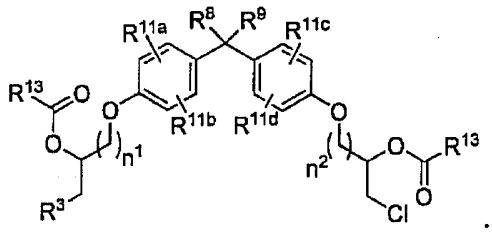
(Iq)

;



(Ir)

or



(Is)

10. The compound of claim 9, wherein R3 is –OR12.

11. The compound of claim 10, wherein R12 is C1-C6 alkyl.

12. The compound of claim 11, wherein R12 is methyl, isopropyl or n-butyl.

13. The compound of claim 9, wherein R3 is halo.

14. The compound of claim 13, wherein R3 is fluoro.

15. The compound of any one of claim 1-14, wherein each R13 is independently C1-C6 alkyl.

16. The compound of claim 15, wherein each R13 is independently methyl, ethyl or propyl.

17. The compound of claim 16, wherein each R13 is methyl.

18. The compound of any one of claims 1-17, wherein R8 and R9 are each independently C1-C6 alkyl.

19. The compound of claim 18, wherein R8 and R9 are each methyl.

20. The compound of any one of claims 1-19, wherein at least one R11 is H or at least one of R11a, R11b, R11c or R11d is H.

21. The compound of claim 20, wherein each R11 is H or each of R11a, R11b, R11c and R11d is H.

22. The compound of any one of claims 1-21, wherein n1 and n2 are each 1.

23. The compound of any one of claims 1-22, wherein R4 and R5 are each H.

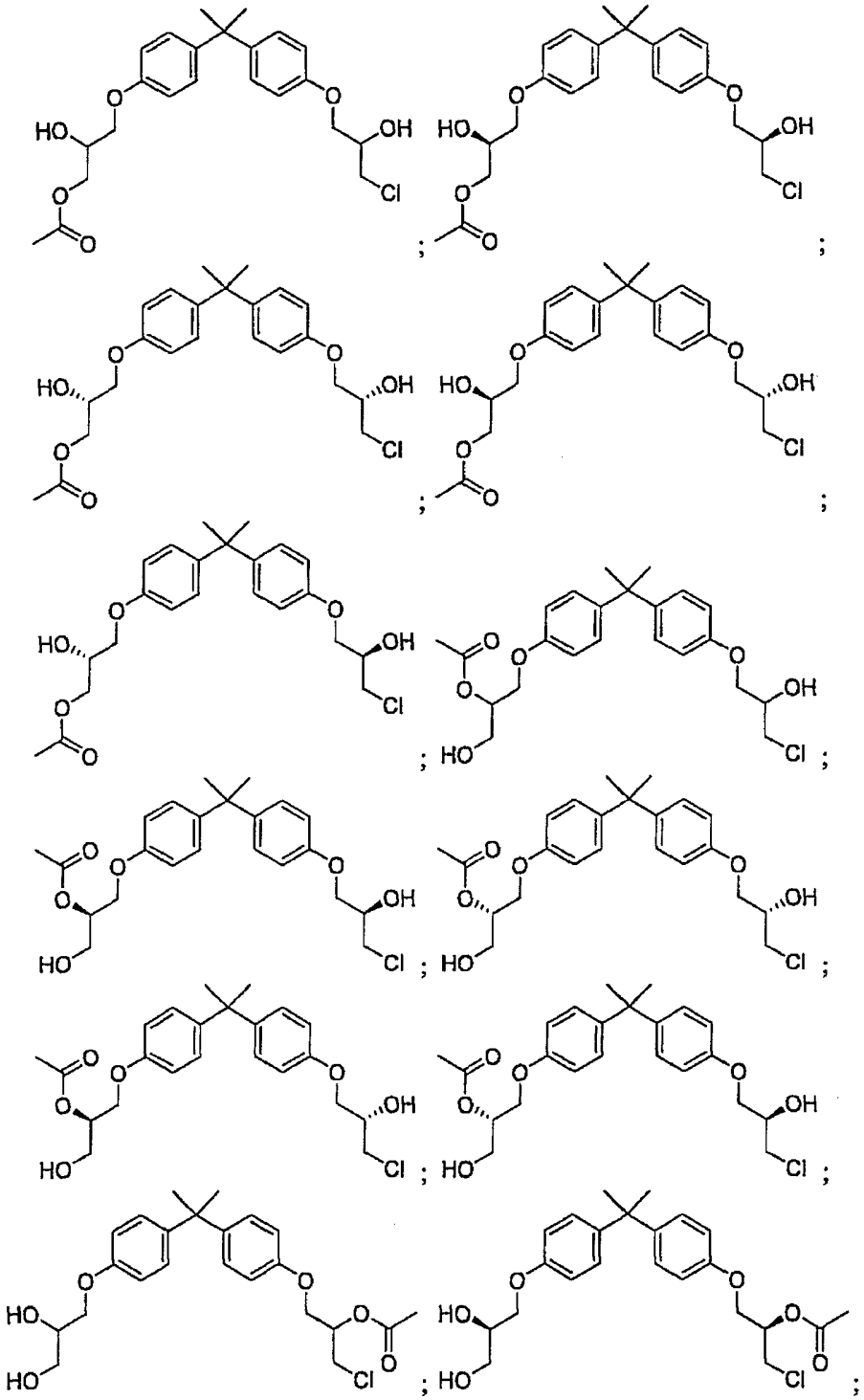
24. The compound of any one of claims 1-22, wherein R4 and R5 are each halo.

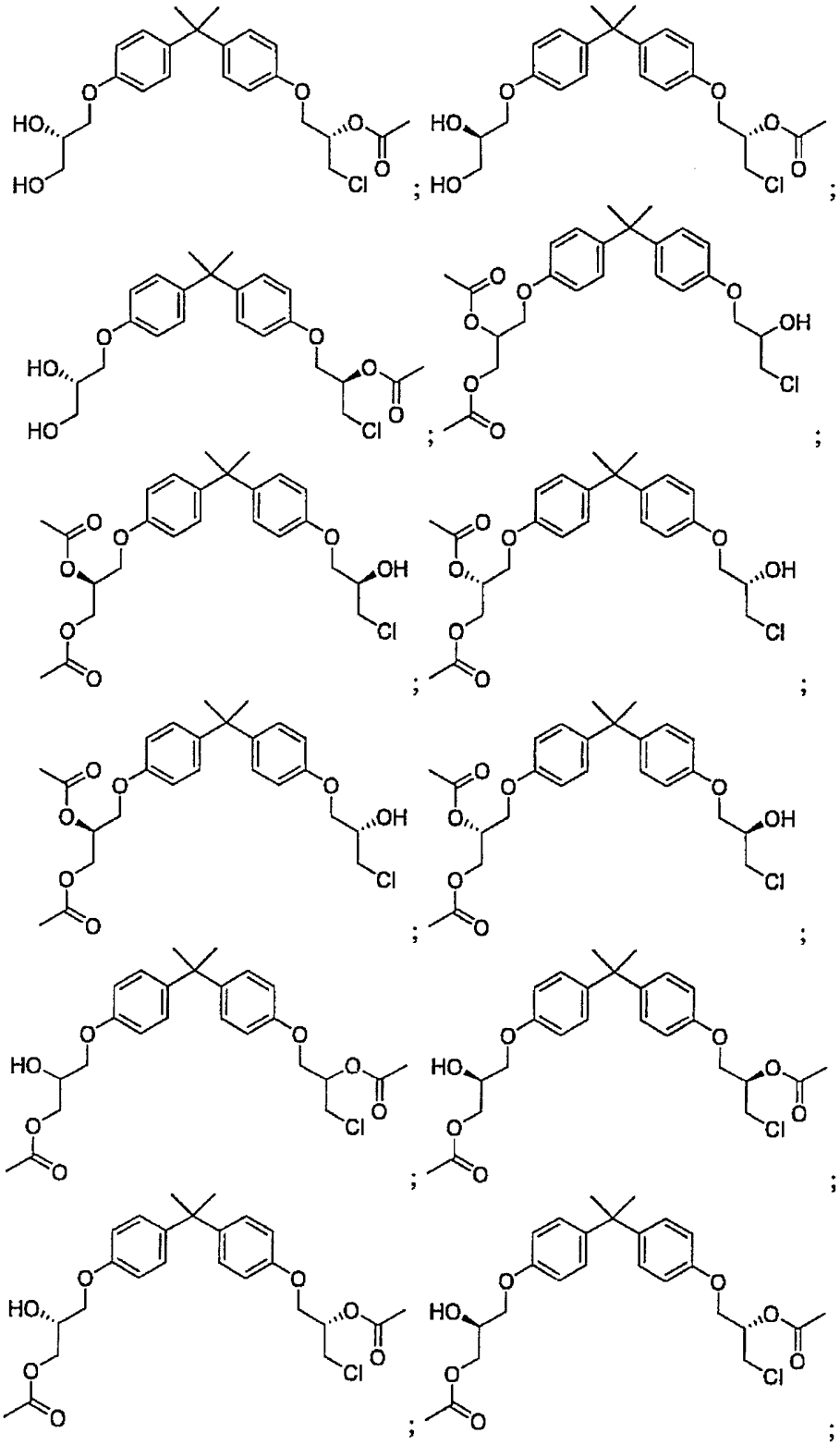
25. The compound of claim 24, wherein halo is fluoro.

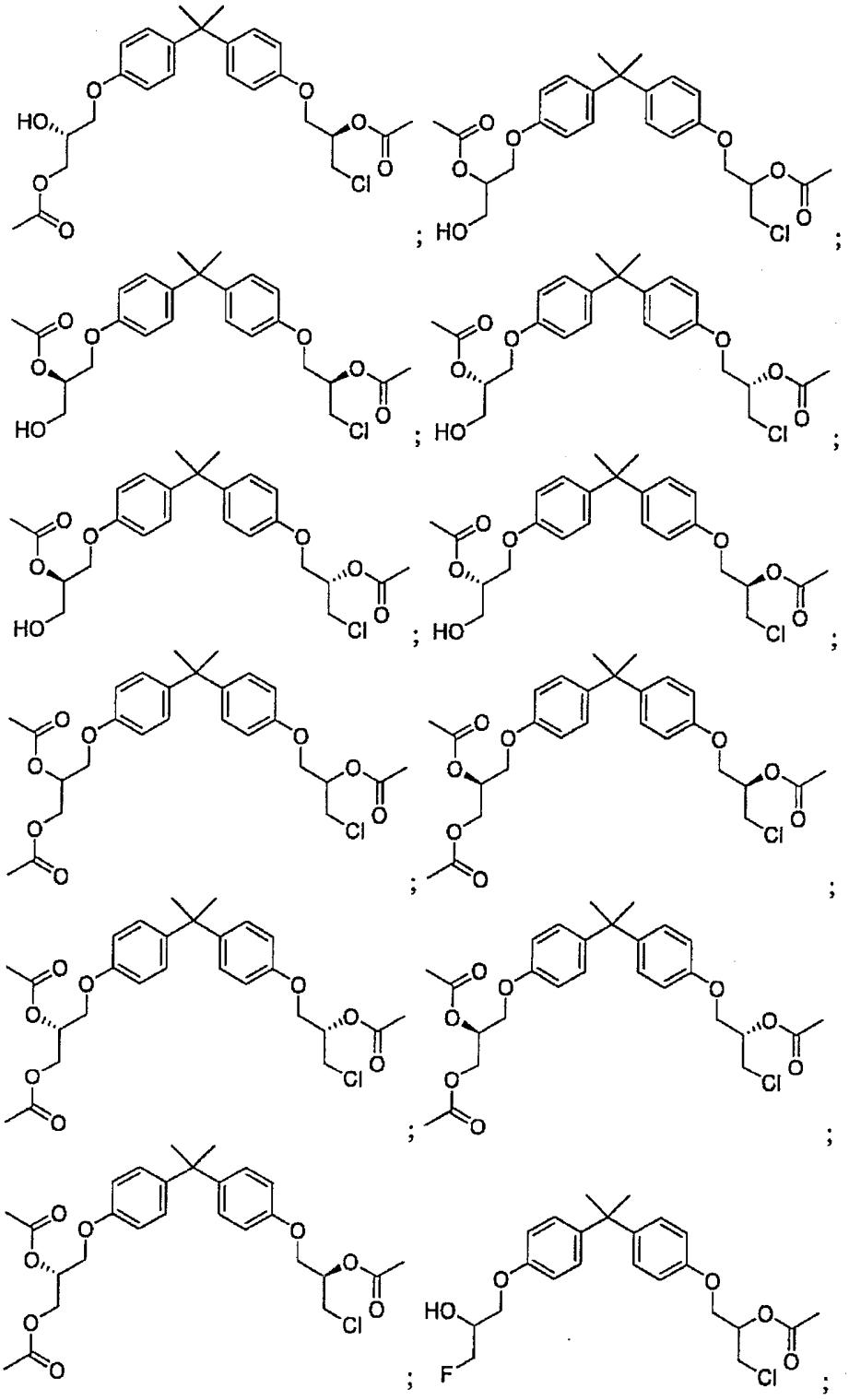
26. The compound of any one of claims 1-14, wherein R13 is C1-C20 alkyl, C2-C20 alkenyl or aralkyl, and at least one of the aliphatic carbons of the C1-C20 alkyl, C2-C20 alkenyl or aralkyl group is substituted with a substituent selected from hydroxyl, halo, oxo and alkoxy.

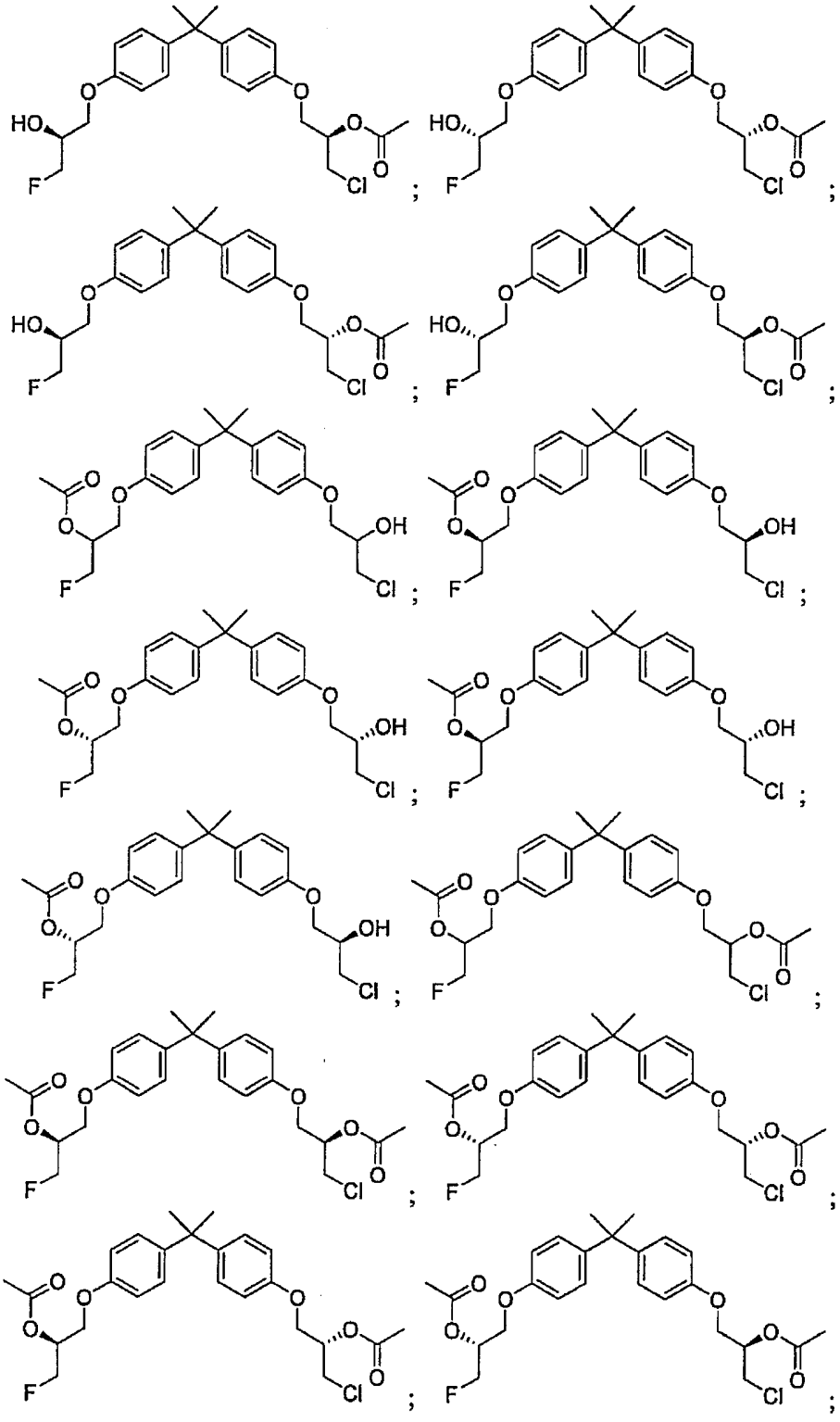
27. The compound of any one of claims 1-14, wherein R13 is aryl or aralkyl, and at least one of the aromatic carbons of the aryl or aralkyl group is substituted with a substituent selected from hydroxyl, halo and alkoxy.

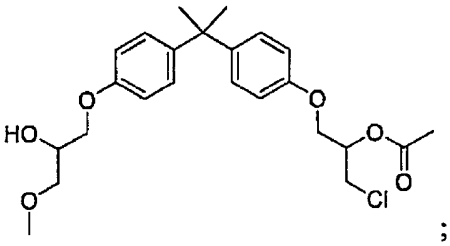
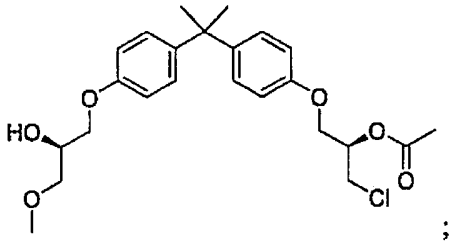
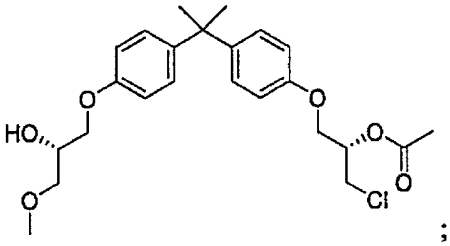
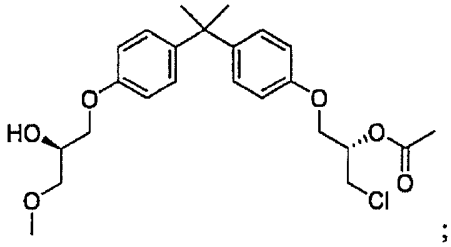
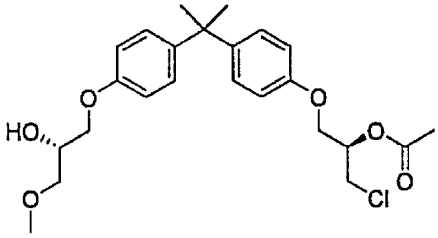
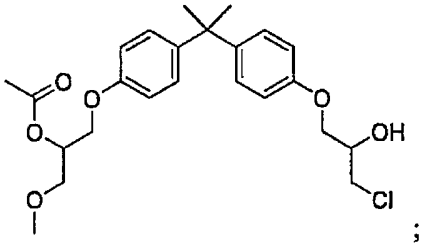
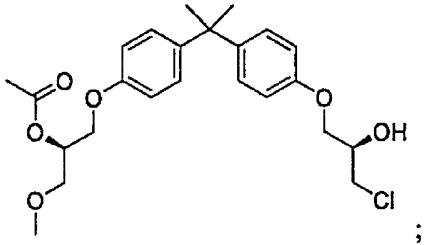
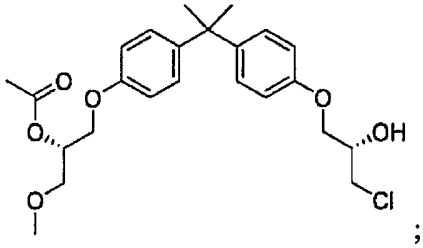
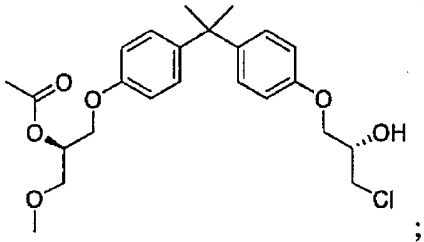
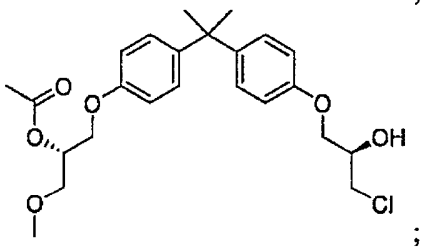
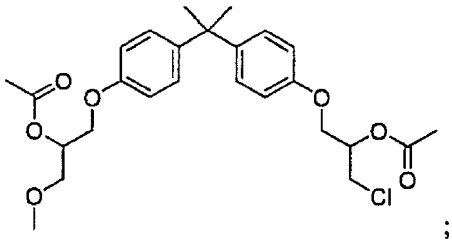
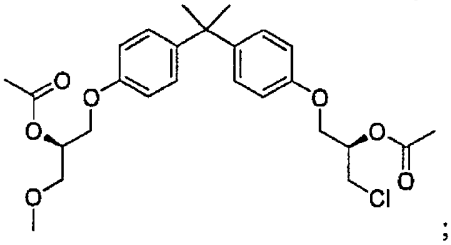
28. The compound of claim 1, wherein the compound has one of the following structures:

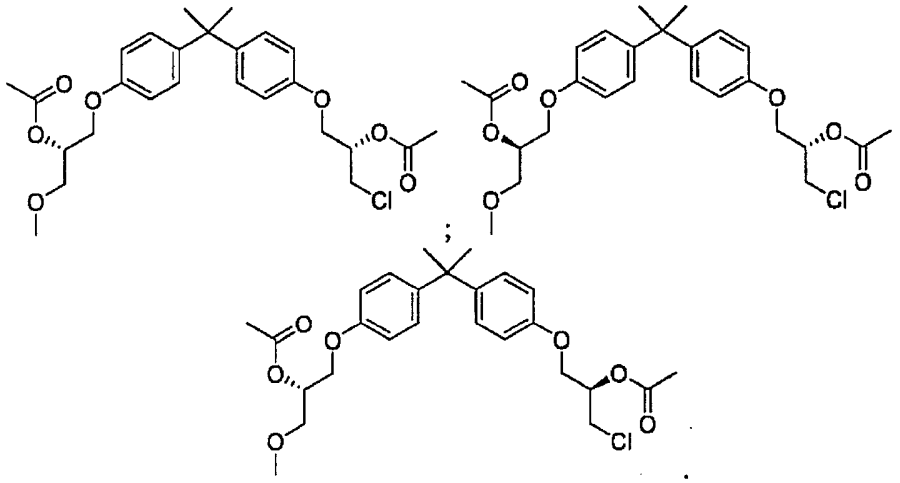









;

;

;

;

;

;

;

;

;

;

;

;



29. A pharmaceutical composition comprising a compound of any one of claims 1 to 28 and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition comprising a compound of any one of claims 1 to 28, an additional therapeutic agent and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, wherein the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy or age-related macular degeneration.

32 The pharmaceutical composition of claim 30, wherein the additional therapeutic agent is enzalutamide, TOK 001, TOK 001; ARN-509; abiraterone, bicalutamide, nilutamide, flutamide, cyproterone acetate, docetaxel, Bevacizumab (Avastin), OSU-HDAC42, VITAXIN, sunitumib, ZD-4054, VN/124-1, Cabazitaxel (XRP-6258), MDX-010 (Ipilimumab), OGX 427, OGX 011, finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111 or a related compound thereof.

33. Use of the pharmaceutical composition of any one of claims 29-32, for modulating androgen receptor (AR) activity.

34. The use of claim 33, wherein modulating androgen receptor (AR) activity is in a mammalian cell.

35. The use of any one of claims 33 or 34, wherein modulating androgen receptor (AR) activity is for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration.

36. The use of claim 35, wherein the indication is prostate cancer.

37. The use of claim 36, wherein the prostate cancer is castration resistant prostate cancer.

38. The use of claim 36, wherein the prostate cancer is androgen-dependent prostate cancer.

39. A method for modulating androgen receptor (AR) activity, the method comprising administering the pharmaceutical composition of any one of claims 29-32 to a subject in need thereof.

40. The method of claim 39, wherein modulating androgen receptor (AR) activity is for the treatment of one or more of the following: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration.

41. The method of claim 40, wherein the method is for treatment of prostate cancer.

42. The method of claim 41, wherein the prostate cancer is castration resistant prostate cancer.

43. The method of claim 41, wherein the prostate cancer is androgen-dependent prostate cancer.

44. A method for increasing the bioavailability of a hydroxyl-containing androgen receptor modulator, the method comprising replacing at least one hydroxyl moiety with an alkyl, alkenyl, aryl or aralkyl ester.

45. The method of claim 44, wherein the method is for increasing oral bioavailability.

46. The method of claim 44, wherein the alky ester is a methyl ester.

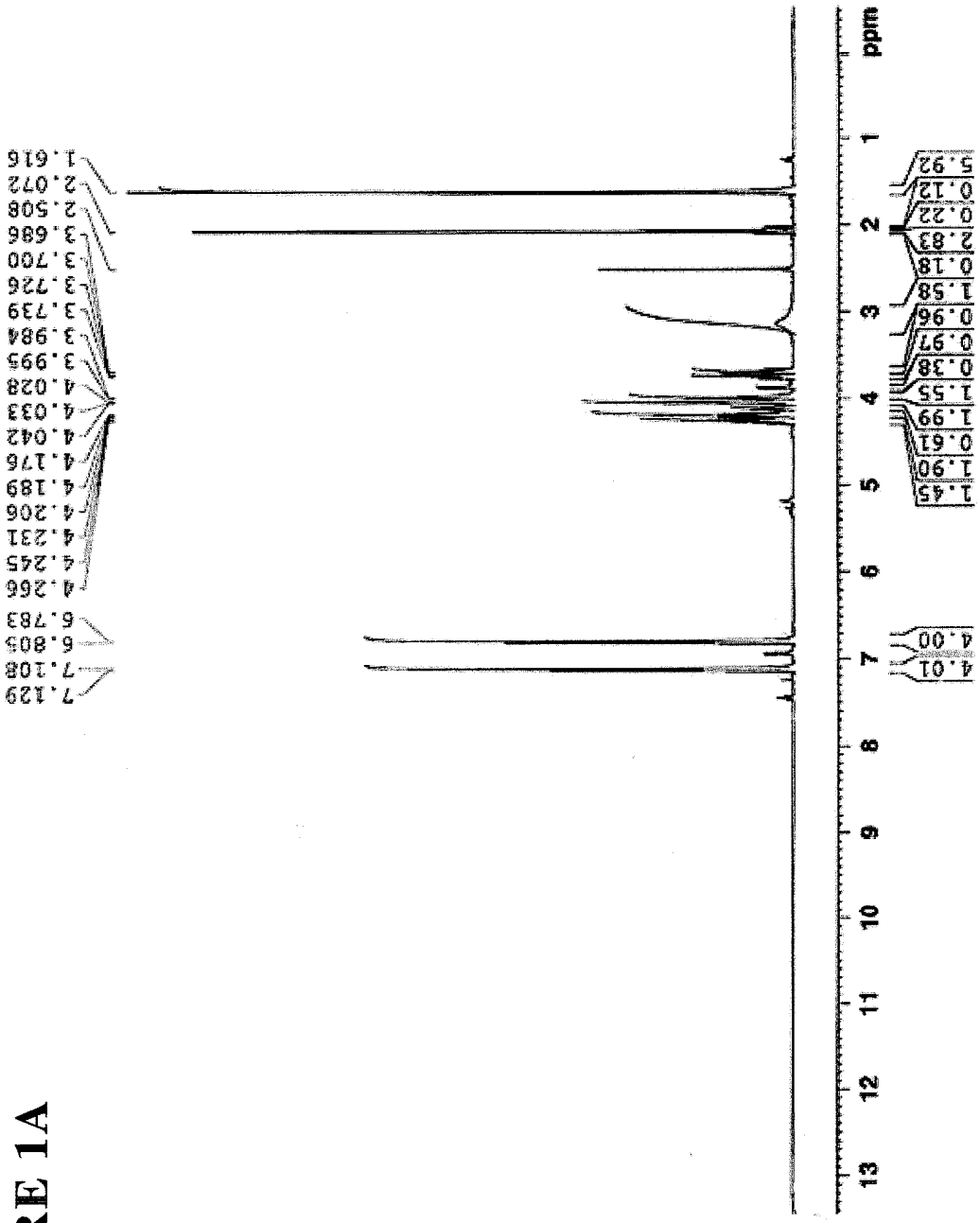

ppm
1 2 3 4 5 6 7 8 9 10 11 12 13
1.616
2.072
2.508
3.686
3.700
3.726
3.739
3.984
3.995
4.028
4.033
4.042
4.176
4.189
4.206
4.231
4.245
4.266
6.783
6.805
7.108
7.129
5.92
0.12
0.22
2.83
0.18
1.58
0.96
0.97
0.38
1.55
1.99
0.61
1.90
1.45
4.00
4.01

FIGURE 1A

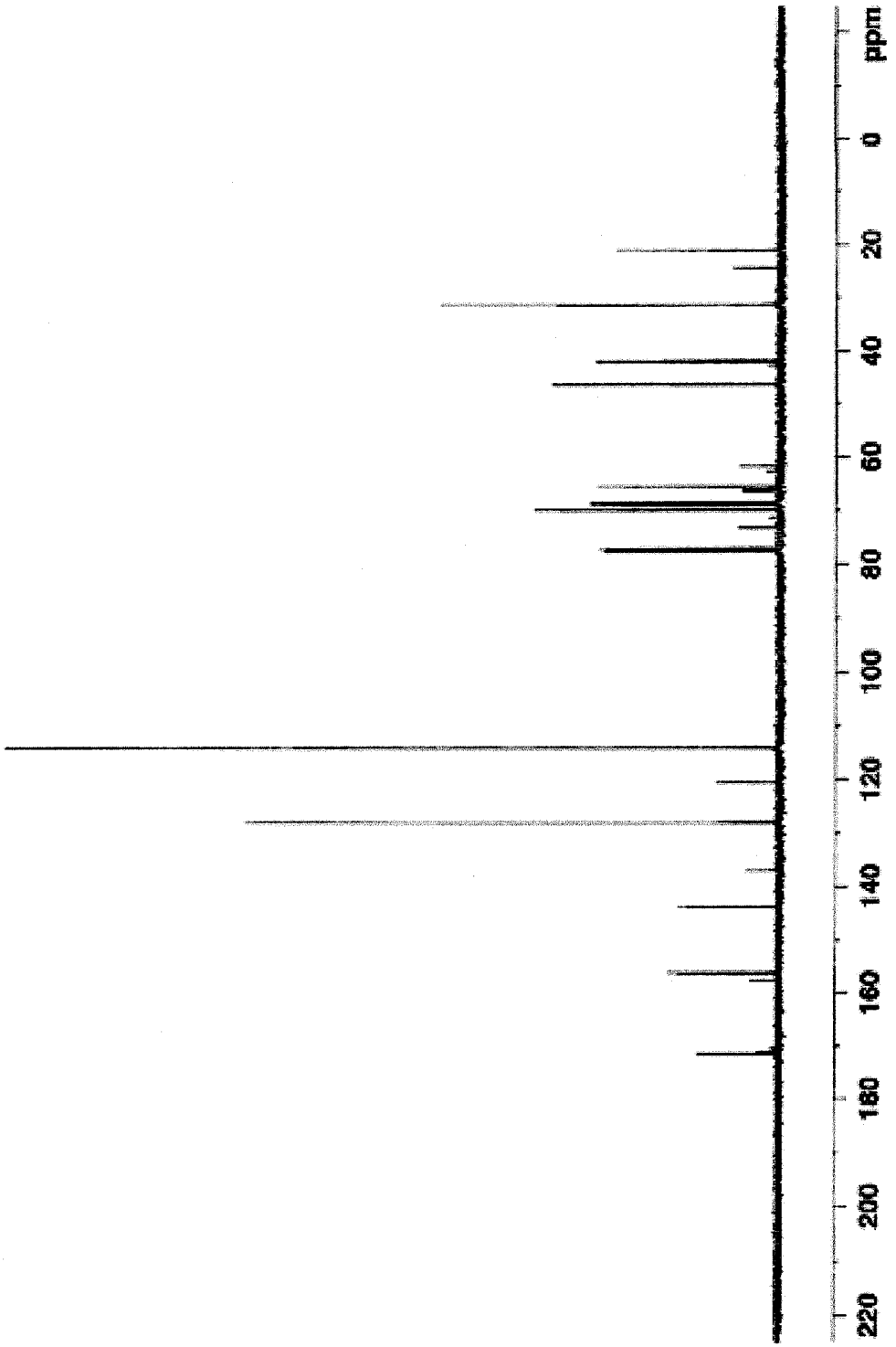


FIGURE 1B

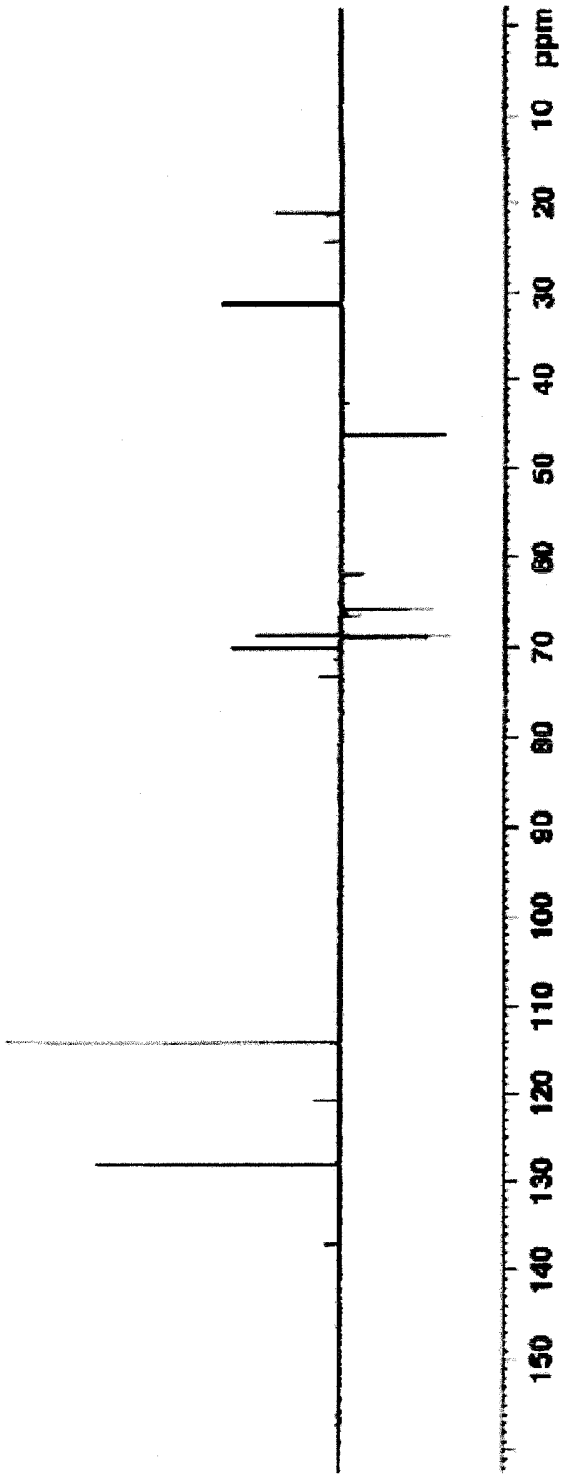


FIGURE 1C

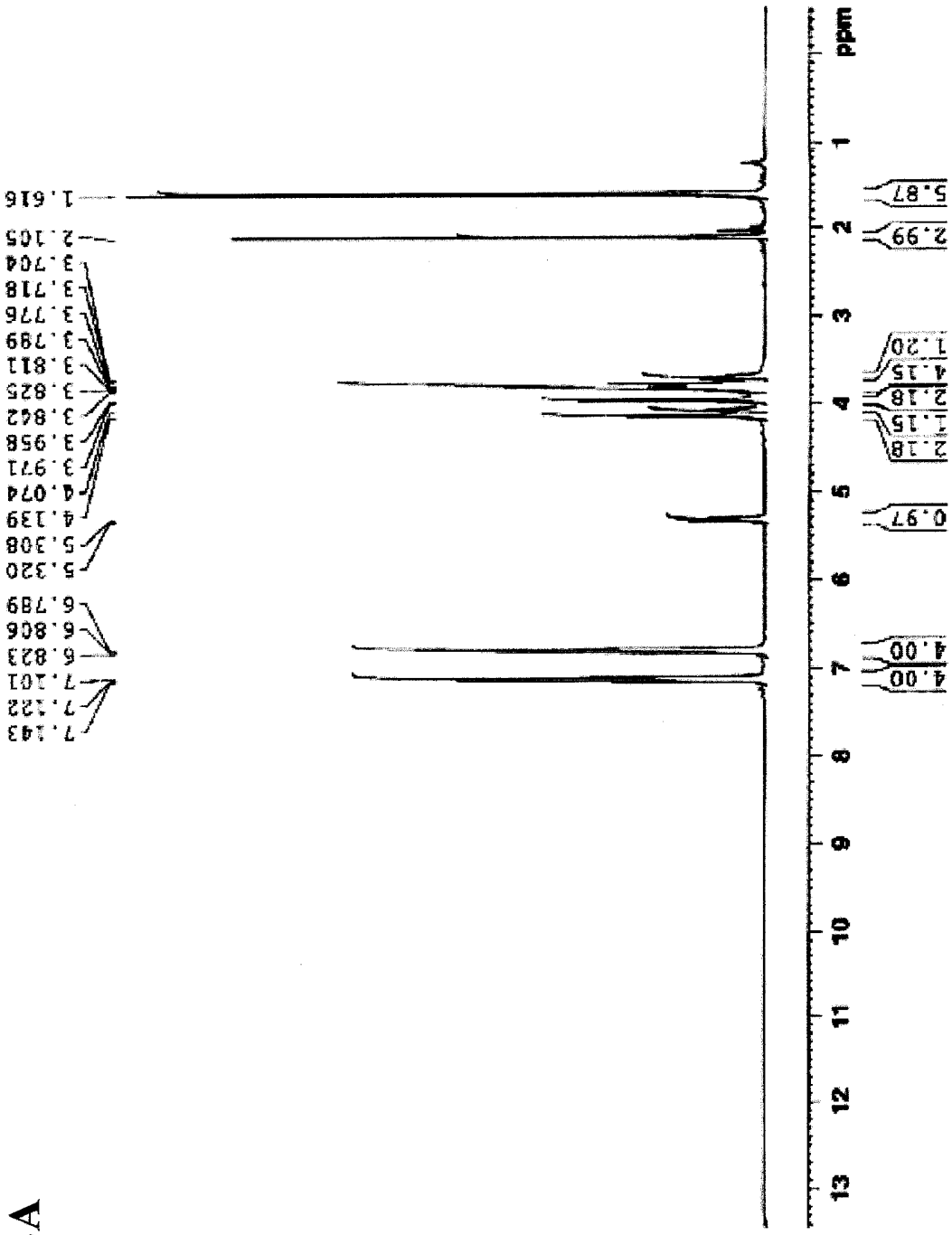

1.616
2.105
3.704
3.718
3.776
3.789
3.811
3.825
3.842
3.958
3.971
4.074
4.139
5.308
5.320
6.789
6.806
6.823
7.101
7.122
7.143
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
5.87
2.99
1.20
4.15
2.18
1.15
2.18
0.97
4.00
4.00

FIGURE 2A

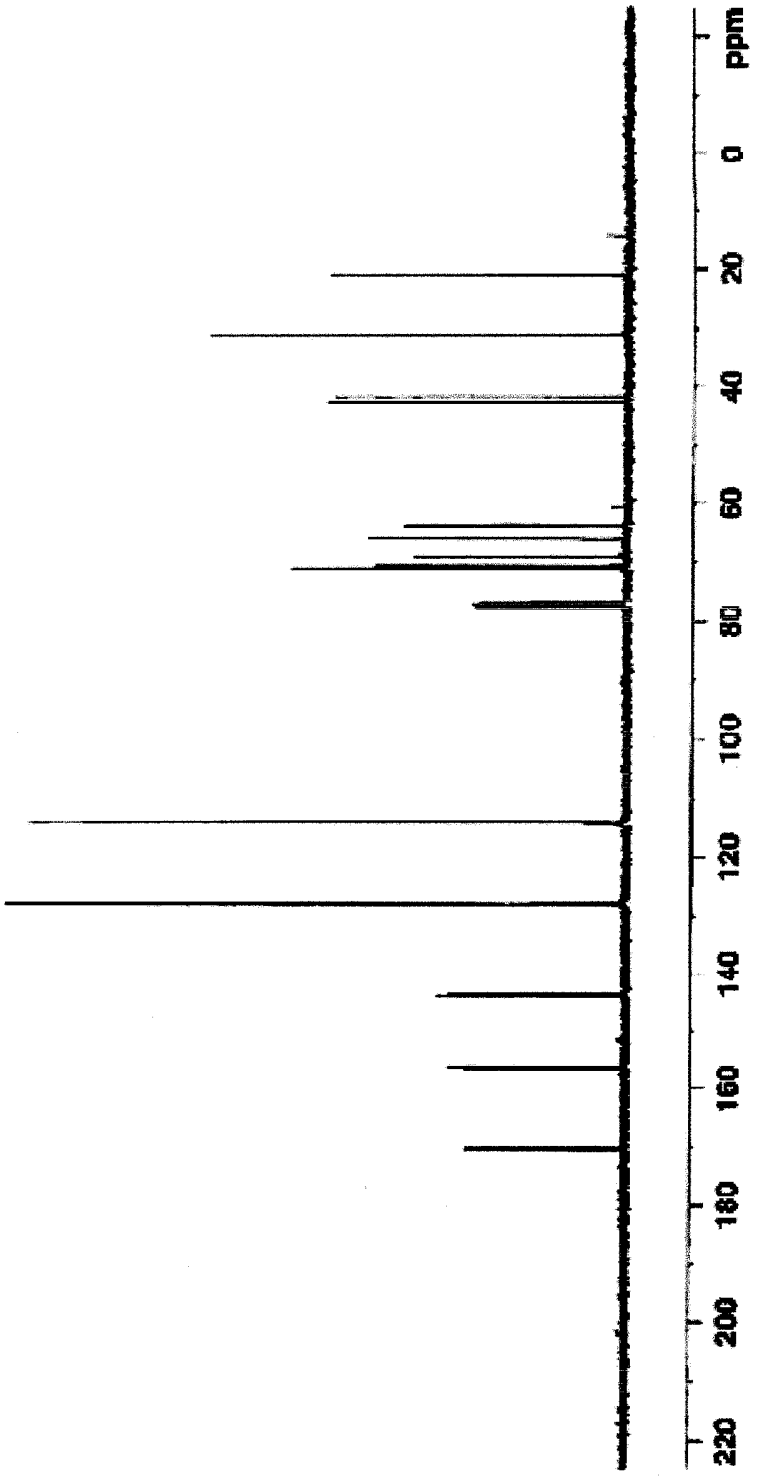


FIGURE 2B

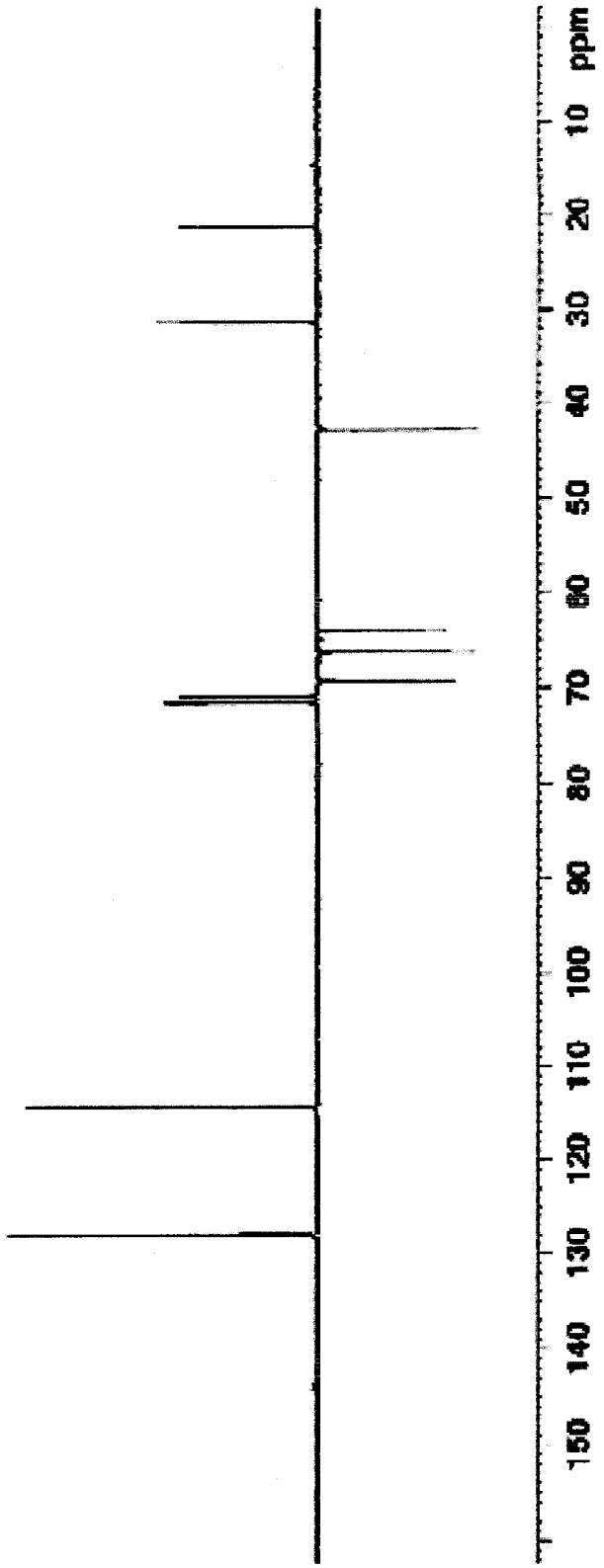


FIGURE 2C

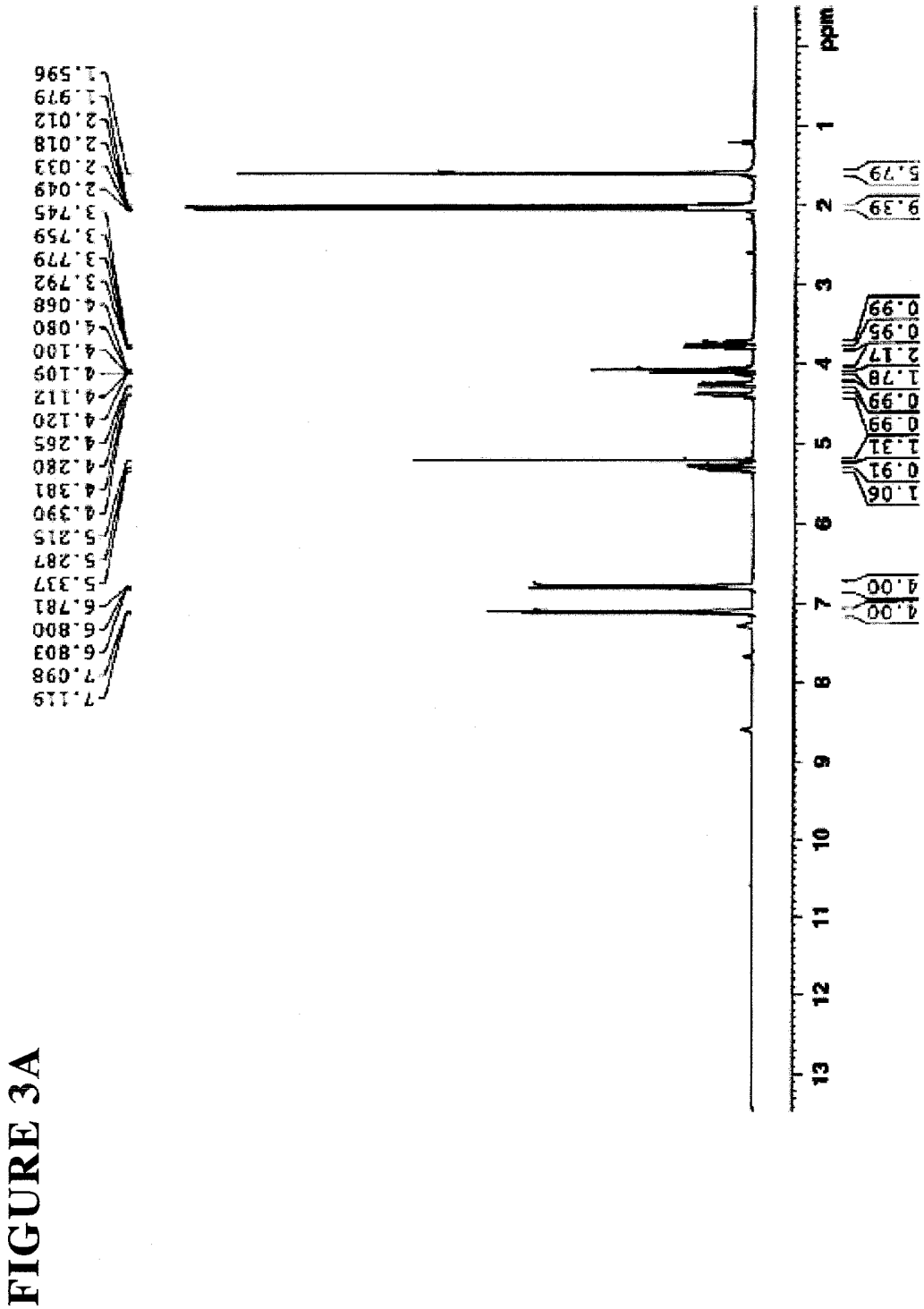

1.596
1.979
2.012
2.018
2.033
2.049
3.745
3.759
3.779
3.792
4.068
4.080
4.100
4.109
4.112
4.120
4.265
4.280
4.381
4.390
5.215
5.287
5.337
6.781
6.800
6.803
7.098
7.119
5.79
9.39
0.99
0.95
2.17
1.78
0.99
0.99
1.31
0.91
1.06
4.00
4.00
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13

FIGURE 3A

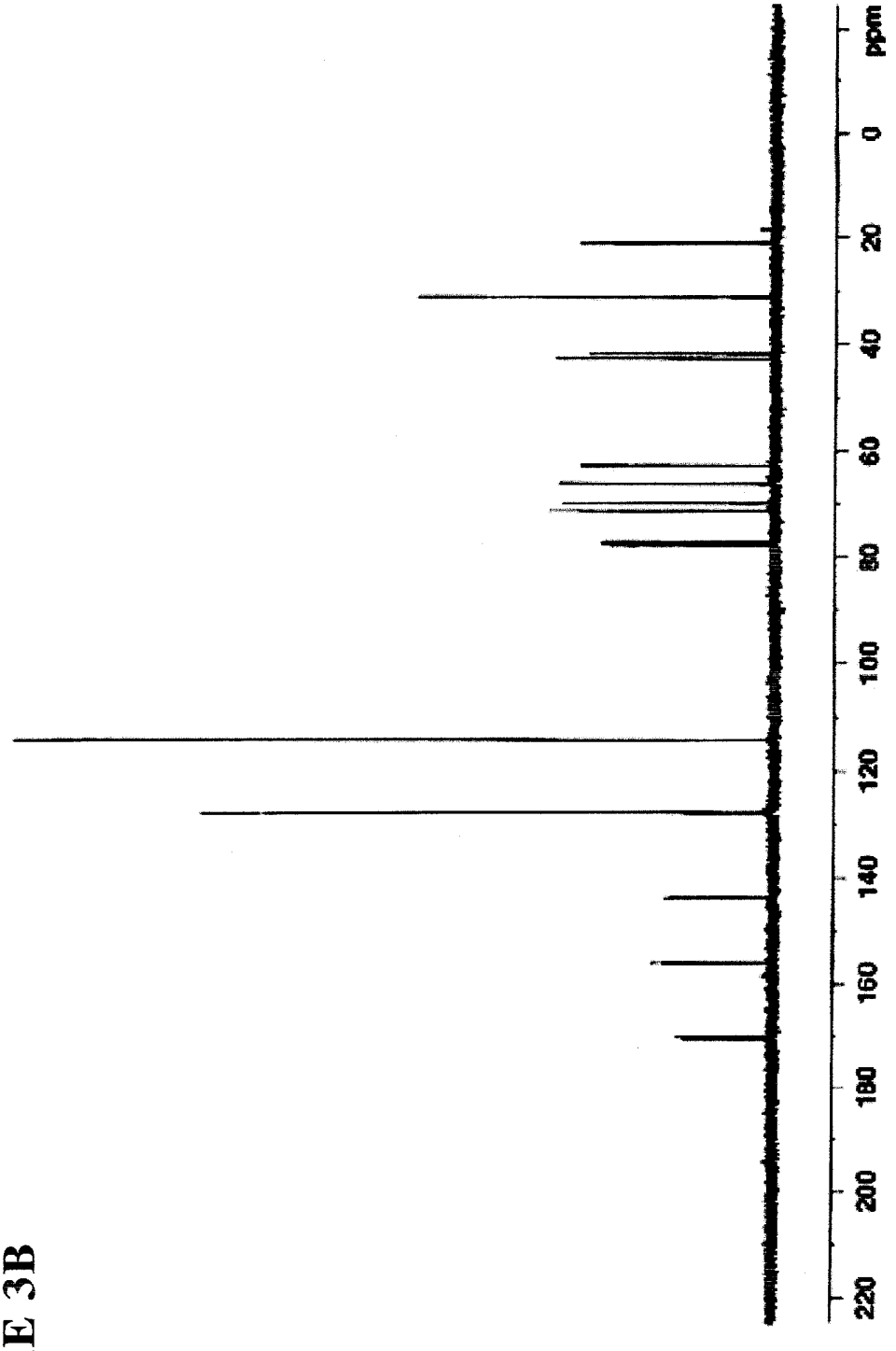


FIGURE 3B

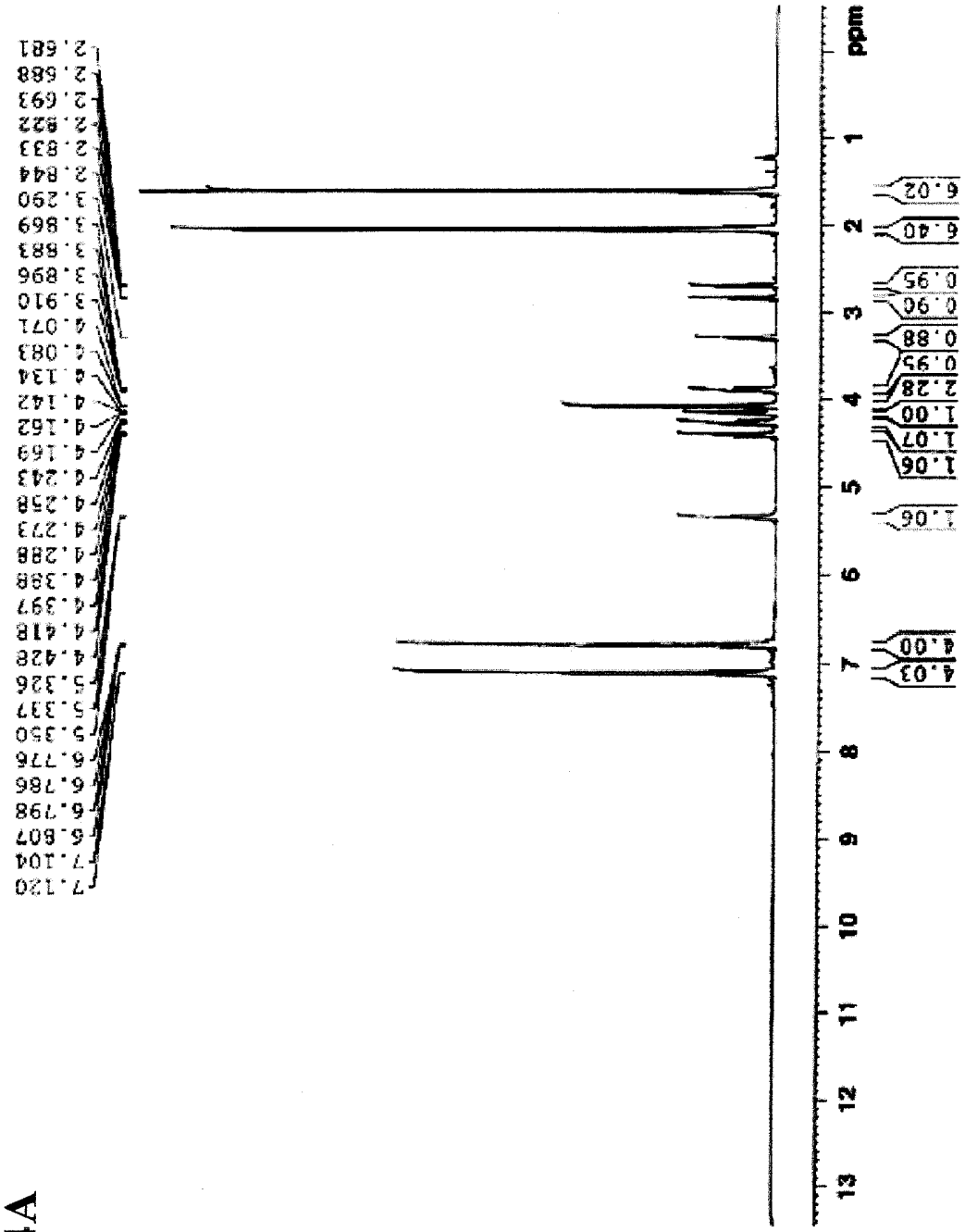

ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
6.02
6.40
0.95
0.90
0.88
0.95
2.28
1.00
1.07
1.06
1.06
4.00
4.03
2.681
2.688
2.693
2.822
2.833
2.844
3.290
3.869
3.883
3.896
3.910
4.071
4.083
4.134
4.142
4.162
4.169
4.243
4.258
4.273
4.288
4.388
4.397
4.418
4.428
5.326
5.337
5.350
6.776
6.786
6.798
6.807
7.104
7.120

FIGURE 4A

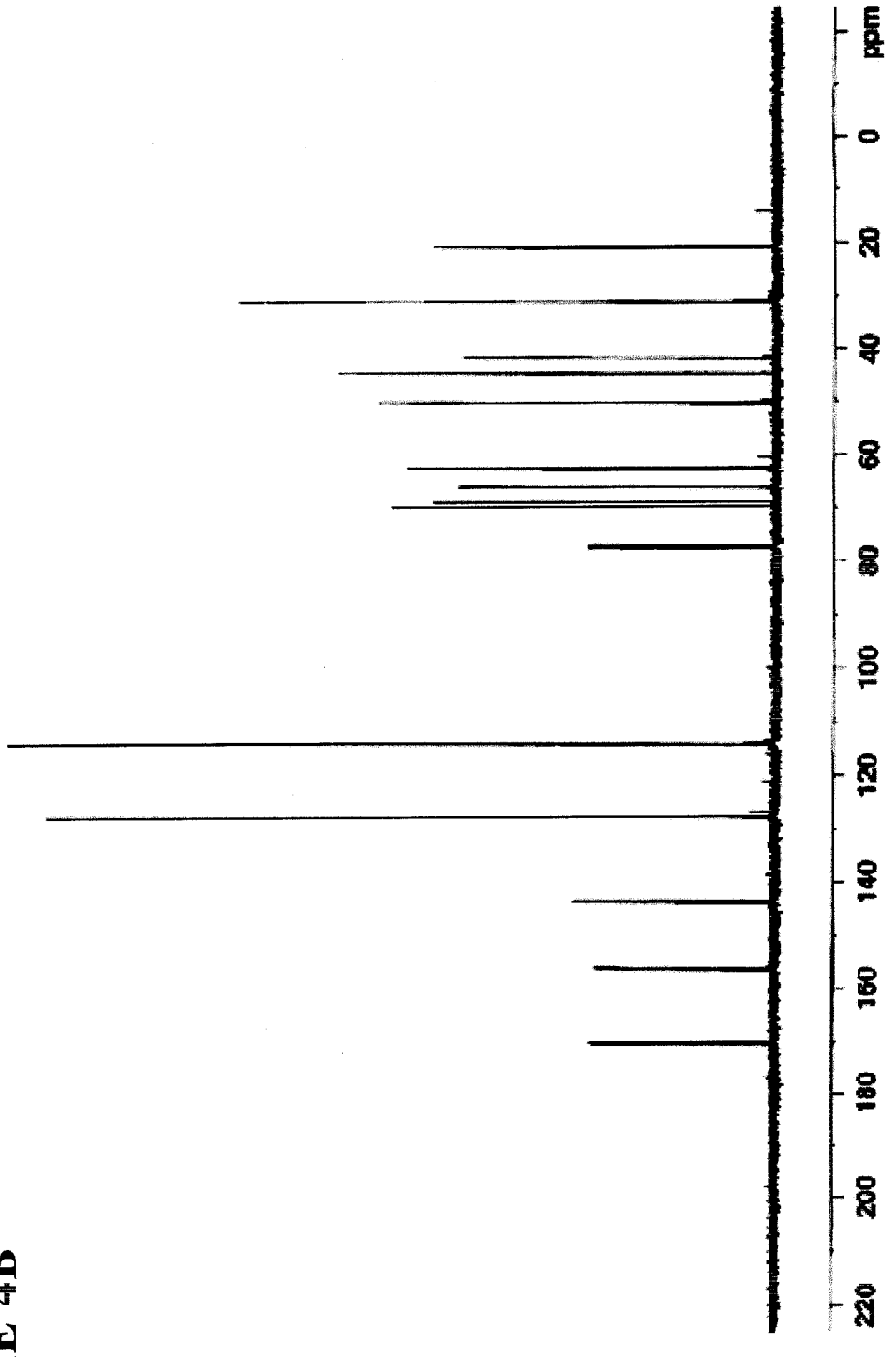


FIGURE 4B

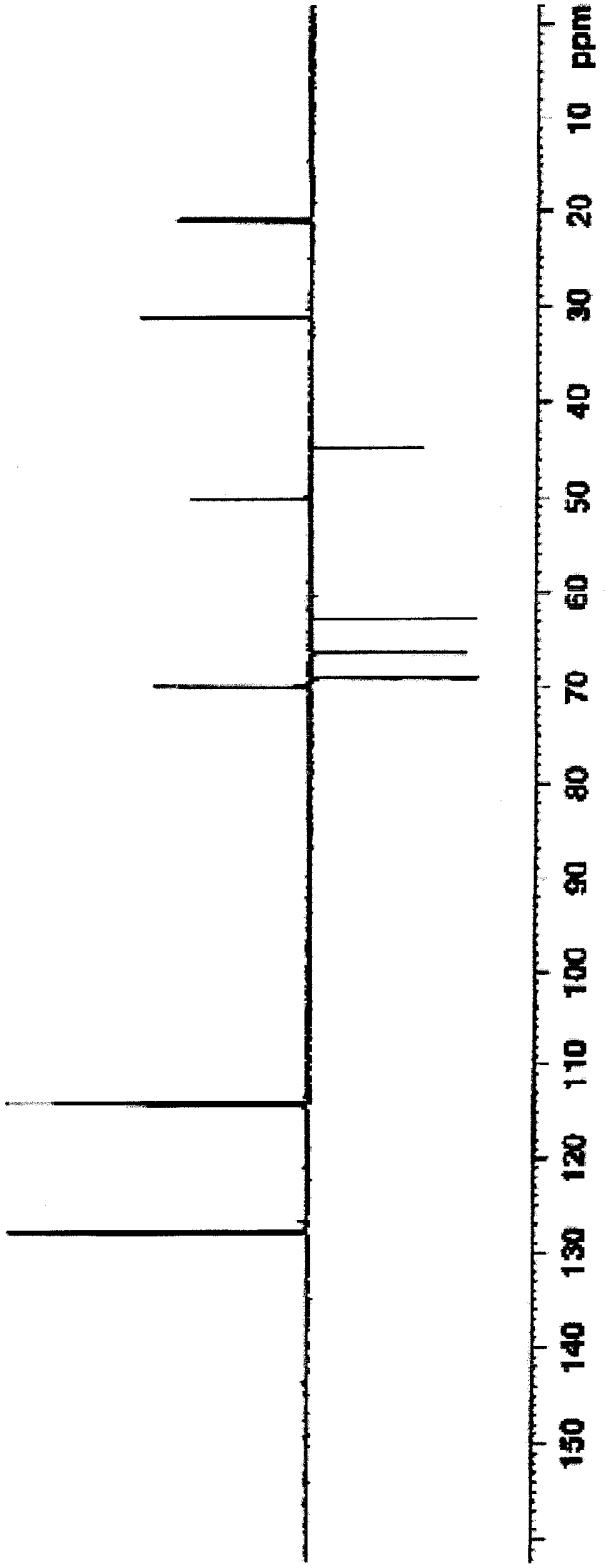


FIGURE 4C

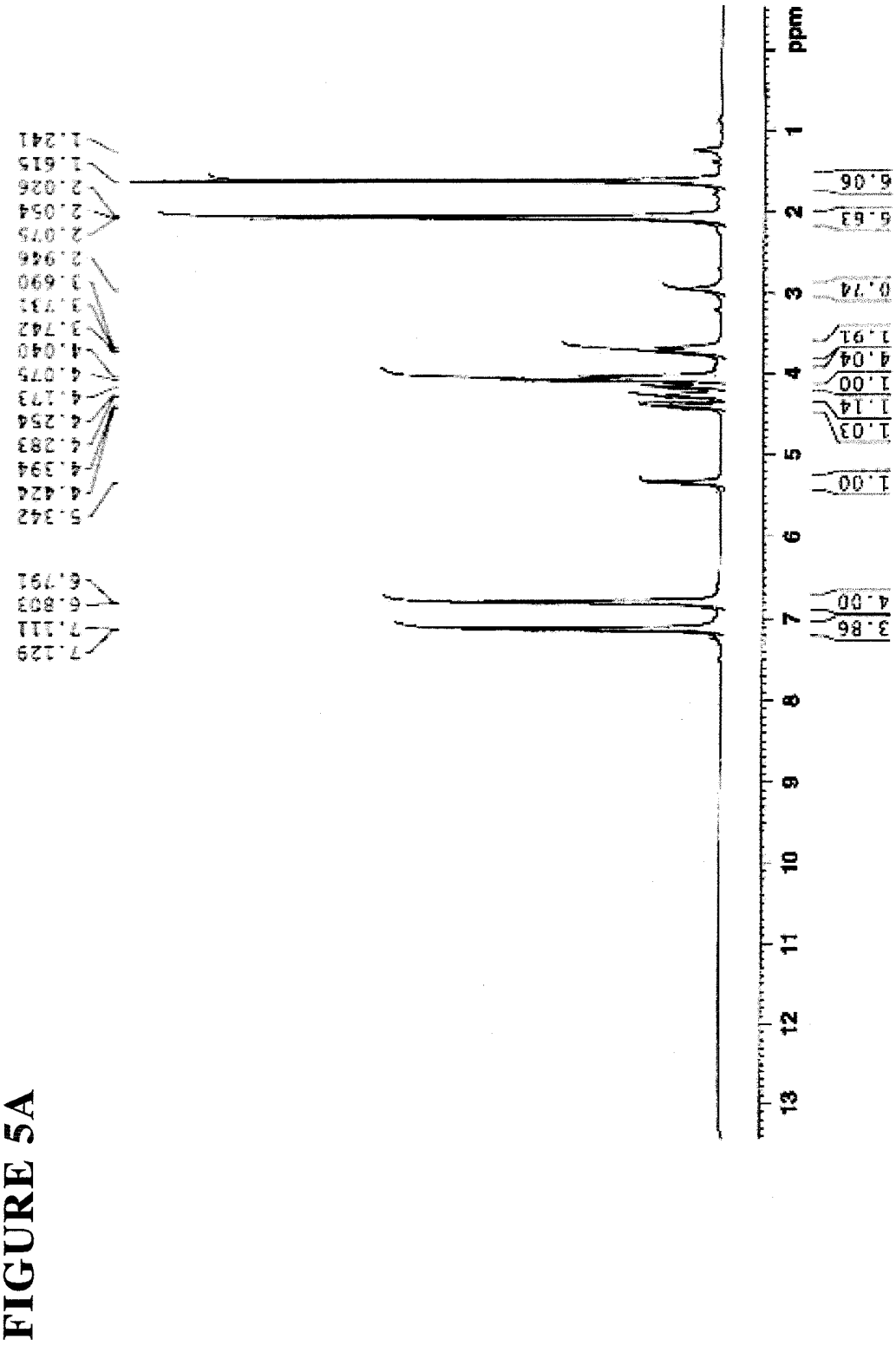

ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
6.06
5.63
0.74
1.91
4.04
1.00
1.14
1.03
1.00
4.00
3.86
1.241
1.615
2.026
2.054
2.075
2.966
3.690
3.731
3.742
4.040
4.075
4.173
4.254
4.283
4.394
4.424
5.342
6.791
6.803
7.111
7.129

