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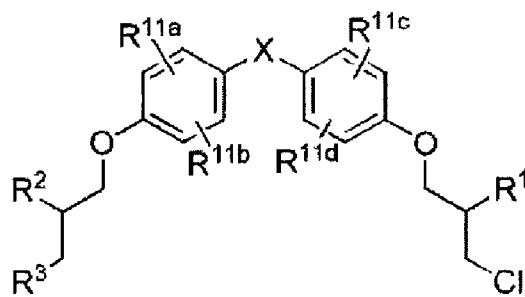
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[Continued on next page]

(54) **Title:** BISPHENOL DERIVATIVES AND THEIR USE AS ANDROGEN RECEPTOR ACTIVITY MODULATORS

(I)

(57) **Abstract:** Compounds having a structure of Formula I or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein R¹, R², R³, R^{11a}, R^{11b}, R^{11c}, R^{11d}, and X, are as defined herein, are provided. Uses of such compounds for modulating androgen receptor activity, imaging diagnostics in cancer and therapeutics, and methods for treatment of subjects in need thereof, including prostate cancer are also provided.



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**BISPHENOL DERIVATIVES AND THEIR USE AS ANDROGEN RECEPTOR
ACTIVITY MODULATORS**

STATEMENT OF GOVERNMENT INTEREST

5 [001] This invention 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 invention.

CROSS-REFERENCE TO RELATED APPLICATION

10 10 [002] This application claims the benefit of priority to U.S. Provisional Application No. 62/323,196, filed on April 15, 2016 and entitled "BISPHENOL DERIVATIVES AND THEIR USE AS ANDROGEN RECEPTOR ACTIVITY MODULATORS," the disclosure of which is hereby incorporated by reference in its entirety for all purposes.

15 15 **Technical Field**

[003] This invention generally relates to bisphenol-related compounds and their use for treatment of various indications. In particular the invention relates to bisphenol ether compounds having halogenated phenyl groups and/or sulfone linking groups and their use for treatment of various cancers, for example prostate cancer, including but not limited to, 20 primary/localized prostate cancer (newly diagnosed), locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer (CRPC), and hormone-sensitive prostate cancer. This invention also relates to bisphenol-related compounds and their use for modulating androgen receptor (AR) activity including truncated AR.

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Description of the Related 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. 30 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. 5 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. *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, 10 *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 diseases such as polycystic ovary syndrome as well as cancers. One example is ovarian cancer where elevated levels of androgens are 15 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 AR 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. 20 Clinton & W. Hua, *Crit Rev Oncol Hematol* 25, 1-9 (1997)), whereas estrogen receptor-alpha (ER α) and the progesterone receptor are detected in less than 50% of ovarian tumors.

[006] The only effective treatment available for advanced prostate cancer is the withdrawal of androgens which are essential for the survival of prostate luminal cells. Androgen ablation therapy causes a temporary reduction in tumor burden concomitant with a decrease in serum 25 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 that is still driven by AR 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 30 patients succumb to their disease within two years.

[007] The AR 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 two transcriptional activation units (tau1 and tau5) within activation function-1 (AF-1). Binding of androgen (ligand) to the LBD

of the AR 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 androgen regulated genes, such as PSA, to initiate transcription. The AR can be activated in the absence of androgen by stimulation of the cAMP-dependent protein kinase 5 (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).

[008] Clinically available inhibitors of the AR include nonsteroidal antiandrogens such as 10 bicalutamide (CasodexTM), nilutamide, flutamide, and enzalutamide. There is also a class of steroidal antiandrogens, such as cyproterone acetate and spironolactone. Both steroidal and non-steroidal antiandrogens target the LBD of the AR and predominantly fail presumably due to poor affinity, mutations that lead to activation of the AR by these same antiandrogens (Taplin, M.E., Bubley, G.J., Kom Y.J., Small E.J., Uptonm M., Rajeshkumarm B., Balkm S.P., 15 *Cancer Res.*, 59, 2511-2515 (1999)), and constitutively active AR splice variants. Antiandrogens have no effect on the constitutively active AR splice variants that lack the ligand-binding domain (LBD) and are associated with castration-recurrent 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 20 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) and resistant to abiraterone and enzalutamide (Antonarakis *et al.*, *N Engl J Med.* 2014, 371, 1028-38; Scher et al *JAMA Oncol.* 2016 doi: 10.1001).

[009] AR antagonists other than the bisphenol ether derivatives previously reported (see, WO 25 2010/000066, WO 2011/082487; WO 2011/082488; WO 2012/145330; WO 2015/031984; WO 2016/058080; WO 2016/058082, WO 2016/112455, and WO 2016/141458 which are hereby incorporated by reference in their entireties, to the British Columbia Cancer Agency 30 Branch and The University of British Columbia) that bind to full-length AR and/or truncated AR splice variants that are currently being developed include: AR degraders such as niclosamide (Liu C et al 2014), galeterone (Njar et al 2015; Yu Z et al 2014), and ARV-330/Androgen receptor PROTAC (Neklesa et al 2016 *J Clin Oncol* 34 suppl 2S; abstr 267); AR DBD inhibitor VPC-14449 (Dalal K et al 2014 *J Biol Chem.* 289(38):26417-29; Li H et al 2014 *J Med Chem.* 57(15):6458-67); antiandrogens apalutamide (Clegg NJ et al 2012), ODM-201 (Moilanen AM et al 2015), ODM-204 (Kallio et al *J Clin Oncol* 2016 vol. 34 no. 2 suppl

230), TAS3681 (Minamiguchi et al 2015 *J Clin Oncol* 33, suppl 7; abstr 266); and AR NTD inhibitors 3E10-AR441bsAb (Goicochea NL et al 2015), and sintokamide (Sadar et al 2008; Banuelos et al 2016).

[010] The AR-NTD is also a target for drug development (e.g. WO 2000/001813), since the 5 NTD contains Activation-Function-1 (AF-1) which is the essential region required for AR transcriptional activity (Jenster et al 1991. *Mol Endocrinol.* 5, 1396-404). The AR-NTD importantly plays a role in activation of the AR 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; 10 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).

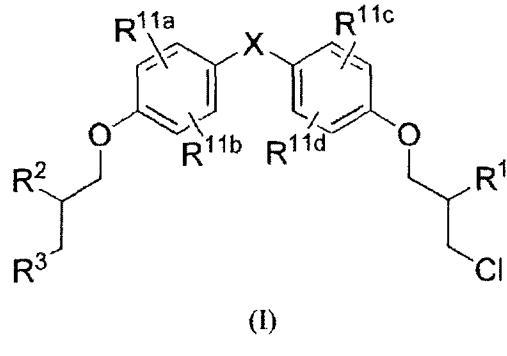
[011] While the crystal structure has been resolved for the AR C-terminus LBD, this has not 15 been the case for the NTD due to its high flexibility and intrinsic disorder in solution (Reid et al 2002 *J. Biol. Chem.* 277, 20079-20086) thereby hampering virtual docking drug discovery approaches.

[012] While significant advances have been made in this field, there remains a need for 20 improved treatment for prostate cancer, especially metastatic castration-resistant prostate cancer.

BRIEF SUMMARY

[013] The present disclosure is based in part on the surprising discovery that the compounds described herein, can be used to modulate AR activity either in vivo or in vitro for both research 25 and therapeutic uses. In some embodiments, certain compounds disclosed herein are useful for imaging the prostate. The imaging can be for any number of diagnostic purposes. For example, in certain embodiments the compounds are useful for imaging benign prostate cancer diseases. In other embodiments, the compounds find utility for imaging of certain cancers, including prostate cancer since certain embodiments of the compounds localize in prostate tumor sites. 30 Other imaging agents are androgen mimics; however, in one embodiment, the compounds are useful for imaging AR splice variants or any AR species (i.e., those mutated in other domains or regions). The AR can be mammalian. For example, the AR can be human. The prostate cancer can be castration-resistant prostate cancer. The prostate cancer can be androgen-dependent prostate cancer.

[014] In one embodiment, the present disclosure relates to compounds of Formula (I):



[015] or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

- 5 [016] X is $-\text{S}(\text{O})_n-$ or $-\text{C}(\text{R}^8\text{R}^9)-$;
- [017] R¹ is H, hydroxyl or $\text{OC}(=\text{O})\text{R}^{13}$;
- [018] R² is hydroxyl or $\text{OC}(=\text{O})\text{R}^{13}$;
- [019] R³ is halo, -OH, -OR⁴; $\text{OC}(=\text{O})\text{R}^{13}$, -NH₂, -NHS(O)_nR⁵, -N(C₁-C₆ alkyl)S(O)_nR⁵, -S(O)_nR⁵, -N₃, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R₆;
- 10 [020] R⁴ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R₆;
- [021] R⁵ is each independently C₁-C₆ alkyl or aryl which are optionally substituted with one or more R⁶;
- 15 [022] R⁶ is each independently selected from the group consisting of H, F, Cl, Br, I, ¹²³I, hydroxyl, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₆-C₁₂ aryl, wherein each R⁶ is optionally substituted with one or more of halogen, ¹²³I, ¹⁸F, hydroxyl, -OS(O)₂-aryl, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;
- [023] R⁸ and R⁹ are each independently H or C₁-C₆ alkyl;
- 20 [024] R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, F, Cl, Br, I, or ¹²³I;
- [025] R¹³ is C₁-C₆ alkyl; and
- [026] n is 0, 1, or 2;
- [027] wherein at least one of R^{11a}, R^{11b}, R^{11c} and R^{11d} is methyl F, Cl, Br, I, or ¹²³I.
- [028] In some embodiments, at least two of R^{11a}, R^{11b}, R^{11c} and R^{11d} in Formula I are independently methyl, F, Cl, Br, I, or ¹²³I. In other embodiments, any two of R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently methyl, F, Cl, Br, I, or ¹²³I and the remaining two of R^{11a}, R^{11b}, R^{11c} and R^{11d} are each H. In one embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each independently methyl, F, Cl, Br, I, or ¹²³I. In another embodiment, R^{11a} and R^{11b} are

each H, and R^{11c} and R^{11d} are each independently methyl, Cl, or Br. In a certain embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each Cl.

[029] In one embodiment, R^{11a} and R^{11c} in Formula I are each H, and R^{11b} and R^{11d} in Formula I are each independently methyl, F, Cl, Br, I, or ¹²³I. In some embodiments, R^{11a} and 5 R^{11c} are each H, and R^{11b} and R^{11d} are each independently methyl, Cl, or Br. In another embodiment, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each Cl.

[030] In some embodiments, X in Formula I is -S(O)₂- In another embodiment, X in Formula I is -C(R⁸R⁹)- and R₈ and R⁹ are each independently C₁-C₃ alkyl. In one embodiment, X is -C(R⁸R⁹)- and R₈ and R⁹ are each methyl.

10 [031] In some embodiments, R¹ in Formula I is hydroxyl or -OC(=O)R¹³. In another embodiment R¹ is H.

[032] In some embodiments, R³ in Formula I is -OH. In another embodiment, R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In one embodiment, R³ is -OR⁴ and R⁴ is C₁-C₆ alkyl. In other embodiments, R³ is -OR⁴ and R⁴ is methyl.

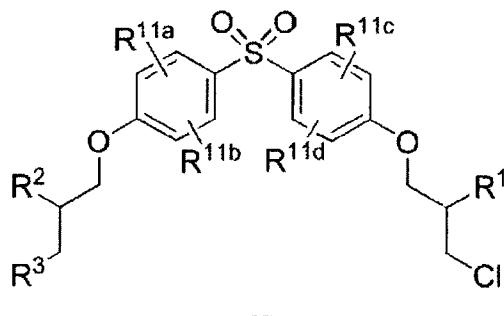
15 [033] In one embodiment, R³ in Formula I is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom. In another embodiment, R³ is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, 20 isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine.

[034] In one embodiment, each R¹³ in Formula I when present is C₁-C₃ alkyl. In a further embodiment, each R¹³ when present is methyl.

25 [035] In one embodiment, R¹ and R² in Formula I are each independently -OH or -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, at least one of R¹, R² and R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In another embodiment, any two of R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl. In one embodiment, R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

30 [036] In one embodiment of the present disclosure relates to compounds disclosed in Tables 1, 2, 3, and 4 or a pharmaceutically acceptable salt thereof.

[037] In one embodiment, the present disclosure relates to compounds of Formula (I):



(II)

[038] or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

[039] R¹ is H, hydroxyl or -OC(=O)R¹³;

5 [040] R² is hydroxyl or -OC(=O)R¹³;

[041] R³ is halo, -OH, -OR⁴, -OC(=O)R¹³, -NH₂, -NHS(O)_nR⁵, -N(C₁-C₆ alkyl)S(O)_nR⁵, -S(O)_nR⁵, -N₃, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R⁶;

10 [042] R⁴ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R⁶;

[043] R⁵ is each independently C₁-C₆ alkyl or aryl which are optionally substituted with one or more R⁶;

15 [044] R⁶ is each independently selected from the group consisting of H, F, Cl, Br, I, ¹²³I, hydroxyl, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₆-C₁₂ aryl, wherein each R⁶ is optionally substituted with one or more of halogen, ¹²³I, ¹⁸F, hydroxyl, -OS(O)₂-aryl, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

[045] R⁸ and R⁹ are each independently H or C₁-C₆ alkyl;

[046] n is 0, 1, or 2; and

[047] R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, F, Cl, Br, I, or ¹²³I.

20 [048] In one embodiment, R³ in Formula II is -OH. In another embodiment, R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In other embodiments, R³ is -OR⁴, wherein R⁴ is C₁-C₆ alkyl. In some embodiments, R³ is -OR⁴, wherein R⁴ is methyl.

[049] In some embodiments, R¹ in Formula II is hydroxyl or OC(=O)R¹³. In another embodiment R¹ in Formula II is H.

25 [050] In one embodiment, R³ in Formula II is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom. In some embodiments, R³ is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine,

pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine.

5 [051] In one embodiment, R^{11a}, R^{11b}, R^{11c} and R^{11d} in Formula II are each H.

[052] In one embodiment, each R¹³ in Formula II when present is C₁-C₃ alkyl. In a further embodiment, each R¹³ when present is methyl.

[053] In one embodiment, R¹ and R² in Formula II are each independently -OH or -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, at least one of R¹, R² and R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In another embodiment, any two of R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl. In one embodiment, R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

10 [054] In one embodiment of the present disclosure relates to compounds disclosed in Table 5 or a pharmaceutically acceptable salt thereof.

15 [055] In one embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula I or Formula II or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. In one embodiment, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier and an additional therapeutic agent.

20 [056] In some embodiments, a pharmaceutical composition comprising a compound of Formula I or Formula II or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, and an additional therapeutic agent is provided. In one embodiment, the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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. In another embodiment, the additional therapeutic agent is enzalutamide, galeterone, abiraterone, bicalutamide, nilutamide, flutamide, cyproterone acetate, docetaxel, bevacizumab (Avastin), OSU-HDAC42, VITAXIN, 25 sunitumib, ZD-4054, cabazitaxel (XRP-6258), MDX-010 (Ipilimumab), OGX 427, OGX 011, finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111, ODM-30 201, radium 233, ODM-204, niclosamide, apalutamide, ARV-330, VPC-14449, TAS3681, 3E10-AR441bsAb, sintokamide, or related compounds thereof.

[057] In one embodiment, the present disclosure provides a method for modulating androgen receptor activity, comprising administering a compound of Formula I or Formula II or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, or a pharmaceutical composition comprising a compound of Formula I or Formula II or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a patient in need thereof. In some embodiments, the method of modulating androgen receptor activity is inhibiting androgen receptor.

[058] In one embodiment, the present disclosure provides a method for treating a condition or disease that is responsive to modulation of androgen receptor activity, comprising: 10 administering a compound of Formula I or Formula II or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, or a pharmaceutical composition comprising a compound of Formula I or Formula II or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a patient in need thereof. In one embodiment, the condition or disease is selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, bladder cancer, 15 pancreatic cancer, hepatocellular 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 one embodiment, the condition is prostate cancer. In another embodiment, the condition or disease is castration-resistant prostate cancer. In some embodiments, the condition or disease is androgen-dependent 20 prostate cancer.

[059] Some embodiments of the compounds described herein can be used for diagnostic purposes to investigate diseases of the prostate, including cancer. In particular embodiments, the compounds are useful for imaging diagnostics in cancer. In some embodiments, such imaging allows for the detection and/or location of cancer sites (e.g., tumor sites). Furthermore, 25 these compounds can be used individually or as part of a kit for such purposes.

BRIEF DESCRIPTION OF THE FIGURES

[060] **Figure 1** shows a ^{13}C NMR spectrum of Compound 3a.

30 [061] **Figure 2** shows a dose-response for selected compounds of the present disclosure in LNCaP cells transfected with the PSA (6.1 kb)-luciferase reporter and treated with androgen.

[062] **Figure 3** shows tumor volume of LNCaP xenografts in SCID-NOD mice treated with Compound 1a or CMC-treated mice (control) in the course of 26 day treatment.

[063] **Figure 4** shows tumor volume of LNCaP xenografts at the start and the finish (day 26) for Compound **1a** treated mice and CMC-treated mice.

[064] **Figure 5** shows body weight at the start and the finish (day 26) for Compound **1a** treated mice and CMC-treated mice.

5 [065] **Figure 6** shows tissues levels of *PSA* mRNA in five representative xenografts from each treatment group measured by QPCR.

DETAILED DESCRIPTION

[066] Definitions

10 [067] 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 invention can 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 15 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 invention.

[068] Reference throughout this specification to “one embodiment” or “an embodiment” 20 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 can be combined in any suitable manner in one or more 25 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.

[069] The terms below, as used herein, have the following meanings, unless indicated 30 otherwise:

[070] “Amino” refers to the -NH₂ radical.

[071] “Cyano” refers to the -CN radical.

[072] “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo radical.

[073] “Hydroxy” or “hydroxyl” refers to the -OH radical.

- [074] “Imino” refers to the =NH substituent.
- [075] “Nitro” refers to the -NO₂ radical.
- [076] “Oxo” refers to the =O substituent.
- [077] “Thioxo” refers to the =S substituent.
- 5 [078] “Acetyl” or “Ac” refers to -C(=O)CH₃ substituent.
- [079] “Alkyl” or “alkyl group” refers to a fully saturated, straight or branched hydrocarbon chain radical having from one to twelve 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 12 are included. An alkyl comprising up to 12 carbon atoms is a C₁-C₁₂ alkyl, an alkyl comprising up
- 10 to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls and C₁ alkyl (*i.e.*, methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and
- 15 C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.
- 20 [080] “Alkylene” or “alkylene chain” refers to a fully saturated, straight or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C₁-C₁₂ alkylene include methylene, ethylene, propylene, *n*-butylene, ethylene, propylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a
- 25 single 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 can be optionally substituted.
- [081] “Alkenyl” or “alkenyl group” refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds.
- 30 Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkenyl, an alkenyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C₂-C₆ alkenyl and an alkenyl comprising up to 5 carbon atoms is a C₂-C₅ alkenyl. A C₂-C₅ alkenyl includes

C₅ alkenyls, C₄ alkenyls, C₃ alkenyls, and C₂ alkenyls. A C₂-C₆ alkenyl includes all moieties described above for C₂-C₅ alkenyls but also includes C₆ alkenyls. A C₂-C₁₀ alkenyl includes all moieties described above for C₂-C₅ alkenyls and C₂-C₆ alkenyls, but also includes C₇, C₈, C₉ and C₁₀ alkenyls. Similarly, a C₂-C₁₂ alkenyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkenyls. Non-limiting examples of C₂-C₁₂ alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Examples of C₁-C₃ alkyl includes methyl, ethyl, *n*-propyl, and *i*-propyl. Examples of C₁-C₄ alkyl includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *sec*-butyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[082] “Alkenylene” or “alkenylene chain” refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Non-limiting examples of C₂-C₁₂ alkenylene include ethene, propene, butene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkenylene 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 alkenylene chain can be optionally substituted.

[083] “Alkynyl” or “alkynyl group” refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl group comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkynyl, an alkynyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C₂-C₆ alkynyl and an alkynyl comprising up to 5 carbon atoms is a C₂-C₅ alkynyl. A C₂-C₅ alkynyl includes C₅ alkynyls, C₄ alkynyls, C₃ alkynyls, and C₂ alkynyls. A C₂-C₆ alkynyl includes all moieties described above for C₂-C₅ alkynyls but also includes C₆ alkynyls. A C₂-C₁₀ alkynyl includes

all moieties described above for C₂-C₅ alkynyls and C₂-C₆ alkynyls, but also includes C₇, C₈, C₉ and C₁₀ alkynyls. Similarly, a C₂-C₁₂ alkynyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkynyls. Non-limiting examples of C₂-C₁₂ alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[084] “Alkynylene” or “alkynylene chain” refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Non-limiting examples of C₂-C₁₂ alkynylene include ethynylene, propargylene and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkynylene 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 alkynylene chain can be optionally substituted.

[085] “Alkoxy” refers to a radical of the formula -OR_a where R_a is an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[086] “Alkylamino” refers to a radical of the formula -NHR_a or -NR_aR_a where each R_a is, independently, an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group can be optionally substituted.

[087] “Alkylcarbonyl” refers to the -C(=O)R_a moiety, wherein R_a is an alkyl, alkenyl or alkynyl radical as defined above. A non-limiting example of an alkyl carbonyl is the methyl carbonyl (“acetal”) moiety. Alkylcarbonyl groups can also be referred to as “C_w-C_z acyl” where w and z depicts the range of the number of carbon in R_a, as defined above. For example, “C₁-C₁₀ acyl” refers to alkylcarbonyl group as defined above, where R_a is C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, or C₁-C₁₀ alkynyl radical as defined above. Unless stated otherwise specifically in the specification, an alkyl carbonyl group can be optionally substituted.

[088] “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 invention, the aryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can 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” is meant to include aryl radicals that are optionally substituted.

[089] “Aralkyl” refers to a radical of the formula -R_b-R_c where R_b is an alkylene, alkenylene or alkynylene group 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 can be optionally substituted.

[090] “Carbocyclic,” “carbocyclic ring” or “carbocycle” refers to a rings structure, wherein the atoms which form the ring are each carbon. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include aryls and cycloalkyl, cycloalkenyl and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclic group can be optionally substituted.

[091] “Cycloalkyl” refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl 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 can be optionally substituted.

[092] “Cycloalkenyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon double bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkenyl radicals include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like. Polycyclic cycloalkenyl radicals include, for example, bicyclo[2.2.1]hept-2-enyl and the like. Unless otherwise stated specifically in the specification, a cycloalkenyl group can be optionally substituted.

[093] “Cycloalkynyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon triple bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkynyl radicals include, for example,

cycloheptynyl, cyclooctynyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkynyl group can be optionally substituted.

[094] “Cycloalkylalkyl” refers to a radical of the formula -R_b-R_a where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_a is a cycloalkyl, cycloalkenyl, 5 cycloalkynyl radical as defined above. Unless stated otherwise specifically in the specification, a cycloalkylalkyl group can be optionally substituted.

[095] “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 10 like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[096] “Haloalkenyl” refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 1-fluoropropenyl, 1,1-difluorobutenyl, and the like. Unless stated otherwise specifically in the specification, a haloalkenyl group can be 15 optionally substituted.

[097] “Haloalkynyl” refers to an alkynyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 1-fluoropropynyl, 1-fluorobutynyl, and the like. Unless stated otherwise specifically in the specification, a haloalkenyl group can be optionally substituted.

20 [098] “Heterocyclyl,” “heterocyclic ring” or “heterocycle” refers to a stable 3- to 20-membered non-aromatic 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. Heterocyclyl or heterocyclic rings include heteroaryls as defined below. Unless stated otherwise specifically in the specification, the heterocyclyl radical can be a monocyclic, 25 bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl radical can be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, 30 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 heterocycl group can be optionally substituted.

[099] “*N*-heterocycl” refers to a heterocycl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocycl radical to the rest of the molecule is through a nitrogen atom in the heterocycl radical. Unless stated otherwise specifically in the specification, a *N*-heterocycl group can be optionally substituted.

[100] “Heterocyclalkyl” refers to a radical of the formula -R_b-R_e where R_b is an alkylene, alkenylene, or alkynylene chain as defined above and R_e is a heterocycl radical as defined above, and if the heterocycl is a nitrogen-containing heterocycl, the heterocycl can be attached to the alkyl, alkenyl, alkynyl radical at the nitrogen atom. Unless stated otherwise specifically in the specification, a heterocyclalkyl group can be optionally substituted.

[101] “Heteroaryl” refers to a 5- to 20-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 invention, the heteroaryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzoxazolyl, 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 can be optionally substituted.

[102] “*N*-heteroaryl” refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule

is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an *N*-heteroaryl group can be optionally substituted.

[103] "Heteroarylalkyl" refers to a radical of the formula -R_b-R_f where R_b is an alkylene, alkenylene, or alkynylene chain as defined above and R_f is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkyl group can be optionally substituted.

[104] "¹²³I" refers to the radioactive isotope of iodine having atomic mass 123. The compounds of Formula I can comprise at least one ¹²³I moiety. Throughout the present application, where structures depict a ¹²³I moiety at a certain position it is meant that the I moiety at this position is enriched for ¹²³I. In other words, the compounds contain more than the natural abundance of ¹²³I at the indicated position(s). It is not required that the compounds comprise 100% ¹²³I at the indicated positions, provided ¹²³I is present in more than the natural abundance. Typically the ¹²³I isotope is enriched to greater than 50%, greater than 60%, greater than 70%, greater than, 80% or greater than 90%, relative to ¹²⁷I.

[105] "¹⁸F" refers to the radioactive isotope of fluorine having atomic mass 18. "F" or "¹⁹F" refers to the abundant, non-radioactive fluorine isotope having atomic mass 19. The compounds of Formula I can comprise at least one ¹⁸F moiety. Throughout the present application, where structures depict a ¹⁸F moiety at a certain position it is meant that the F moiety at this position is enriched for ¹⁸F. In other words, the compounds contain more than the natural abundance of ¹⁸F at the indicated position(s). It is not required that the compounds comprise 100% ¹⁸F at the indicated positions, provided ¹⁸F is present in more than the natural abundance. Typically the ¹⁸F isotope is enriched to greater than 50%, greater than 60%, greater than 70%, greater than 80% or greater than 90%, relative to ¹⁹F.

[106] "Thioalkyl" refers to a radical of the formula -SR_a where R_a is an alkyl, alkenyl, or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group can be optionally substituted.

[107] The term "substituted" used herein means any of the above groups (*i.e.*, alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, alkoxy, alkylamino, alkylcarbonyl, thioalkyl, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl) 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, 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, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, “substituted” includes any of the above groups in which one or more hydrogen atoms are replaced

5 with -NR_gR_h, -NR_gC(=O)R_h, -NR_gC(=O)NR_gR_h, -NR_gC(=O)OR_h, -NR_gSO₂R_h, -OC(=O)NR_gR_h, -OR_g, -SR_g, -SOR_g, -SO₂R_g, -OSO₂R_g, -SO₂OR_g, =NSO₂R_g, and -SO₂NR_gR_h. “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, -CH₂SO₂R_g, -CH₂SO₂NR_gR_h. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, 10 alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocycl, N-heterocycl, heterocyclalkyl, heteroaryl, N-heteroaryl and/or heteroarylalkyl. “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, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, 15 aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocycl, N-heterocycl, heterocyclalkyl, heteroaryl, N-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

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[108] As used herein, the symbol “” (hereinafter can 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. 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 can be specified by inference. For example, the compound CH₃-R³, wherein R³ is H or “”

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$XY-\overset{\text{R}^3}{\text{C}}-$ " 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 .

[109] "Fused" refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring is a heterocycl ring or a 5 heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocycl ring or the fused heteroaryl ring can be replaced with a nitrogen atom.

[110] The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products can result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered 10 compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising administering a compound of this invention 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 invention in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing 15 sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[111] "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.

20 [112] As used herein, a "subject" can be a human, non-human primate, mammal, rat, mouse, cow, horse, pig, sheep, goat, dog, cat and the like. The subject can 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 25 puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration. Diagnostic methods for various cancers, such as prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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 30 atrophy, or age-related macular degeneration and the clinical delineation of cancer, such as prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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.

[113] "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 5 animals such as wildlife and the like.

[114] "Optional" or "optionally" means that the subsequently described event of circumstances can or cannot 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 can or cannot be substituted and that the description includes 10 both substituted aryl radicals and aryl radicals having no substitution.

[115] "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 15 Drug Administration as being acceptable for use in humans or domestic animals.

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

[117] "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, 20 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, 25 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 30 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.

[118] “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, 5 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, 10 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, 15 tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

[119] Often crystallizations produce a solvate of the compound of the invention. As used herein, the term “solvate” refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent can be water, 20 in which case the solvate can be a hydrate. Alternatively, the solvent can be an organic solvent. Thus, the compounds of the present invention can 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 invention can be true solvates, while in other cases, the compound of the invention can merely retain adventitious water or be a mixture 25 of water plus some adventitious solvent.

[120] A “pharmaceutical composition” refers to a formulation of a compound of the invention 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.

30 [121] “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 can 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 can 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. 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 a castration-resistant form. Typically, a prophylactic dose is used in subjects prior to or at an earlier stage of disease, so that a prophylactically effective amount can be less than a therapeutically effective amount.

5 [122] “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;
- 10 (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”

15 and “condition” can be used interchangeably or can be different in that the particular malady or condition cannot 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.

[123] The compounds of the invention, or their pharmaceutically acceptable salts can contain

20 one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms whether or not they are specifically depicted herein. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers

25 can 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 centers 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.

[124] 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 invention contemplates various stereoisomers and mixtures thereof and includes “enantiomers”, which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[125] A “tautomer” refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

[126] 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, ChemDraw Ultra Version 11.0.1 and/or ChemDraw Ultra Version 14.0 and/or ChemDraw Professional 16.0.0.82 software naming program (CambridgeSoft), or the like. 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.

[127] Throughout the present specification, the terms “about” and/or “approximately” can be used in conjunction with numerical values and/or ranges. The term “about” is understood to mean those values near to a recited value. For example, “about 40 [units]” can mean within \pm 25% of 40 (e.g., from 30 to 50), within \pm 20%, \pm 15%, \pm 10%, \pm 9%, \pm 8%, \pm 7%, \pm 6%, \pm 5%, \pm 4%, \pm 3%, \pm 2%, \pm 1%, less than \pm 1%, or any other value or range of values therein or therebelow. Furthermore, the phrases “less than about [a value]” or “greater than about [a value]” should be understood in view of the definition of the term “about” provided herein. The terms “about” and “approximately” can be used interchangeably.

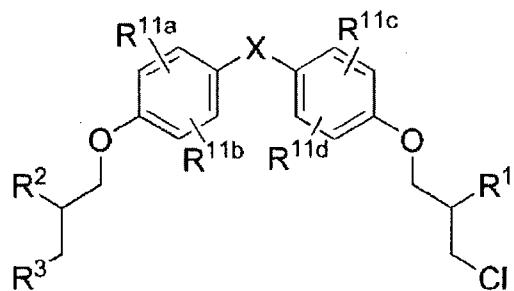
[128] Throughout the present specification, numerical ranges are provided for certain quantities. It is to be understood that these ranges comprise all subranges therein. Thus, the range “from 50 to 80” includes all possible ranges therein (e.g., 51-79, 52-78, 53-77, 54-76, 55-75, 60-70, etc.). Furthermore, all values within a given range can be an endpoint for the range encompassed thereby (e.g., the range 50-80 includes the ranges with endpoints such as 55-80, 50-75, etc.).

II. Compounds and Pharmaceutical Compositions

[129] As noted above, certain embodiments of the present invention are directed to compounds useful for treatment of various cancers, including various types of prostate cancers. While not wishing to be bound by theory, it is believed that binding of the compounds to the androgen receptor (for example at the N-terminal domain) can contribute to the activity of the disclosed compounds. The compounds of the present invention include halogenated phenyl groups (i.e., R^{11a}-R^{11d} in Formula I) and/or sulfone bridging groups (i.e., X in Formula I is -S(O)₂- or compounds of Formula II) which impart improved properties to the compounds compared to compounds lacking the described R³ moiety. For example, the improved properties include improved drug-like properties such as improved activity (e.g., androgen receptor (AR) modulation), longer half-life (e.g., *in vivo*); decreased toxicity; better solubility, improved formulation, better bioavailability, better pharmacokinetic profile; reduction in unwanted metabolites and the like.

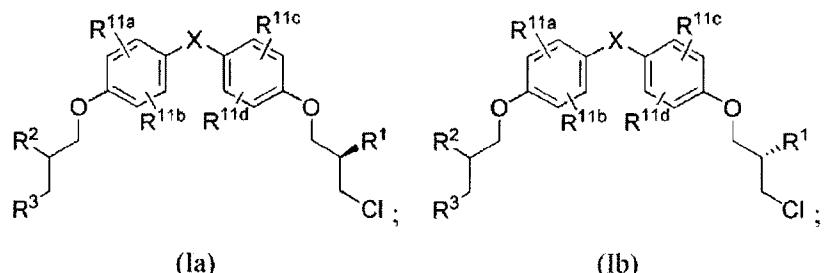
[130] In one embodiment the invention includes compounds which form covalent bonds with the androgen receptor (AR) (e.g., at the N-terminal domain), thus resulting in irreversible (or substantially irreversible) inhibition of the same. In this regard, the certain compounds of the present invention are designed to include functional groups capable of forming covalent bonds with a nucleophile under certain *in vivo* conditions. For example, in some embodiments the reactivity of compounds of the present invention is such that they will not substantially react with various nucleophiles (e.g., glutathione) when the compounds are free in solution. However, when the free mobility of the compounds is restricted, and an appropriate nucleophile is brought into close proximity to the compound, for example when the compounds associate with, or bind to, the androgen receptor, the compounds are capable of forming covalent bonds with certain nucleophiles (e.g., thiols).