FIGURE 5A

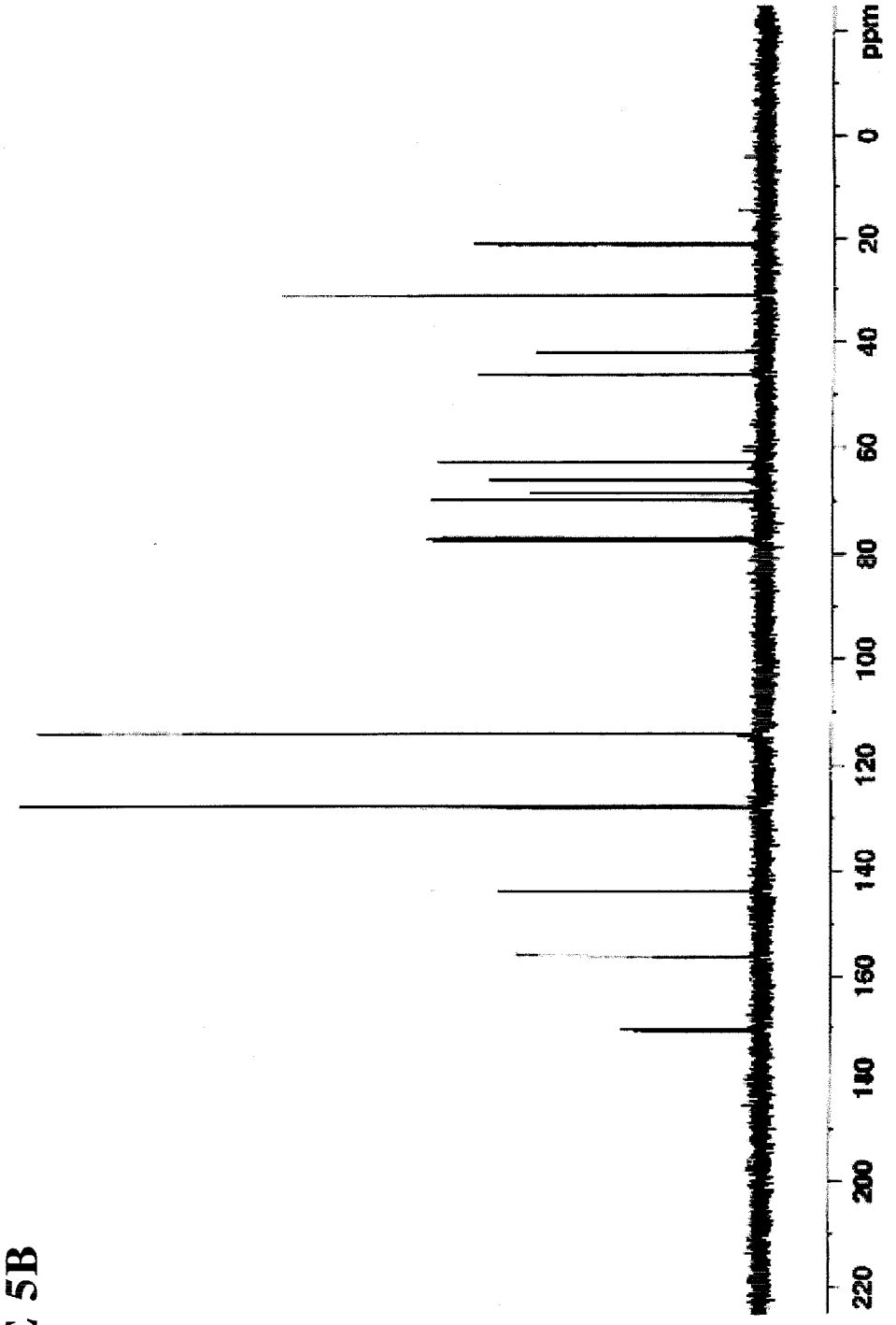


FIGURE 5B

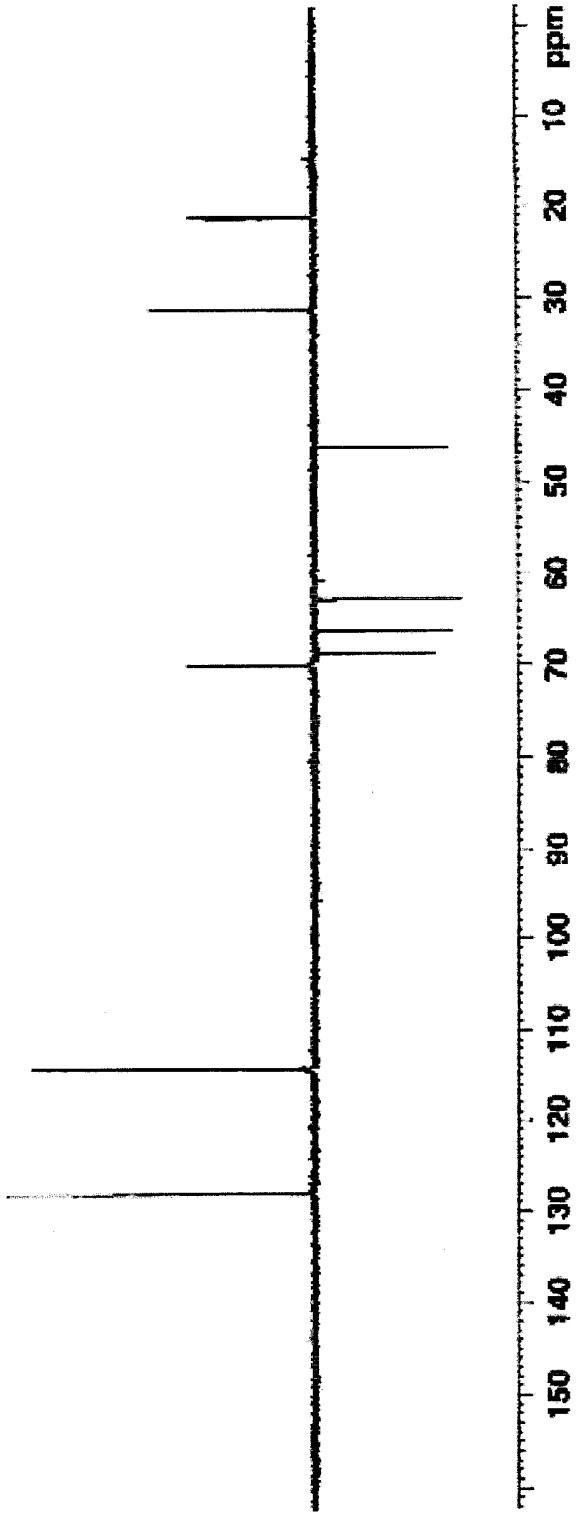


FIGURE 5C

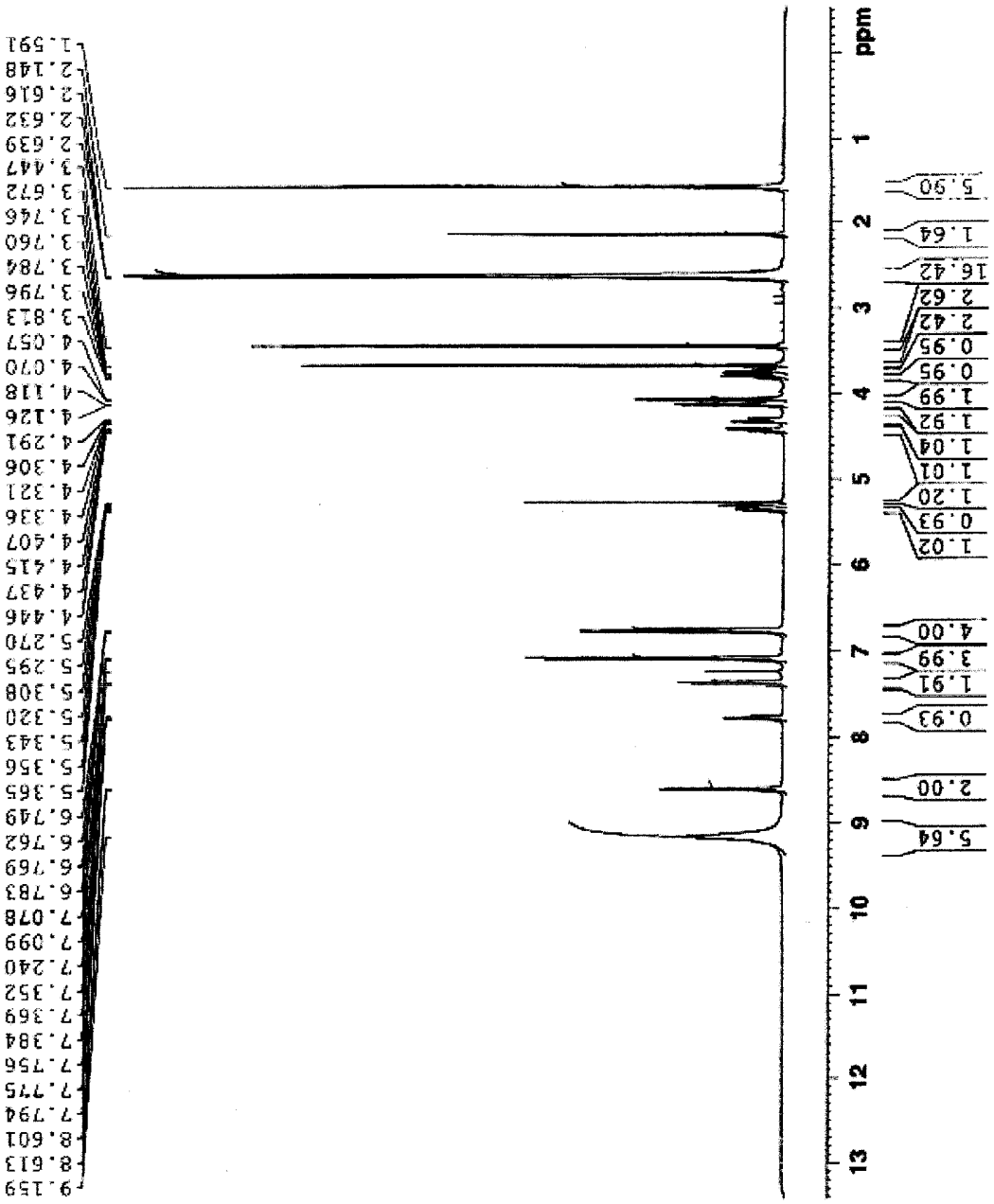

ppm
1 2 3 4 5 6 7 8 9 10 11 12 13
5.90
1.64
16.42
2.62
2.42
0.95
0.95
1.99
1.92
1.04
1.01
1.20
0.93
1.02
4.00
3.99
1.91
0.93
2.00
5.64

FIGURE 6A

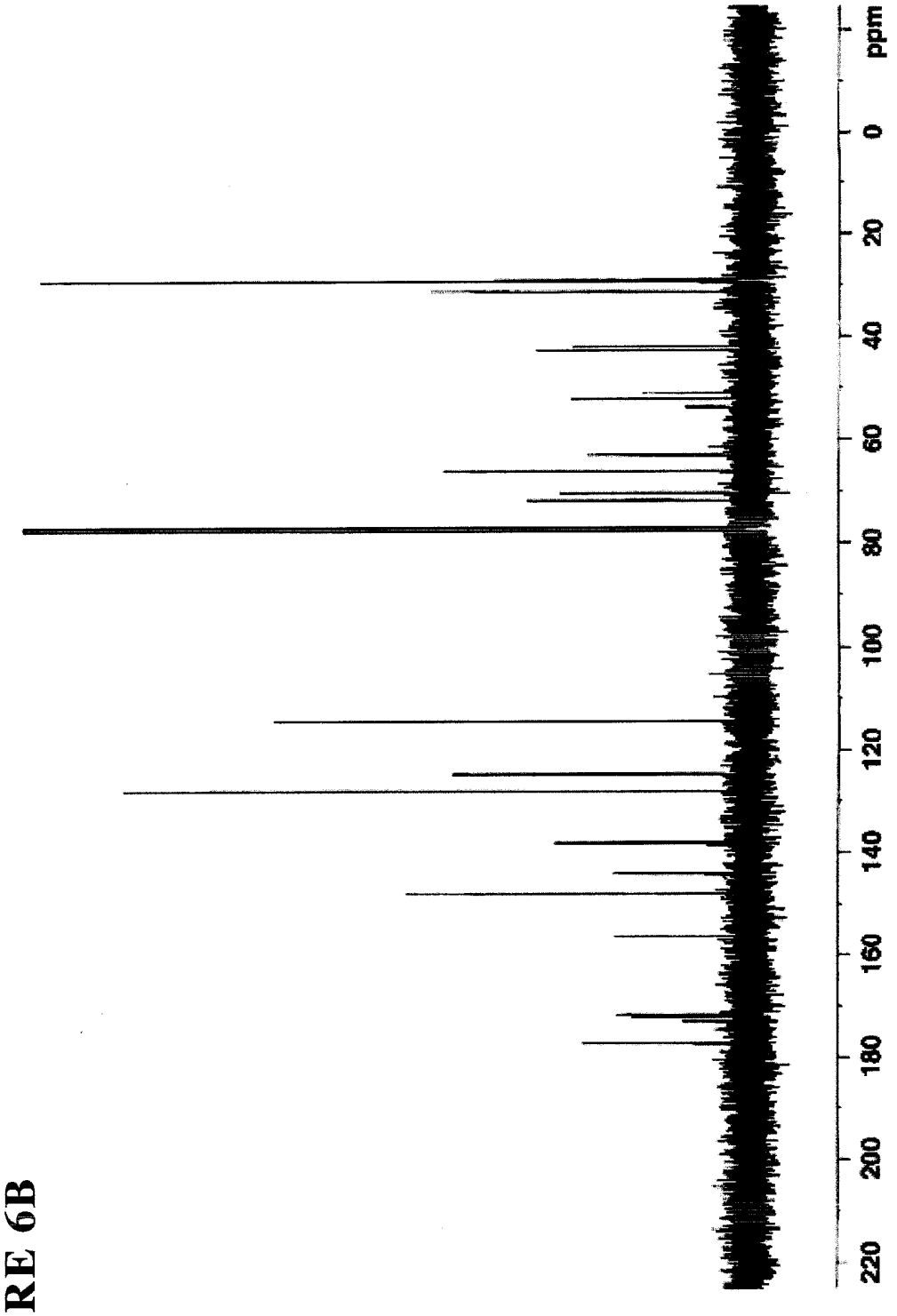


FIGURE 6B

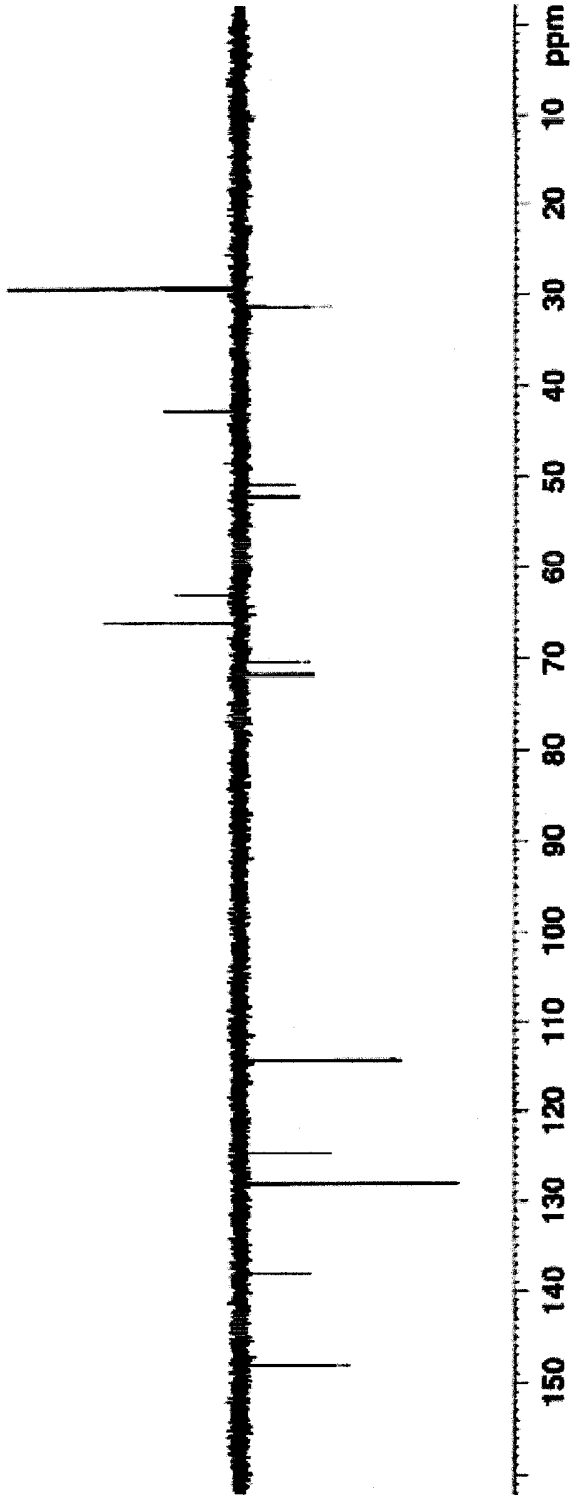


FIGURE 6C

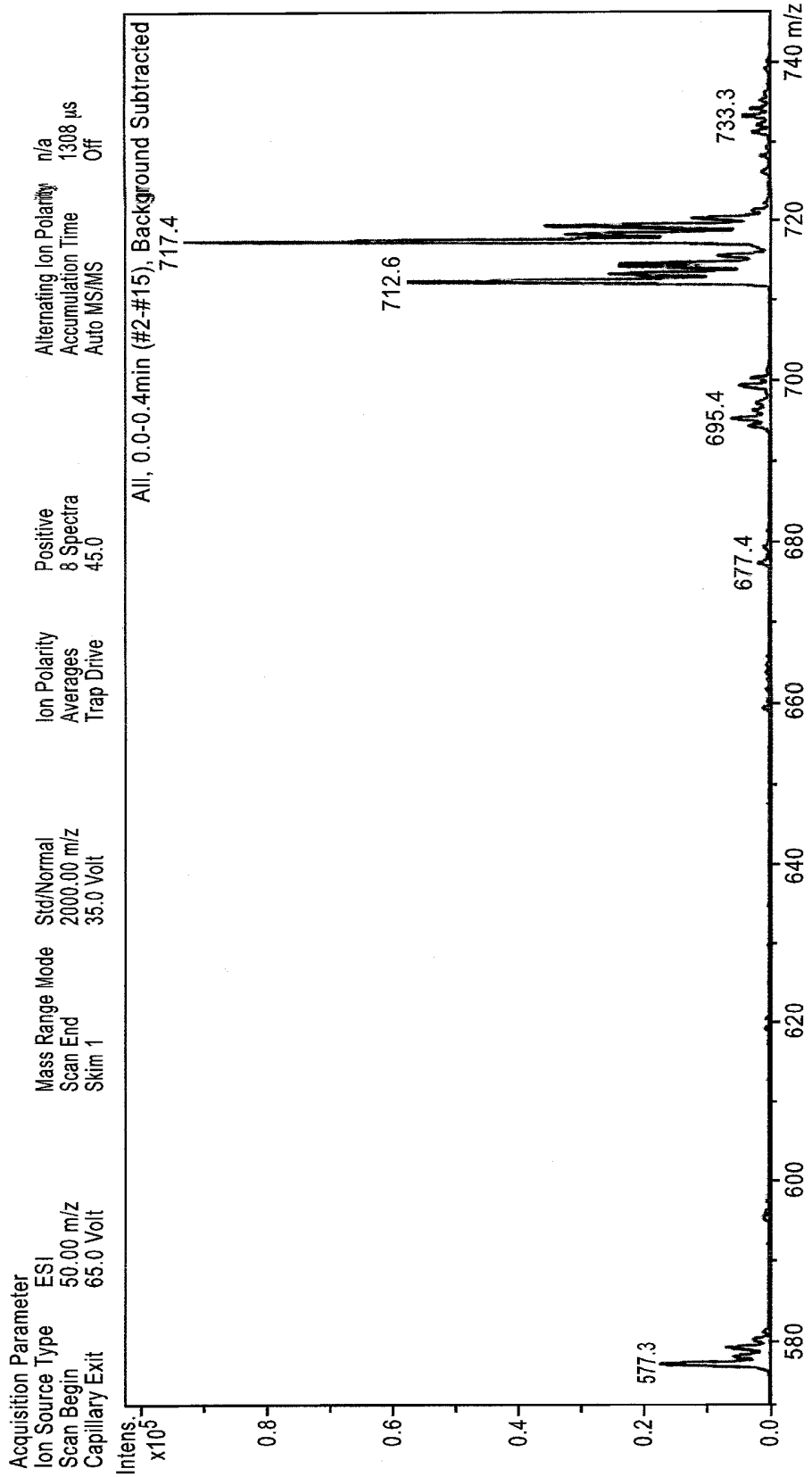

Acquisition Parameter
Ion Source Type ESI
Scan Begin 50.00 m/z
Capillary Exit 65.0 Volt
Mass Range Mode
Scan End
Skim 1
Std/Normal
2000.00 m/z
35.0 Volt
Ion Polarity
Averages
Trap Drive
Positive
8 Spectra
45.0
Alternating Ion Polarity n/a
Accumulation Time 1308 µs
Auto MS/MS Off
All, 0.0-0.4min (#2-#15), Background Subtracted
Intens.
x10^5
0.8
0.6
0.4
0.2
0.0
577.3
677.4
695.4
712.6
717.4
733.3
580
600
620
640
660
680
700
720
740 m/z

FIGURE 6D

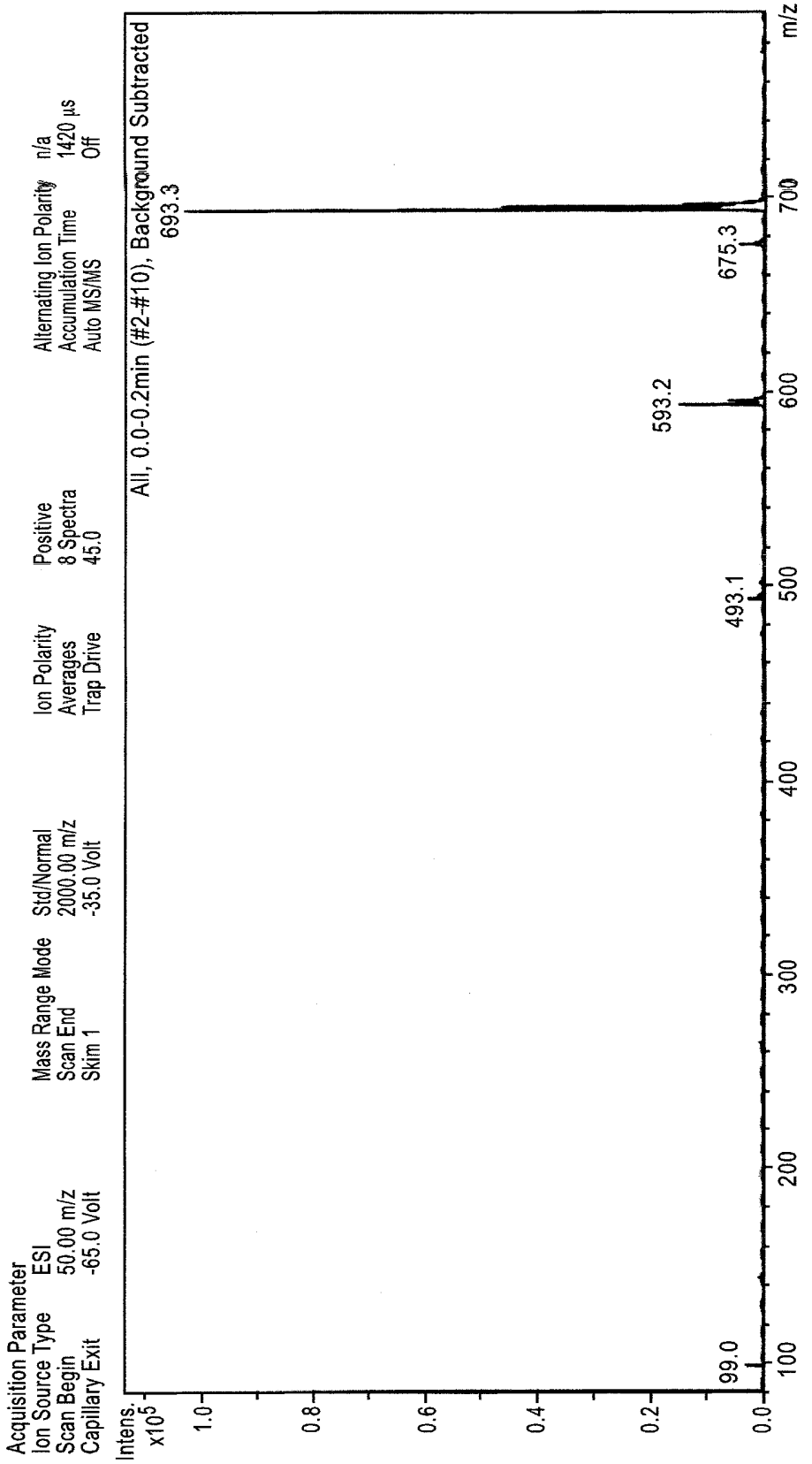

Acquisition Parameter
Ion Source Type ESI
Scan Begin 50.00 m/z
Capillary Exit -65.0 Volt
Mass Range Mode
Scan End
Skim 1
Std/Normal
2000.00 m/z
-35.0 Volt
Ion Polarity
Averages
Trap Drive
Positive
8 Spectra
45.0
Alternating Ion Polarity n/a
Accumulation Time 1420 µs
Auto MS/MS Off
All, 0.0-0.2min (#2-#10), Background Subtracted
693.3
675.3
593.2
493.1
99.0
Intens.
x10^5
1.0
0.8
0.6
0.4
0.2
0.0
100
200
300
400
500
600
700
m/z

FIGURE 6E

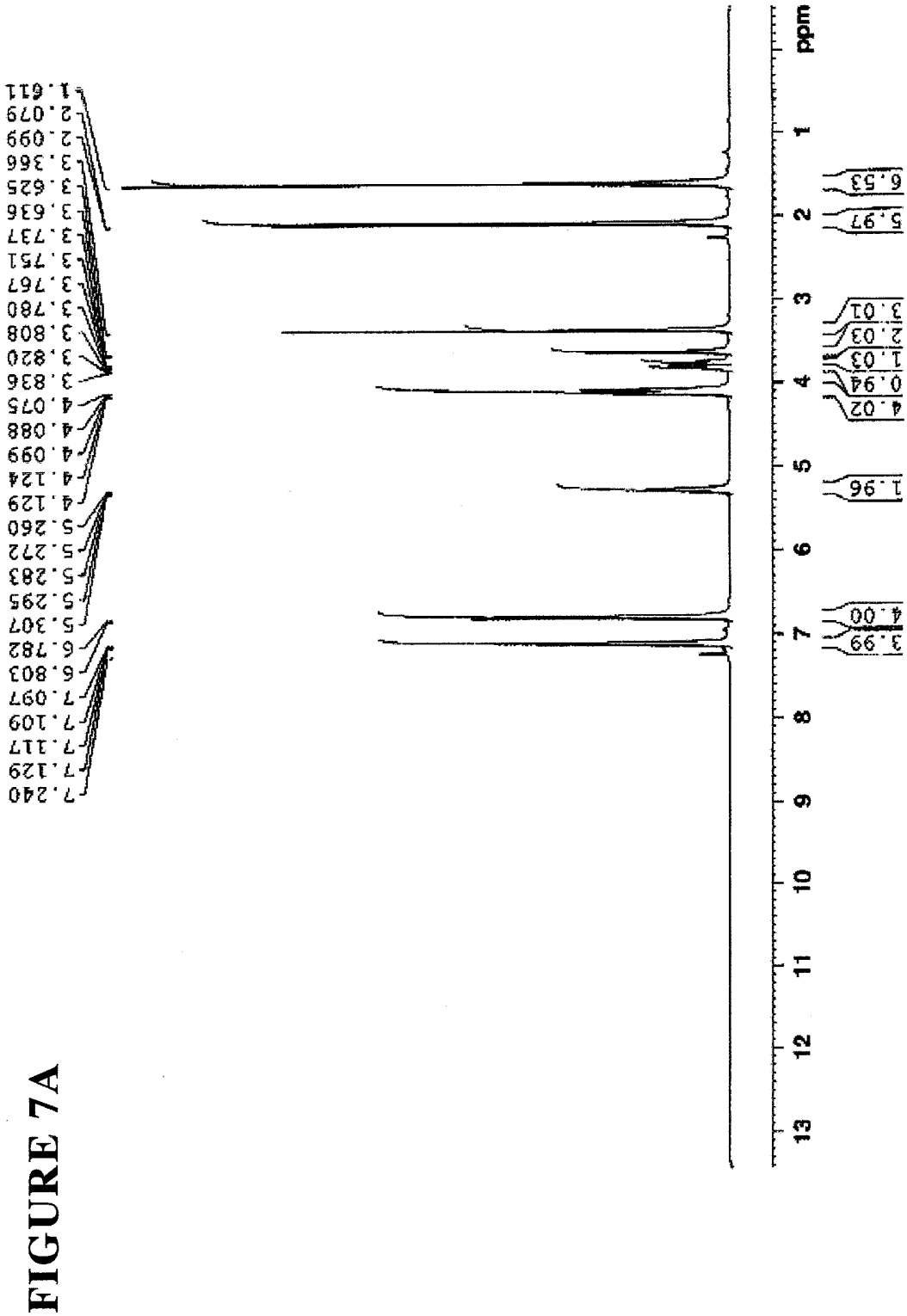

ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
6.53
5.97
3.01
2.03
1.03
0.94
4.02
1.96
4.00
3.99
1.611
2.079
2.099
3.366
3.625
3.636
3.737
3.751
3.767
3.780
3.808
3.820
3.836
4.075
4.088
4.099
4.124
4.129
5.260
5.272
5.283
5.295
5.307
6.782
6.803
7.097
7.109
7.117
7.129
7.240

FIGURE 7A

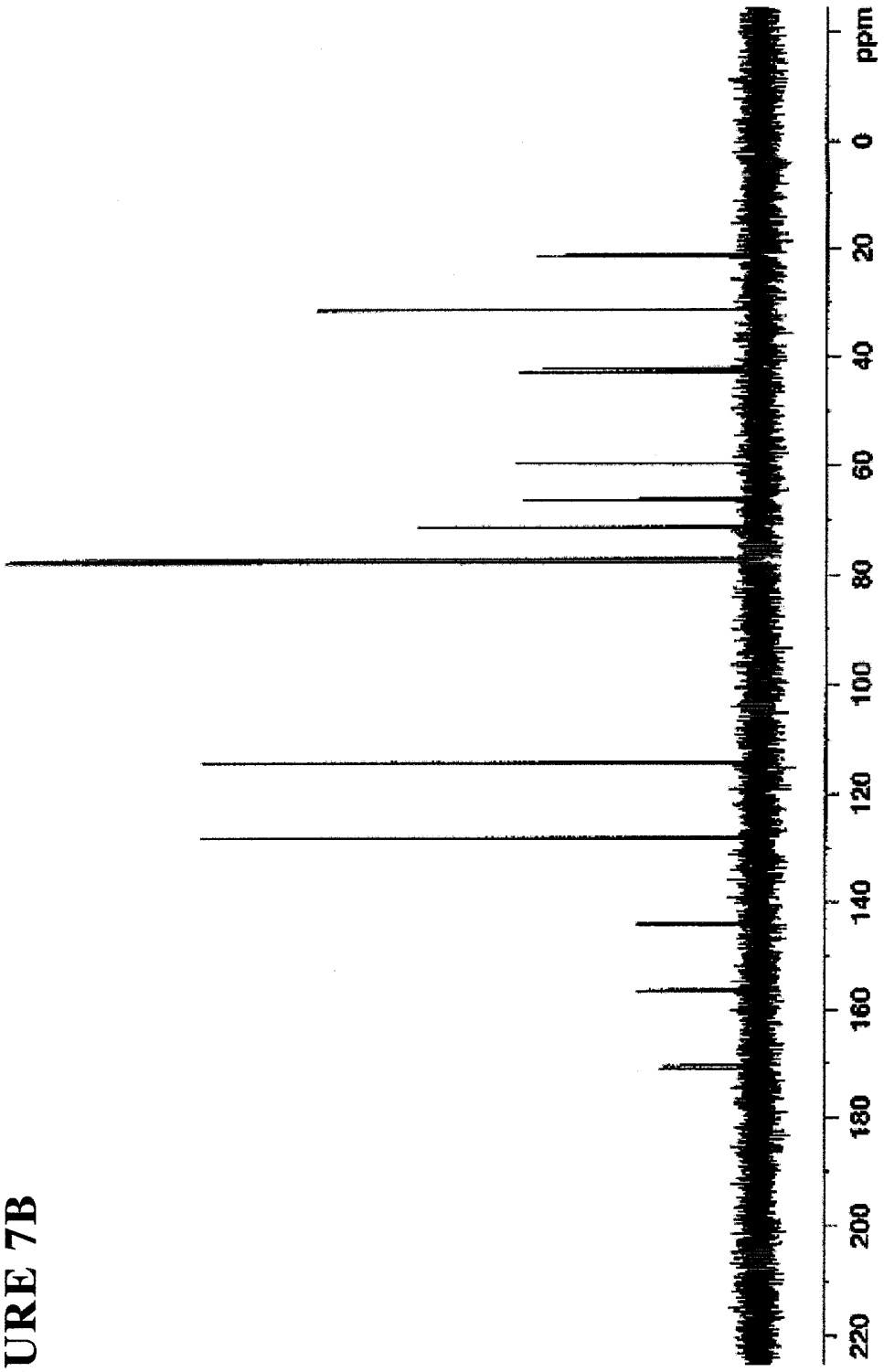


FIGURE 7B

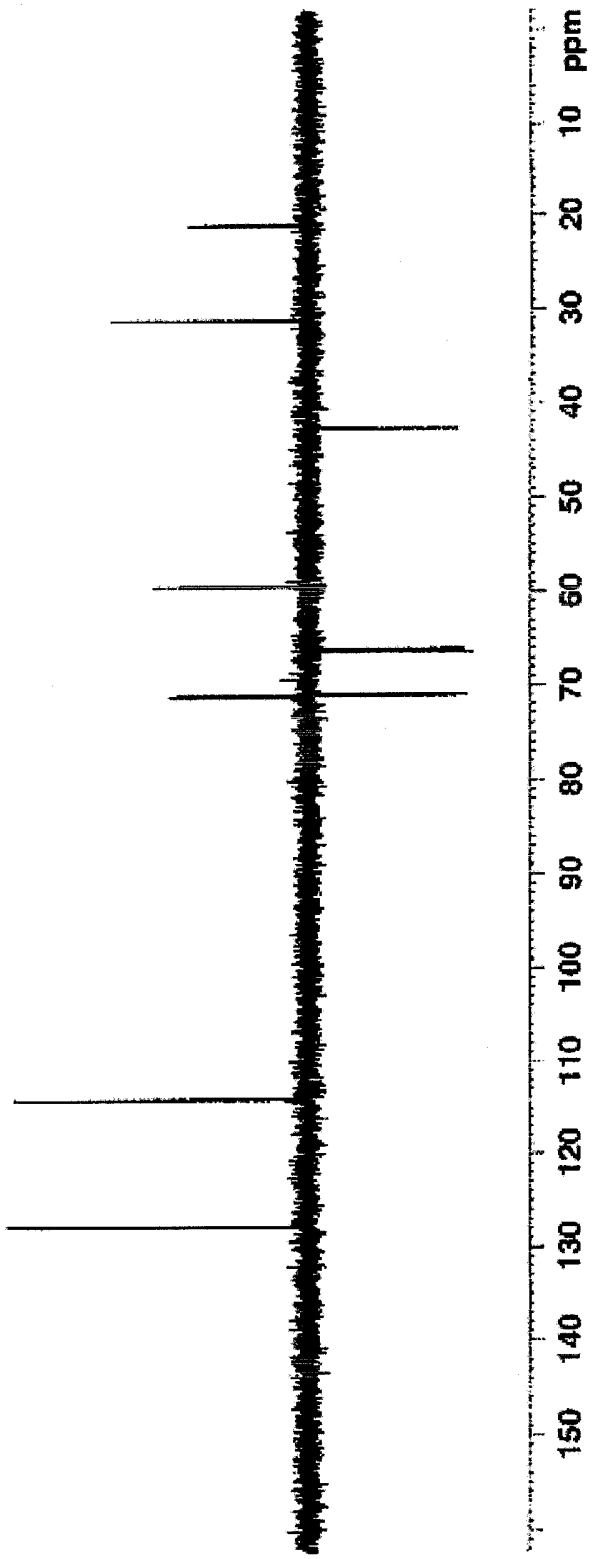


FIGURE 7C

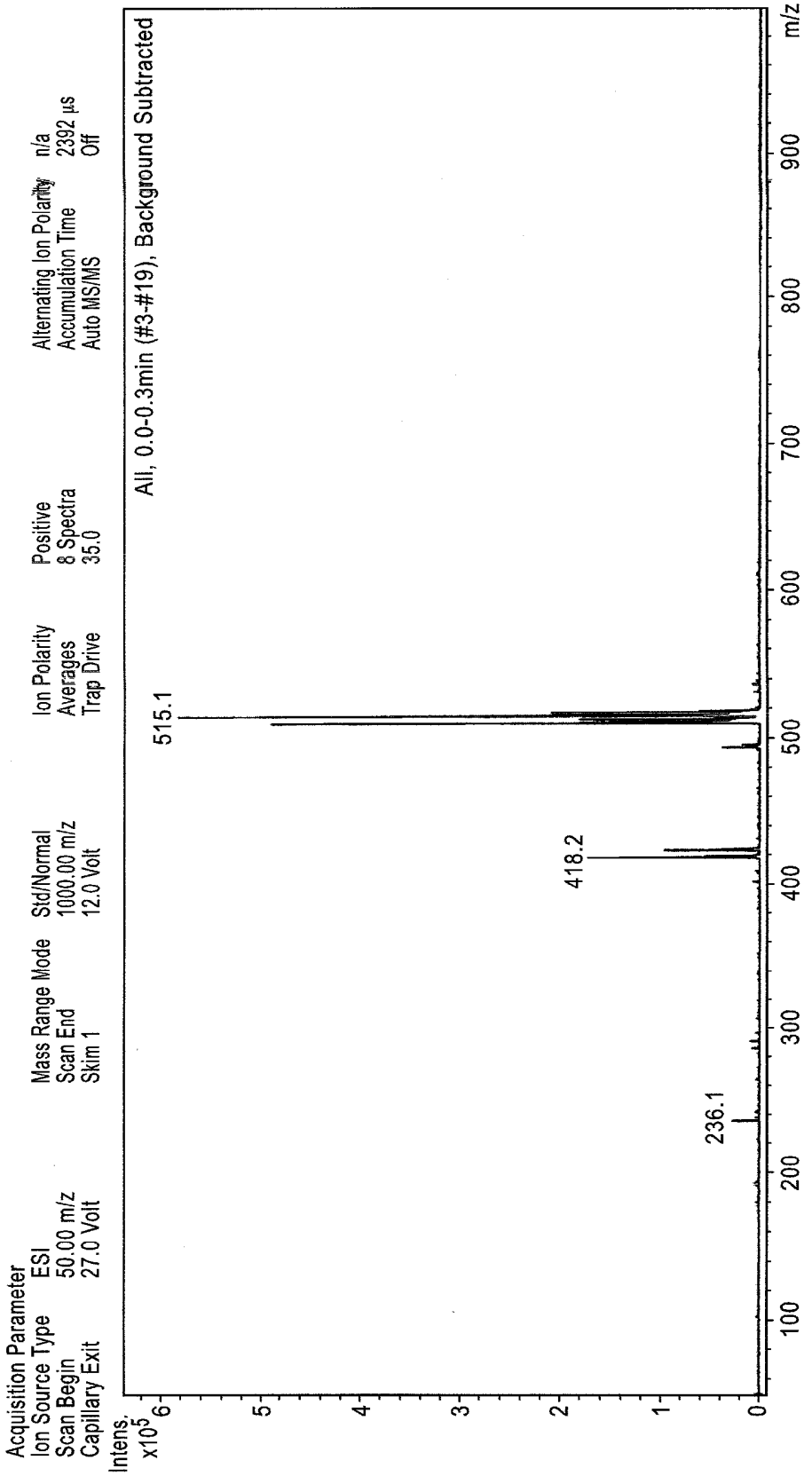

Acquisition Parameter
Ion Source Type ESI
Scan Begin 50.00 m/z
Capillary Exit 27.0 Volt
Mass Range Mode
Scan End
Skim 1
Std/Normal
1000.00 m/z
12.0 Volt
Ion Polarity
Averages
Trap Drive
Positive
8 Spectra
35.0
Alternating Ion Polarity n/a
Accumulation Time 2392 µs
Auto MS/MS Off
All, 0.0-0.3min (#3-#19), Background Subtracted
Intens.
x10^5
515.1
418.2
236.1
m/z

FIGURE 7D

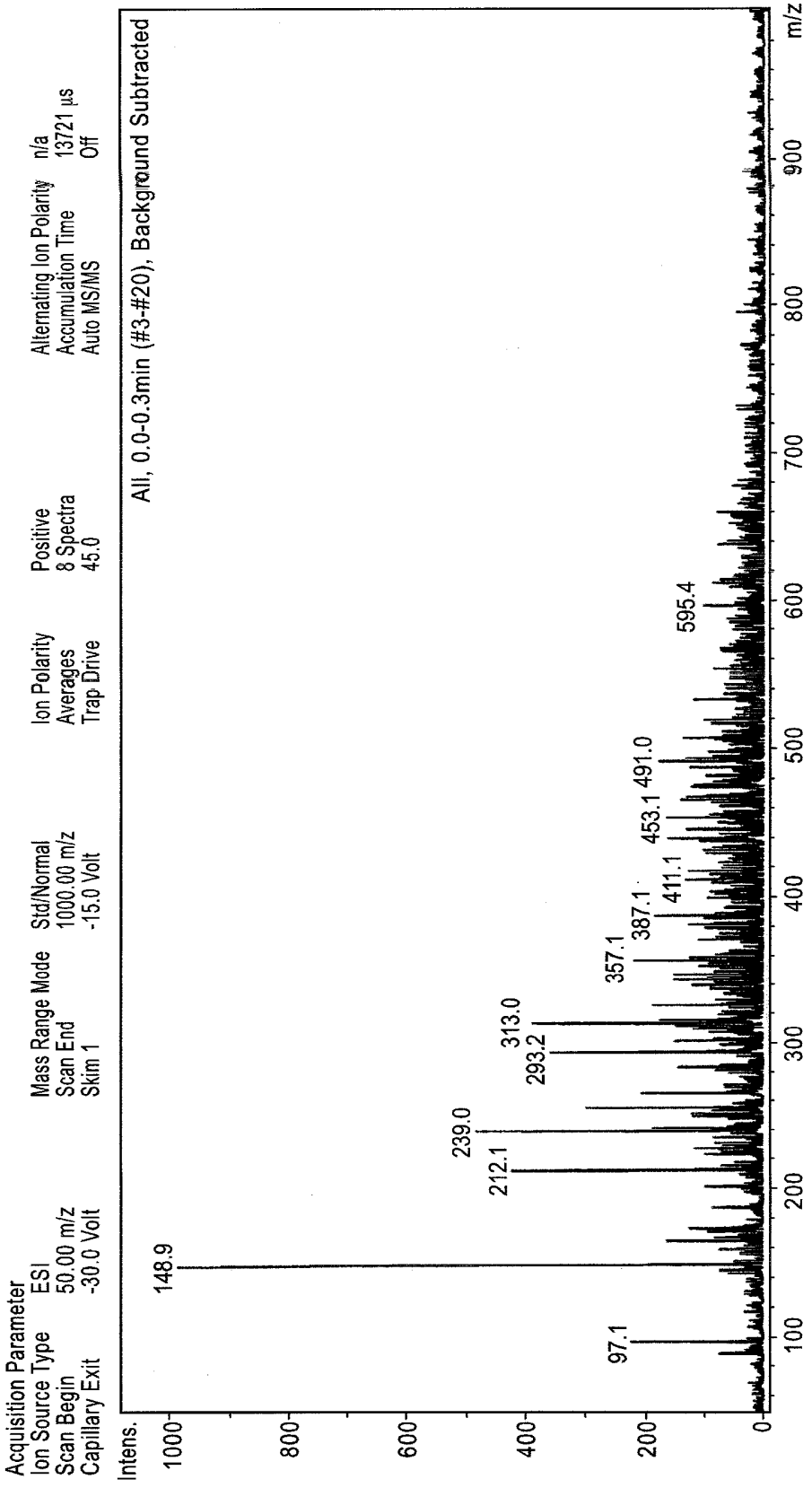

Acquisition Parameter
Ion Source Type ESI
Scan Begin 50.00 m/z
Capillary Exit -30.0 Volt
Mass Range Mode
Scan End
Skim 1
Std/Normal
1000.00 m/z
-15.0 Volt
Ion Polarity
Averages
Trap Drive
Positive
8 Spectra
45.0
Alternating Ion Polarity n/a
Accumulation Time 13721 µs
Auto MS/MS Off
All, 0.0-0.3min (#3-#20), Background Subtracted
Intens.
1000
800
600
400
200
0
100
200
300
400
500
600
700
800
900
m/z
148.9
97.1
239.0
212.1
313.0
293.2
357.1
387.1
411.1
453.1
491.0
595.4

FIGURE 7E

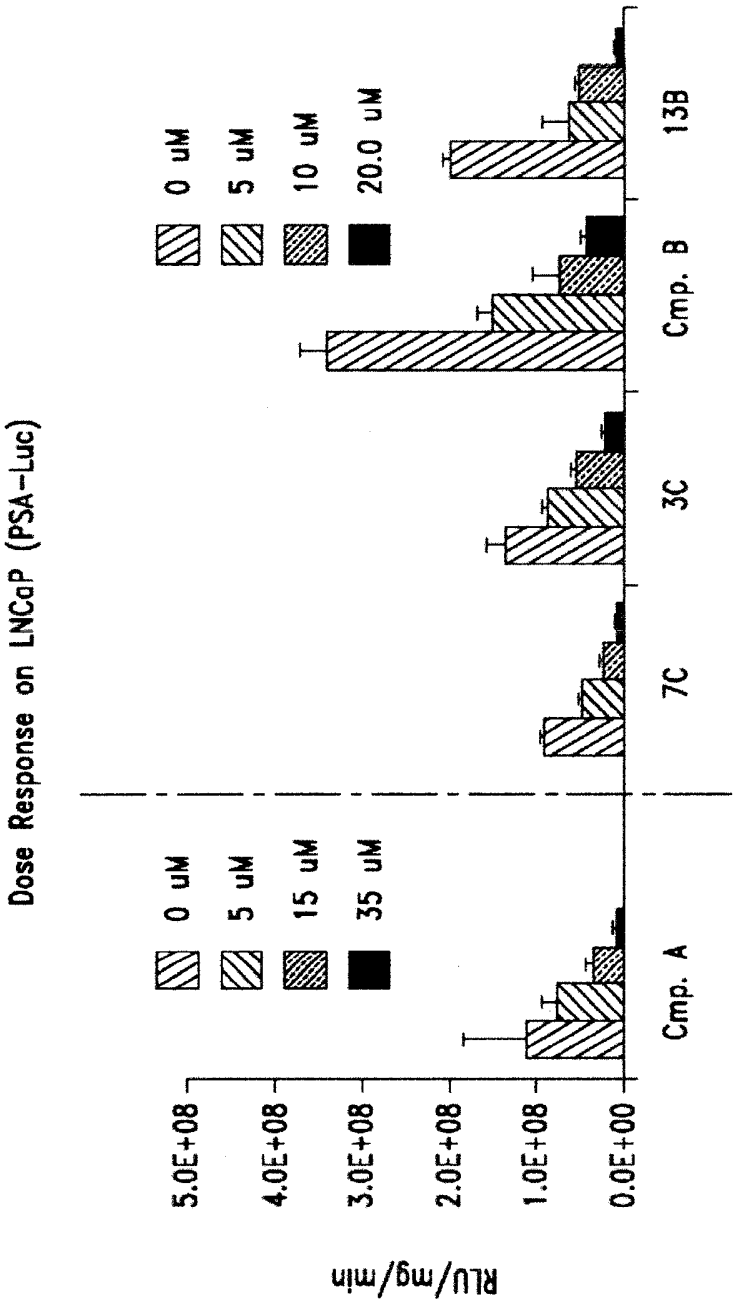

Dose Response on LNCaP (PSA-Luc)
RLU/mg/min
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
0 uM
5 uM
15 uM
35 uM
0 uM
5 uM
10 uM
20.0 uM
Cmp. A
7C
3C
Cmp. B
13B

FIGURE 8

FIGURE 9

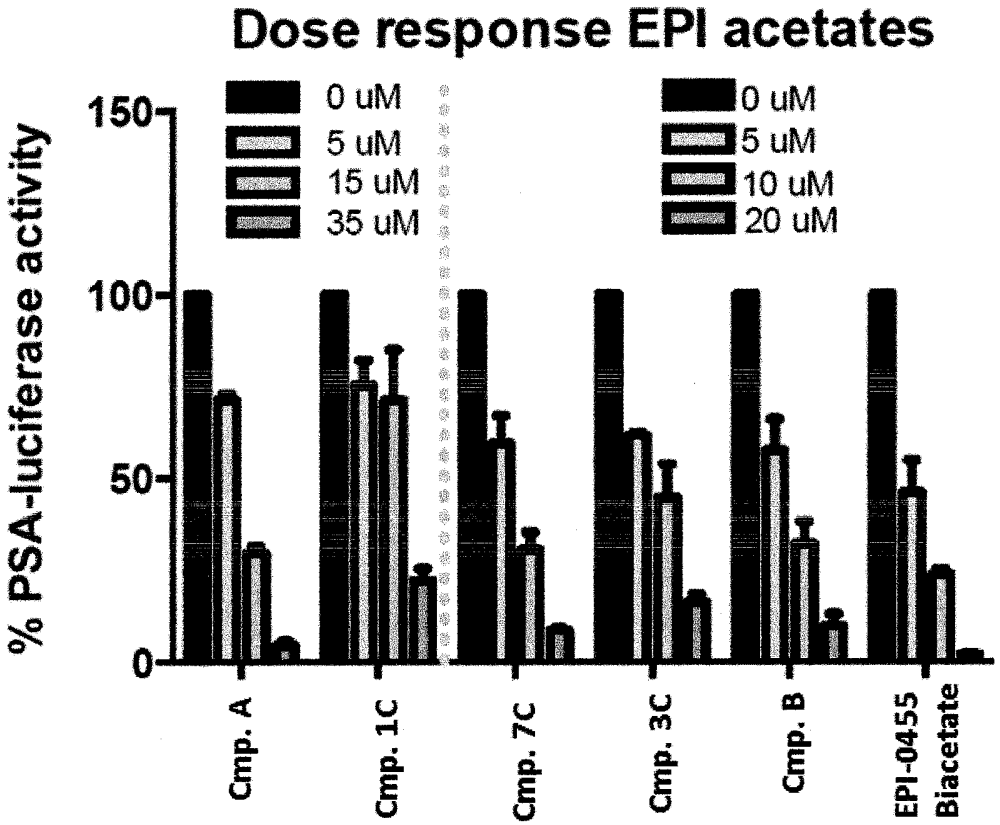
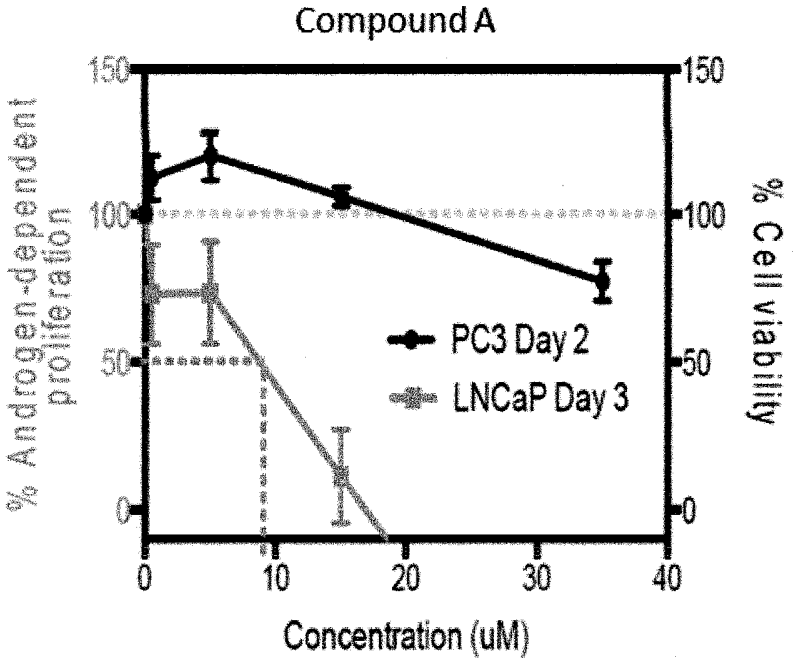

Dose response EPI acetates
% PSA-luciferase activity
150
100
50
0
0 uM
5 uM
15 uM
35 uM
0 uM
5 uM
10 uM
20 uM
Cmp. A
Cmp. 1C
Cmp. 7C
Cmp. 3C
Cmp. B
EPI-0455 Biacetate

FIGURE 10


Compound A
% Androgen-dependent proliferation
% Cell viability
150
100
50
0
0
10
20
30
40
PC3 Day 2
LNCaP Day 3
Concentration (uM)

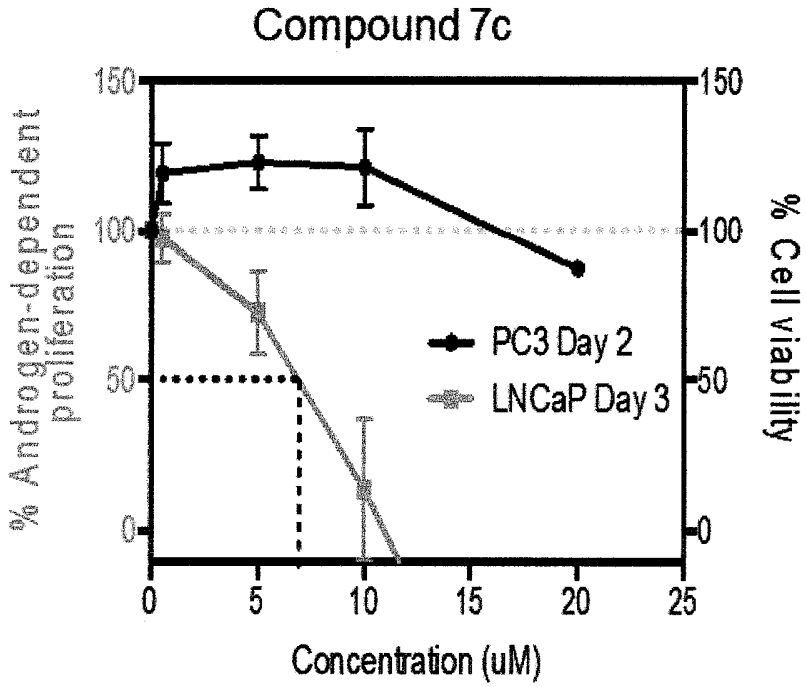
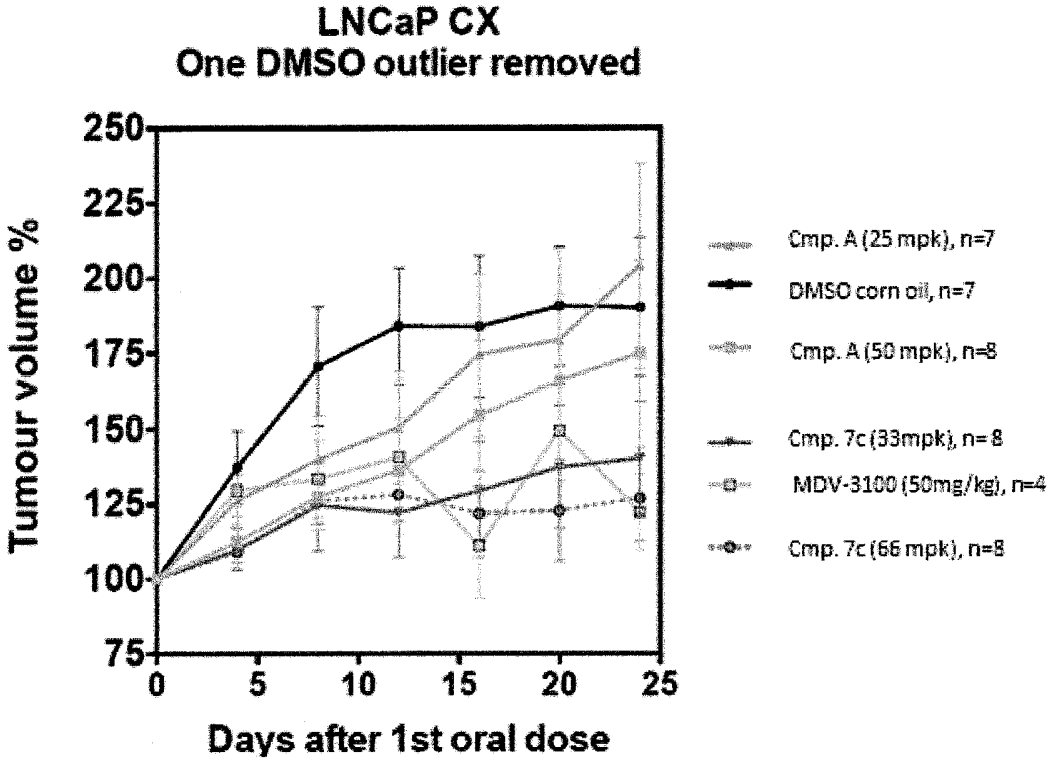

Compound 7c
% Androgen-dependent proliferation
% Cell viability
150
100
50
0
0
5
10
15
20
25
PC3 Day 2
LNCaP Day 3
Concentration (uM)

FIGURE 11


LNCaP CX
One DMSO outlier removed
Tumour volume %
250
225
200
175
150
125
100
75
0
5
10
15
20
25
Days after 1st oral dose
Cmp. A (25 mpk), n=7
DMSO corn oil, n=7
Cmp. A (50 mpk), n=8
Cmp. 7c (33mpk), n=8
MDV-3100 (50mg/kg), n=4
Cmp. 7c (66 mpk), n=8

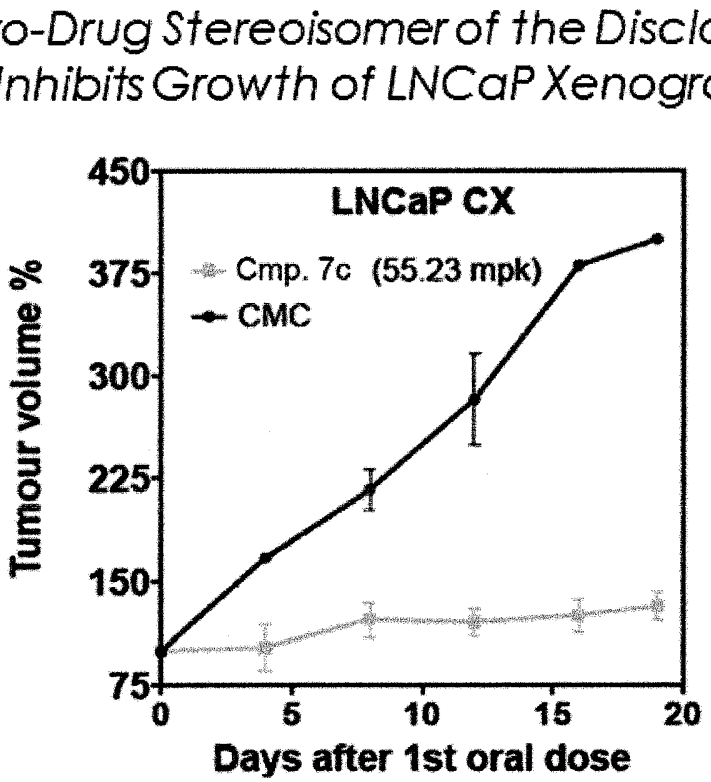

Pro-Drug Stereoisomer of the Disclosure Inhibits Growth of LNCaP Xenografts
LNCaP CX
Cmp. 7c (55.23 mpk)
CMC
Tumour volume %
450
375
300
225
150
75
0
5
10
15
20
Days after 1st oral dose

FIGURE 12

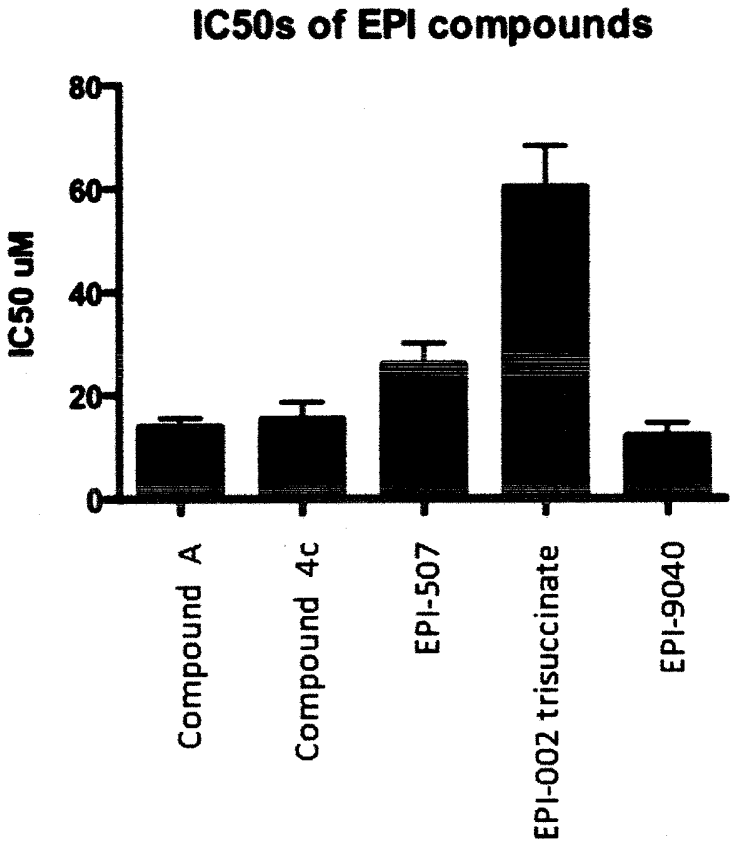

IC50s of EPI compounds
IC50 uM
80
60
40
20
0
Compound A
Compound 4c
EPI-507
EPI-002 trisuccinate
EPI-9040

FIGURE 13

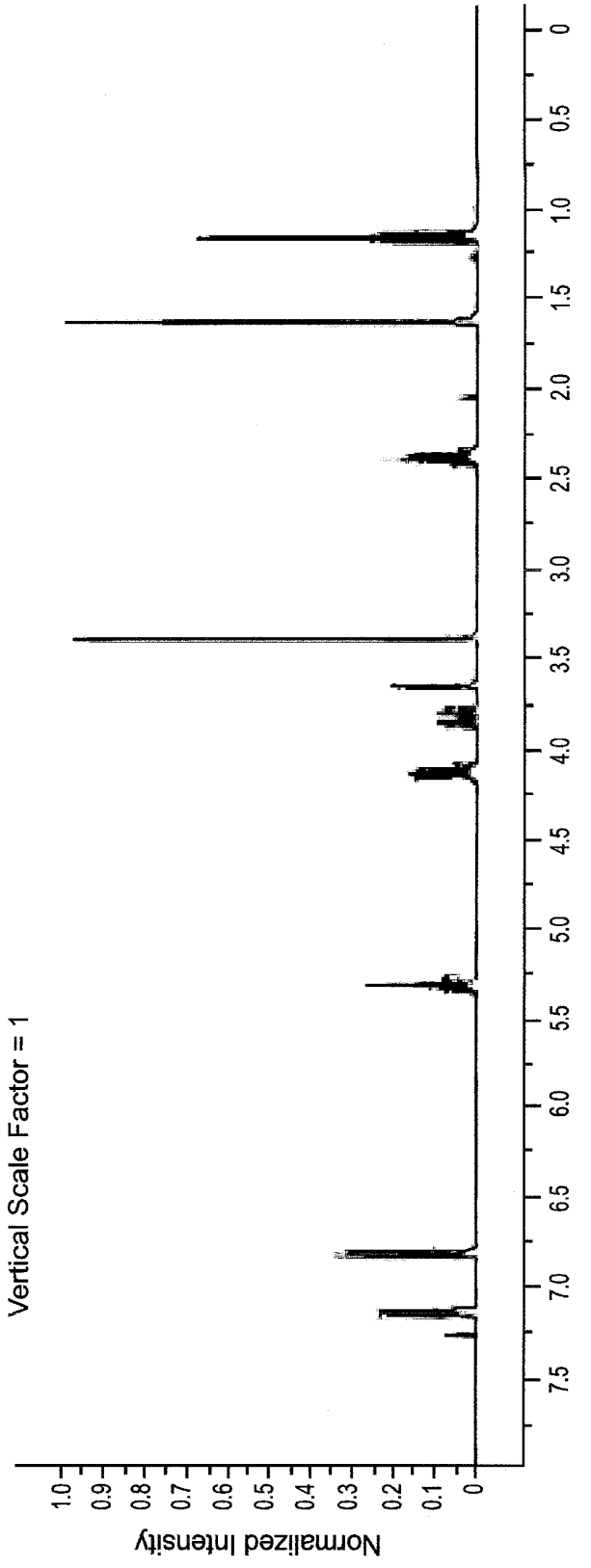

Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Vertical Scale Factor = 1
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

FIGURE 14A

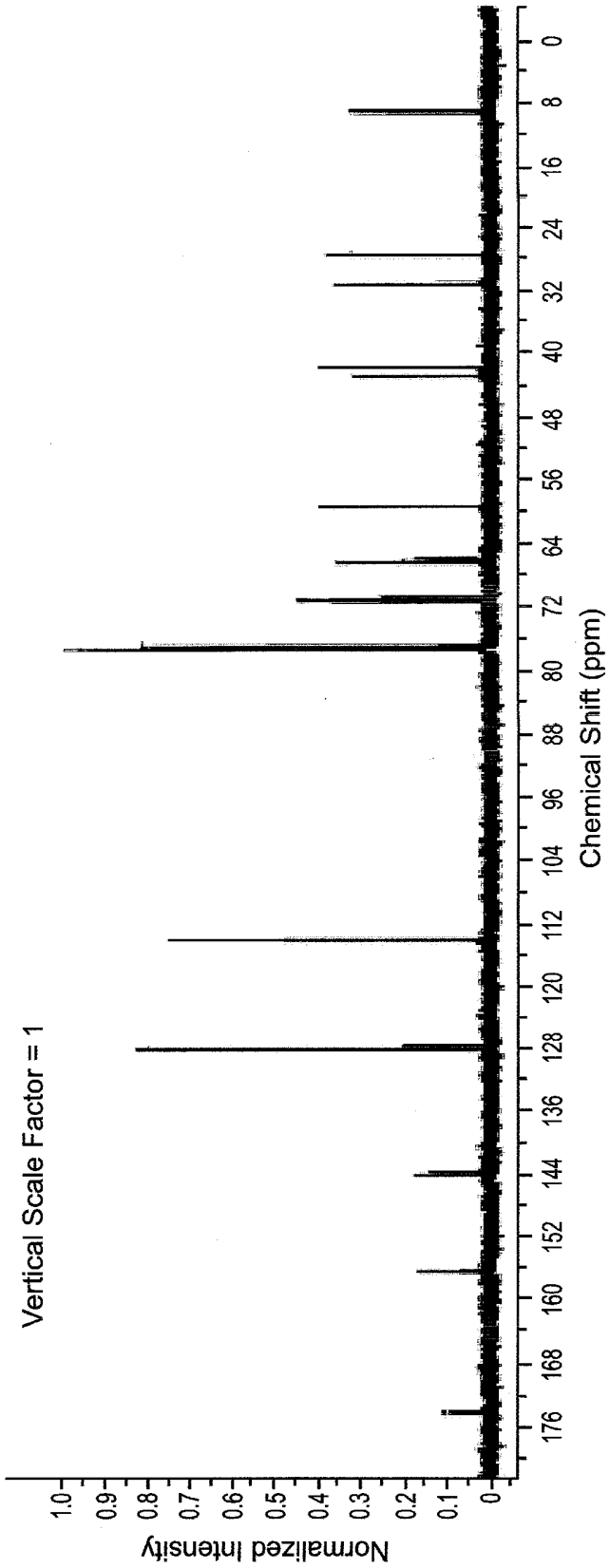

Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Vertical Scale Factor = 1
Chemical Shift (ppm)
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
152
160
168
176

FIGURE 14B

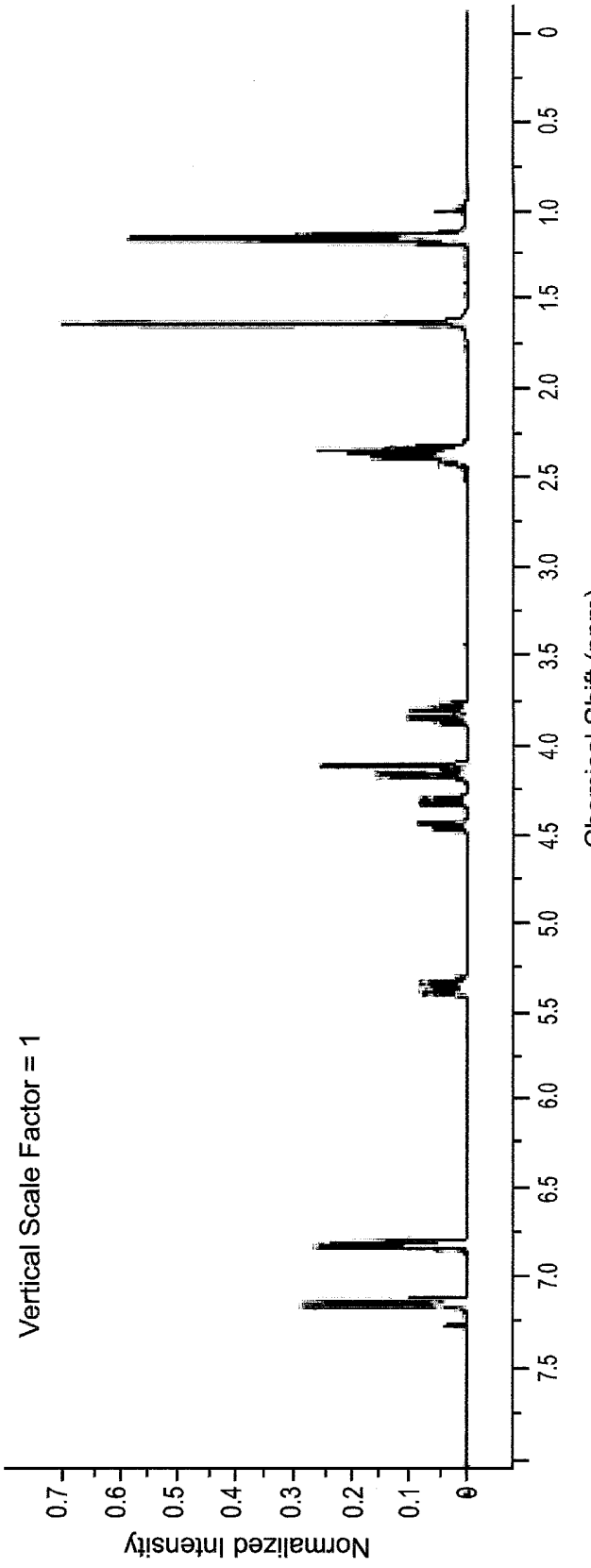

Vertical Scale Factor = 1
Normalized Intensity
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

FIGURE 15A

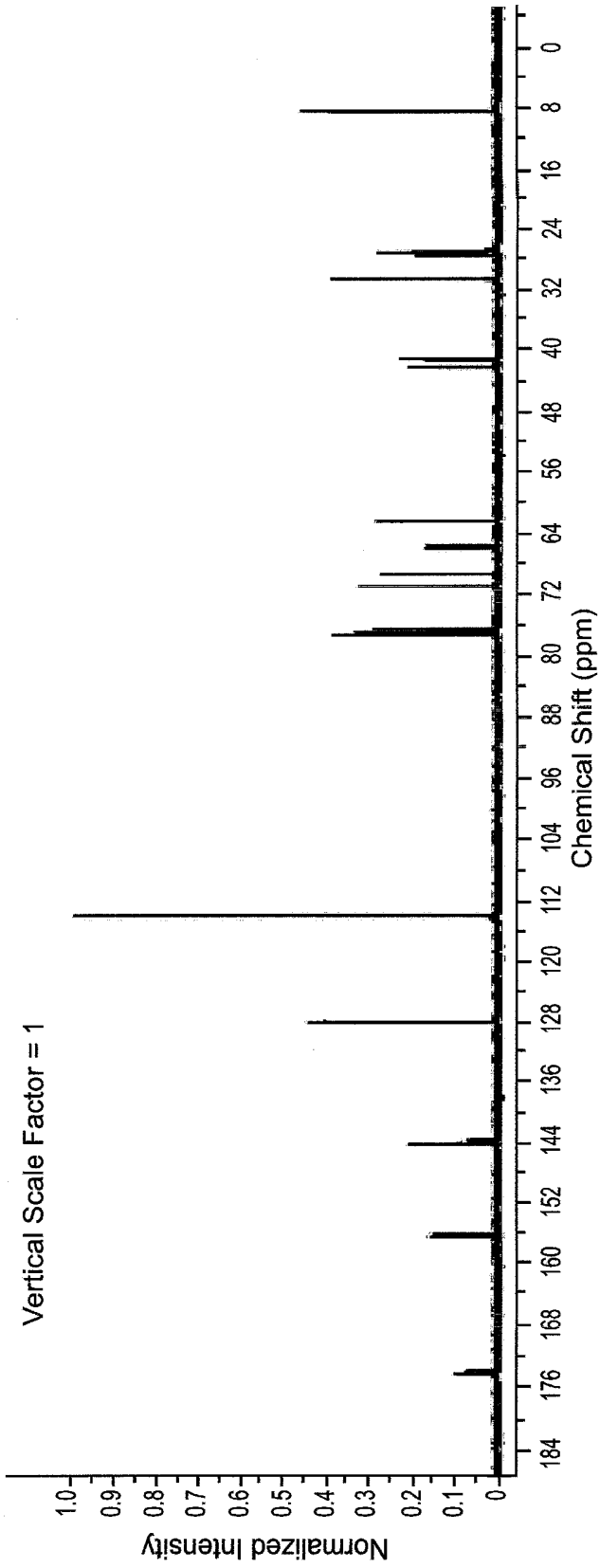

Vertical Scale Factor = 1
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Chemical Shift (ppm)
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

FIGURE 15B

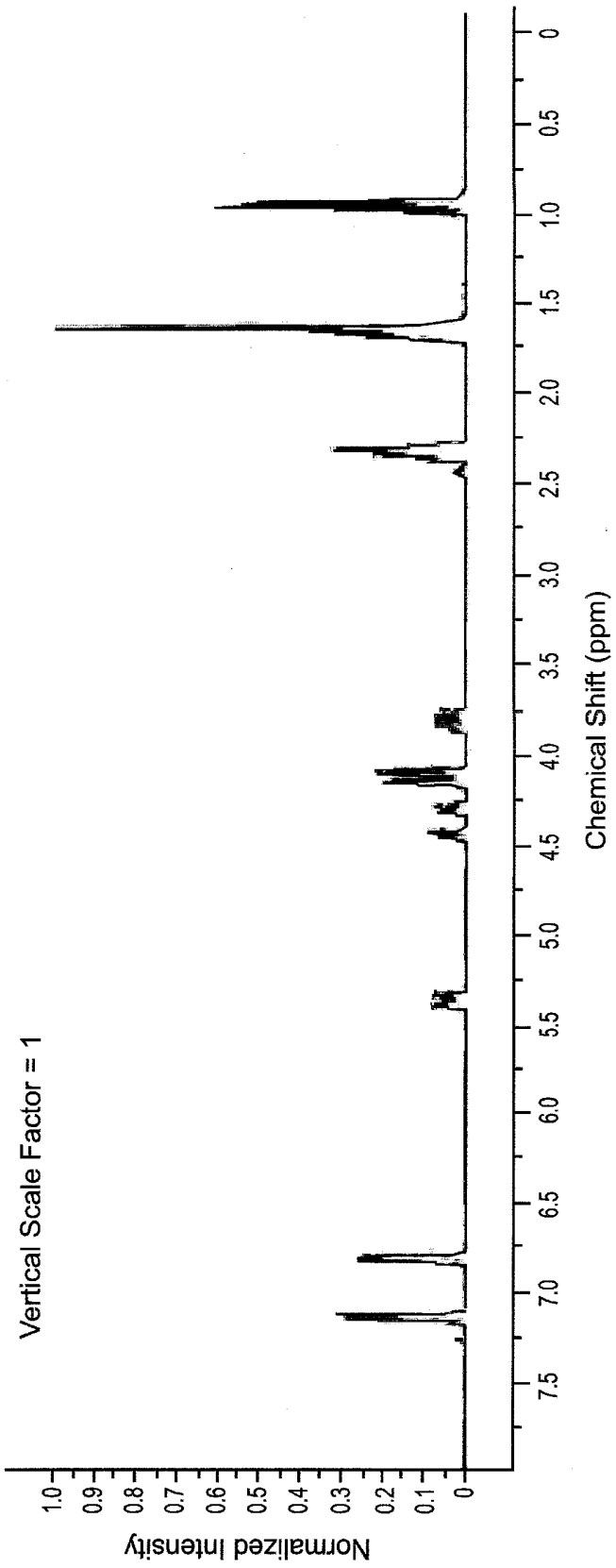

Vertical Scale Factor = 1
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

FIGURE 16A

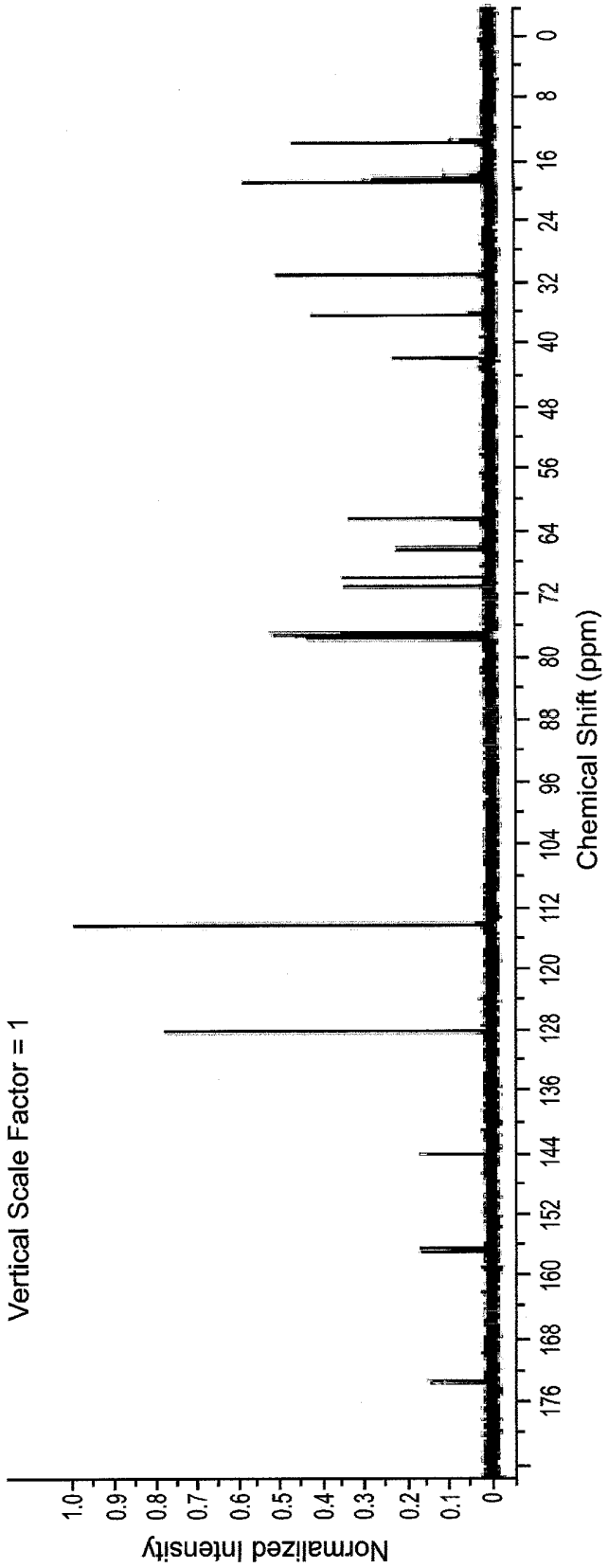

Vertical Scale Factor = 1
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Chemical Shift (ppm)
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
152
160
168
176

FIGURE 16B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2014/000414

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07C 69/18*** (2006.01), ***A61K 31/25*** (2006.01), ***A61P 35/00*** (2006.01), ***C07C 69/16*** (2006.01)

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)
See IPC classes listed above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
C07C, A61K, A61P

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN, Canadian Patent Database, Scopus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RUSU, E. et al.: "Photosensitive compounds with chloromethyl groups" *Revue Roumaine de Chimie*, Vol. 45(5), 2000, pages 451-456 *compound with CAS 344958-53-8*	1-7, 9, 13, 18-23
X	JP 09176240 (URANO, T. et al.) 08 July 1997 (08-07-1997) *compound with CAS 192652-72-5*	1-7, 9, 13, 18-23
Y	CA 2,728,219 (SADAR, M. D. et al.) 07 January 2010 (07-01-2010) *polyols and esters on page 12*	1-46

☑ 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 another 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
25 July 2014 (25-07-2014)

Date of mailing of the international search report
05 August 2014 (05-08-2014)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001-819-953-2476

Authorized officer

Genevieve Fortier, PhD (819) 994-3433

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/082488 (SADAR, M. D. et al.) 14 July 2011 (14-07-2011) *polyols and esters on pages 73-75*	1-46
Y	WO 2012/139039 (ANDERSEN, R. J. et al.) 11 October 2012 (11-10-2012) *esters on page 39*	1-46
Y	CA 2,786,319 (SADAR, M. D. et al.) 14 July 2011 (14-07-2011) *esters on page 114*	1-46

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
JP 09176240	08 July 1997 (08-07-1997)	none	
CA2728219	07 January 2010 (07-01-2010)	CA2728219A1	07 January 2010 (07-01-2010)
		AU2009266379A1	07 January 2010 (07-01-2010)
		CN102083780A	01 June 2011 (01-06-2011)
		CO6351774A2	20 December 2011 (20-12-2011)
		EP2307342A1	13 April 2011 (13-04-2011)
		EP2307342A4	20 July 2011 (20-07-2011)
		IL210120D0	28 February 2011 (28-02-2011)
		JP2011526250A	06 October 2011 (06-10-2011)
		KR20110044216A	28 April 2011 (28-04-2011)
		MX2010014372A	20 June 2011 (20-06-2011)
		NZ589759A	21 December 2012 (21-12-2012)
		RU2011103538A	10 August 2012 (10-08-2012)
		TR201011157T1	21 October 2011 (21-10-2011)
		US2013245129A1	19 September 2013 (19-09-2013)
		US8686050B2	01 April 2014 (01-04-2014)
		US2011230556A1	22 September 2011 (22-09-2011)
		WO2010000066A1	07 January 2010 (07-01-2010)
WO2011082488	14 July 2011 (14-07-2011)	WO2011082488A1	14 July 2011 (14-07-2011)
		AR079975A1	07 March 2012 (07-03-2012)
		US2013109758A1	02 May 2013 (02-05-2013)
WO2012139039	11 October 2012 (11-10-2012)	WO2012139039A2	11 October 2012 (11-10-2012)
		WO2012139039A3	25 April 2013 (25-04-2013)
		EP2693875A2	12 February 2014 (12-02-2014)
CA2786319	14 July 2011 (14-07-2011)	CA2786319A1	14 July 2011 (14-07-2011)
		AR079846A1	22 February 2012 (22-02-2012)
		EP2521707A1	14 November 2012 (14-11-2012)
		EP2521707A4	24 July 2013 (24-07-2013)
		JP2013516435A	13 May 2013 (13-05-2013)
		US2013131167A1	23 May 2013 (23-05-2013)
		WO2011082487A1	14 July 2011 (14-07-2011)
		WO2011082487A8	17 January 2013 (17-01-2013)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2014/000414

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☑ Claim Nos.: 39-43
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 39-43 are directed to a method of treatment of the human or animal body by surgery or therapy, which this Authority is not required to search. However, this Authority has nevertheless carried out a search based on the alleged effects or purposes/uses.

2. ☑ Claim Nos.: 44-46
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:

Claims 44-46 relate to an extremely large number of possible compounds/drugs. Support within the meaning of Article 6 of the PCT and/or disclosure within the meaning of Article 5 of the PCT is to be found, however, only for a very small portion of the compounds/drugs defined. In the current case, the claims so lack support, and the application so lack disclosure, that a meaningful search over the whole scope of the claims is not possible. (see extra sheet)

3. ☐ Claim 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 additional 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 additional fees, this Authority did not invite payment of additional fees.

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 claim 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 claim 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.

(Continuation from Box II.2)

Therefore, the search has been carried out for those parts of the claims which appear to be fully supported and disclosed, namely those parts relating to the compounds clearly identified in the claims and in the examples.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 105358522 A
(43)申请公布日 2016.02.24

(21)申请号 201480026227.1

(22)申请日 2014.05.09

(30)优先权数据
61/822,186 2013.05.10 US

(85)PCT国际申请进入国家阶段日
2015.11.09

(86)PCT国际申请的申请数据
PCT/CA2014/000414 2014.05.09

(87)PCT国际申请的公布数据
WO2014/179867 EN 2014.11.13

(71)申请人 不列颠哥伦比亚癌症局分支机构
地址 加拿大不列颠哥伦比亚省
申请人 英属哥伦比亚大学工业联络处

(72)发明人 纳斯林·R·穆基 王军
卡门·阿德里亚娜·巴纽埃洛斯
雷蒙德·约翰·安德森
哈维尔·加西亚·费尔南德斯
玛丽安娜·桃乐茜·萨达尔

(74)专利代理机构 中科专利商标代理有限责任公司 11021
代理人 陈晓娜

(51)Int.Cl.
C07C 69/18(2006.01)
A61K 31/25(2006.01)
A61P 35/00(2006.01)
C07C 69/16(2006.01)

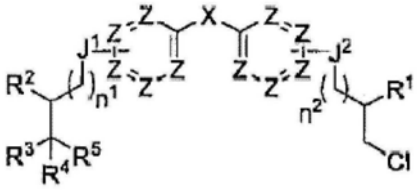
权利要求书12页 说明书53页 附图36页

(54)发明名称

雄激素受体调节剂的酯衍生物及其使用方法

(57)摘要

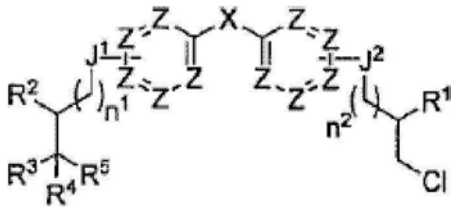
本发明提供了具有结构I的结构的化合物：



I或其药学上可接受的盐、互变异构体、或立体异构体，其中R^1、R^2、R^3、R^4、R^5、J^1、J^2、X、Z、n^1和n^2如本文所定义，并且其中R^1、R^2或R^3中的至少一个为烷基、烯基、芳基或芳烷基酯。也提供了此类化合物用于治疗包括前列腺癌的各种适应症的用途以及涉及此类化合物治疗的方法。

CN 105358522 A

1.一种具有下列结构(I)的化合物：



(I)

或其药学上可接受的盐、互变异构体或立体异构体，其中：

J1和J2各自独立地为-O-、-S(O)m-、-NR6-或-(CR6R7)-；

X为直接键、-C(R8R9)-、-C(=CR8R9)-、-C(R8R9)-芳基-C(R8R9)-、-C(=CR8R9)-芳基-C(=CR8R9)-、-C(=CR8R9)-芳基-C(R8R9)-、-C(R8R9)-芳基-C(=CR8R9)-、-O-、-S(O)m-、-N(R6)-、-CH(NR6R7)-、-C(=NOR6)-、-C(=N-NHR10)-、-C(=NR6)-或-C(=O)-；

Z在每次出现时独立地为-C(R11)-或-N-；

R1为羟基、-OR12或-OC(=O)R13；

R2和R3各自独立地为羟基、卤代、-OR12或-OC(=O)R13；

R4和R5各自独立地为H或卤代；

R6和R7在每次出现时独立地为H或C1-10烷基；

R8和R9在每次出现时独立地为H、羟基、卤代、C1-C10烷基、C1-C10卤代烷基、C1-C10氘化烷基、C1-C10烷氧基、芳基、芳烷基、-S(O)mR14或-NR6R7，或R8和R9可联接以形成含有3至20个碳原子的单环、二环或三环碳环或杂环；

R10为H、C1-C10烷基、芳基、氨基羰基、C1-C10烷基羰基或C1-C10烷基氨基羰基；

R11在每次出现时独立地为H、卤代或C1-C10烷基；

R12在每次出现时独立地为C1-C20烷基或C2-C20烯基；

R13在每次出现时独立地为C1-C20烷基、C2-C20烯基、芳基或芳烷基，其中所述C1-C20烷基不包括任选的氨基或烷基氨基取代基并且C1-C20烷基、C2-C20烯基或芳烷基中的每个脂族碳可任选地被-O-或-S(O)m-取代；

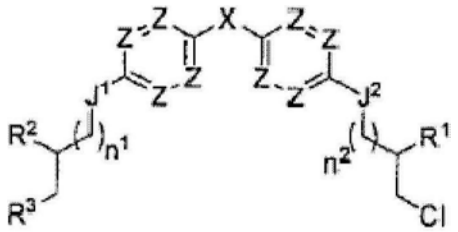
R14为H、C1-C10烷基或芳基；

m在每次出现时独立地为0、1或2；

n1和n2各自独立地为0、1、2、3、4或5，

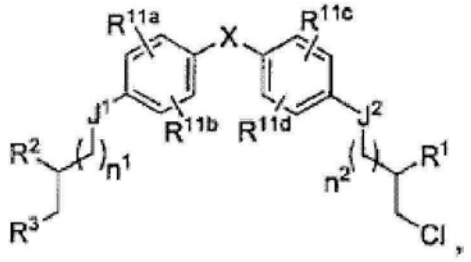
其中R1、R2或R3中的至少一个为-OC(=O)R13。

2.如权利要求1所述的化合物，其中所述化合物具有下列结构(Ia)：



(Ia)

3.如权利要求1或2中任一项所述的化合物，其中所述化合物具有下列结构(Ib)：



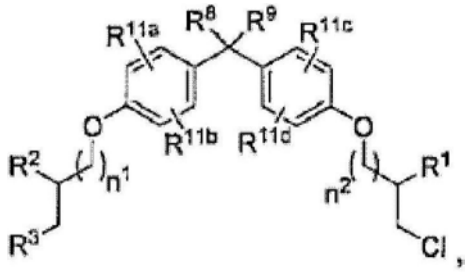
(Ib)

其中 R11a、R11b、R11c 和 R11d 各自独立地为 H、卤代或 C1-C10 烷基。

4. 如权利要求 1-3 中任一项所述的化合物，其中 J1 和 J2 各自为 -O-。

5. 如权利要求 1-4 中任一项所述的化合物，其中 X 为 -C(R8R9)-。

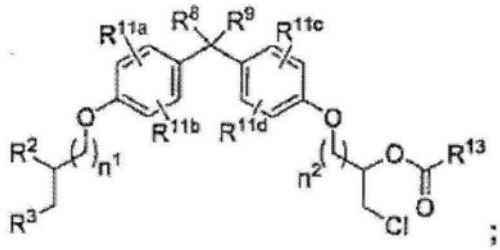
6. 如权利要求 1-5 中任一项所述的化合物，其中所述化合物具有下列结构 (Ic)：



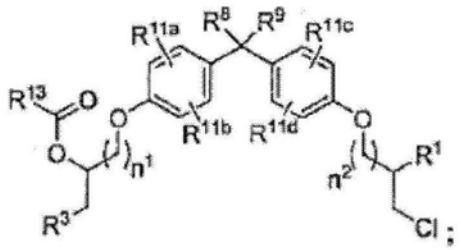
(Ic)

其中 R11a、R11b、R11c 和 R11d 各自独立地为 H、卤代或 C1-C10 烷基。

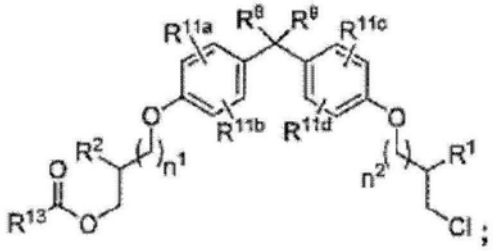
7. 如权利要求 1-6 中任一项所述的化合物，其中所述化合物具有下列结构 (Id)、(Ie)、(If)、(Ig)、(Ih)、(Ii) 或 (Ij) 中的一个：



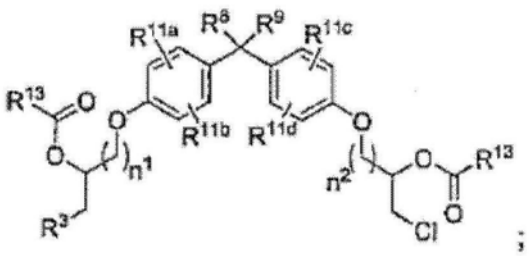
(Id)



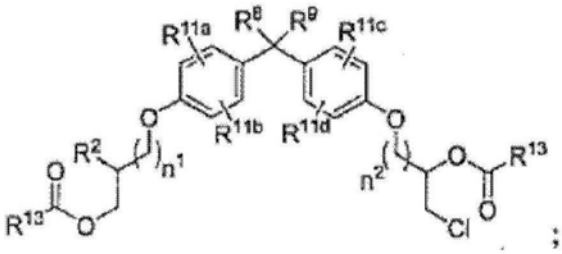
(Ie)



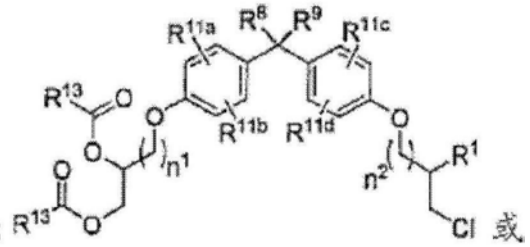
(If)



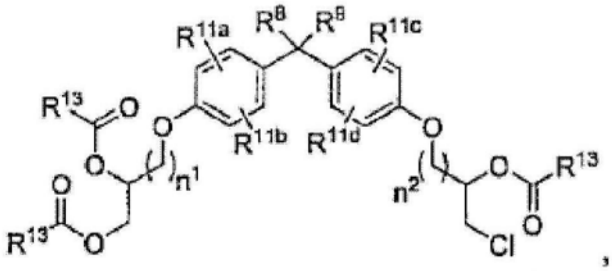
(Ig)



(Ih)



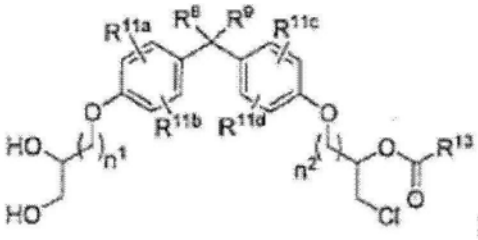
(Ii)



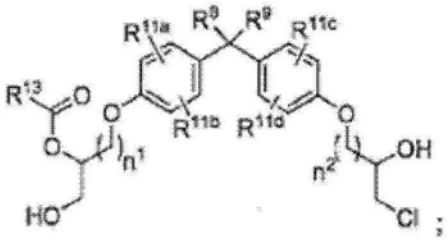
(Ij)

其中 R11a、R11b、R11c 和 R11d 各自独立地为 H、卤代或 C1-C10 烷基。

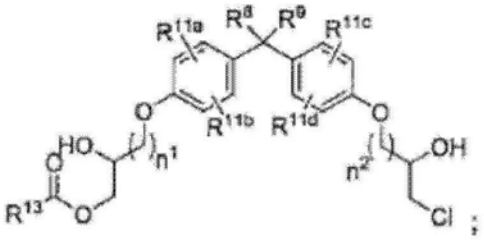
8. 如权利要求 1-7 中任一项所述的化合物，其中所述化合物具有下列结构 (Ik)、(Il)、(Im)、(In)、(Io) 或 (Ip) 中的一个：



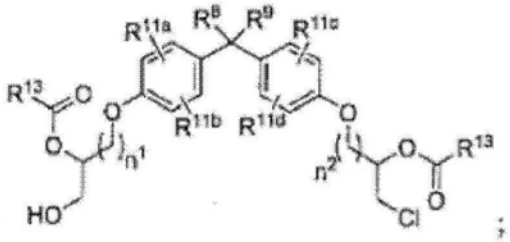
(Ik)



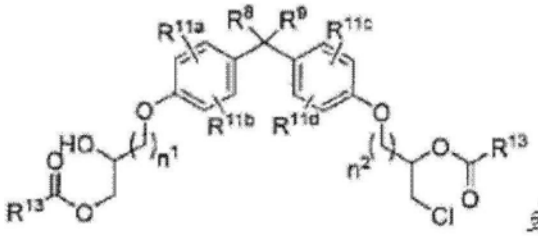
(Il)



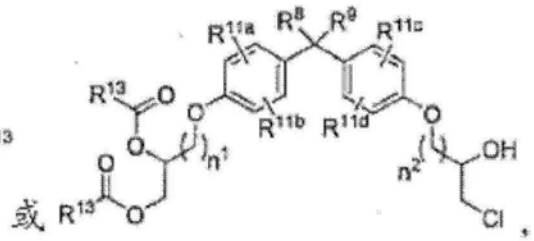
(Im)



(In)



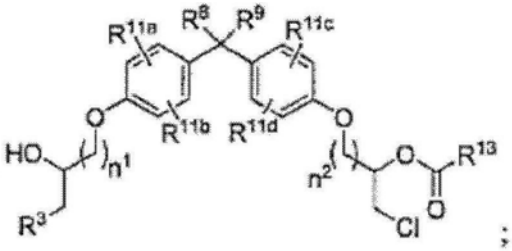
(Io)



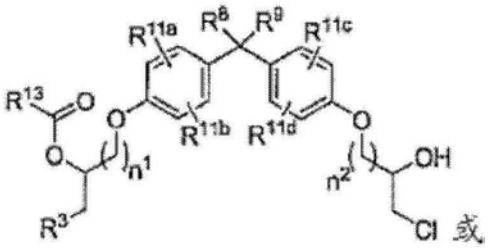
(Ip)

其中 R11a、R11b、R11c 和 R11d 各自独立地为 H、卤代或 C1-C10 烷基。

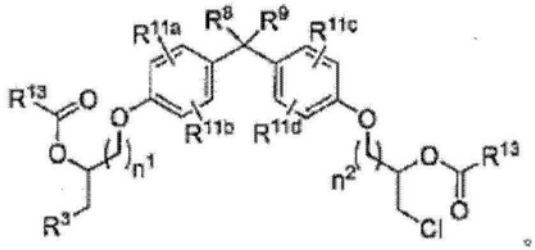
9. 如权利要求 1-7 中任一项所述的化合物，其中所述化合物具有下列结构 (Iq)、(Ir) 或 (Is) 中的一个：



(Iq)



(Ir)



(Is)

10. 如权利要求 9 所述的化合物，其中 R3 为 -OR12。

11. 如权利要求 10 所述的化合物，其中 R12 为 C1-C6 烷基。

12. 如权利要求 11 所述的化合物，其中 R12 为甲基、异丙基或正丁基。

13. 如权利要求 9 所述的化合物，其中 R3 为卤代。

14. 如权利要求 13 所述的化合物，其中 R3 为氟。

15. 如权利要求 1-14 中任一项所述的化合物，其中每个 R13 独立地为 C1-C6 烷基。

16. 如权利要求 15 所述的化合物，其中每个 R13 独立地为甲基、乙基或丙基。

17. 如权利要求 16 所述的化合物，其中每个 R13 为甲基。

18. 如权利要求 1-17 中任一项所述的化合物，其中 R8 和 R9 各自独立地为 C1-C6 烷基。

19. 如权利要求 18 所述的化合物，其中 R8 和 R9 各自为甲基。

20. 如权利要求 1-19 中任一项所述的化合物，其中至少一个 R11 为 H 或者 R11a、R11b、R11c 或 R11d 中的至少一个为 H。

21. 如权利要求 20 所述的化合物，其中每个 R11 为 H 或 R11a、R11b、R11c 和 R11d 中的每个为 H。

22. 如权利要求 1-21 中任一项所述的化合物，其中 n1 和 n2 各自为 1。

23. 如权利要求 1-22 中任一项所述的化合物，其中 R4 和 R5 各自为 H。

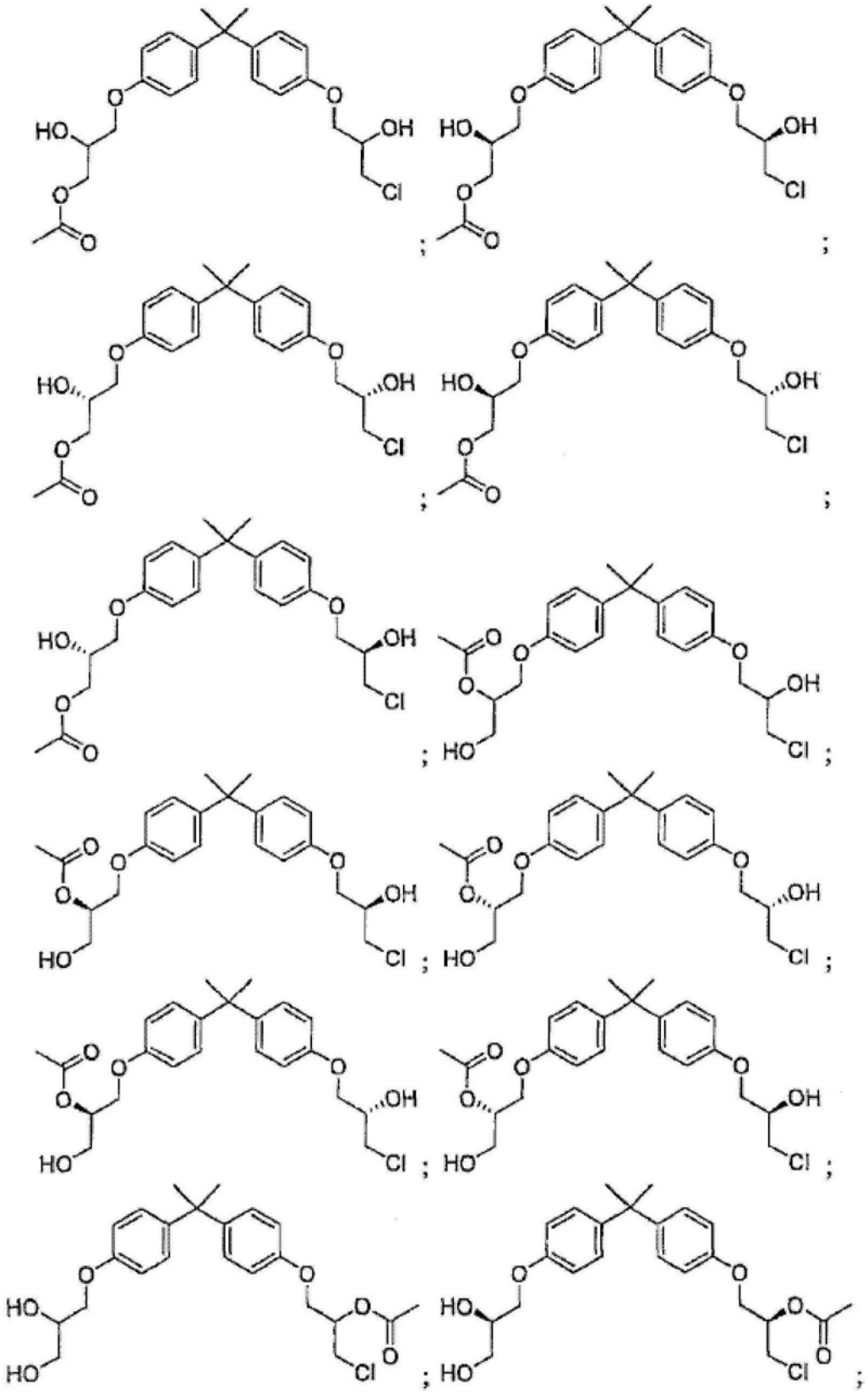
24. 如权利要求 1-22 中任一项所述的化合物，其中 R4 和 R5 各自为卤代。

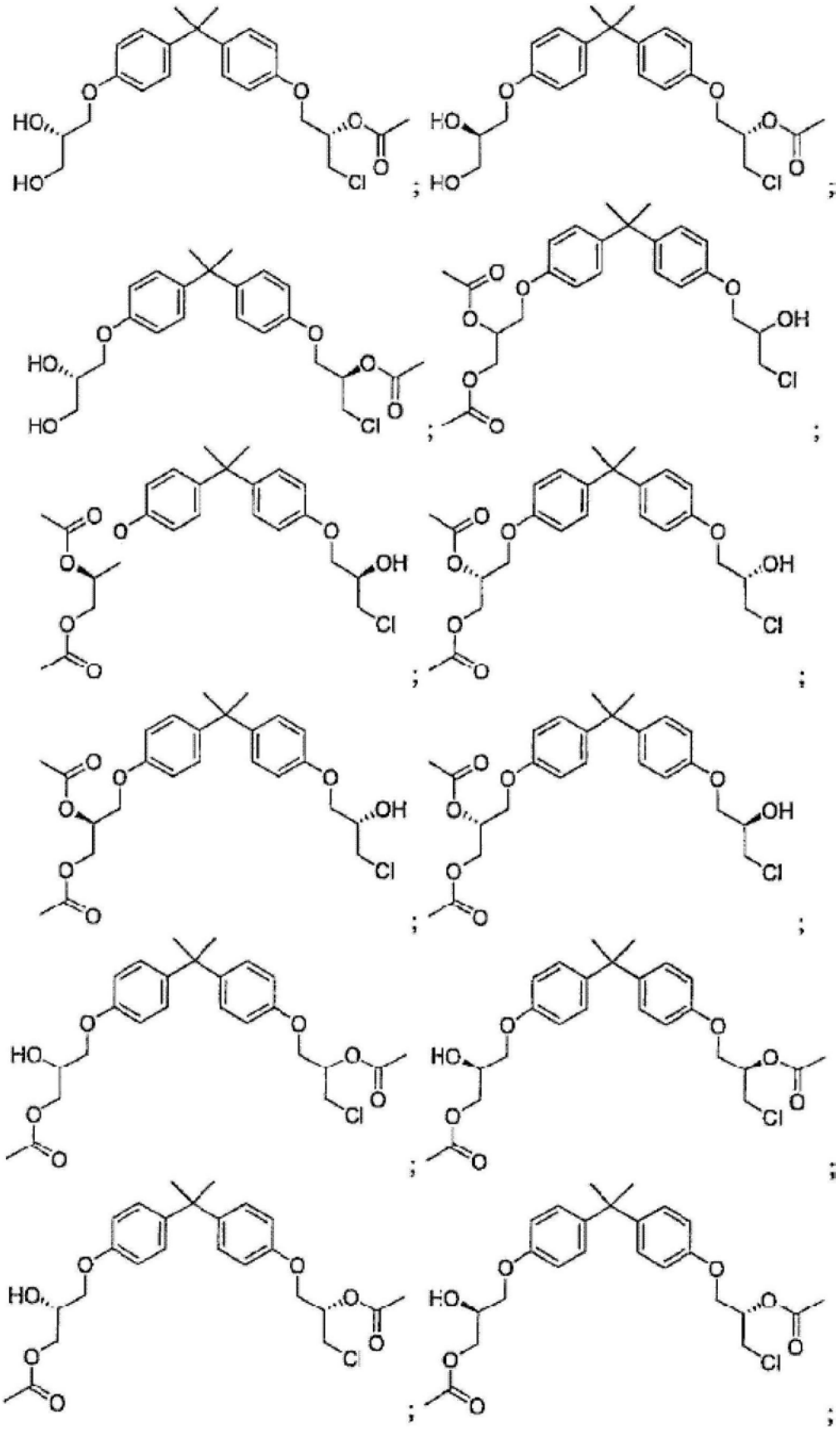
25. 如权利要求 24 所述的化合物，其中卤代为氟代。

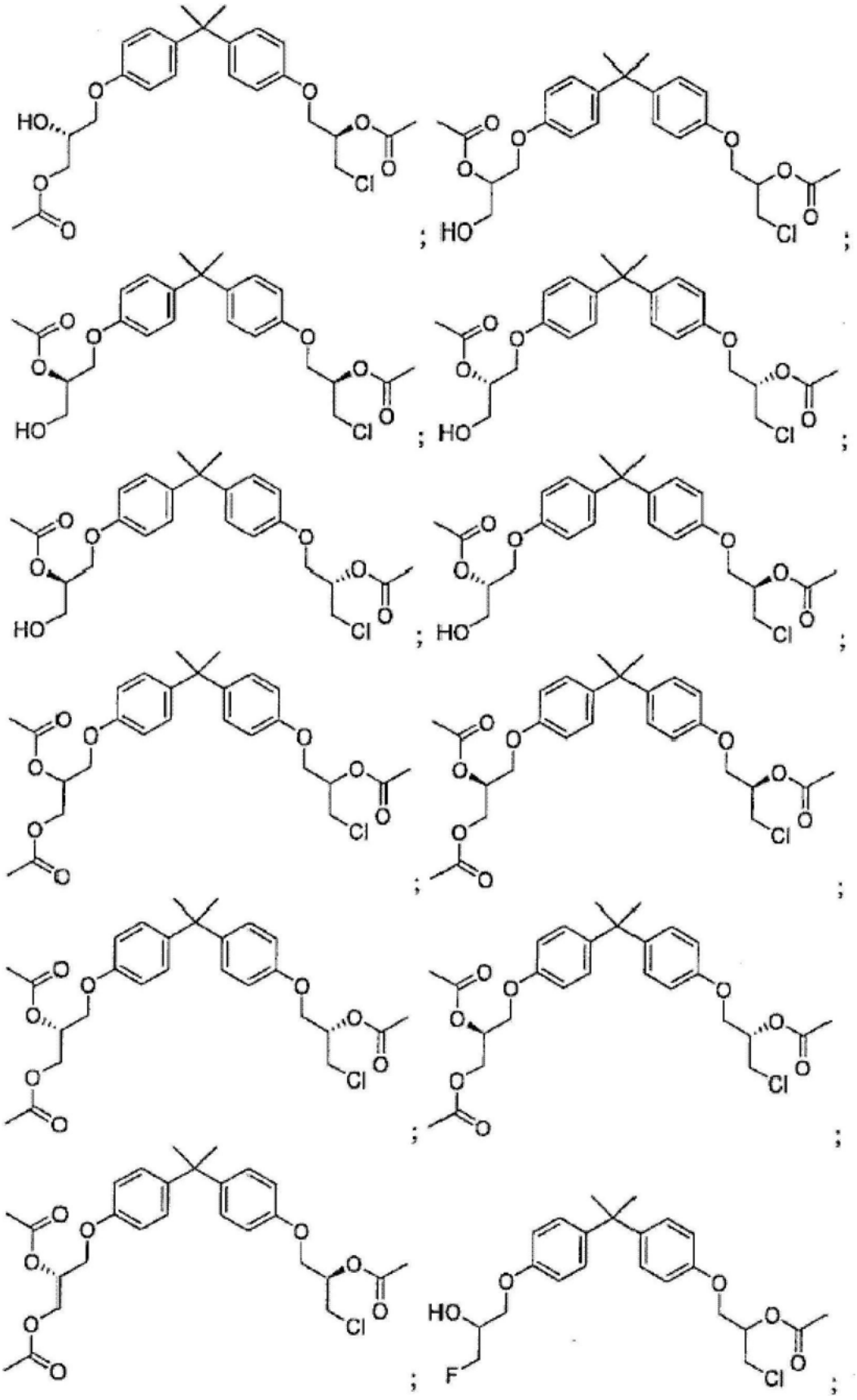
26. 如权利要求 1-14 中任一项所述的化合物，其中 R13 为 C1-C20 烷基、C2-C20 烯基或芳烷基，且所述 C1-C20 烷基、C2-C20 烯基或芳烷基的至少一个脂族碳被选自羟基、卤代、氧代基和烷氧基的取代基取代。

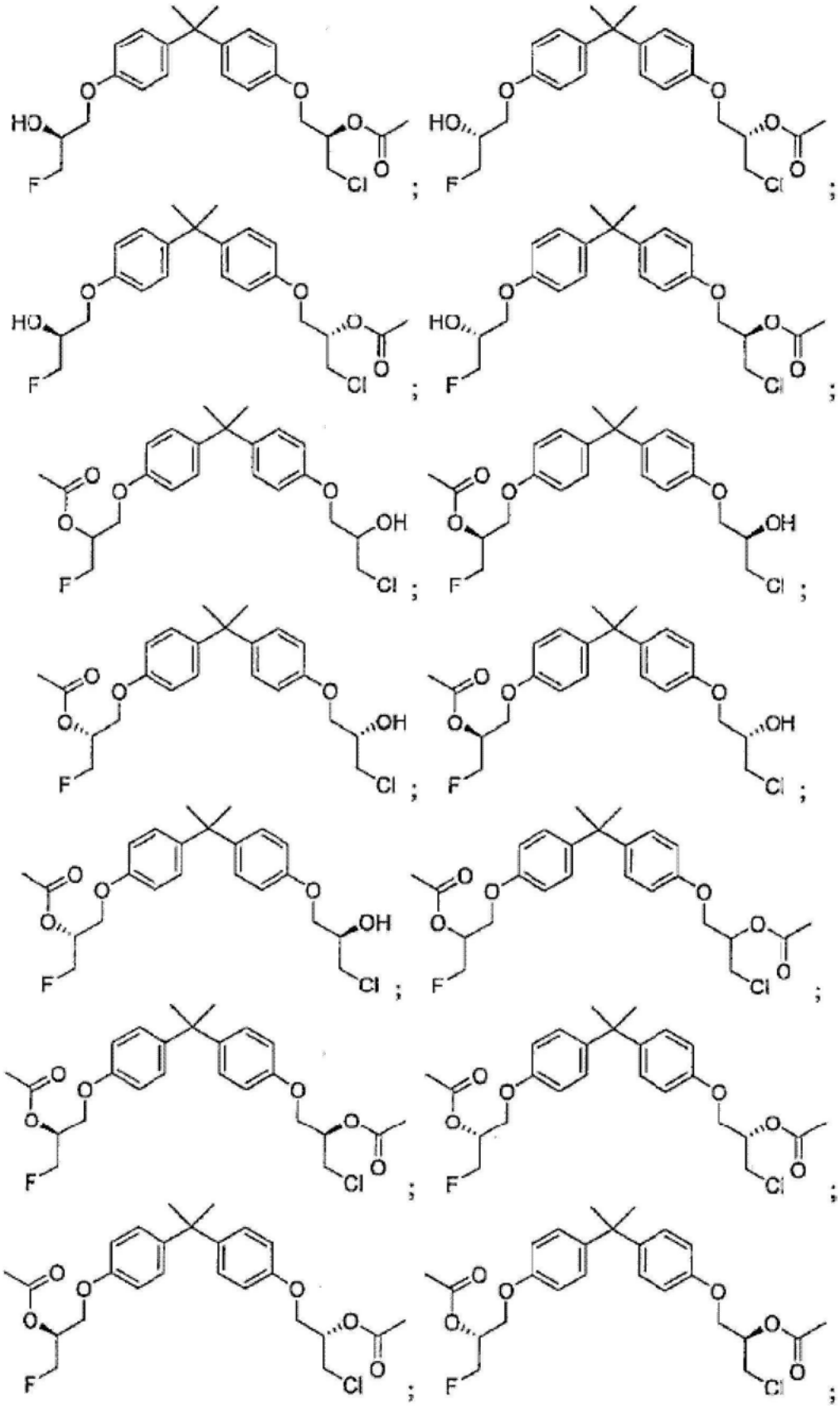
27. 如权利要求 1-14 中任一项所述的化合物，其中 R13 为芳基或芳烷基、且所述芳基或芳烷基的至少一个芳族碳被选自羟基、卤代和烷氧基的取代基取代。

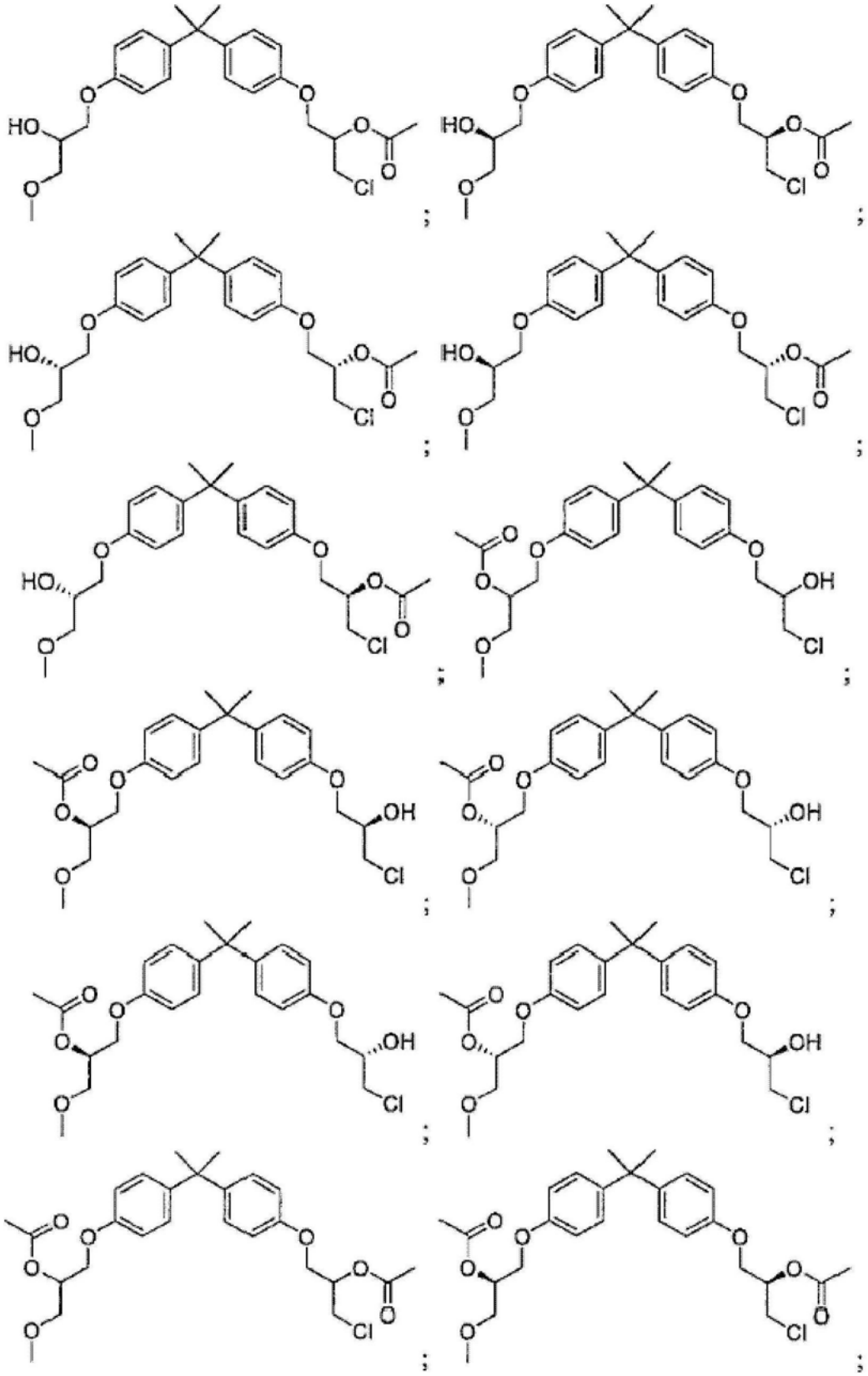
28. 如权利要求 1 所述的化合物，其中所述化合物具有下列结构之一 ：

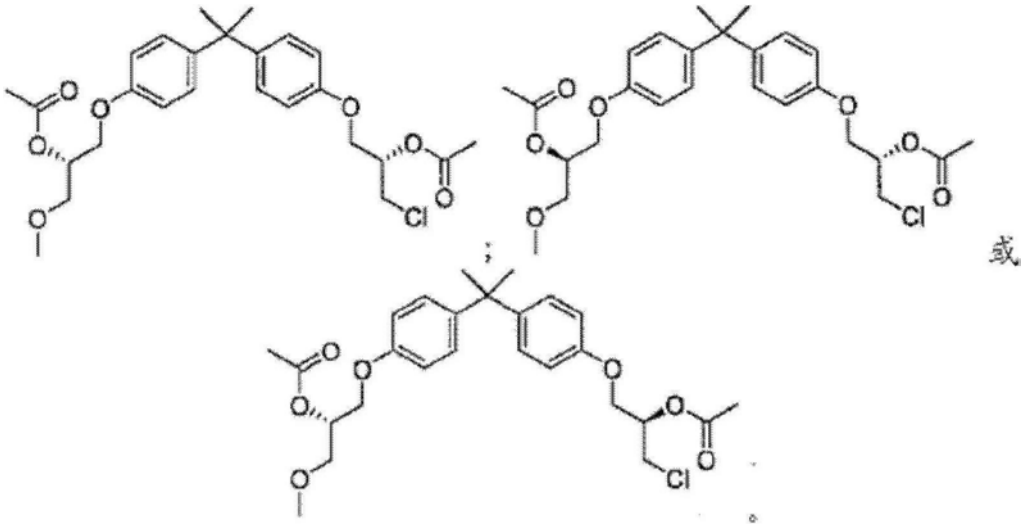












29. 一种药物组合物，其包含如权利要求 1 至 28 中任一项所述的化合物和药学上可接受的载体。

30. 一种药物组合物，其包含如权利要求 1 至 28 中任一项所述的化合物、额外治疗剂和药学上可接受的载体。

31. 如权利要求 30 所述的药物组合物，其中所述额外治疗剂用于治疗前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症或年龄相关性黄斑变性。

32. 如权利要求 30 所述的药物组合物，其中所述额外治疗剂是恩杂鲁胺、TOK 001、TOK 001 ;ARN-509 ;阿比特龙、比卡鲁胺、尼鲁米特、氟他胺、醋酸环丙孕酮、多西他赛、贝伐单抗 (Avastin)、OSU-HDAC42、VITAXIN、舒尼替尼、ZD-4054、VN/124-1、卡巴他赛 (XRP-6258)、MDX-010 (伊匹单抗)、OGX 427、OGX 011、非那雄胺、度他雄胺、妥罗雄胺、倍氯特来、艾宗特来、FCE 28260、SKF105，111 或其相关化合物。