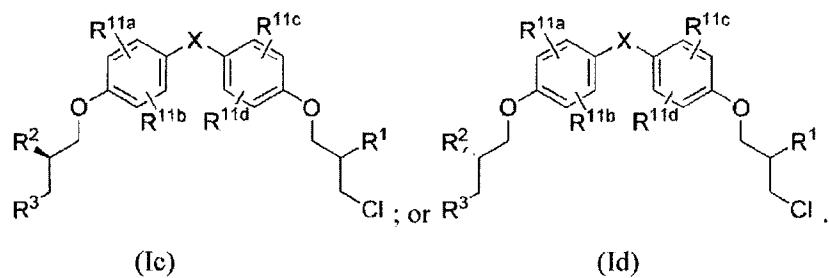
[131] The present invention includes all compounds which have the above described properties (i.e., binding and/or inhibiting to androgen receptor (AR)). In one embodiment, the present invention is directed to a compound having a structure of Formula I:



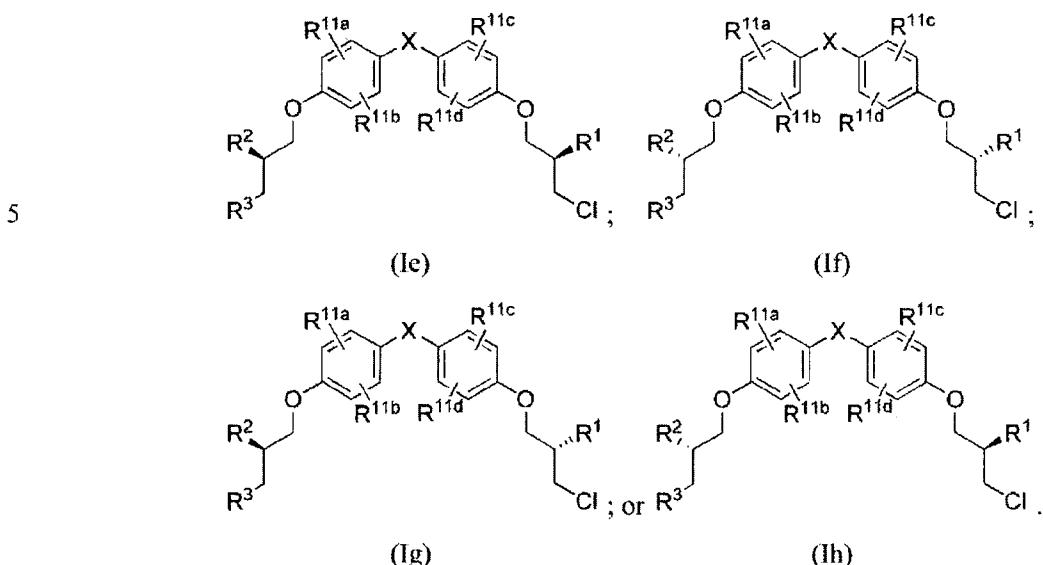
(I)

- [132] or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:
- [133] X is -S(O)_n- or -C(R⁸R⁹)-;
- [134] R¹ is H, -OH, or -OC(=O)R¹³;
- 5 [135] R² is -OH, or -OC(=O)R¹³;
- [136] R³ is halo, -OH, -OR⁴, -OC(=O)R¹³, -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), -N(C₁-C₆ alkyl)(S(O)_nR⁵), -S(O)_nR⁵, -N₃, aryl, carbocycll, heteroaryl or heterocycll which are optionally substituted with one or more R⁶;
- 10 [137] R⁴ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, carbocycll, heteroaryl or heterocycll which are optionally substituted with one or more R⁶;
- [138] R⁵ is each independently C₁-C₆ alkyl or aryl which are optionally substituted with one or more R⁶;
- [139] R⁶ is each independently selected from the group consisting of H, F, Cl, Br, I, ¹²³I, -OH, 15 oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₆-C₁₂ aryl, wherein each R⁶ is optionally substituted with one or more of halogen, ¹²³I, ¹⁸F, -OH, -OS(O)₂-aryl, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;
- [140] R⁸ and R⁹ are each independently H or C₁-C₆ alkyl;
- [141] R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, F, Cl, Br, I, or ¹²³I;
- 20 [142] R¹³ is C₁-C₆ alkyl; and
- [143] n is 0, 1, or 2;
- [144] wherein at least one of R^{11a}, R^{11b}, R^{11c} and R^{11d} is methyl, F, Cl, Br, I, or ¹²³I.
- [145] In various embodiments, different stereoisomers of the compound of structure (I) are provided, for example in some embodiments the compound has one of the following structures
- 25 (Ia), (Ib), (Ic) or (Id):





[146] In still other embodiments, the compound has one of the following structures (Ie), (If), (Ig) or (Ih):



[147] In one embodiment, X is $-S(O)_{m-}$. In some embodiments, X is $-S(O)_{2-}$. In another embodiment, X is $-C(R^8R^9)-$. In one embodiment X is $-C(R^8R^9)-$, wherein R⁸ and R⁹ are each independently H or C₁-C₃ alkyl. In another embodiment, X is $-C(R^8R^9)-$, wherein R⁸ and R⁹ are each C₁ alkyl. In some embodiments, X is $-S(O)_{2-}$ or $-C(CH_3)_{2-}$.

[148] In one embodiment, R¹ is -OH. In another embodiment, R¹ is $-OC(=O)R^{13}$. In some embodiments, R¹ is $-OC(=O)R^{13}$, wherein R¹³ is C₁-C₄ alkyl. In other embodiments, R¹ is $-OC(=O)R^{13}$, wherein R¹³ is methyl. In one embodiment, R¹ is H.

[149] In one embodiment, R² is -OH. In another embodiment, R² is $-OC(=O)R^{13}$. In some embodiments, R² is $-OC(=O)R^{13}$, wherein R¹³ is C₁-C₄ alkyl. In other embodiments, R² is $-OC(=O)R^{13}$, wherein R¹³ is methyl.

[150] In one embodiment, R³ is -OH. In another embodiment, R³ is $-OC(=O)R^{13}$. In some embodiments, R³ is $-OC(=O)R^{13}$, wherein R¹³ is C₁-C₄ alkyl. In other embodiments, R³ is $-OC(=O)R^{13}$, wherein R¹³ is methyl.

[151] In some embodiments, at least one of R¹, R², or R³ is -OH. In some embodiments, at least two of R¹, R², or R³ are each -OH. In other embodiments, R¹ and R² are each -OH. In another embodiment, R¹, R², and R³ are each -OH.

[152] In some embodiments, at least one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, at least one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, at least two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, at least two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is methyl. In other embodiments, R¹ and R² are each -OC(=O)R¹³, wherein R¹³ is methyl.

10 [153] In some embodiments, one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, R¹ and R² are each -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, R¹ and R² are each -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

20 [154] In other embodiments, R³ is -OR⁴. In one embodiment, R³ is -OR⁴, wherein R⁴ is C₁-C₆ alkyl. In another embodiment, R³ is -OR⁴, wherein R⁴ is C₁-C₃ alkyl. In one embodiment, R³ is -OR⁴, wherein R⁴ is methyl, ethyl, *n*-propyl, or *i*-propyl. In one embodiment, R³ is -OR⁴, wherein R⁴ is methyl. In another embodiment, R³ is -OR⁴, wherein R⁴ is *i*-propyl.

[155] In other embodiments, R³ is a halogen. In other embodiments, R³ is F, Cl, Br, or I. In one embodiment, R³ is F.

25 [156] In other embodiments, R³ is -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), or -N(C₁-C₆ alkyl)(S(O)_nR⁵). In one embodiment, R³ is a -NH₂. In one embodiment, R³ is a -NHC(=O)R¹³. In one embodiment, R³ is a -N(C(=O)R¹³)₂. In another embodiment, R³ is a -NHS(O)_nR⁵. In some embodiments, R³ is a -NHS(O)₂R⁵. In other embodiments, R³ is a -NHS(O)₂R⁵, wherein R⁵ is C₁-C₃ alkyl. In one embodiment, R³ is a -NHS(O)₂R⁵, wherein R⁵ is C₁ alkyl. In one embodiment, R³ is a -N(C(=O)R¹³)(S(O)_nR⁵). In one embodiment, R³ is a -N(C₁-C₆ alkyl)(S(O)_nR⁵).

30 [157] In other embodiments, R³ is -NH₂, -NHC(=O)(C₁-C₄ alkyl), -N[(C(=O)(C₁-C₄ alkyl)]₂, -NHS(O)_n(C₁-C₃ alkyl), -N[C(=O)(C₁-C₄ alkyl)][(S(O)_n(C₁-C₃ alkyl)], or -N[C₁-C₆ alkyl][(S(O)_n(C₁-C₃ alkyl)]. In some embodiments, R³ is -NH(C(=O)CH₃) or -N(C(=O)CH₃)₂.

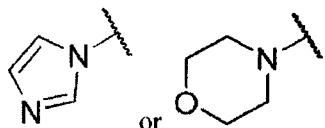
In other embodiments, R^3 is $-NHS(O)_2CH_3$. In other embodiments, R^3 is $-N(C(=O)CH_3)(S(O)_2CH_3)$.

[158] In another embodiment, R^3 is a $-S(O)_nR^5$. In one embodiment, R^3 is a $-S(O)_2R^5$. In another embodiment, R^3 is a $-S(O)_2(C_1-C_3$ alkyl). In other embodiments, R^3 is a $-S(O)_2CH_3$.

5 In other embodiments, R^3 is a $-S(O)_2CH_2CH_3$.

[159] In some embodiments, R^3 is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom in the ring. In one embodiment, R^3 is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine,

10 pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine. In a certain embodiment, R^3 is



15 [160] In one embodiment, at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is Cl. In another embodiment, at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is Br. In some embodiments, at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is methyl.

[161] In one embodiment, at least two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are methyl, F, Cl, Br, I, or ^{123}I . In another embodiment, exactly two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are methyl, F, Cl, Br, I, or ^{123}I .

[162] In some embodiments, R^{11a} and R^{11b} are each H and R^{11c} and R^{11d} are each independently methyl, F, Cl, Br, I, or ^{123}I . In one embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each Cl. In one embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each Br. In one embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each methyl.

25 [163] In some embodiments, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each independently methyl, F, Cl, Br, I, or ^{123}I . In one embodiment, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each Cl. In one embodiment, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each Br. In one embodiment, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each methyl.

[164] In some embodiments, R^{13} is C_1-C_3 alkyl. In other embodiments, R^{13} is methyl, ethyl, 30 or propyl. In one embodiment, R^{13} is a methyl.

[165] In one embodiment, n is 0. In another embodiment n is 1. In some embodiments, n is 2.

[166] The compounds for use in the imaging and treatment methods are described herein. In some embodiments, the compounds comprise one F, Cl, Br, I, or ^{123}I substitution. For example in certain other embodiments, any three of $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{11\text{c}}$ and $\text{R}^{11\text{d}}$ are each H, and the remaining one of $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{11\text{c}}$ or $\text{R}^{11\text{d}}$ is F, Cl, Br, I or ^{123}I . In some embodiments, the 5 compounds comprise two F, Cl, Br, I or ^{123}I substitutions on the phenyl rings (*i.e.*, two of $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{11\text{c}}$ and $\text{R}^{11\text{d}}$ are H, and the other two of $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{11\text{c}}$ or $\text{R}^{11\text{d}}$ are F, Cl, Br, I or ^{123}I). In other embodiments, the compounds comprise three F, Cl, Br, I or ^{123}I substitutions (*i.e.*, any one of $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{11\text{c}}$ and $\text{R}^{11\text{d}}$ is H, and the remaining $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{11\text{c}}$ or $\text{R}^{11\text{d}}$ is F, Cl, Br, I or ^{123}I) and in other embodiments the compounds comprise four F, Cl, Br, I or ^{123}I substitutions 10 (*i.e.*, each of $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{11\text{c}}$ and $\text{R}^{11\text{d}}$ are F, Cl, Br, I or ^{123}I).

[167] In another embodiment, the compound comprises one or more of F, Cl, Br, I or ^{123}I substitutions for R^3 . In one embodiment, the compound comprises one or more of I or ^{123}I substitutions for R^3 .

[168] In some embodiments, the compound comprises at least one R^6 substituent on R^3 , 15 wherein at least one R^6 is further substituted with at least one of F, Cl, Br, I or ^{123}I . In another embodiment, R^6 substituent on R^3 is further substituted with at least one of I or ^{123}I .

[169] Favorable imaging and/or AR NTD modulating results can be obtained by substitution with F, Cl, Br, I or ^{123}I at any of the “ R^{11} ” positions. In some of the foregoing embodiments, $\text{R}^{11\text{a}}$ is ^{123}I . In other embodiments, $\text{R}^{11\text{c}}$ is ^{123}I .

20 [170] In some more specific embodiments of the compound of Formula I, the compound has one of the following structures from Table 1, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof:

Table 1. Compounds

No.	Structure	Name
1		3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
1a		(<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol

No.	Structure	Name
1b		(S)-3-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
1c		(S)-3-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
1d		(R)-3-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
2		3-(2-chloro-4-(2-(3-chloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
2a		(R)-3-(2-chloro-4-(2-(3-chloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
2b		(S)-3-(2-chloro-4-(2-(3-chloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
2c		(S)-3-(2-chloro-4-(2-(3-chloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol

No.	Structure	Name
2d		(<i>R</i>)-3-(2-chloro-4-(2-(3-chloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
3		3-(4-(2-(3,5-dibromo-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
3a		(<i>R</i>)-3-(4-(2-(3,5-dibromo-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
3b		(<i>S</i>)-3-(4-(2-(3,5-dibromo-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
3c		(<i>S</i>)-3-(4-(2-(3,5-dibromo-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
3d		(<i>R</i>)-3-(4-(2-(3,5-dibromo-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
4		3-(4-(2-(4-(3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol

No.	Structure	Name
4a		(<i>R</i>)-3-(4-(2-(4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol
4b		(<i>S</i>)-3-(4-(2-(4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol
4c		(<i>S</i>)-3-(4-(2-(4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol
4d		(<i>R</i>)-3-(4-(2-(4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol
5		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
5a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
5b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
5c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
5d		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
6		1-chloro-3-(2-chloro-4-(2-(3-chloro-4-(2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
6a		(S)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((R)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
6b		(R)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((S)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
6c		(S)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((S)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
6d		(<i>R</i>)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((<i>R</i>)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
7		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
7a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
7b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
7c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
7d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
8		1-chloro-3-(2,6-dichloro-4-(2-(4-(3-fluoro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
8a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-3-fluoro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
8b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-3-fluoro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
8c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-3-fluoro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
8d		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-3-fluoro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
9		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
9a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
9b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
9c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
9d		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
10		1-chloro-3-(2-chloro-4-(2-(3-chloro-4-(2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
10a		(S)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((R)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
10b		(R)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((S)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
10c		(S)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((S)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
10d		(R)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((R)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
11		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
11a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
11b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
11c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
11d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
12		1-amino-3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
12a		(<i>R</i>)-1-amino-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
12b		(<i>S</i>)-1-amino-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
12c		(<i>S</i>)-1-amino-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
12d		(<i>R</i>)-1-amino-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
13		<i>N</i> -(3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide

No.	Structure	Name
13a		<i>N</i> -((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide
13b		<i>N</i> -((<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide
13c		<i>N</i> -((<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide
13d		<i>N</i> -((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide
14		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
14a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
14b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
14c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
14d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
15		1-chloro-3-(2-chloro-4-(2-(3-chloro-4-(2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
15a		(<i>S</i>)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-(2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
15b		(<i>R</i>)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-(2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

No.	Structure	Name
15c		(S)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((R)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
15d		(R)-1-chloro-3-(2-chloro-4-(2-(3-chloro-4-((S)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
16		3-(2,6-dichloro-4-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
16a		(R)-3-(2,6-dichloro-4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
16b		(S)-3-(2,6-dichloro-4-(2-(4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
16c		(S)-3-(2,6-dichloro-4-(2-(4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
16d		(R)-3-(2,6-dichloro-4-(2-(4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol

No.	Structure	Name
17		1-chloro-3-(4-(2-(3,5-dichloro-4-(3-ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
17a		(S)-1-chloro-3-(4-(2-(3,5-dichloro-4-((S)-3-ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
17b		(R)-1-chloro-3-(4-(2-(3,5-dichloro-4-((R)-3-ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
17c		(S)-1-chloro-3-(4-(2-(3,5-dichloro-4-((R)-3-ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
17d		(R)-1-chloro-3-(4-(2-(3,5-dichloro-4-((S)-3-ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol
18		3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol

No.	Structure	Name
18a		(<i>R</i>)-3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
18b		(<i>S</i>)-3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
19		1-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
19a		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
19b		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
20		3-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol

No.	Structure	Name
20a		(<i>R</i>)-3-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
20b		(<i>S</i>)-3-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
21		1-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
21a		(<i>S</i>)-1-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
21b		(<i>R</i>)-1-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
22		3-(4-(2-(4-(3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol

No.	Structure	Name
22a		(<i>R</i>)-3-(4-(2-(4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol
22b		(<i>S</i>)-3-(4-(2-(4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol
22c		(<i>S</i>)-3-(4-(2-(4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol
22d		(<i>R</i>)-3-(4-(2-(4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol

[171] In some embodiments of the compound of Formula I, the compound has one of the following structures from Table 2, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

5 Table 2. Compounds

No.	Structure	Name
A1		3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)propane-1,2-diyil diacetate
A1a		(<i>S</i>)-3-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)propane-1,2-diyil diacetate

No.	Structure	Name
A1b		(<i>R</i>)-3-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
A1c		(<i>R</i>)-3-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
A1d		(<i>S</i>)-3-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
B1		1-(4-(2-(4-(3-acetoxy-2-hydroxypropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
B1a		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-3-acetoxy-2-hydroxypropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
B1b		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-3-acetoxy-2-hydroxypropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
B1c		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-3-acetoxy-2-hydroxypropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate

No.	Structure	Name
B1d		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-3-acetoxy-2-hydroxypropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
C1		1-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
C1a		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
C1b		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
C1c		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
C1d		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
D1		3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyi diacetate

No.	Structure	Name
D1a		(<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
D1b		(<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
D1c		(<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
D1d		(<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
E1		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
E1a		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
E1b		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate

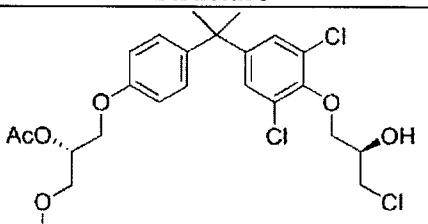
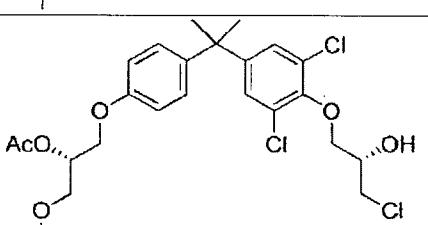
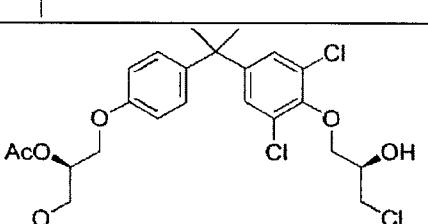
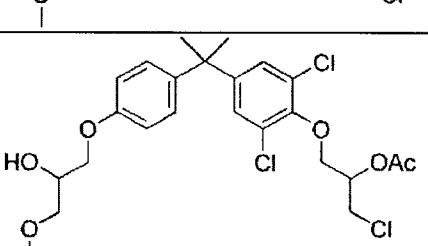
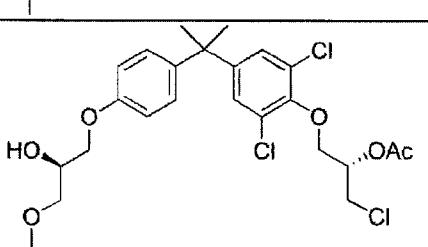
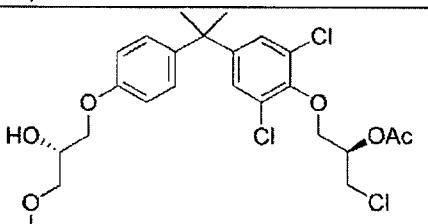
No.	Structure	Name
E1c		(S)-1-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
E1d		(R)-1-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-hydroxypropan-2-yl acetate
F1		3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate
F1a		(S)-3-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate
F1b		(R)-3-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate
F1c		(R)-3-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate
F1d		(S)-3-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl acetate

No.	Structure	Name
G1		1-chloro-3-(2,6-dichloro-4-(2-(4-(2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
G1a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
G1b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
G1c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
G1d		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2,3-dihydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
A2		3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)propane-1,2-diy diacetate
A2a		(S)-3-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)propane-1,2-diy diacetate

No.	Structure	Name
A2b		(<i>R</i>)-3-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)propane-1,2-diyI diacetate
A2c		(<i>R</i>)-3-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)propane-1,2-diyI diacetate
A2d		(<i>S</i>)-3-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)propane-1,2-diyI diacetate
A3		3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3,5-dibromophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
A3a		(<i>S</i>)-3-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dibromophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
A3b		(<i>R</i>)-3-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dibromophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
A3c		(<i>R</i>)-3-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dibromophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate

No.	Structure	Name
A3d		(S)-3-(4-(2-(4-((R)-2-acetoxy-3-chloropropoxy)-3,5-dibromophenyl)propan-2-yl)phenoxy)propane-1,2-diyI diacetate
A4		3-(4-(2-(4-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diyI diacetate
A4a		(S)-3-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diyI diacetate
A4b		(R)-3-(4-(2-(4-((R)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diyI diacetate
A4c		(R)-3-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diyI diacetate
A4d		(S)-3-(4-(2-(4-((R)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diyI diacetate
A5		1-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate

No.	Structure	Name
A5a		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
A5b		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
A5c		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
A5d		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
B5		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
B5a		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate

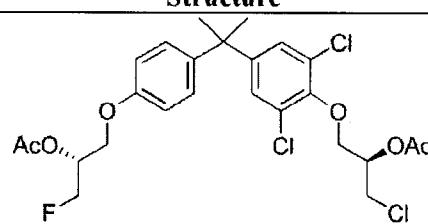
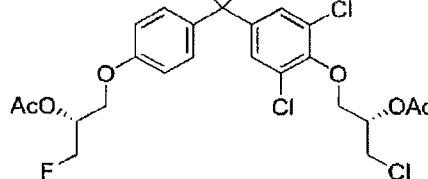
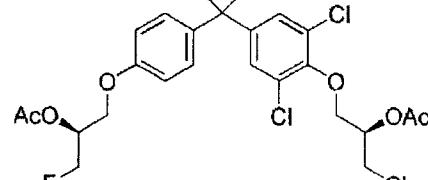
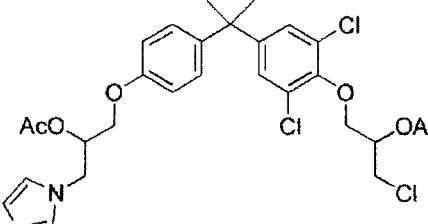
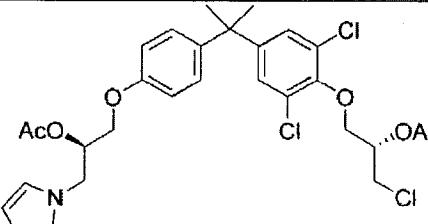
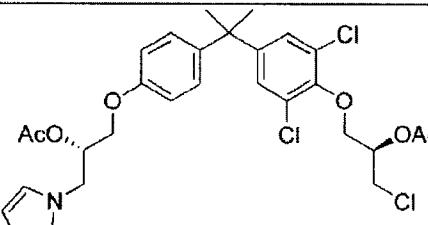
No.	Structure	Name
B5b		(S)-1-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
B5c		(S)-1-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
B5d		(R)-1-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate
C5		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C5a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C5b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate

No.	Structure	Name
C5c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C5d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
A6		1-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A6a		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A6b		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A6c		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate

No.	Structure	Name
A6d		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A7		1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
A7a		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
A7b		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
A7c		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
A7d		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate

No.	Structure	Name
B7		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
B7a		(R)-1-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
B7b		(S)-1-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
B7c		(S)-1-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
B7d		(R)-1-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate
C7		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate

No.	Structure	Name
C7a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C7b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C7c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C7d		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
A8		1-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-fluoropropan-2-yl acetate
A8a		(S)-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-fluoropropan-2-yl acetate

No.	Structure	Name
A8b		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-fluoropropan-2-yl acetate
A8c		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-fluoropropan-2-yl acetate
A8d		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-fluoropropan-2-yl acetate
A9		1-(4-(2-(4-(2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A9a		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A9b		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate

No.	Structure	Name
A9c		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A9d		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
B9		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(1 <i>H</i> -imidazol-1-yl)propan-2-yl acetate
B9a		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-(<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(1 <i>H</i> -imidazol-1-yl)propan-2-yl acetate
B9b		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-(<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(1 <i>H</i> -imidazol-1-yl)propan-2-yl acetate
B9c		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-(<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(1 <i>H</i> -imidazol-1-yl)propan-2-yl acetate

No.	Structure	Name
B9d		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(1H-imidazol-1-yl)propan-2-yl acetate
C9		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C9a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C9b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C9c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C9d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate

No.	Structure	Name
A10		1-(4-(2-(4-(2-acetoxy-3-(1H-imidazol-1-yl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A10a		(S)-1-(4-(2-(4-(R)-2-acetoxy-3-(1H-imidazol-1-yl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A10b		(R)-1-(4-(2-(4-(S)-2-acetoxy-3-(1H-imidazol-1-yl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A10c		(S)-1-(4-(2-(4-(S)-2-acetoxy-3-(1H-imidazol-1-yl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A10d		(R)-1-(4-(2-(4-(R)-2-acetoxy-3-(1H-imidazol-1-yl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A11		1-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate

No.	Structure	Name
A11a		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
A11b		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
A11c		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
A11d		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
B11		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate

No.	Structure	Name
B11a		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
B11b		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
B11c		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
B11d		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate
C11		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C11a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate

No.	Structure	Name
C11b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C11c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C11d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
A12		1-(4-(2-(4-(2-acetoxy-3-(<i>N</i> -acetylacetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A12a		<i>N</i> -acetyl- <i>N</i> -((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide
A12b		<i>N</i> -acetyl- <i>N</i> -((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide

No.	Structure	Name
A12c		<i>N</i> -acetyl- <i>N</i> -((<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide
A12d		<i>N</i> -acetyl- <i>N</i> -((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide
B12		1-(4-(2-(4-(3-acetamido-2-acetoxypropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
B12a		<i>N</i> -((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide
B12b		<i>N</i> -((<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide
B12c		<i>N</i> -((<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide
B12d		<i>N</i> -((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)acetamide

No.	Structure	Name
A13		1-(4-(2-(4-(2-acetoxy-3-(N-methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy-3-chloropropan-2-yl acetate
A13a		(S)-1-(4-(2-(4-(R)-2-acetoxy-3-(N-methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy-3-chloropropan-2-yl acetate
A13b		(R)-1-(4-(2-(4-(S)-2-acetoxy-3-(N-methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy-3-chloropropan-2-yl acetate
A13c		(S)-1-(4-(2-(4-(S)-2-acetoxy-3-(N-methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy-3-chloropropan-2-yl acetate
A13d		(R)-1-(4-(2-(4-(R)-2-acetoxy-3-(N-methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy-3-chloropropan-2-yl acetate

No.	Structure	Name
B13		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-(N-(methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
B13a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-(N-(methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
B13b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-(N-(methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
B13c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-(N-(methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
B13d		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-(N-(methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate

No.	Structure	Name
C13		1-(4-(2-(4-(2-acetoxy-3-(methylsulfonamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
C13a		(S)-1-(4-(2-(4-((R)-2-acetoxy-3-(methylsulfonamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
C13b		(R)-1-(4-(2-(4-((S)-2-acetoxy-3-(methylsulfonamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
C13c		(S)-1-(4-(2-(4-((S)-2-acetoxy-3-(methylsulfonamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
C13d		(R)-1-(4-(2-(4-((R)-2-acetoxy-3-(methylsulfonamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
D13		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(N-(methylsulfonyl)acetamido)propan-2-yl acetate

No.	Structure	Name
D13a		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(N-methylsulfonyl)acetamido)propan-2-yl acetate
D13b		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(N-methylsulfonyl)acetamido)propan-2-yl acetate
D13c		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(N-methylsulfonyl)acetamido)propan-2-yl acetate
D13d		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(N-methylsulfonyl)acetamido)propan-2-yl acetate
E13		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(methylsulfonamido)propan-2-yl acetate
E13a		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(methylsulfonamido)propan-2-yl acetate

No.	Structure	Name
E13b		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(methylsulfonamido)propan-2-yl acetate
E13c		(<i>S</i>)-1-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(methylsulfonamido)propan-2-yl acetate
E13d		(<i>R</i>)-1-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(methylsulfonamido)propan-2-yl acetate
F13		N-(3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)-N-(methylsulfonyl)acetamide
F13a		N-((<i>R</i>)-3-(4-(2-(3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)-N-(methylsulfonyl)acetamide
F13b		N-((<i>S</i>)-3-(4-(2-(3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)-N-(methylsulfonyl)acetamide

No.	Structure	Name
F13c		N-((S)-3-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenoxy)-2-hydroxypropyl)-N-(methylsulfonyl)acetamide
F13d		N-((R)-3-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenoxy)-2-hydroxypropyl)-N-(methylsulfonyl)acetamide
G13		1-chloro-3-(2,6-dichloro-4-(2-(4-(2-hydroxy-3-(methylsulfonamido)propoxy)phenoxy)propan-2-yl)phenoxy)propan-2-yl acetate
G13a		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-(methylsulfonamido)propoxy)phenoxy)propan-2-yl)phenoxy)propan-2-yl acetate
G13b		(R)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-(methylsulfonamido)propoxy)phenoxy)propan-2-yl)phenoxy)propan-2-yl acetate
G13c		(S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-2-hydroxy-3-(methylsulfonamido)propoxy)phenoxy)propan-2-yl)phenoxy)propan-2-yl acetate

No.	Structure	Name
G13d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-2-hydroxy-3-(methylsulfonamido)propoxy)phenoxy)propan-2-yl)phenoxy)propan-2-yl acetate
A14		1-(4-(2-(4-(2-acetoxy-3-(ethylsulfonamido)propoxy)phenoxy)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A14a		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-(ethylsulfonamido)propoxy)phenoxy)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A14b		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-(ethylsulfonamido)propoxy)phenoxy)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A14c		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-(ethylsulfonamido)propoxy)phenoxy)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A14d		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-(ethylsulfonamido)propoxy)phenoxy)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate

No.	Structure	Name
B14		1-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
B14a		(S)-1-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
B14b		(R)-1-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
B14c		(R)-1-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
B14d		(S)-1-(4-(2-(3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
C14		1-chloro-3-(2,6-dichloro-4-(2-(4-(3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate

No.	Structure	Name
C14a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C14b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C14c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>R</i>)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
C14d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-(2-(4-((<i>S</i>)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-yl acetate
A15		1-(4-(2-(4-(2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A15a		(<i>S</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate

No.	Structure	Name
A15b		(<i>R</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A15c		(<i>S</i>)-1-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A15d		(<i>R</i>)-1-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)propan-2-yl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A16		3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)propane-1,2-diyil diacetate
A16a		(<i>S</i>)-3-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)propane-1,2-diyil diacetate
A16b		(<i>R</i>)-3-(4-(2-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)propane-1,2-diyil diacetate
A16c		(<i>R</i>)-3-(4-(2-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)propane-1,2-diyil diacetate

No.	Structure	Name
A16d		(S)-3-(4-(2-(4-((R)-2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)propane-1,2-diyldiacetate
A17		1-(4-(2-(4-(2-acetoxy-3-ethylsulfonyl)propoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy-3-chloropropan-2-yl acetate
A17a		(S)-1-(4-(2-(4-((S)-2-acetoxy-3-ethylsulfonyl)propoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy-3-chloropropan-2-yl acetate
A17b		(R)-1-(4-(2-(4-((R)-2-acetoxy-3-ethylsulfonyl)propoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy-3-chloropropan-2-yl acetate
A17c		(S)-1-(4-(2-(4-((R)-2-acetoxy-3-ethylsulfonyl)propoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy-3-chloropropan-2-yl acetate
A17d		(R)-1-(4-(2-(4-((S)-2-acetoxy-3-ethylsulfonyl)propoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy-3-chloropropan-2-yl acetate

No.	Structure	Name
A18		3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate
A18a		(S)-3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate
A18b		(R)-3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate
A19		1-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
A19a		(S)-1-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
A19b		(R)-1-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate

No.	Structure	Name
A20		3-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate
A20a		(S)-3-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate
A20b		(R)-3-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate
A21		1-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
A21a		(S)-1-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
A21b		(R)-1-(2,6-dichloro-4-(2-(4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate

No.	Structure	Name
A22		3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diy diacetate
A22a		(S)-3-(4-(2-(4-(S)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diy diacetate
A22b		(R)-3-(4-(2-(4-(R)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diy diacetate
A22c		(R)-3-(4-(2-(4-(S)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diy diacetate
A22d		(S)-3-(4-(2-(4-(R)-2-acetoxy-3-chloropropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diy diacetate

[172] In some more specific embodiments of the compound of Formula I, the compound has one of the following structures from Table 3, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof:

5

Table 3. Compounds

No.	Structure	Name
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40		3-(4-((3-chloro-4-(3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
40a		(R)-3-(4-((3-chloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
40b		(S)-3-(4-((3-chloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
40c		(S)-3-(4-((3-chloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
40d		(R)-3-(4-((3-chloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
41		3-(4-((3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
41a		(R)-3-(4-((3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol

41b		(S)-3-(4-((3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
41c		(S)-3-(4-((3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
41d		(R)-3-(4-((3,5-dichloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
42		3-(2-chloro-4-((3-chloro-4-(3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
42a		(R)-3-(2-chloro-4-((3-chloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
42b		(S)-3-(2-chloro-4-((3-chloro-4-((R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
42c		(S)-3-(2-chloro-4-((3-chloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol

42d		(<i>R</i>)-3-(2-chloro-4-((3-chloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
43		1-chloro-3-(2,6-dichloro-4-((4-(2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
43a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-(<i>R</i>)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
43b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-(<i>S</i>)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
43c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-(<i>S</i>)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
43d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-(<i>R</i>)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol

44		1-chloro-3-(2-chloro-4-((3-chloro-4-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
44a		(S)-1-chloro-3-(2-chloro-4-((3-chloro-4-((R)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
44b		(R)-1-chloro-3-(2-chloro-4-((3-chloro-4-((S)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
44c		(S)-1-chloro-3-(2-chloro-4-((3-chloro-4-((S)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
44d		(R)-1-chloro-3-(2-chloro-4-((3-chloro-4-((R)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
45		1-amino-3-(4-((3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol

45a		(<i>R</i>)-1-amino-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
45b		(<i>S</i>)-1-amino-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
45c		(<i>S</i>)-1-amino-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
45d		(<i>R</i>)-1-amino-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
46		<i>N</i> -(3-(4-((3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)methanesulfonamide
46a		<i>N</i> -((<i>R</i>)-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)methanesulfonamide
46b		<i>N</i> -((<i>S</i>)-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)methanesulfonamide

46c		<i>N</i> -((<i>S</i>)-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)methanesulfonamide
46d		<i>N</i> -((<i>R</i>)-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)methanesulfonamide
47		1-chloro-3-(2,6-dichloro-4-((4-(2-hydroxy-3-morpholinopropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
47a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-(<i>R</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
47b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-(<i>S</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
47c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-(<i>S</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol

47d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>R</i>)-2-hydroxy-3-morpholinopropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
48		1-chloro-3-(2,6-dichloro-4-((4-(2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
48a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>R</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
48b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>S</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
48c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>S</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
48d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>R</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol

49		1-chloro-3-(2-chloro-4-((3-chloro-4-(2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
49a		(<i>S</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>R</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
49b		(<i>R</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>S</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
49c		(<i>S</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>S</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
49d		(<i>R</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>R</i>)-2-hydroxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
50		1-chloro-3-(2,6-dichloro-4-((4-(2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol

50a		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenoxy)sulfonyl)phenoxy)propan-2-ol
50b		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>R</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenoxy)sulfonyl)phenoxy)propan-2-ol
50c		(<i>S</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>R</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenoxy)sulfonyl)phenoxy)propan-2-ol
50d		(<i>R</i>)-1-chloro-3-(2,6-dichloro-4-((4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenoxy)sulfonyl)phenoxy)propan-2-ol
51		1-chloro-3-(2-chloro-4-((3-chloro-4-(2-hydroxy-3-(ethylsulfonyl)propoxy)phenoxy)sulfonyl)phenoxy)propan-2-ol
51a		(<i>S</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenoxy)sulfonyl)phenoxy)propan-2-ol

51b		(<i>R</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>R</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
51c		(<i>S</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
51d		(<i>R</i>)-1-chloro-3-(2-chloro-4-((3-chloro-4-((<i>S</i>)-2-hydroxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
52		3-(2,6-dichloro-4-((4-(3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
52a		(<i>R</i>)-3-(2,6-dichloro-4-((4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
52b		(<i>S</i>)-3-(2,6-dichloro-4-((4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol

52c		(S)-3-(2,6-dichloro-4-((4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
52d		(R)-3-(2,6-dichloro-4-((4-((R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
53		1-chloro-3-(4-((3,5-dichloro-4-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
53a		(S)-1-chloro-3-(4-((3,5-dichloro-4-((S)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
53b		(R)-1-chloro-3-(4-((3,5-dichloro-4-((R)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
53c		(S)-1-chloro-3-(4-((3,5-dichloro-4-((R)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol

53d		(<i>R</i>)-1-chloro-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol
54		3-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
54a		(<i>R</i>)-3-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
54b		(<i>S</i>)-3-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
55		1-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
55a		(<i>S</i>)-1-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-ol

55b		(R)-1-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
56		3-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
56a		(R)-3-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
56b		(S)-3-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol
57		1-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
57a		(S)-1-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-ol

57b		(<i>R</i>)-1-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-ol
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[173] In some more specific embodiments of the compound of Formula I, the compound has one of the following structures from Table 4, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof:

5 [174] **Table 4.** Compounds

No.	Structure	Name
A40		3-((4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)phenoxy)propane-1,2-diy1 diacetate
A40a		(<i>S</i>)-3-((4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)phenoxy)propane-1,2-diy1 diacetate
A40b		(<i>R</i>)-3-((4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)phenoxy)propane-1,2-diy1 diacetate
A40c		(<i>R</i>)-3-((4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)phenoxy)propane-1,2-diy1 diacetate

A40d		(<i>S</i>)-3-(4-((4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A41		3-(4-((4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A41a		(<i>S</i>)-3-(4-((4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A41b		(<i>R</i>)-3-(4-((4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A41c		(<i>R</i>)-3-(4-((4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A41d		(<i>S</i>)-3-(4-((4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A42		3-(4-((4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)propane-1,2-diyI diacetate

A42a		(S)-3-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)propane-1,2-diyldiacetate
A42b		(R)-3-(4-((4-((R)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)propane-1,2-diyldiacetate
A42c		(R)-3-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)propane-1,2-diyldiacetate
A42d		(S)-3-(4-((4-((R)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)propane-1,2-diyldiacetate
A43		1-(4-((4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-methoxypropan-2-yl acetate
A43a		(R)-1-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-methoxypropan-2-yl acetate
A43b		(S)-1-(4-((4-((R)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-methoxypropan-2-yl acetate

A43c		(S)-1-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-methoxypropan-2-yl acetate
A43d		(R)-1-(4-((4-((R)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-methoxypropan-2-yl acetate
A44		1-(4-((4-(2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A44a		(R)-1-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A44b		(S)-1-(4-((4-((R)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A44c		(S)-1-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate

A44d		(<i>R</i>)-1-(4-((4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-methoxypropan-2-yl acetate
A45		1-(4-((4-(2-acetoxy-3-(<i>N</i> -acetylacetamido)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A45a		<i>N</i> -acetyl- <i>N</i> -((<i>R</i>)-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxyl)-2-hydroxypropyl)acetamide
A45b		<i>N</i> -acetyl- <i>N</i> -((<i>S</i>)-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxyl)-2-hydroxypropyl)acetamide
A45c		<i>N</i> -acetyl- <i>N</i> -((<i>S</i>)-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxyl)-2-hydroxypropyl)acetamide
A45d		<i>N</i> -acetyl- <i>N</i> -((<i>R</i>)-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxyl)-2-hydroxypropyl)acetamide
B45		1-(4-((4-(3-acetamido-2-acetoxypropoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate

B45a		<i>N</i> -((<i>R</i>)-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)acetamide
B45b		<i>N</i> -((<i>S</i>)-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)acetamide
B45c		<i>N</i> -((<i>S</i>)-3-(4-((3,5-dichloro-4-((<i>S</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)acetamide
B45d		<i>N</i> -((<i>R</i>)-3-(4-((3,5-dichloro-4-((<i>R</i>)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)acetamide
A46		1-(4-((4-(2-acetoxy-3-(<i>N</i> -(methylsulfonyl)acetamido)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A46a		(<i>S</i>)-1-(4-((4-((<i>R</i>)-2-acetoxy-3-(<i>N</i> -(methylsulfonyl)acetamido)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A46b		(<i>R</i>)-1-(4-((4-((<i>S</i>)-2-acetoxy-3-(<i>N</i> -(methylsulfonyl)acetamido)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate

A46c		(S)-1-(4-((4-((S)-2-acetoxy-3-(N-methylsulfonyl)acetamido)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy-3-chloropropan-2-yl acetate
A46d		(R)-1-(4-((4-((R)-2-acetoxy-3-(N-methylsulfonyl)acetamido)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy-3-chloropropan-2-yl acetate
A47		1-(4-((4-(2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-morpholinopropan-2-yl acetate
A47a		(R)-1-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-morpholinopropan-2-yl acetate
A47b		(S)-1-(4-((4-((R)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-morpholinopropan-2-yl acetate
A47c		(S)-1-(4-((4-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-morpholinopropan-2-yl acetate

A47d		(<i>R</i>)-1-(4-((4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-morpholinopropan-2-yl acetate
A48		1-(4-((4-(2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A48a		(<i>S</i>)-1-(4-((4-((<i>R</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A48b		(<i>R</i>)-1-(4-((4-((<i>S</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A48c		(<i>S</i>)-1-(4-((4-((<i>S</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A48d		(<i>R</i>)-1-(4-((4-((<i>R</i>)-2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate

A49		1-(4-((4-(2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A49a		(<i>S</i>)-1-(4-((4-(2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A49b		(<i>R</i>)-1-(4-((4-(2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A49c		(<i>S</i>)-1-(4-((4-(2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A49d		(<i>R</i>)-1-(4-((4-(2-acetoxy-3-(1 <i>H</i> -imidazol-1-yl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A50		1-(4-((4-(2-acetoxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate

A50a		(S)-1-(4-((4-((S)-2-acetoxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A50b		(R)-1-(4-((4-((R)-2-acetoxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A50c		(S)-1-(4-((4-((R)-2-acetoxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A50d		(R)-1-(4-((4-((S)-2-acetoxy-3-(ethylsulfonyl)propoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate
A51		1-(4-((4-(2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A51a		(S)-1-(4-((4-((S)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate

A51b		(R)-1-(4-((4-((R)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A51c		(S)-1-(4-((4-((R)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A51d		(R)-1-(4-((4-((S)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3-chlorophenyl)sulfonyl)-2-chlorophenoxy)-3-chloropropan-2-yl acetate
A52		3-(4-((4-(2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)propane-1,2-diyi diacetate
A52a		(S)-3-(4-((4-((S)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)propane-1,2-diyi diacetate
A52b		(R)-3-(4-((4-((R)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)propane-1,2-diyi diacetate

A52c		(<i>R</i>)-3-(4-((<i>S</i>)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)propane-1,2-diyil diacetate
A52d		(<i>S</i>)-3-(4-((<i>R</i>)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)-2,6-dichlorophenoxy)propane-1,2-diyil diacetate
A53		1-(4-((4-(2-acetoxy-3-ethylsulfonyl)propoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-chloropropan-2-yl acetate
A53a		(<i>S</i>)-1-(4-((<i>S</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-chloropropan-2-yl acetate
A53b		(<i>R</i>)-1-(4-((<i>R</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-chloropropan-2-yl acetate
A53c		(<i>S</i>)-1-(4-((<i>R</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-chloropropan-2-yl acetate

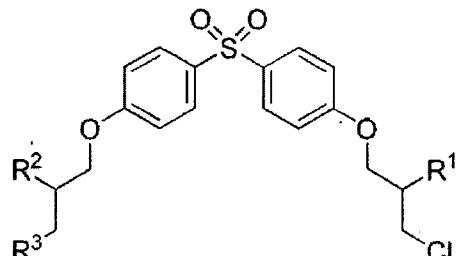
A53d		(<i>R</i>)-1-(4-((4-((<i>S</i>)-2-acetoxy-3-(ethylsulfonyl)propoxy)-3,5-dichlorophenyl)sulfonyl)phenoxy)-3-chloropropan-2-yl acetate
A54		3-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A54a		(<i>S</i>)-3-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A54b		(<i>R</i>)-3-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A55		1-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
A55a		(<i>S</i>)-1-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate

A55b		(<i>R</i>)-1-(4-((3,5-dichloro-4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
A56		3-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A56a		(<i>S</i>)-3-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A56b		(<i>R</i>)-3-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A57		1-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate
A57a		(<i>S</i>)-1-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxy)-3-(ethylsulfonyl)propan-2-yl acetate

A57b		<i>(R)</i> -1-(2,6-dichloro-4-((4-(3-chloropropoxy)phenyl)sulfonyl)phenoxyl)-3-(ethylsulfonyl)propan-2-yl acetate
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[175] In some embodiments of the compound of Formula I, the compound has one of the following structures from Tables 1, 2, 3, or 4, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

5 [176] The present invention includes all compounds which have the above described properties (i.e., binding to androgen receptor (AR)). In one embodiment, the present invention is directed to a compound having a structure of Formula II:



(II)

10 [177] or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

[178] R¹ is H, hydroxyl or -OC(=O)R¹³;

[179] R² is hydroxyl or -OC(=O)R¹³;

[180] R³ is halo, -OH, -OR⁴, -OC(=O)R¹³, -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), -N(C₁-C₆ alkyl)(S(O)_nR⁵), -S(O)_nR⁵, -N₃, aryl, 15 carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R⁶;

[181] R⁴ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R⁶;

[182] R⁵ is each independently C₁-C₆ alkyl or aryl which are optionally substituted with one or more R⁶;

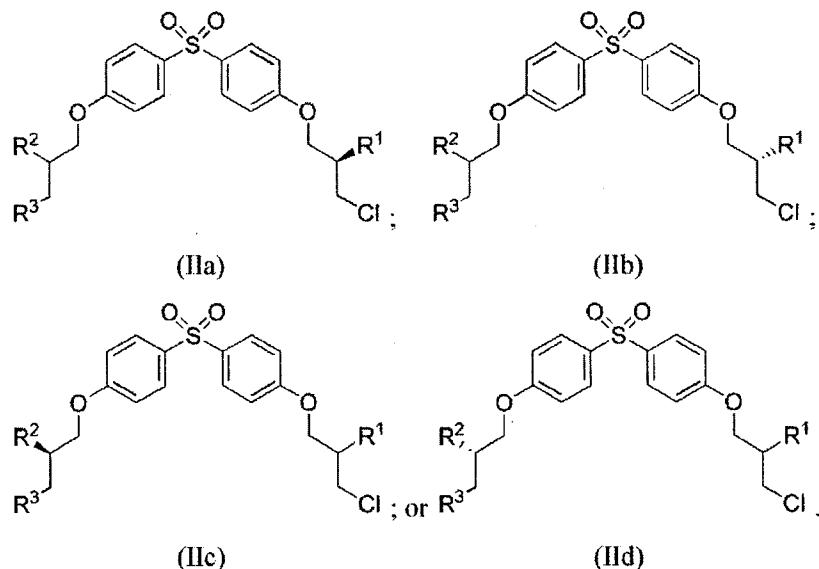
20 [183] R⁶ is each independently selected from the group consisting of H, F, Cl, Br, I, ¹²³I, hydroxyl, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₆-C₁₂ aryl, wherein each R⁶ is optionally substituted with one or more of halogen, ¹²³I, ¹⁸F, hydroxyl, -OS(O)₂-aryl, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

[184] R^{13} is C₁-C₆ alkyl; and

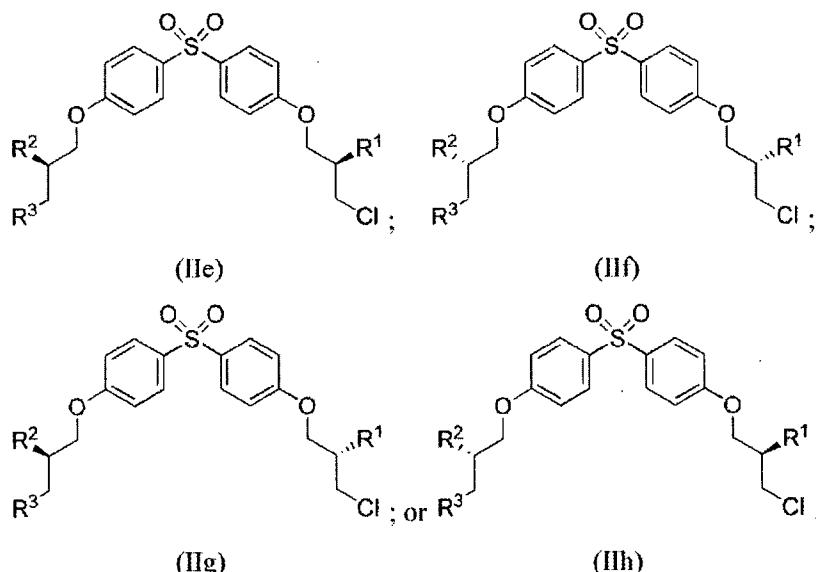
[185] n is 0, 1, or 2.

[186] In various embodiments, different stereoisomers of the compound of structure (II) are provided, for example in some embodiments the compound has one of the following structures

5 (IIa), (IIb), (IIc) or (IId):



10 [187] In still other embodiments, the compound has one of the following structures (IIe), (IIf),
(IIg) or (IIh):



[188] In one embodiment, R¹ is hydroxyl. In another embodiment, R¹ is -OC(=O)R¹³. In some embodiments, R¹ is -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In other embodiments, R¹ is -OC(=O)R¹³, wherein R¹³ is methyl. In one embodiment, R¹ is H.

[189] In one embodiment, R² is hydroxyl. In another embodiment, R² is -OC(=O)R¹³. In some embodiments, R² is -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In other embodiments, R² is -OC(=O)R¹³, wherein R¹³ is methyl.

[190] In one embodiment, R³ is -OH. In another embodiment, R³ is -OC(=O)R¹³. In some embodiments, R³ is -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In other embodiments, R³ is -OC(=O)R¹³, wherein R¹³ is methyl.

10 [191] In some embodiments, at least one of R¹, R², or R³ is -OH. In another embodiment, at least one of R¹, R², or R³ is -OH. In some embodiments, at least two of R¹, R², or R³ are each -OH. In another embodiment, R¹ and R² are each -OH. In one embodiment, R¹, R², or R³ are each -OH.

15 [192] In some embodiments, at least one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, at least one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, at least two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, at least two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

20 [193] In some embodiments, one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, one of R¹, R², or R³ is -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, two of R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is methyl. In some embodiments, R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is C₁-C₄ alkyl. In another embodiment, R¹, R², or R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

25 [194] In other embodiments, R³ is -OR⁴. In one embodiment, R³ is -OR⁴, wherein R⁴ is C₁-C₆ alkyl. In another embodiment, R³ is -OR⁴, wherein R⁴ is C₁-C₃ alkyl. In one embodiment, R³ is -OR⁴, wherein R⁴ is C₁ alkyl. In another embodiment, R³ is -OR⁴, wherein R⁴ is isopropyl.

[195] In other embodiments, R³ is a halogen. In one embodiment, R³ is F.

[196] In other embodiments, R³ is -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -30 N(C(=O)R¹³)(S(O)_nR⁵), or -N(C₁-C₆ alkyl)(S(O)_nR⁵). In one embodiment, R³ is a -NH₂. In one embodiment, R³ is a -NHC(=O)R¹³. In one embodiment, R³ is a -N(C(=O)R¹³)₂. In another embodiment, R³ is a -NHS(O)_nR⁵. In some embodiments, R³ is a -NHS(O)₂R⁵. In other embodiments, R³ is a -NHS(O)₂R⁵, wherein R⁵ is C₁-C₃ alkyl. In one embodiment, R³ is a -

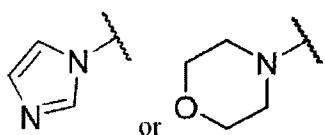
NHS(O)₂R⁵, wherein R⁵ is methyl. In one embodiment, R³ is a -N(C(=O)R¹³)(S(O)_nR⁵). In one embodiment, R³ is a -N(C₁-C₆ alkyl)S(O)_nR⁵.

[197] In other embodiments, R³ is -NH₂, -NHC(=O)(C₁-C₄ alkyl), -N[(C(=O)(C₁-C₄ alkyl))₂, -NHS(O)_n(C₁-C₃ alkyl), -N[C(=O)(C₁-C₄ alkyl)][(S(O)_n(C₁-C₃ alkyl)], or -N[C₁-C₆ alkyl][S(O)_n(C₁-C₃ alkyl)]. In some embodiments, R³ is -NH(C(=O)CH₃) or -N(C(=O)CH₃)₂. In other embodiments, R³ is -NHS(O)₂CH₃. In other embodiments, R³ is -N(C(=O)CH₃)(S(O)₂CH₃).

[198] In another embodiment, R³ is a -S(O)_nR⁵. In one embodiment, R³ is a -S(O)₂R⁵. In another embodiment, R³ is a -S(O)₂(C₁-C₃ alkyl). In other embodiments, R³ is a -S(O)₂CH₃.
10 In other embodiments, R³ is a -S(O)₂CH₂CH₃.

[199] In another embodiment, R³ is a -S(O)_nR⁵. In one embodiment, R³ is a -S(O)₂R⁵. In some embodiments, R³ is a -S(O)₂R⁵, wherein R⁵ is C₁-C₃ alkyl. In other embodiments, R³ is a -S(O)₂R⁵, wherein R⁵ is C₁ alkyl.

[200] In some embodiments, R³ is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprises at least one N atom in the ring. In one embodiment, R³ is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, 20 pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine. In a certain embodiment, R³ is



[201] In some embodiments, R¹³ is C₁-C₄ alkyl. In other embodiments, R¹³ is methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, or *sec*-butyl. In one embodiment, R¹³ is a methyl.

25 [202] In one embodiment, n is 0. In another embodiment n is 1. In some embodiments, n is 2.
[203] The compounds for use in the imaging and treatment methods described herein. In some embodiments, the compounds comprise one F, Cl, Br, I, or ¹²³I substitution.

[204] In another embodiment, the compound comprise one or more of F, Cl, Br, I or ¹²³I substitutions for R³. In one embodiment, the compound comprise one or more of I or ¹²³I substitutions for R³.
30

[205] In some embodiments, the compound comprises at least one R⁶ substituent on R³, wherein at least one R⁶ is further substituted with at least one of F, Cl, Br, I or ¹²³I. In another embodiment, R⁶ substituent on R³ is further substituted with at least one of I or ¹²³I.

[206] In some more specific embodiments of the compound of Formula II, the compound has 5 one of the following structures from Table 5, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof:

Table 5. Compounds

No.	Structure	Name
80		3-(4-((4-(3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenyl)propane-1,2-diol
80a		(R)-3-(4-((4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenyl)propane-1,2-diol
80b		(S)-3-(4-((4-(R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenyl)propane-1,2-diol
80c		(S)-3-(4-((4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenyl)propane-1,2-diol
80d		(R)-3-(4-((4-(R)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenyl)propane-1,2-diol

No.	Structure	Name
A80		3-(4-((4-(2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A80a		(S)-3-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A80b		(R)-3-(4-((R)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A80c		(R)-3-(4-((S)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate
A80d		(S)-3-(4-((R)-2-acetoxy-3-chloropropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diyI diacetate

[207] In one embodiment, the present invention is directed to a pharmaceutical composition, comprising a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as described herein. In one embodiment, the present 5 invention is directed to a pharmaceutical composition, comprising a compound of Formula I or Formula II, or a pharmaceutically acceptable salt or stereoisomer thereof, as described herein.

[208] In some embodiment, the pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or 10 stereoisomer thereof, further comprises a pharmaceutically acceptable carrier. In another

embodiment, the pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, further comprises an additional therapeutic agent. In one embodiment, the pharmaceutical composition comprising a compound having a structure of Formula I or 5 Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, further comprises a pharmaceutically acceptable carrier and an additional therapeutic agent.

[209] In another embodiment, the pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, further comprises an additional therapeutic agent which is for treating 10 prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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.

[210] Accordingly, one embodiment comprises the use of the disclosed compounds in 15 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 cytotoxic in nature, and pharmacological therapies which 20 interfere with the biological production or function of androgen (hereinafter, an “additional therapeutic agent”). By “combination therapy” is meant the administration of any one or more of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, 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 25 contemporaneous, that their effects are synergistic with one another even though dosed sequentially rather than contemporaneously.

[211] Such administration includes without limitation dosing of one or more of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, and one or more of the additional therapeutic agent(s) as separate agents without any 30 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 Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as a pre-mixed formulation. Administration of the compound(s) of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, in combination with the

additional therapeutic agents for treatment of the above disease states also includes dosing by any dosing method including without limitation, intravenous delivery (IV), oral delivery, intra-peritoneal delivery, intra-muscular delivery, or intra-tumoral delivery.

[212] In another aspect of the present disclosure, the one or more of the additional therapeutic agents can be administered to the patient before administration of the compound(s) of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. In another embodiment, the compound(s) of Formula I can be co-administered with one or more of the additional therapeutic agents. In yet another aspect, the one or more additional therapeutic agents can be administered to the patient after administration of the compound(s) of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

[213] The ratio of the doses of compound(s) of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to that of the one or more additional therapeutic agents can be about 1:1 or can vary, e.g., about 2:1, about 3:1, about 4:1, about 5:1, about 6:1, about 7:1, about 8:1, about 9:1, about 10:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, and can be varied accordingly to achieve the optimal therapeutic benefit.

[214] The compound(s) of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, that are combined with the one or more additional therapeutic agents for improved treatment of the above disease states can comprise, but are not limited to any compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, including those compounds shown in Tables 1, 2, 3, 4, or 5.

[215] The additional 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 ODM-201 (also known as BAY1841788) and related compounds, which appears to bind to the AR and blocks its cellular function, and is currently in clinical development as a treatment for prostate cancer; the chemical entity known as ODM-204 and related compounds, which appears to be a dual inhibitor of AR and CYP17A1 and can be useful for treatment of prostate cancer; 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 (AR) LBD and a FDA-approved treatment for prostate cancer; the chemical entity known as Galetetone and related compounds which appears to be a blocker of the androgen receptor (AR) LBD, and a CYP17 lyase inhibitor, and also appears to decrease overall androgen receptor levels in prostate cancer cells. Galetetone is currently in development as a treatment for prostate cancer; the chemical entity known as ARN-509 or apalutamide (4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide) and related compounds which appears to be a blocker of the androgen receptor (AR) 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 FDA-approved treatment for 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 (AR) 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 (AR) LBD and which is currently used to treat prostate cancer, the chemical entities known as cyproterone acetate (6-chloro-1 β ,2 β -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 (AR) LBD and which is currently used to treat prostate cancer, the chemical entity known as docetaxel (Taxotere; 1,7 β ,10 β -trihydroxy-9-oxo-5 β ,20-epoxytax-11-ene-2 α ,4,13 α -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 can be used to treat prostate cancer, the chemical entity known as OSU-HDAC42 ((S)-(+)-N-hydroxy-4-(3-methyl-2-phenylbutyryl)amino)-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 $\alpha\beta 3$ to prevent angiogenesis, and which can 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 5 tyrosine kinases (RTKs) and can 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 can 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 10 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 15 cancer; the chemical entity known as OGX 011 which appears to target clusterin as an antisense agent, and which is currently in development as a treatment for prostate cancer; the chemical entity known as finasteride (Proscar, Propecia; *N*-(1,1-dimethylethyl)-3-oxo-(5 α ,17 β)-4-azaandrost-1-ene-17-carboxamide), and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone, and can be used to treat prostate 20 cancer; the chemical entity known as dutasteride (Avodart; 5 α , 17 β)-*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 can 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-2-ylcarbamoyl)hexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide), 25 and related molecules, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and can 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 30 reductase inhibitor that reduces levels of dihydrotestosterone and can 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 can 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 can 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 can be used for treatment of prostate cancer. The chemical entity known as niclosamide (4,5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide) and related compounds, which appears to be an antihelminitic that is an AR-V7 inhibitor and can be used for treatment of prostate cancer. The chemical entity known as ARV-330 (Arvinas, Inc.) and related compounds, which appears to degrade androgen receptor in LNCaP and VCaP cells and can be useful for treatment of prostate cancer. The chemical entity known as VPC-14449 (4-(4-(4,5-bromo-1*H*-imidazol-1-yl)thiazol-2-yl)morpholine) and related compounds, which appears to target the DNA-binding domain of full-length AR and can be useful for treatment of prostate cancer. The chemical entity known as TAS3681 appears to be an AR antagonist with AR downregulating activity and can be useful for treatment of prostate cancer.

15 The chemical entity known as sintokamides (e.g., sintokamide A also known as N-[(2*R*,4*S*)-5,5,5-trichloro-1-[(2*S*)-2-[(2*S*)-3,3-dichloro-2-methylpropyl]-3-methoxy-5-oxo-2*H*-pyrrol-1-yl]-4-methyl-1-oxopentan-2-yl]propanamide) and related compounds, which appears to be an AR antagonist and can be useful for treating prostate cancer.

20 [216] Accordingly, in some embodiments, the pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, further comprises an additional therapeutic agent selected from the group consisting of enzalutamide, galeterone, 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, 25 finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111, ODM-201, ODM-204, radium 233, niclosamide, apalutamide, ARV-330, VPC-14449, TAS3681, 3E10-AR441bsAb, sintokamide or related compounds thereof.

30 [217] In some embodiments, compounds of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, which result in unstable structures and/or unsatisfied valences are not included within the scope of the invention.

[218] In another embodiment, the present disclosure provides a pharmaceutical composition comprising any of the foregoing compounds of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[219] Compounds as described herein can be in the free form or in the form of a salt thereof. In some embodiments, compounds as described herein can 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 can be, for example, formed as a pharmaceutically acceptable salt. Compounds containing one or more basic functional groups can be capable of forming a pharmaceutically acceptable salt with, for example, a pharmaceutically acceptable organic or inorganic acid. Pharmaceutically acceptable salts can 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, 15 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-naphthalenesulfonic acid, naphthalenedisulphonic acid, p- 20 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 can be capable of forming pharmaceutically acceptable salts with a pharmaceutically acceptable base, 25 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 can be derived from, for example, and without limitation, a hydroxide, 30 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-ephedamine, *N,N*'-dibenzylethylenediamine or polyamine resins. In some embodiments, compounds as described herein can contain both acidic and basic groups and can be in the form of inner salts or zwitterions, for example, and without limitation, betaines. Salts as described herein can 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 can occur *in situ* during isolation and purification of the compounds or preparation of salts can occur by separately reacting an isolated and purified compound.

[220] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, polymorphs, isomeric forms) as described herein can 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 can 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.

[221] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, solvates, isomeric forms) as described herein can 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 can cause a single crystal form to dominate.

[222] 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 formula illustrated for the sake of convenience.

III. Methods

[223] The present compounds find use in any number of methods. For example, in some embodiments the compounds are useful in methods for modulating androgen receptor (AR).

5 Accordingly, in one embodiment, the present disclosure provides the use of any one of the foregoing compounds of Formula 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 (AR) can be in a subject in need thereof (e.g., a mammalian subject) and for treatment of any of the described conditions or diseases.

10 [224] 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, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, age related macular degeneration, and

15 combinations thereof. For example in some embodiments, the indication is prostate cancer. In other embodiments, the prostate cancer is primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, or metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. While in other embodiments, the prostate cancer is androgen dependent prostate cancer.

20 In other embodiments, the spinal and bulbar muscular atrophy is Kennedy's disease.

[225] In some embodiments, compounds as described herein can be administered to a subject. In one embodiment, the present invention is directed to a method of treating primary/localized prostate cancer comprising administering a pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, 25 tautomer or stereoisomer thereof. In some embodiments, the present invention is directed to a method of treating locally advanced prostate cancer comprising administering a pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. In other embodiments, the present invention is directed to a method of treating recurrent prostate cancer comprising 30 administering a pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. In other embodiments, the present invention is directed to a method of treating metastatic prostate cancer comprising administering a pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable

salt, tautomer or stereoisomer thereof. In other embodiments, the present invention is directed to a method of treating advanced prostate cancer comprising administering a pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. In other embodiments, the 5 present invention is directed to a method of treating metastatic castration-resistant prostate cancer (CRPC) comprising administering a pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. In other embodiments, the present invention is directed to a method of treating hormone-sensitive prostate cancer comprising administering a 10 pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

[226] In other embodiments, the present disclosure provides a method of modulating androgen receptor (AR) activity, the method comprising administering any one of the foregoing compounds of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or 15 stereoisomer thereof, or pharmaceutical composition of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as described herein (including compositions comprising a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, and an additional therapeutic agent), to a subject (e.g., mammal) in need thereof. In some embodiments, 20 modulating androgen receptor (AR) activity is in a mammalian cell. In other embodiments, modulating androgen receptor (AR) activity is in a mammal. In one embodiment, modulating androgen receptor (AR) activity is in a human.

[227] The modulating androgen receptor (AR) activity can be for inhibiting AR N-terminal domain activity. The modulating androgen receptor (AR) activity can be for inhibiting 25 androgen receptor (AR) activity. The modulating can be *in vivo*. The modulating androgen receptor (AR) activity can be for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy 30 (e.g., Kennedy's disease), and age related macular degeneration. The indication can be prostate cancer. The prostate cancer can be castration-resistant prostate cancer. In one embodiment, the prostate cancer is primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, or metastatic castration-

resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. The prostate cancer can be CRPC.

[228] In accordance with another embodiment, there is provided a use of the compounds of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, or pharmaceutical composition of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as described herein for preparation of a medicament for modulating androgen receptor (AR).

[229] Alternatively, in one embodiment, a method of modulating androgen receptor activity, comprising administering Formula I or Formula II, or a pharmaceutically acceptable salt, 10 tautomer or stereoisomer thereof, or pharmaceutical composition of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as described herein, is provided. In some embodiments, the administration can be to a mammal. In other embodiments, the administering can 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 15 cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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), age related macular degeneration, and combinations thereof.

[230] As noted above, the presently disclosed compounds can find utility in a number of 20 medical imaging applications, including imaging of the prostate. Many currently available imaging agents tend to accumulate in the bladder, which decreases their effectiveness as imaging tools specifically for the prostate. While not wishing to be bound by theory, the present applicants believe the disclosed compounds are unexpectedly effective for imaging of the prostate due to their ability to accumulate in the prostate, rather than the bladder, allowing the 25 prostate gland to be seen. Accordingly, the compounds can be used in methods for imaging the prostate, for example to image benign prostate diseases. In other embodiments, the compounds can be used in methods to image cancerous prostate diseases, such as tumors of the prostate.

[231] Androgen ablation therapy causes a temporary reduction in prostate cancer tumor burden, but the malignancy will begin to grow again in the absence of testicular androgens to 30 form castrate resistant prostate cancer (CRPC). A rising titer of serum prostate-specific antigen (PSA) after androgen ablation therapy indicates biochemical failure, the emergence of CRPC, and re-initiation of an androgen receptor (AR) transcription program. Most patients succumb to CRPC within two years of biochemical failure.

[232] In one embodiment, the method identifies the presence of a tumor that expresses AR (both full-length and truncated AR lacking LBD) and then treats the tumor by radiotherapy. In another embodiment, the imaging methods provide information to determine if a tumor expresses AR species.