33. 如权利要求 29-32 中任一项所述的药物组合物的用途，其用于调节雄激素受体 (AR) 活性。

34. 如权利要求 33 所述的用途，其中在哺乳动物细胞中调节雄激素受体 (AR) 活性。

35. 如权利要求 33 或 34 中任一项所述的用途，其中调节雄激素受体 (AR) 活性是用于治疗至少一种选自由以下组成的组的适应症 :前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。

36. 如权利要求 35 所述的用途，其中所述适应症是前列腺癌。

37. 如权利要求 36 所述的用途，其中所述前列腺癌是去势抗性前列腺癌。

38. 如权利要求 36 所述的用途，其中所述前列腺癌是雄激素 - 依赖性前列腺癌。

39. 一种用于调节雄激素受体 (AR) 活性的方法，所述方法包括向需要其的受试者施用如权利要求 29-32 中任一项所述的药物组合物。

40. 如权利要求 39 所述的方法，其中调节雄激素受体 (AR) 活性是用于治疗下列的一种或多种 :前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。

41. 如权利要求 40 所述的方法，其中所述方法用于治疗前列腺癌。

42. 如权利要求 41 所述的方法，其中所述前列腺癌是去势抗性前列腺癌。

43. 如权利要求 41 所述的方法，其中所述前列腺癌是雄激素 - 依赖性前列腺癌。

44. 一种用于增加含羟基雄激素受体调节剂的生物利用度的方法，所述方法包括用烷基、烯基、芳基或芳烷基酯取代至少一个羟基部分。

45. 如权利要求 44 所述的方法，其中所述方法用于增加口服生物利用度。

46. 如权利要求 44 所述的方法，其中所述烷基酯为甲基酯。

雄激素受体调节剂的酯衍生物及其使用方法

[0001] 相关申请的交叉引用

[0002] 本申请要求于2013年5月10日提交的美国临时申请号61/822,186的权益，其全部内容为了所有目的通过引用整体并入本文。

[0003] 政府利益的申明

[0004] 本公开部分通过政府资助在由美国国家癌症研究所授予的拨款号2R01 CA105304下完成的。美国政府具有本公开的某些权利。

[0005] 背景

技术领域

[0006] 本公开一般涉及双酚相关的化合物的酯衍生物及其用于治疗各种适应症的用途。特别地，本公开涉及双酚相关的化合物的酯衍生物及其用于治疗各种癌症例如所有阶段的前列腺癌（包括雄激素依赖性、雄激素敏感性和去势抗性前列腺癌）的用途。

[0007] 背景描述

[0008] 雄激素通过雄激素受体(AR)介导它们的作用。雄激素在广泛的发育和生理响应中发挥作用并且参与男性性分化、维持精子发生和男性促性腺激素调节(R.K.Ross，G.A.Coetzee，C.L.Pearce、J.K.Reichardt，P.Bretsky，L.N.Kolonel，B.E.Henderson，E.Lander，D.Altshuler&G.Daley，Eur Urol 35,355-361(1999)；A.A.Thomson、Reproduction 121,187-195(2001)；N.Tanji，K.Aoki&M.Yokoyama，Arch Androl 47，1-7(2001))。数条证据显示雄激素与前列腺癌发生相关。首先，雄激素在啮齿类动物模型中诱导前列腺癌发生(R.L.Noble,Cancer Res 37,1929-1933(1977)；R.L.Noble,Oncology 34,138-141(1977))并且以合成代谢类固醇的形式接受雄激素的男性具有更高的前列腺癌发病率(J.T.Roberts&D.M.Essenhigh，Lancet 2,742(1986)；J.A.Jackson、J.Waxman&A.M.Spiekerman，Arch Intern Med 149,2365-2366(1989)；P.D.Guinan，W.Sadoughi，H.Alsheik、R.J.Ablin，D.Alrenga&I.M.Bush，Am J Surg 131,599-600(1976))。其次，如果人或狗在青春期前去势，则前列腺癌不会发展(J.D.Wilson&C.Roehrborn、J Clin Endocrinol Metab 84,4324-4331(1999)；G.Wilding，Cancer Surv 14,113-130(1992))。成年男性的去势导致前列腺退化和前列腺上皮凋亡，而没有引发对其它男性外部生殖器的影响(E.M.Bruckheimer&N.Kyprianou，Cell Tissue Res 301,153-162(2000)；J.T.Isaacs,Prostate 5,545-557(1984))。这种对于雄激素的依赖性提供了用化学或手术去势（雄激素阻断）治疗前列腺癌的理论基础。

[0009] 雄激素还在女性癌症中发挥作用。一个实例是卵巢癌，其中升高水平的雄激素与发展卵巢癌的增加风险相关(K.J.Helzlsouer，A.J.Alberg，G.B.Gordon，C.Longcope，T.L.Bush，S.C.Hoffman&G.W.Comstock、JAMA 274,1926-1930(1995)；R.J.Edmondson、J.M.Monaghan&B.R.Davies，Br J Cancer 86,879-885(2002))。已经在大多数卵巢癌中检测到雄激素受体(H.A.Risch、J Natl Cancer Inst 90,1774-1786(1998)；B.R.Rao&B.J.Slotman，Endocr Rev 12,14-26(1991)；G.M.Clinton&W.Hua，Crit Rev Oncol Hematol

25,1-9(1997)),而雌激素受体-α(ERa)和孕酮受体在少于50%的卵巢肿瘤中检测到。

[0010] 可用于晚期前列腺癌的有效治疗是撤回雄激素,雄激素对于前列腺上皮细胞的存活是关键性的。雄激素阻断治疗导致肿瘤负荷的暂时减轻,伴随着血清前列腺特异性抗原(PSA)的减少。不幸的是,前列腺癌可以最终在缺乏睾丸雄激素的情况下再次生长(去势抗性疾病)(Huber等人1987ScandJ.Urol Nephrol.104,33-39)。去势抗性前列腺癌在生物化学上的特征在于,在症状发作前血清PSA滴度升高(Miller等人1992J.Urol.147,956-961)。一旦该疾病变成去势抗性,大多数患者就在两年内死于他们的疾病。

[0011] 雄激素受体具有清楚的功能结构域,包括羧基末端配体-结合结构域(LBD)、包含两个锌指基序的DNA-结合结构域(DBD)和含有一个或多个转录活化结构域的N-末端结构域(NTD)。雄激素(配体)与雄激素受体的LBD的结合导致其活化,使得受体可有效地结合于其在"正常"雄激素调节基因诸如PSA的启动子和增强子区域上的特异性DNA共有位点(称为雄激素应答元件(ARE)),以引发转录。在缺乏雄激素下,雄激素受体可通过刺激cAMP-依赖性蛋白激酶(PKA)途径、用白介素-6(IL-6)和通过各种生长因子来激活(Culig等人1994Cancer Res.54,5474-5478;Nazareth等人1996J.Biol.Chem.271,19900-19907;Sadar 1999J.Biol.Chem.274,7777-7783;Ueda等人2002 A J.Biol.Chem.277,7076-7085;和Ueda等人2002 B J.Biol.Chem.277,38087-38094)。已显示雄激素受体AR的配体-非依赖性转化的机制涉及:1)增加的核雄激素受体蛋白,表明核易位;2)增加的雄激素受体/ARE复合物形成;和3)AR-NTD(Sadar 1999J.Biol.Chem.274,7777-7783;Ueda等人2002 A J.Biol.Chem.277,7076-7085;和Ueda等人2002 B J.Biol.Chem.277,38087-38094)。在去势抗性疾病中,雄激素受体可在缺乏睾丸雄激素下通过备选的信号转导途径被活化,这与以下发现一致:核雄激素受体蛋白存在于继发前列腺癌肿瘤中(Kim等人2002Am.J.Pathol.160,219-226;和van der Kwast等人1991Inter.J.Cancer48,189-193)。

[0012] 可用的雄激素受体抑制剂包括非甾类抗雄激素诸如比卡鲁胺、尼鲁米特、氟他胺、恩杂鲁胺和测试药物ARN-509,以及甾类抗雄激素、醋酸环丙孕酮。这些抗雄激素靶向雄激素受体的LBD并且推测主要由于亲和力差和突变而失效,所述突变导致雄激素受体被这些相同抗雄激素活化(Taplin,M.E.,Bubley,G.J.,Kom Y.J.,Small E.J.,Uptonm M.,Rajeshkumarm B.,Balkm S.P.,Cancer Res.,59,2511-2515(1999))。这些抗雄激素对于最近发现的雄激素受体剪接变体也没有作用,所述雄激素受体剪接变体缺乏配体-结合结构域(LBD)来产生组成性活性受体,其促进雄激素-非依赖性前列腺癌的进展(Dehm SM,Schmidt LJ,Heemers HV,Vessella RL,Tindall DJ.,Cancer Res68,5469-77,2008;Guo Z、Yang X,Sun F、Jiang R,Linn DE,Chen H,Chen H,Kong X,Melamed J,Tepper CG,Kung HJ,Brodie AM,Edwards J,Qiu Y.,Cancer Res.69,2305-13,2009;Hu等人2009Cancer Res.69,16-22;Sun等人2010 J Clin Invest.2010120,2715-30)。

[0013] 常规治疗已集中在雄激素受体通过其C-末端结构域的雄激素-依赖性活化。最近开发针对雄激素受体的拮抗剂的研究已集中在C-末端并且具体地:1)别构袋和AF-2活性(Estébanez-Perpiñá等人2007,PNAS104,16074-16079);2)计算机"药物再利用"程序,用于鉴定非甾类拮抗剂(Bisson等人2007,PNAS104,11927-11932);和共激活剂或共遏抑剂相互作用(Chang等人2005,Mol Endocrinology19,2478-2490;Hur等人2004,PLoS Biol2,E274;Estébanez-Perpiñá等人2005、JBC280,8060-8068;He等人2004,Mol

Cell16,425-438)。

[0014] AR-NTD 也是药物开发的靶标（例如 WO 2000/001813),因为 NTD 含有为对于雄激素受体转录活性所需的必需区的活化－功能 -1(AF-1)(Jenster 等人 1991.Mol Endocrinol.5,1396-404)。在缺乏雄激素下，AR-NTD 在活化雄激素受体中起重要的作用 (Sadar，M.D.1999J.Biol.Chem.274,7777-7783 ;Sadar MD 等 人 1999Endocr Relat Cancer.6,487-502 ;Ueda 等 人 2002J.Biol.Chem.277,7076-7085 ;Ueda 2002J.Biol.Chem.277,38087-38094 ;Blaszczyk等人2004Clin CancerRes.10,1860-9 ;Dehm等人2006J Biol Chem.28,27882-93 ;Gregory等人2004J Biol Chem.279,7119-30)。AR-NTD在前列腺癌的激素进展中是重要的,如通过施加诱饵分子所显示(Quayle等人2007,Proc Natl Acad Sci USA.104,1331-1336)。

[0015] 尽管雄激素受体 C- 末端 LBD 的晶体结构已得到解析,但是 NTD 的晶体结构还未解析,这是因为它在溶液中具有高柔性和内在无序性 (Reid 等人 2002J.Biol.Chem.277,20079-20086),由此阻碍了虚拟对接药物开发方法。

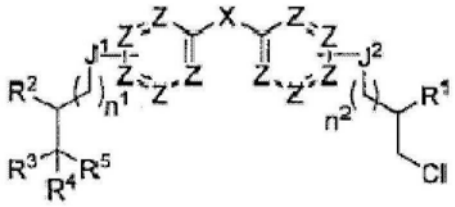
[0016] 尽管已取得进展,但是本领域仍需要调节雄激素受体的另外的和 / 或改进的化合物。本公开提供这些和相关优势。

[0017] 概述

[0018] 本公开部分是基于偶然发现,即双酚相关的化合物的某些酯具有用作雄激素受体调节剂的期望性质。特别地,本文所述的酯是有效力的雄激素受体调节剂。也希望涉及所述酯用于调节雄激素受体（体外或体内）的用途的另外优势。

[0019] 根据一个实施方案,提供了具有结构 I 的结构的化合物：

[0020]



I

[0021] 或其药学上可接受的盐、互变异构体或立体异构体,其中 R^1、R^2、R^3、R^4、R^5、J^1、J^2、X、Z、n^1和 n^2如本文所定义,并且其中 R^1、R^2或 R^3中的至少一个为烷基、烯基、芳基或芳烷基酯。也提供了包含结构 I 化合物、药学上可接受的载体和任选的额外治疗剂的药物组合物。

[0022] 在其它实施方案中,本公开提供结构 I 化合物或包含其的组合物用于调节雄激素受体 (AR) 活性的用途。也提供了用于调节雄激素受体的相关方法。

[0023] 本公开的这些和其它方面在参考下列详述后将是明显的。为此,本文阐述了各篇参考文献,它们更详细地描述了某些背景信息、程序、化合物和 / 或组合物并且各自据此通过引用整体并入。

[0024] 附图简述

[0025] 图 1A 是化合物乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基)-2- 羟丙基酯的 ^1H NMR 光谱。

[0026] 图 1B 是化合物乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）

丙 -2- 基) 苯氧基)-2- 羟丙基酯的 ^{13}C NMR 光谱。

[0027] 图 1C 是化合物乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基)-2- 羟丙基酯的 ^{13}C APT NMR 光谱。

[0028] 图 2A 是化合物乙酸 (S)-1- 氯 -3-(4-(2-(4-((R)-2,3- 二羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙 -2- 基酯的 ^{1}H NMR 光谱。

[0029] 图 2B 是化合物乙酸 (S)-1- 氯 -3-(4-(2-(4-((R)-2,3- 二羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙 -2- 基酯的 ^{13}C NMR 光谱。

[0030] 图 2C 是光谱化合物乙酸 (S)-1- 氯 -3-(4-(2-(4-((R)-2,3- 二羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙 -2- 基酯的 ^{13}C APT NMR。

[0031] 图 3A 是化合物二乙酸 (S)-3-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{1}H NMR 光谱。

[0032] 图 3B 是化合物二乙酸 (S)-3-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{13}C NMR 光谱。

[0033] 图 4A 是化合物二乙酸 (S)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{1}H NMR 光谱。

[0034] 图 4B 是化合物二乙酸 (S)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{13}C NMR 光谱

[0035] 图 4C 是化合物二乙酸 (S)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{13}C APT NMR 光谱。

[0036] 图 5A 是化合物二乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{1}H NMR 光谱。

[0037] 图 5B 是化合物二乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{13}C NMR 光谱。

[0038] 图 5C 是化合物二乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{13}C APT NMR 光谱。

[0039] 图 6A 是化合物三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二醇酯的 ^{1}H NMR 光谱。

[0040] 图 6B 是化合物三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二醇酯的 ^{13}C NMR 光谱。

[0041] 图 6C 是化合物三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二醇酯的 ^{13}C APT NMR 光谱。

[0042] 图 6D 举例说明了具有正离子极性的三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二醇酯的电喷雾电离质谱法数据。

[0043] 图 6E 举例说明了具有负离子极性的三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二醇酯的电喷雾电离质谱法数据

[0044] 图 7A 是化合物乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯的 ^{1}H NMR 光谱。

[0045] 图 7B 是化合物乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯的 ^{13}C NMR 光谱。

[0046] 图 7C 是化合物乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯的 ^{13}C APT NMR 光谱。

[0047] 图 7D 举例说明了具有正离子极性的乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯的电喷雾电离质谱法数据

[0048] 图 7E 举例说明了具有负离子极性的乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯的电喷雾电离质谱法数据

[0049] 图 8 举例说明了本公开的各个化合物 (3c、7c 和 13b) 和比较化合物的剂量响应数据。

[0050] 图 9 举例说明了本公开的各个化合物 (1c、3c、7c、乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯 (实施例 21)) 和比较化合物的剂量响应数据。

[0051] 图 10 描绘了细胞增殖测定,其表明本公开化合物 (7c) 的效力为其活性化合物 (化合物 A) 的两倍。

[0052] 图 11 举例说明了本公开化合物 (7c) 在减少异种移植模型的肿瘤体积方面有效。

[0053] 图 12 举例说明了本公开化合物 (7c) 在抑制 LNCaP 异种移植肿瘤生长方面有效。

[0054] 图 13 举例说明了本公开的各个化合物的 IC50。

[0055] 图 14A 是化合物二丙酸 1- 氯 -3-(4-(2-(4-(2- 羟基 -3- 甲氧基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙 -2- 醇酯的 ^{1}H NMR 光谱。

[0056] 图 14B 是化合物二丙酸 1- 氯 -3-(4-(2-(4-(2- 羟基 -3- 甲氧基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙 -2- 醇酯的 ^{13}C NMR 光谱。

[0057] 图 15A 是化合物二丙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2-(丙酰氧基) 丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{1}H NMR 光谱。

[0058] 图 15B 是化合物二丙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2-(丙酰氧基) 丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{13}C NMR 光谱。

[0059] 图 16A 是化合物二丁酸 (S)-3-(4-(2-(4-((S)-2-(丁酰氧基)-3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{1}H NMR 光谱。

[0060] 图 16B 是化合物二丁酸 (S)-3-(4-(2-(4-((S)-2-(丁酰氧基)-3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^{13}C NMR 光谱。

[0061] 详述

[0062] I. 定义

[0063] 在下列描述中,为了提供对各种实施方案的彻底理解阐述某些具体细节。然而,本领域技术人员应理解,本公开可在没有这细节下实践。在其它情况下,未示出或未详细描述熟知结构以避免不必要地模糊实施方案的描述。除非上下文另有需要,否则在下面的说明书和权利要求中,词语“包含 (comprise)”及其变型诸如“包含 (comprises)”和“包含 (comprising)”应以开放的包含性意义被解释,即为“包括但不限于”。此外,本文提供的标题仅出于方便的目的并且不解释公开的权利要求的范围或含义。

[0064] 在整篇说明书中参考“一个实施方案”或“实施方案”意指在至少一个实施方案中

包括结合实施方案描述的特定特征、结构或特性。因此，在整篇说明书中的各个地方出现的短语“在一个实施方案中”或“在实施方案中”不一定都是指相同的实施方案。此外，特定特征、结构、或特性可以任何适合的方式在一个或多个实施方案中组合。同样，如在本说明书和所附权利要求中使用，单数形式“一个 / 种 (a)”、“一个 / 种 (an)”和“该 (the)”包括复数指示物，除非上下文另有明确指示。也应认识到，除非上下文另有明确指明，否则术语“或”一般以其含义使用，包括“和 / 或”。

[0065] 除非另有指示，否则本文所使用的以下术语具有下列含义：

[0066] “氨基”是指 $-NH_2$基团。

[0067] “氰基”是指 -CN 基团。

[0068] “羟基”或“羟基”是指 -OH 基团。

[0069] “亚氨基”是指＝ NH 取代基。

[0070] “硝基”是指 $-NO_2$基团。

[0071] “氧代基”是指＝ O 取代基。

[0072] “硫代基”是指＝ S 取代基。

[0073] “烷基”是指直链、支链或非芳族环状烃（“环烷基”）链基团，其为饱和的或不饱和的（即，含有一个或多个双键和 / 或三键），具有一至二十个碳原子（例如，一个至是个、或一个至六个碳原子），并且其通过单键连接至分子的其余部分。包括包含 1 至 20 的任何数量的碳原子的烷基。包含至多 10 个碳原子的烷基是 C_1-C_{10}烷基。C_1-C_{10}烷基包括 C_{10}烷基、C_9烷基、C_8烷基、C_7烷基、C_6烷基、C_5烷基、C_4烷基、C_3烷基、C_2烷基和 C_1烷基（即，甲基）并且包括，例如但不限于，饱和 C_1-C_{10}烷基、C_2-C_{10}烯基和 C_2-C_{10}炔基。饱和 C_1-C_{10}烷基的非限制性实例包括甲基、乙基、正丙基、异丙基、仲丙基、正丁基、异丁基、种丁基、叔丁基和正戊基、正己基、正庚烷等。C_2-C_{10}烯基的非限制性实例包括乙烯基、烯丙基、异丙烯基、1- 丙烯 -2- 基、1- 丁烯 -1- 基、1- 丁烯 -2- 基、1- 丁烯 -3- 基、2- 丁烯 -1- 基、2- 丁烯 -2- 基、戊烯基、己烯基等。C_2-C_{10}炔基的非限制性实例包括乙炔基、丙炔基、丁炔基、戊炔基、己炔基等。除非在说明书中另有明确指明，否则烷基可任选地被取代（即，烷基中的氢原子可被任选的取代基取代）。烷基包括如下定义的环烷基。

[0074] “亚烷基”或“亚烷基链”是指仅由碳和氢组成的将分子的其余部分与该基团的直链或支链二价烃链，其为饱和的或不饱和的（即，含有一个或多个双键和 / 或三键），且具有一至二十个碳原子，例如，亚甲基、亚乙基、亚丙基、亚正丁基、亚乙烯基、亚丙烯基、亚正丁烯基、亚丙炔基、亚正丁炔基等。亚烷基链通过单键或双键连接至分子的其余部分并且通过单键或双键连接至该基团。亚烷基链与分子的其余部分和该基团的连接点可以是通过链内的一个碳或任意两个碳。除非在说明书中另有明确指明，否则亚烷基链可任选地被取代。

[0075] “脂族碳”是指非芳族的碳原子。

[0076] “烷基氨基羰基”是指式 $-C(=O)NR_aR_b$的基团，其中 R_a和 R_b各自独立地为含有一至二十个碳原子的上文定义的的烷基。除非在说明书中另有明确指明，否则烷基氨基羰基可任选地被取代。

[0077] “烷基羰基”是指式 $-C(=O)R_a$的基团，其中 R_a为含有一至二十个碳原子的上文定义的烷基。除非在说明书中另有明确指明，否则烷基羰基可任选地被取代。

[0078] “烷氧基”是指式 $-OR_a$的基团，其中 R_a为含有一至二十个碳原子的上文定义的烷

基。除非在说明书中另有明确指明，否则烷氧基可任选地被取代。

[0079] “烷基氨基”是指式 -NHR$_a$或 -NR $_a$R$_a$的基团，其中每个 R $_a$独立地为含有一至二十个碳原子的上文定义的烷基。除非在说明书中另有明确指明，否则烷基氨基可任选地被取代。

[0080] “氨基羰基”是指式 -C(= O)NH$_2$的基团。除非在说明书中另有明确指明，否则烷基羰基可任选地被取代。

[0081] “芳族碳”是指为芳族环的一部分的碳原子。芳族碳为 SP^{2}杂化的且来自在 pi 轨道中具有 4n+2 个电子的共轭的不饱和环系统的一部分。例如，芳族碳可以是本文所定义的芳基或杂芳基环上的成员。

[0082] “芳基”是指包含氢、6 至 18 个碳原子和至少一个芳族环的烃环系统基团。为了本公开的目的，芳基可以为单环、双环、三环或四环状环系统，其可以包括稠环或桥环系统。芳基包括，但不限于，芳基源自醋蒽烯、苊烯、醋菲烯、蒽、蒽、苯、□、荧蒽、芴、不对称引达省、对称引达省、茚满、茚、萘、非那烯、菲、七曜烯、苉和苯并菲。除非在说明书中另有明确指明，否则术语“芳基”或前缀“ar- “（诸如在“芳烷基”中）意在包括任选取代的芳基。

[0083] “芳烷基”是指式 -R$_b$-R$_c$的基团，其中 R $_b$为上文定义的亚烷基链且 R $_c$为上文定义的一个或多个芳基，例如，苄基、二苯基甲基等。除非在说明书中另有明确指明，否则芳烷基可任选地被取代。

[0084] “碳环”是指环状结构，其中形成环的键为各个碳 - 碳键。碳环一般在环内含有 3 至 20 个碳原子并且可以为单环、二环或三环状。二环和三环状碳环可以是稠合的（即，共享一个多两个共用碳原子），螺接的（即，共享一个共用碳原子）或者经由一个或两个接头原子连接的。碳环包括如本文所定义的环烷基和芳基。除非在说明书中另有明确指明，否则碳环基可任选地被取代。

[0085] “环烷基”是指仅由碳和氢原子组成的稳定的非芳族单环或多环烃基，其可以包括稠环或桥环系统，具有三至十五个碳原子，优选具有三至十个碳原子，且为饱和的或不饱和的，通过单键连接至分子的其余部分。单环基团包括，例如，环丙基、环丁基、环戊基、环己基、环庚基和环辛基。多环基团包括，例如，金刚烷基、降冰片基、十氢萘基、7,7- 二甲基 - 二环 [2.2.1] 庚烷基等。除非在说明书中另有明确说明，否则环烷基可任选地被取代。

[0086] “氘化烷基”是指上文定义的烷基，其中氢原子中的至少一个被氘原子取代。除非在说明书中另有明确指明，否则氘化烷基可任选地被取代。

[0087] “稠合”是指与本公开化合物中的现有环结构稠合的本文所述的任何环结构。当稠环为杂环基环或杂芳基环时，现有环结构上的任何碳原子变成稠合的杂环基环或稠合的杂芳基环的一部分，可被氮原子取代。

[0088] “卤素”或“卤代”是指氟 (F)、氯 (Cl)、溴 (Br) 和碘 (I) 取代基。卤素取代基也包括卤素放射性同位素。

[0089] “卤代烷基”是指上文定义的的烷基，其被一个或多个上文定义的卤代取代，例如，三氟甲基、二氟甲基、三氯甲基、2,2,2- 三氟乙基、1,2- 二氟乙基、3- 溴 -2- 氟丙基、1,2- 二溴乙基等。除非在说明书中另有明确指明，否则卤代烷基可任选地被取代。

[0090] “杂环基”或“杂环”是指稳定的 3- 至 18- 元环基团，其由二至十二个碳原子和一至六个选自氮、氧和硫的杂原子组成。除非在说明书中另有明确指明，否则杂环基可以为单环、双环、三环或四环状环系统，其可以包括稠环或桥环系统；并且杂环基中的氮、碳或硫

原子可任选地被氧化；氮原子可任选地被季铵化；并且杂环基可为部分或完全饱和的。此类杂环基的实例包括，但不限于，二氧戊环基、噻吩基 [1,3] 二噻烷基、十氢异喹啉基、咪唑啉基、咪唑烷基、异噻唑烷基、异噁唑烷基、吗啉基、八氢吲哚基、八氢异吲哚基、2- 氧代哌嗪基、2- 氧代哌啶基、2- 氧代吡咯烷基、噁唑烷基、哌啶基、哌嗪基、4- 哌啶酮基、吡咯烷基、吡唑烷基、奎宁环基、噻唑烷基、四氢呋喃基、三噻烷基、四氢吡喃基、硫代吗啉基、硫吗啉基、1- 氧代 - 硫代吗啉基和 1,1- 二氧代 - 硫代吗啉基。除非在说明书中另有明确指明，否则杂环基可任选地被包括如下定义的杂芳基的杂环取代。

[0091] “杂芳基”是指包含氢原子、一至十三个碳原子、一个六个选自氮、氧和硫的杂原子，和至少一个芳族环的 5- 至 14- 元环系统基团。为了本公开的目的，杂芳基可以为单环、双环、三环或四环状环系统，其可以包括稠环或桥环系统；并且杂芳基中的氮、碳或硫原子可任选地被氧化；氮原子可任选地被季铵化。实例包括，但不限于，氮杂䓬基、吖啶基、苯并咪唑基、苯并噻唑基、苯并吲哚基、苯并二氧杂环戊烯基、苯并呋喃基、苯并噁唑基、苯并噻唑基、苯并噻二唑基、苯并 [b][1,4] 二氧杂䓬基、1,4- 苯并二噁烷基、苯并萘并呋喃基、苯并噁唑基、苯并二氧杂环戊烯基、苯并二氧杂环己二烯基、苯并吡喃基、苯并吡喃酮基、苯并呋喃基、苯并呋喃酮基、苯并噻吩基（苯并噻吩基）、苯并三唑基、苯并 [4,6] 咪唑并 [1,2-a] 吡啶基、咔唑基、噌啉基、二苯并呋喃基、二苯并噻吩基、呋喃基、呋喃酮基、异噻唑基、咪唑基、吲唑基、吲哚基、吲唑基、异吲哚基、吲哚啉基、异吲哚啉基、异喹啉基、吲哚啉基、异噁唑基、萘啶基、噁二唑基、2- 氧氮杂䓬、噁唑基、环氧乙烷基、1- 氧代吡啶基、1- 氧代嘧啶基、1- 氧代吡嗪基、1- 氧代哒嗪基、1- 苯基 -1H- 吡咯基、吩嗪基、吩噻嗪基、吩噁嗪基、酞嗪基、蝶啶基、嘌呤基、吡咯基、吡唑基、吡啶基、吡嗪基、嘧啶基、哒嗪基、喹唑啉基、喹喔啉基、喹啉基、奎宁环基、异喹啉基、四氢喹啉基、噻唑基、噻二唑基、三唑基、四唑基、三嗪基和噻吩基（即噻吩基）。除非在说明书中另有明确指明，否则杂芳基可任选地被取代。

[0092] 本文所使用的术语“取代的”意指其中至少一个氢原子被连接至非氢原子的键取代的任何上述基团（即，烷基、亚烷基、烷基氨基羰基、烷基羰基、烷氧基、烷基氨基、氨基羰基、环烷基、芳基、芳烷基、碳环、氘化烷基、卤代烷基、杂环基、和 / 或杂芳基），所述非氢原子诸如，但不限于：卤素原子诸如 F、Cl、Br 和 I；诸如羟基、烷氧基和酯基的基团中的氧原子；诸如巯基、硫代烷基、砜基、磺酰基和亚砜基的基团中的硫原子；诸如胺、酰胺、烷基胺、二烷基胺、芳基胺、烷基芳基胺、二芳基胺、N- 氧化物、亚酰胺、甘氨酸和烯胺的基团中的氮原子；诸如三烷基甲硅烷基、二烷基芳基甲硅烷基、烷基二芳基甲硅烷基和三芳基甲硅烷基中的硅原子；和各种其它基团中的其它杂原子。“取代的”也意指其中一个或多个氢原子被高级键（例如，双键或三键）取代成杂原子的任何上述基团，所述杂原子诸如氧代基（即，C = O）、羰基、羧基和酯基中的氧；以及诸如亚胺、肟、腙和腈的基团中的氮。

[0093] 例如，“取代的”包括其中一个或多个氢原子被 $-NR_gR_h$、$-NR_gC(=O)R_h$、$-NR_gC(=O)NR_gR_h$、$-NR_gC(=O)OR_h$、$-NR_gSO_2R_h$、$-OC(=O)NR_gR_h$、$-OR_g$、$-SR_g$、$-SOR_g$、$-SO_2R_g$、$-OSO_2R_g$、$-SO_2OR_g$、$=NSO_2R_g$ 和 $-SO_2NR_gR_h$ 取代的任何上述基团。

[0094] “取代的也意指意指其中一个或多个氢原子被 $-C(=O)R_g$、$-C(=O)OR_g$、$-C(=O)NR_gR_h$、$-CH_2SO_2R_g$、$-CH_2SO_2NR_gR_h$ 取代的任何上述基团。在前述中，R_g 和 R_h 相同或不同且独立地为氢、烷基、烷氧基、烷基氨基、硫代烷基、芳基、芳烷基、环烷基、环烷基烷基、卤代烷基、杂环基、N- 杂环基、杂环基烷基、杂芳基、N- 杂芳基和 / 或杂芳基烷基。

[0095] “取代的”还意指其中一个或多个氢原子被连接至氨基、氰基、羟基、亚氨基、硝基、氧代基、硫代基、卤代、烷基、烷氧基、烷基氨基、硫代烷基、芳基、芳烷基、环烷基、环烷基烷基、卤代烷基、杂环基、N- 杂环基、杂环基烷基、杂芳基、N- 杂芳基和 / 或杂芳基烷基的键取代的任何上述基团。此外，每个前述取代基也可任选地被一个或多个上述取代基取代。

[0096] “前药”意在指示可在生理条件下或通过溶剂分解转化为生物活性化合物的化合物。因此，术语“前药”是指本公开化合物的代谢前体，其为药学上可接受的。前药当向需要其的受试者施用时可以为活性或无活性的，但在体内转化成活性（或更具活性的）化合物。前药通常在体内快速转化以产生母体化合物，例如通过在血液中的水解。前药化合物经常提供在哺乳动物生物体中的溶解性、组织相容性或延迟释放的优点（参见，Bundgard，H.，Design of Prodrugs(1985)，第 7-9 页，21-24(Elsevier，Amsterdam)）。对前药的讨论于 Higuchi，T. 等人，A.C.S.Symposium Series，第 14 卷，和于 Bioreversible Carriers in Drug Design，编者 Edward B.Roche，American Pharmaceutical Association and Pergamon Press，1987 中提供。本公开意在涵盖所有结构 I 化合物，不论作为前药还是活性化合物自身、或两者起作用。

[0097] 本文公开的本公开也意指涵盖通过含有一个或多个被具有不同原子质量或质量数的原子取代的原子而被同位素标记的所有药学上可接受的结构 (I) 的化合物。可掺入公开的化合物的同位素的实例包括氢、碳、氮、氧、磷、氟、氯和碘的同位素，诸如分别为 ^{2}H、^{3}H、^{11}C、^{13}C、^{14}C、^{13}N、^{15}N、^{15}O、^{17}O、^{18}O、^{31}P、^{32}P、^{35}S、^{18}F、^{36}Cl、^{123}I 和 ^{125}I。同位素标记的这些化合物可用于通过表征例如作用位点或模式、或对药理学上重要的作用位点的结合亲和力来帮助确定或测量化合物的有效性。某些同位素标记的结构 (I) 化合物，例如，掺入放射性同位素的那些，可用于药物和 / 或底物组织分布研究。放射性同位素氚即 ^{3}H 和碳 -14 即 ^{14}C 鉴于它们掺入的容易性和迅速的检测方式可特别用于该目的，。

[0098] 被较重的同位素诸如氘即 ^{2}H 取代可提供由较高的代谢稳定性产生的某些治疗优势（例如增加的体内半衰期或减少的剂量需求），且因此在一些情况下可以是优选的。

[0099] 被正电子发射同位素诸如 ^{11}C、^{18}F、^{15}O、I^{123}和 ^{13}N 取代可用于正电子发射拓扑学 (PET) 或单电子发射计算机断层摄影术 (SPECT) 研究，以用于检查底物受体占有率。同位素标记的结构 (I) 的化合物一般可通过本领域技术人员已知的常规技术或通过与下面列出的制备例和实施例中描述的那些程序类似的程序使用适当的同位素标记的试剂代替先前采用的未标记的试剂来制备。

[0100] 本文公开的本公开也意图涵盖公开的化合物的体内代谢产物。此类产物可由例如所施用的化合物的氧化、还原、水解、酰胺化、酯化等产生，主要由于酶促过程。因此，本公开包括通过包括本公开化合物向哺乳动物施用足以产生其代谢产物的时间段的方法生成的化合物。通常，通过向动物诸如大鼠、小鼠、豚鼠、猴或向人以可检测的剂量施用放射性标记的本公开化合物，允许足够的时间以使代谢发生以及从尿液、血液或其它生物样品中分离其转化产物来对此类产物进行鉴定。

[0101] “稳定的化合物”和“稳定的结构”意在指示化合物足够鲁棒以承受从反应混合物中分离至可用的纯度以及配制成有效的治疗剂。

[0102] “哺乳动物”包括人和家养动物诸如实验室动物和家庭宠物（例如，猫、狗、猪、牛、绵羊、山羊、马、兔）、以及非家养动物诸如野生动物等二者。

[0103] “任选的”或“任选地”意指随后描述的事件或情形可能发生或可能不发生，并且该描述包括所述事件或情形发生的例子和所述事件或情形不发生的例子。例如，“任选取代的芳基”意指芳基可以被取代或可以不被取代，并且该描述包括取代的芳基和未取代的芳基二者。

[0104] “药学上可接受的载体、稀释剂或赋形剂”包括但不限于已被美国食品药品监督局批准为可接受地用于人或家养动物的任何佐剂、载体、赋形剂、助流剂、增甜剂、稀释剂、防腐剂、染料 / 着色剂、增味剂 (flavor enhancer)、表面活性剂、润湿剂、分散剂、悬浮剂、稳定剂、等渗剂、溶剂或乳化剂。

[0105] “药学上可接受的盐”包括酸式和碱式加成盐二者。

[0106] “药学上可接受的酸加成盐”是指保持游离碱的生物学效能和性质的那些盐，其在生物学或其它方面不是不合需要的并且与无机酸和有机酸形成，所述无机酸诸如但不限于，盐酸、氢溴酸、硫酸、硝酸、磷酸等，而所述有机酸诸如但不限于，乙酸、2,2- 二氯乙酸、己二酸、藻酸、抗坏血酸、天冬氨酸、苯磺酸、苯甲酸、4- 乙酰胺基苯甲酸、樟脑酸、樟脑 -10- 磺酸、癸酸、己酸、辛酸、碳酸、肉桂酸、柠檬酸、环己氨磺酸 (cyclamic acid)、十二烷基硫酸、乙烷 -1,2- 二磺酸、乙磺酸、2- 羟基乙磺酸、甲酸、富马酸、半乳糖二酸、龙胆酸、葡庚糖酸、葡糖酸、葡糖醛酸、谷氨酸、戊二酸、2- 氧代 - 戊二酸、甘油磷酸、乙醇酸、马尿酸、异丁酸、乳酸、乳糖酸、月桂酸、马来酸、苹果酸、丙二酸、扁桃酸、甲磺酸、粘酸、萘 -1,5- 二磺酸、萘 -2- 磺酸、1- 羟基 -2- 萘甲酸、烟酸、油酸、乳清酸、草酸、棕榈酸、扑酸、丙酸、焦谷氨酸、丙酮酸、水杨酸、4- 氨基水杨酸、癸二酸、硬脂酸、琥珀酸、酒石酸、硫氰酸、对甲苯磺酸、三氟乙酸、十一碳烯酸等。

[0107] “药学上可接受的碱加成盐”是指保持游离酸的生物学效能和性质的那些盐，其在生物学或其它方面不是不合需要的。这些盐可以通过向游离酸加入无机碱或有机碱而制备。衍生自无机碱的盐包括但不限于，钠、钾、锂、铵、钙、镁、铁、锌、铜、锰、铝盐等。优选的无机盐为铵、钠、钾、钙和镁盐。衍生自有机碱的盐包括但不限于，下列有机碱的盐 :伯胺、仲胺和叔胺、取代的胺 (包括天然存在的取代的胺)、环胺和碱性离子交换树脂，诸如氨、异丙胺、三甲胺、二乙胺、三乙胺、三丙胺、二乙醇胺、乙醇胺、二乙醇胺、2- 二甲基氨基乙醇、2- 二乙基氨基乙醇、二环己基胺、赖氨酸、精氨酸、组氨酸、咖啡因、普鲁卡因、哈胺、胆碱、甜菜碱、苯乙苄胺 (benethamine)、苄星青霉素、乙二胺、氨基葡萄糖、甲基葡糖胺、可可碱、三乙醇胺、氨丁三醇、嘌呤、哌嗪、哌啶、N- 乙基哌啶、聚胺树脂等。特别是优选的有机碱为异丙胺、二乙胺、乙醇胺、三甲胺、二环己基胺、胆碱和咖啡因。

[0108] 结晶通常能够产生本公开化合物的溶剂化物。本文所使用的术语“溶剂化物”是指含有一个或多个本公开化合物分子以及一个或多个溶剂分子的聚集体。溶剂可以是水，在这种情况下，溶剂化物为水合物。可选地，溶剂可以是有机溶剂。因此，本公开化合物可以以水合物存在，包括单水合物、二水合物、半水合物、倍五水合物、三水合物、四水合物等，也可以以相应的溶剂化形式存在。本公开化合物可以是纯的溶剂化物，而在其它情况下，本公开化合物可以仅仅保留不定的水，或者是水加上某些不定溶剂的混合物。

[0109] “药物组合物”是指本公开化合物和用于将生物活性化合物递送到哺乳动物例如人中的本领域中通常可接受的介质的制剂。此类介质包括所有药学上可接受的载体、稀释剂或赋形剂。

[0110] “有效量”是指治疗有效量或预防有效量。“治疗有效量”是指在所需剂量下和所需时间段内有效获得所需治疗结果（如减小的肿瘤尺寸、增加的寿命或增加的预期寿命）的量。化合物的治疗有效量可以根据诸如以下因素改变：受试者的疾病状态、年龄、性别和重量，和化合物在受试者中引发所需反应的能力。剂量给药方案可以进行调整以提供最佳的治疗反应。治疗有效量也是其中化合物的任何毒性或有害作用被治疗有益作用超过的量。

[0111] “预防有效量”是指在所需剂量下和所需时间段内有效获得所需预防结果（诸如较小的肿瘤、增加的寿命、增加的预期寿命或防止前列腺癌向雄激素非依赖性形式进展）的量。典型地，在疾病之前或疾病早期在受试者中使用预防剂量，因此预防有效量可以少于治疗有效量。

[0112] 本文所使用的“治疗”包括在具有关注的疾病或疾患的哺乳动物（优选人）中治疗关注的疾病或疾患，并且包括：

[0113] (i) 预防疾病或疾患在哺乳动物中发生，特别是当此类哺乳动物易患所述疾患但还未诊断出时；

[0114] (ii) 抑制疾病或疾患，即，阻止其发展；

[0115] (iii) 减轻疾病或疾患，即，引起疾病或疾患退化；或

[0116] (iv) 减轻由疾病或疾患产生的症状，即，减轻疼痛但不解决根本的疾病或疾患。本文所使用的术语“疾病”和“疾患”可交换使用或可以不同，因为特定的疾病或疾患可能不具有已知的致病物（以使病因尚未确定），因而其尚未确认为疾病，而是仅仅视为不希望的疾患或综合征，其中临床医师已鉴定出或多或少的一组具体症状。

[0117] 本公开化合物、或其药学上可接受的盐可含有一个或多个不对称中心并且可由此产生对映异构体、非对映异构体和其它立体异构形式，根据绝对立体化学的观点，它们可被定义为 (R)- 或 (S)- 或 (D)- 或 (L)-（就氨基酸而言）。本公开意在包括所有此类可能的异构体、以及它们的外消旋和光学纯形式。

[0118] 光学活性 (+) 和 (-)、(R)- 和 (S)-、或 (D)- 和 (L)- 异构体可使用手性合成子或手性试剂制备，或使用常规技术例如色谱和分步结晶进行拆分。用于制备 / 分离个别对映异构体的常规技术包括从适合的光学纯前体进行手性合成或使用例如手性高效液相色谱 (HPLC) 拆分外消旋体（或盐或衍生物的外消旋体）。当本文所述的化合物含有烯属双键或其它几何不对称中心时，且除非另有说明，否则该化合物意在包括 E 和 Z 几何异构体二者。同样，也意图包括所有互变异构形式。

[0119] “立体异构体”是指由通过相同键结合的相同原子组成的但是具有不同的三维结构的化合物，它们是不可互换的。本发明设想各种立体异构体及其混合物，包括“对映异构体”，它是指两种立体异构体，它们的分子彼此为不重叠的镜像。

[0120] “互变异构体”是指质子从分子的一个原子至同一分子的另一原子的迁移，伴有单键和相邻双键的切换。本公开包括任何所述化合物的互变异构体。

[0121] 本文所使用的化学命名方案和结构图是使用 ACD/Name 第 9.07 版软件程序和 / 或 ChemDraw Ultra 第 11.0.1 版软件命名程序 (CambridgeSoft) 的 I.U.P.A.C. 命名系统的改进形式，其中本公开化合物在本文被命名为中心核结构的衍生物。对于本文采用的复杂化学名，在所连接的基团之前命名取代基。例如，环丙基乙基包含具有环丙基取代基的乙基骨架。除下面所述的之外，本文的化学结构图中的所有键均被鉴定，而一些碳原子例外，因为

它们被假定与足够的氢原子键合以完成化合价。

[0122] 本文所使用的符号“  ”(在下文可被称为“连接键的点”)表示为两个化学实体之间的连接点的键,其中一个化学实体被描绘成连接至连接键的点,而另一个化学实体未被描绘成连接至连接键的点。

[0123] 例如,“  ”表示化学实体“XY”经由连接键的点与另一个化学实体键合。此外,未描述的化学实体的具体连接点可通过推断来指定。

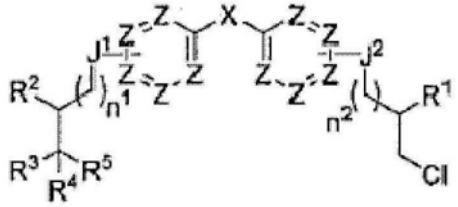
[0124] 例如,其中 R^3 为 H 或“  ”的化合物 CH_3-R^3 推断当 R^3 为“XY”时,连接键的点是与 R^3 被描绘成与 CH_3 键合的键相同的键。

[0125] II. 化合物和组合物

[0126] 如上所述,本公开的某些实施方案涉及化合物可用于调节雄激素受体。因而,所述化合物具有用于治疗各种癌症(包括各种类型的前列腺癌)的效用。期望本文所述的酯衍生物相对于其它不含所述的酯部分的已知雄激素受体调节剂具有改善的性质。

[0127] 因此,本公开的一个实施方案涉及具有结构 I 的结构的化合物:

[0128]



(I)

[0129] 或其药学上可接受的盐、互变异构体或立体异构体,其中:

[0130] J^1 和 J^2 各自独立地为 -O-、-S(O)$_m$-、-NR^6- 或 -(CR^6R^7)-;

[0131] X 为直接键、-C(R^8R^9)-、-C(=CR^8R^9)-、-C(R^8R^9)- 芳基 -C(R^8R^9)-、-C(=CR^8R^9)- 芳基 -C(=CR^8R^9)-、-C(=CR^8R^9)- 芳基 -C(R^8R^9)-、-C(R^8R^9)- 芳基 -C(=CR^8R^9)-、-O-、-S(O)$_m$-、-N(R^6)-、-CH(NR^6R^7)-、-C(=NOR^6)-、-C(=N-NHR^{10})-、-C(=NR^6)- 或 -C(=O)-;

[0132] Z 在每次出现时独立地为 -C(R^{11})- 或 -N-;

[0133] R^1 为羟基、-OR^{12} 或 -OC(=O)R^{13};

[0134] R^2 和 R^3 各自独立地为羟基、卤代、-OR^{12} 或 -OC(=O)R^{13};

[0135] R^4 和 R^5 各自独立地为 H 或卤代;

[0136] R^6 和 R^7 在每次出现时独立地为 H 或 C_{1-10} 烷基;

[0137] R^8 和 R^9 在每次出现时独立地为 H、羟基、卤代、C_1-C_{10} 烷基、C_1-C_{10} 卤代烷基、C_1-C_{10} 氘化烷基、C_1-C_{10} 烷氧基、芳基、芳烷基、-S(O)$_m$$R^{14}$ 或 -NR^6R^7,或 R^8 和 R^9 可联接以形成含有 3 至 20 个碳原子的单环、二环或三环碳环或杂环;

[0138] R^{10} 为 H、C_1-C_{10} 烷基、芳基、氨基羰基、C_1-C_{10} 烷基羰基或 C_1-C_{10} 烷基氨基羰基;

[0139] R^{11} 在每次出现时独立地为 H、卤代或 C_1-C_{10} 烷基;

[0140] R^{12} 在每次出现时独立地为 C_1-C_{20} 烷基或 C_2-C_{20} 烯基;

[0141] R^{13}在每次出现时独立地为C_1-C_{20}烷基、C_2-C_{20}烯基、芳基或芳烷基，其中所述C_1-C_{20}烷基不包括任选的氨基或烷基氨基取代基并且C_1-C_{20}烷基、C_2-C_{20}烯基或芳烷基中的每个脂族碳可任选地被 -O- 或 $-S(O)_m-$ 取代；

[0142] R^{14}为 H、C_1-C_{10}烷基或芳基；

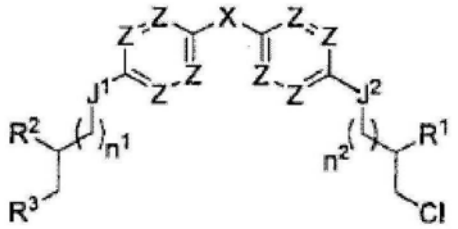
[0143] m 在每次出现时独立地为 0、1 或 2；

[0144] n^1和 n^2各自独立地为 0、1、2、3、4 或 5，

[0145] 其中 R^1、R^2或 R^3中的至少一个为 $-OC(=O)R^{13}$。

[0146] 在其它实施方案中，所述化合物具有下列结构（Ia）：

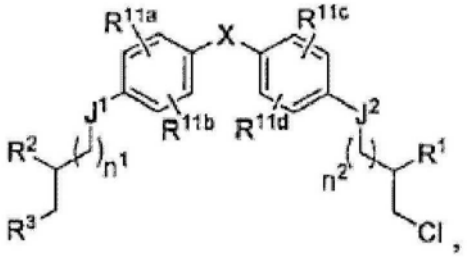
[0147]



(Ia)

[0148] 在又其它实施方案中，所述化合物具有下列结构（Ib）：

[0149]



(Ib)

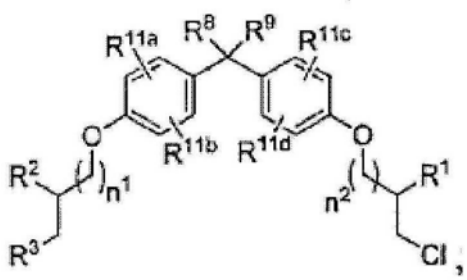
[0150] 其中 R^{11a}、R^{11b}、R^{11c}和 R^{11d}各自独立地为 H、卤代或 C_1-C_{10}烷基。

[0151] 在任何前述实施方案中，J^1和 J^2各自为 -O-。

[0152] 在任何前述实施方案的其它实施方案中，X 为 $-C(R^8R^9)-$。

[0153] 在任何前述实施方案的又其它实施方案中，所述化合物具有下列结构（Ic）：

[0154]

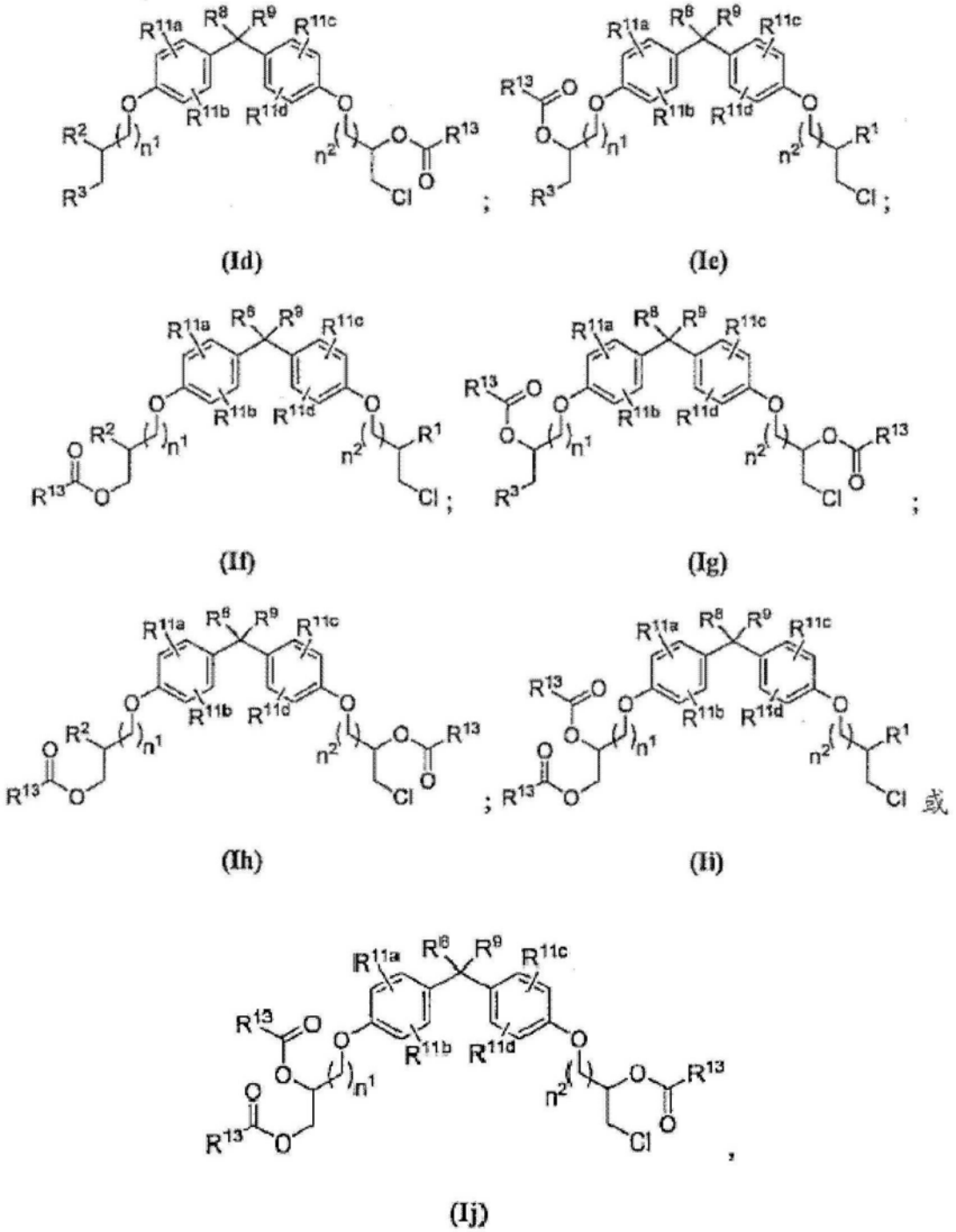


(Ic)

[0155] 其中 R^{11a}、R^{11b}、R^{11c}和 R^{11d}各自独立地为 H、卤代或 C_1-C_{10}烷基。

[0156] 在前述实施方案的再其它实施方案中，所述化合物具有下列结构(Id)、(Ie)、(If)、(Ig)、(Ih)、(Ii)或(Ij)之一：

[0157]



(Id) (Ie)

(If) (Ig)

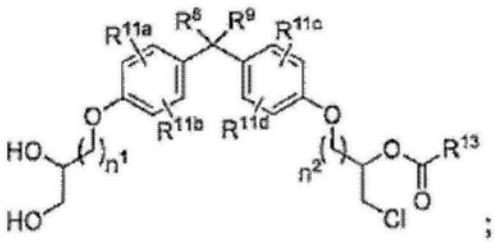
(Ih) (Ii)

(Ij)

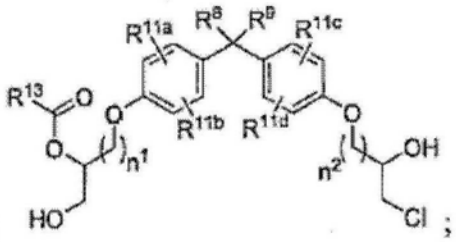
[0158] 其中R^{11a}、R^{11b}、R^{11c}和R^{11d}各自独立地为H、卤代或C_1-C_{10}烷基。

[0159] 在前述实施方案的又更多实施方案中，所述化合物具有下列结构(Ik)、(Il)、(Im)、(In)、(Io)或(Ip)之一：

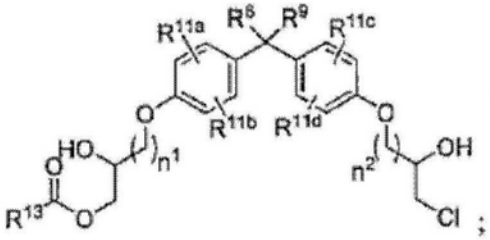
[0160]



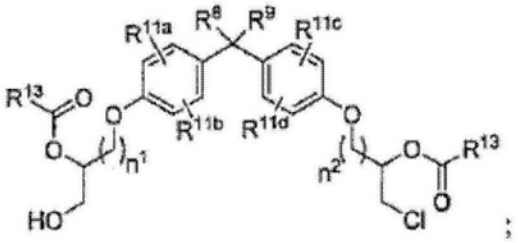
(Ik)



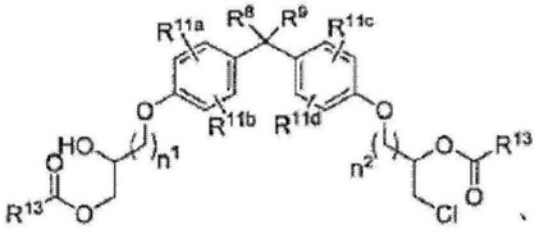
(Il)



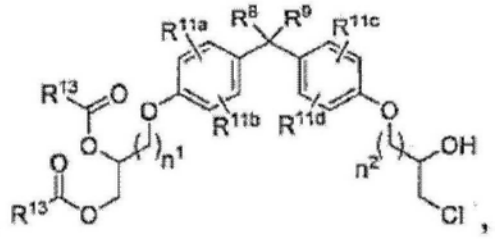
(Im)



(In)



(Io)

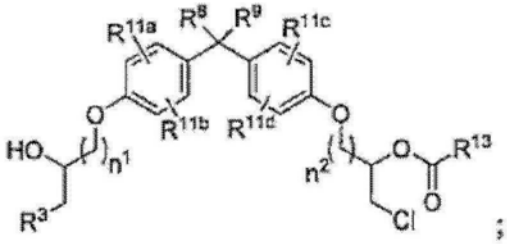


(Ip)

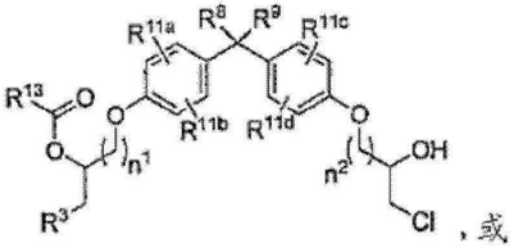
[0161] 其中 R^{11a}、R^{11b}、R^{11c}和 R^{11d}各自独立地为 H、卤代或 C_1-C_{10}烷基。

[0162] 在任何前述的其它实施方案中，所述化合物具有下列结构 (Iq)、(Ir) 或 (Is) 之一：

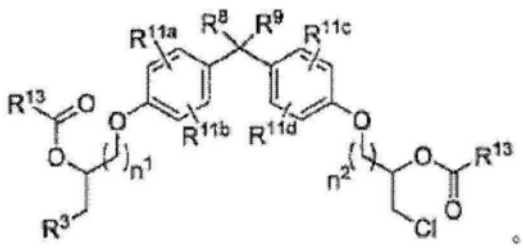
[0163]



(Iq)



(Ir)



(Is)

[0164] 在前述的一些实施方案中，R^3为-OR^{12}。例如，在一些实施方案中，R^{12}为C_1-C_6烷基。在其它实施方案中，R^{12}为甲基、异丙基或正丁基。

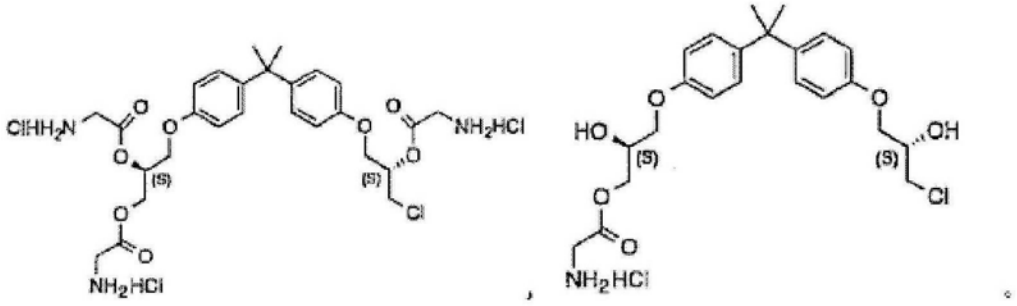
[0165] 在任何前述的又其它实施方案中，R^3为卤代。例如，在一些实施方案中，R^3为氟。

[0166] 在某些实施方案中，所述化合物包括至少一个烷基酯。因此，在一些实施方案中每个R^{13}独立地为C_1-C_{20}烷基、例如C_1-C_6烷基。在这些实施方案的一些中，C_1-C_{20}或C_1-C_6烷基是未被取代的。在一些进一步的实施方案中，每个R^{13}独立地为甲基、乙基或丙基。在更进一步的实施方案中，每个R^{13}为甲基。

[0167] 在另外其它实施方案中，R^{13}是被取代的。例如，在某些实施方案中，R^{13}为取代的C_1-C_{20}烷基或取代的C_1-C_6烷基。在特定实施方案中，R^{13}取代的烷基包含氮取代基。在一方面，氮取代的R^{13}烷基为甲基，其与相邻羰基一起形成甘氨酸取代基。在特定方面中，所述R^{13}取代的烷基为具有氮和末端氯的甲基，即NH_2HCl。

[0168] 在特定实施方案中，具有末端氯的所述甘氨酸取代的化合物如下：

[0169]



[0170] 在任何前述的结构I化合物的更多实施方案中，R^8和R^9各自独立地为C_1-C_6烷基。例如，在一些实施方案中R^8和R^9各自为甲基。

[0171] 在任何前述的结构I化合物的又其它实施方案中，至少一个R^{11}为H或R^{11a}、R^{11b}、R^{11c}或R^{11d}中的至少一个为H。例如，在一些实施方案中每个R^{11}为H或R^{11a}、R^{11b}、R^{11c}和R^{11d}中的每一个为H。

[0172] 在前述的更多实施方案中，n^1或n^2中的至少一个为1。在前述的其它实施方案中，n^1和n^2各自为1。在一些实施方案中，n^1为2。在一些实施方案中，n^1为3。在一些实施方案中，n^1为4。在一些实施方案中，n^1为2。在一些实施方案中，n^2为2。在一些实施方案中，n^1为3。在一些实施方案中，n^1为4。在一些实施方案中，n^1为5。

[0173] 在其它实施方案中，R^4和R^5各自为H。在一些不同实施方案中，R^4或R^5中的至少一个为卤代。例如，在一些实施方案中R^4和R^5各自为卤代。在这些前述实施方案的一些中，卤代为氟。

[0174] 在前述实施方案的一些中，R^{13}为C_1-C_{20}烷基、C_2-C_{20}烯基或芳烷基，并且C_1-C_{20}烷基、C_2-C_{20}烯基或芳烷基中的至少一个脂族碳被取代基取代。例如，所述取代基可选自羟基、卤代、氧代基和烷氧基。在其它实施方案中，C_1-C_{20}烷基、C_2-C_{20}烯基或芳烷基是未被取代的。

[0175] 在一些其它实施方案中，R^{13}为芳基或芳烷基，芳基或芳烷基中的至少一个芳族碳被取代基取代。例如，在一些实施方案中，所述取代基选自羟基、卤代和烷氧基。在其它实施方案中，芳基或芳烷基是未被取代的。

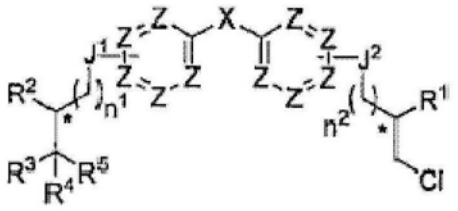
[0176] 本文所述的化合物意在包括所有外消旋混合物和所有个别对映异构体或其组合，

不管它们是否在本文明确描绘。因此，所述化合物包括任何本文所述的化合物的外消旋混合物、对映异构体和非对映异构体。任何结构 I 化合物的互变异构体也包括本公开的范围之内。

[0177] 如上指出，本公开化合物（即，结构 1 化合物）可含有一个或多个不对称中心。因此，在一些实施方案中，所述化合物为不同对映异构体（例如，R 和 S）或不同非对映异构体的混合物。在其它实施方案中，所述化合物为纯（或富集的）对映异构体或非对映异构体。为了清楚的目的，不总在化合物中描绘手性碳；然而，本公开包括所有结构 I 化合物的所有立体异构体（纯的和混合物）。

[0178] 作为实例，结构 I 化合物含有下面用 * 标记的至少两个立体中心：

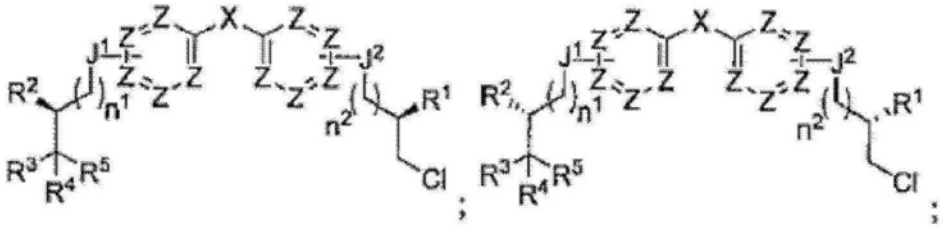
[0179]



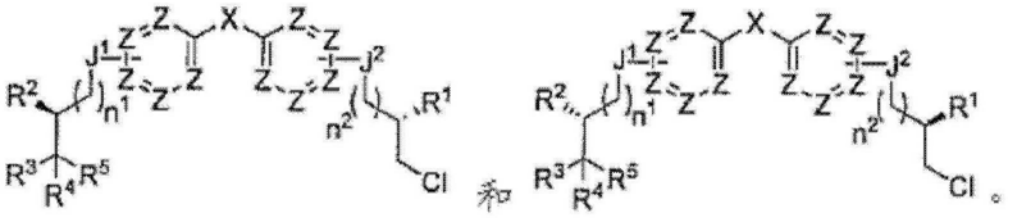
(I)

[0180] 尽管一般如上描绘化合物，但是本公开的范围包括所有可能的立体异构体。例如，关于结构 I，本公开也包括下列立体异构体 (I′)、(I″)、(I″′) 和 (I″″)：

[0181]



(I′) (I″)



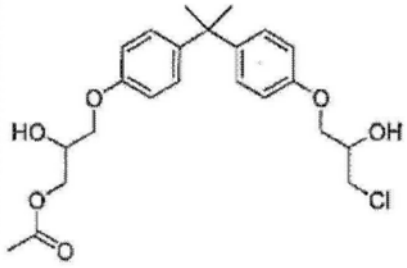
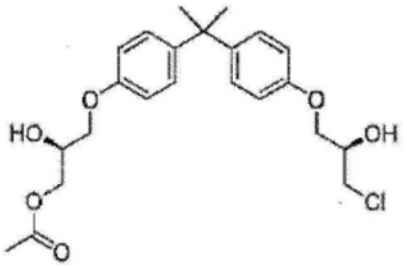
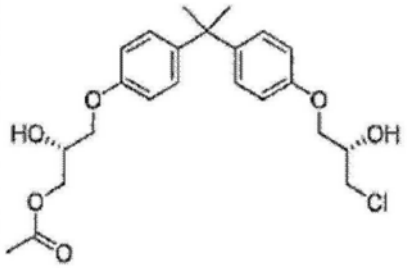
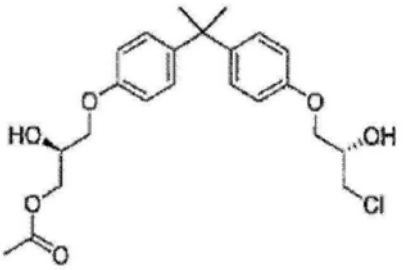
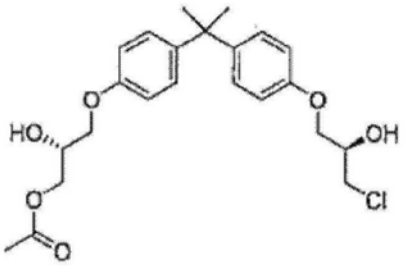
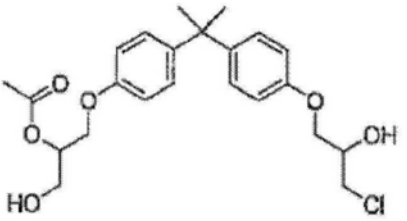
(I‴) (I⁗)

[0182] 在类似方式中，本公开包括所有结构 I 化合物（例如，Ia、Ib、Ic、Id、Ie、If、Ig、Ih、Ii、Ij、Ik、Il、Im、In、Io、Ip、Iq、Ir 和 Is）的所有可能的立体异构体，所述结构 I 化合物包括表 1 中提供的化合物。本领域普通技术人员将容易理解如何获得所有可能的立体异构体，尤其参考上述实施例。

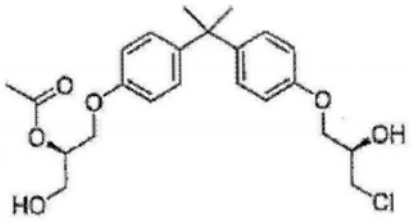
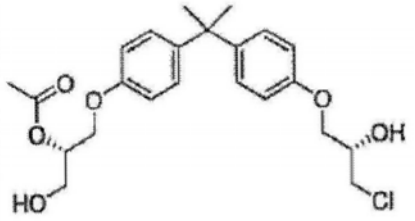
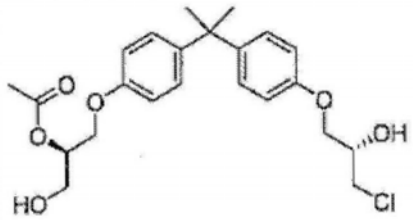
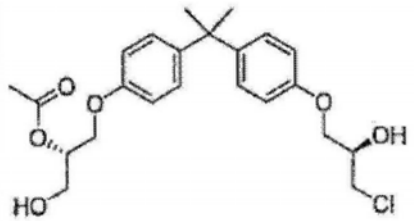
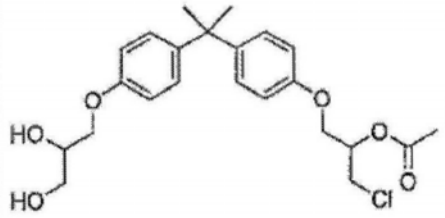
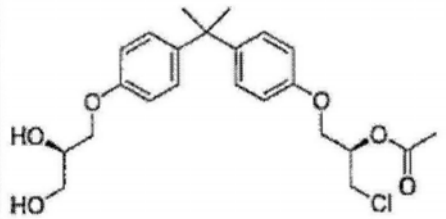
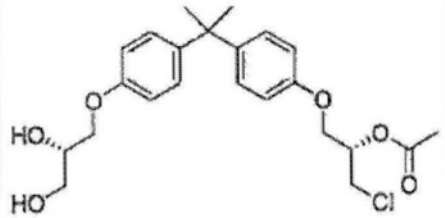
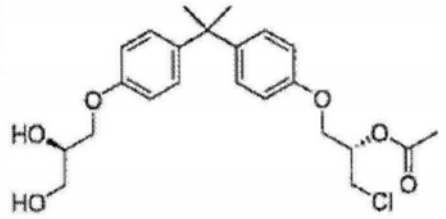
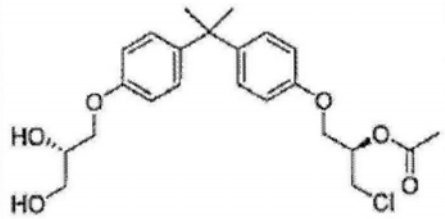
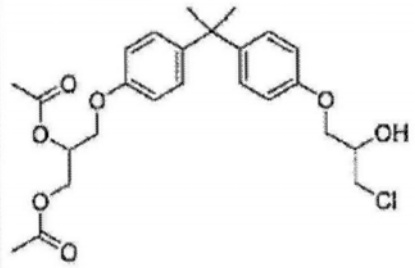
[0183] 在化合物的其它特定实施方案中，如在本文他处描述的，提供了表 1 中的下列化合物。

[0184] 表 1. 代表性化合物

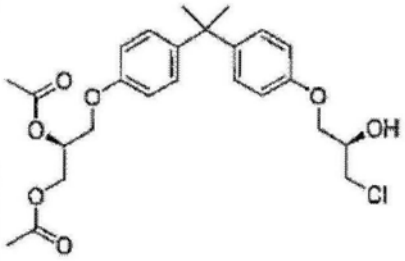
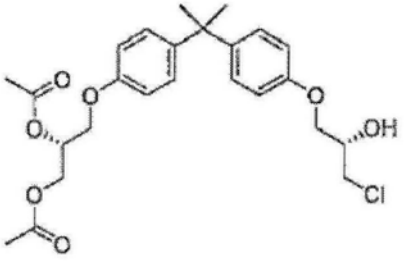
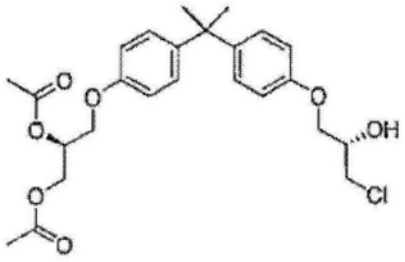
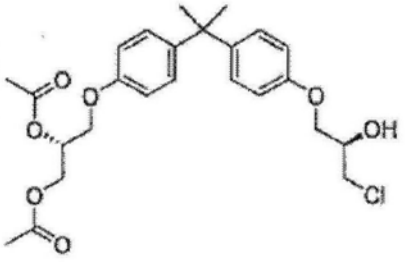
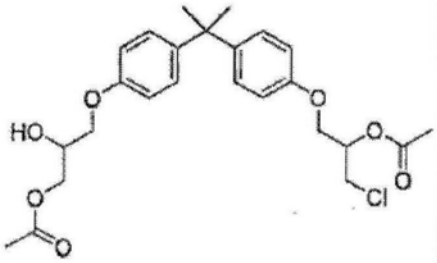
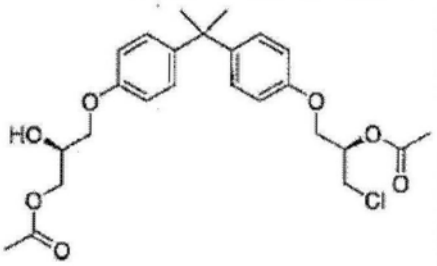
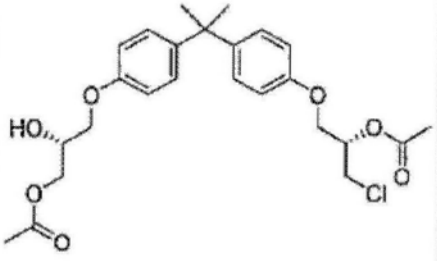
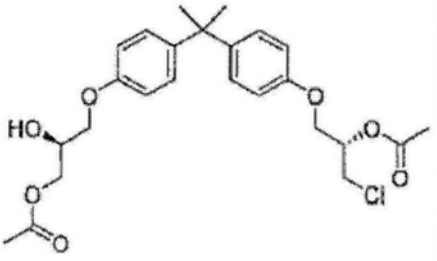
[0185]

编号	结构	编号	结构
1		1a	
1b		1c	
1d		2	

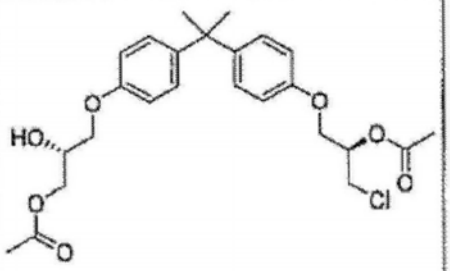
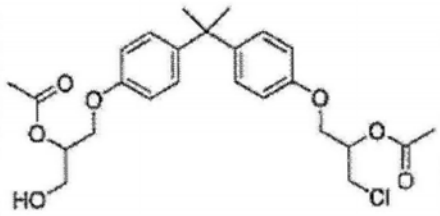
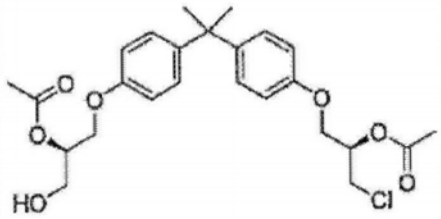
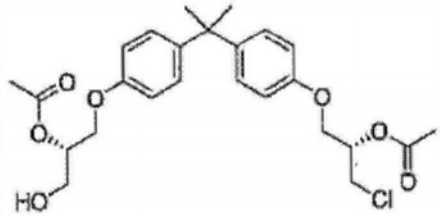
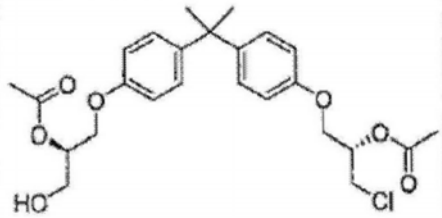
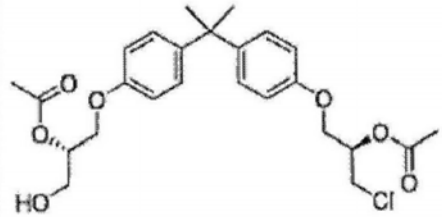
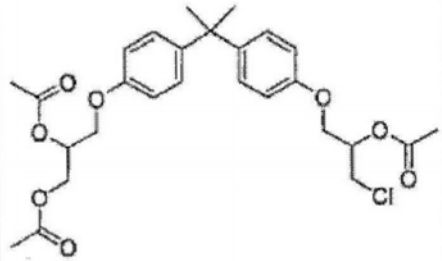
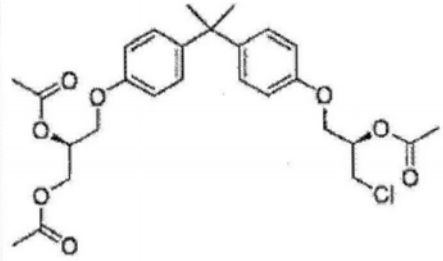
[0186]

编号	结构	编号	结构
2a		2b	
2c		2d	
3		3a	
3b		3c	
3d		4	

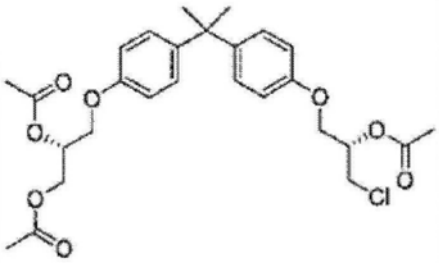
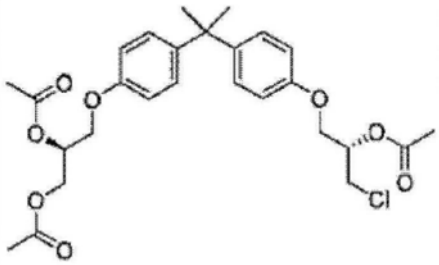
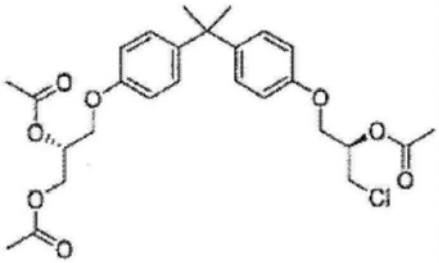
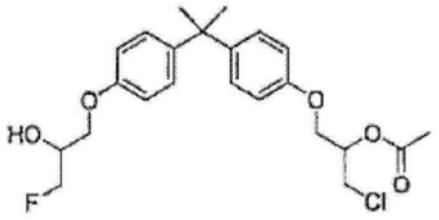
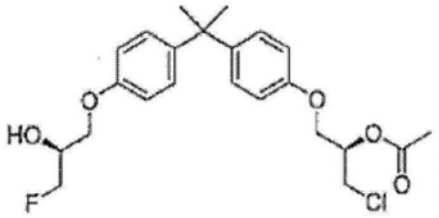
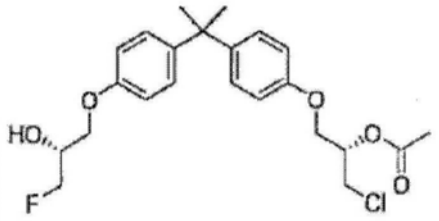
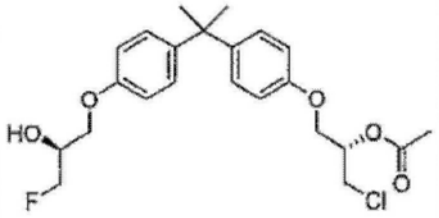
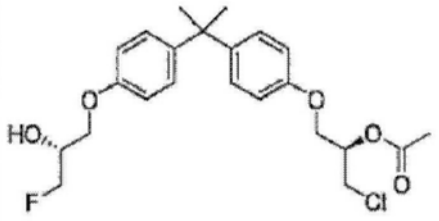
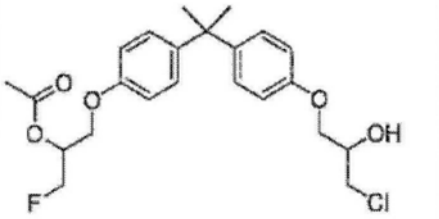
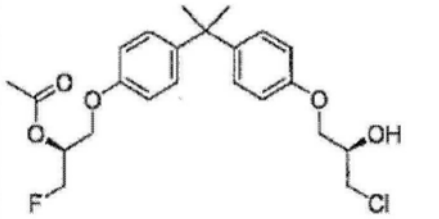
[0187]

编号	结构	编号	结构
4a		4b	
4c		4d	
5		5a	
5b		5c	

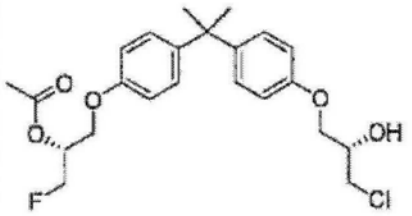
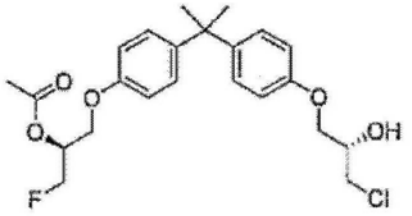
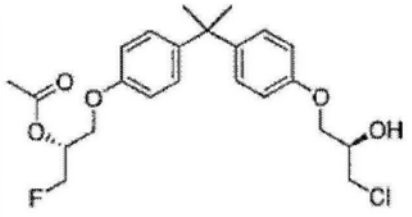
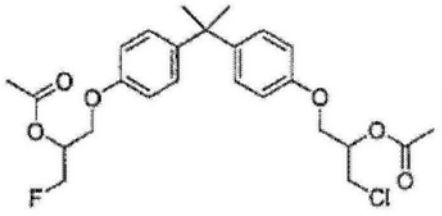
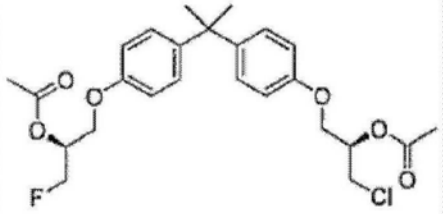
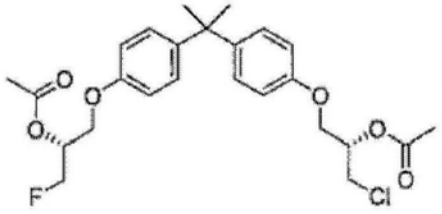
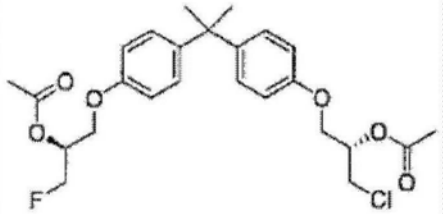
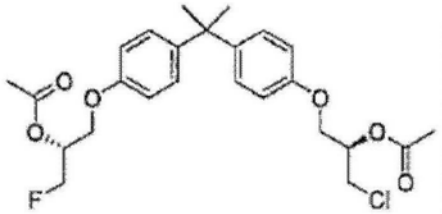
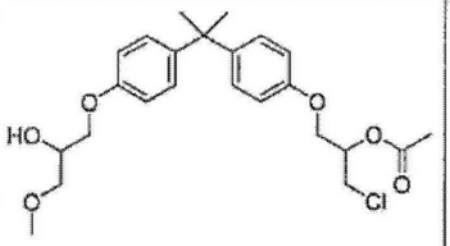
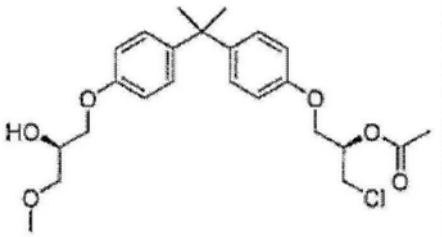
[0188]

编号	结构	编号	结构
5d		6	
6a		6b	
6c		6d	
7		7a	

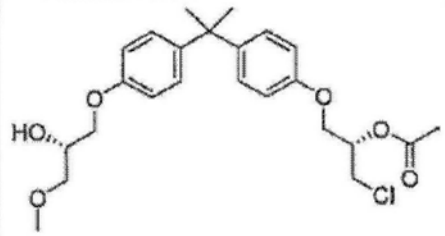
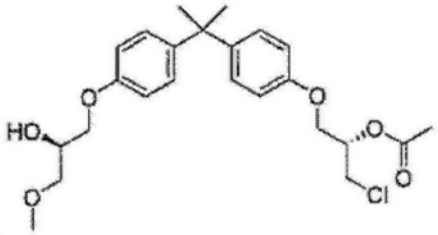
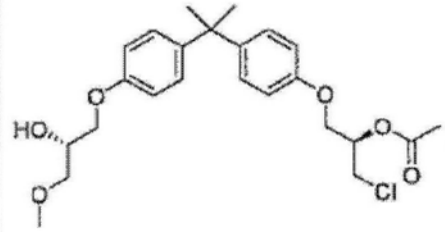
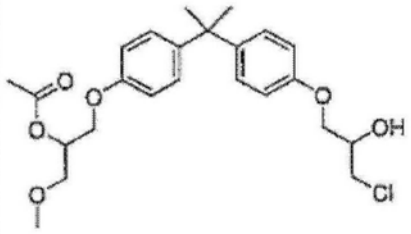
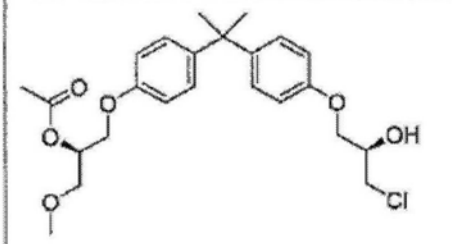
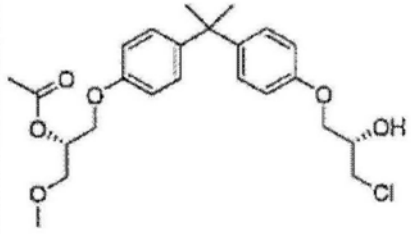
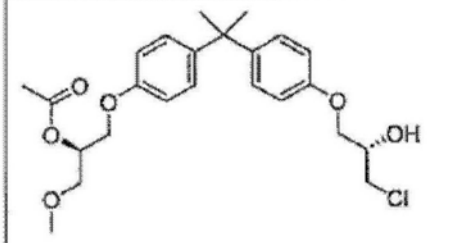
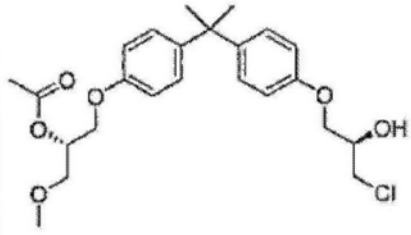
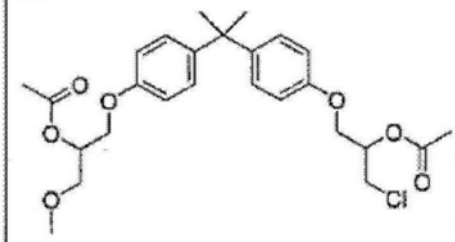
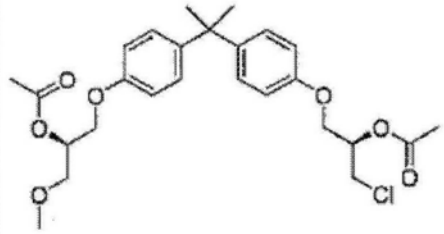
[0189]

编号	结构	编号	结构
7b		7c	
7d		8	
8a		8b	
8c		8d	
9		9a	

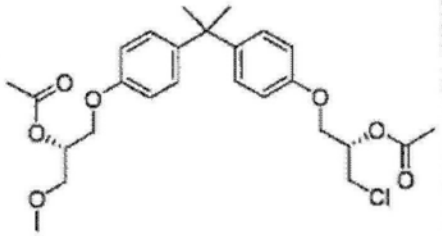
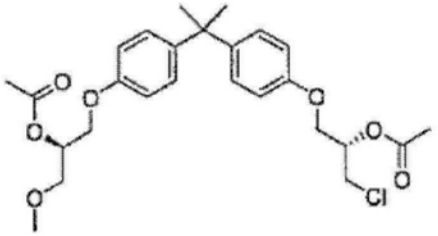
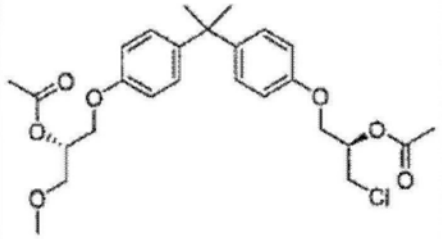
[0190]

编号	结构	编号	结构
9b		9c	
9d		10	
10a		10b	
10c		10d	
11		11a	

[0191]

编号	结构	编号	结构
11b		11c	
11d		12	
12a		12b	
12c		12d	
13		13a	

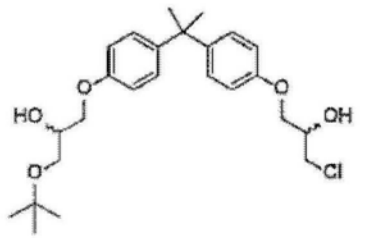
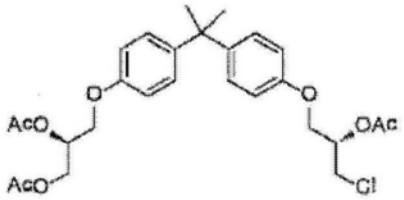
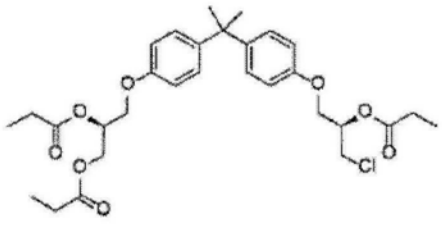
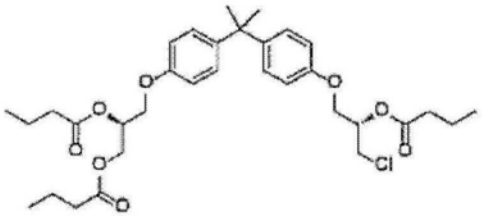
[0192]

编号	结构	编号	结构
13b		13c	
13d		N/A	N/A

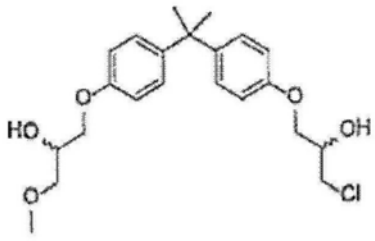
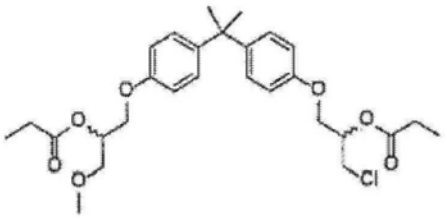
[0193] 在化合物的其它特定实施方案中，如在本文他处描述的，提供了表 2 中的下列化合物。

[0194] 表 2. 代表性化合物

[0195]

结构	结构
	
	

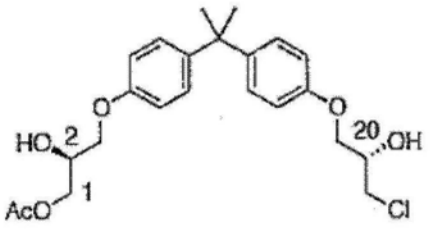
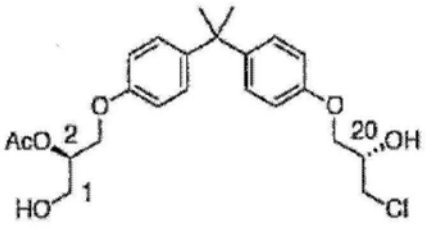
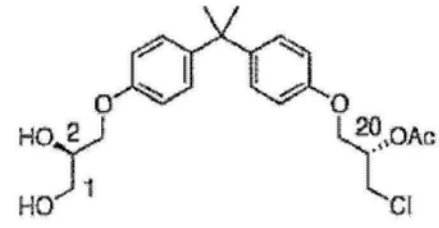
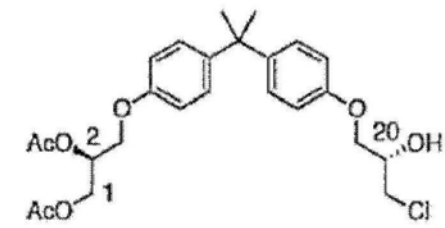
[0196]

结构	结构
	

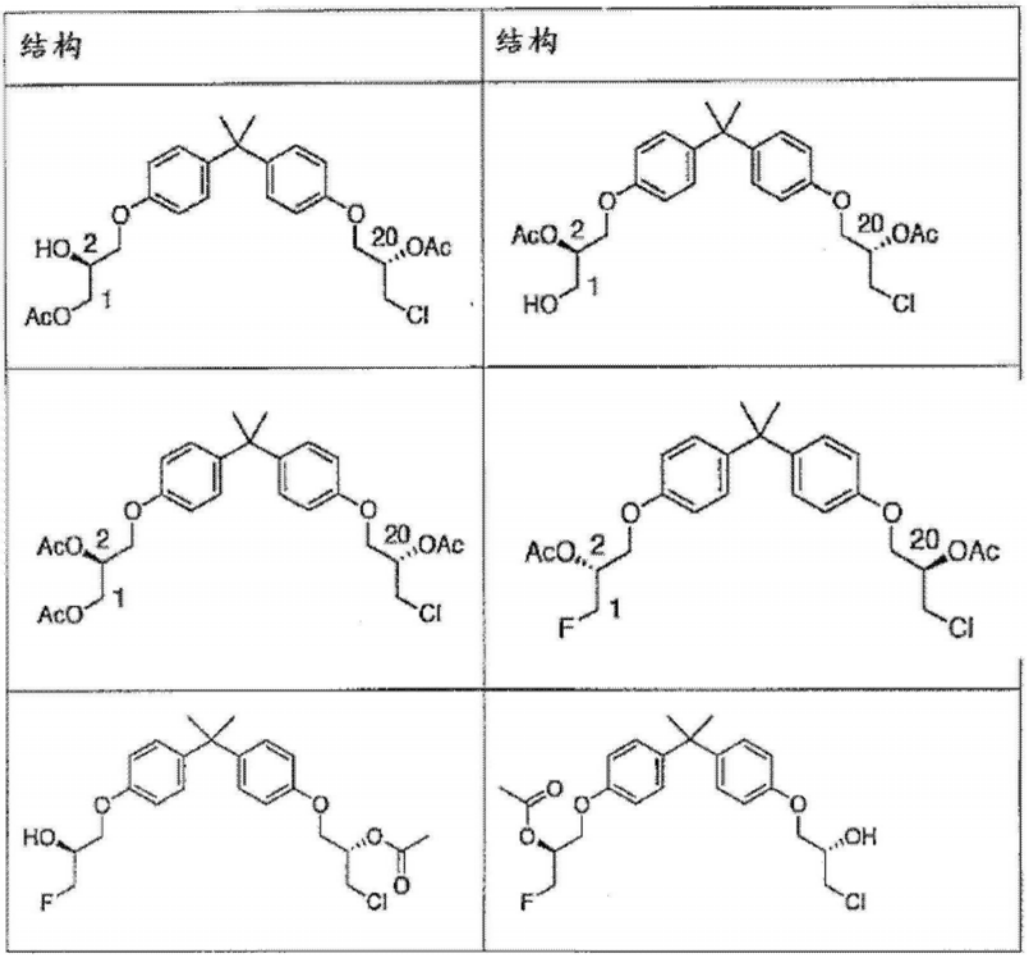
[0197] 在化合物的其它特定实施方案中，如在本文他处描述的，提供了表 3 中的下列化合物，大多数化合物具有 1、2 和 20 位编号。

[0198] 表 3. 代表性化合物

[0199]

结构	结构
	
	

[0200]



[0201] 本文所述的化合物可以呈游离形式或其盐的形式。在一些实施方案中，本文所述的化合物可以呈药学上可接受的盐的形式，其在本领域中是已知的 (Berge 等人、J.Pharm.Sci.1977,66,1)。本文所使用的药学上可接受的盐包括，例如，具有母体化合物的所需药理学活性的盐（保持母体化合物的生物学效能和 / 或性质并且在生物学和 / 或其它方面不是不合需要的盐）。具有一个或多个能够成盐的官能团的本文所述的化合物可以例如形成为药学上可接受的盐。含有一个或多个碱性官能团的化合物可能能够与例如药学上可接受的有机酸或无机酸形成药学上可接受的盐。药学上可接受的盐可衍生自，例如但不限于，乙酸、己二酸、藻酸、天冬氨酸、抗坏血酸、苯甲酸、苯磺酸、丁酸、肉桂酸、柠檬酸、樟脑酸、樟脑磺酸、环戊烷丙酸、二乙基乙酸、二葡糖酸、十二烷基磺酸、乙磺酸、甲酸、富马酸、葡庚糖酸、葡糖酸、甘油磷酸、乙醇酸、半磺酸、庚酸、己酸、盐酸、氢溴酸、氢碘酸、2- 羟基乙磺酸、异烟酸、乳酸、苹果酸、马来酸、丙二酸、扁桃酸、甲磺酸、2- 萘磺酸、萘二磺酸、对甲苯磺酸、烟酸、硝酸、草酸、扑酸、果胶酸、3- 苯基丙酸、磷酸、苦味酸、庚二酸、特戊酸、丙酸、丙酮酸、水杨酸、琥珀酸、硫酸、氨基磺酸、酒石酸、硫氰酸或十一烷酸。含有一个或多个酸性官能团的化合物可能能够与例如药学上可接受的碱形成药学上可接受的盐，所述药学上可接受的碱例如但不限于，基于碱金属或碱土金属的无机碱，或诸如伯胺化合物、仲胺化合物、叔胺化合物、季胺化合物、取代胺、天然存在的取代胺、环状胺或碱性离子交换树脂的有机碱。药学上可接受的盐可衍生自，例如但不限于，药学上可接受的金属阳离子诸如铵、钠、钾、锂、钙、镁、铁、锌、铜、锰或铝的氢氧化物、碳酸盐或碳酸氢盐、氨、苄星青霉素、葡甲胺、甲基胺、二甲胺、三甲胺、乙基胺、二乙胺、三乙胺、异丙胺、三丙胺、三丁基胺、乙醇胺、二乙醇胺、2- 二

甲基氨基乙醇、2- 二乙基氨基乙醇、二环己基胺、赖氨酸、精氨酸、组氨酸、咖啡因、哈胺、胆碱、甜菜碱、乙二胺、氨基葡萄糖、葡糖胺、甲基葡糖胺、可可碱、嘌呤、哌嗪、哌啶、普鲁卡因、N- 乙基哌啶、可可碱、四甲基铵化合物、四乙基铵化合物、吡啶、N,N- 二甲基苯胺、N- 甲基哌啶、吗啉、N- 甲基吗啉、N- 乙基吗啉、二环己基胺、二苄基胺、N,N- 二苄基苯乙基胺、1- 二苯羟甲胺 (ephenamine)、N,N′ - 二苄基乙二胺或聚胺树脂。在一些实施方案中，本文所述的化合物可以含有酸性基团和碱性基团二者，并且可以呈内盐或两性离子形式，例如但不限于，甜菜碱。本文所述的盐可以通过本领域技术人员已知的常规方法制备，例如但不限于，通过将游离形式与有机酸或无机酸或碱反应，或通过从其它盐进行阴离子交换或阳离子交换。本领域技术人员将理解，盐的制备可以在分离和纯化化合物过程中原位进行，或者盐的制备可以通过单独使分离和纯化的化合物反应来进行。

[0202] 在一些实施方案中，本文所述的化合物及其所有不同形式（例如，游离形式、盐、多晶型物、异构形式）可以呈溶剂加合物形式，例如溶剂化物形式。溶剂化物含有化学计算或非化学计算量的与化合物或其盐物理缔合的溶剂。所述溶剂可以例如但不限于药学上可接受的溶剂。例如，当溶剂是水时形成水合物，或当溶剂是醇时形成醇化物。

[0203] 在一些实施方案中，本文所述的化合物及其所有不同形式（例如，游离形式、盐、溶剂化物、异构形式）可以包括结晶和无定形形式，例如多晶型物，假多晶型物，构象假多晶型物，无定形形式，或它们的组合。多晶型物包括相同元素组成的化合物的不同晶体堆积排列。多晶型物通常具有不同的 X- 射线衍射图、红外光谱、熔点、密度、硬度、晶形、光学和电学性质、稳定性和 / 或溶解性。本领域技术人员将理解，包括重结晶溶剂、结晶速率和贮存温度的各种因素可以导致单一晶型占优势。

[0204] 在一些实施方案中，本文所述的化合物及其所有不同形式（例如，游离形式、盐、溶剂化物、异构形式）包括异构体诸如几何异构体、基于不对称碳的旋光异构体、立体异构体、互变异构体、个别异构对映体、个别非异构对映体、外消旋体、非对映体混合物、和它们的组合，并且不限于为了便利目的而图示的结构的描述。

[0205] 本公开也提供药物组合物，其包含本文公开的任何一种或多种化合物（例如，结构 I 化合物）和药学上可接受的载体。在一些实施方案中，药物组合物可用于治疗下列的一种或多种 :前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。

[0206] 在一些实施方案中，根据本公开的药物组合物可以包含结构 I 化合物、或此类化合物的盐，优选药学上或生理上可接受的盐和药学上可接受的载体。药物制剂将典型地包含一种或多种载体、赋形剂或稀释剂，其适于制剂的施用模式、例如通过注射、吸入、局部施用、灌洗或适于所选治疗的其它模式。

[0207] 适合的载体、赋形剂或稀释剂是本领域中已知的以此类施用模式使用的那些。

[0208] 适合的药物组合物可以通过本领域已知的方法配制，并且它们的施用模式和剂量由熟练的专业人员确定。关于肠胃外施用，可以将化合物溶解在无菌水或盐水或药学上可接受的载体中，所述药用载体用于非水溶性化合物的施用，诸如用于维生素 K 的那些。对于经肠施用，化合物可以是以片剂、胶囊或溶解在液体形式中施用。片剂或胶囊可以是肠包衣的，或者于持续释放的制剂中。许多适当的制剂是已知的，包括包封待释放的化合物的聚合物或蛋白微粒、软膏剂、糊剂、凝胶、水凝胶、或可以局部或区域使用以施用化合物的溶液。

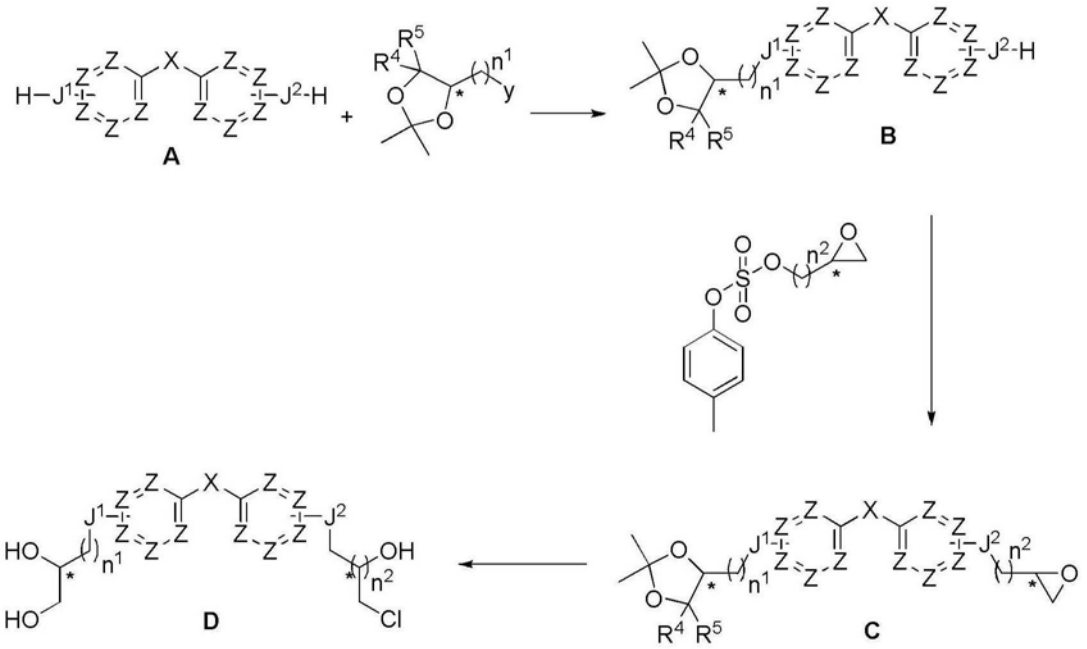
持续释放贴片或植入物可以用于提供延长的时段内的释放。许多本领域技术人员已知的技术描述在Remington :the Science&Practice of Pharmacy by Alfonso Gennaro,第20版,Lippencott Williams&Wilkins,(2000) 中。用于肠胃外施用的制剂可以例如含有赋形剂、聚亚烷基二醇如聚乙二醇、植物来源的油或氢化萘。生物相容的、生物可降解的丙交酯聚合物、丙交酯 / 乙交酯共聚物、或聚氧乙烯 - 聚氧丙烯共聚物可以用于控制化合物的释放。其它潜在有用的用于调节化合物的肠胃外递送系统包括乙烯 - 醋酸乙烯酯共聚物颗粒、渗透泵、可植入输注系统和脂质体。用于吸入的制剂可以含有赋形剂例如乳糖,或者可以是含有例如聚氧乙烯 -9- 月桂醚、甘胆酸盐和去氧胆酸盐的水溶液,或者可以是用于以滴鼻剂或作为凝胶形式施用的油性溶液。

[0209] 本公开中使用的化合物可获自医药资源或使用已知方法由天然存在的化合物进行修饰。此外,已参考已知的化学合成原理例如在 PCT 公布号 WO 2010/000066 ;WO 2011/082487、WO 2011/082488、WO 2012/145330、WO 2012/139039、WO 2012/145328 中、在共同待决的 PCT 申请号 US 2012/051481 中和以及在共同待决的美国申请号 13/863,849 和 61/667,355 中列出的合成程序,本领域技术人员将理解制备或合成本公开化合物的方法,所述申请用于所有目的据此通过引用整体并入。Auzou 等人 1974European Journal of Medicinal Chemistry9(5),548-554 也描述了可被考虑且适合地适于制备以上列出的结构 I 化合物的适合合成程序。可以有用的其它参考文献包括 :Debasish Das、Jyh-Fu Lee 和 Soofin Cheng“Sulfonic acid functionalized mesoporous MCM-41 silica as a convenient catalyst for Bisphenol-A synthesis”Chemical Communications,(2001)2178-2179 ;美国专利 2571217 Davis,Orris L. ;Knight,Horace S. ;Skinner、John R.(Shell Development Co.)“Halohydrin ethers of phenols.”(1951) ;和 Rokicki,G. ;Pawlicki、J. ;Kuran,W. “4- 氯甲基 -1,3- 二氧戊环 -2- 酮与苯酚的反应作为多元醇和环状碳酸酯的新路径”Journal fuer Praktische Chemie(Leipzig)(1985)327,718-722。每个以上参考文献为了所有目的据此通过引用整体并入。

[0210] 例如,本公开化合物的某些实施方案可参考下列一般反应方案 I 来制备 :

[0211] 一般反应方案 I

[0212]



[0213] 结构 I 化合物可参考一般反应方案 1 来制备，其中 R^3、R^4、J^1、J^2、n^1、n^2和 x 如结构 I 所述，y 为离去基团诸如氯，且＊指示立体中心。结构 A 化合物可购自商业来源或根据本领域中已知的方法来制备。A 与适当取代的 1,3- 二氧戊环的反应产生结构 B 的化合物。可采用任选纯的或外消旋的二氧戊环以产生所需立体化学。用适当的试剂例如适当取代的甲苯磺酸缩水甘油基酯使 B 环氧化，得到结构 C 的化合物。可采用各种环氧化试剂（包括光学纯的试剂）产生光学纯的环氧化物（例如，+ 或 - 甲苯磺酸缩水甘油基酯）。用适当的开环试剂例如 $CeCl_3x7H_2O$ 处理 C，产生 D。

[0214] 结构 D 的化合物可用作用于制备各个结构 I 化合物的中间体。例如，通过用适当的酰基氯（例如，乙酰氯等）处理，化合物 D 可在伯醇处被修饰以包括酯。可选地，1,2- 二羟基部分可通过如下被保护成缩酮：与 2,2- 二甲氧基丙烷反应、随后用适当的酸酐（例如乙酸酐等）处理以及使缩酮脱保护而使游离仲醇转化成酯。结构 I 的三酯化合物可通过用适当的酸酐处理化合物 D 来制备。最终，使用实施例 9-11 中所示的对上述方案的改进可使 1,2- 二羟基都转化成所需酯基团。基于上述描述，本领域普通技术人员容易制备其它结构 I 化合物。

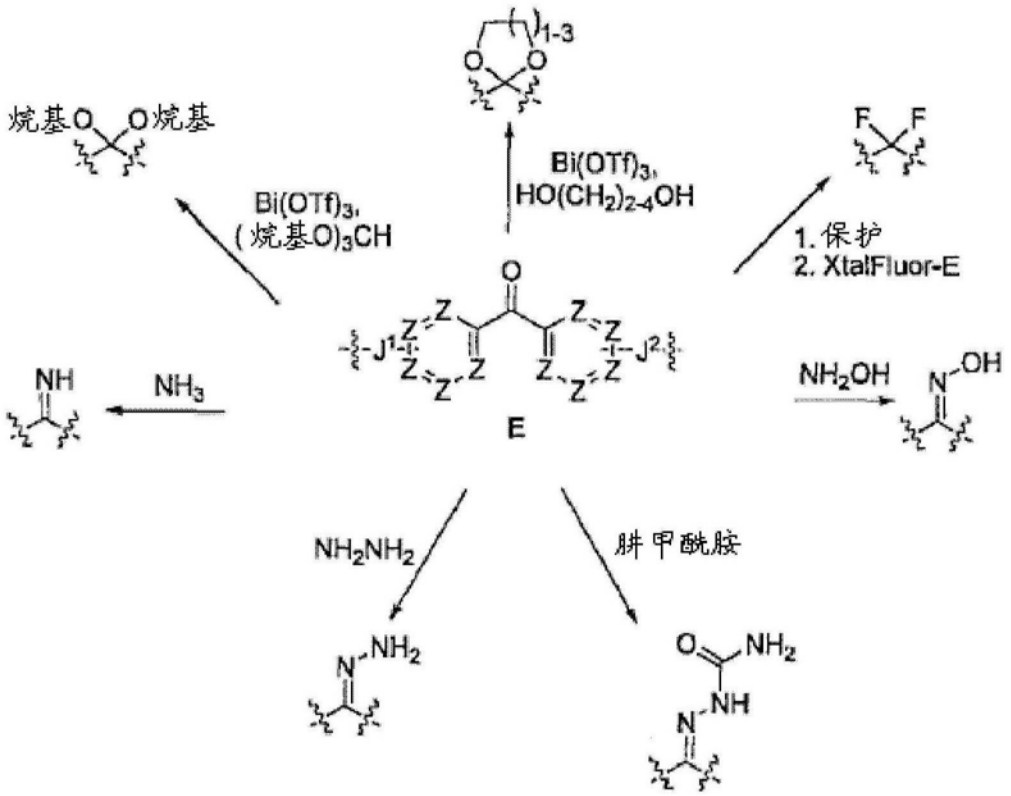
[0215] 通过对上述方案的改进，可容易制备其中 R^3为卤代的结构 I 化合物。例如，用适当的卤化试剂处理 D，随后如上所述酯化，产生其中 R^3为卤代（例如，氟）的结构 I 化合物。例如，在一个实施方案中，氟原子通过用二乙基氨基三氟化硫 (DAST) 或 Xtalfluor-E 或 M 来引入（参见 J.Org.Chem.2010,75,3401-3411，其据此通过引用整体并入）。在其它实施方案中，例如通过与对甲苯磺酰氯或甲磺酸酐反应，随后与 [K^+/2,2,2- 穴状配体]F^-或四丁基氟化铵反应可使 D 中的伯羟基部分转化成适当的离去基团。其它用于将 D 氟化的方法为本领域技术人员已知。对于氟化程序的描述，参见 J.Org.Chem.2010,75,3401-3411,Bioorg.Med.Chem.2009,17,7441-7448，和 J.Med.Chem.1990,33,2430-2437，其各自据此通过引用整体并入。

[0216] 其中 R^3为 $-OR^{12}$的结构 I 化合物可通过如下制备：用 2 当量的适当环氧化试剂例如适当取代的甲苯磺酸缩水甘油基酯处理结构 A 化合物，以产生二环氧化物。这些环氧化

物中的一个可用醇（即，R^3OH）打开，随后用 $CeCl_3x7H_2O$ 使剩余环氧化物开环，并如上所述进行酯化，以产生结构 I 化合物。

[0217] 一般反应方案 II

[0218]



[0219] 具有各种桥接基团（即，“X”）的结构 I 化合物可根据一般反应方案 II 来制备。可使用结构 E 化合物制备任何数量的各个结构 I 化合物。用于一般反应方案 II 中所示的反应为本领域熟知的。可使用本领域普通技术人员熟知的技术和方法对一般反应方案 II 中描绘的任何官能团进一步官能化。

[0220] 本领域技术人员将认识到，关于上述合成方案而讨论的步骤次序和试剂的变化是可能的。此外，也可采用适当的保护基团策略，诸如于 Greene’s Protective Groups in Organic Synthesis，第 4 版，Peter G.M.Wuts 和 Theodora W.Greene、John Wiley and Sons，Inc.，2007（其据此通过引用整体并入）描述的那些。此外，具有各种取代（例如，针对 R^1、R^2、R^3、R^4、J^1、J^2等的不同值）的结构 I 化合物和不同位置异构体可通过改变上述起始材料和 / 或程序来制备。此类改变在本领域普通技术人员的能力范围之内。

[0221] III. 方法

[0222] 本化合物可用于任何数量的方法。例如，在一些实施方案中，所述化合物可在用于调节雄激素受体的方法中有用。

[0223] 因此，在一个实施方案中，本公开提供包含任一种前述结构 (I) 化合物的组合物用于调节雄激素受体 (AR) 活性的用途。例如在一些实施方案中，在哺乳动物细胞中调节雄激素受体 (AR) 活性。可在需要其的受试者（例如，哺乳动物受试者）中调节雄激素受体并且用于治疗任何所述疾患或疾病。

[0224] 在其它实施方案中，调节雄激素受体 (AR) 活性是用于治疗至少一种选自以下的

适应症：前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。例如在一些实施方案中，所述适应症是前列腺癌。在其它实施方案中，前列腺癌是去势抗性前列腺癌（也被称为激素难治性、雄激素－非依赖性、抗雄激素剥夺性、抗雄激素去势型、雄激素耗竭－非依赖性、去势－复发型、抗雄激素－复发型）。而在其它实施方案中，前列腺癌是雄激素－依赖性前列腺癌。

[0225] 在其它实施方案中，本公开提供调节雄激素受体（AR）活性的方法，所述方法包括向需要其的受试者（例如，哺乳动物）施用包括任一种前述结构（I）化合物或其药学上可接受的盐、立体异构体或互变异构体的组合物。

[0226] 在前述方法的其它进一步实施方案中，调节雄激素受体（AR）活性是用于治疗下列的一种或多种：前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。例如在一些实施方案中，前列腺癌是去势抗性前列腺癌（也被称为激素难治性、雄激素－非依赖性、抗雄激素剥夺性、抗雄激素去势型、雄激素耗竭－非依赖性、去势－复发型、抗雄激素－复发型）。在其它实施方案中，前列腺癌是雄激素－依赖性前列腺癌。

[0227] 根据另一实施方案，提供在本文他处描述的结构（I）化合物在制备用于调节雄激素受体（AR）的药物中的用途。

[0228] 在其它实施方案中，本公开提供了用于提高含羟基雄激素受体调节剂的生物利用度（例如，口服生物利用度）的方法，所述方法包括用烷基（例如甲基）、烯基、芳基或芳烷基酯取代至少一个羟基部分。

[0229] 根据进一步实施方案，提供了筛选雄激素受体调节化合物的方法，其中所述化合物筛选选自在本文他处描述的化合物。

[0230] 可在哺乳动物细胞中调节雄激素受体（AR）活性。可在哺乳动物细胞中调节雄激素受体（AR）活性。哺乳动物可以为人。

[0231] 可选地，可向哺乳动物施用。可向需要其的哺乳动物和以用于治疗至少一种选自以下的适应症的有效量施用：前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症（例如，肯尼迪氏病）和年龄相关性黄斑变性。

[0232] 哺乳动物细胞可以为人细胞。调节雄激素受体活性可以是用于抑制雄激素受体N-端结构域活性。调节雄激素受体活性可以是用于抑制雄激素受体活性。所述调节可以在体内。调节雄激素受体活性可以用于治疗至少一种选自以下的适应症：前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症（例如，肯尼迪氏病）和年龄相关性黄斑变性。所述适应症可以是前列腺癌。前列腺癌可以是去势抗性前列腺癌。前列腺癌可以是雄激素－依赖性前列腺癌。

[0233] 在一些实施方案中，化合物及如本文所述的其所有不同形式可以例如但不限于与其它治疗方法组合用于至少一种选自以下的适应症：前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。例如，化合物及如本文所述的其所有不同形式可用作新辅助疗法（之前）、辅助（期间）和/或手术辅助性疗法（之后）、辐射疗法（短程疗法或外部束）、

或其它疗法（例如，HIFU)，以及与化学疗法、雄激素去势、抗雄激素或任何其它治疗方法组合。

[0234] 关于组合疗法，本公开的一个实施方案提供了任何一种或多种结构 I 化合物与用于或可用于治疗任何上述疾病状态（例如，雄激素－非依赖性前列腺癌或肯尼迪氏病）的一种或多种目前使用的或实验性药理学疗法的组合。还提供了方法、用途和包含上述组合的药物组合物。

[0235] 在一些实施方案中，本公开涉及用于调节雄激素受体（例如，用于治疗任何上述条件）的方法通过向需要其的受试者施用包含结构 I 化合物和额外治疗剂的药物组合物。还提供了包含任一种前述式 (I) 化合物、额外治疗剂和药学上可接受的载体的药物组合物（及其用途）。例如，在一些实施方案中，额外治疗剂用于治疗前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症或年龄相关性黄斑变性。

[0236] 公开的化合物被认为主要通过结合于雄激素受体的 N- 末端来干扰雄激素受体，期望所述化合物当与现有的已获批的和处于开发中的试剂配合使用时显示优异的协同疗效。即，使用彼此配合的试剂的生物影响产生生物效果和治疗效果，其大于它们每一种单独的简单添加效应。

[0237] 因此，一个实施方案包括在组合疗法中使用公开的化合物和用于治疗上述疾病状态的一种或多种目前使用的或实验性药理学疗法（不考虑此类药理学疗法的生物作用机制如何），所述药理学疗法包括但不限于直接或间接抑制雄激素受体的药理学疗法、本质上有细胞毒性的药理学疗法和干扰雄激素的生物产生或功能的药理学疗法（在下文，“其它治疗剂”）。所谓的“组合疗法”意指向同一患者施用任何一种或多种结构 I 化合物和一种或多种另一治疗剂以使它们的药理效应彼此同时发生，或如果不是同时发生的话，即它们的效应彼此协同，即使相继而不是同时给药。

[0238] 此类施用包括但不限于一种或多种结构 I 化合物和一种或多种其它治疗剂作为在给药前无任何掺混的单独试剂，以及包括与一种或多种结构 I 化合物混合的一种或多种其它雄激素－阻断治疗剂的制剂作为预混制剂的给药。一种或多种结构 I 化合物与用于治疗上述疾病状态的其它治疗剂的施用包括通过包括但不限于，静脉内递送、口服递送、腹膜内递送、肌内递送或瘤内递送的任何给药方法进行给药。

[0239] 在本公开的另一方面，一种或多种其它治疗剂可在施用一种或多种结构 I 化合物之前向患者施用。在另一个实施方案中，一种或多种结构 I 化合物可以与一种或多种其它治疗剂共施用。在又另一方面，一种或多种其它治疗剂可以在施用一种或多种结构 I 化合物之后向患者施用。

[0240] 一种或多种结构 I 化合物的剂量与一种或多种其它治疗剂的剂量的比率可以或可以不等于 1 并且可以相应地变化以实现最佳治疗益处，这完全在本公开的范围之内。

[0241] 为了清楚起见，与一种或多种其它治疗剂组合用于改善对上述疾病状态的治疗的一种或多种结构 I 化合物可以包含，但不限于具有结构 I 的结构的任何化合物，包括表 2 中所示的那些化合物。

[0242] 其它治疗剂包括但不限于目前被美国 FDA（或在其它地方通过任何其它监管机构）批准用作任何上述疾病状态的药理学治疗、或目前在实验上用作临床测试程序

的一部分的任何药理学试剂。其它药理学试剂的非限制性实例包含但不限于：称为恩杂鲁胺（4-(3-(4-氰基-3-(三氟甲基)苯基)-5,5-二甲基-4-氧代-2-硫代咪唑烷-1-基)-2-氟-N-甲基苯甲酰胺）及相关化合物的化学实体，其看似为雄激素受体LBD的阻断剂并且目前在开发作为用于前列腺癌的治疗；称为Galeterone及相关化合物的化学实体，其看似为雄激素受体LBD的阻断剂，和CYP17裂解酶抑制剂，并且也看似减少前列腺癌细胞中的总体雄激素受体水平。Galeterone目前在开发作为用于前列腺癌的治疗；称为ARN-509及相关化合物的化学实体，其看似为雄激素受体LBD的阻断剂并且目前在开发作为用于前列腺癌的治疗；称为阿比特龙（或CB-7630；(3S,8R,9S,10R,13S,14S)-10,13-二甲基-17-(吡啶-3-基)2,3,4,7,8,9,10,11,12,13,14,15-十二氢-1H-环戊[a]菲-3-醇）及相关分子的化学实体，其看似阻断雄激素生成且用于治疗前列腺癌；称为比卡鲁胺（N-[4-氰基-3-(三氟甲基)苯基]-3-[(4-氟苯基)磺酰基]-2-羟基-2-甲基丙酰胺）及相关化合物的化学实体，其看似为雄激素受体LBD的阻断剂且其目前用于治疗前列腺癌；称为尼鲁米特（5,5-二甲基-3-[4-硝基-3-(三氟甲基)苯基]咪唑烷-2,4-二酮）及相关化合物的化学实体，其看似为AR LBD的阻断剂且其目前用于治疗前列腺癌；称为氟他胺（2-甲基-N-[4-硝基-3-(三氟甲基)苯基]-丙酰胺）及相关化合物的化学实体，其看似为雄激素受体LBD的阻断剂且其目前用于治疗前列腺癌；称为醋酸环丙孕酮（6-氯-1β,2β-二氢-17-羟基-3′ H-环丙并[1,2]孕甾-4,6-二烯-3,20-二酮）及相关化合物的化学实体，其看似为雄激素受体LBD的阻断剂且其目前用于治疗前列腺癌，称为多西他赛（泰素帝；1,7β,10β-三羟基-9-氧代-5β,20-乙氧基紫衫-11-烯-2α,4,13α-三基4-乙酸酯2-苯甲酸酯13-{(2R,3S)-3-[(叔丁氧基羰基)氨基]-2-羟基-3-苯基丙酸酯}）及相关化合物的化学实体，其看似为细胞毒性的抗微管剂并且目前用于与泼尼松组合来治疗前列腺癌；称为贝伐单抗（Avastin）的化学实体，一种识别并阻断血管内皮生长因子A(VEGF-A)且可用于治疗前列腺癌的单克隆抗体；称为OSU-HDAC42((S)-(+)-N-羟基-4-(3-甲基-2-苯基丁酰基氨基)-苯甲酰胺）及相关化合物的化学实体，其看似充当组蛋白脱乙酰酶抑制剂，并且目前正在开发成用于前列腺癌的治疗；称为VITAXIN的化学实体，其看似为对抗血管整合素αvβ3以预防血管发生的的单克隆抗体，并且其可用于治疗前列腺癌；称为舒尼替尼（sunitumib)(N-(2-二乙基氨基乙基)-5-[(Z)-(5-氟-2-氧代-1H-吲哚-3-亚基)甲基]-2,4-二甲基-1H-吡咯-3-甲酰胺）及相关化合物的化学实体，其看似抑制多个受体酪氨酸激酶（RTK）且可用于治疗前列腺癌；称为ZD-4054(N-(3-甲氧基-5-甲基吡嗪-2-基)-2-[4-(1,3,4-噁二唑-2-基)苯基]吡啶-3-磺酰胺）及相关化合物的化学实体，其看似阻断edta受体且其可用于治疗前列腺癌；称为卡巴他赛（XRP-6258）及相关化合物的化学实体，其看似为细胞毒性的微管抑制剂，且其目前用于治疗前列腺癌；称为MDX-010（伊匹单抗）的化学实体，一种结合于并阻断CTLA-4活性的完全人单克隆抗体，其目前在开发作为用于治疗前列腺癌的免疫治疗剂；称为OGX 427的化学实体，其看似作为反义剂靶向HSP27，并且其目前在开发用于治疗前列腺癌；称为OGX 011的化学实体，其看似作为反义剂靶向clusterin；称为非那雄胺（Proscar，Propeci a；N-(1,1-二甲基乙基)-3-氧代-(5α,17β)-4-氮杂雄甾-1-烯-17-甲酰胺）及相关化合物的化学实体，其看似为减少二氢睾酮水平的5-α还原酶抑制剂，且可用于治疗前列腺癌；称为度他雄胺（Avodart；5α,17β)-N-{2,5双（三氟

甲基）苯基}-3- 氧代 -4- 氮杂雄甾 -1- 烯 -17- 甲酰胺）及相关分子的化学实体，其看似为减少二氢睾酮水平的 5- α 还原酶抑制剂，并且可用于治疗前列腺癌；称为妥罗雄胺（(4aR，4bS，6aS，7S，9aS，9bS，11aR)-1，4a，6a- 三甲基 -2- 氧代 -N-（丙 -2- 基）-N-（丙 -2 基氨基甲酰基）十六氢 -1H- 茚并 [5，4-f] 喹啉 -7- 甲酰胺）及相关分子的化学实体，其看似为减少二氢睾酮水平的 5- α 还原酶抑制剂并且可用于治疗前列腺癌；称为倍氯特来 (LY-191，704；(4aS，10bR)-8- 氯 -4- 甲基 -1，2，4a，5，6，10b- 六氢苯并 [f] 喹啉 -3- 酮）及相关化合物的化学实体，其看似为减少二氢睾酮水平的 5- α 还原酶抑制剂并且可用于治疗前列腺癌；称为艾宗特来 (LY-320，236；(4aR，10bR)-8-[(4- 乙基 -1，3- 苯并噻唑 -2- 基）硫烷基]-4，10b- 二甲基 -1，4，4a，5，6，10b- 六氢苯并 [f] 喹啉 -3(2H)- 酮）及相关化合物的化学实体，其看似为减少二氢睾酮水平的 5- α 还原酶抑制剂并且可用于治疗前列腺癌；称为 FCE 28260 及相关化合物的化学实体，其看似为减少二氢睾酮水平的 5- α 还原酶抑制剂并且可用于治疗前列腺癌；称为 SKF105，111 及相关化合物的化学实体，其看似为减少二氢睾酮水平的 5- α 还原酶抑制剂并且可用于治疗前列腺癌。

[0243] 因此，在某些实施方案中额外治疗剂是恩杂鲁胺、Galeterone；ARN-509；阿比特龙、比卡鲁胺、尼鲁米特、氟他胺、醋酸环丙孕酮、多西他赛、贝伐单抗 (Avastin)、OSU-HDAC42、VITAXIN、舒尼替尼、ZD-4054、卡巴他赛 (XRP-6258)、MDX-010（伊匹单抗）、OGX 427、OGX 011、非那雄胺、度他雄胺、妥罗雄胺、倍氯特来、艾宗特来、FCE 28260、SKF105，111、Radium 233、或其相关化合物。

[0244] 在另一个实施方案中，本公开提供了任何一种前述药物组合物（包括包含结构 I 化合物和额外治疗剂的组合物）用于调节雄激素受体 (AR) 活性的用途。例如在一些实施方案中，在哺乳动物细胞中调节雄激素受体 (AR) 活性。