5 [233] AR is a transcription factor and a validated target for prostate cancer therapy. Current therapies include androgen ablation and administration of antiandrogens. Most CRPC is suspected to be AR-dependent. AR has distinct functional domains that include the C-terminus ligand-binding domain (LBD), a DNA-binding domain (DBD), and an amino-terminal domain (NTD). AR NTD contains activation function- 1 (AF-1) that contributes most of the
10 transcriptional activity to the AR. Recently, splice variants of the AR that lack the LBD have been reported in prostate cancer cell lines (VCaP, LNCaP95 and 22Rv1), and in CRPC tissues. To date more than 20 splice variants of AR have been detected. Splice variants V7 and V567es are clinically relevant with levels of expression correlated to poor survival and CRPC. AR
15 V567es is solely expressed in 20% of metastases. Abiraterone resistance is associated with expression of AR splice variants. Enzalutamide also increases levels of expression of these constitutively active AR splice variants. These splice variants lack LBD and thereby would not be inhibited by current therapies that target the AR LBD such as antiandrogens or androgen ablation therapy. A single patient with advanced prostate cancer can have many lesions throughout the body and skeleton and each tumor can have differing levels of expression of
20 AR.

[234] Biopsy of metastatic tumors in a patient to determine AR species is neither widely accessible nor feasible to sample tumors in a patient that can have multiple metastases. Thus it is essential to develop approaches to detect the expression of all AR species for the molecular classification of tumors based on the level and extent of expression of AR splice variants, or
25 other AR species that cannot be detected using an imaging agent that interacts with the LBD, to identify patients with potentially aggressive disease and poor prognosis, or to identify patients that will not respond to hormone therapies that target the AR LBD. Accordingly, certain embodiments of the present invention provide an AR NTD-targeted molecular imaging probe (e.g., compound of formula I) which can be used to monitor response to therapy and
30 provide insight into the role of AR in resistance mechanisms.

[235] One current approach to image AR in prostate cancer uses positron emission tomography (PET) with 16β -[^{18}F]-fluoro-5 α dihydrotestosterone (^{18}F -FDHT) that binds to AR LBD. Unfortunately this imaging agent cannot detect splice variants lacking LBD. In some embodiments, the invention employs sequential imaging with ^{18}F -FDHT to detect full-length

AR and gamma radiation emitting probes to specifically detect the AR NTD which would be the sum of both full-length AR and variant AR. In other embodiments, the invention employs sequential imaging with two different PET imaging agents to detect only full-length AR and another to specifically detect the AR NTD which would be the sum of both full-length AR and variant AR. Together these data reveal patients with tumors that express variant AR (NTD of variant plus full-length AR detected with NTD isotope minus full-length AR detected with ¹⁸F-FDHT). By using sequential imaging, a discordant distribution or discordant level of uptake between ¹⁸F-FDHT and a radiolabeled compound of this invention (*i.e.*, compound of Formula I) indicates the presence of overexpression of splice variants lacking the LBD.

5 [236] As described above, radioactive ¹⁸F labeled compounds have found use as imaging agents not only to image AR in prostate cancer but for imaging various organs and various tumors. Similarly, radioactive ¹²³I labeled compounds have been known for the use as imaging agents. In one embodiment, the compounds of the present disclosure comprise at least one ¹²³I.

10 [237] In one embodiment, the present invention is directed to a method of imaging cancer by administering a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a subject. In another embodiment, the present invention is directed to a method of imaging cancer by administering a pharmaceutical composition comprising a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a subject.

15 [238] In some embodiment, the method of imaging cancer by administering a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, or a pharmaceutical composition comprising Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a subject and detecting the presence or absence of cancer by use of SPECT or PET. In other embodiments,

20 the method of imaging cancer by administering a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a subject and the method identifies the presence or absence of a tumor. In one embodiment, the method of imaging cancer by administering a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a subject and the method identifies the location of a tumor. In one embodiment, the method of imaging cancer by administering a compound having a structure of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, to a subject and the method identifies a presence of a prostate cancer. In other embodiments, the prostate cancer is

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androgen-dependent prostate cancer. In some embodiments, the subject is a mammal such as a human.

[239] In some other embodiments, the method is useful for detecting the presence of AR splice variants or other AR species that cannot be detected by imaging agents that interact with the AR LBD (i.e., mutations, truncations). Without wishing to be bound by any particular theory, since the present compounds bind to the AR N-terminal domain (NTD), even mutants or variants which lack the AR LBD can be imaged employing the present compounds. Thus, the present methods can be useful for detecting AR species, including mutants and variants, which lack the LBD or have LBD mutations, but do comprise the AR NTD. In other embodiments the method detects the presence or overexpression of AR splice variants lacking the ligand-binding domain. For example, the method can include sequential imaging with ¹⁸F-FDHT and a compound of the invention and a discordant distribution or discordant level of uptake between ¹⁸F-FDHT and the compound of the invention indicates the presence or overexpression of splice variants lacking the ligand-binding domain.

[240] In other embodiments, the compounds of the invention are used in single photon emission computed tomography methods to monitor a patient's response to therapy. In other embodiments, the methods comprise use of a compound of the invention to detect the AR NTD.

[241] In accordance with a further embodiment, the method of imaging a cancer is by administering a compound as described anywhere herein. In one embodiment, the method of imaging a cancer is by administering a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein said compound comprises at least one ¹²³I.

[242] The administering and imaging can be to a mammal in need of diagnosis of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, benign prostatic hyperplasia, 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 imaging can be for imaging AR splice variants, mutants or other AR species which contain AR NTD.

[243] In some embodiments, the compounds as described herein or pharmaceutically acceptable salts thereof can be used for imaging and diagnosis of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, benign prostatic hyperplasia, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease,

precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration.

In some embodiments, the compounds as described herein or acceptable salts thereof above can be used in the preparation of a medicament or a composition for imaging the prostate, for example for imaging benign prostate conditions or for imaging prostate cancer in a subject in

5 need of such imaging (for example for diagnosis and/or location of prostate tumors).

[244] In some embodiments, pharmaceutical compositions useful in modulating androgen receptor (AR) activity or useful for imaging, in accordance with this invention can comprise a salt of such a compound, preferably a pharmaceutically or physiologically acceptable salt.

Pharmaceutical preparations will typically comprise one or more carriers, excipients or diluents

10 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. Suitable carriers, excipients or diluents are those known in the art for use in such modes of administration.

[245] In one embodiment, the imaging method disclosed herein is directed to imaging prostate

15 cancer. In some embodiments, the prostate cancer is primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, or metastatic castration-resistant prostate cancer (CRPC), and hormone-sensitive prostate cancer. In some embodiments the prostate cancer is CRPC. In other

20 embodiments, the imaging is for imaging benign prostate conditions such as benign prostatic hyperplasia. Methods of imaging and/or treating any of the indications described herein are also provided. Such methods may include administering a compound as described herein or a composition of a compound as described herein, or an effective amount of a compound as described herein or composition of a compound as described herein to a subject in need thereof.

In one embodiment, a pharmaceutical composition suitable for imaging is administered

25 intravenously.

[246] Suitable pharmaceutical compositions can 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 can be dissolved in sterile water or saline or a pharmaceutically acceptable vehicle used for administration of non-water soluble compounds such as those used

30 for vitamin K. For enteral administration, the compound can be administered in a tablet, capsule or dissolved in liquid form. The tablet or capsule can 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 can 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 can, for example, contain excipients, polyalkylene

5 glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes.

Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers can 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

10 systems, and liposomes. Formulations for inhalation can contain excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or can be oily solutions for administration in the form of nasal drops, or as a gel.

[247] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein, and an additional therapeutic agent and/or a pharmaceutically acceptable carrier. In some embodiments, the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer,

hepatocellular cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy

20 or age related macular degeneration. In other embodiments, the additional therapeutic agent is enzalutamide, galeterone, ODN-201 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, ODM-
25 201 ODM-204, niclosamide, apalutamide, ARV-330, VPC-14449, TAS3681, 3E10-AR441bsAb, sintokamide, or related compounds thereof.

[248] Compounds described herein can 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 30 research purposes. Ligand-independent activation of the androgen receptor (AR) refers to transactivation of the full-length androgen receptor (AR) in the absence of androgen (ligand) by, for examples, stimulation of the cAMP dependent protein kinase (PKA) pathway or the interleukin-6 (IL6)/STAT3 pathway. Such compounds should block a mechanism that is common to both ligand-dependent and ligand-independent activation of the androgen receptor

(AR), as well as constitutively active splice variants of the androgen receptor (AR) that lack ligand-binding domain. This could involve any step in activation of the androgen receptor (AR) including dissociation of heatshock proteins, essential posttranslational modifications (e.g., acetylation, phosphorylation), nuclear translocation, protein-protein interactions, formation of 5 the transcriptional complex, release of co repressors, and/or increased degradation. 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 can be used to treat such conditions.

[249] Compounds or pharmaceutical compositions in accordance with this invention or for 10 use in this invention can be administered by means of a medical device or appliance such as an implant, graft, prosthesis, stent, etc. Also, implants can 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.

[250] It is to be noted that dosage values can vary with the exact imaging protocol. For any 15 particular subject, specific dosage regimens can 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 can be selected by medical practitioners. The amount of active compound(s) in the composition can vary according to factors such as the disease state, age, 20 sex, and weight of the subject. Dosage regimens can be adjusted to provide the optimum imaging result. For example, a single bolus can be administered, several divided doses can be administered over time or the dose can be proportionally reduced or increased as indicated by the imaging results. It can be advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage.

[251] In general, compounds of the invention should be used without causing substantial 25 toxicity. Toxicity of the compounds of the invention 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, such as in 30 severe disease conditions, substantial excesses of the compositions can be administered for therapeutic effects. Some compounds of this invention can be toxic at some concentrations. Titration studies can be used to determine toxic and non-toxic concentrations. Toxicity can be evaluated by examining a particular compound's or composition's specificity across cell lines using PC3 or DU145 cells as possible negative controls since these cells do not express

functional AR. Animal studies can 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 castration, antiandrogens and androgen insensitivity syndrome are not fatal.

5 [252] Compounds for use in the present invention can 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 invention will be understood by a person of skill in the art having reference to known chemical synthesis principles. For example, Auzou *et al* 1974 *European Journal of Medicinal Chemistry* 9(5), 548-554 describes
10 suitable synthetic procedures that can be considered and suitably adapted for preparing compounds of any one of the compounds of structure (I) as set out above. Other references that can 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,
15 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.

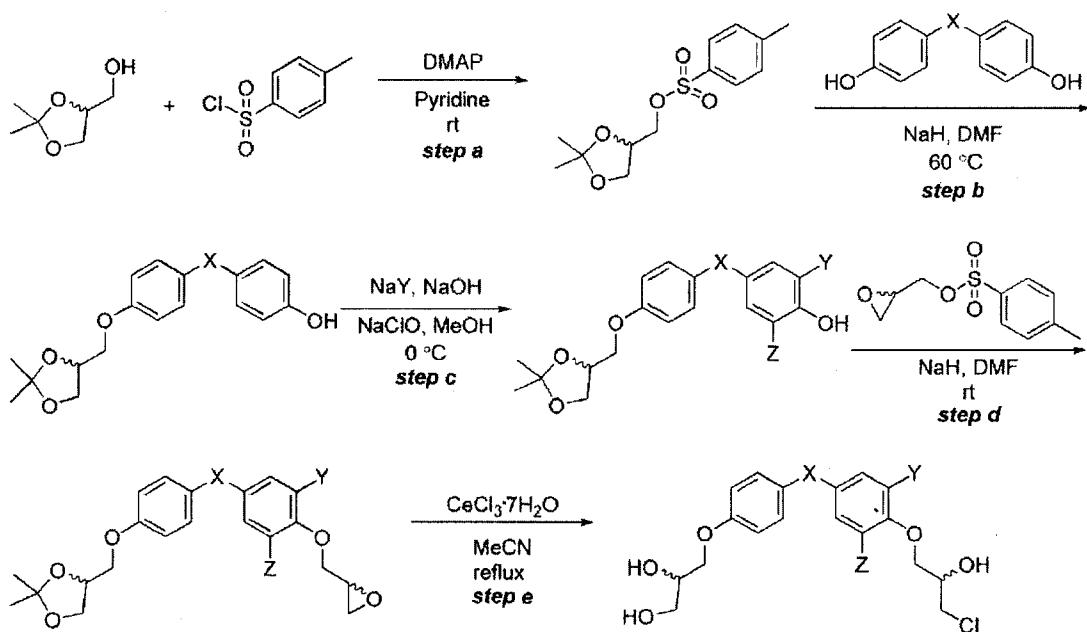
[253] In some embodiments, compounds and all different forms thereof as described herein
20 can be used, for example, and without limitation, in combination with other treatment methods for at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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.
25 For example, compounds and all their different forms as described herein can be used as neoadjuvant (prior), adjunctive (during), and/or adjuvant (after) therapy with surgery, radiation (brachytherapy or external beam), or other therapies (eg. HIFU), and in combination with chemotherapies, androgen ablation, antiandrogens or any other therapeutic approach.

[254] In an exemplary embodiment for imaging the prostate, a dose of the disclosed
30 compounds in solution (typically 5 to 10 millicuries or 200 to 400 MBq) is typically injected rapidly into a saline drip running into a vein, in a patient. Then, the patient is placed in the SPECT for a series of one or more scans which can take from 20 minutes to as long as an hour (often, only about one quarter of the body length can be imaged at a time). Methods for SPECT scanning are well known in the art.

[255] The compounds described herein can 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 androgen receptor (AR)). Furthermore, these compounds can 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.

[256] For example, exemplary compounds of the present invention can be prepared with reference to the following General Reaction Scheme I:

10 [257] General Reaction Scheme I



[258] It should be noted that, although General Reaction Scheme I depicts a racemic synthesis, one skilled in the art would recognize that different stereoisomers and diastereomers 15 can be synthesized by using starting materials of different stereochemistry, e.g., stereospecific (2,2-dimethyl-1,3-dioxolan-4-yl)methanol and/or stereospecific oxiran-2-ylmethyl 4-methylbenzenesulfonate.

[259] Referring to General Reaction Scheme I, (2,2-dimethyl-1,3-dioxolan-4-yl)methanol is tosylated under basic conditions as shown in step a. In step b, tosyl group (*p*-toluenesulfonate) 20 is displaced with bisphenol derivatives under basic conditions (X can be -S(O)_n- where n = 0, 1, or 2, or divalent linear or branched C₁-C₆ alkyl). Optionally, in step c, the bisphenol derivative is halogenated on the phenyl ring (e.g., Y and Z can be Cl or Br). In step d, the

unreacted phenol portion undergoes another elimination reaction to afford a bisphenol derivative with an epoxide on one side and a protected diol on the other. In step e, epoxide is opened using CeCl₃·7H₂O and the diol is deprotected *in situ*.

[260] One skilled in the art will recognize that variations to the order of the steps and reagents 5 discussed in reference to the above General Synthetic Schemes I are possible.

[261] In addition, protecting group strategies can be employed for preparation of the compounds disclosed herein. Such strategies are well known to those of skill in the art. Exemplary protecting groups and related strategies are disclosed in Greene's Protective Groups 10 in Organic Synthesis, Wiley-InterScience; 4 edition (October 30, 2006), which is hereby incorporated by reference in its entirety. In certain embodiments, a protecting group is used to mask an alcohol moiety while performing other chemical transformations. After removal of the protecting group, the free hydroxyl is obtained. Such protecting groups and strategies are well known in the art.

[262] Various alternative embodiments and examples of the invention are described herein. 15 These embodiments and examples are illustrative and should not be construed as limiting the scope of the invention. The following examples are provided for purposes of illustration, not limitation.

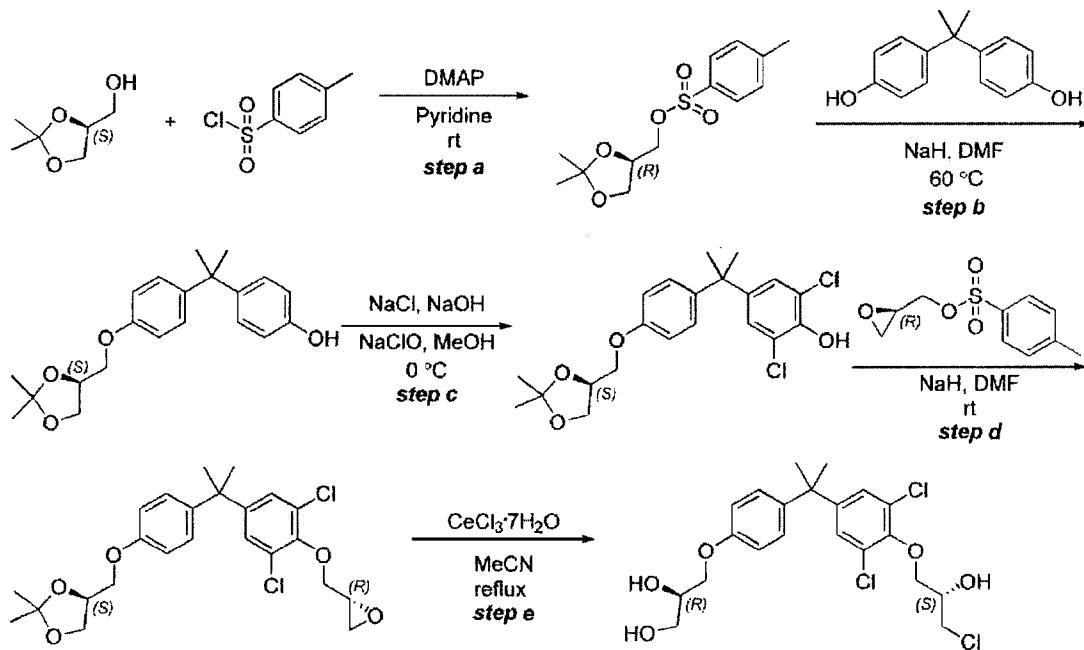
EXAMPLES

[263] All non-aqueous reactions were performed in flame-dried round bottomed flasks. The 20 flasks 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 aluminum plates pre-coated with 25 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 molybdate 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 30 pressure (15-30 torr, house vacuum) at 25-40 °C.

Commercial reagents and solvents were used as received. All solvents used for extraction and chromatography were HPLC grade. Normal-phase Si gel Sep paksTM were purchased from

waters, Inc. Thin-layer chromatography plates were Kieselgel 60F₂₅₄. All synthetic reagents were purchased from Sigma Aldrich and Fisher Scientific Canada.

[264] EXAMPLE 1: Synthesis of (R)-3-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (Compound 1a)



[265] Steps a and b: Synthesis of (S)-4-(2-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)propan-2-yl)phenol

10 [266] The titled compound was synthesized as previously reported. See, WO 2014/179867.

[267] Step c: (S)-2,6-dichloro-4-(2-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)propan-2-yl)phenol

[268] To a solution of (S)-4-(2-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)propan-2-yl)phenol (500 mg, 1.46 mmol, 1.0 equiv) in MeOH (12 mL) was added NaCl (256 mg, 4.38 mmol, 3.0 equiv) and NaOH (87.6 mg, 2.19 mmol, 1.5 equiv). Aqueous sodium hypochlorite (6035 mg, 5.4% in H₂O, 4.38 mmol, 3.0 equiv) was then added dropwise over 2 min at 0 °C. After 2 hours, the mixture was extracted with ethyl acetate (2 x 30 mL). The organic layer was washed with deionized water (2 x 30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash 15 Si gel column chromatography (elution: 10% ethyl acetate in hexane to 20% ethyl acetate in hexane) to provide the title compound (454 mg, 75.6%) as a sticky oil. ¹H NMR (600 MHz,

DMSO-D₆) δ (ppm) = 9.92 (s, 1H), 7.11 (d, J = 9.0 Hz, 2H), 7.07 (s, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.38-4.34 (m, 1H), 4.08-4.05 (m, 1H), 3.97-3.91 (m, 2H), 3.74-3.70 (m, 1H), 1.55 (s, 6H), 1.33 (s, 3H), 1.28 (s, 3H). ¹³C NMR (150 MHz, DMSO-D₆) δ (ppm) = 156.33, 146.75, 143.77, 141.55, 127.47, 126.58, 121.78, 114.03, 108.79, 73.69, 68.60, 65.78, 41.36, 30.23, 26.59, 25.37.

5 [269] **Step d:** (S)-4-((4-(2-(3,5-dichloro-4-((R)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)methyl)-2,2-dimethyl-1,3-dioxolane

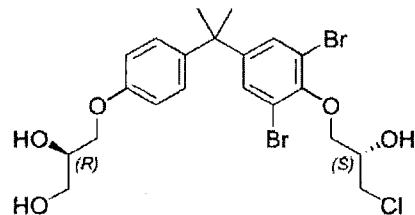
[270] Sodium hydride (60% dispersion in mineral oil, 63.6 mg, 1.59 mmol, 1.5 equiv) was added slowly to a stirred solution of (S)-2,6-dichloro-4-(2-(4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)propan-2-yl)phenol (434 mg, 1.06 mmol, 1.0 equiv) in anhydrous DMF (8 mL) at room temperature and the contents were stirred under an atmosphere of argon for 10 min. A solution of (2R)-(-)-glycidyl tosylate (363 mg, 1.59 mmol, 1.5 equiv) in anhydrous DMF (4 mL) was added via syringe and the mixture was allowed to react at 60 °C for 16 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (1 mL), and the mixture was extracted with ethyl acetate (60 mL). The organic layer was washed with deionized water (2 x 30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash Si gel column chromatography (elution: 10% ethyl acetate in hexane to 20% ethyl acetate in hexane) to provide the titled compound (476 mg, 96.1%) as a sticky oil. ¹H NMR (600 MHz, DMSO-D₆) δ (ppm) = 7.20 (s, 2H), 7.13 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 4.38-4.34 (m, 1H), 4.25-4.22 (m, 1H), 4.07-4.05 (m, 1H), 3.98-3.91 (m, 2H), 3.82-3.80 (m, 1H), 3.74-3.70 (m, 1H), 3.35-3.32 (m, 1H), 2.79-2.77 (m, 1H), 2.62-2.60 (m, 1H), 1.58 (s, 6H), 1.32 (s, 3H), 1.28 (s, 3H). ¹³C NMR (150 MHz, DMSO-D₆) δ (ppm) = 156.46, 149.15, 148.21, 141.01, 127.77, 127.54, 127.24, 114.10, 108.80, 75.01, 73.68, 68.61, 65.77, 49.88, 43.42, 41.80, 30.08, 26.59, 25.37.

25 [271] **Step e:** Synthesis of (R)-3-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (Compound 1a)

[272] To a solution of (S)-4-((4-(2-(3,5-dichloro-4-((R)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)methyl)-2,2-dimethyl-1,3-dioxolane (560 mg, 1.2 mmol, 1.0 equiv) in MeCN (12 mL) was added CeCl₃·7H₂O (1118 mg, 3.0 mmol, 2.5 equiv) and the mixture was heated to reflux for 16 h. The resulting white paste was collected by filtration and washed with ethyl acetate and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by column chromatography to provide the titled compound (512 mg, 92%) as a sticky oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.15-7.12 (m, 4H), 6.86 (d, J = 9.0 Hz, 2H), 4.26-4.23 (m, 1H), 4.21-4.15 (m, 2H), 4.15-4.11 (m,

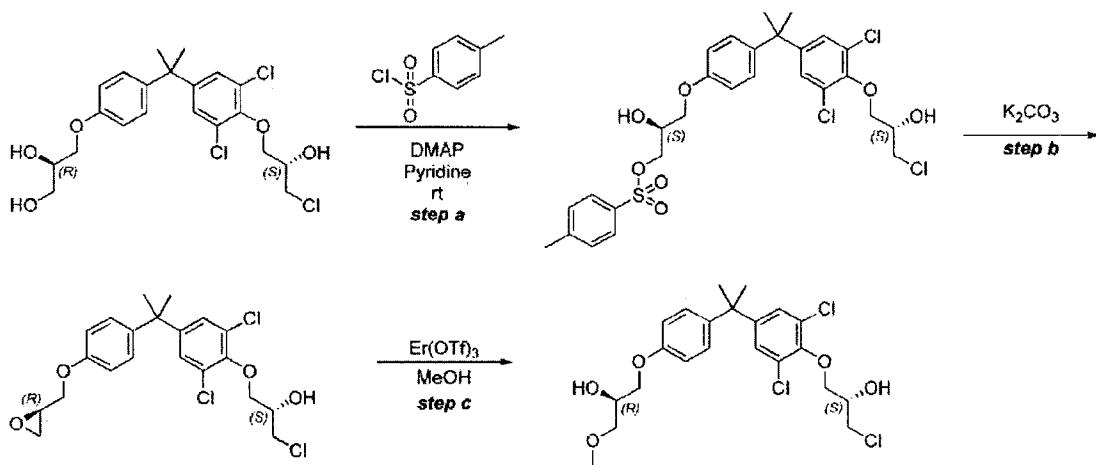
1H), 4.08-4.03 (m, 2H), 3.86 (dd, J = 4.8 Hz, 10.8 Hz, 2H), 3.78 (dd, J = 6.6 Hz, 12.6 Hz, 2H), 1.64 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) = 156.76, 149.30, 148.26, 141.84, 128.52, 127.87, 127.67, 114.35, 73.69, 70.48, 69.26, 63.78, 45.55, 42.34, 30.79; ESI-LRMS calcd for $[\text{M} + \text{Na}]^+$ 485.1, found 485.4.

5 [273] EXAMPLE 2: Synthesis of (*R*)-3-(4-(2-(3,5-dibromo-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (Compound 3a)



[274] Compound 3a was synthesized according to Example 1 by using NaBr instead of NaCl in step c. ^1H NMR (400 MHz, DMSO-D_6) δ (ppm) = 7.39 (s, 1H), 7.30 (dd, J = 2.0 Hz, 34.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.57-5.54 (m, 1H), 4.91 (d, J = 4.8 Hz, 1H), 4.64 (t, J = 5.6 Hz, 1H), 4.10-4.08 (m, 1H), 3.98-3.92 (m, 3H), 3.86-3.81 (m, 2H), 3.79-3.76 (m, 1H), 3.71 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.45-3.42 (m, 2H), 1.60 (s, 6H). ^{13}C NMR spectrum of Compound 3a as synthesized is shown in Figure 1.

15 [275] EXAMPLE 3: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*R*)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 5a)



[276] Step a: Synthesis of (*S*)-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl 4-methylbenzenesulfonate

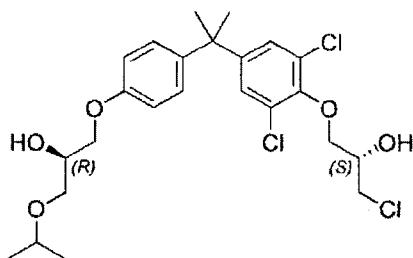
[277] The titled compound was synthesized by tosylation of Compound **1a** under basic conditions according to commonly known protocol, such as the protocol referenced for step **a** in Example 1.

[278] **Step b:** Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol The titled compound was synthesized via epoxidation reaction commonly known in the art under basic conditions. ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.13-7.10 (m, 4H), 6.86 (d, J = 6.8 Hz, 2H), 4.24-4.12 (m, 4H), 3.99-3.94 (m, 1H), 3.85 (dd, J = 5.2 Hz, 11.2 Hz, 1H), 3.77 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.38-3.33 (m, 1H), 2.93-2.89 (m, 1H), 2.76 (dd, J = 2.4 Hz, 4.8 Hz, 1H), 1.62 (s, 6H).

[279] **Step c:** Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **5a**)

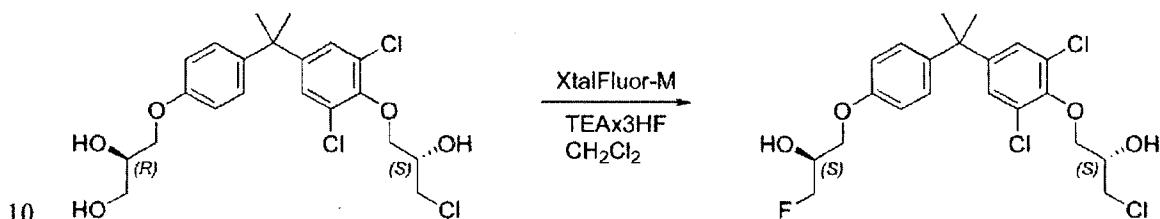
[280] To a solution of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (15 mg, 0.034 mmol, 1.0 equiv) in anhydrous methanol (2 mL) was added Erbium (III) trifluoromethanesulfonate (2.1 mg, 0.0034 mmol, 0.1 equiv) and the mixture was stirred at room temperature for 40 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (0.5 ml) and the mixture was extracted with ethyl acetate (2 x 10 ml). The organic layer was washed with deionized water (2 x 10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on silica gel (elution: 30% ethyl acetate in hexane to 50% ethyl acetate in hexane) to provide Compound **5a** (12.5 mg, 77.1%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.14-7.10 (m, 4H), 6.87 (d, J = 6.0 Hz, 2H), 4.26-4.22 (m, 1H), 4.21-4.15 (m, 3H), 4.06-4.01 (m, 2H), 3.87 (dd, J = 6.0 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 5.4 Hz, 11.4 Hz, 1H), 3.61 (dd, J = 4.2 Hz, 9.6 Hz, 1H), 3.57 (dd, J = 6.0 Hz, 9.6 Hz, 1H), 3.44 (s, 3H), 1.64 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 156.37, 148.81, 147.69, 141.04, 127.95, 127.25, 127.05, 113.81, 73.13, 73.00, 69.93, 68.58, 68.44, 58.88, 45.00, 41.78, 30.25.

[281] EXAMPLE 4: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **7a**)



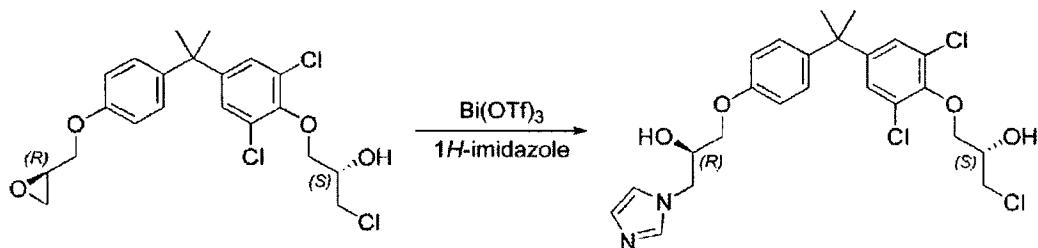
[282] Compound 7a was synthesized according to Example 2 by using isopropanol in step c instead of methanol. ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.13-7.10 (m, 4H), 6.86 (d, J = 8.8 Hz, 2H), 4.25-4.12 (m, 4H), 4.03-3.98 (m, 2H), 3.85 (dd, J = 5.2 Hz, 10.8 Hz, 1H), 3.77 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.67-3.53 (m, 3H), 2.83 (s, 1H), 2.57 (s, 1H), 1.62 (s, 6H), 1.18 (d, J = 6.0 Hz, 6H).

[283] EXAMPLE 5: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-((S)-3-fluoro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 8a)



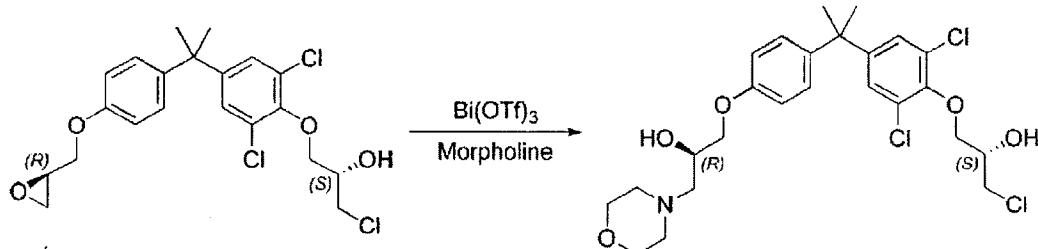
[284] To a solution of Compound 1a (1 equiv; synthesized according to Example 1) in dichloromethane were successively added triethylamine trihydrofluoride (2 equiv) and XtalFluor-M (2 equiv). After 3 h, the reaction mixture was quenched at room temperature with 15 a 5% aqueous sodium bicarbonate solution 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 chromatography to provide Compound 8a. ^1H NMR (600 MHz, CDCl_3) δ (ppm) = 7.16-7.14 (m, 4H), 6.87 (d, J = 8.4 Hz, 2H), 4.69-4.56 (m, 2H), 4.30-20 4.22 (m, 2H), 4.22-4.16 (m, 2H), 4.10-4.09 (m, 2H), 3.87 (dd, J = 6.0 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 5.4 Hz, 10.8 Hz, 1H), 1.64 (s, 6H).

[285] EXAMPLE 6: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-((R)-2-hydroxy-3-(1*H*-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 9a)



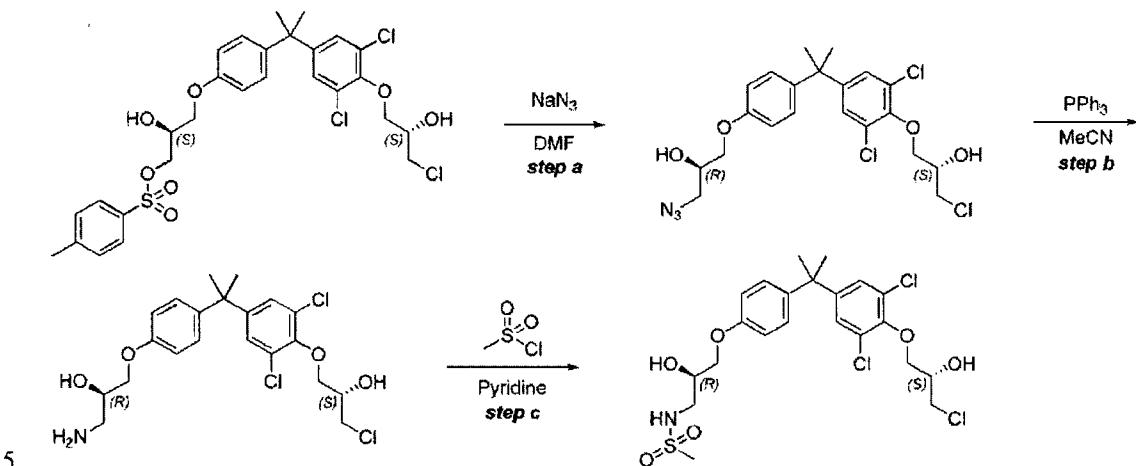
[286] To a solution of (S)-1-chloro-3-(2,6-dichloro-4-(2-((R)-oxiran-2-yl)methoxy)phenyl)propan-2-ol (12.6 mg, 0.028 mmol, 1.0 equiv) in anhydrous MeCN (2 mL) was added Bismuth (III) trifluoromethanesulfonate (1.8 mg, 0.0028 mmol, 0.1 equiv) and the mixture was stirred at room temperature for 40 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (0.5 mL) and the mixture was extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with deionized water (2 x 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to provide Compound 9a (8.7 mg, 60.4%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.56 (s, 1H), 7.16-7.14 (m, 4H), 7.04 (s, 1H), 7.01 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 4.29-4.23 (m, 3H), 4.22-4.13 (m, 3H), 3.98-3.92 (m, 2H), 3.87 (dd, J = 6.0 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 4.8 Hz, 10.8 Hz, 1H), 1.65 (s, 6H).