[0245] 在其它实施方案中，调节雄激素受体 (AR) 活性是用于治疗至少一种选自以下的适应症：前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。例如在一些实施方案中，所述适应症是前列腺癌。例如，在一些实施方案中，前列腺癌是去势抗性前列腺癌，且在其它实施方案中前列腺癌是雄激素 - 依赖性前列腺癌。

[0246] 在又一实施方案中，本公开提供了调节雄激素受体 (AR) 活性的方法，所述方法包括向需要其的受试者施用任何一种前述药物组合物（包括包含结构 I 化合物和额外治疗剂的组合物）。例如在一些实施方案中，调节雄激素受体 (AR) 活性是为了治疗下列的一种或多种：前列腺癌、乳腺癌、卵巢癌、子宫内膜癌、唾液腺癌、脱发、痤疮、多毛症、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症和年龄相关性黄斑变性。在又其它实施方案中，所述适应症是前列腺癌。例如，在一些实施方案中，前列腺癌是去势抗性前列腺癌，而在其它实施方案中，前列腺癌是雄激素 - 依赖性前列腺癌。

[0247] 通常，本公开化合物应当在不导致实质毒性情况下使用。本公开化合物的毒性可以使用标准技术测定，例如通过在细胞培养物或实验动物中测试和确定治疗指数，即 LD50(50％群体致死剂量）和 LD100(100％群体致死剂量）之间的比率。然而，在一些情况下，诸如在重病情况下，可能需要施用显著过量的组合物。本公开的一些化合物可以在一些浓度下是有毒性的。可以使用滴定研究来测定毒性和非毒性浓度。可以如下评估毒性：使用不表达功能性 AR 的 PC3 细胞作为阴性对照，检查特定化合物或组合物对细胞系的特异

性。可以使用动物研究来提供化合物是否对于其它组织具有任何影响的指示。靶向 AR 的系统疗法将不大可能对其它组织导致重大问题，因为抗雄激素药和雄激素不敏感综合征不是致命的。

[0248] 本文所述的化合物可以向受试者施用。如本文所用，“受试者”可以是人、非人灵长类、大鼠、小鼠、牛、马、猪、绵羊、山羊、狗、猫等。受试者可以疑似患有癌症（诸如前列腺癌、乳腺癌、卵巢癌或子宫内膜癌）或处于患上所述癌症的风险，或疑似患有以下疾病或处于患上其的风险：痤疮、多毛症、脱发、良性前列腺肥大、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症或年龄相关的黄斑变性。本领域普通技术人员已知用于各种癌症（诸如前列腺癌、乳腺癌、卵巢癌、唾液腺癌或子宫内膜癌）的诊断方法和用于痤疮、多毛症、脱发、良性前列腺肥大、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症或年龄相关的黄斑变性的诊断方法，和癌症（诸如前列腺癌、乳腺癌、卵巢癌、唾液腺癌或子宫内膜癌）的临床叙述，痤疮、多毛症、脱发、良性前列腺肥大、卵巢囊肿、多囊卵巢病、性早熟、脊髓延髓肌肉萎缩症或年龄相关的黄斑变性的诊断和临床叙述。

[0249] 本文所述的化合物也可以用于测定和研究目的。所用的定义包括通过雄激素诸如二氢睾酮 (DHT) 或用于研究目的的合成雄激素 (R1881) 对雄激素受体 (AR) 的配体 - 依赖性活化。对 AR 的配体 - 非依赖性活化是指在缺乏雄激素（配体）的情况下通过例如用毛喉素 (FSK) 刺激 cAMP- 依赖性蛋白激酶 (PKA) 途径而进行的 AR 的反式激活。本公开的一些化合物和组合物可以抑制 FSK 和雄激素（例如 R1881，合成雄激素）两者诱导 ARE- 萤光素酶 (ARE-luc)。AR 的组成性活性是指缺少 AR 配体 - 结合结构域的剪接变体。此类化合物可以阻断 AR 的配体 - 依赖性活化和配体 - 非依赖性活化两者所共有的机制，以及缺少配体 - 结合结构域的 AR 的组成性活性剪接变体。这可以包括 AR 活化中的任何步骤，包括热休克蛋白的解离、必需的翻译后修饰（例如乙酰化，磷酸化）、核易位、蛋白 - 蛋白相互作用、转录复合物形成、辅助阻抑物的释放，和 / 或增加的降解。本公开的一些化合物和组合物可仅抑制配体的活性并且可以干扰配体 - 依赖性活化特异的机制（例如，配体结合结构域 (LBD) 对雄激素的可及性）。除了前列腺癌以外，许多病症涉及雄激素轴线（例如，痤疮、多毛症、脱发、良性前列腺肥大）和干扰该机制的化合物可以用于治疗这些疾患。本公开的一些化合物和组合物可以仅抑制 FSK 诱导，并且可以是 AR 的配体的非依赖性激活的特异性抑制剂。这些化合物和组合物可以干扰事件级联或任何可以对 AR 起作用的下游作用（例如 FSK 增加 MAPK 活性，MAPK 活性对于 AR 活性具有强力作用），所述事件通常伴随 FSK 和 / 或 PKA 活性发生。实例可以包括 cAMP 和 / 或 PKA 或其它激酶的抑制剂。本公开的一些化合物和组合物可以诱导基础水平的 AR 活性（无雄激素或刺激 PKA 途径）。本公开的一些化合物和组合物可以增加 R1881 或 FSK 的诱导。此类化合物和组合物可以刺激 AR 的转录或反式激活。

[0250] 本公开的一些化合物和组合物可抑制雄激素受体的活性。白介素 -6(IL-6) 也导致 LNCaP 细胞中 AR 的配体 - 非依赖性活可以和 FSK 一起使用。

[0251] 根据本公开或用于本公开的化合物或药物组合物可借助于医疗设备或器具诸如植入物、移植物、假体、支架等来施用。同样，可以设计意图含有且释放此类化合物或组合物的植入物。实例为由适于在一段时间内释放化合物的聚合物材料制成的植入物。

[0252] 应当注意，剂量值可以随将要缓解的病症的严重性而变化。对于任何具体的受试

者，具体的剂量给药方案可以随时间根据个体需要和施用组合物或监督组合物给药的人的专业判断进行调整。本文列出的剂量范围仅是示例性的，并且不限制医学从业者可以选择的剂量范围。在组合物中活性化合物的量可以按照诸如以下因素而改变：受试者的疾病状态、年龄、性别和重量。给药方案可以进行调整以提供最佳的治疗响应。例如，可以施用单次推注，可以随时间施用数个分剂量，或者剂量可以根据治疗情形的紧急情况要求而成比例的减少或增加。以单位剂量形式配制肠胃外组合物可以是有利的，以便易于施用和剂量一致性。

[0253] 本文所述的化合物可用于体内或体外研究用途（即非临床的）以调查孤儿受体和核受体（包括类固醇受体如雄激素受体）的机制。此外，使用重组蛋白、保持在培养物中的细胞、和/或动物模型，这些化合物可以单独地使用或者作为试剂盒的一部分，用于体内或体外研究以调查信号转导途径和/或孤儿受体和核受体的激活。

[0254] 本公开的各种替代实施方案和实施例如本文所述。这些实施方案和实施例是例证性的且不应解释为限制本公开的范围。提供下列实施例用于举例说明性而非限制。

实施例

[0255] 所有非水性反应在火焰干燥的圆底烧瓶中进行。除非另有规定，否则烧瓶配备有橡胶隔片并且反应在氩气正压下进行。使用不锈钢注射器转移空气-和水分-敏感性液体。快速柱色谱如 Still 等人 (Still,W.C. ;Kahn,M. ;Mitra,A.J.Org.Chem.1978,43,2923) 所述那样，使用 230-400 目硅胶来进行。薄层色谱使用预涂敷有 0.25mm 230-400 目硅胶（用荧光指示剂浸渍）的铝板进行 (254nm)。薄层色谱板通过暴露于紫外线和“Seebach”染色溶液 (700mL 水、10.5g 硫酸铈 (IV) 十水合物、15.0g 钼合磷酸、17.5g 硫酸、之后用加热枪（～ 250℃）加热（～ 1 分钟）来显色。有机溶液在 25-40℃下在 Büchi R-114 旋转蒸发仪上减压 (15-30 托，室内真空）浓缩。

[0256] 商业试剂和溶剂按原样使用。用于提取和色谱的所有溶剂为 HPLC 级的。正相硅胶 Sep paks™购自 waters，Inc。薄层色谱板为 Kieselgel 60F_{254}。所有合成试剂购自 Sigma Aldrich and Fisher Scientific Canada。

[0257] 质子核磁共振 (^{1}H NMR) 光谱于 25℃下使用具有反向探针的 Bruker 400 和 Bruker 400 光谱仪来记录，并在 δ 级上以百万分率报道，并且参考 NMR 溶剂中的残余氕 ($CDCl_3$：δ 7.24($CHCl_3$))。碳 -13 核磁共振 (^{13}C NMR) 光谱用 Bruker 400 光谱仪记录，并在 δ 级上以百万分率报道，并且参考溶剂的碳共振 ($CDCl_3$：δ 77.23)。光谱特征以下列顺序列出：化学位移（δ，ppm）；多重性 (s ＝单重峰，d ＝双重峰，t ＝三重峰，m ＝多重峰，br ＝宽峰）；耦合常数 (J，Hz，质子数）。

[0258] LNCaP 细胞用于实验，因为它们是良好分化的人前列腺癌细胞，其中已表征 FSK 对 AR 的配体-依赖性和配体-非依赖性活化 (Nazareth 等人 1996J.Biol.Chem.271，19900-19907；和 Sadar 1999J.Biol.Chem.274,7777-7783)。LNCaP 细胞表达内源性 AR 并且分泌前列腺特异性抗原 (PSA)(Horoszewicz 等人 1983CancerRes.43,1809-1818)。LNCaP 细胞可于细胞培养基中作为单层或在充分表征的异种移植模型中作为肿瘤生长，所述异种移植模型在去势宿主中发展为去势抗性前列腺癌 (CRPC)(Sato 等人 1996J.Steroid Biochem.Mol.Biol.58,139-146；Gleave 等人 1991Cancer Res.51,3753-3761；Sato 等人

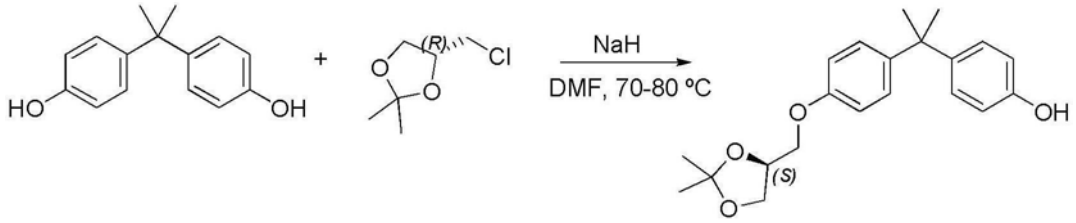
1997Cancer Res.57,1584-1589;和 Sadar 等人 2002Mol.Cancer Ther.1(8),629-637)。采用 R1881(一种合成雄激素)是因为其是稳定的并且避免与不稳定的生理配体二氢睾酮(DHT)相关的问题。

[0259] 已被广泛使用的一个充分表征的 ARE-驱动的报告基因基因构建体为 PSA(6.1kb)增强子/启动子,其含有数个 ARE 并且通过雄激素以及 FSK 高度诱导(Ueda 等人 2002 A J.Biol.Chem.277,7076-7085)。

[0260] 实施例 1

[0261] (S)-4-(2-(4-((2,2-二甲基-1,3-二氧戊环-4-基)甲氧基)苯基)丙-2-基)苯酚的合成

[0262]

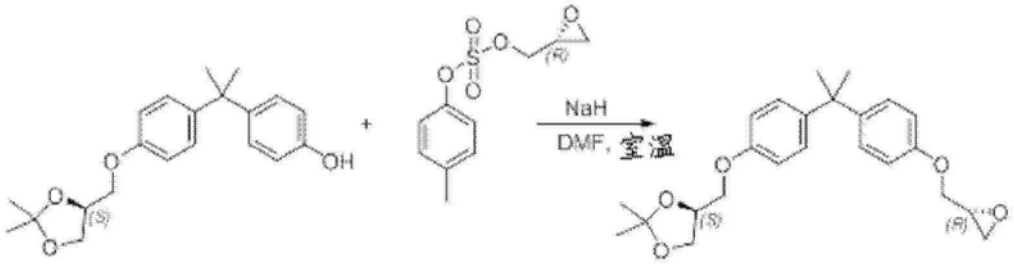


[0263] 在室温将氢化钠(60%于矿物油中的分散体,1750mg,43.80mmol,1.0 当量)缓慢地加至双酚 A(10000mg,43.80mmol,1 当量)于无水二甲基甲酰胺(30mL)中的搅拌溶液,并将内容物在氩气氛下搅拌 20 分钟。经由注射器加入(R)-(+)-4-氯甲基-2,2-二甲基-1,3-二氧戊环 98%(7.10mL,52.56mmol,1.2 当量)并使混合物在 70-80℃反应 40h。然后,通过添加氯化铵饱和溶液(10mL)来猝灭反应物,且混合物用乙酸乙酯萃取(3x 20mL)。将有机层用去离子水(25mL)洗涤,经无水硫酸镁干燥,过滤且在减压下浓缩。所得残余物通过硅胶快速柱色谱(洗脱液:含 10%乙酸乙酯的己烷)纯化以提供呈泡沫的标题化合物(3560mg,24%,25-30%转化率)。

[0264] 实施例 2

[0265] (S)-2,2-二甲基-4-((4-(2-(4-((R)-环氧乙烷-2-基甲氧基)苯基)丙-2-基)苯氧基)甲基)-1,3-二氧戊环的合成

[0266]



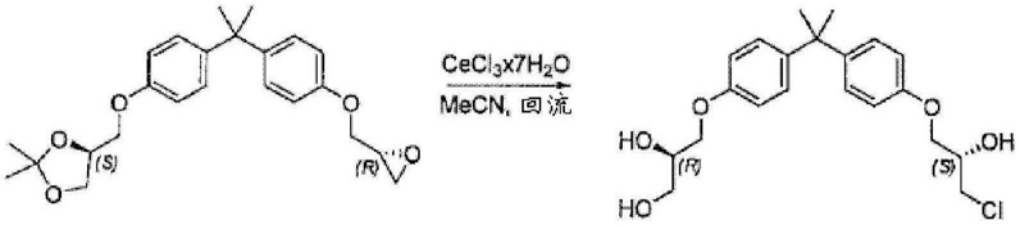
[0267] 在室温将氢化钠(60%于矿物油中的分散体,391mg,9.78mmol,1.5 当量)缓慢地加至(S)-4-(2-(4-((2,2-二甲基-1,3-二氧戊环-4-基)甲氧基)苯基)丙-2-基)苯酚(2230mg,6.52mmol,1 当量)于无水二甲基甲酰胺(15mL)中的搅拌溶液,并将内容物在氩气氛下搅拌 30 分钟。经由注射器加入(2R)-(-)-甲苯磺酸缩水甘油基酯 98%(2230mg,9.78mmol,1.5 当量)于无水二甲基甲酰胺(5mL)中的溶液并将混合物在室温反应 16h。然后,通过添加氯化铵饱和溶液(10mL)来猝灭反应物,且混合物用乙酸乙酯萃取(3x 20mL)。

将有机层用去离子水 (20mL) 洗涤，经无水硫酸镁干燥，过滤且在减压下浓缩。所得残余物通过硅胶快速柱色谱（洗脱液：含 20％至 40％乙酸乙酯的己烷）纯化以呈透明泡沫的标题化合物 (2.53g，94％)。

[0268] 实施例 3

[0269] (R)-3-(4-(2-(4-((S)-3-氯-2-羟基丙氧基)苯基)丙-2-基)苯氧基)丙烷-1，2-二醇的合成

[0270]

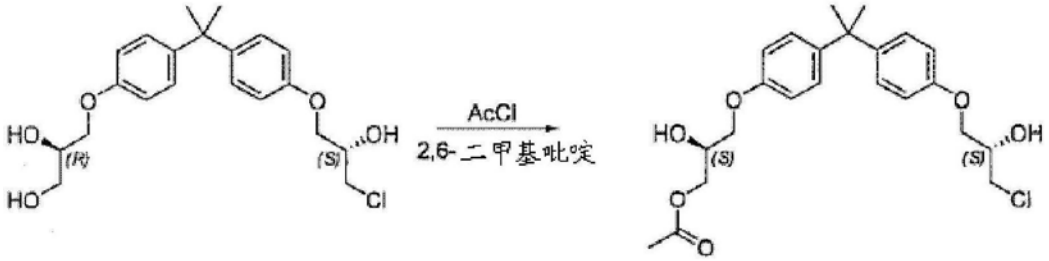


[0271] 向 (S)-2,2-二甲基-4-((4-(2-(4-((R)-环氧乙烷-2-基甲氧基)苯基)丙-2-基)苯氧基)甲基)-1,3-二氧戊环 (2530mg，6.34mmol，1 当量）于乙腈 (25mL) 中的溶液加入 $CeCl_3 \cdot 7H_2O$(5910mg，15.87mmol，2.5 当量）并将混合物回流 20h。将所得白色糊剂过滤并用乙酸乙酯洗涤，并将澄清悬浮液在减压下浓缩。所得残余物通过硅胶快速柱色谱（洗脱液：含 20％己烷的乙酸乙酯至 100％乙酸乙酯）和硅胶 Sep pak(10g，洗脱液：含 50％己烷的乙酸乙酯至 80％乙酸乙酯）纯化以提供呈透明泡沫的标题化合物 (2250mg，90％)。

[0272] 实施例 4

[0273] 乙酸 (S)-3-(4-(2-(4-((S)-3-氯-2-羟基丙氧基)苯基)丙-2-基)苯氧基)-2-羟丙基酯的合成

[0274]



[0275] 在 -78℃向 (R)-3-(4-(2-(4-((S)-3-氯-2-羟基丙氧基)苯基)丙-2-基)苯氧基)丙烷-1，2-二醇 (1000mg，2.53mmol) 于无水二氯甲烷 (8.0mL) 中的溶液连续逐滴加入 2，6-二甲基吡啶 (590μL，5.06mmol) 和乙酰氯 (144μL，2.02mmol)。1h 后，将反应混合物用氯化钠水溶液猝灭并搅拌 15 分钟，且所得混合物用二氯甲烷萃取两次。将有机相合并，经无水硫酸镁干燥并过滤。蒸发溶剂，并将所得粗材料通过硅胶快速色谱（洗脱液：含 2％甲醇的二氯甲烷）纯化以提供呈粘性固体的标题化合物 (300mg，27％)。

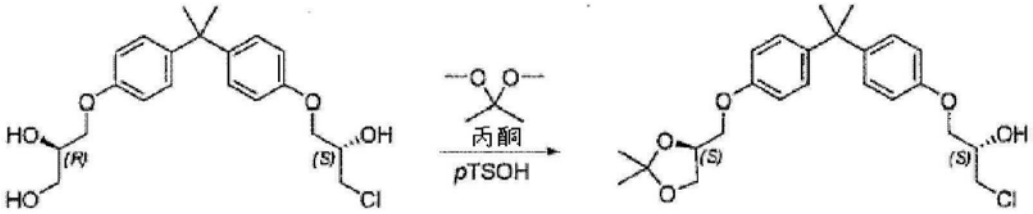
[0276] 图 1(A)-(C) 举例说明了标题化合物乙酸 (S)-3-(4-(2-(4-((S)-3-氯-2-羟基丙氧基)苯基)丙-2-基)苯氧基)-2-羟丙基酯的 ^1H 和 ^{13}C-NMR 数据。

[0277] 实施例 5

[0278] (S)-1-氯-3-(4-(2-(4-(((S)-2,2-二甲基-1,3-二氧戊环-4-基)甲氧基)苯

基）丙-2-基）苯氧基）丙-2-醇的合成

[0279]

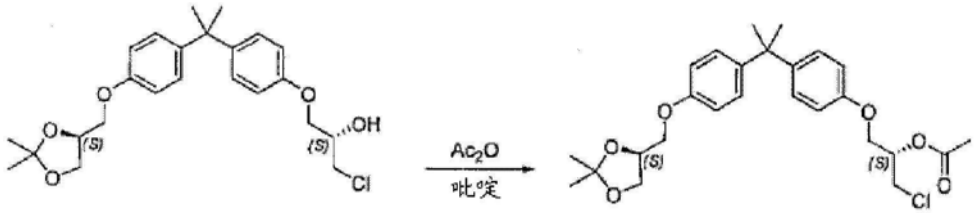


[0280] 向(R)-3-(4-(2-(4-((S)-3-氯-2-羟基丙氧基）苯基）丙-2-基）苯氧基）丙烷-1,2-二醇(1000mg,2.53mmol)于丙酮(8.0mL)中的溶液加入2,2-二甲氧基丙烷(630μL,5.06mmol)和催化量的对甲苯磺酸。14h后,将反应混合物用氯化钠水溶液猝灭并搅拌15分钟,且将所得混合物用乙酸乙酯萃取两次。将有机相合并,经无水硫酸镁干燥并过滤。蒸发溶剂,并将所得粗材料通过硅胶快速色谱(洗脱液:含2%甲醇的二氯甲烷)纯化以提供标题化合物。

[0281] 实施例6

[0282] 乙酸(S)-1-氯-3-(4-(2-(4-(((S)-2,2-二甲基-1,3-二氧戊环-4-基）甲氧基）苯基）丙-2-基）苯氧基）丙-2-基酯的合成

[0283]

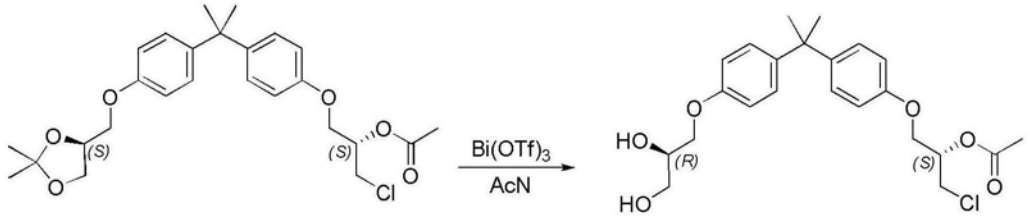


[0284] 向(S)-1-氯-3-(4-(2-(4-(((S)-2,2-二甲基-1,3-二氧戊环-4-基）甲氧基）苯基）丙-2-基）苯氧基）丙-2-醇(850mg,1.95mmol)于无水吡啶(6.0mL)中的溶液连续加入乙酸酐(280μL,2.93mmol)和催化量的DMAP。3h后,将反应混合物用氯化钠水溶液猝灭并搅拌15分钟,且将所得混合物用乙酸乙酯萃取两次。将有机相合并,经无水硫酸镁干燥并过滤。蒸发溶剂,且所得粗材料不经进一步纯化即可使用。

[0285] 实施例7

[0286] 乙酸(S)-1-氯-3-(4-(2-(4-((R)-2,3-二羟基丙氧基）苯基）丙-2-基）苯氧基）丙-2-基酯的合成

[0287]



[0288] 向粗的乙酸(S)-1-氯-3-(4-(2-(4-(((S)-2,2-二甲基-1,3-二氧戊环-4-基）甲氧基）苯基）丙-2-基）苯氧基）丙-2-基酯于无水乙腈(8.0mL)中的溶液一次性加入三氟甲磺酸铋(300mg,0.46mmol)。0.5h后,将反应混合物用碳酸氢钠和乙酸乙酯分配两次。将有机相合并,经无水硫酸镁干燥,且过滤。蒸发溶剂,且所得粗材料通过硅胶快速色

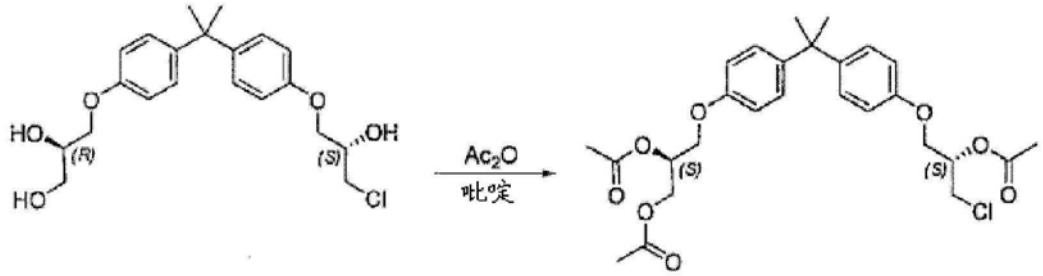
谱（洗脱液：含 2％至 5％甲醇的二氯甲烷）纯化以提供呈粘性固体的标题化合物（734mg，86％）。

[0289] 图 2(A)-(C) 举例说明了标题化合物乙酸 (S)-1- 氯 -3-(4-(2-(4-((R)-2,3- 二羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 基酯的 ^{1}H 和 ^{13}C-NMR 数据。

[0290] 实施例 8

[0291] 二乙酸 (S)-3-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯的合成

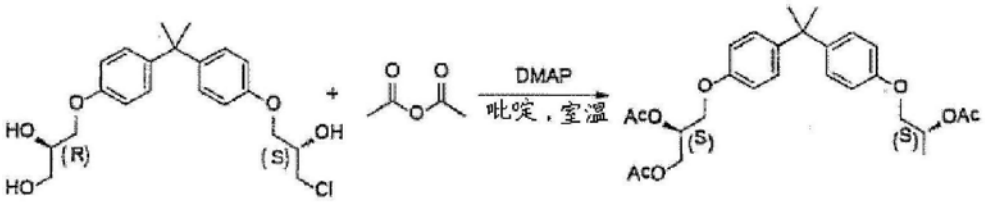
[0292]



[0293] 向 (R)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇 (500mg,1.27mmol) 于无水吡啶 (6.0mL) 中的溶液连续加入乙酸酐 (605μL,6.35mmol) 和催化量的 DMAP。14h 后，将反应混合物用氯化钠水溶液猝灭并搅拌 15 分钟，且所得混合物用二氯甲烷萃取两次。将有机相合并，经无水硫酸镁干燥，且过滤。蒸发溶剂，并将所得粗材料通过硅胶快速色谱（洗脱液：含 2％甲醇的二氯甲烷）纯化以提供呈粘性固体的标题化合物 (621mg,94％)。

[0294] 在另一个实施方案中，标题化合物二乙酸 (S)-3-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯可经由下列反应方案合成。

[0295]



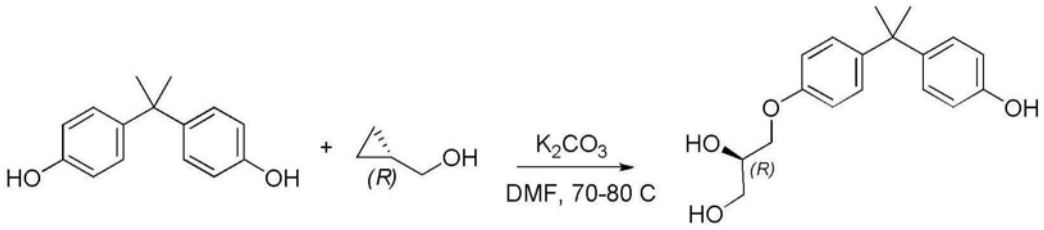
[0296] 将乙酸酐 (4.3g,41.7mmol) 加入至在水浴中的 (R)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇 (2.8g,6.95mmol) 和 DMAP(30mg,0.25mmol) 于无水吡啶 (24mL) 中的溶液。将所得溶液搅拌过夜。在减压下除去吡啶且残余物用乙酸乙酯 (50mL) 稀释，随后用水洗涤 (2x 40mL)，然后用冷的 1M HCl 水溶液 (40mL)、饱和的 $NaHCO_3$(40mL) 和水 (40mL) 洗涤。将有机层经 Mg_2SO_4 干燥，过滤且浓缩以得到浅黄色油状物。粗产物通过柱色谱（洗脱液：含 5％乙酸乙酯的己烷至含 20％乙酸乙酯的己烷）纯化以提供呈无色粘稠油的标题化合物 (3.30g,91.5％产率)。

[0297] 图 3(A)-(B) 举例说明了标题化合物二乙酸 (S)-3-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯的 ^{1}H 和 ^{13}C-NMR 数据。

[0298] 实施例 9

[0299] (R)-3-(4-(2-(4- 羟基苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇的合成

[0300]

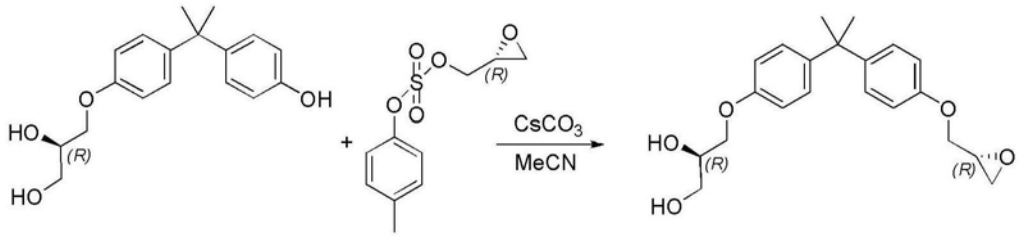


[0301] 向双酚 A(10g,43.84mmol,1.0 当量）于无水二甲基甲酰胺 (35mL) 中的搅拌溶液在室温加入 K_2CO_3(9.1g,65.76mmol,1.5 当量），并将混合物在氩气氛下搅拌 20 分钟。加入 R(+) 缩水甘油 (3.8mL,56.99mmol,1.3 当量）并将混合物在 70-80℃搅拌 5h。在室温将氯化铵饱和溶液 (10mL) 加入至所得橙棕色溶液。混合物用乙酸乙酯萃取 (3x 15mL)。有机层用去离子水 (10mL) 洗涤，经无水硫酸镁干燥，过滤，且在减压下浓缩。所得残余物通过硅胶快速柱色谱（洗脱液：含 40％至 90％乙酸乙酯的己烷）纯化以提供呈透明泡沫的标题化合物 (3.77g,28％）。

[0302] 实施例 10

[0303] (R)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇的合成

[0304]

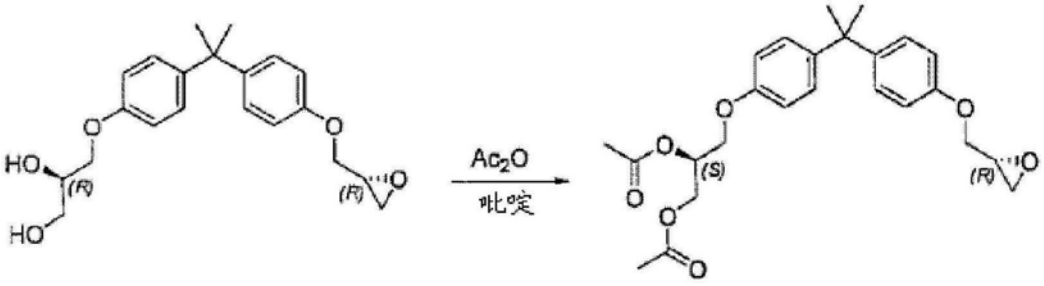


[0305] 向 (R)-3-(4-(2-(4- 羟基苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇 (3.77g,12.49mmol,1.0 当量）于无水乙腈 (35mL) 中的搅拌溶液在室温加入碳酸铯 (6.1g,18.73mmol,1.5 当量），并将混合物在氩气氛下搅拌 20 分钟。经由注射器缓慢加入 (2R)-(-)- 甲苯磺酸缩水甘油基酯 98％ (4.3g,18.73mmol,1.5 当量）于无水乙腈 (8mL) 中的溶液，且使混合物在 30℃反应 120h。在室温用氯化铵饱和溶液 (5mL) 来猝灭反应物混合物。混合物用乙酸乙酯萃取 (3x 10mL)。有机层用去离子水 (10mL) 洗涤，经无水硫酸镁干燥，过滤且在减压下浓缩。所得残余物通过硅胶快速柱色谱（洗脱液：含 5％至 10％甲醇的二氯甲烷）纯化以提供呈透明泡沫的标题化合物 (4.1g,91％）。

[0306] 实施例 11

[0307] 二乙酸 (S)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯的合成

[0308]



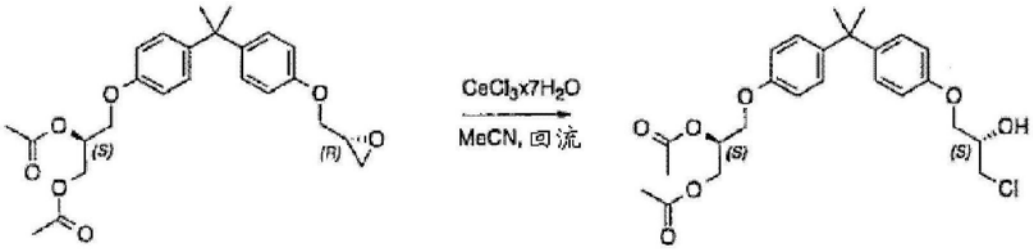
[0309] 向 (R)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇 (3000mg,8.37mmol) 于无水吡啶 (15.0mL) 中的溶液连续加入乙酸酐 (1.97mL,20.92mmol) 和催化量的 DMAP。14h 后,将反应混合物用氯化钠水溶液猝灭并搅拌 15 分钟,且所得混合物用二氯甲烷萃取两次。将有机相合并,经无水硫酸镁干燥并过滤。蒸发溶剂,并将所得粗材料通过硅胶快速色谱（洗脱液 :含 2％甲醇的二氯甲烷）纯化以提供呈粘性固体的标题化合物 (3.3g,89％）。

[0310] 图 4(A)-(C) 举例说明了标题化合物二乙酸 (S)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯的 ^{1}H 和 ^{13}C-NMR 数据。

[0311] 实施例 12

[0312] 二乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯的合成

[0313]



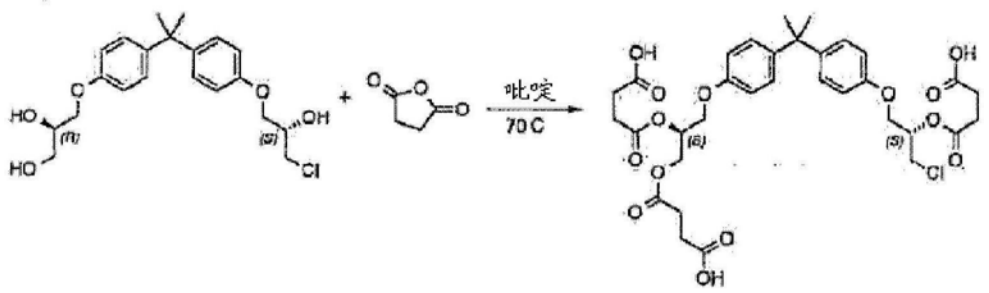
[0314] 向二乙酸 (S)-3-(4-(2-(4-((R)- 环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯 (180mg,0.41mmol,1 当量）于乙腈 (6mL) 中的溶液加入 $CeCl_3 \cdot 7H_2O$(227mg,0.61mmol,1.5 当量）并将混合物回流 6h。将所得白色糊剂过滤且用乙酸乙酯洗涤,并在减压下浓缩澄清悬浮液。所得残余物通过硅胶快速柱色谱（洗脱液 :含 20％己烷的乙酸乙酯至 60％乙酸乙酯）纯化以提供呈粘性团块的标题化合物 (172mg,88％）。

[0315] 图 5(A)-(C) 是标题化合物二乙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯的 ^{1}H、^{13}C 和 ^{13}C APT NMR 光谱。

[0316] 实施例 13

[0317] 三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇酯 :

[0318]

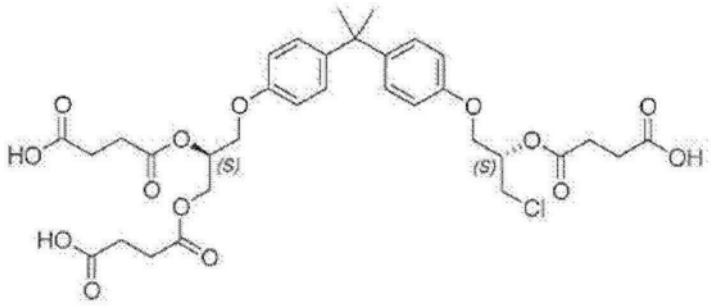


[0319] 向 (R)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇 (700mg,1.77mmol) 于无水吡啶 (6.0ml) 中的溶液加入琥珀酸酐 (710mg,7.10mmol) 且将混合物在 70℃加热。3h 后,将反应混合物用氯化钠水溶液猝灭并搅拌 15 分

钟，且将所得混合物用乙酸乙酯萃取两次。将有机相合并，经无水硫酸镁干燥，且过滤。蒸发溶剂，且所得粗材料通过硅胶快速色谱（洗脱液：含 5％至 30％甲醇的二氯甲烷）纯化以提供标题化合物。

[0320] 标题化合物的分子式也可如下所示：

[0321]



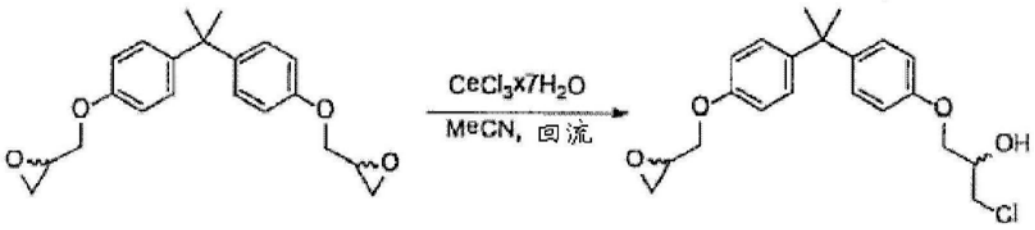
[0322] 图 6(A)-(C) 是标题化合物三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇酯的 ^{1}H 和 ^{13}C 以及 ^{13}C APT NMR 光谱。

[0323] 图 6(D) 和 (E) 是三琥珀酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇酯的 ESI MS 光谱。

[0324] 实施例 14

[0325] (2S)-1- 氯 -3-(4-(2-(4-（环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇的合成

[0326]

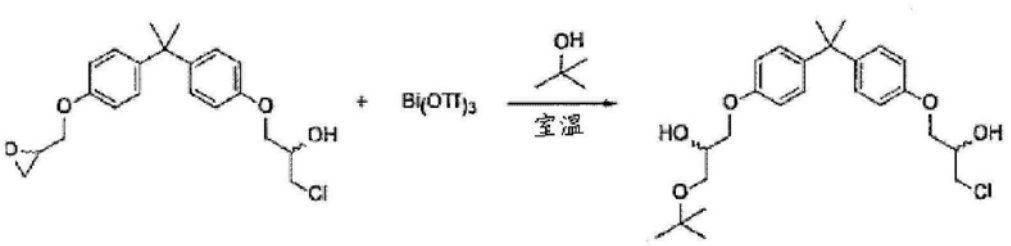


[0327] 向外消旋衍生物双酚 A 二缩水甘油基醚 (13.30g,39.27mmol,1 当量）于乙腈 (30mL) 中的溶液加入 $CeCl_3 \cdot 7H_2O$(7.30g,19.63mmol,1/2 当量）并将混合物回流 3.5h。将所得白色糊剂过滤且用乙酸乙酯洗涤，并在减压下浓缩澄清悬浮液。所得残余物通过硅胶快速柱色谱（洗脱液：含 10％乙酸乙酯的己烷）纯化以提供呈灰色液体的 (2S)-1- 氯 -3-(4-(2-(4-（环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇 (2.12g,14％）。

[0328] 实施例 15

[0329] 1-（叔丁氧基）-3-(4-(2-(4-(3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇的合成

[0330]

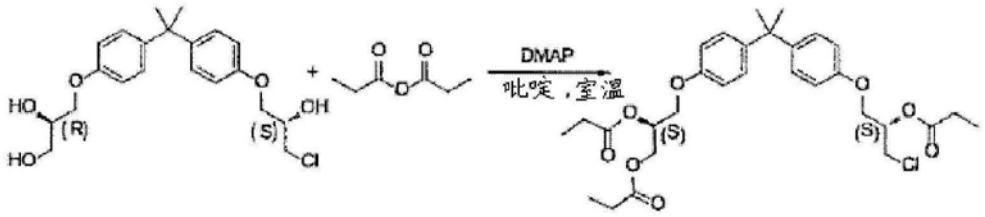


[0331] 向外消旋 1- 氯 -3-(4-(2-(4-(环氧乙烷 -2- 基甲氧基) 苯基) 丙 -2- 基) 苯氧基) 丙 -2- 醇 (300mg,0.8mmol,1 当量) 于叔丁醇 (5mL) 中的溶液一次性加入固体三氟甲烷磺酸铋 (III)(10mg,0.015mmol,1/50 当量) 并将混合物在室温搅拌 12h。加入碳酸氢钠 (0.5mL),在减压下蒸发有机溶剂,且残余物用二氯甲烷萃取 (3x 10mL)。有机层用去离子水洗涤 (2x 10mL),经无水硫酸镁干燥,过滤,且在减压下浓缩。所得残余物通过硅胶快速柱色谱 (洗脱液 :含 40％至 80％乙酸乙酯的己烷) 纯化以提供呈泡沫的 1-(叔丁氧基)-3-(4-(2-(4-(3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙 -2- 醇 (100mg,28％)。

[0332] 实施例 16

[0333] 二丙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2-(丙酰氧基) 丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的合成

[0334]



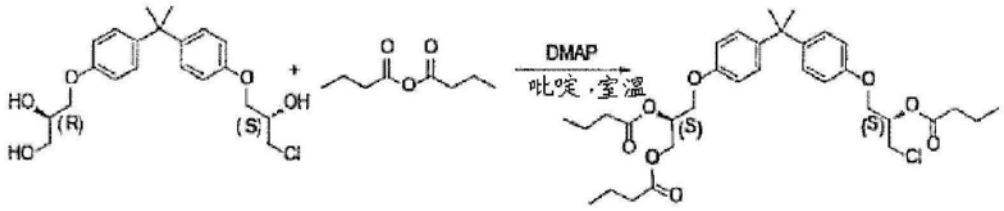
[0335] 将丙酸酐 (4.3g,41.7mmol) 加入至水浴中的 (R)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二醇 (2.8g,6.95mmol) 和 DMAP(30mg,0.25mmol) 于无水吡啶 (24mL) 中的溶液。将所得溶液搅拌过夜。在减压下除去吡啶且残余物用乙酸乙酯 (50mL) 稀释,随后用水洗涤 (2x 40mL),然后用冷的 1M HCl 水溶液 (40mL)、饱和 $NaHCO_3$(40mL) 和水 (40mL) 洗涤。将有机层经 Mg_2SO_4干燥,过滤且浓缩以得到浅黄色油状物。粗产物通过柱色谱 (洗脱液 :含 5％乙酸乙酯的己烷至含 20％乙酸乙酯的己烷) 纯化以提供呈无色粘稠油的标题化合物 (3.30g,91.5％产率)。

[0336] 图 15A 和 15B 是二丙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2-(丙酰氧基) 丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的 ^1H 和 ^{13}C NMR 光谱。

[0337] 实施例 17

[0338] 二丁酸 (S)-3-(4-(2-(4-((S)-2-(丁酰氧基)-3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基) 丙烷 -1,2- 二基酯的合成

[0339]



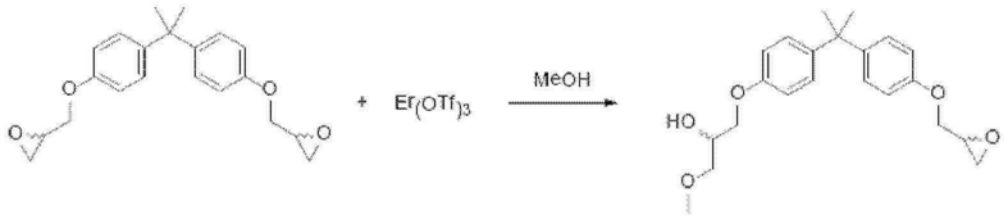
[0340] 将丁酸酐 (4.3g,41.7mmol) 加入至水浴中的 (R)-3-(4-(2-(4-((S)-3- 氯 -2- 羟基丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二醇 (2.8g,6.95mmol) 和 DMAP(30mg,0.25mmol) 于无水吡啶 (24mL) 中的溶液。将所得溶液搅拌过夜。在减压下除去吡啶且残余物用乙酸乙酯 (50mL) 稀释，随后用水洗涤 (2x 40mL)，然后用冷的 1M HCl 水溶液 (40mL)、饱和 $NaHCO_3$(40mL) 和水 (40mL) 洗涤。将有机层经 Mg_2SO_4干燥，过滤且浓缩以得到浅黄色油状物。粗产物通过柱色谱（洗脱液：含 5％乙酸乙酯的己烷至含 20％乙酸乙酯的己烷）纯化以提供呈无色粘稠油状物的标题化合物 (3.30g,91.5％产率）。

[0341] 图 16A 和 16B 是二丁酸 (S)-3-(4-(2-(4-((S)-2-（丁酰氧基）-3- 氯丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯的 ^1H 和 ^{13}C NMR 光谱。

[0342] 实施例 18

[0343] 1- 甲氧基 -3-(4-(2-(4-（环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇的合成

[0344]



[0345] 向外消旋衍生物双酚 A 二缩水甘油基醚 (500mg,1.46mmol,1 当量）于甲醇 (5mL) 中的溶液一次性加入固体三氟甲烷磺酸铒 (III)(90mg,0.146mmol,1/10 当量）并将混合物在室温搅拌 1h。加入碳酸氢钠 (1mL)，在减压下蒸发有机溶剂且残余物用二氯甲烷萃取 (3x 5mL)。将有机层用去离子水洗涤 (2x 5mL)，经无水硫酸镁干燥，过滤，且在减压下浓缩。所得残余物通过硅胶快速柱色谱（洗脱液：含 10％至 40％乙酸乙酯的己烷）纯化以提供呈灰白泡沫的标题化合物 (128mg,23％）。

[0346] 实施例 19

[0347] 1- 氯 -3-(4-(2-(4-(2- 羟基 -3- 甲氧基丙氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇的合成

[0348]

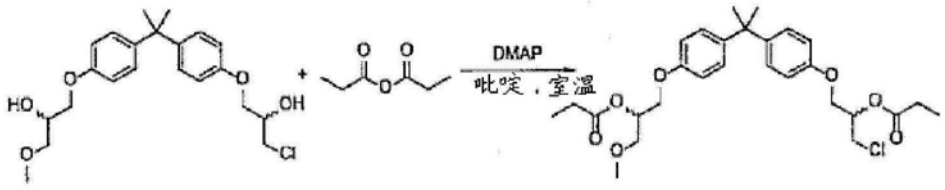
[0349] 向外消旋衍生物 1- 甲氧基 -3-(4-(2-(4-（环氧乙烷 -2- 基甲氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇 (64mg,0.17mmol,1 当量）于乙腈 (2mL) 中的溶液加入

$CeCl_3 \cdot 7H_2O$(96mg,0.25mmol,1.5 当量）并将混合物回流 17h。将所得白色糊剂过滤且用乙酸乙酯洗涤，并在减压下浓缩澄清悬浮液。所得残余物通过硅胶快速柱色谱（洗脱液：含 40％乙酸乙酯的己烷）纯化以提供呈灰白泡沫的标题化合物（70mg,99％）。

[0350] 实施例 20

[0351] 二丙酸 1- 氯 -3-(4-(2-(4-(2- 羟基 -3- 甲氧基丙氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇酯的合成

[0352]



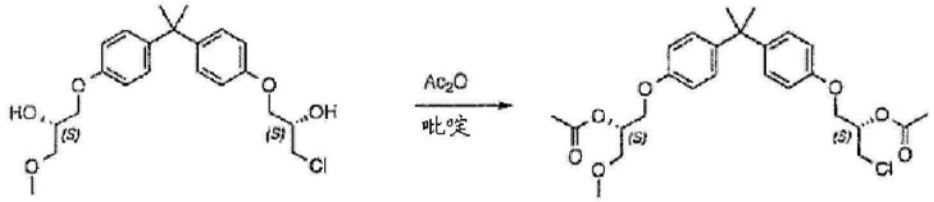
[0353] 如实施例 17 中对于二丙酸 (S)-3-(4-(2-(4-((S)-3- 氯 -2-（丙酰氧基）丙氧基）苯基）丙 -2- 基）苯氧基）丙烷 -1,2- 二基酯所述进行制备。

[0354] 图 14A 和 14B 是二丙酸 1- 氯 -3-(4-(2-(4-(2- 羟基 -3- 甲氧基丙氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇酯的 ^1H 和 ^{13}C NMR 光谱。

[0355] 实施例 21

[0356] 乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基）苯基）丙 -2- 基）苯氧基）-3- 甲氧基丙 -2- 基酯的合成

[0357]



[0358] 向 (S)-1- 氯 -3-(4-(2-(4-((S)-2- 羟基 -3- 甲氧基丙氧基）苯基）丙 -2- 基）苯氧基）丙 -2- 醇（15mg,0.036mmol）于无水吡啶（1.0ml）中的溶液连续加入乙酸酐（9μL,0.091mmol）和催化量的 DMAP。5h 后，将反应混合物用氯化钠水溶液猝灭并搅拌 15 分钟，且所得混合物用二氯甲烷萃取两次。将有机相合并，经无水硫酸镁干燥，且过滤。蒸发溶剂，且所得粗材料通过硅胶快速色谱（洗脱液：含 10 至 20％乙酸乙酯的己烷）纯化以提供呈粘性固体的标题化合物。

[0359] 图 7(A)-(C) 是标题化合物乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基）苯基）丙 -2- 基）苯氧基）-3- 甲氧基丙 -2- 基酯的 ^1H、^{13}C 和 ^{13}C APT NMR 光谱。

[0360] 图 6(D) 和 (E) 是乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基）苯基）丙 -2- 基）苯氧基）-3- 甲氧基丙 -2- 基酯的 ESI MS 光谱。

[0361] 化合物的体外活性

[0362] 实施例 22

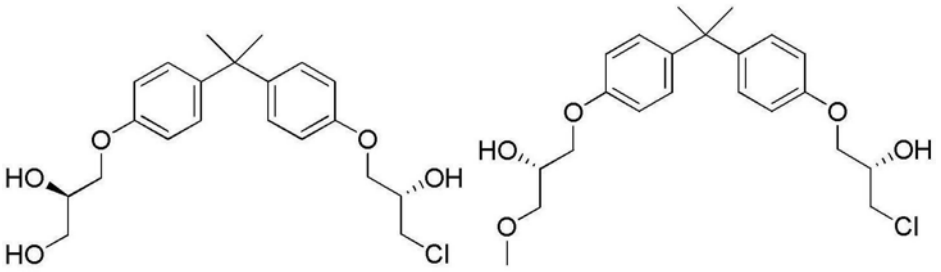
[0363] 将 LNCaP($2.4x10^4$个细胞 / 孔）细胞接种于 24- 孔板中过夜，然后用 PSA(6.1kb)- 荧光素酶质粒 (0.25ug/ 孔）于无血清无酚红的培养基中转染。次日，将细胞用本公开化合物预处理 1 小时，然后添加合成雄激素、R1881(1nM) 以反式激活雄激素受体。

在用R1881孵育48h后，收集细胞，并将相对荧光素酶活性确定为雄激素受体转录活性的读数。将测试化合物以各种浓度加入至细胞并且将每种处理的活性标准化至所预测的最大活性诱导（在缺乏测试化合物下，仅媒介物）。使用一式三份的孔进行转染实验。

[0364] 图8示出本公开的各个化合物(7c、3c和13b)相对于比较化合物A和B的体外剂量响应。

[0365] 如图8中看出，每个本公开的测试化合物显示剂量响应。

[0366]

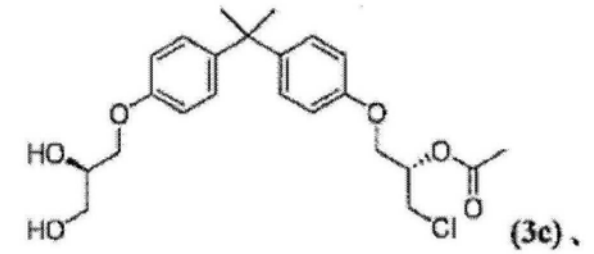


化合物A **化合物B**

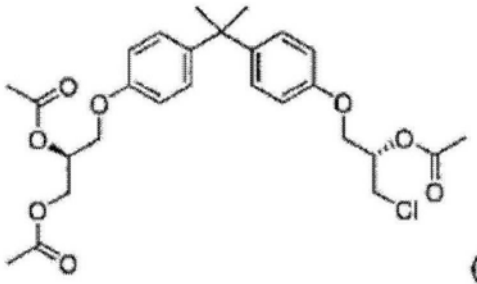
[0367] 此外，通过显微镜检查和降低蛋白质水平来评估毒性。通过目视（混浊培养基）和通过显微镜（颗粒或晶体的形成）二者来评估溶解度。

[0368] 因此，测试化合物

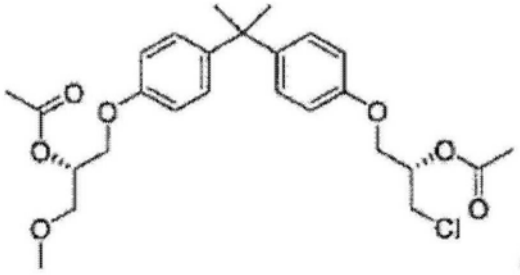
[0369]



(3c)、



(7c)和



(13b)

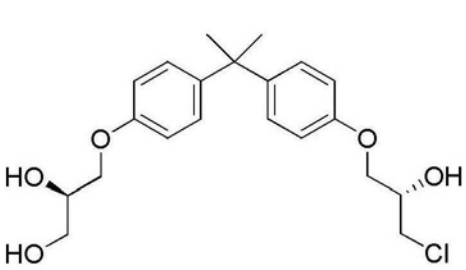
[0370] 在本文公开的治疗方法方面有效并表明在5μM、10μM和20μM下的剂量响应。

[0371] 实施例 23

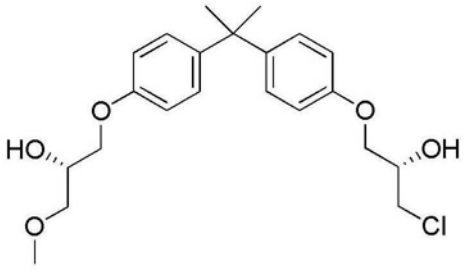
[0372] 如实施例 22 中概述的进一步实验利用用 PSA- 荧光素酶质粒转染的 LNCaP 细胞进行，以评价本公开的特定化合物的剂量响应。

[0373] 本公开化合物与化合物 A 和 B 比较，如在实施例 22 中 ：

[0374]



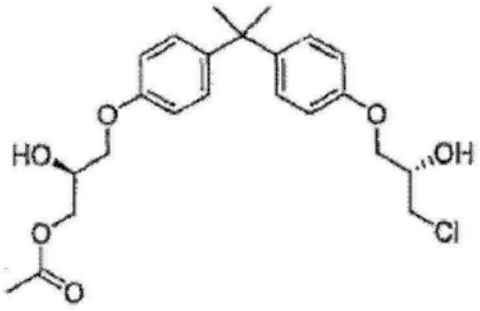
化合物 A



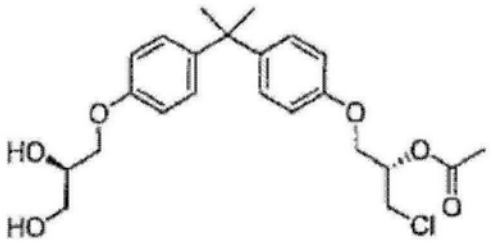
化合物 B

[0375] 所评价的本公开化合物如下 ：

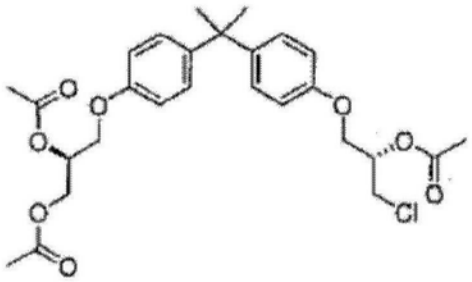
[0376]



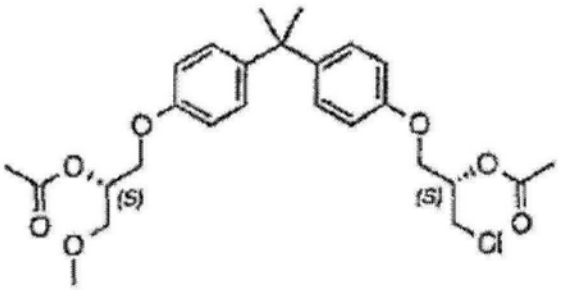
(1c)、



(3c)、



(7c)和



[0377] 乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯 (实施例 21)

[0378] 图 9 示出本公开的各个化合物 (1c、3c 7c 和乙酸 (S)-1-(4-(2-(4-((S)-2- 乙酰氧基 -3- 氯丙氧基) 苯基) 丙 -2- 基) 苯氧基)-3- 甲氧基丙 -2- 基酯 (实施例 21)) 相对于比较化合物 A 和 B 的体外剂量响应。

[0379] 下列表 4 也举例说明了图 9 中含有的数据并且表明本公开化合物展现出剂量响应。

[0380] 表 4.

[0381]

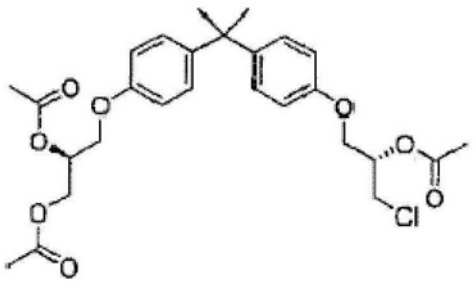
类似物	IC50 (μM +标准偏差)
化合物 A	15.02 + 1.25
化合物 1C	25.58 + 6.89
化合物 3C	11.61 + 2.6
化合物 7C	8.81 + 0.93
化合物 B	9.80 + 2.28
乙酸(S)-1-(4-(2-(4-((S)-2-乙酰氧基-3-氯丙氧基)苯基)丙-2-基)苯氧基)-3-甲氧基丙-2-基酯(实施例 21)	8.07 + 1.48

[0382] 实施例 24

[0383] 进行活力和增殖测定,且表明本公开的前药化合物的效力为其活性化合物的两倍。

[0384] 本公开化合物 :

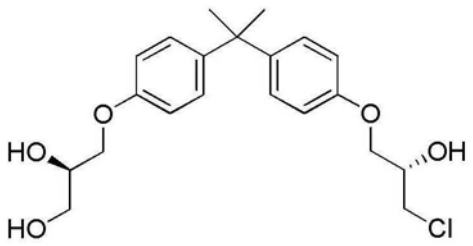
[0385]



(7c),

[0386] 与化合物 A 比较 :

[0387]



化合物 A。

[0388] 方案 :使用 AlamarBlue 的增殖测定,其中雄激素 - 依赖性增殖%表示与基础水平比较,响应于 R1881 的 LNCaP 细胞的增殖。PC3 细胞不表达功能性雄激素受体且活力%提供与雄激素受体无关的细胞毒性或脱靶效应的指示。

[0389] 活力和增殖测定。将 PC3 和 LNCaP 细胞于各自培养基 +0.5% FBS 中在 96- 孔板中铺板。第二天,将 PC3 细胞用媒介物和递增浓度的化合物 A 或化合物 7c 处理 2 天,且将 LNCaP 细胞用媒介物和化合物 A 预处理 1 小时,之后用 0.1nM R1881 处理 3 天。使用 alamarBlue

细胞活力测定（Invitrogen）按照制造商的方案来测量细胞活力。

[0390] 结果于图 10 中示出并且表明本公开的前药化合物（即 7c）的效力是其活性化合物（即化合物 A）的两倍。

[0391] 实施例 25

[0392] 异种移植实验

[0393] 当肿瘤体积为约 100mm3 时对携带皮下肿瘤的雄性 NOD-SCID 小鼠进行去势。

[0394] 每天通过口服管饲法用化合物 7c、化合物 A 或 10％ DMSO/ 玉米油媒介物对照对携带 LNCaP 异种移植物的动物给药。

[0395] 使用卡尺测量肿瘤并通过应用式 (LxWxH)*0.5236 计算体积。

[0396] 如从图 11 可见，本公开化合物（即化合物 7c）在减少肿瘤体积方面有效。

[0397] 此外，图 11 表明本公开的前药化合物（即化合物 7c）在减少异种移植小鼠模型的肿瘤体积方面比其活性化合物（即化合物 A）更有效。

[0398] 实施例 26

[0399] 进一步的异种移植实验

[0400] 当肿瘤体积为约 100mm3 时对携带皮下肿瘤的雄性 NOD-SCID 小鼠进行去势。

[0401] 每天通过口服管饲法用 55.23mg/kg 体重的化合物 7c 或 CMC/10％ DMSO/Tween-20 媒介物对照对携带 LNCaP 异种移植物的动物给药。

[0402] 使用卡尺测量肿瘤并通过应用式 (LxWxH)*0.5236 雄性计算体积

[0403] 如从图 12 可见，本公开化合物的前药立体异构体（即化合物 7c）在减少肿瘤体积方面有效。

[0404] 实施例 27

[0405] 本公开的前药的 IC50

[0406] 表 5 举例说明了本公开的各个前药相较于化合物 A 的 IC50。

[0407] 图 13 进一步说明了本公开的各个化合物的 IC50。

[0408] 表 5

[0409]

化合物	PSA-luc IC50 (uM) 平均值	SD	n
化合物 A	14.0	0.8	5
化合物 4c	15.3	3.4	4
二乙酸	26.0	4.1	4

[0410]

(S)-3-(4-(2-(4-((R)-环氧乙烷-2-基甲氧基)苯基)丙-2-基)苯氧基)丙烷-1,2-二基酯			
三琥珀酸(S)-3-(4-(2-(4-((S)-3-氯-2-羟基丙氧基)苯基)丙-2-基)苯氧基)丙烷-1,2-二醇酯	60.2	8.1	2
2-氨基乙酸(S)-3-(4-(2-(4-((S)-3-氯-2-羟基丙氧基)苯基)丙-2-基)苯氧基)-2-羟丙基酯	12.1	2.5	4

[0411] 通过引用并入

[0412] 在本说明书中提及的和/或在申请数据表中列出的所有美国专利、美国专利申请公开、美国专利申请、外国专利、外国专利申请和非专利出版物为了所有目的通过引用整体并入本文。

[0413] 如有需要，可对实施方案的各方面进行改变以采用通过引用并入本文的各种专利、申请和出版物的概念，从而提供更进一步的实施方案。依据以上详细描述可对实施方案进行这些和其它变化。

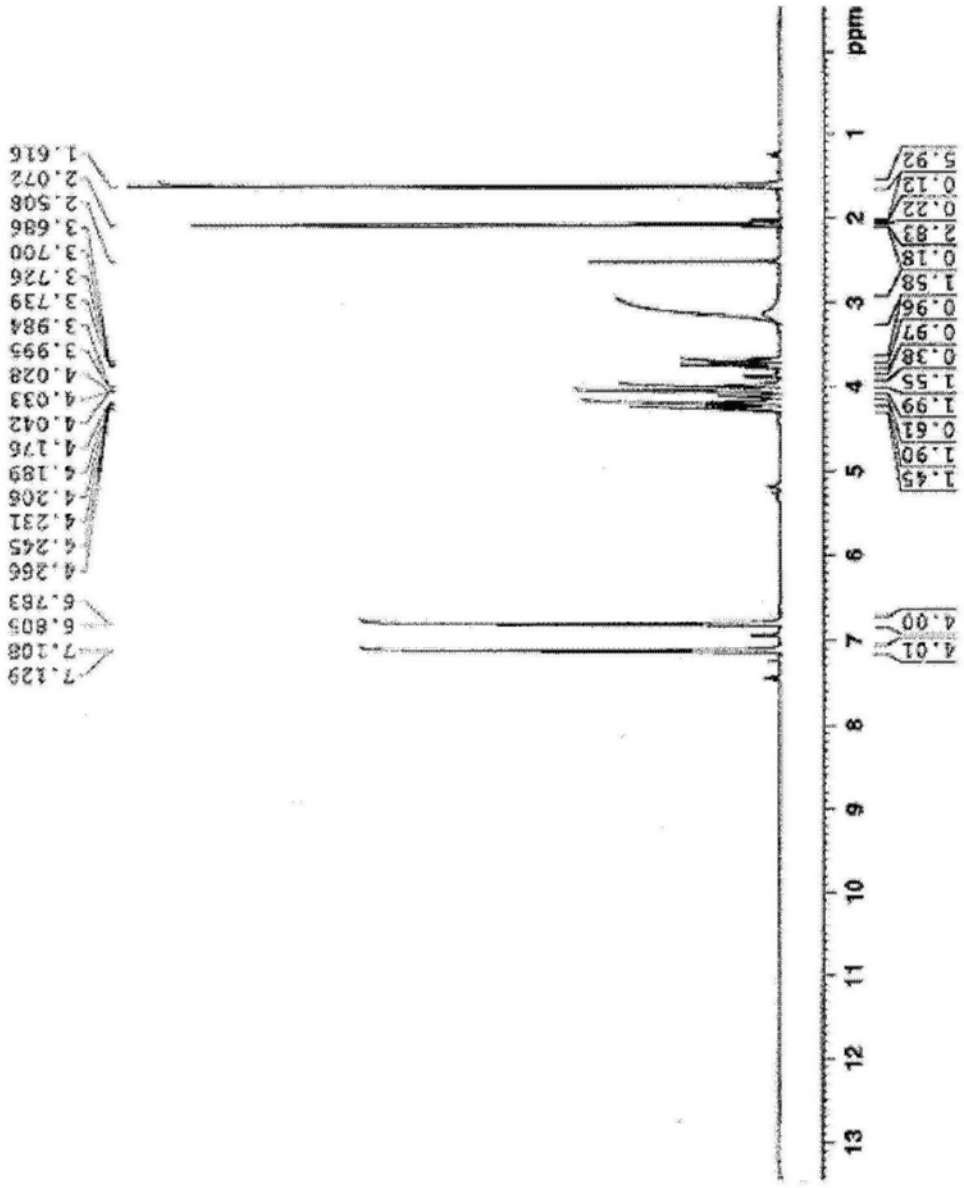

ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
1.616
2.072
2.508
3.686
3.700
3.726
3.739
3.984
3.995
4.028
4.033
4.042
4.176
4.189
4.206
4.231
4.245
4.266
6.783
6.805
7.108
7.129
5.92
0.13
0.22
2.83
0.18
1.58
0.96
0.97
0.38
1.55
1.99
0.61
1.90
1.45
4.00
4.01

图 1A

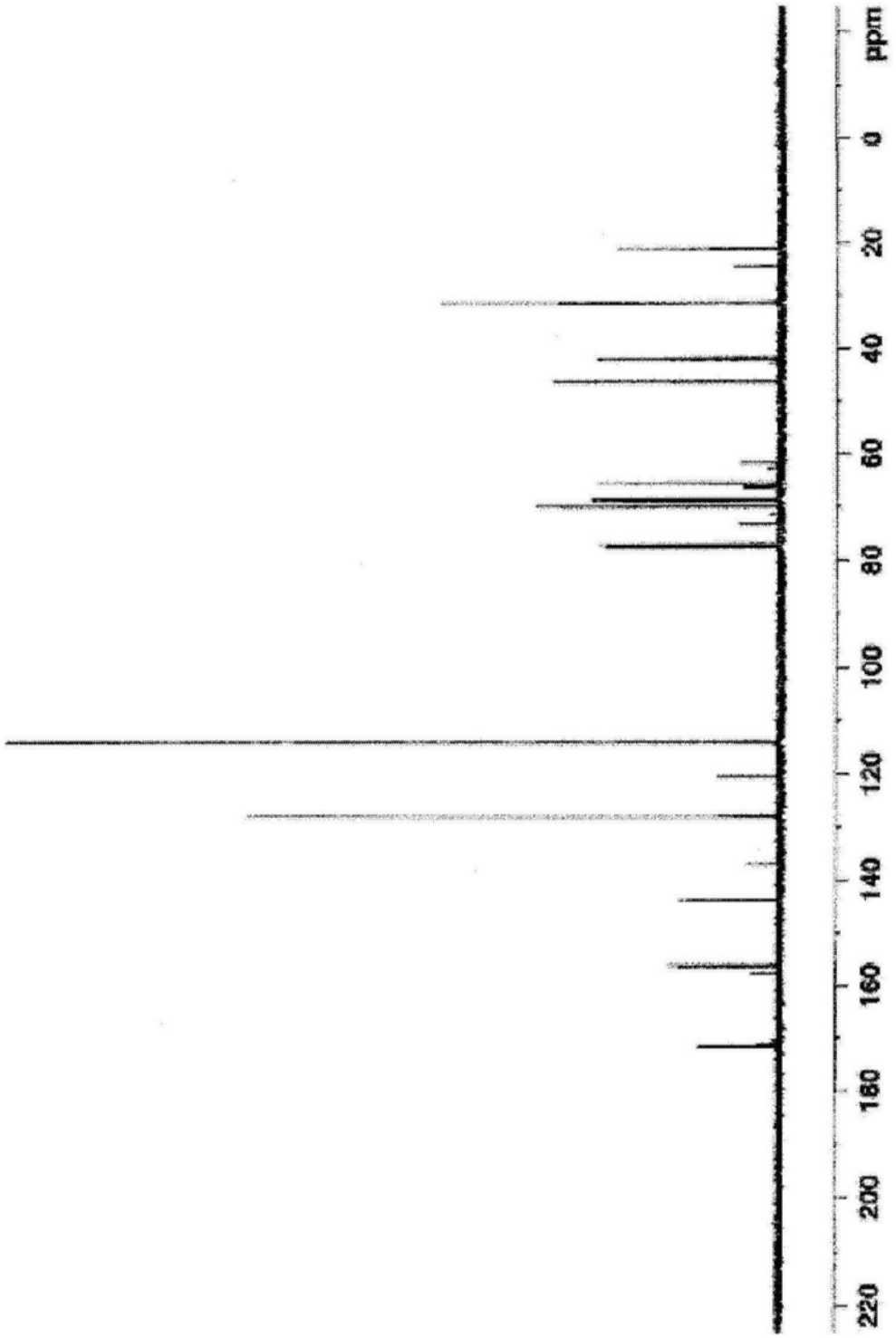


图 1B

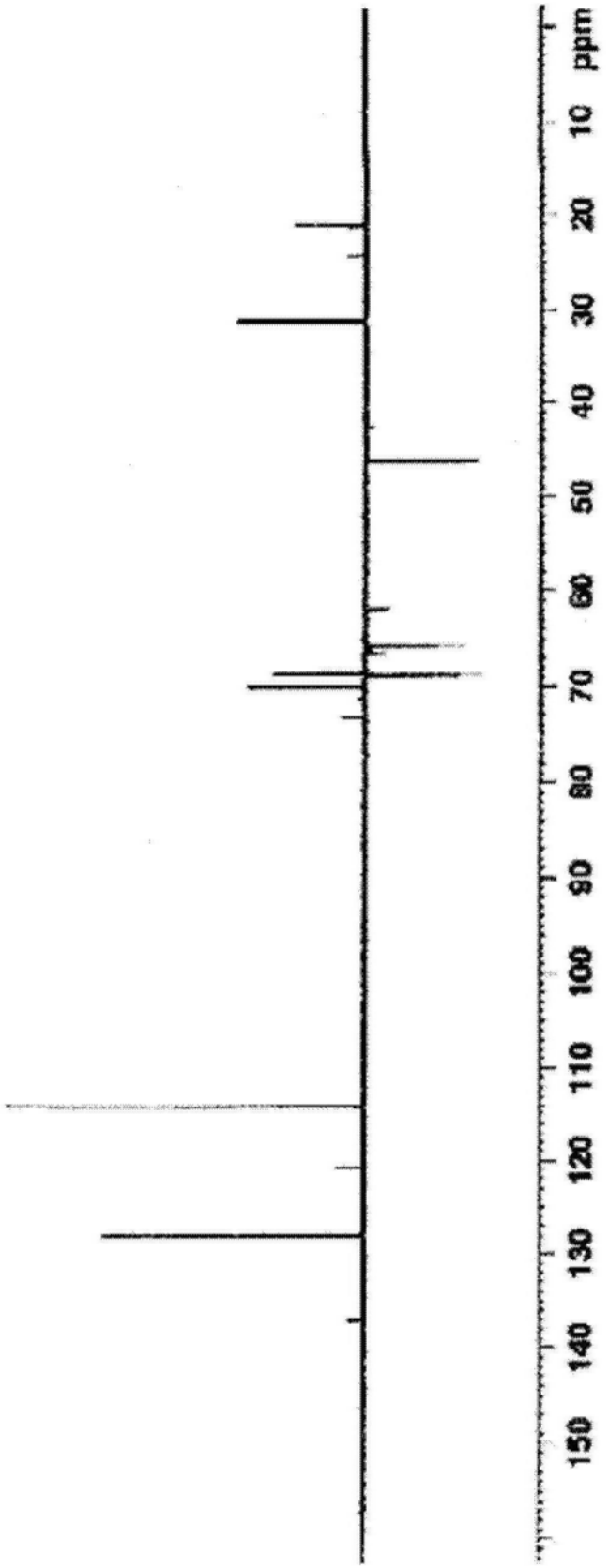


图 1C

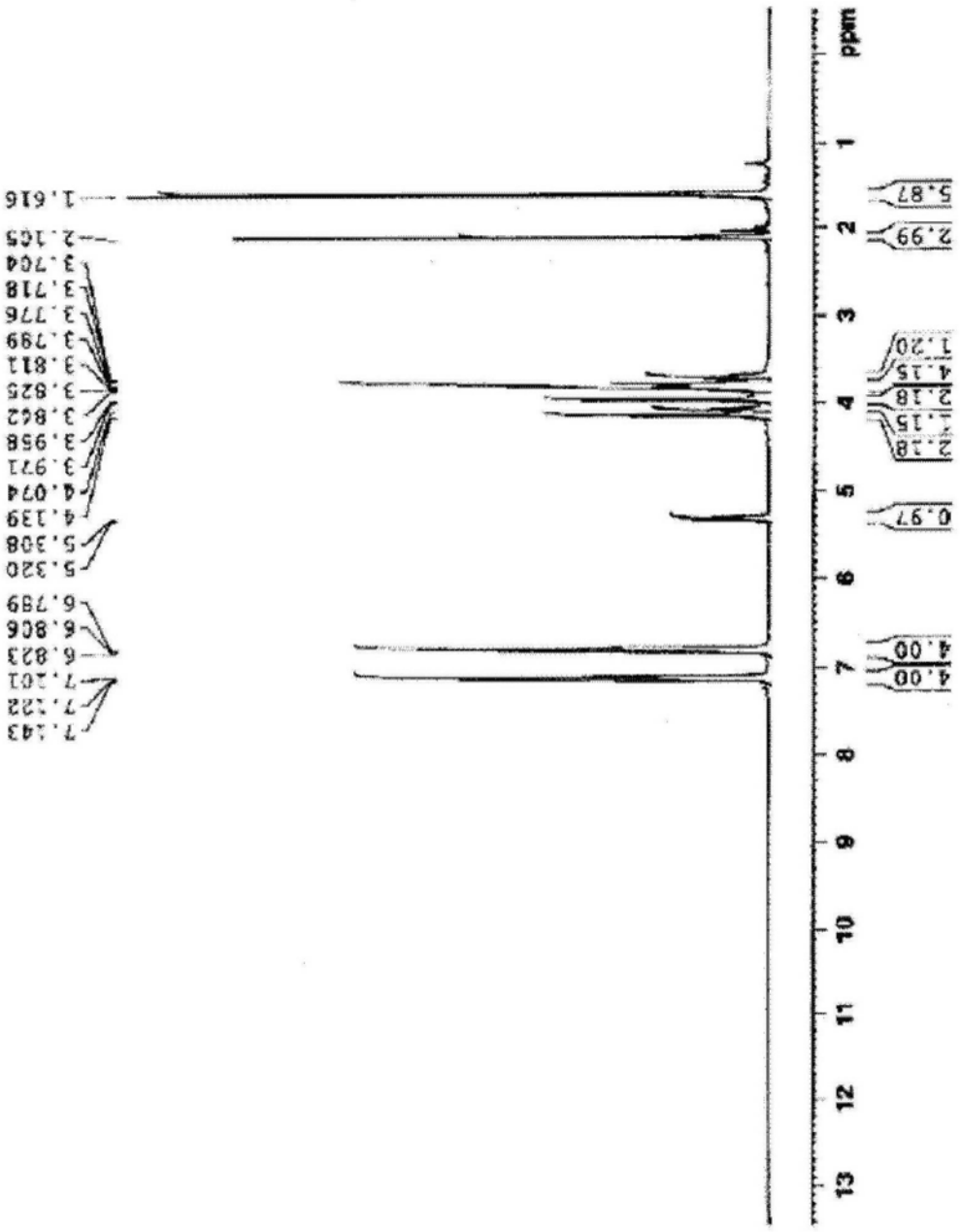

1.616
2.165
3.704
3.718
3.776
3.799
3.811
3.825
3.862
3.958
3.971
4.074
4.139
5.308
5.320
6.789
6.806
6.823
7.161
7.222
7.243
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
5.87
2.99
1.20
4.15
2.18
4.15
2.18
0.97
4.00
4.00

图 2A

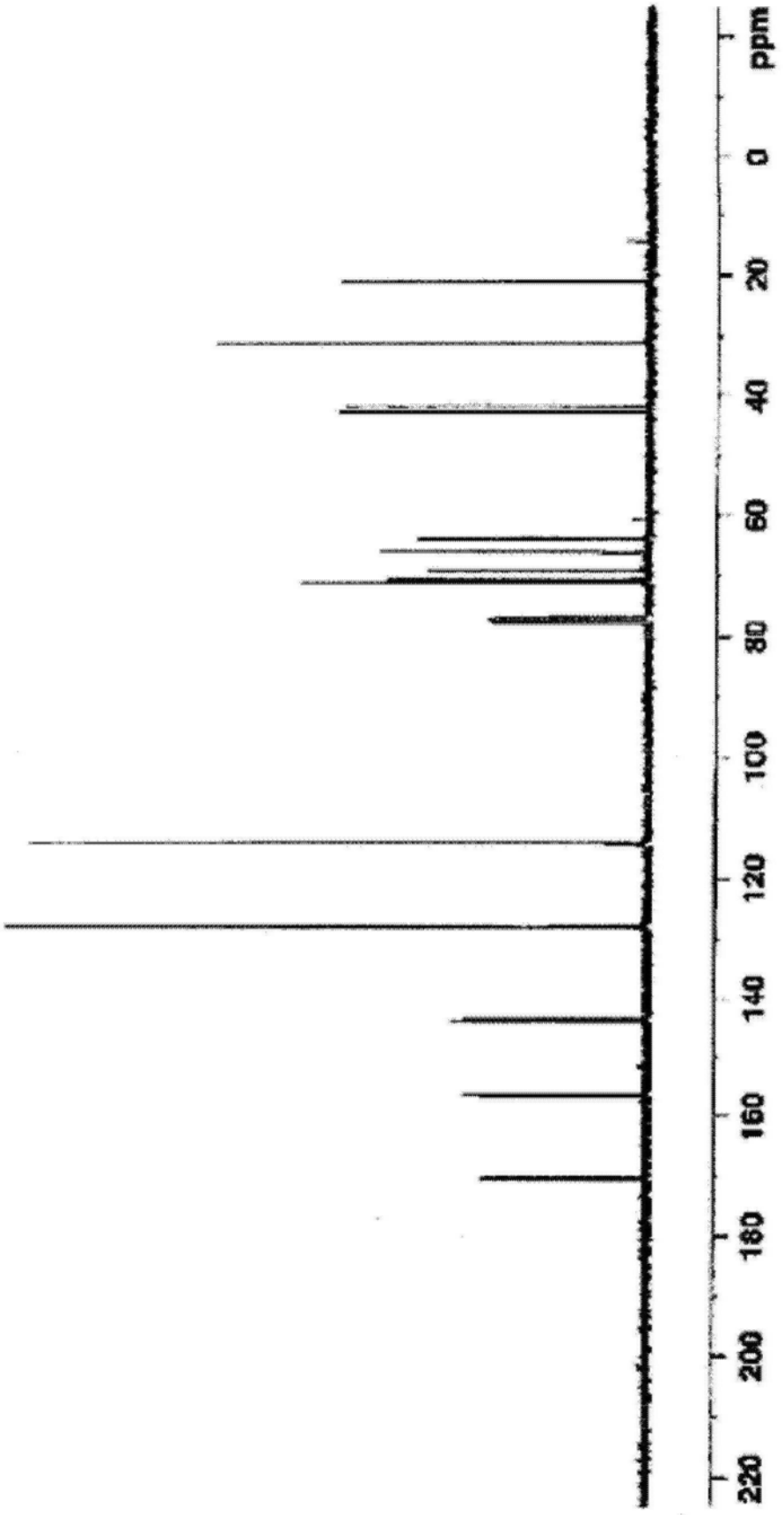


图 2B

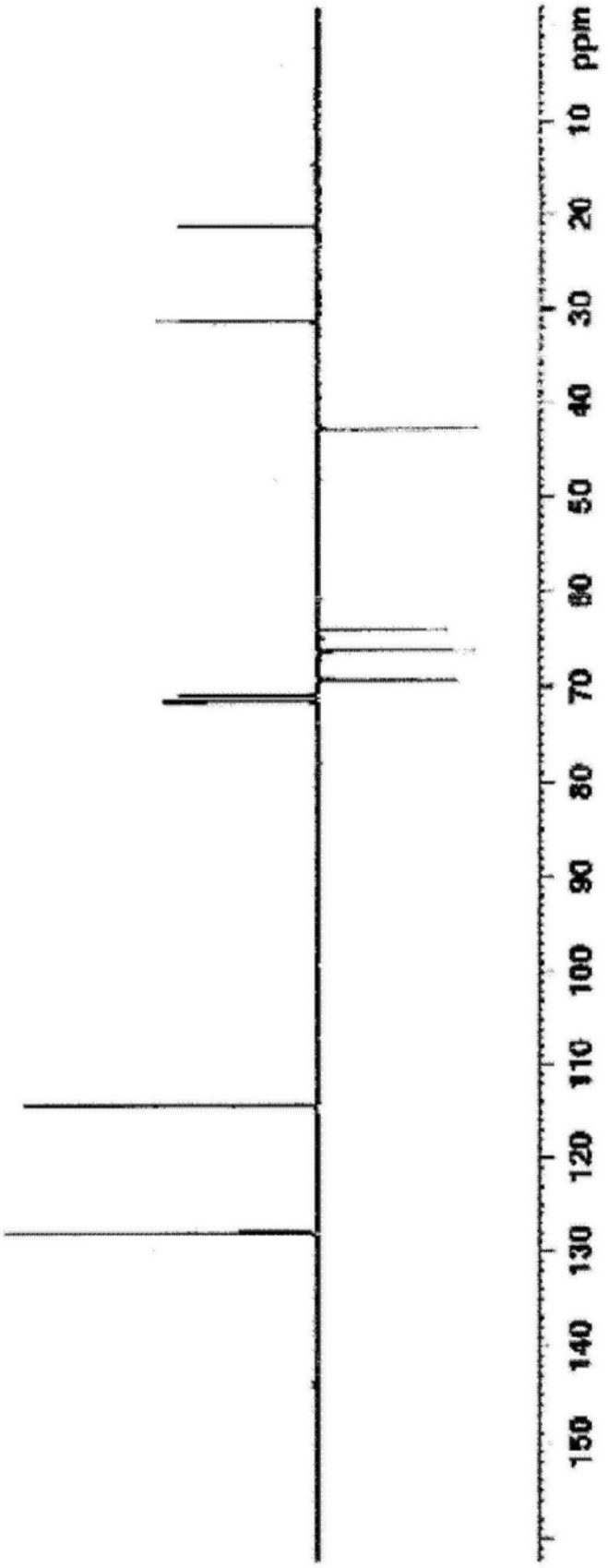


图 2C

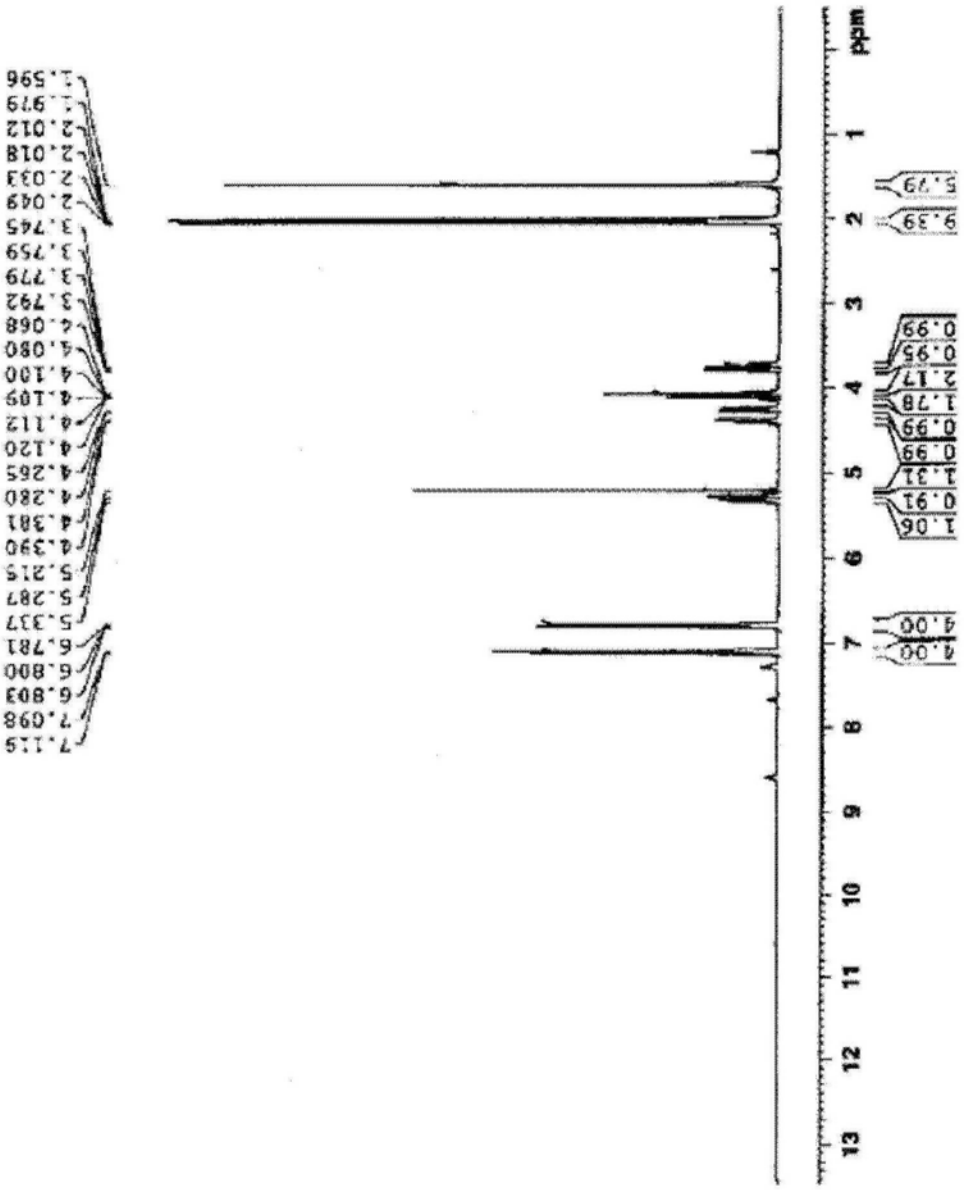

1.596
1.979
2.012
2.018
2.033
2.049
3.745
3.759
3.779
3.792
4.068
4.080
4.100
4.109
4.112
4.120
4.265
4.280
4.381
4.390
5.215
5.287
5.337
6.781
6.800
6.803
7.098
7.115
5.79
9.39
0.99
0.95
2.17
1.78
0.99
0.99
1.31
0.91
1.06
4.00
4.00
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13

图 3A

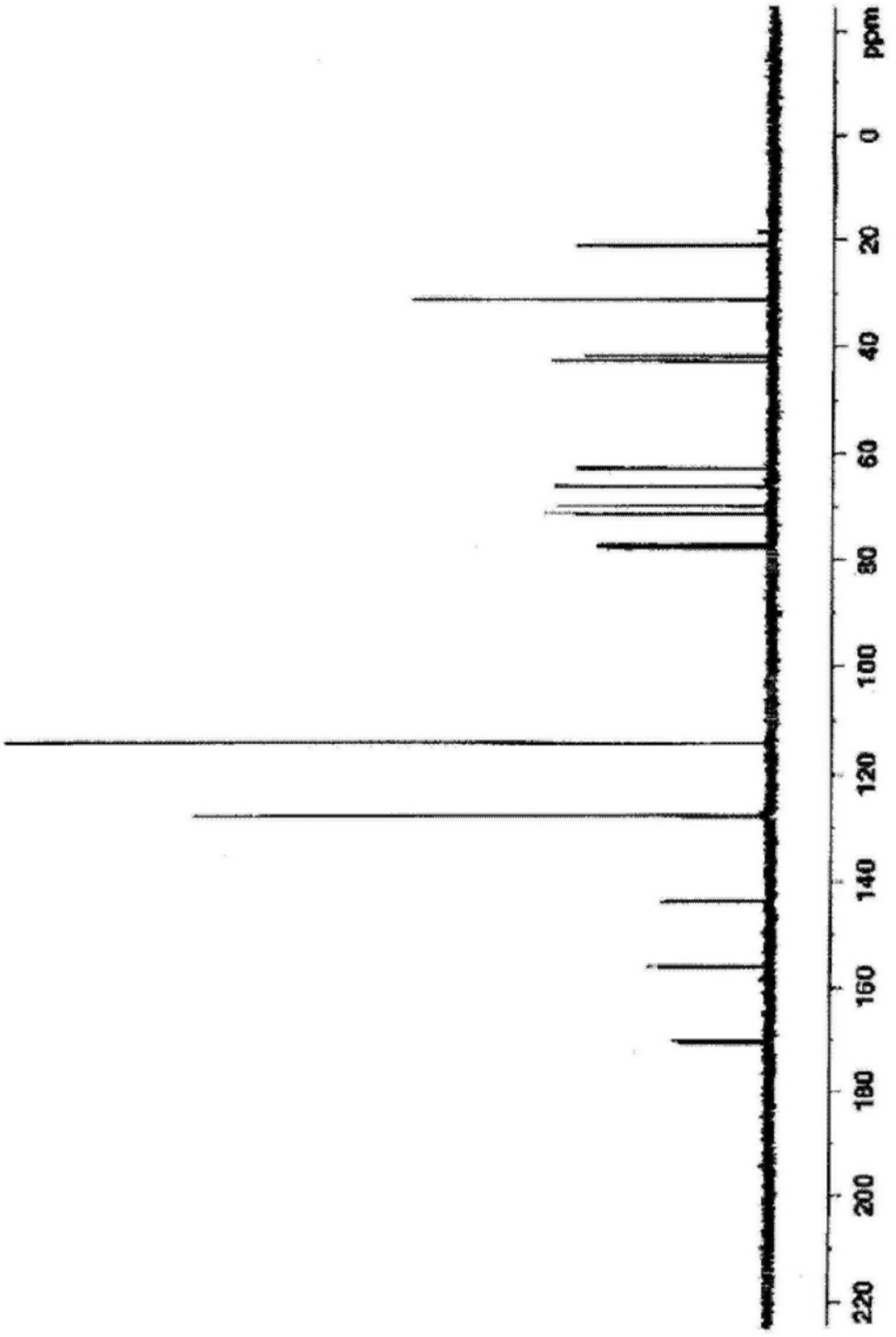


图 3B

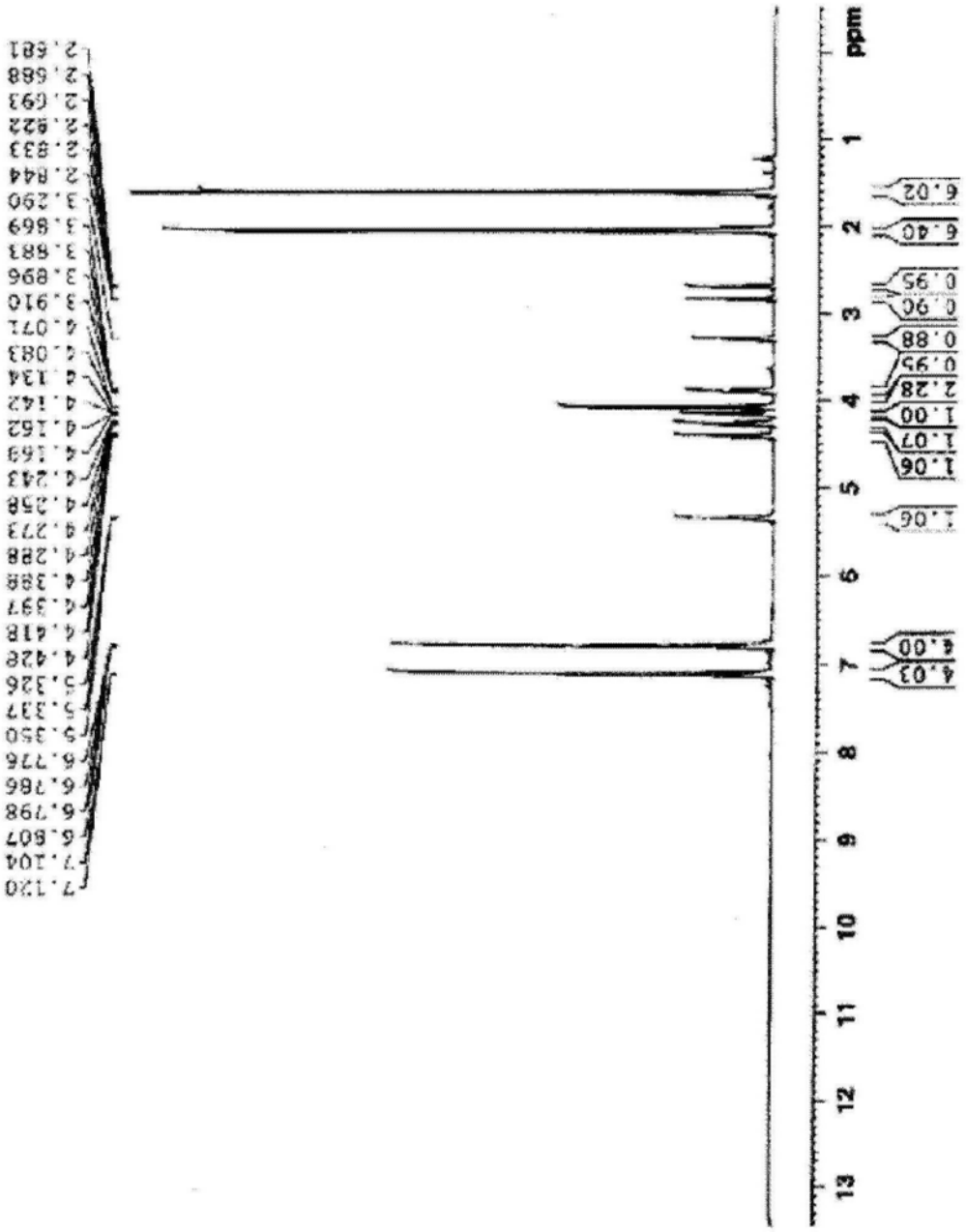

ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
6.02
6.40
0.95
0.90
0.88
0.95
2.28
1.00
1.07
1.06
1.06
4.00
4.03

图 4A

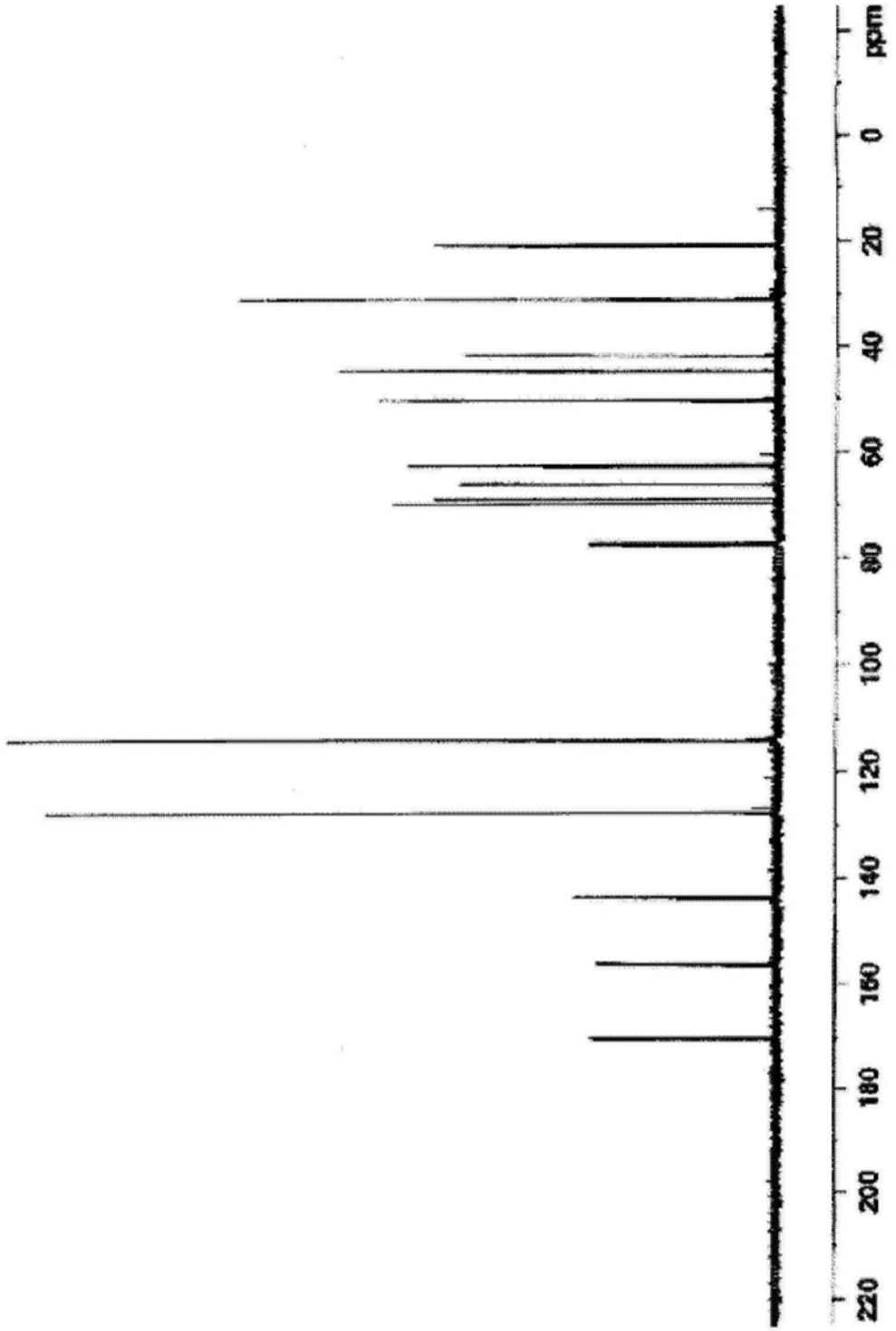


图 4B

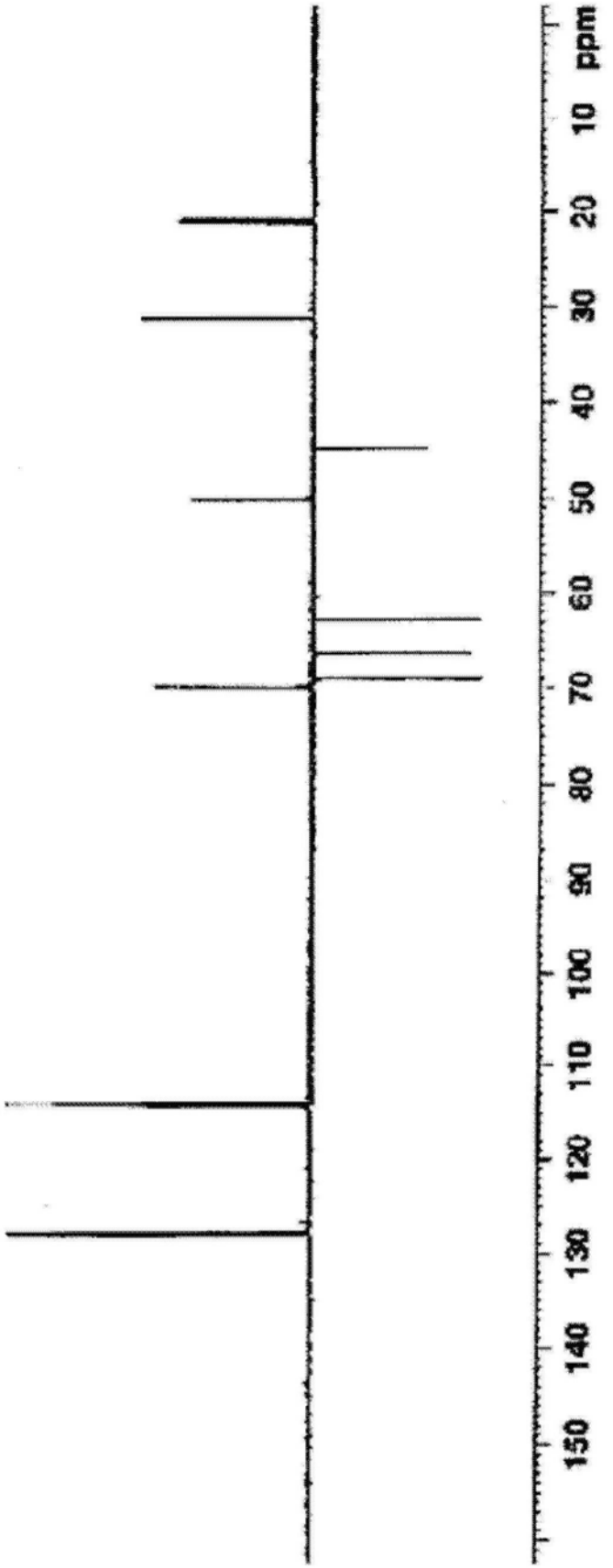


图 4C

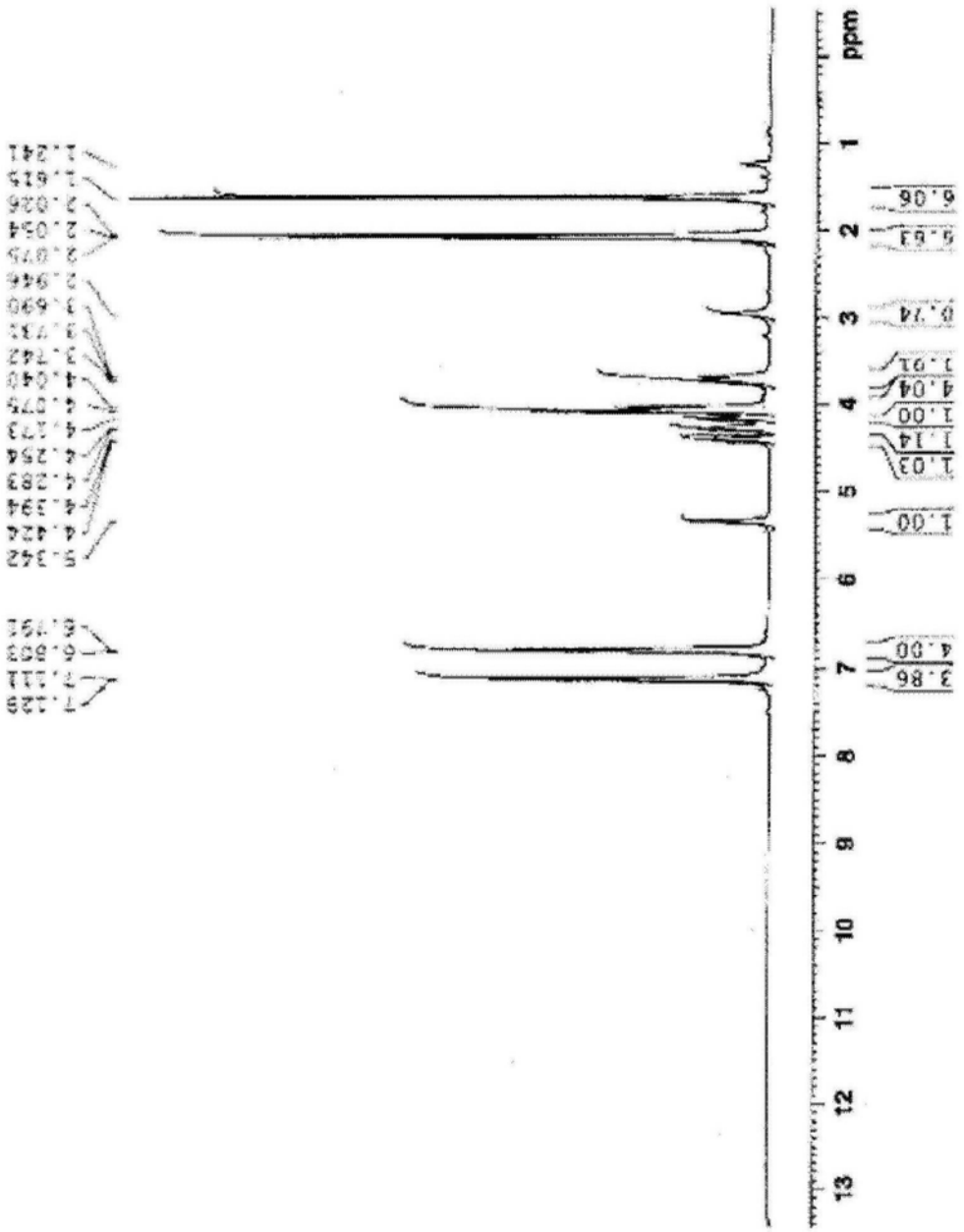

ppm
1 2 3 4 5 6 7 8 9 10 11 12 13
6.06
5.83
0.74
1.91
4.04
1.00
1.14
1.03
1.00
4.00
3.86

图 5A

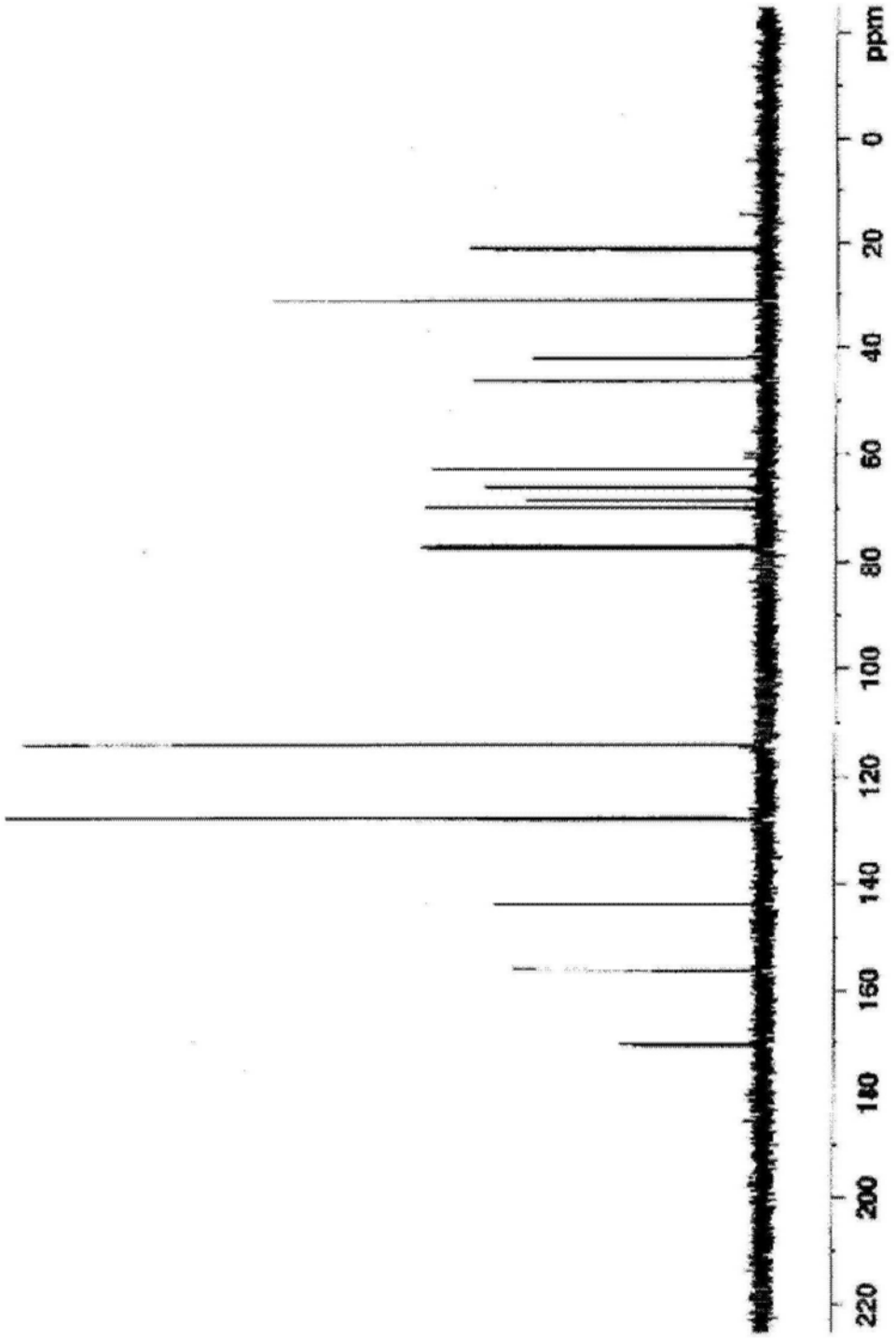


图 5B

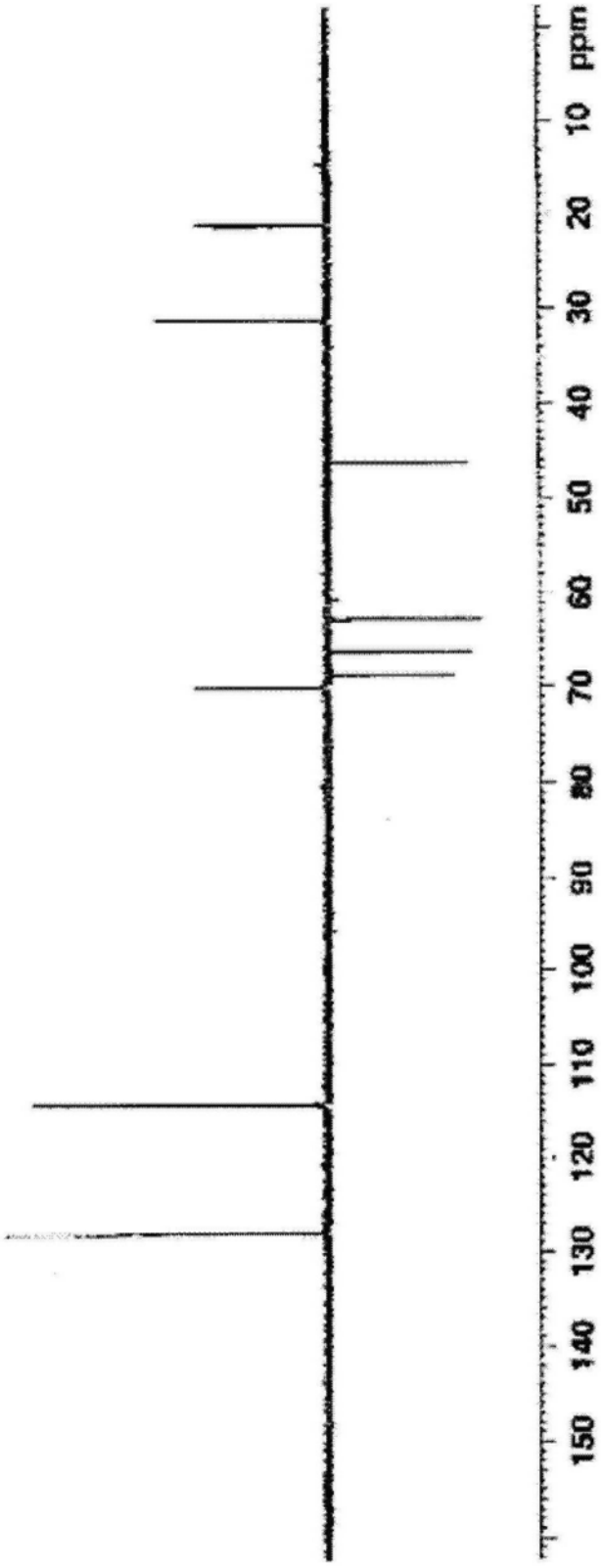


图 5C

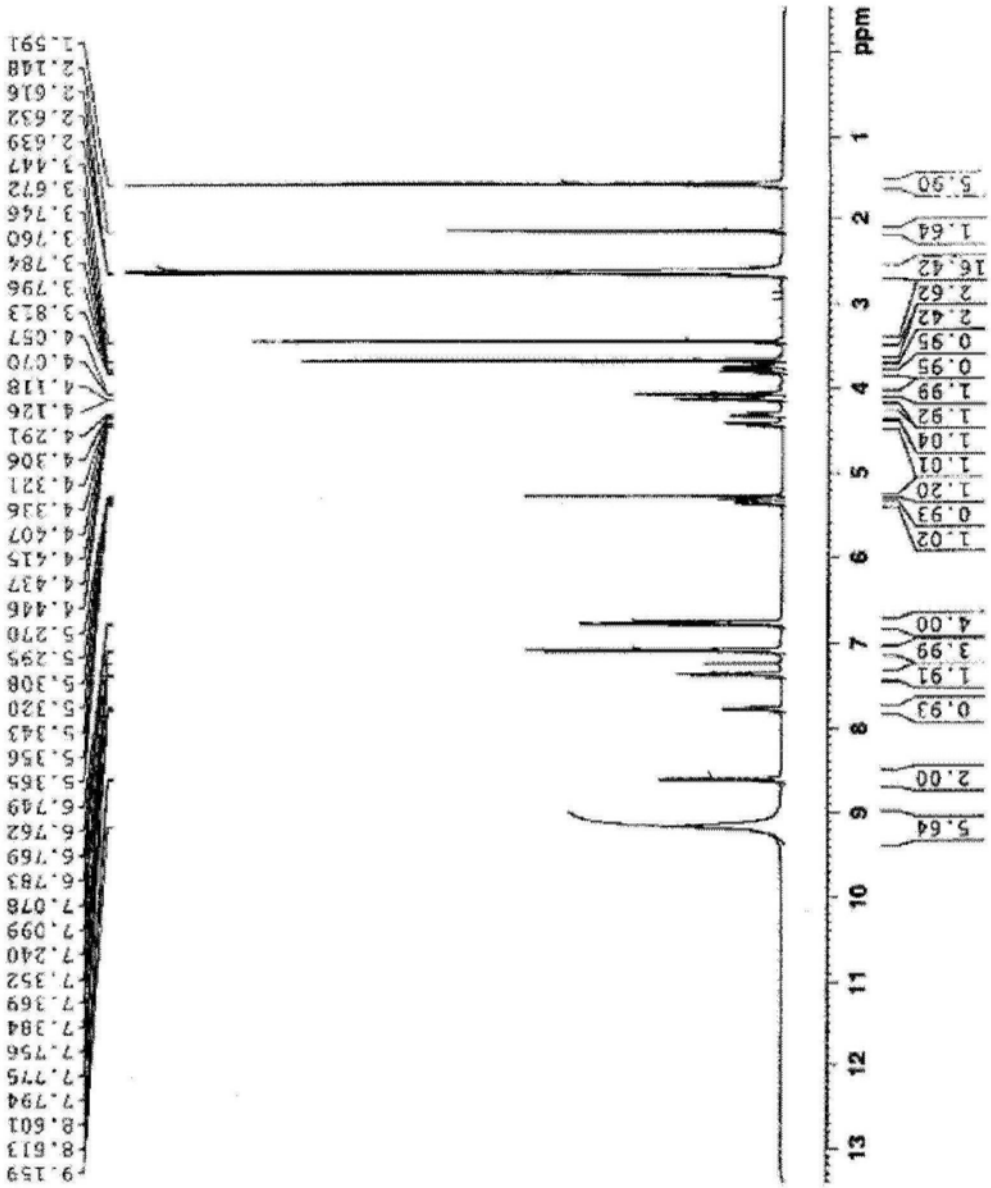

ppm
1 2 3 4 5 6 7 8 9 10 11 12 13
5.90
1.64
16.42
2.62
2.42
0.95
0.95
1.99
1.92
1.04
1.01
1.20
0.93
1.02
4.00
3.99
1.91
0.93
2.00
5.64

图 6A

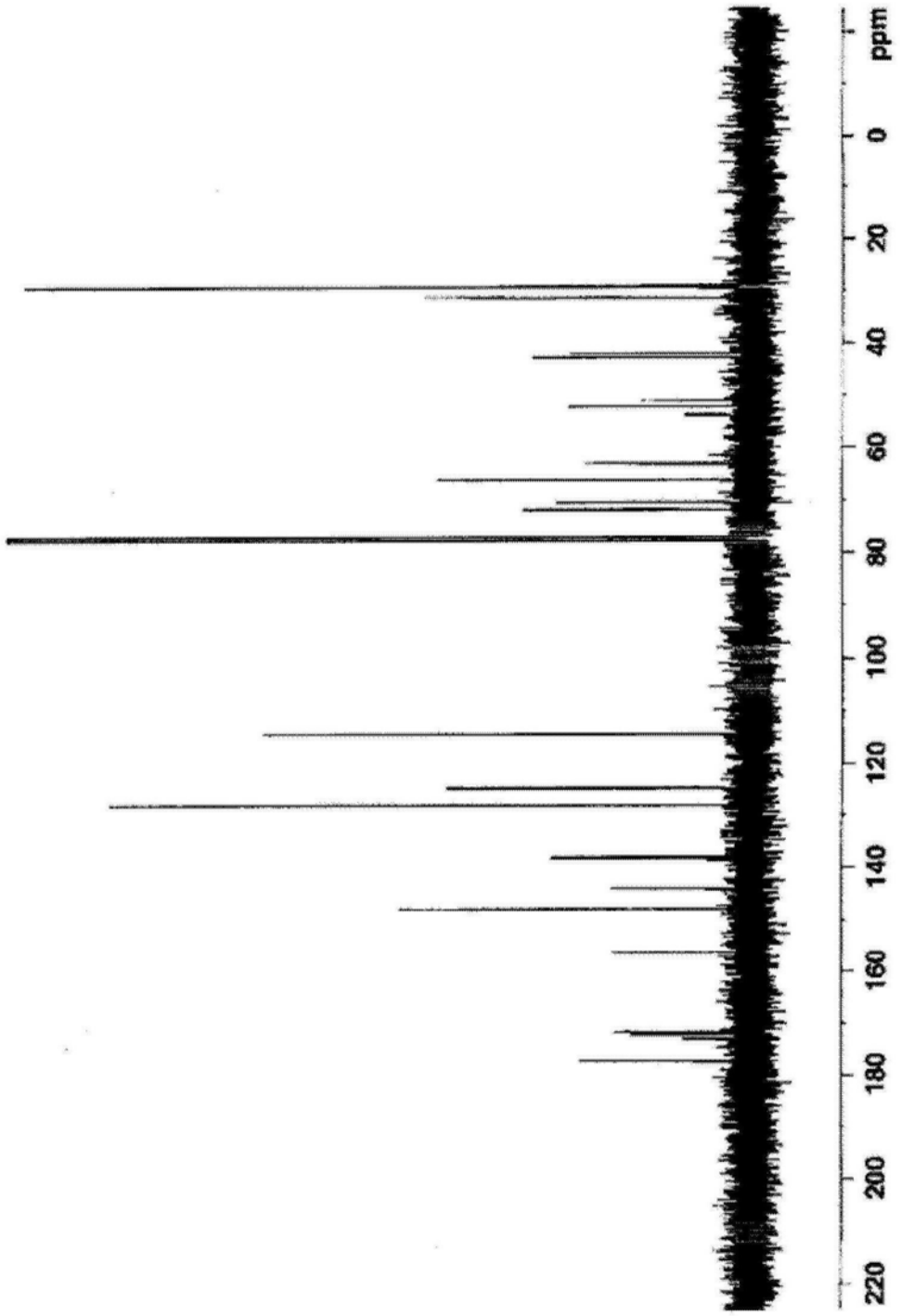


图 6B

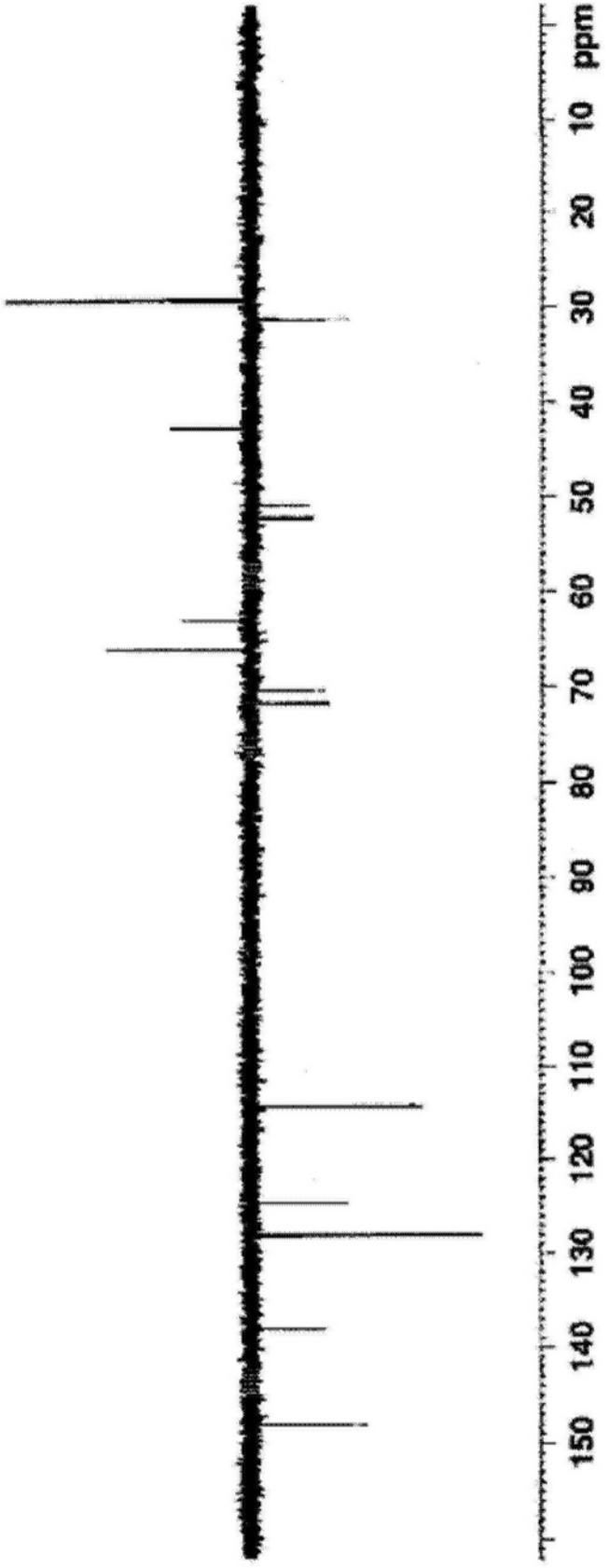


图 6C

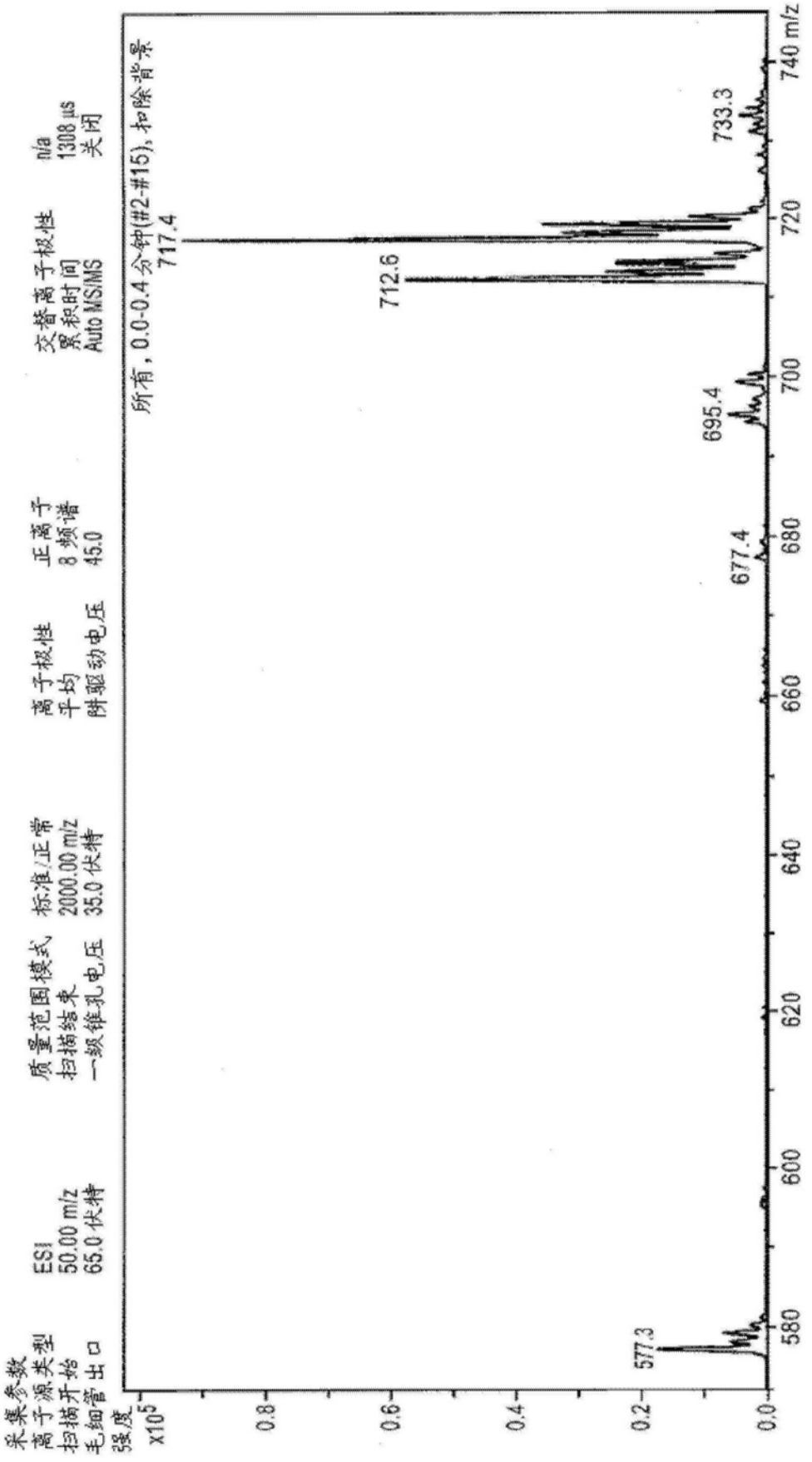

采集参数
离子源类型 ESI
扫描开始 50.00 m/z
毛细管出口 65.0 伏特
强度
x10^5
质量范围模式 标准/正常
扫描结束 2000.00 m/z
一级锥孔电压 35.0 伏特
离子极性 正离子
平均 8 频谱
附驱动电压 45.0
交替离子极性 n/a
累积时间 1308 µs
Auto MS/MS 关闭
所有，0.0-0.4 分钟(#2-#15)，扣除背景
717.4
712.6
733.3
695.4
677.4
577.3
0.0
0.2
0.4
0.6
0.8
580
600
620
640
660
680
700
720
740 m/z