[287] EXAMPLE 7: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-((R)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 11a)



[288] Compound 11a was synthesized according to Example 6 by using morpholine instead of 1H-imidazole. ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.16-7.11 (m, 4H), 6.88 (d, J = 8.8 Hz, 2H), 4.27-4.13 (m, 4H), 4.07-3.98 (m, 2H), 3.90-3.77 (m, 6H), 2.84-2.80 (m, 2H), 2.73-2.72 (m, 2H), 2.71-2.67 (m, 2H), 1.65 (s, 6H); ESI-LRMS calcd for [M + H]⁺ 532.1, found 534.6.

[289] EXAMPLE 8: Synthesis of *(R)*-1-amino-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 12a) and *N*-(*(R*)-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide (Compound 13a)



[290] Step a: Synthesis of *(R)*-1-azido-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

[291] To a solution of (*S*)-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl 4-methylbenzenesulfonate (90 mg, 0.146 mmol, 1.0 equiv) in anhydrous DMF (3 mL) was added sodium azide (9.5 mg, 0.146 mmol, 1.0 equiv) and the mixture was heated to 60-70 °C for 16 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and the mixture was extracted with ethyl acetate (2 x 30 mL). The organic layer was washed with deionized water (2 x 30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on Si gel (elution: 20% ethyl acetate in hexane to 50% ethyl acetate in hexane) to provide the titled compound (57.4 mg, 80.1%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.15-7.13 (m, 4H), 6.86 (d, J = 9.0 Hz, 2H), 4.25-4.23 (m, 1H), 4.21-4.12 (m, 3H), 4.03-4.01 (m, 2H), 3.86 (dd, J = 5.4 Hz, 10.8 Hz, 1H), 3.78 (dd, J = 5.4 Hz, 11.4 Hz, 1H), 3.58-3.50 (m, 2H), 3.01 (s, 1H), 2.78 (s, 1H), 1.64 (s, 6H).

[292] Step b: Synthesis of *(R)*-1-amino-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 12a)

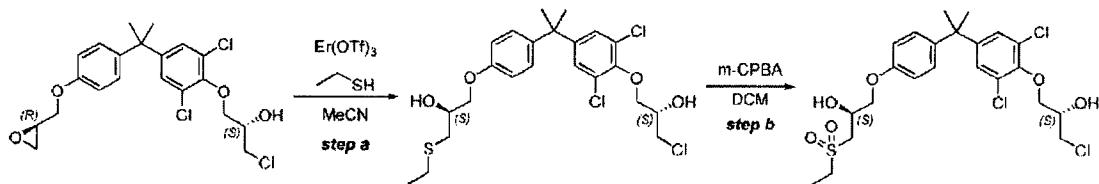
[293] To a solution of (*R*)-1-azido-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (57 mg, 0.117 mmol, 1.0 equiv) in

MeCN (6 mL) was added triphenylphosphine (36.7 mg, 0.14 mmol, 1.2 equiv) and the mixture was heated to reflux for 16 h. The reaction was quenched by deionized water (2 ml) and the mixture was extracted with ethyl acetate (2 x 30 ml). The organic layer was washed with deionized water (2 x 30 ml), dried over anhydrous magnesium sulfate, filtered, and 5 concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on Si gel (elution: 2% methanol in dichloromethane to 30% methanol in dichloromethane) to provide Compound **12a** (24.3 mg, 44.9%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.12-7.09 (m, 4H), 6.84 (d, J = 8.4 Hz, 2H), 4.24-4.21 (m, 1H), 4.17-4.13 (m, 2H), 3.97 (m, 3H), 3.84 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.76 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.00-2.85 (m, 2H), 1.61 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 157.00, 149.35, 148.31, 141.60, 128.52, 127.81, 127.61, 114.37, 73.78, 70.47, 70.42, 70.14, 45.65, 44.11, 42.34, 30.25; ESI-LRMS calcd for [M + H]⁺ 462.1, found 463.9.

[294] **Step c:** Synthesis of *N*-(*(R*)-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide
15 (Compound **13a**)

[295] To a solution of (*R*)-1-azido-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (14.3 mg, 0.031 mmol, 1.0 equiv) in anhydrous dichloromethane (3 mL) was treated triethylamine (12.5 mg, 0.124 mmol, 4.0 equiv) and methane sulfonyl chloride (3.6 mg, 0.031 mmol, 1.0 equiv) sequentially at 0 °C for 20 10 minutes. Then it was warmed to room temperature for 16 hours. The reaction was quenched by the addition of a saturated solution of ammonium chloride (2 ml) and the mixture was extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with deionized water (2 x 20 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on silica 25 gel (elution: 50% ethyl acetate in hexane to 75% ethyl acetate in hexane) to provide Compound **13a** (9.7 mg, 57.9%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.15-7.13 (m, 4H), 6.87 (d, J = 5.4 Hz, 2H), 4.93-4.90 (m, 1H), 4.26-4.23 (m, 1H), 4.21-4.13 (m, 3H), 4.06-4.01 (m, 2H), 3.87 (dd, J = 5.4 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 5.4 Hz, 10.8 Hz, 1H), 3.50-3.45 (m, 1H), 3.26-3.31 (m, 1H), 3.03 (s, 3H), 1.64 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 155.94, 148.69, 147.73, 141.57, 127.99, 127.39, 127.05, 113.81, 73.14, 69.92, 68.85, 68.54, 30.22.

[296] EXAMPLE 9: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 14a)



5

[297] Step a: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-3-(ethylthio)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol

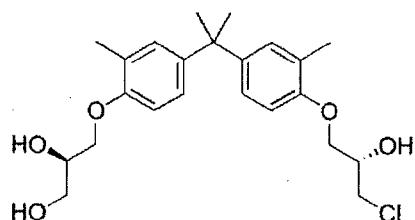
[298] To a solution of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((R)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (50 mg, 0.081 mmol, 1.0 equiv) in anhydrous DMF (3 mL) was added sodium ethanethiolate (6.8 mg, 0.081 mmol, 1.0 equiv) and the mixture was heated to 60-70 °C for 16 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (2 ml) and the mixture was extracted with ethyl acetate (2 x 30 ml). The organic layer was washed with deionized water (2 x 30 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on silica gel (elution: 20% ethyl acetate in hexane to 50% ethyl acetate in hexane) to provide the titled compound (16.4 mg, 39.5%) as a colorless oil.

[299] Step b: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound 14a)

[300] To a solution of (S)-1-chloro-3-(2,6-dichloro-4-(2-(4-((S)-3-(ethylthio)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (14.6 mg, 0.029 mmol, 1.0 equiv) in anhydrous dichloromethane (3 mL) was treated 3-chloroperbenzoic acid (14.0 mg, 0.081 mmol, 2.8 equiv) at 0 °C for 10 minutes. Then it was warmed to room temperature for 3 hours. The reaction was quenched by the addition of a saturated solution of ammonium chloride (2 ml) and the mixture was extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with saturated NaHCO₃ (20 ml), deionized water (2 x 20 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on Si gel (elution: 30% ethyl acetate in hexane to 75% ethyl acetate in hexane) to provide Compound 14a (4.7 mg, 31.0%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.18-7.15 (m, 4H), 6.88 (d, J = 8.8 Hz, 2H), 4.69-4.67 (m, 1H), 4.27-4.15 (m, 3H), 4.10-4.07 (m, 2H), 3.88 (dd, J = 5.2 Hz, J = 11.2 Hz, 1H), 3.80 (dd, J

= 5.2 Hz, J = 10.8 Hz, 1H), 3.39-3.20 (m, 4H), 1.66 (s, 6H), 1.48 (t, J = 7.2 Hz, 3H); ESI-LRMS calcd for [M + Na]⁺ 561.1, found 561.5.

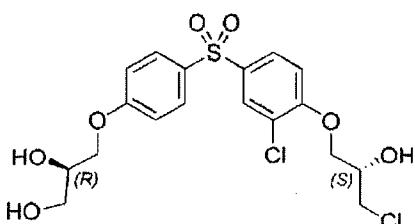
[301] EXAMPLE 10: Synthesis of (*R*)-3-(4-(2-((*S*)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol (Compound 22a)



[302] Compound 22a was synthesized according to Example 1 by using 4,4'-(Propane-2,2-diyl)bis(2-methylphenol) (commercially available) instead of 4,4'-(propane-2,2-diyl)diphenol and omitting step c. ¹H NMR (400 MHz, DMSO-D₆) δ (ppm) = 6.97-6.94 (m, 4H), 6.81-6.76 (m, 2H), 5.50 (d, J = 4.8 Hz, 1H), 4.86 (s, 1H), 4.61 (s, 1H), 4.06-4.00 (m, 1H), 3.97-3.89 (m, 3H), 3.86-3.76 (m, 3H), 3.69 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.50-3.44 (m, 2H), 2.10 (s, 6H), 1.55 (s, 6H); ¹³C NMR (100 MHz, DMSO-D₆) δ (ppm) = 155.14, 154.74, 143.23, 142.75, 129.32, 129.23, 125.66, 125.62, 125.22, 125.16, 111.28, 111.16, 70.67, 70.02, 69.48, 69.32, 63.43, 55.50, 47.53, 31.42, 16.86, 16.79.

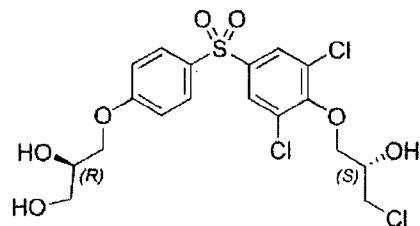
15

[303] EXAMPLE 11: Synthesis of (*R*)-3-(4-((3-chloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol (Compound 40a)



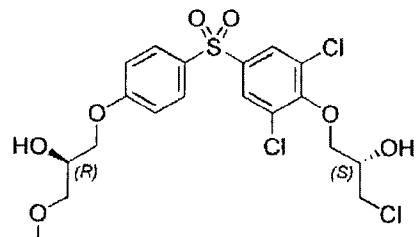
[304] Compound 40a was synthesized according to Example 1 by using 4,4'-sulfonyldiphenol instead of 4,4'-(propane-2,2-diyl)diphenol and with only 1 equiv of NaCl in step c. ¹H NMR (400 MHz, MeOD) δ (ppm) = 7.92-7.82 (m, 4H), 7.26 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 4.23-4.12 (m, 4H), 4.08-4.03 (m, 1H), 4.00-3.96 (m, 1H), 3.81 (dd, J = 4.8 Hz, 11.6 Hz, 1H), 3.72 (dd, J = 5.2 Hz, 11.2 Hz, 1H), 3.68-3.61 (m, 2H); ¹³C NMR (100 MHz, MeOD) δ (ppm) = 163.24, 157.96, 135.21, 133.24, 129.56, 128.90, 127.82, 123.46, 115.12, 113.49, 70.23, 70.16, 69.62, 69.30, 62.64, 45.28; ESI-LRMS calcd for [M + Na]⁺ 473.0, found 472.8.

[305] EXAMPLE 12: Synthesis of (R)-3-(4-((3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol (Compound 41a)



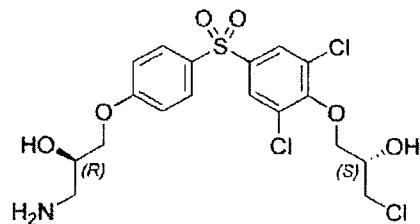
5 [306] Compound 41a was synthesized according to Example 1 by using 4,4'-sulfonyldiphenol instead of 4,4'-(propane-2,2-diyl)diphenol. ¹H NMR (400 MHz, MeOD) δ (ppm) = 7.94-7.89 (m, 4H), 7.14 (d, J = 8.8 Hz, 2H), 4.21-4.13 (m, 4H), 4.09-4.04 (m, 1H), 4.01-3.95 (m, 1H), 3.84 (dd, J = 4.4 Hz, 11.6 Hz, 1H), 3.72 (dd, J = 5.2 Hz, 11.2 Hz, 1H), 3.69-3.62 (m, 2H); ¹³C NMR (100 MHz, MeOD) δ (ppm) = 165.08, 156.38, 141.20, 133.48, 10 131.65, 131.46, 129.37, 116.74, 75.60, 71.62, 71.46, 71.11, 64.06, 46.76; ESI-LRMS calcd for [M + Na]⁺ 506.9, found 506.9.

[307] EXAMPLE 13: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-((4-((R)-2-hydroxy-3-methoxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol (Compound 43a)



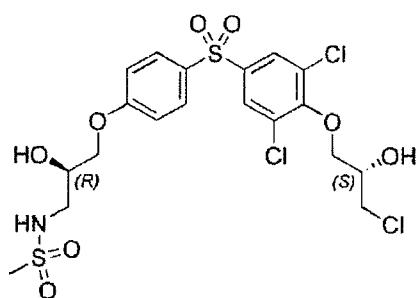
15 [308] Compound 43a was synthesized according to Examples 3 by starting with Compound 41a. ¹H NMR (600 MHz, CD₃Cl) δ (ppm) = 7.91-7.85 (m, 4H), 7.06 (d, J = 9.0 Hz, 2H), 4.27-4.16 (m, 4H), 4.13-4.07 (m, 2H), 3.85 (dd, J = 4.8 Hz, 10.8 Hz, 1H), 3.79 (dd, J = 5.4 Hz, 11.4 Hz, 1H), 3.62-3.54 (m, 2H), 3.43 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ (ppm) = 163.22, 154.58, 139.94, 132.47, 130.56, 130.47, 128.37, 115.67, 74.18, 73.31, 70.42, 69.70, 20 69.01, 59.62, 45.56; ESI-LRMS calcd for [M + Na]⁺ 521.0, found 520.9.

[309] EXAMPLE 14: Synthesis of (R)-1-amino-3-(4-((3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol (Compound 45a)



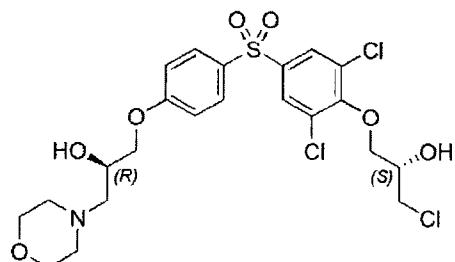
[310] Compound **45a** was synthesized according to Examples 3 and 8 by starting with Compound **41a**. ^1H NMR (400 MHz, MeOD) δ (ppm) = 7.93-7.90 (m, 4H), 7.14 (d, J = 9.2 Hz, 2H), 4.19-4.13 (m, 3H), 4.10-4.01 (m, 2H), 3.95-3.91 (m, 1H), 3.85-3.80 (m, 1H), 3.74-5 3.69 (m, 1H), 2.85 (dd, J = 4.4 Hz, 13.2 Hz, 1H), 2.74 (dd, J = 5.2 Hz, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) = 165.08, 156.51, 141.32, 133.70, 131.76, 131.57, 129.46, 116.86, 75.71, 72.15, 71.73, 71.57, 46.83, 45.26; ESI-LRMS calcd for $[\text{M} + \text{Na}]^+$ 506.0, found 507.9.

10 [311] EXAMPLE 15: Synthesis of N-((*R*)-3-(4-((3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)-2-hydroxypropyl)methanesulfonamide (Compound **46a**)



[312] Compound **46a** was synthesized according to Examples 3 and 8 by starting with Compound **41a**. ^1H NMR (600 MHz, MeOD) δ (ppm) = 7.93-7.90 (m, 4H), 7.14 (d, J = 9.0 Hz, 2H), 4.18-4.10 (m, 4H), 4.07-4.01 (m, 2H), 3.82 (dd, J = 4.2 Hz, 11.4 Hz, 1H), 3.71 (dd, J = 4.8 Hz, 10.8 Hz, 1H), 3.30-3.27 (m, 1H), 3.20 (dd, J = 6.0 Hz, 13.2 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (150 MHz, MeOD) δ (ppm) = 165.01, 156.49, 141.31, 133.74, 131.75, 131.56, 129.46, 116.86, 75.68, 71.55, 71.47, 70.27, 46.81, 46.70, 40.22; ESI-LRMS calcd for $[\text{M} + \text{Na}]^+$ 584.0, 20 found 584.0.

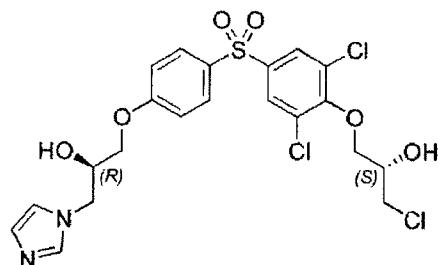
[313] EXAMPLE 16: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-((4-((R)-2-hydroxy-3-morpholinopropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol (Compound 47a)



[314] Compound 47a was synthesized according to Examples 3 and 7 by starting with
5 Compound 41a. ^1H NMR (600 MHz, CDCl_3) δ (ppm) = 7.90-7.86 (m, 4H), 7.06 (d, $J = 9.0$ Hz, 2H), 4.28-4.19 (m, 4H), 4.08-4.07 (m, 2H), 3.87-3.77 (m, 6H), 2.77-2.58 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) = 162.51, 153.88, 139.21, 131.79, 129.85, 129.75, 127.66, 114.97, 73.48, 70.03, 69.71, 66.14, 64.45, 60.50, 53.26, 44.85; ESI-LRMS calcd for $[\text{M} + \text{H}]^+$ 554.1, found 556.0.

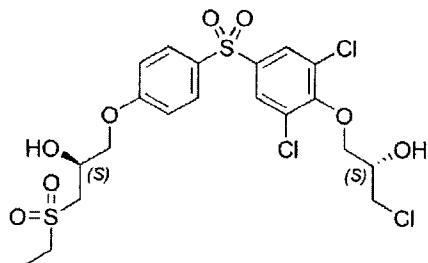
10

[315] EXAMPLE 17: Synthesis of (S)-1-chloro-3-(2,6-dichloro-4-((4-((R)-2-hydroxy-3-(1H-imidazol-1-yl)propoxy)phenyl)sulfonyl)phenoxy)propan-2-ol (Compound 48a)



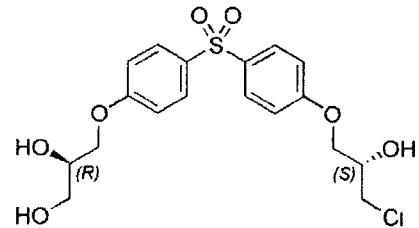
[316] Compound 48a was synthesized according to Examples 3 and 6 by starting with
15 Compound 41a. ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.88-7.83 (m, 4H), 7.65 (s, 1H), 7.03-6.97 (m, 4H), 4.27-4.10 (m, 6H), 4.02 (dd, $J = 4.8$ Hz, 9.6 Hz, 1H), 3.96-3.90 (m, 1H), 3.82 (dd, $J = 4.8$ Hz, 11.2 Hz, 1H), 3.75 (dd, $J = 5.2$ Hz, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 162.53, 154.66, 139.49, 137.72, 132.85, 130.46, 130.40, 128.24, 128.00, 120.24, 115.50, 74.12, 70.14, 69.22, 68.64, 50.29, 45.48; ESI-LRMS calcd for $[\text{M} + \text{H}]^+$ 535.0, found
20 535.0.

[317] EXAMPLE 18: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-((4-((*S*)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propan-2-ol (Compound **50a**)



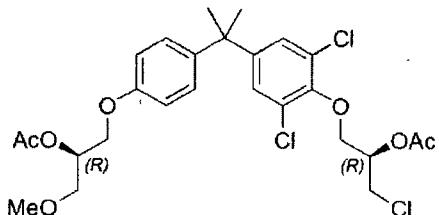
[318] Compound **50a** was synthesized according to Examples 3 and 9 by starting with
 5 Compound **41a**. ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.89 (d, J = 9.2 Hz, 2H), 7.85 (s, 2H),
 7.04 (d, J = 9.2 Hz, 2H), 4.72-4.66 (m, 1H), 4.26-4.19 (m, 3H), 4.14-4.09 (m, 2H), 3.83 (dd, J
 = 5.2 Hz, 11.2 Hz, 1H), 3.77 (dd, J = 4.8 Hz, 11.2 Hz, 1H), 3.35-3.14 (m, 4H), 1.45 (t, J = 7.6
 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 162.37, 154.56, 139.59, 133.08, 130.46,
 130.43, 128.27, 115.56, 74.08, 70.82, 70.29, 65.20, 54.87, 49.39, 45.41, 6.70; ESI-LRMS calcd
 10 for $[\text{M} + \text{Na}]^+$ 583.0, found 582.9.

[319] EXAMPLE 19: Synthesis of (*R*)-3-(4-((4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)sulfonyl)phenoxy)propane-1,2-diol (Compound **80a**)



[320] Compound **80a** was synthesized according to Examples 1 by using 4,4'-sulfonyldiphenol instead of 4,4'-(propane-2,2-diyl)diphenol and omitting step c. ^1H NMR (400 MHz, MeOD) δ (ppm) = 7.84 (dd, J = 2.8 Hz, 9.2 Hz, 4H), 7.09 (dd, J = 2.0 Hz, 9.2 Hz, 4H), 4.15-4.08 (m, 4H), 4.05-4.01 (m, 1H), 3.99-3.93 (m, 1H), 3.76-3.71 (m, 1H), 3.70-3.60 (m, 3H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) = 164.50, 164.17, 135.74, 135.40, 130.89, 130.87,
 20 116.52, 71.78, 71.12, 70.97, 70.87, 64.19, 46.74; ESI-LRMS calcd for $[\text{M} + \text{Na}]^+$ 439.1, found 438.9.

[321] EXAMPLE 20: Synthesis *(R)*-1-(4-(2-(4-((*R*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Compound A5d)

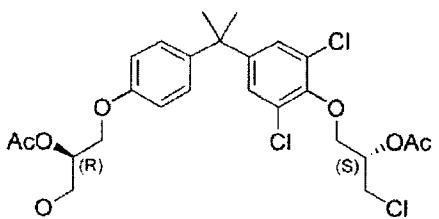


[322] Ac₂O (128 mg, 1.26 mmol, 6.0 equiv.), Et₃N (127 mg, 1.26 mmol, 6.0 equiv.) and 5 DMAP (26 mg, 0.21 mmol, 1.0 equiv.) were added to a solution of Compound 5a (100 mg, 0.21 mmol, 1.0 equiv., see Example 3) in anhydrous DCM (5 mL) at room temperature and the resultant mixture was stirred at the same temperature overnight. The mixture was diluted with EtOAc (30 mL) and the organic layer was washed with water (15 mL) and brine (15 mL). The organic layer was further dried over anhydrous MgSO₄ and evaporated under reduced pressure. 10 The crude was loaded onto a silica gel column and eluted with Hexane/EtOAc (13/1 to 6/1) to give 111 mg of the titled compound as colorless oil (yield: 95.0%).

[323] ¹H NMR (600 MHz, CHLOROFORM-d) δ 7.11 - 7.12 (m, 2H), 7.09 - 7.11 (m, 2H), 6.82 - 6.87 (m, 2H), 5.32 - 5.35 (m, 1H), 5.28 - 5.32 (m, 1H), 4.18 - 4.26 (m, 2H), 4.09 - 4.16 (m, 2H), 3.97 (dd, *J* = 5.14, 11.74 Hz, 1H), 3.88 (dd, *J* = 5.14, 11.74 Hz, 1H), 3.66 (dd, *J* = 2.20, 4.40 Hz, 2H), 3.40 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.61 (s, 6H).

[324] ¹³C NMR (151 MHz, CHLOROFORM-d) δ 170.8, 170.4, 156.9, 149.4, 148.4, 141.8, 128.7, 127.9, 127.7, 114.5, 71.9, 71.1, 70.9, 66.4, 59.6, 42.7, 42.4, 30.9, 21.4, 21.2.

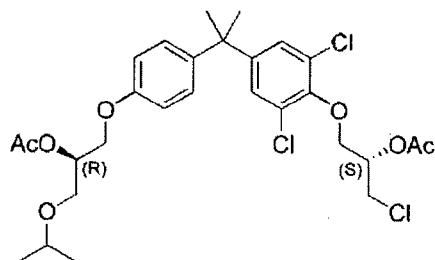
[325] EXAMPLE 21: Synthesis *(R)*-1-(4-(2-(4-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Compound A5a)



[326] Acetic Anhydride (4.1 mg, 0.04 mmol, 4.0 equiv) was added to a solution of Compound 5a (5.0 mg, 0.01 mmol, 1.0 equiv, see Example 3), DMAP (0.1 mg, 0.001 mmol, 0.1 equiv) and Et₃N (4.1 mg, 0.04 mmol, 4.0 equiv) in anhydrous dichloromethane (1 mL). The resulting 25 solution was stirred overnight at room temperature. Dichloromethane was removed under reduced pressure and the residue was purified by column chromatography to afford the title

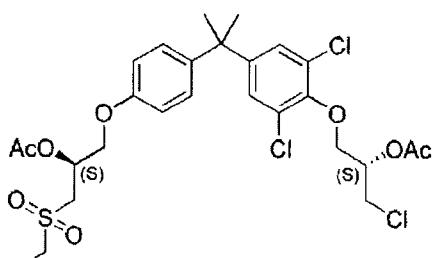
compound as a colorless oil (5.8 mg, 98.6%). ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.11-7.08 (m, 4H), 6.83 (d, $J=8.8$, 2H), 5.35-5.26 (m, 2H), 4.26-4.17 (m, 2H), 4.16-4.07 (m, 2H), 3.96 (dd, $J=5.2$ Hz, 11.6 Hz, 1H), 3.86 (dd, $J=5.6$ Hz, 11.6 Hz, 1H), 3.66-3.61 (m, 2H), 3.38 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.60 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) = 170.80, 170.45, 156.96, 149.41, 148.39, 141.80, 128.69, 127.90, 127.70, 114.54, 71.91, 71.12, 70.54, 66.44, 59.62, 42.73, 42.43, 30.90, 21.38, 21.18; ESI-LRMS calcd for $[\text{M} + \text{H}]^+$ 561.1, found 561.1.

[327] EXAMPLE 22: Synthesis of (*R*)-1-(4-(2-((*S*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate (Compound A7a)



10 [328] Compound A7a was synthesized according to Examples 21 by using Compound 7a prepared according to Example 4. Compound A7a was obtained as a colorless oil (6.4 mg, 96.2%). ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.12-7.08 (m, 4H), 6.85 (d, $J=8.8$, 2H), 5.36-5.30 (m, 1H), 5.28-5.22 (m, 1H), 4.27-4.09 (m, 4H), 3.97 (dd, $J=5.2$ Hz, 11.6 Hz, 1H), 3.87 (dd, $J=5.6$ Hz, 11.6 Hz, 1H), 3.71-3.57 (m, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 1.61 (s, 6H), 1.15 (dd, $J=2.0$ Hz, 6.0 Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) = 170.16, 169.78, 156.42, 148.77, 147.72, 141.03, 128.02, 127.20, 127.03, 113.91, 71.97, 71.25, 70.98, 70.30, 66.01, 65.72, 42.06, 41.76, 30.24, 21.60, 21.54, 20.74, 20.52; ESI-LRMS calcd for $[\text{M} + \text{Na}]^+$ 611.1, found 611.1.

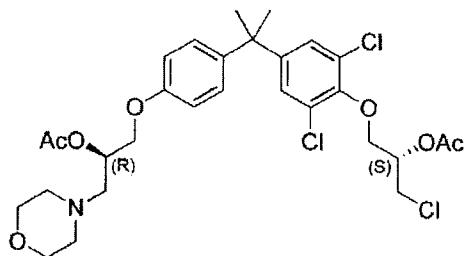
20 [329] EXAMPLE 23: Synthesis of (*S*)-1-(4-(2-((*S*)-2-acetoxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate (Compound A14a)



[330] Compound **A14a** was synthesized according to Examples 21 by using Compound **14a** prepared according to Example 9. Compound **A14a** was obtained as a colorless oil (3.4 mg, 97.3%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.13-7.08 (m, 4H), 6.84 (d, J=8.8, 2H), 5.63-5.57 (m, 1H), 5.36-5.30 (m, 1H), 4.29-4.18 (m, 4H), 3.97 (dd, J=5.2 Hz, 12.0 Hz, 1H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.54-3.40 (m, 2H), 3.10 (q, J=7.2 Hz, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 1.61 (s, 6H), 1.44 (t, J=7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.41, 170.16, 158.50, 154.94, 142.86, 142.39, 128.70, 128.03, 127.66, 114.48, 71.87, 71.46, 67.79, 67.05, 52.48, 48.82, 42.69, 42.44, 30.86, 21.15, 20.90, 6.80; ESI-LRMS calcd for [M + Na]⁺ 645.1, found 645.1.

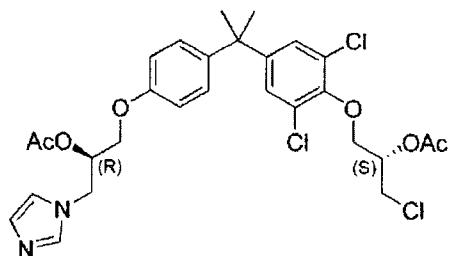
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[331] EXAMPLE 24: Synthesis of (*R*)-1-(4-(2-(4-((*S*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate (Compound **A11a**)



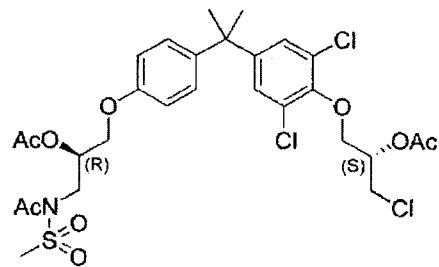
[332] Compound **A11a** was synthesized according to Examples 21 by using Compound **11a** prepared according to Example 7. Compound **A11a** was obtained as a colorless oil (6.8 mg, 97.6%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.14-7.07 (m, 4H), 6.83 (d, J=8.8, 2H), 5.72-5.70 (m, 1H), 5.36-5.30 (m, 1H), 4.47-4.40 (m, 1H), 4.39-4.32 (m, 1H), 4.29-4.14 (m, 4H), 3.99-3.94 (m, 3H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.58-3.37 (m, 4H), 2.97 (m, 2H), 2.23 (s, 3H), 2.14 (s, 3H), 1.61 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.54, 170.37, 156.02, 149.12, 148.39, 142.61, 128.67, 128.06, 127.60, 114.34, 71.81, 70.90, 67.26, 65.89, 63.60, 58.52, 53.17, 52.58, 42.64, 42.40, 30.78, 29.87, 21.56, 21.11; ESI-LRMS calcd for [M + H]⁺ 616.1, found 616.1.

[333] EXAMPLE 25: Synthesis of (*S*)-1-(4-(2-(4-((*R*)-2-acetoxy-3-(1*H*-imidazol-1-yl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate (Compound **A9a**)



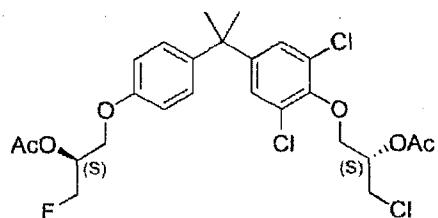
[334] Compound **A9a** was synthesized according to Examples 21 by using Compound **9a** prepared according to Example 6. Compound **A9a** was obtained as a colorless oil (5.6 mg, 93.6%). ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 9.40 (s, 1H), 7.39 (s, 1H), 7.20 (s, 1H), 7.14-5.10 (m, 4H), 6.82 (d, $J=8.4$, 2H), 5.50 (m, 1H), 5.35-5.31 (m, 1H), 4.78-4.70 (m, 2H), 4.27-4.18 (m, 4H), 3.96 (dd, $J=5.6$ Hz, 11.6 Hz, 1H), 3.87 (dd, $J=5.6$ Hz, 11.6 Hz, 1H), 2.14 (s, 3H), 2.11 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) = 170.21, 169.67, 155.72, 148.93, 142.61, 136.02, 128.53, 127.97, 127.46, 121.62, 120.13, 114.19, 71.66, 70.76, 69.72, 65.27, 49.70, 42.49, 42.26, 30.65, 20.96, 20.91; ESI-LRMS calcd for $[\text{M} + \text{H}]^+$ 597.1, found 10 597.1.

[335] EXAMPLE 26: Synthesis of (*S*)-1-(4-(2-((*R*)-2-acetoxy-3-(*N*-methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate (Compound **A13a**)



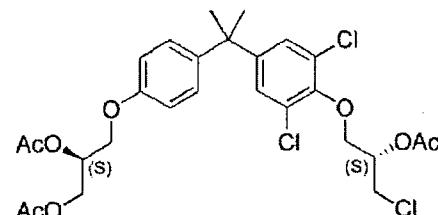
[336] Compound **A13a** was synthesized according to Examples 21 by using Compound **13a** prepared according to Example 8. Compound **A13a** was obtained as a colorless oil (6.0 mg, 100%). ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.13-7.08 (m, 4H), 6.82 (d, $J=8.4$, 2H), 5.47-5.42 (m, 1H), 5.36-5.30 (m, 1H), 4.29-4.07 (m, 6H), 3.97 (dd, $J=5.2$ Hz, 11.6 Hz, 1H), 3.87 (dd, $J=5.6$ Hz, 11.6 Hz, 1H), 3.33 (s, 3H), 2.44 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) = 171.33, 170.47, 170.29, 156.42, 149.13, 148.29, 142.17, 128.58, 127.88, 127.54, 114.33, 71.74, 70.82, 70.36, 67.19, 46.69, 42.66, 42.57, 42.31, 30.73, 24.49, 21.07, 20.03; ESI-LRMS calcd for $[\text{M} + \text{H}]^+$ 666.1, found 666.1.