图 6D

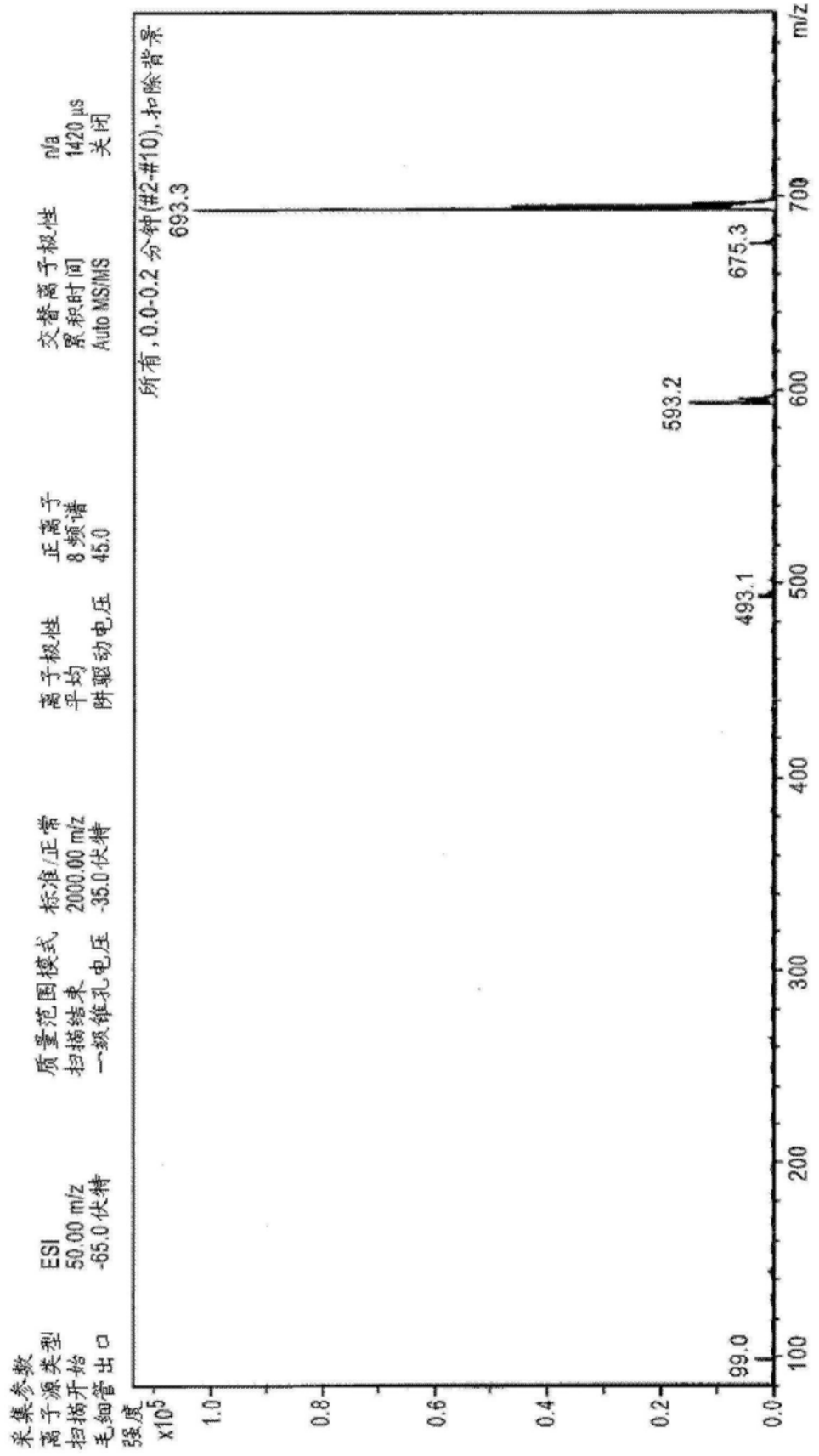

采集参数
离子源类型 ESI
扫描开始 50.00 m/z
毛细管出口 -65.0 伏特
质量范围模式
扫描结束
一级锥孔电压
标准/正常
2000.00 m/z
-35.0 伏特
离子极性
平均
附驱动电压
正离子
8 频谱
45.0
交替离子极性
累积时间
Auto MS/MS
n/a
1420 µs
关闭
所有，0.0-0.2 分钟(#2-#10)，扣除背景
693.3
675.3
593.2
493.1
99.0
强度
x10^5
1.0
0.8
0.6
0.4
0.2
0.0
100
200
300
400
500
600
700
m/z

图 6E

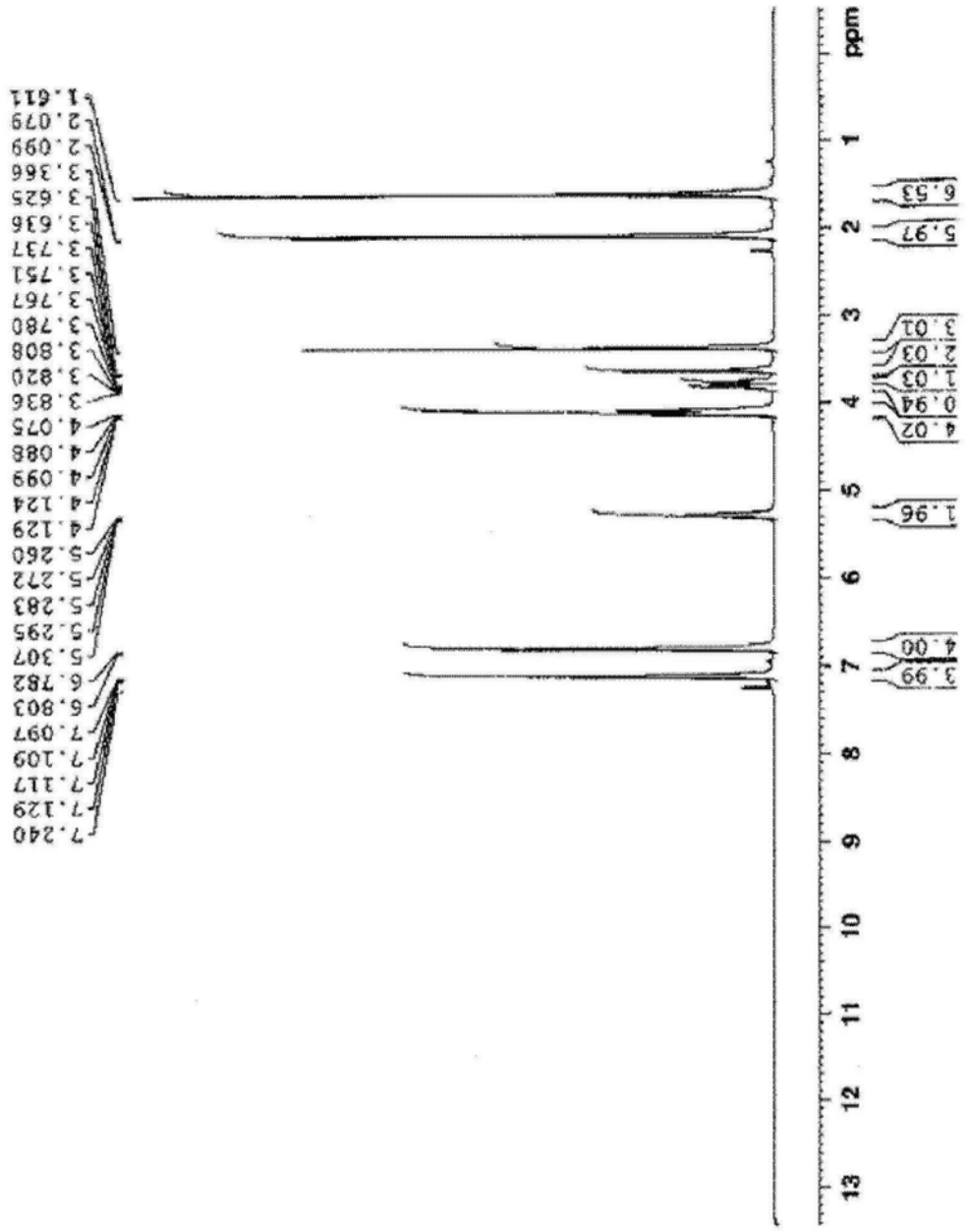

1.611
2.079
2.099
3.366
3.625
3.636
3.737
3.751
3.767
3.780
3.808
3.820
3.836
4.075
4.088
4.099
4.124
4.129
5.260
5.272
5.283
5.295
5.307
6.782
6.803
7.097
7.109
7.117
7.129
7.240
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13
6.53
5.97
3.01
2.03
1.03
0.94
4.02
1.96
4.00
3.99

图 7A

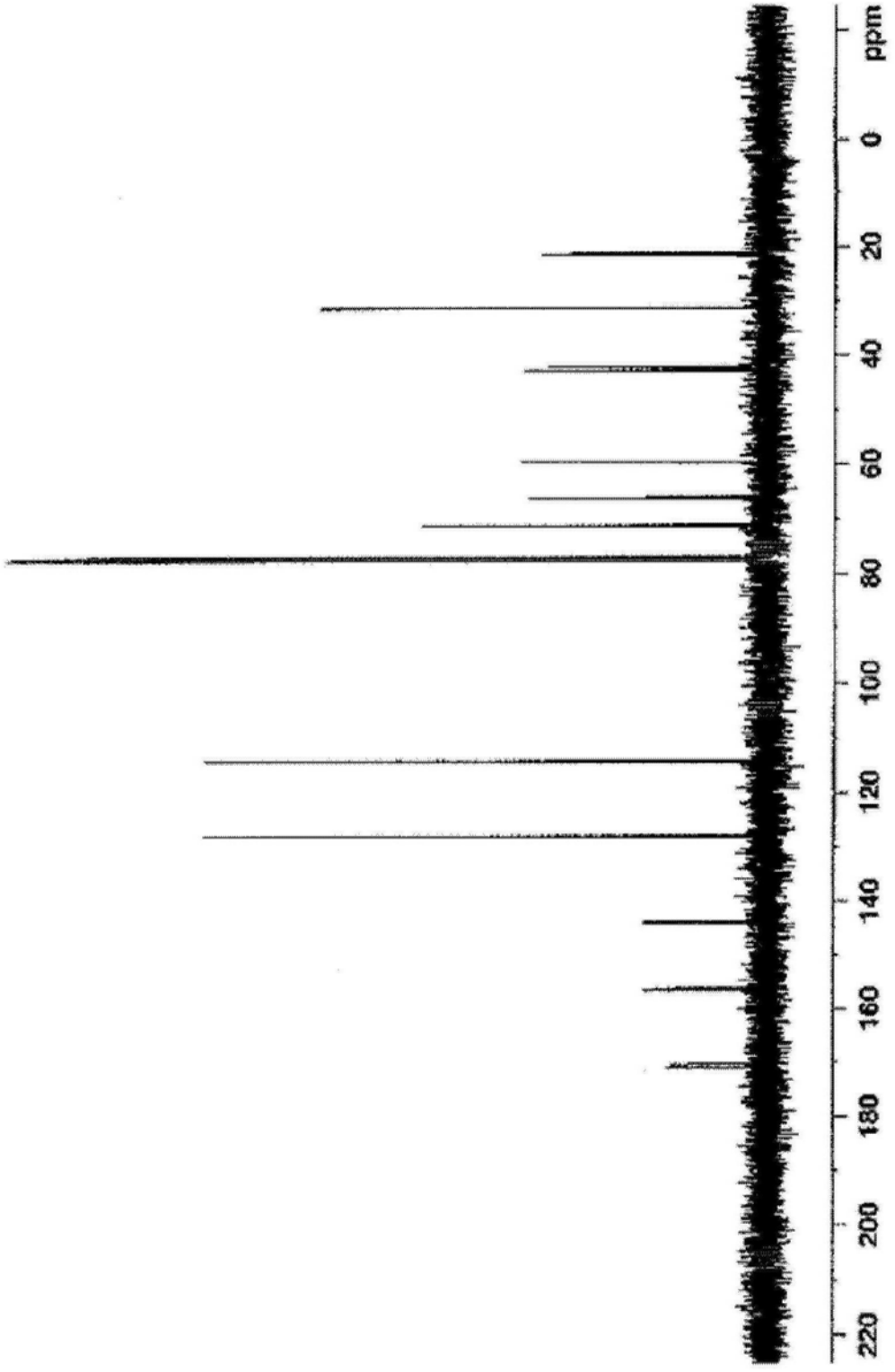


图 7B

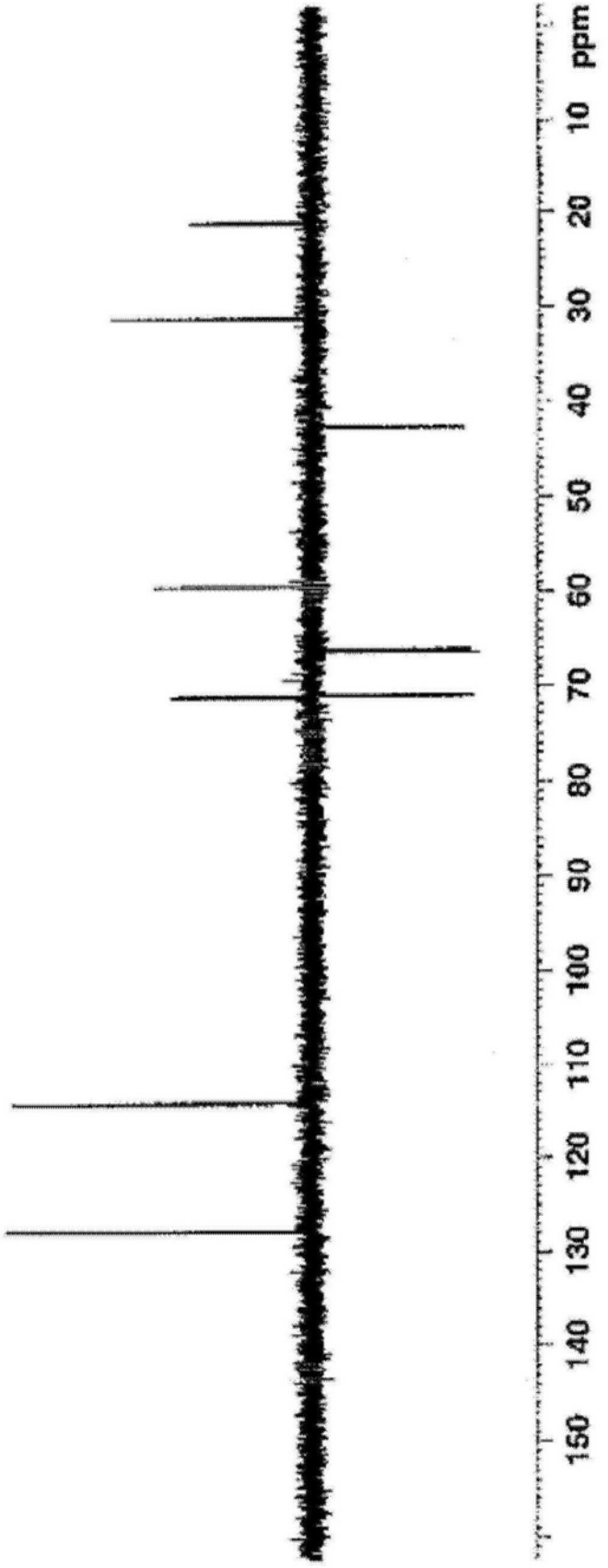


图 7C

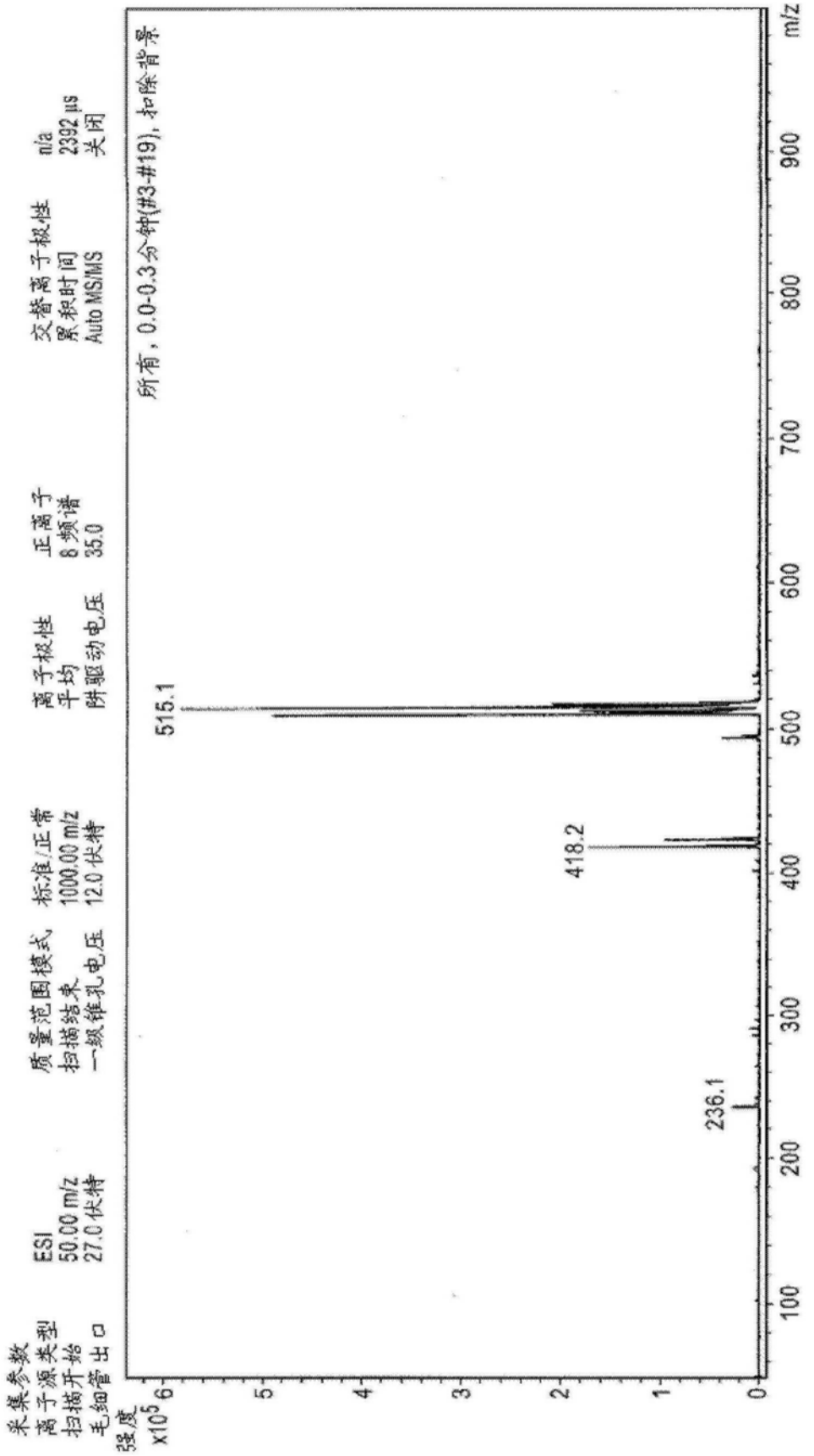

采集参数
离子源类型 ESI
扫描开始 50.00 m/z
毛细管出口 27.0 伏特
质量范围模式 扫描结束
一级锥孔电压
标准/正常 1000.00 m/z
12.0 伏特
离子极性 平均
阱驱动电压
正离子 8 频谱 35.0
交替离子极性 n/a
累积时间 2392 μs
Auto MS/MS 关闭
所有，0.0-0.3 分钟(#3-#19)，扣除背景
515.1
418.2
236.1
强度 x10^5
m/z

图 7D

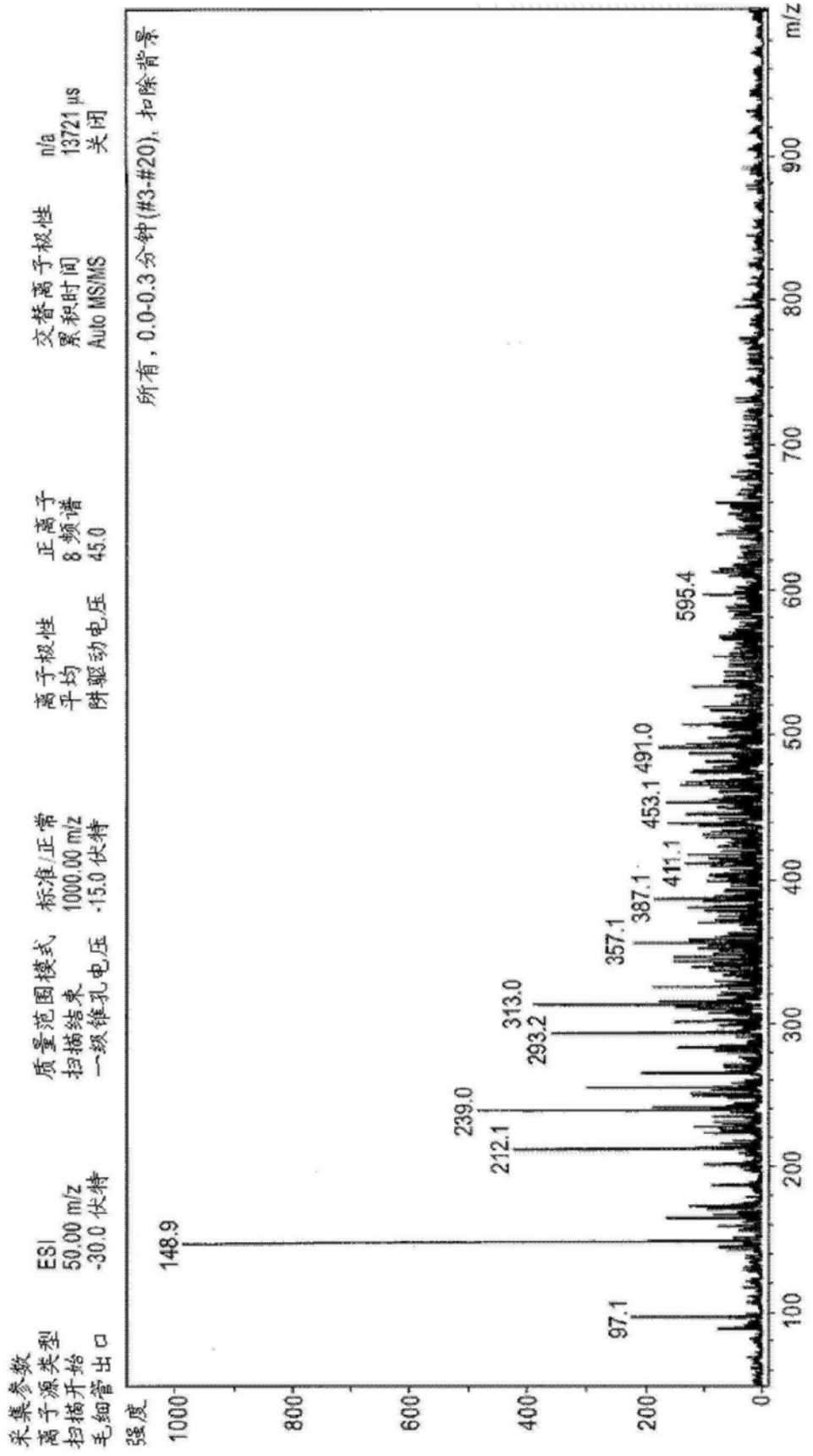

采集参数
离子源类型 ESI
扫描开始 50.00 m/z
毛细管出口 -30.0 伏特
质量范围模式 标准/正常
扫描结束 1000.00 m/z
一级锥孔电压 -15.0 伏特
离子极性 正离子
平均 8 频谱
阱驱动电压 45.0
交替离子极性 n/a
累积时间 13721 μs
Auto MS/MS 关闭
所有，0.0-0.3 分钟(#3-#20)，扣除背景
强度
m/z
148.9
97.1
239.0
212.1
313.0
293.2
357.1
387.1
411.1
453.1
491.0
595.4

图 7E

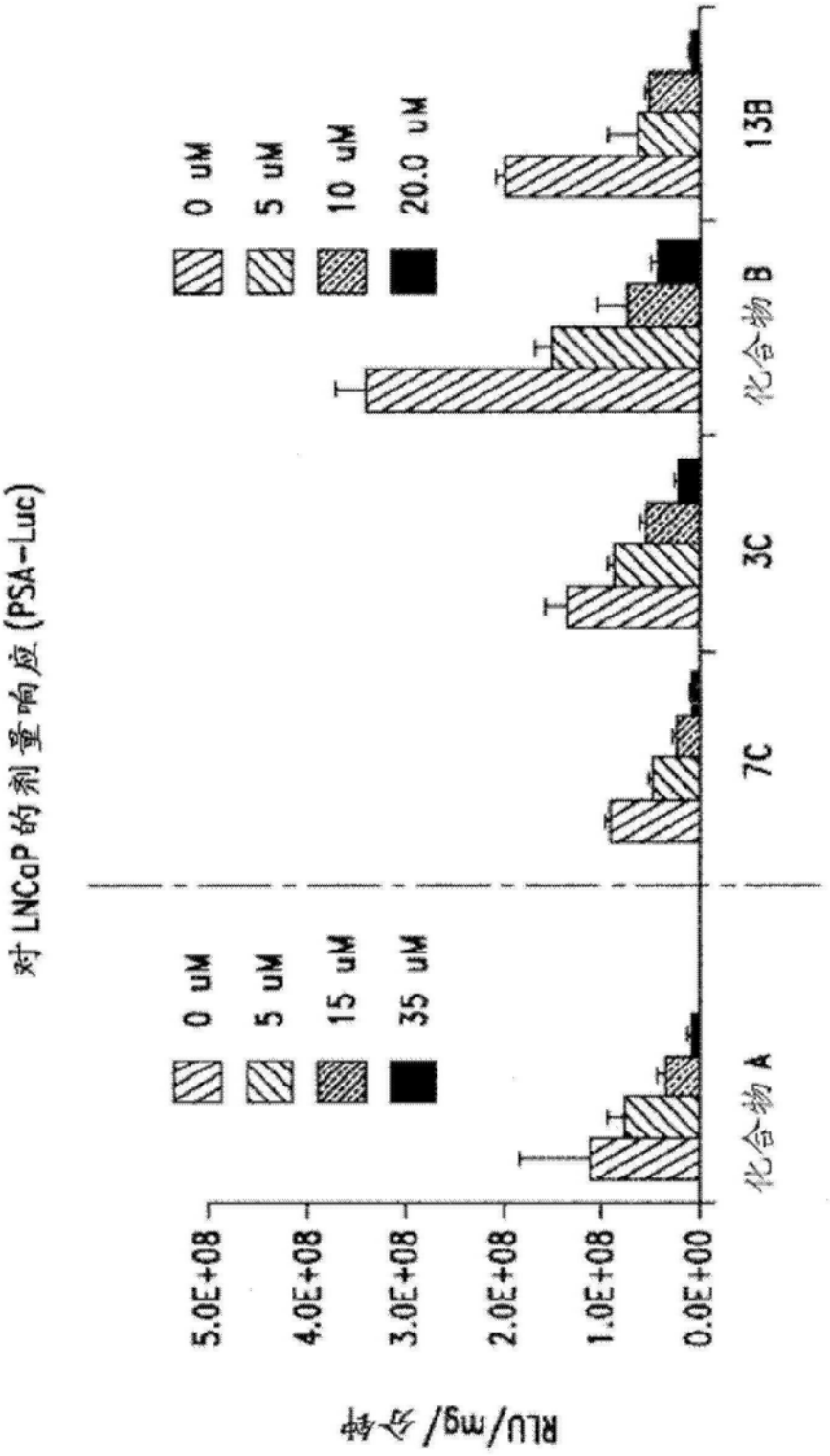

对 LNCaP 的剂量响应 (PSA-Luc)
RLU/mg/分钟
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
0 uM
5 uM
15 uM
35 uM
0 uM
5 uM
10 uM
20.0 uM
化合物 A
7C
3C
化合物 B
13B

图 8

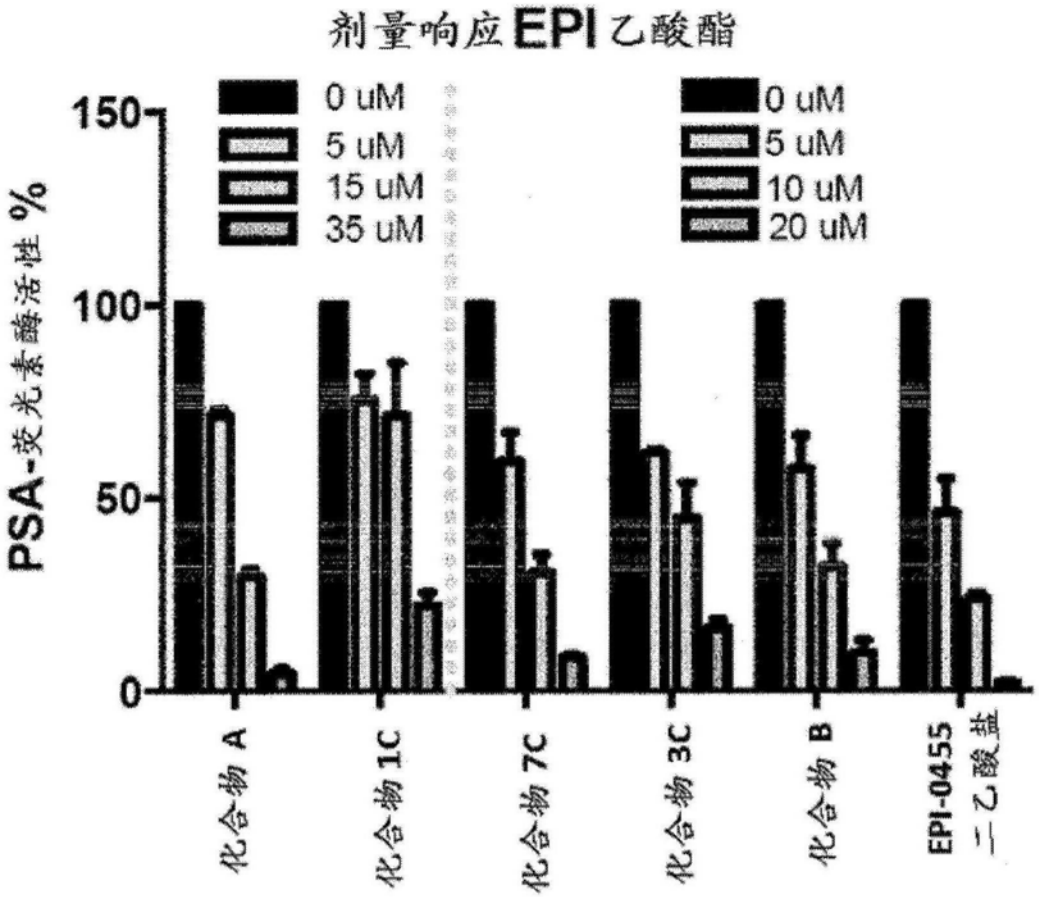

剂量响应EPI乙酸酯
PSA-荧光素酶活性 %
150
100
50
0
0 uM
5 uM
15 uM
35 uM
0 uM
5 uM
10 uM
20 uM
化合物 A
化合物 1C
化合物 7C
化合物 3C
化合物 B
EPI-0455 二乙酸盐

图 9

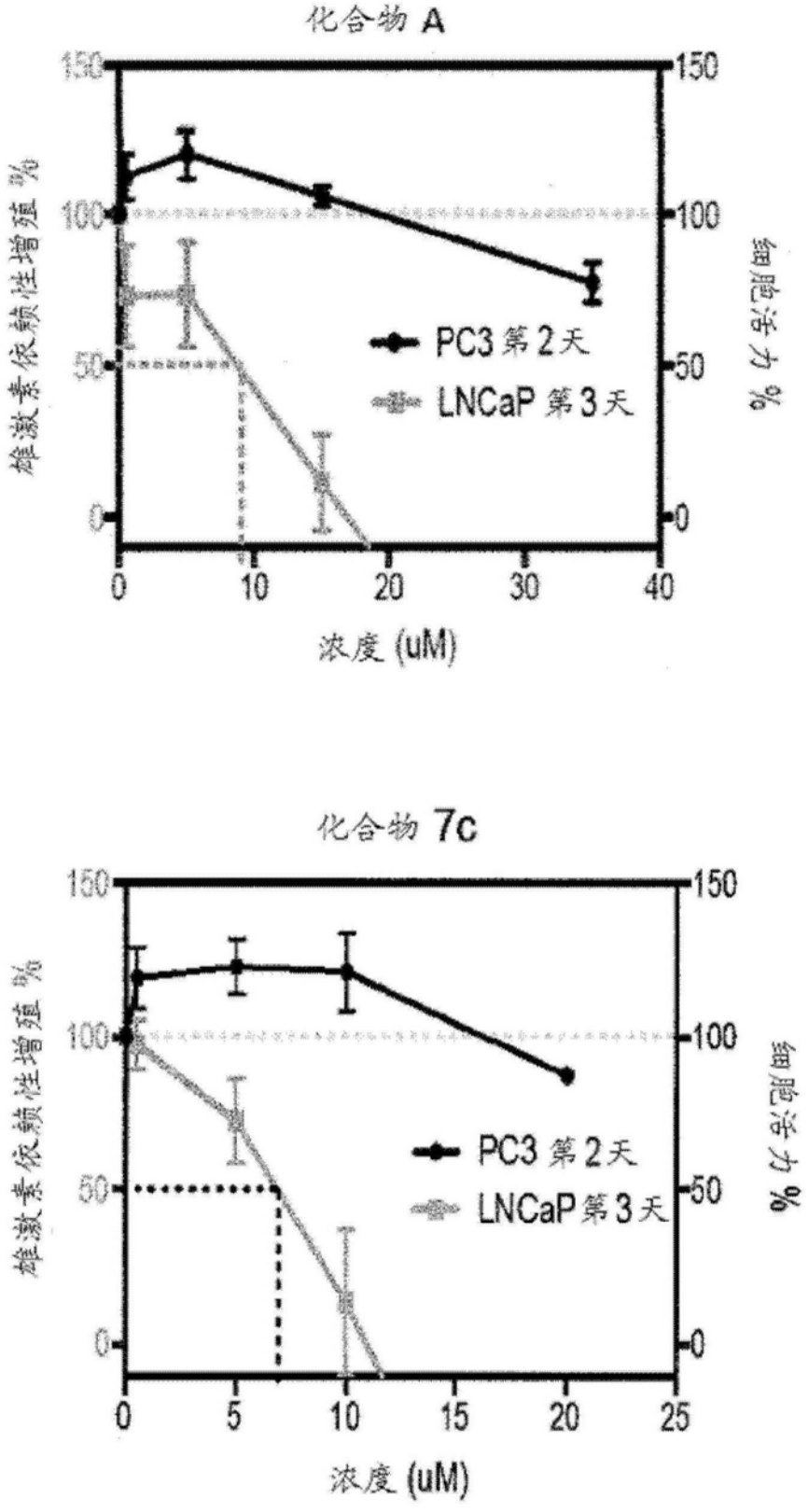

化合物 A
雄激素依赖性增殖 %
细胞活力 %
PC3 第 2 天
LNCaP 第 3 天
浓度 (uM)
化合物 7c
雄激素依赖性增殖 %
细胞活力 %
PC3 第 2 天
LNCaP 第 3 天
浓度 (uM)

图 10

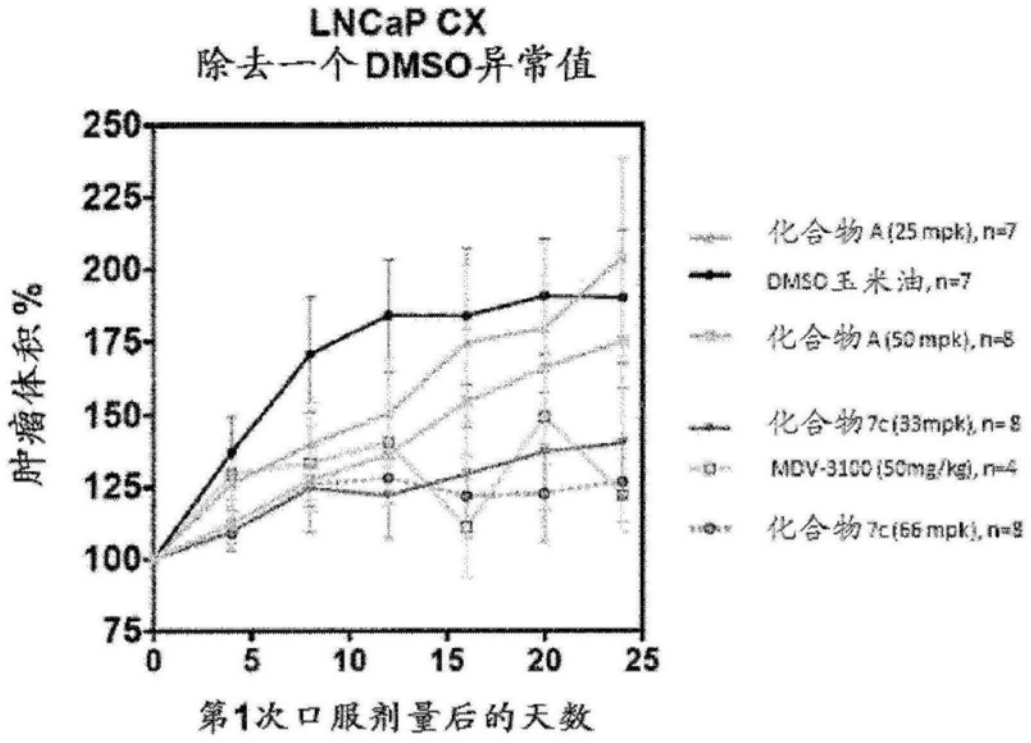

LNCaP CX
除去一个DMSO异常值
肿瘤体积 %
250
225
200
175
150
125
100
75
0
5
10
15
20
25
第1次口服剂量后的天数
化合物A(25 mpk), n=7
DMSO玉米油, n=7
化合物A(50 mpk), n=8
化合物7c(33mpk), n=8
MDV-3100(50mg/kg), n=4
化合物7c(66 mpk), n=8

图 11

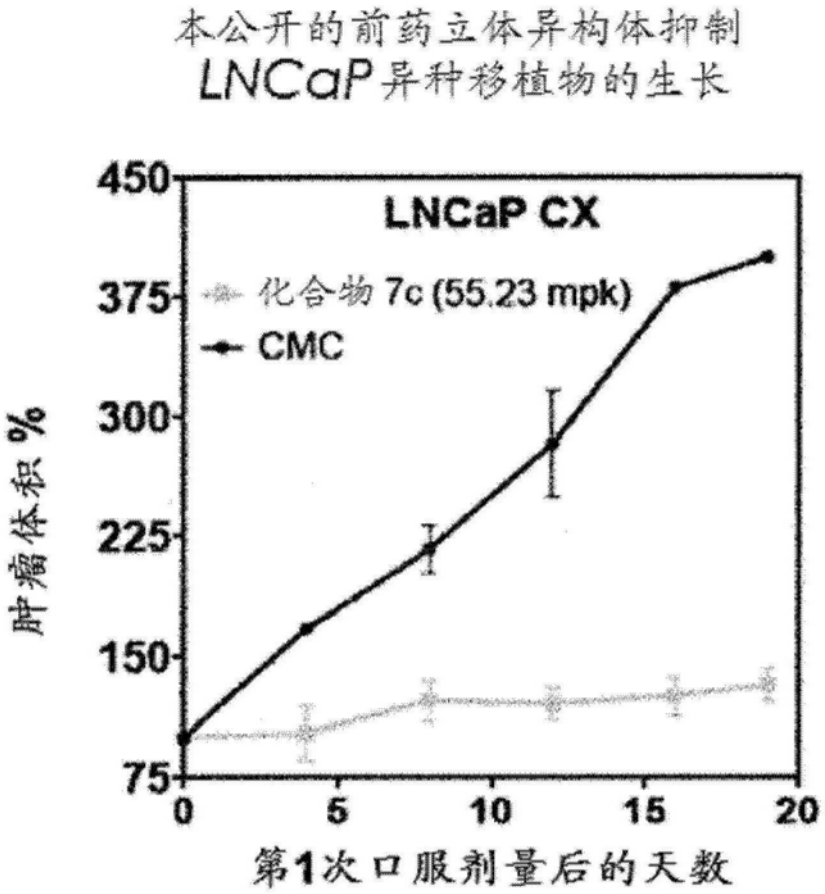

本公开的前药立体异构体抑制
LNCaP异种移植物的生长
LNCaP CX
化合物 7c (55.23 mpk)
CMC
肿瘤体积 %
450
375
300
225
150
75
0
5
10
15
20
第1次口服剂量后的天数

图 12

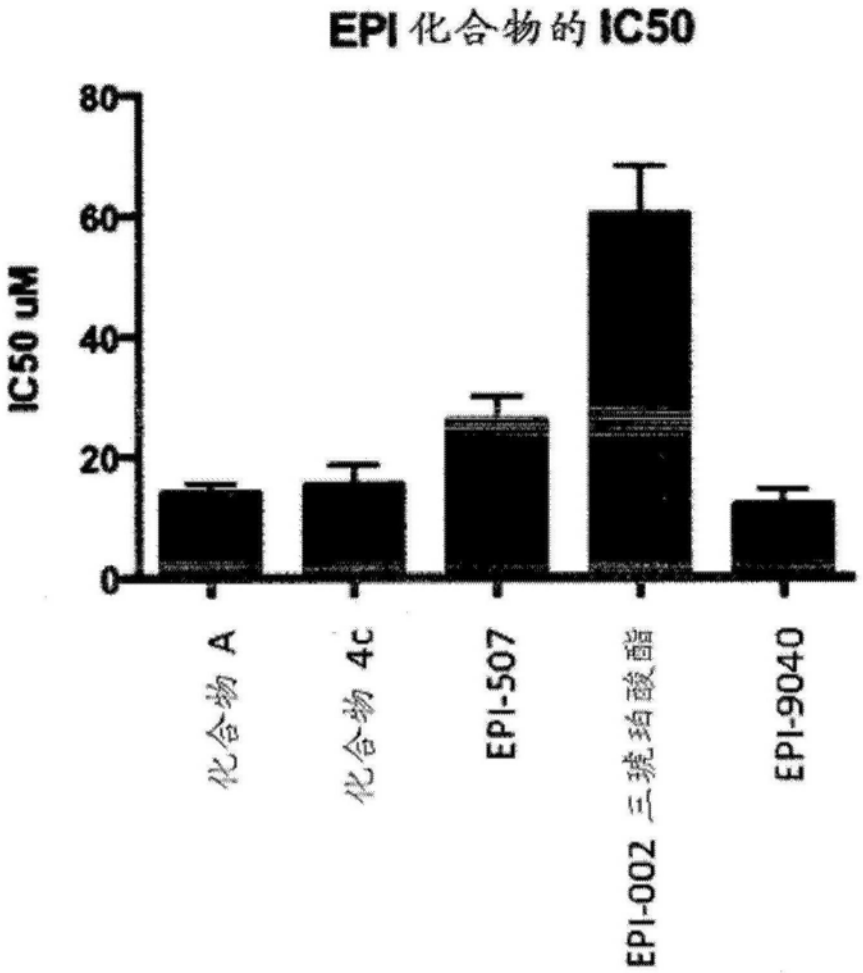

EPI 化合物的 IC50
IC50 uM
80
60
40
20
0
化合物 A
化合物 4c
EPI-507
EPI-002 三琥珀酸盐
EPI-9040

图 13

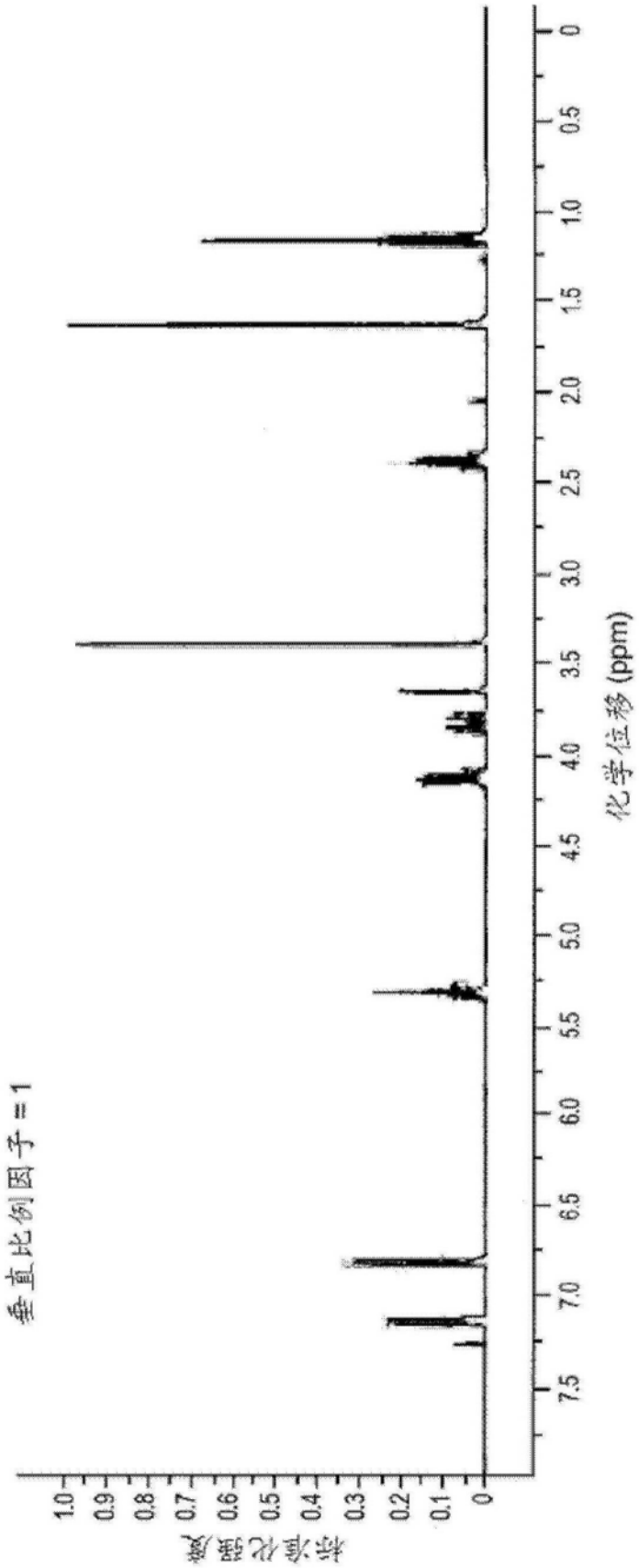

垂直比例因子 = 1
标准化强度
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
化学位移 (ppm)

图 14A

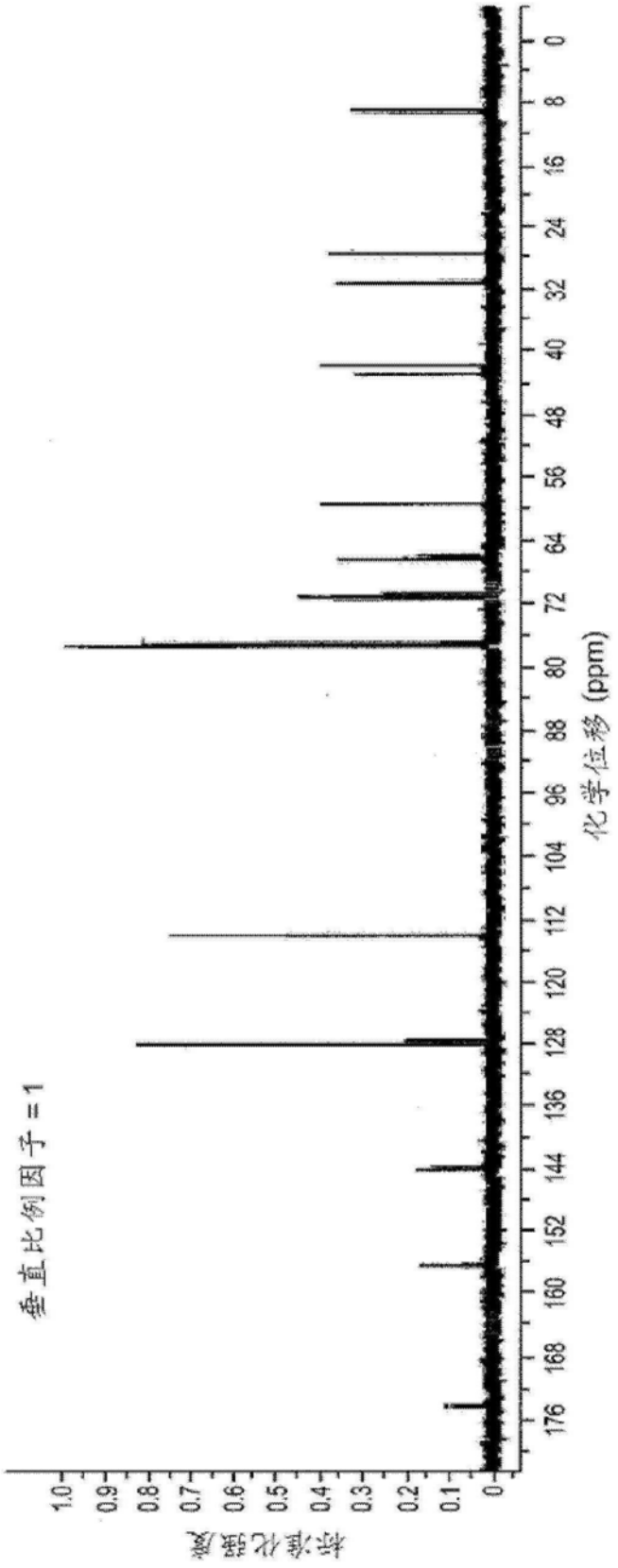

垂直比例因子 = 1
标准化强度
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
化学位移 (ppm)

图 14B

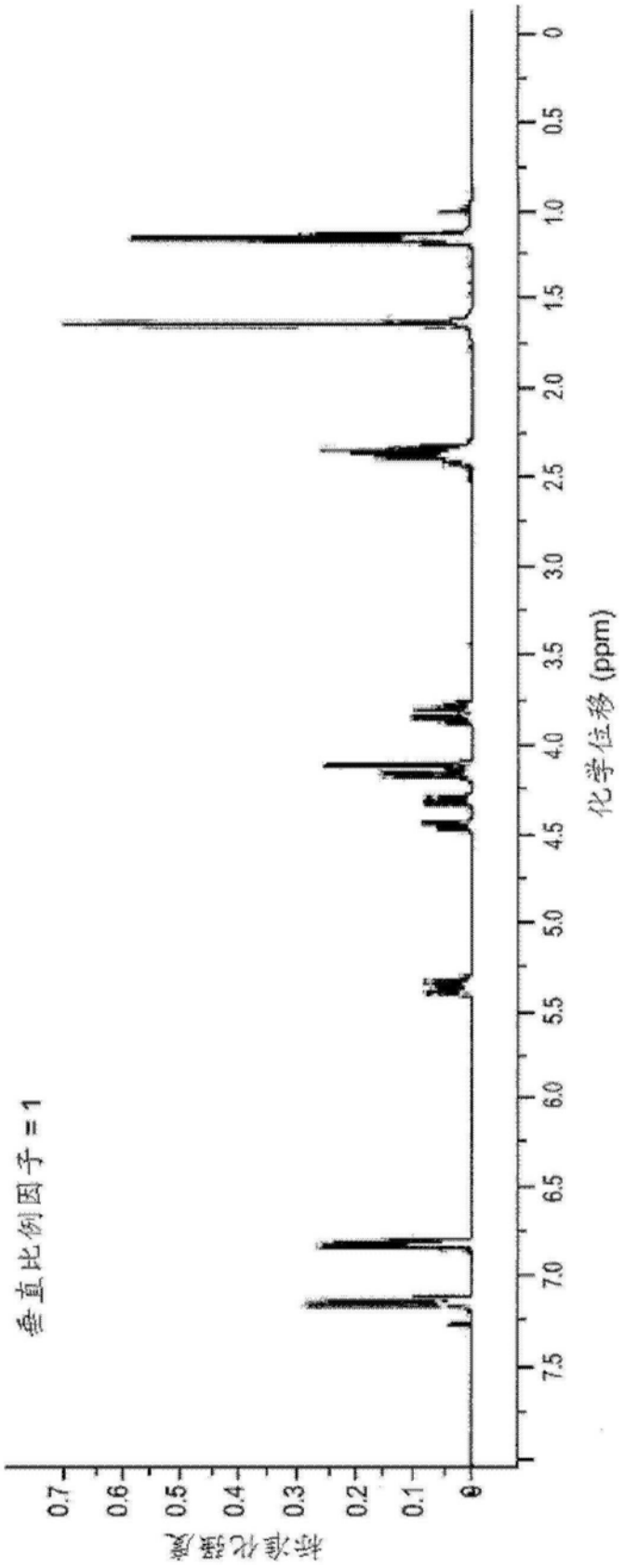

垂直比例因子 = 1
标准化强度
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
化学位移 (ppm)

图 15A

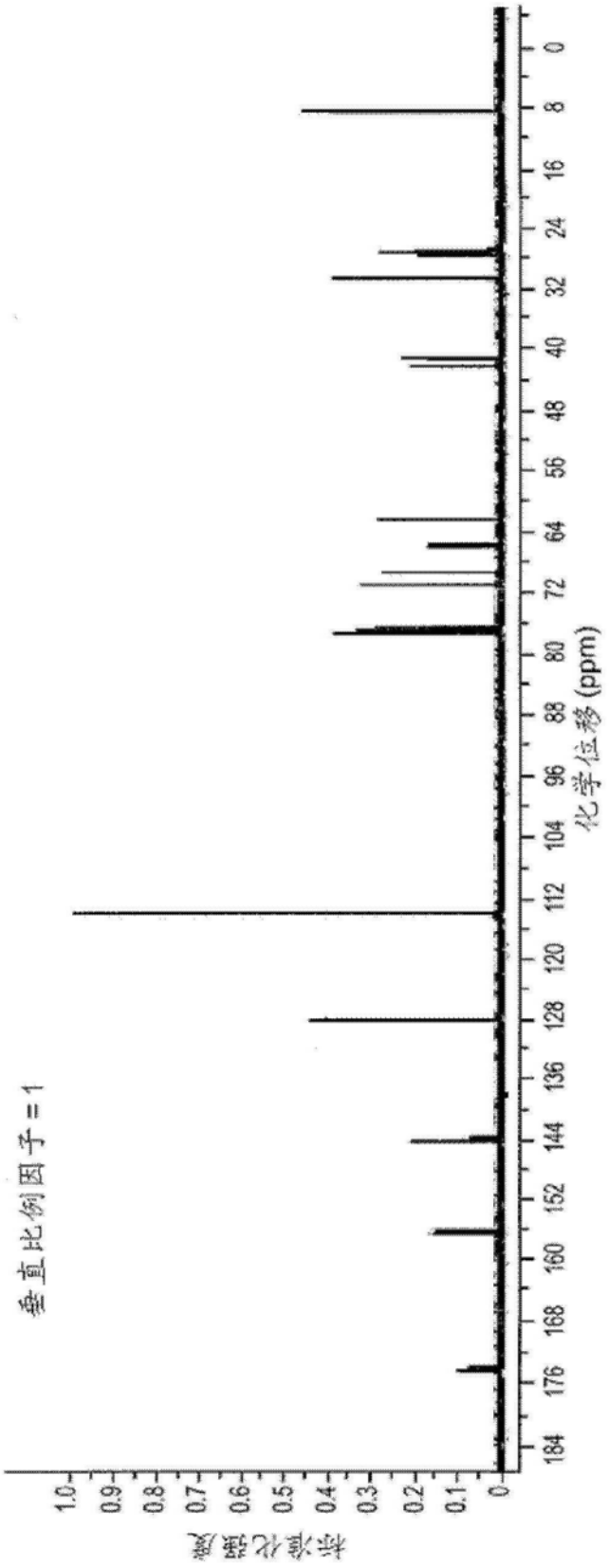

垂直比例因子 = 1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
化学位移 (ppm)

图 15B

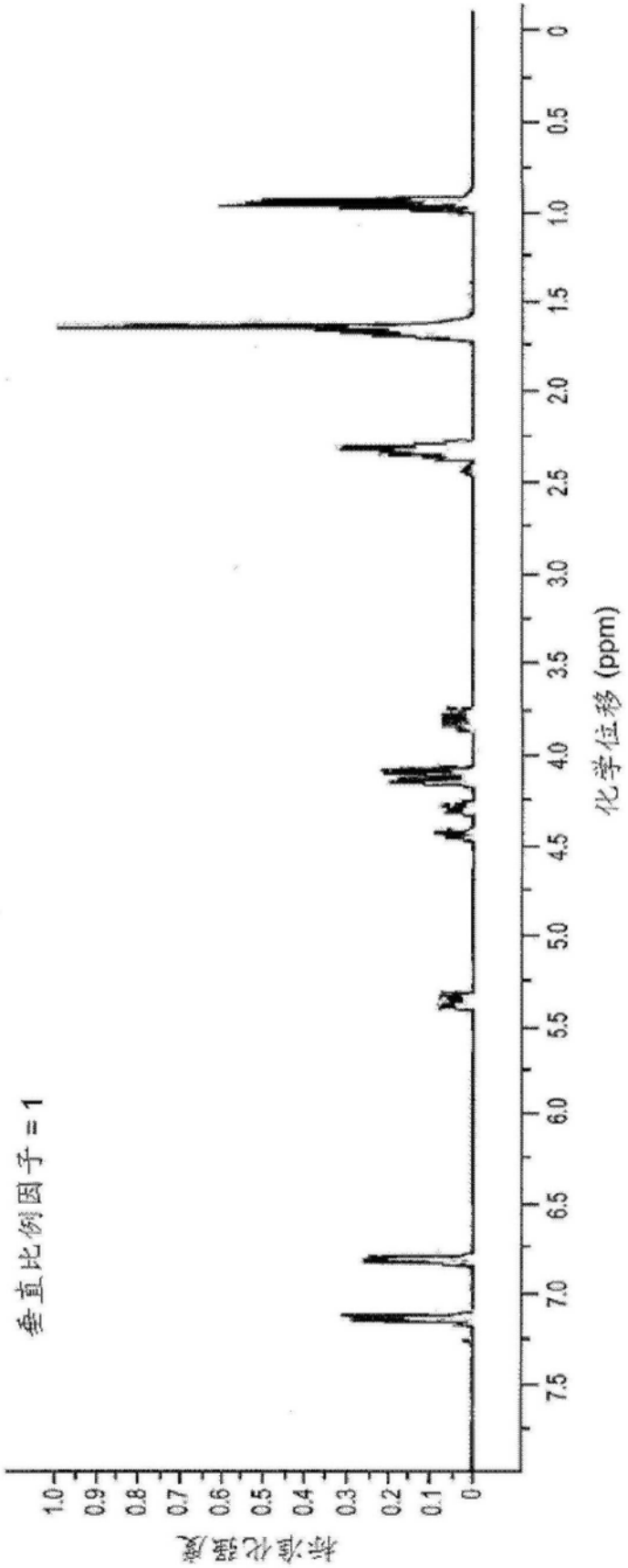

垂直比例因子 = 1
标准化强度
化学位移 (ppm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

图 16A

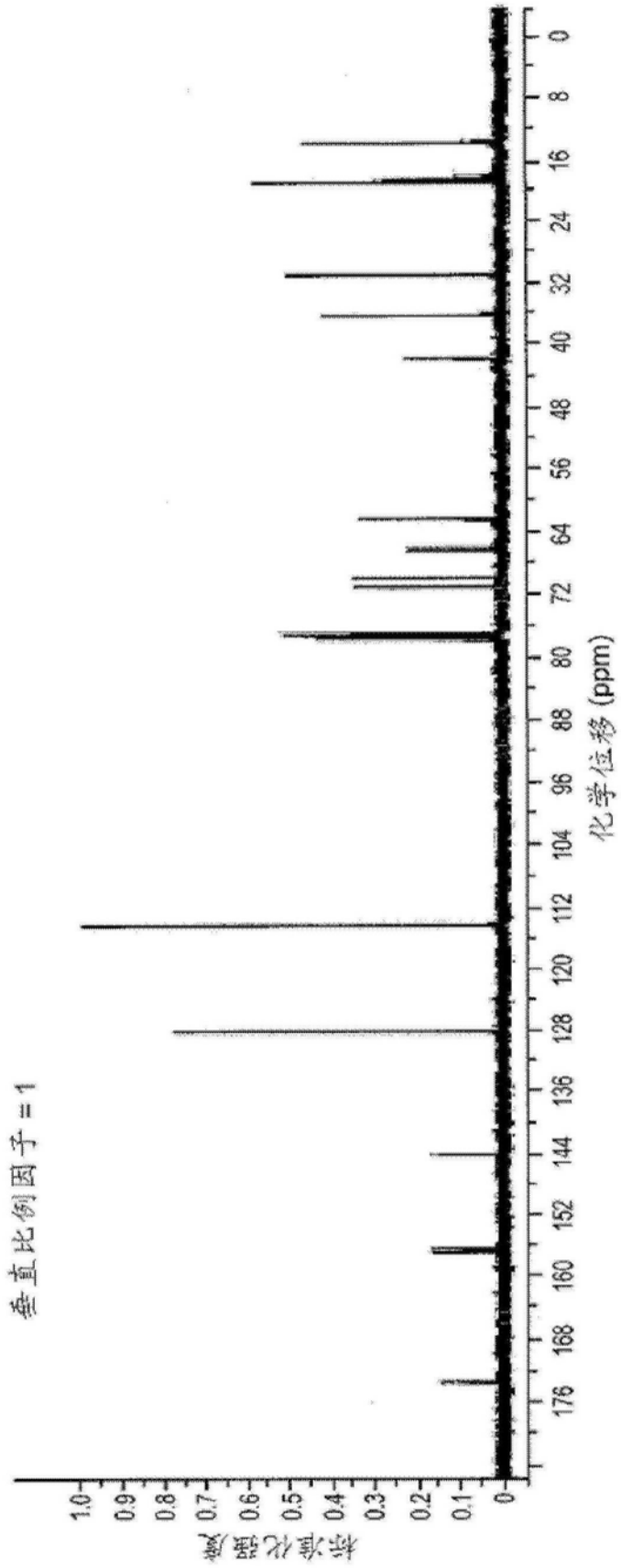

垂直比例因子 = 1
标准化强度
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
化学位移 (ppm)

图 16B

(19)中华人民共和国国家知识产权局

(12)发明专利申请
(扉页更正)

(10)申请公布号 CN 105358522 A8
(43)申请公布日 2016.02.24

(48)更正文献出版日 2016.04.06

(21)申请号 201480026227.1

(22)申请日 2014.05.09

(30)优先权数据
61/822,186 2013.05.10 US

(85)PCT国际申请进入国家阶段日
2015.11.09

(86)PCT国际申请的申请数据
PCT/CA2014/000414 2014.05.09

(87)PCT国际申请的公布数据
WO2014/179867 EN 2014.11.13

(71)申请人 不列颠哥伦比亚癌症局分支机构
地址 加拿大不列颠哥伦比亚省
申请人 英属哥伦比亚大学

(72)发明人 纳斯林·R·穆基 王军
卡门·阿德里亚娜·巴纽埃洛斯
雷蒙德·约翰·安德森
哈维尔·加西亚·费尔南德斯
玛丽安娜·桃乐茜·萨达尔

(74)专利代理机构 中科专利商标代理有限责任公司 11021
代理人 陈晓娜

(51)Int.Cl.
C07C 69/18(2006.01)
A61K 31/25(2006.01)
A61P 35/00(2006.01)
C07C 69/16(2006.01)

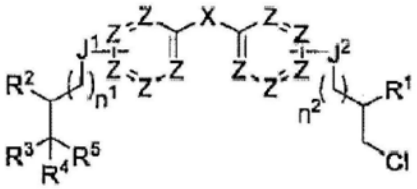
权利要求书 12 页 说明书 53 页 附图 36 页

(54)发明名称

雄激素受体调节剂的酯衍生物及其使用方法

(57)摘要

本发明提供了具有结构 I 的结构的化合物：



I 或其药学上可接受的盐、互变异构体、或立体异构体，其中 R^1、R^2、R^3、R^4、R^5、J^1、J^2、X、Z、n^1和 n^2如本文所定义，并且其中 R^1、R^2或 R^3中的至少一个为烷基、烯基、芳基或芳烷基酯。也提供了此类化合物用于治疗包括前列腺癌的各种适应症的用途以及涉及此类化合物治疗的方法。

CN 105358522 A8