[337] EXAMPLE 27: Synthesis of (S)-1-(4-(2-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-fluoropropan-2-yl acetate (Compound A8a)



[338] Compound A8a was synthesized according to Examples 21 by using Compound 8a prepared according to Example 5. Compound A8a was obtained as a colorless oil (5.8 mg, 95.9%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.13-7.10 (m, 4H), 6.84 (d, J=8.8 Hz, 2H), 5.39-5.29 (m, 2H), 4.79-4.71 (m, 1H), 4.67-4.59 (m, 1H), 4.27-4.18 (m, 2H), 4.16-4.14 (m, 2H), 3.97 (dd, J=5.2 Hz, 11.6 Hz, 1H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 1.61 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.58, 170.46, 156.65, 149.33, 148.43, 142.14, 128.73, 127.99, 127.70, 114.48, 82.13, 80.99 (d, J=513.0 Hz), 71.92, 70.98, 70.77, 70.64 (d, J=19.5 Hz), 65.19, 65.15 (d, J=6.0 Hz), 42.73, 42.46, 30.91, 21.22, 21.19; ESI-LRMS calcd for [M + H]⁺ 549.1, found 549.1.

[339] EXAMPLE 28: Synthesis of (S)-3-(4-(2-((S)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate (Compound A1a)



[340] Compound A1a was synthesized according to Examples 21 by using Compound 1a prepared according to Example 1. Compound A1a was obtained as a colorless oil (63.0 mg, 97.1%). ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.14-7.11 (m, 4H), 6.85 (d, J=12.0 Hz, 2H), 5.39-5.33 (m, 2H), 4.45 (dd, J=4.2 Hz, 12.0 Hz, 1H), 4.32 (dd, J=6.0 Hz, 12.0 Hz, 1H), 4.26 (dd, J=4.8 Hz, 10.2 Hz, 1H), 4.22 (dd, J=4.8 Hz, 10.2 Hz, 1H), 4.13-4.12 (m, 2H), 3.98 (dd, J=5.4 Hz, 12.0 Hz, 1H), 3.89 (dd, J=5.4 Hz, 12.0 Hz, 1H), 2.16 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.63 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.21, 169.90, 169.77, 156.07, 148.66, 147.76, 141.40, 128.04, 127.28, 127.02, 113.88, 71.24, 70.31, 69.30, 65.55, 62.10, 42.05, 41.77, 30.23, 20.56, 20.50, 20.35; ESI-LRMS calcd for [M + Na]⁺ 611.1, found 611.0.

[341] EXAMPLE 29: Compound Activity

[342] LNCaP cells (3×10^4) were seeded into 24-well plates overnight. Next day, LNCaP cells were transiently transfected with 0.25 μ g/well of PSA (6.1 kb)-luciferase reporter plasmid prior to pre-treatment with compounds of the invention or reference compounds (e.g., 5 compounds A, B, C, 1a, 5a, 9a, 11a, 12a, 13a, and 14a) ranging in concentration from 0 μ M to 35 μ M for 1 hour before the addition of vehicle, or synthetic androgen, R1881 (1 nM) to induce luciferase production. After 48 h of exposure, cells were harvested in Passive lysis buffer (Promega). Luciferase activities were measured and normalized to protein concentration determined by the Bradford assay. IC₅₀ calculations were done using OriginPro 8.1 Software (Northampton, MA, USA). Transfection experiments to determine IC₅₀ values were performed in at least 4 independent experiments ("trials") using triplicate wells. Dose responses of 10 representative compounds are shown in Figure 2. Luciferase activity is presented as the mean \pm standard deviation of the technical replicates.

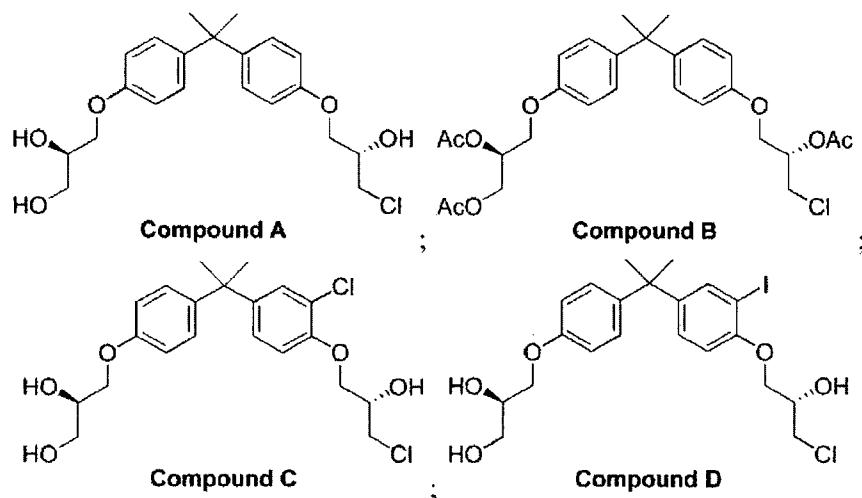


Table 6. IC₅₀ values for selected compounds (μM) with standard error

Compound	Number of Trials	Average IC ₅₀
A	12	13.9 ± 2.6
B	6	10.68 ± 1.04
C	4	2.47 ± 0.26
1a	11	1.41 ± 0.27
5a	6	1.03 ± 0.39

Compound	Number of Trials	Average IC ₅₀
9a	11	3.12 ± 0.68
11a	10	1.05 ± 0.15
12a	4	2.26 ± 0.24
13a	6	1.00±0.16
14a	11	0.95±0.21

[343] EXAMPLE 30: Compound **1a** treatment in LNCaP Xenograft Model

[344] **LNCaP Cell Preparation:** LNCaP cells were passaged prior to seeding in T175 flasks at a concentration of ~2-3x10⁷/mL. The cells were grown for 7 days until 90% confluent. Cell 5 preparations were then prepared in RPMI with 5% FBS/Matrigel (50/50, v/v) yielding a final concentration of 1 x10⁸/mL.

[345] **Tumor Induction and Treatment:** Six to eight week old NOD-SCID mice were received from BC Cancer Research Centre's Animal Resource Centre and acclimated for 28 days. Tumors were initiated with sub-cutaneous back of each animal. Tumors were allowed to 10 grow to an average size of approximately 100 mm³. Mice were then castrated and the tumors allowed to adapt for a period of one week before first dose was administered. Tumor volume was measured as length x width x height in mm multiplied by 0.5236.

[346] **Compound Preparation and Treatment:** Compound **1a** was dissolved in 100% DMSO (ATCC Lot 61908420) to yield a stock solution of 157 mg/mL. Compound **1a** was 15 administered as an oral gavage once per day at dose levels of 10 and 30 mg/kg. Vehicle control animals were administered 1% CMC formulation as an oral gavage once daily. CMC (n = 17 tumours); 10 mg/kg (n = 15 tumours); 30 mg/kg (n = 14 tumours). CMC (n = 9 animals); 10 mg/kg (n = 9 animals); 30 mg/kg (n = 9 animals).

[347] Oral treatment was initiated one week after castration. The start of treatment was 20 designated "Day 1" and animals were treated once daily for a total of 24 doses. Two days after the last dose, the tumours were measured and harvested. Body weight was assessed daily throughout the treatment period. Tumor volume was measured on day -7 (castration day), and again on days 1, 4, 8, 12, 16, 20, 24 and 26.

[348] **Quantitative Real-Time Polymerase Chain Reaction (QPCR) Method:** LNCaP 25 xenografts were homogenized using TRIzol® reagent (Invitrogen™), and total RNA was

extracted using PureLink RNA Mini Kit (Life Technologies). Amplification Grade DNase I treatment (Sigma-Aldrich) was applied to the RNA before RT-PCR using High Capacity RNA-to-DNA kit (Life Technologies) to generate cDNA. cDNA and gene-specific primers were combined with Platinum® SYBR® Green qPCRSuperMix-UDG with ROX (Invitrogen™).

5 Transcripts were measured by quantitative real-time PCR (QPCR) using ABI PRISM 7900 Sequence Detection System (ABI PRISM®, Applied Biosystems by Life Technologies) in triplicates for each biological sample. Gene expression levels were normalized to housekeeping gene RPL13A. Primers for PSA have been previously described (Andersen R. J., *et al. Cancer Cell*. 2010; Myung J. K., *et al. J. Clin. Invest.* 2013).

10 [349] Daily oral treatment of Compound 1a at 10 mg/kg or 30 mg/kg resulted in inhibition of tumor growth and significant reduction of tumor volume at the end of the treatment period (Figures 3 and 4). There was no statistical difference in the tumor volumes between the 10 mg/kg and 30 mg/kg doses of Compound 1a. There were no significant differences between the start and finish body weights for the mice treated with Compound 1a and mice treated with

15 control (CMC formulation) (Figure 5). Since androgen receptor transcriptionally regulates the expression of PSA, the mRNA levels of PSA in the tumors were measured and examined to confirm the *in vivo* on-target activity of Compound 1a (Figure 6). Indeed, Compound 1a demonstrated a dose-dependent inhibition of the mRNA expression of PSA, as 30 mg/kg treatment of Compound 1a caused a significant reduction of PSA expression when compared

20 to the 10 mg/kg dose and control treatment. Together, these data indicated that Compound 1a significantly reduced the castration-resistant growth of LNCaP tumors, while demonstrating on-target activity to block androgen receptor transcriptional activity.

[350] In Figure 6, bars represent mean \pm SEM with n = 5 representative tumors from each treatment group. One-way ANOVA post-hoc Tukey's multiple comparisons test was

25 performed for statistical analysis. *p<0.05; **p<0.01; ***p<0.001.

[351] Although various embodiments of the invention are disclosed herein, many adaptations and modifications can be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the

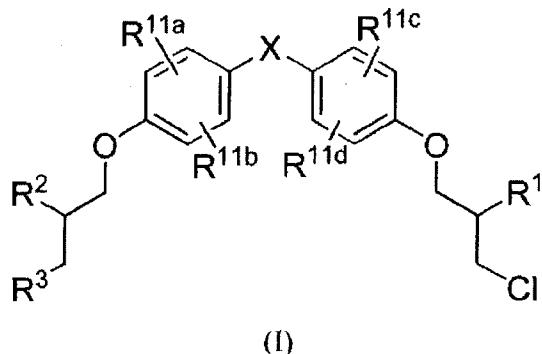
30 substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. The word "comprising" is used herein as an open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. As used herein, the singular forms "a", "an" and "the" include plural referents unless

the context clearly dictates otherwise. Thus, for example, reference to "a thing" includes more than one such thing. Citation of references herein is not an admission that such references are prior art to the present invention. Any priority document(s) and all publications, including but not limited to patents and patent applications, cited in this specification are incorporated herein
5 by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein and as though fully set forth herein. The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings.

Claims

What is claimed is:

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



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

X is $-\text{S}(\text{O})_n-$ or $-\text{C}(\text{R}^8\text{R}^9)-$;

R^1 is H, hydroxyl or $-\text{OC}(=\text{O})\text{R}^{13}$;

R^2 is hydroxyl or $-\text{OC}(=\text{O})\text{R}^{13}$;

R^3 is halo, -OH, -OR⁴; $-\text{OC}(=\text{O})\text{R}^{13}$, -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), -N(C₁-C₆ alkyl)(S(O)_nR⁵), -S(O)_nR⁵, -N₃, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R⁶;

R^4 is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R⁶;

R^5 is each independently C₁-C₆ alkyl or aryl which are optionally substituted with one or more R⁶;

R⁶ is each independently selected from the group consisting of H, F, Cl, Br, I, ¹²³I, hydroxyl, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₆-C₁₂ aryl, wherein each R⁶ is optionally substituted with one or more of halogen, ¹²³I, ¹⁸F, hydroxyl, -OS(O)₂-aryl, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

R^8 and R^9 are each independently H or C₁-C₆ alkyl;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, F, Cl, Br, I, or ¹²³I;

R^{13} is C₁-C₆ alkyl; and

n is 0, 1, or 2;

wherein at least one of R^{11a}, R^{11b}, R^{11c} and R^{11d} is methyl F, Cl, Br, I, or ¹²³I.

2. The compound of claim 1, wherein at least two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are methyl, F, Cl, Br, I, or ^{123}I .
3. The compound of claim 1, wherein any two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are independently methyl, F, Cl, Br, I, or ^{123}I and the remaining two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are each H.
4. The compound of claim 1, wherein R^{11a} and R^{11b} are each H; and R^{11c} and R^{11d} are each independently methyl, F, Cl, Br, I, or ^{123}I .
5. The compound of claim 4, wherein R^{11c} and R^{11d} are each independently methyl, Cl, or Br.
6. The compound of claim 5, wherein R^{11c} and R^{11d} are each Cl.
7. The compound of claim 1, wherein R^{11a} and R^{11c} are each H; and R^{11b} and R^{11d} are each independently methyl, F, Cl, Br, I, or ^{123}I .
8. The compound of claim 7, wherein R^{11b} and R^{11d} are each independently methyl, Cl, or Br.
9. The compound of claim 8, wherein R^{11b} and R^{11d} are each Cl.
10. The compound of claim 1, wherein X is $-S(O)_2-$.
11. The compound of claim 1, wherein X is $-C(R^8R^9)-$ and R^8 and R^9 are each independently C_1-C_3 alkyl.
12. The compound of claim 11, wherein R^8 and R^9 are each methyl.
13. The compound of claim 1, wherein R^1 and R^2 are each independently hydroxyl or $-OC(=O)R^{13}$.

14. The compound of claim 13, wherein R¹ and R² are both hydroxyl.
15. The compound of claim 13, wherein R¹ and R² are both -OC(=O)R¹³.
16. The compound of claim 13, wherein R¹ and R² are both -OC(=O)R¹³, wherein R¹³ is methyl.
17. The compound of claim 1, wherein R¹ is H.
18. The compound of claim 1, wherein R³ is -OH.
19. The compound of claim 1, wherein R³ is -OC(=O)R¹³.
20. The compound of claim 1, wherein R³ is -OC(=O)R¹³, wherein R¹³ is methyl.
21. The compound of claim 1, wherein R³ is -OR⁴ and R⁴ is C₁-C₆ alkyl.
22. The compound of claim 21, wherein R⁴ is a methyl, ethyl, *n*-propyl, or *i*-propyl.
23. The compound of claim 1, wherein R³ is F.
24. The compound of claim 1, wherein R³ is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom.
25. The compound of claim 1, wherein R³ is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine.

26. The compound of claim 1, wherein R³ is -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), -N(C₁-C₆ alkyl)(S(O)_nR⁵) or -S(O)_nR⁵.

27. The compound of claim 26, wherein R³ is -NH₂, -NHC(=O)(C₁-C₄ alkyl), -N[(C(=O)(C₁-C₄ alkyl)]₂, -NHS(O)_n(C₁-C₃ alkyl), -N[C(=O)(C₁-C₄ alkyl)][(S(O)_n(C₁-C₃ alkyl)], -N[C₁-C₆ alkyl][S(O)_n(C₁-C₃ alkyl)], or -S(O)_n(C₁-C₃ alkyl).

28. The compound of claim 1, wherein each R¹³ is C₁-C₄ alkyl.

29. The compound of claim 28, wherein each R¹³ is methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *tert*-butyl, *i*-butyl, or *sec*-butyl.

30. The compound of claim 1, wherein R¹ and R² are each independently -OH or -OC(=O)R¹³, wherein R¹³ is methyl.

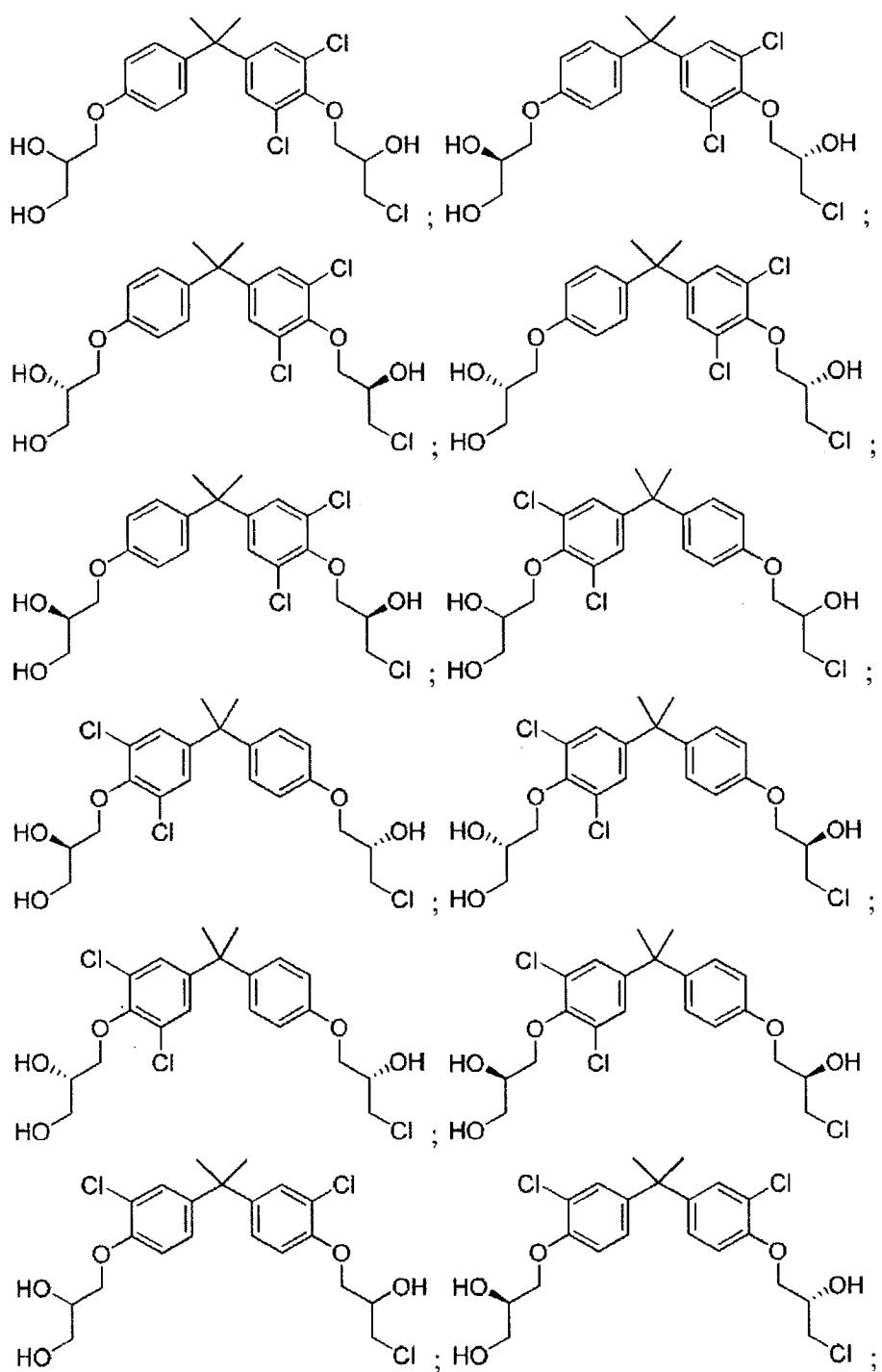
31. The compound of claim 1, wherein at least one of R¹, R² and R³ is -OC(=O)R¹³, wherein R¹³ is methyl.

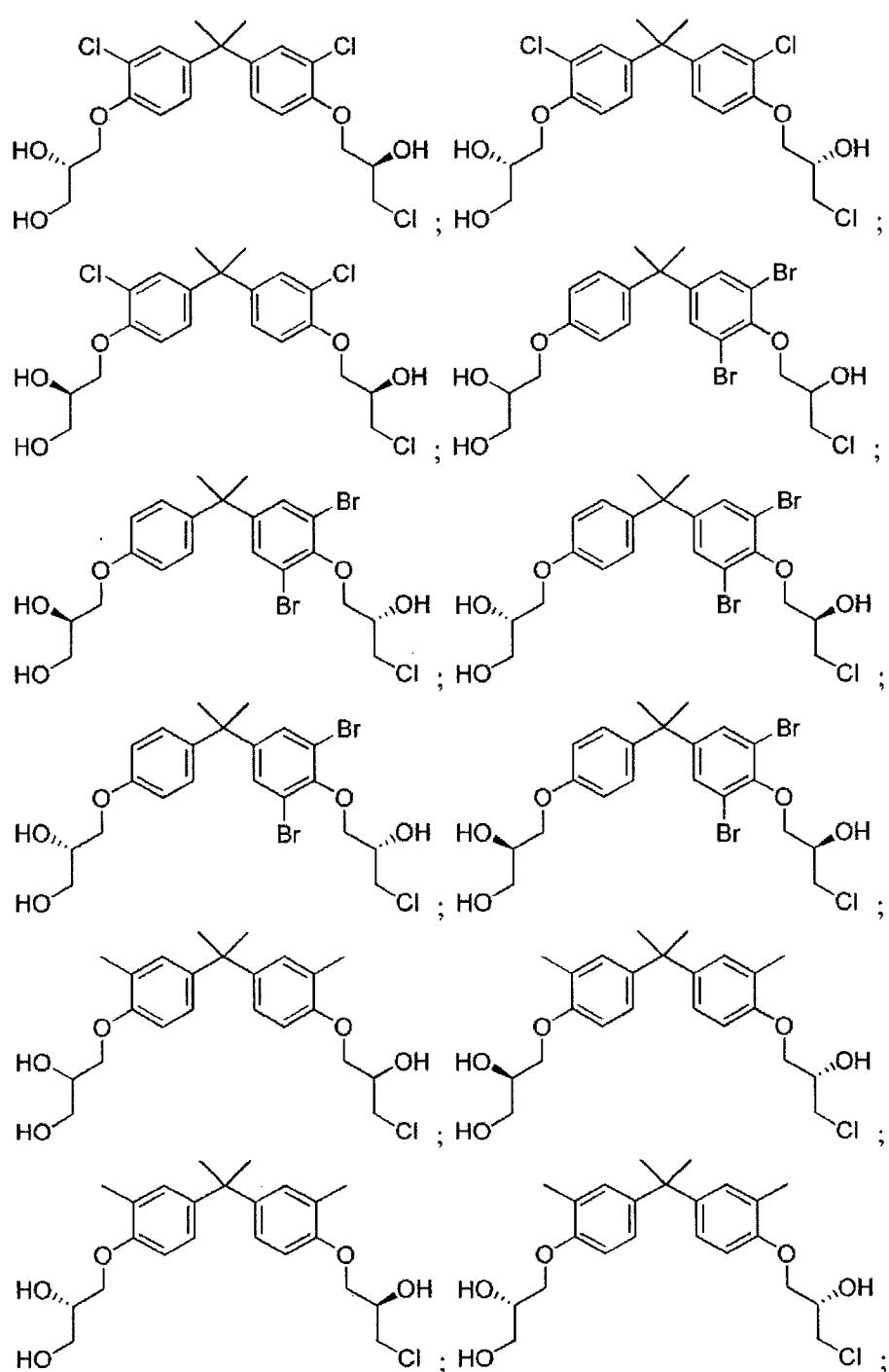
32. The compound of claim 1, wherein any two of R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

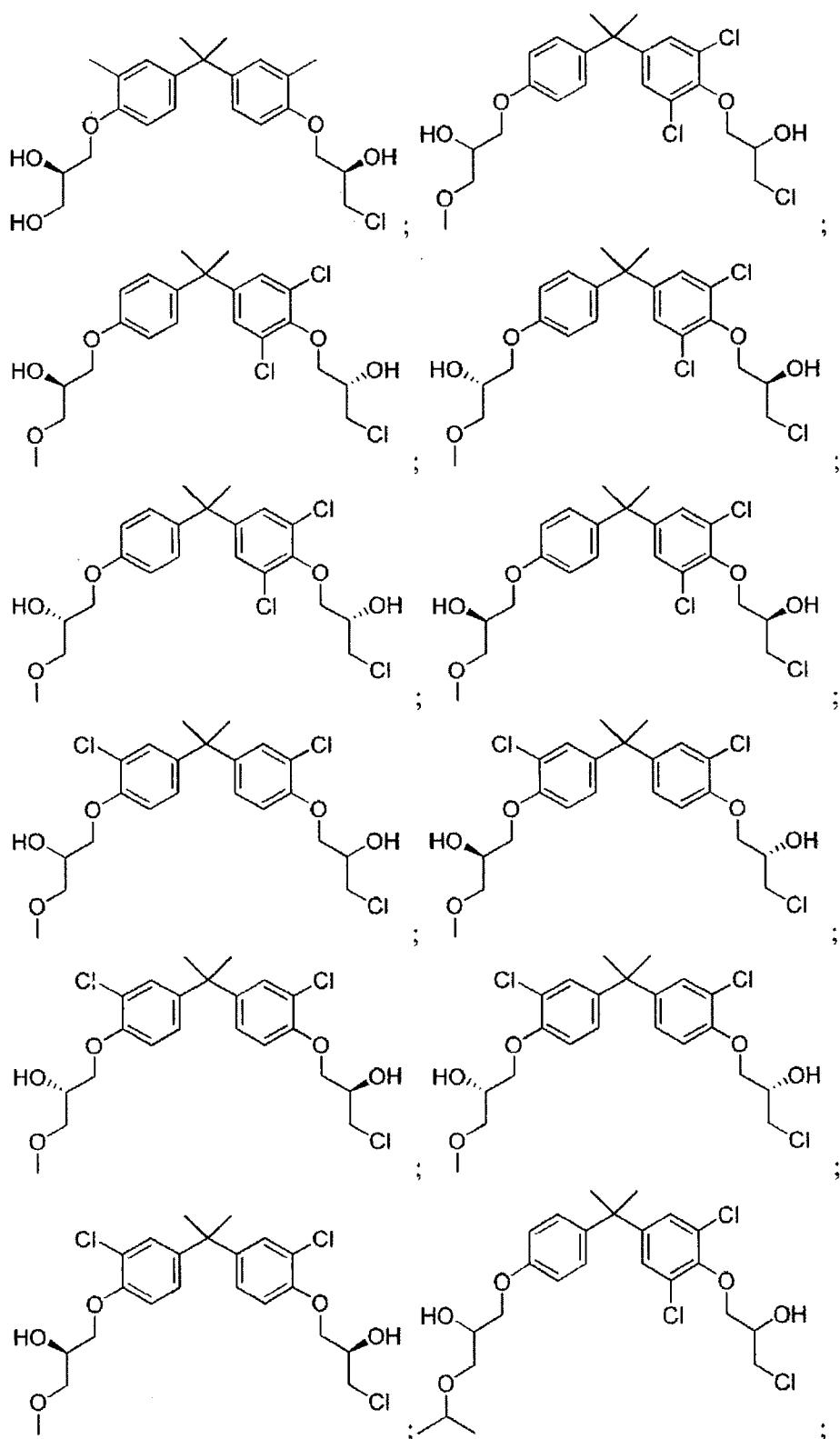
33. The compound of claim 32, wherein R¹ and R² are each -OC(=O)R¹³, wherein R¹³ is methyl.

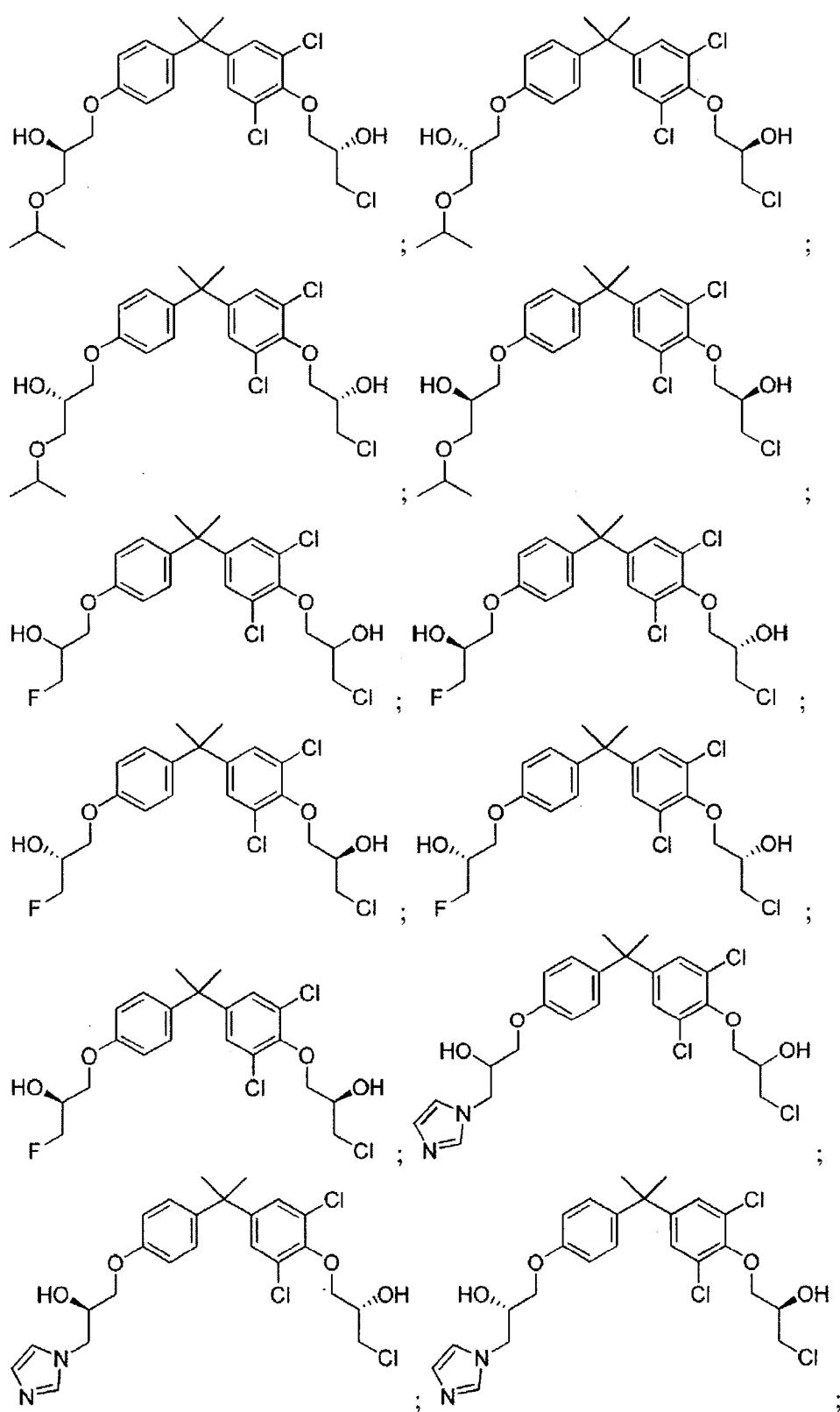
34. The compound of claim 1, wherein R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

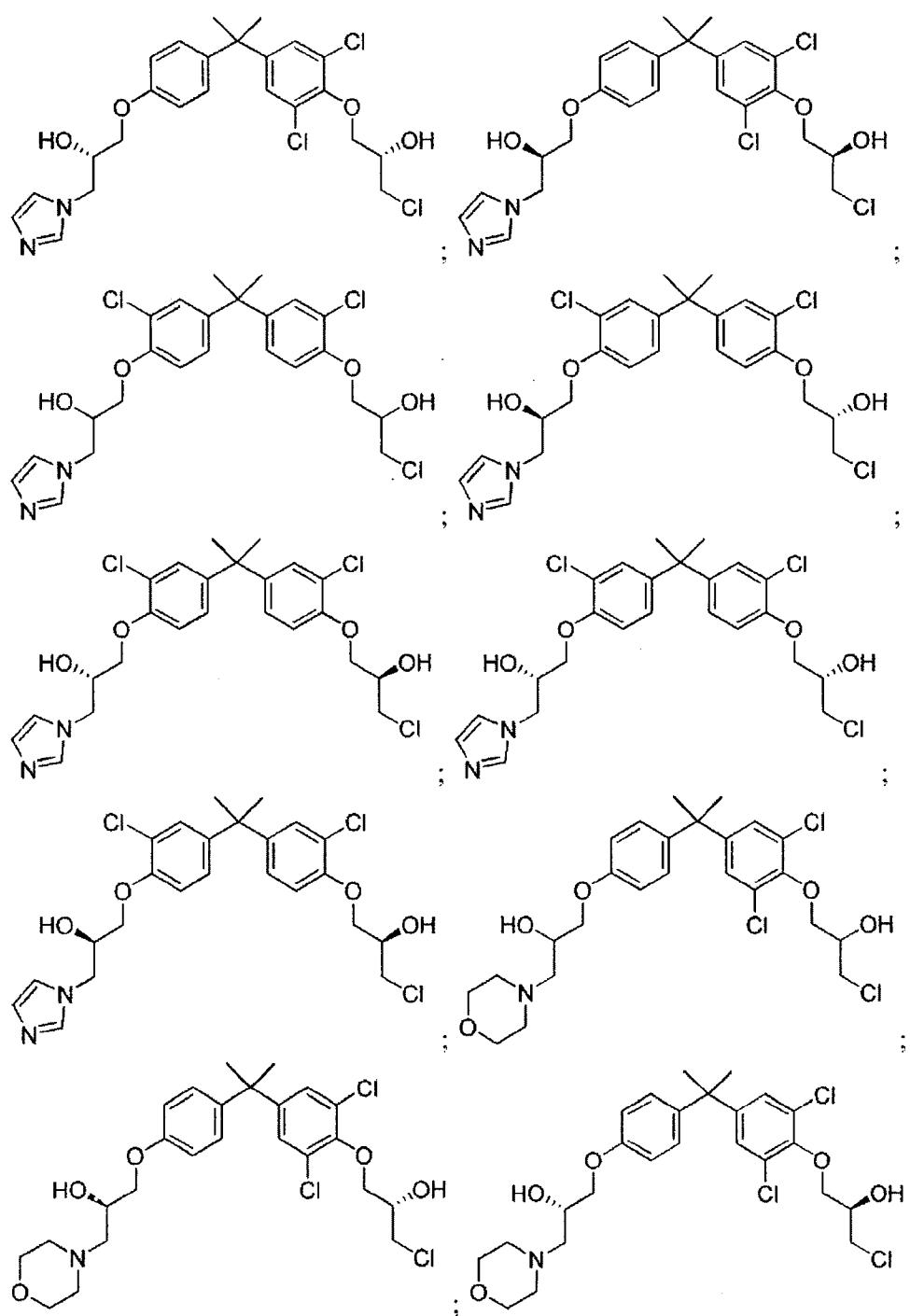
35. The compound of claim 1, wherein the compound has one of the following structures:

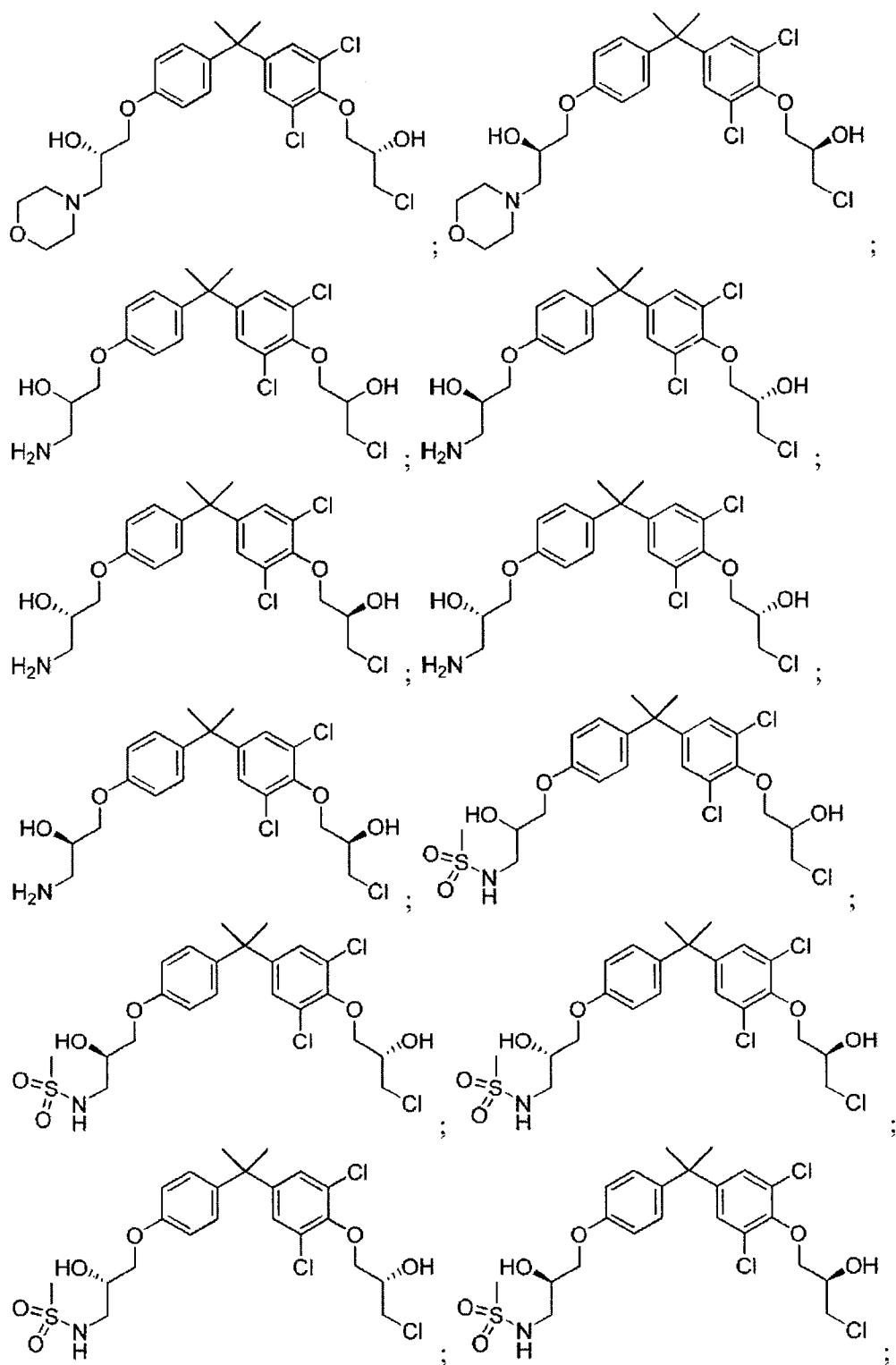


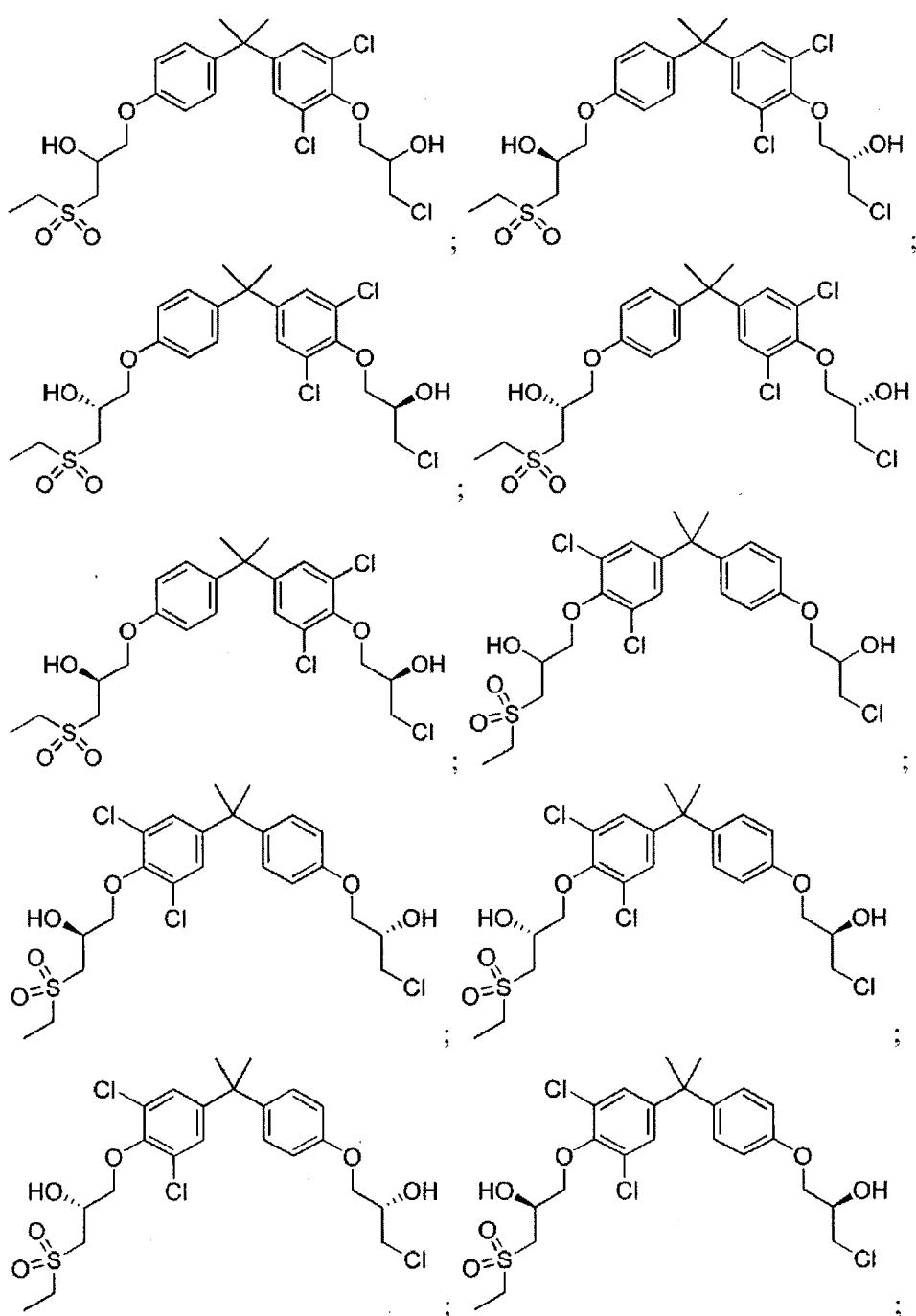


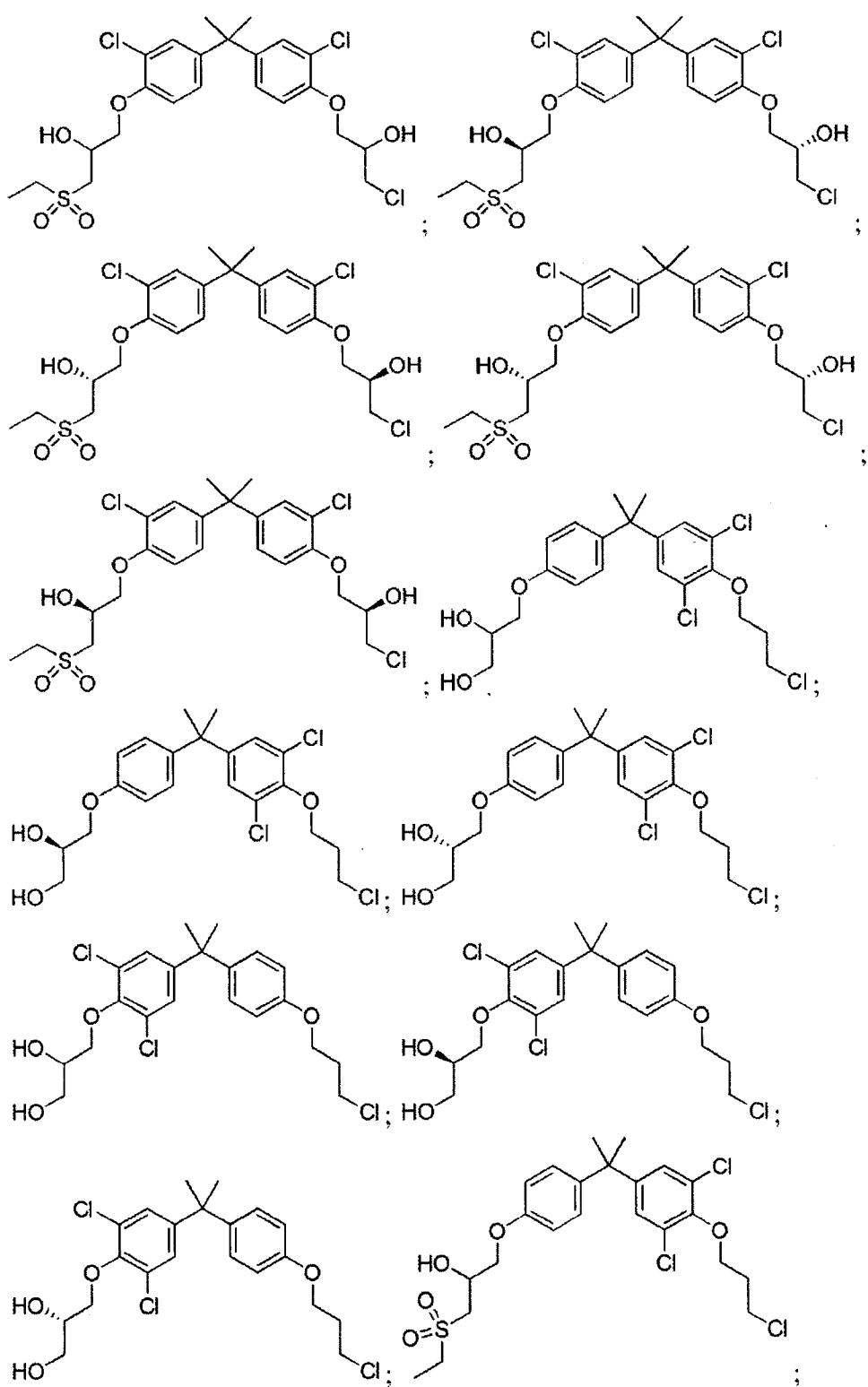


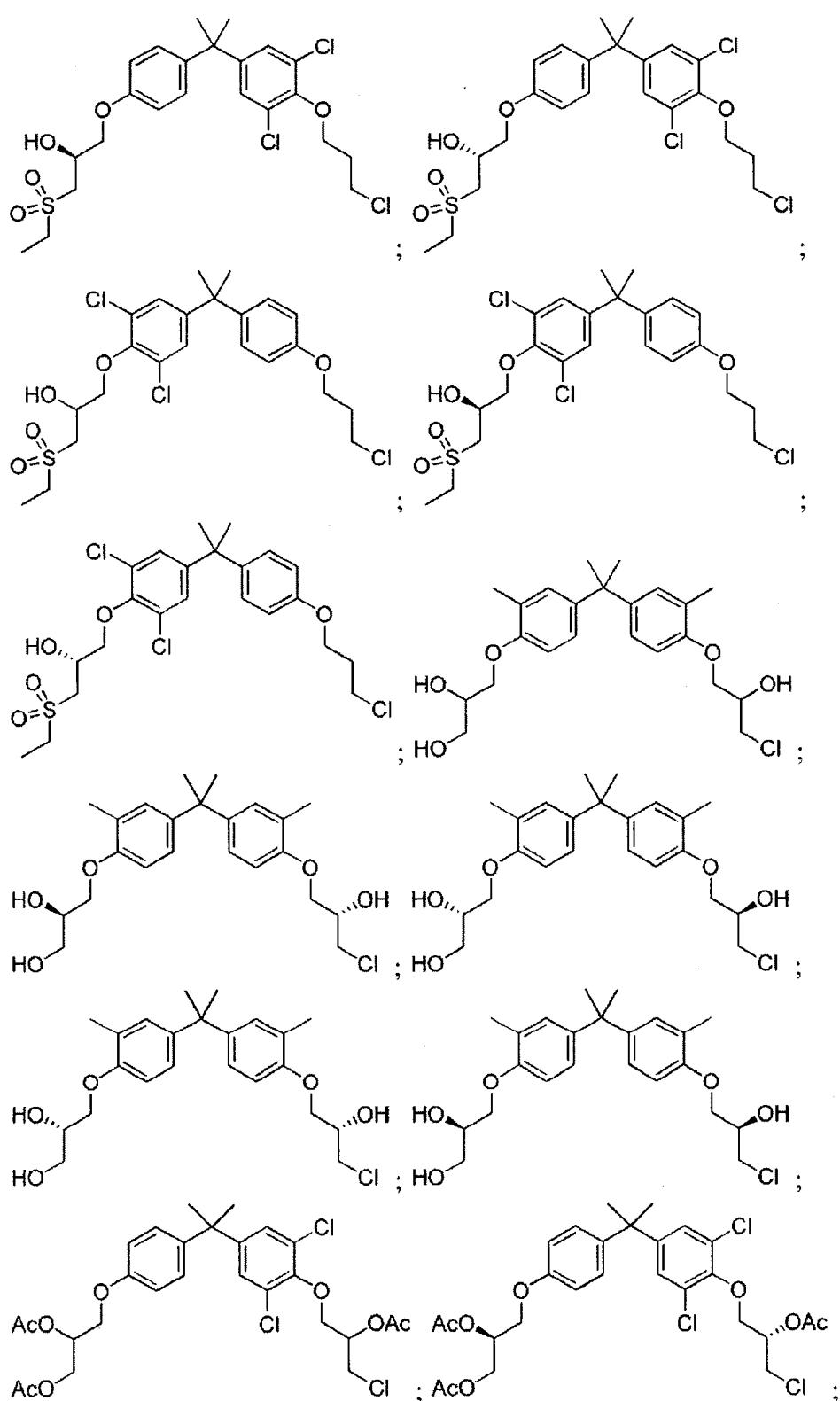


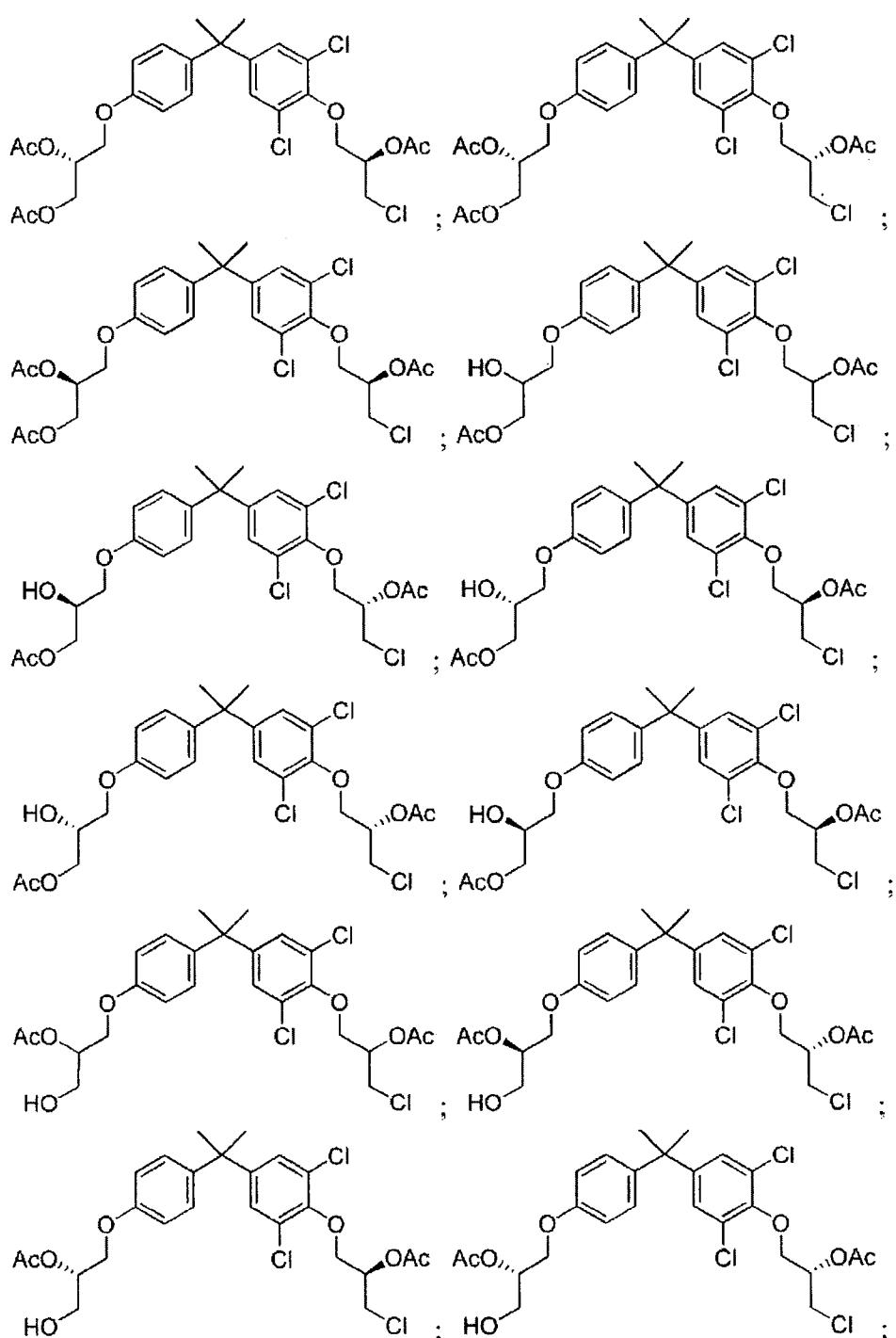


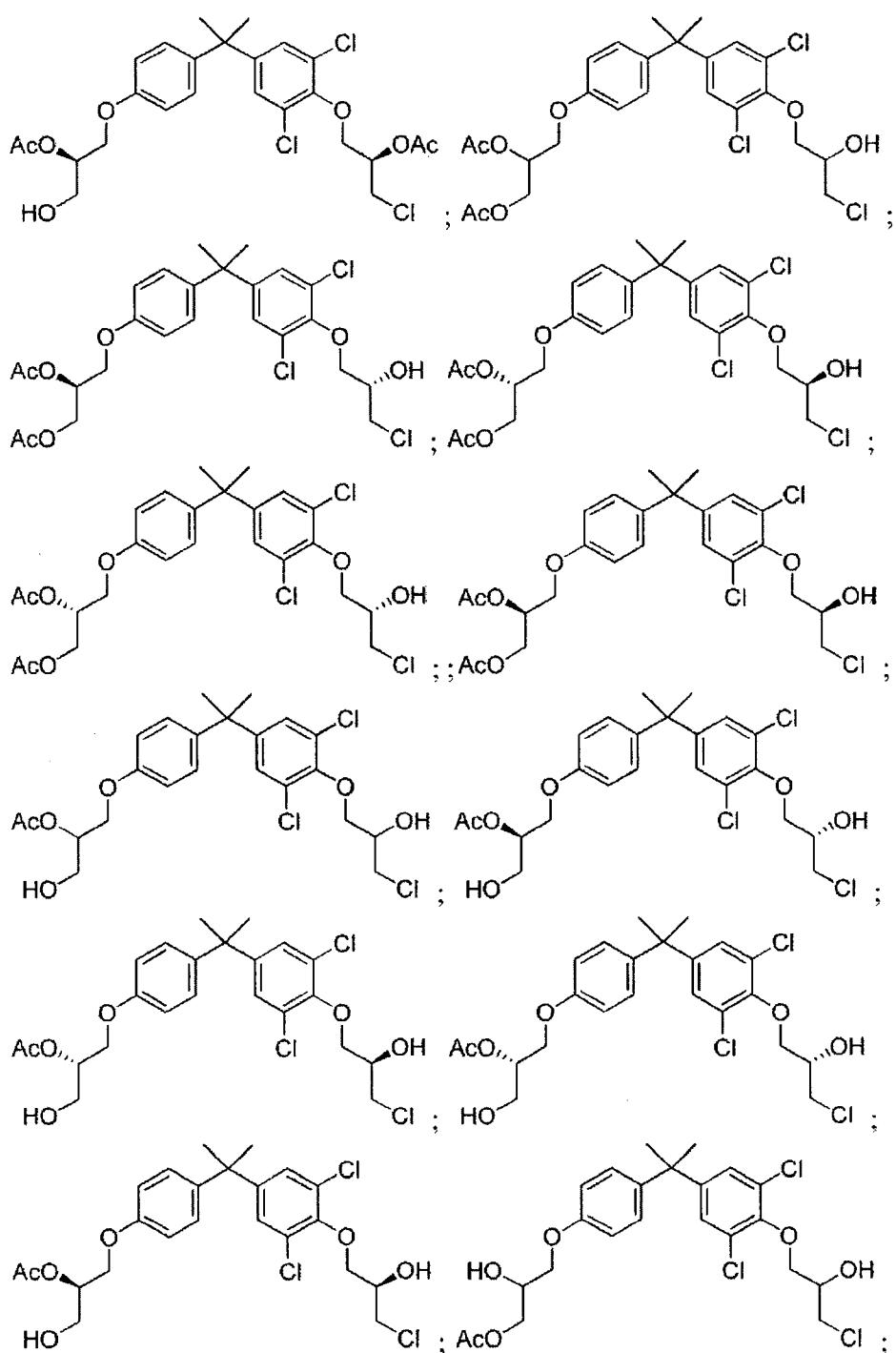


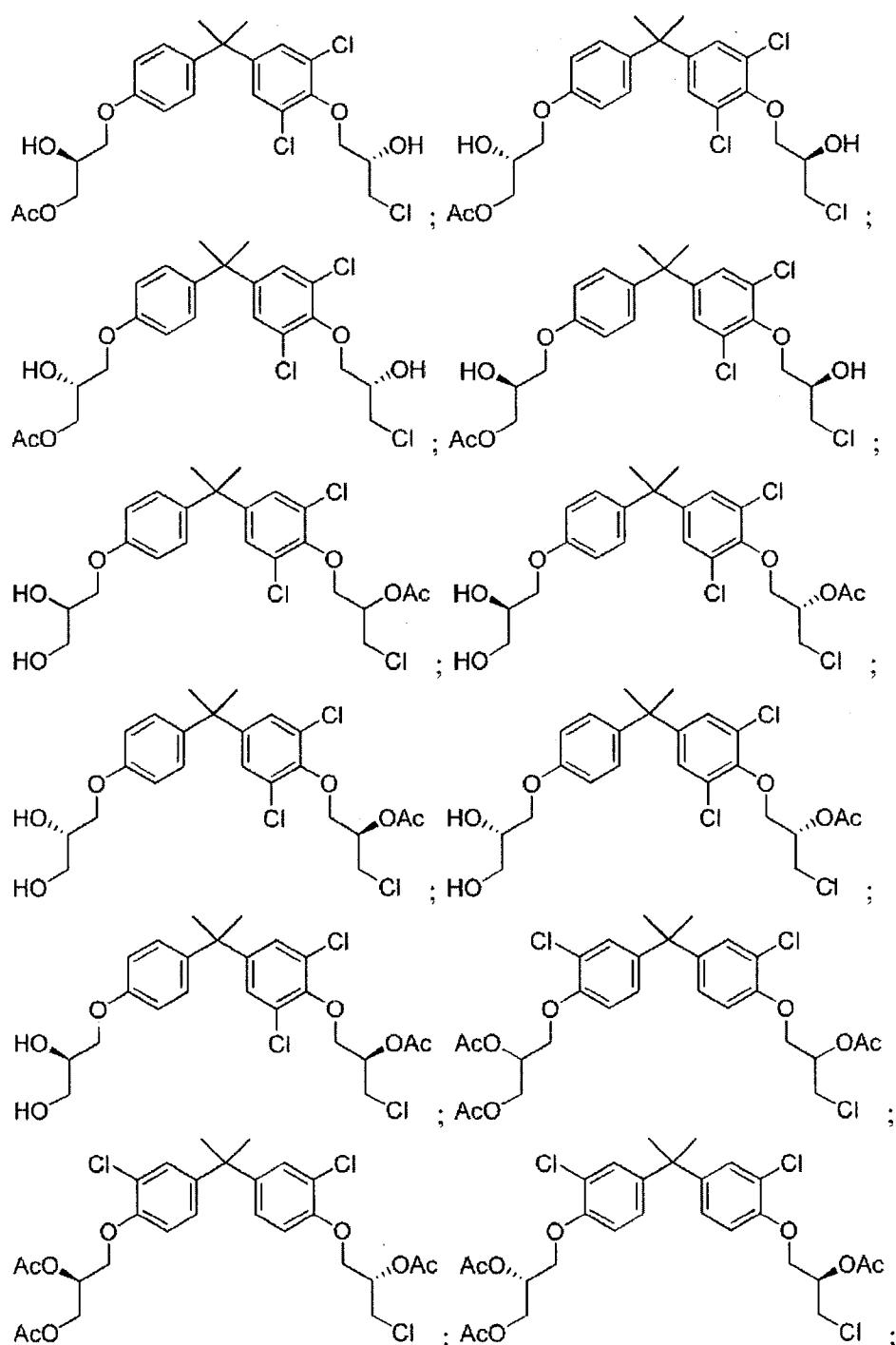


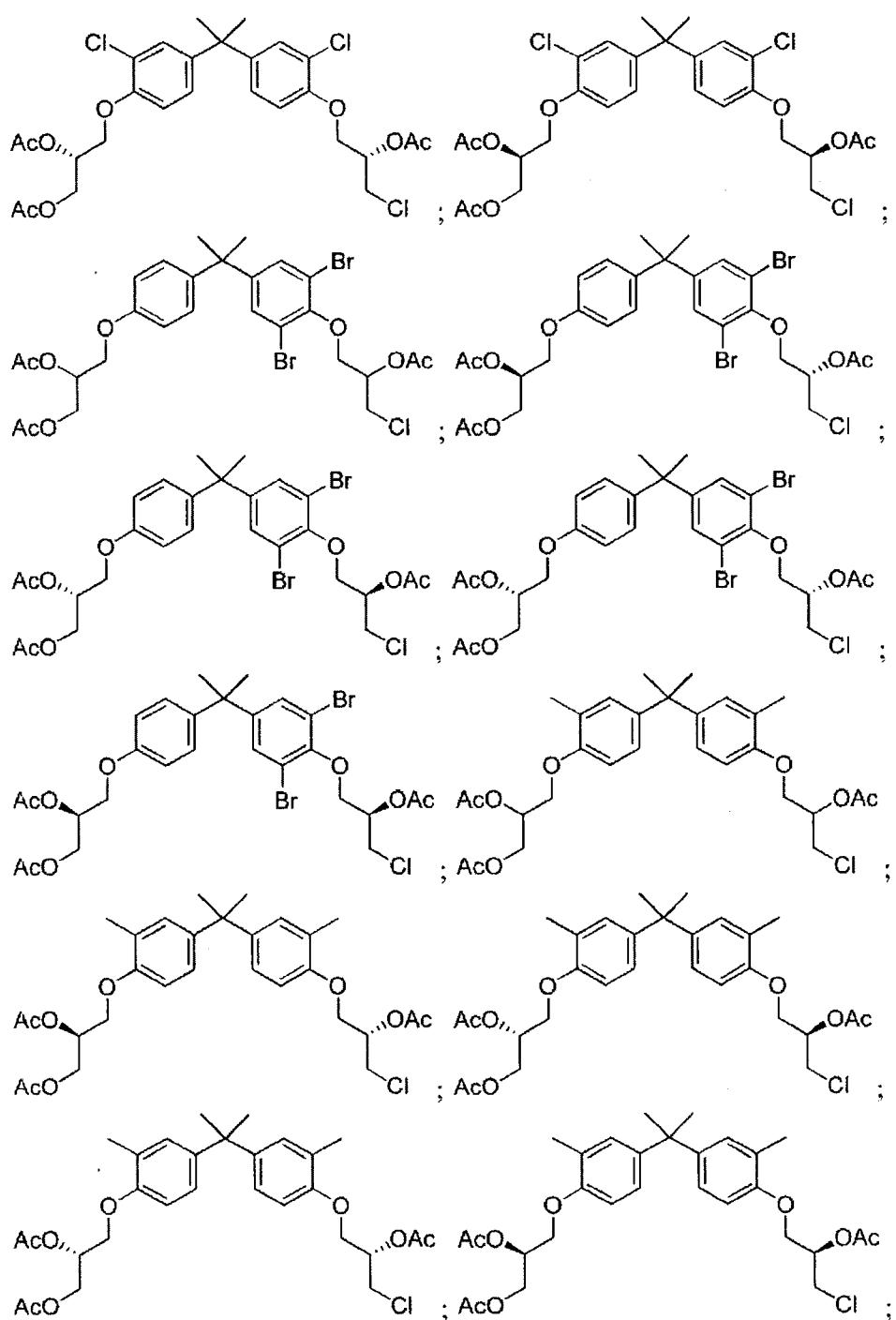


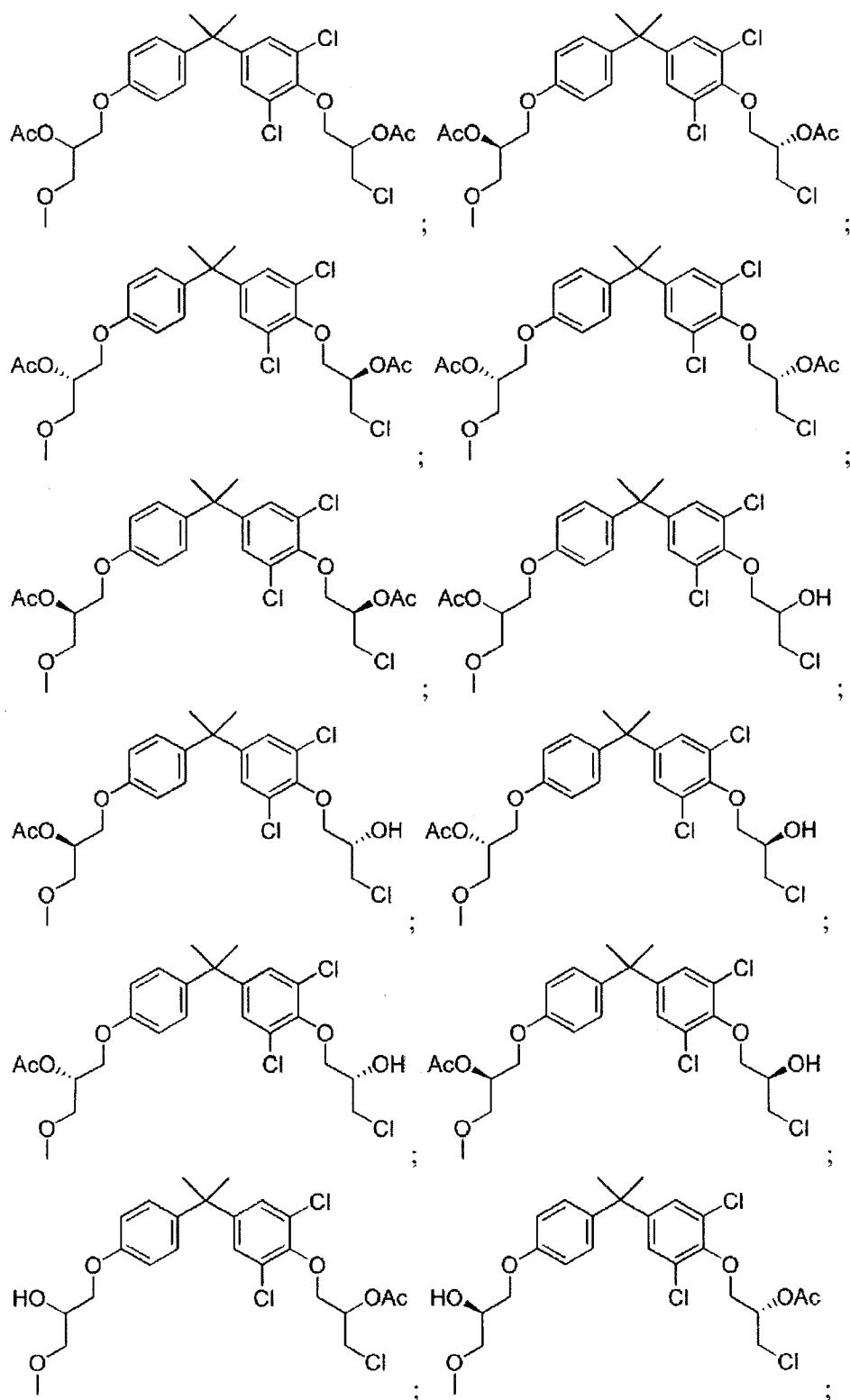


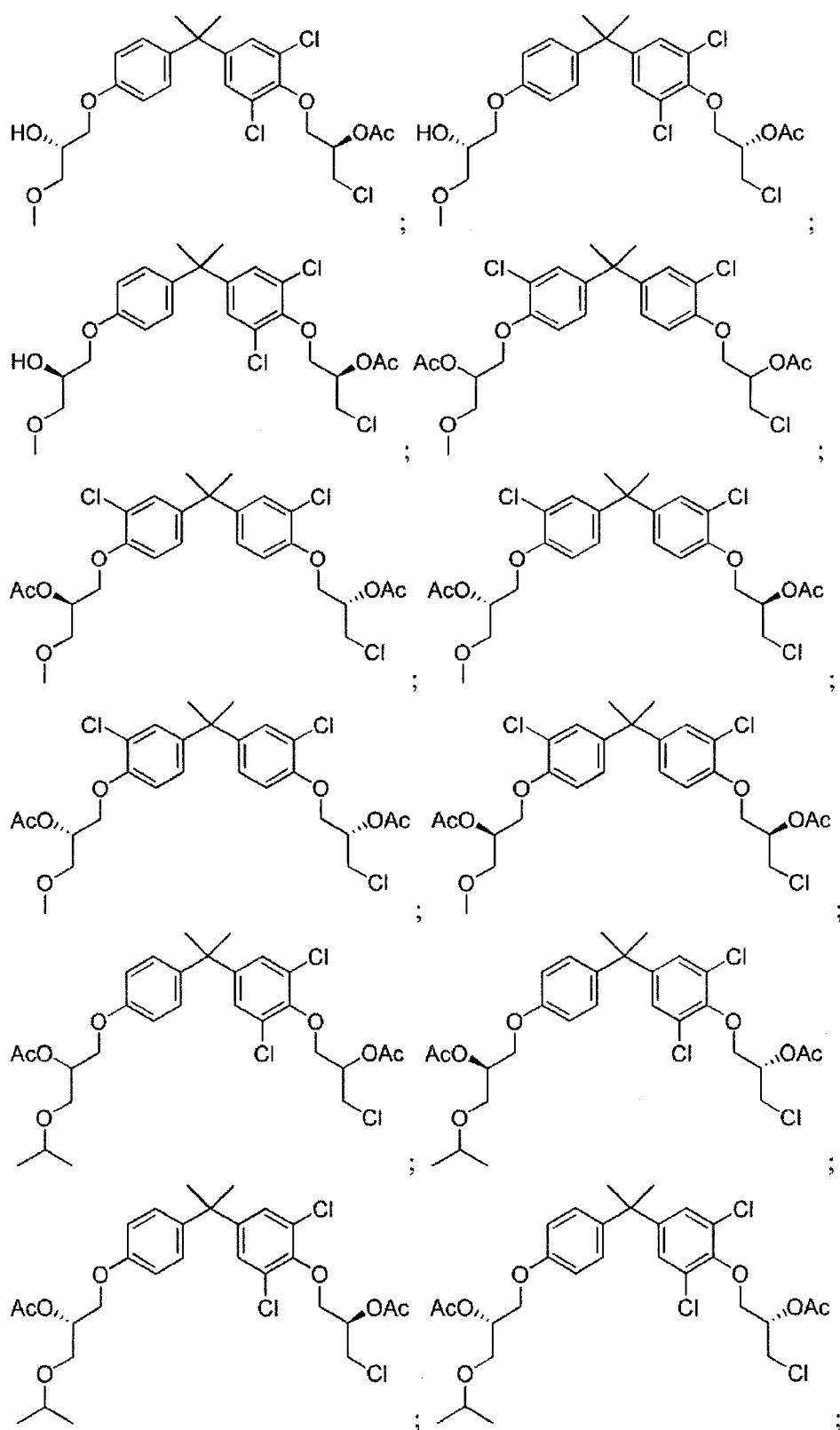


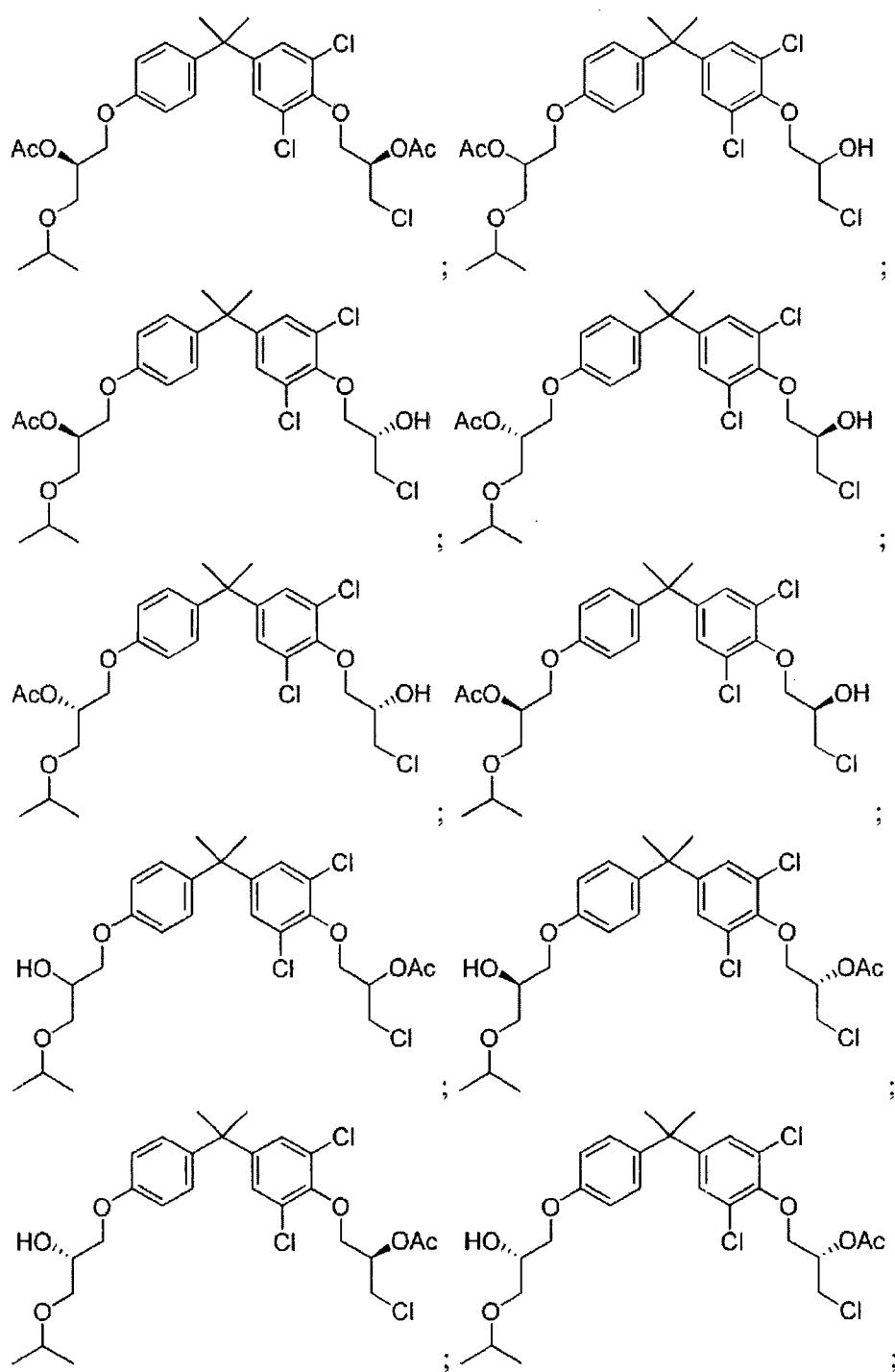


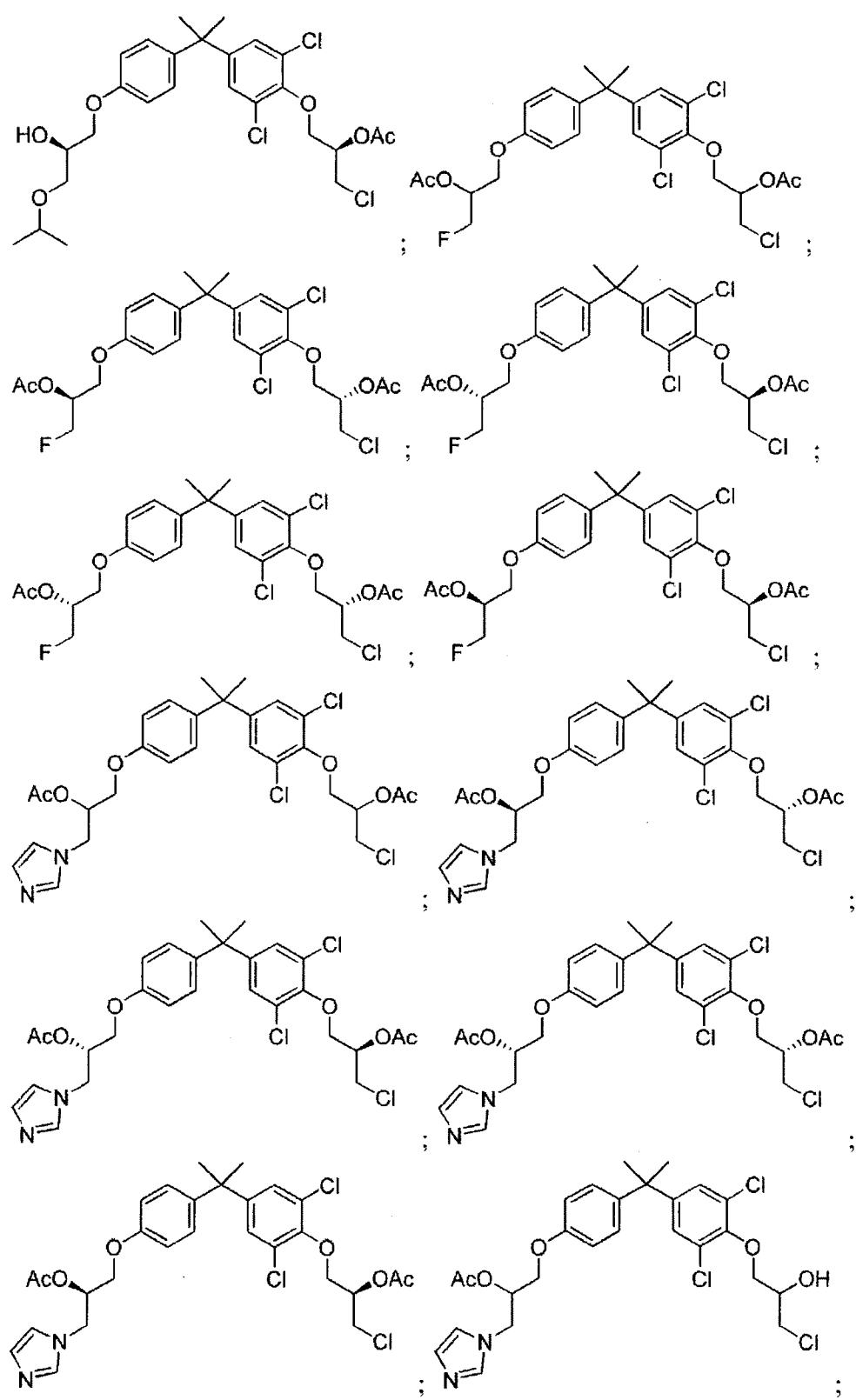


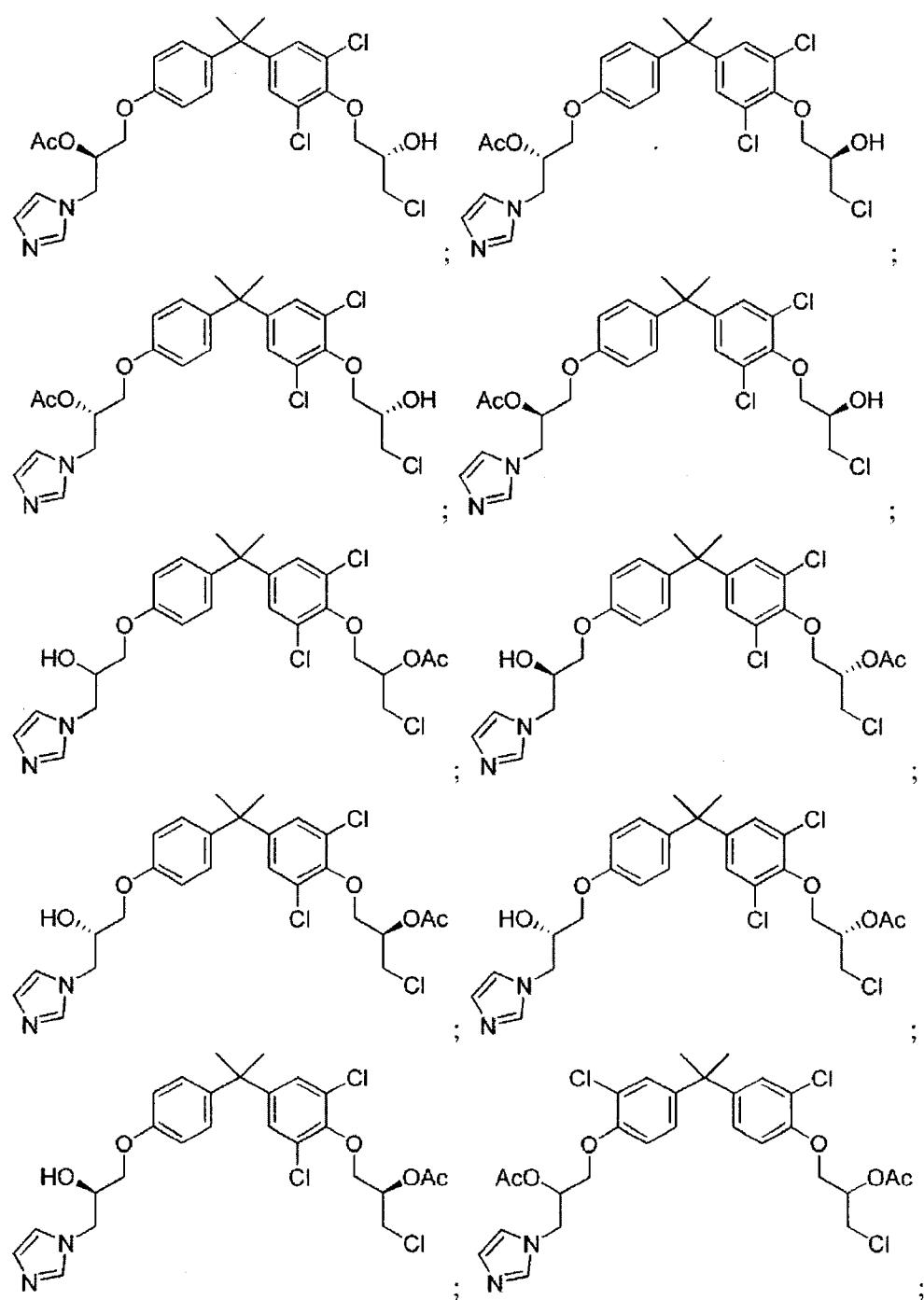


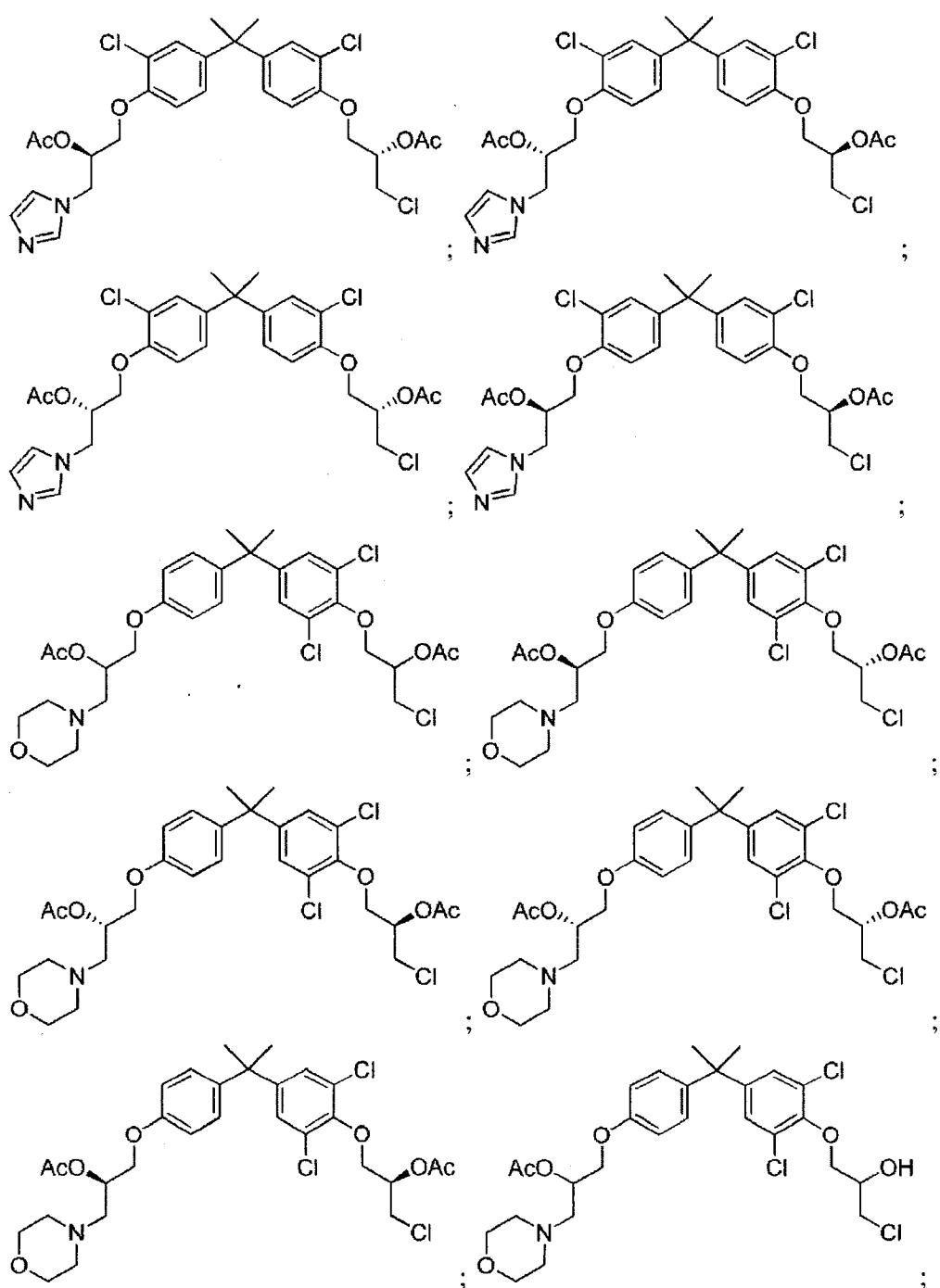


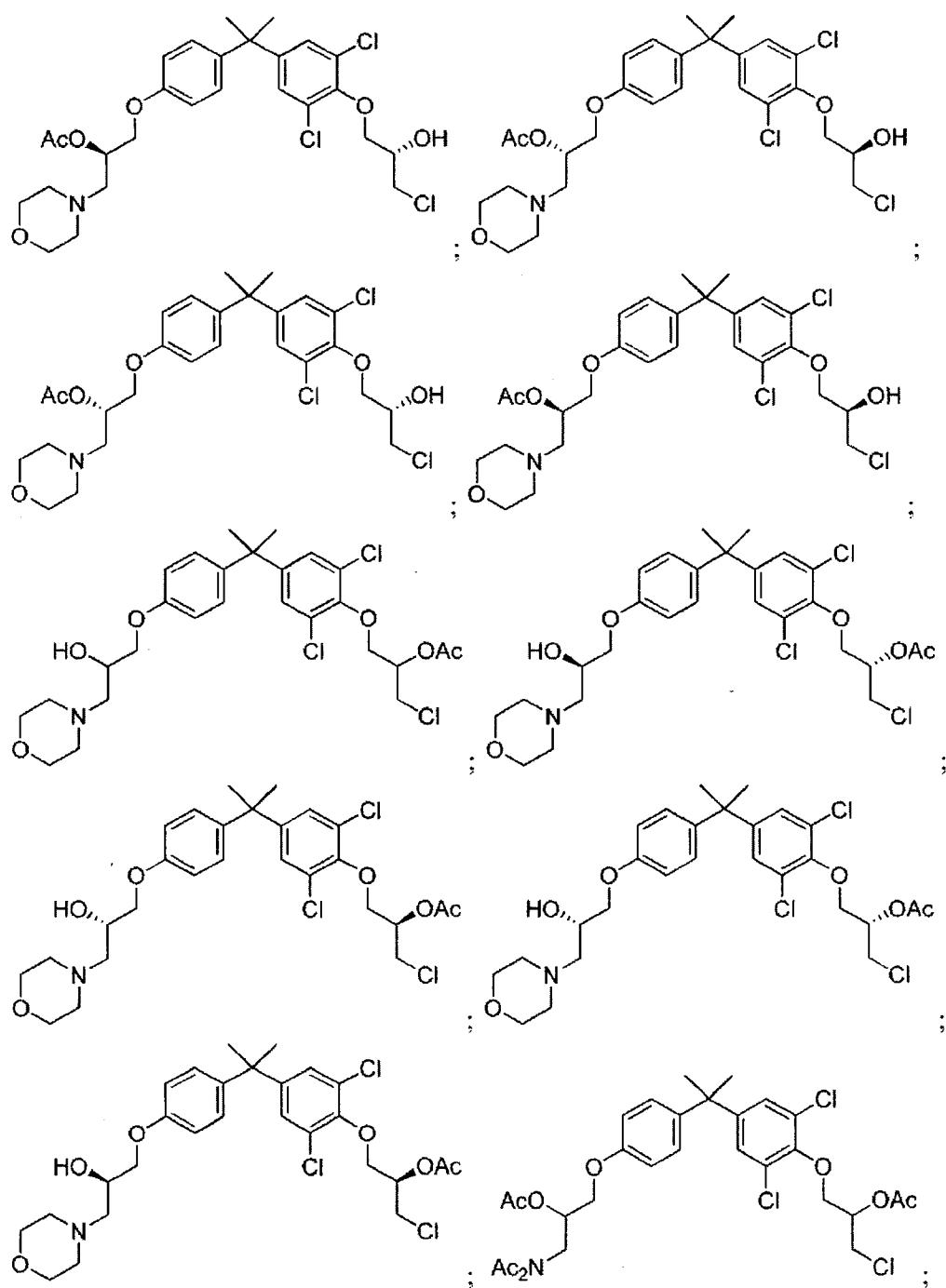


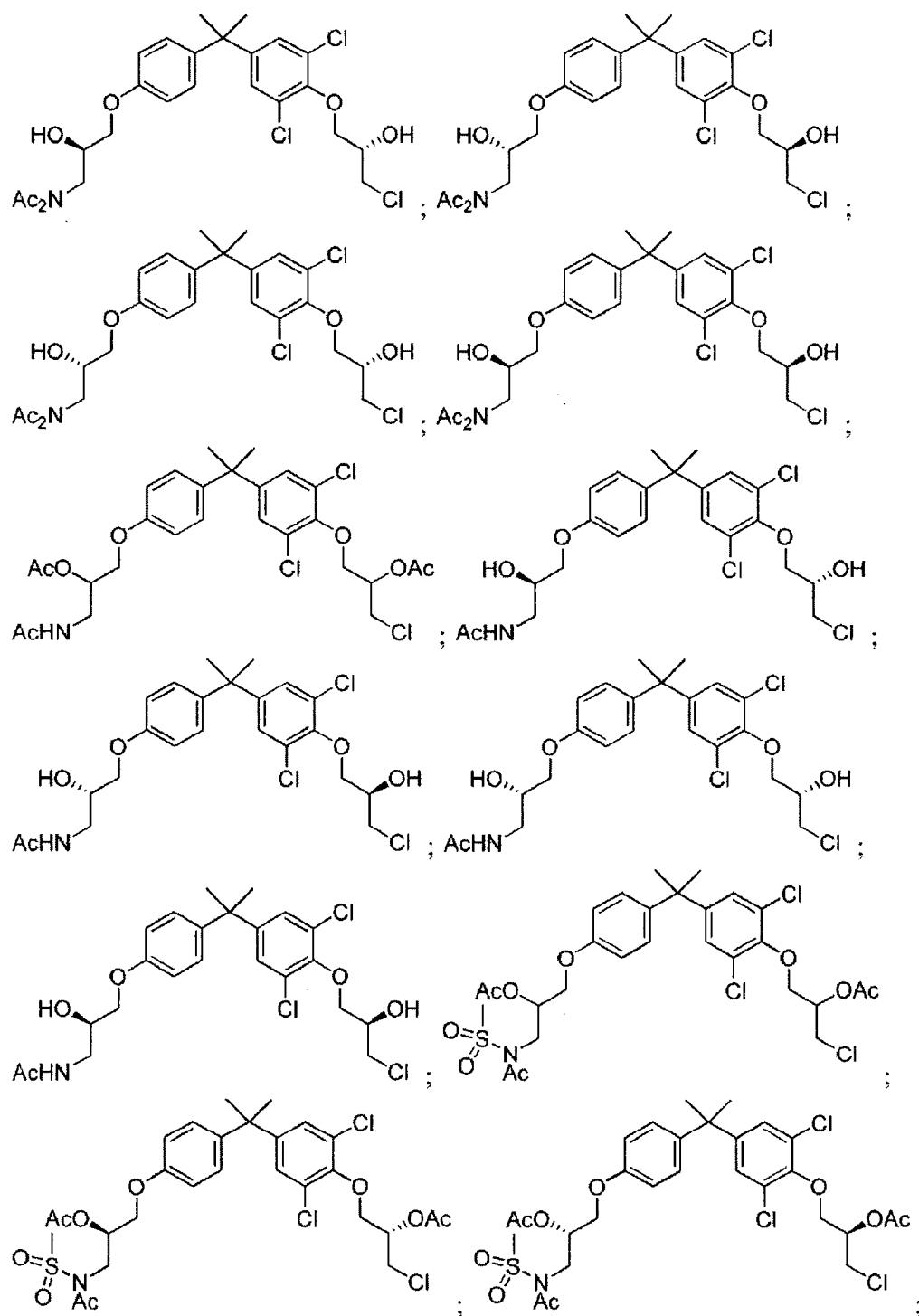


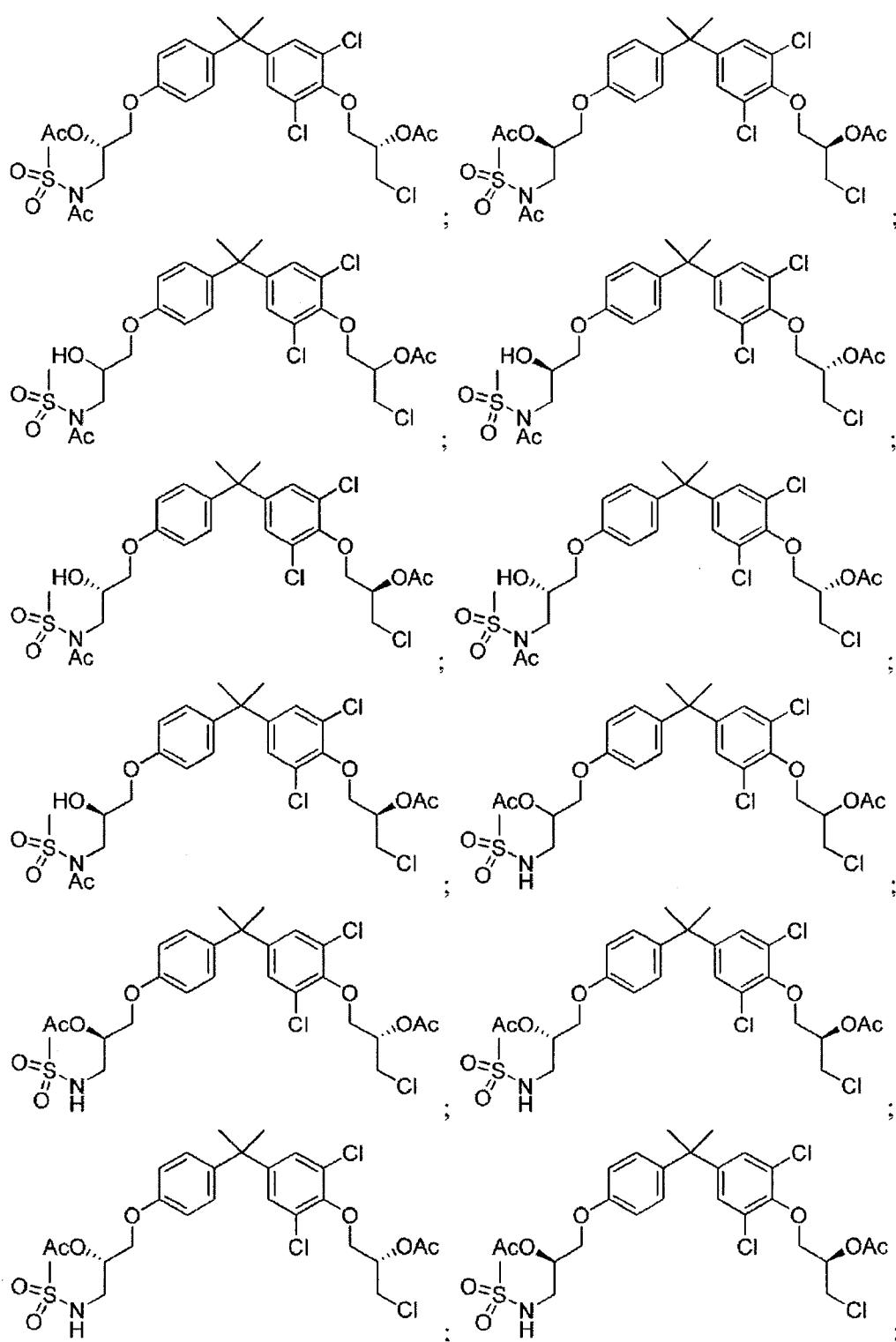


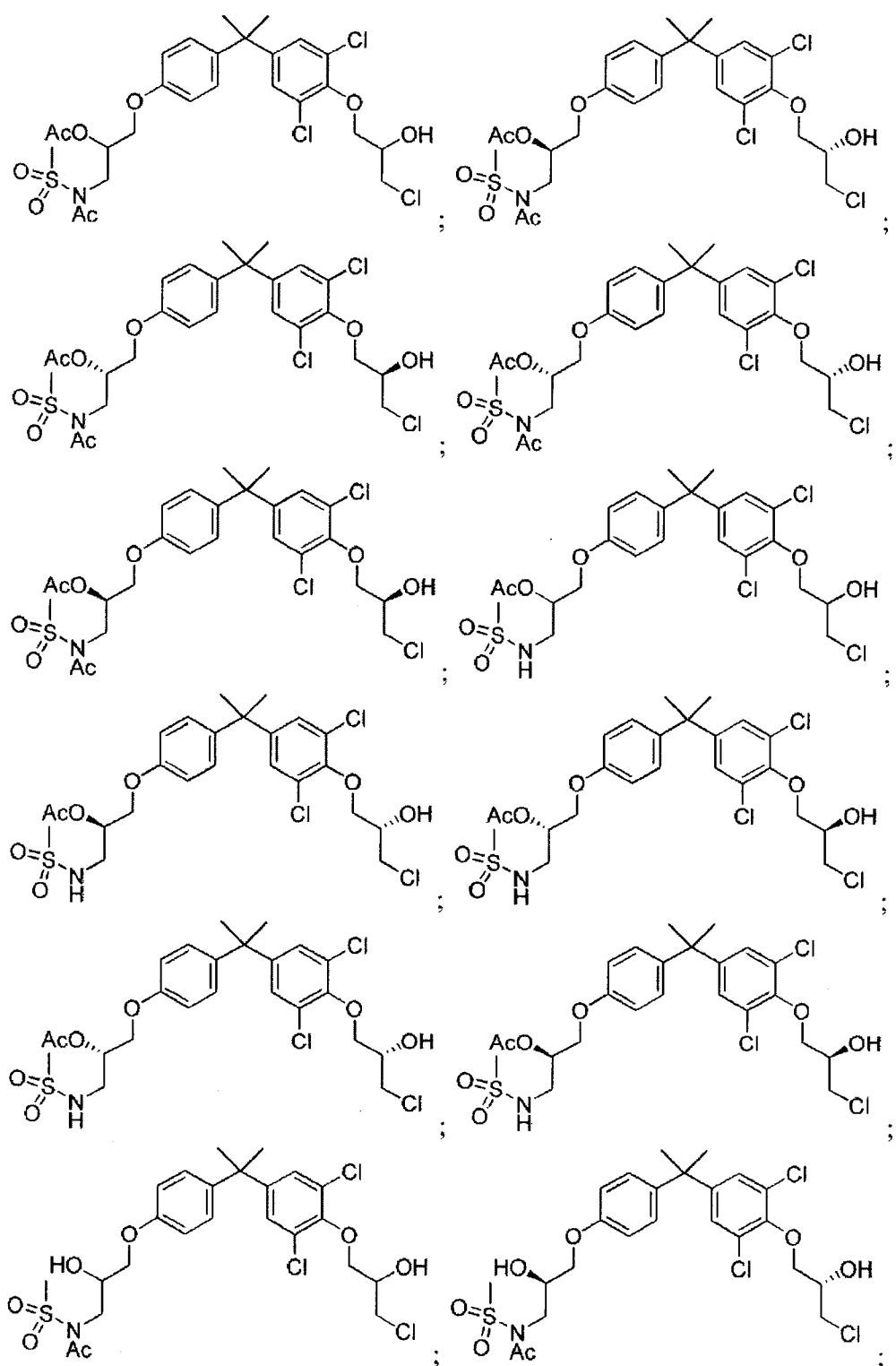


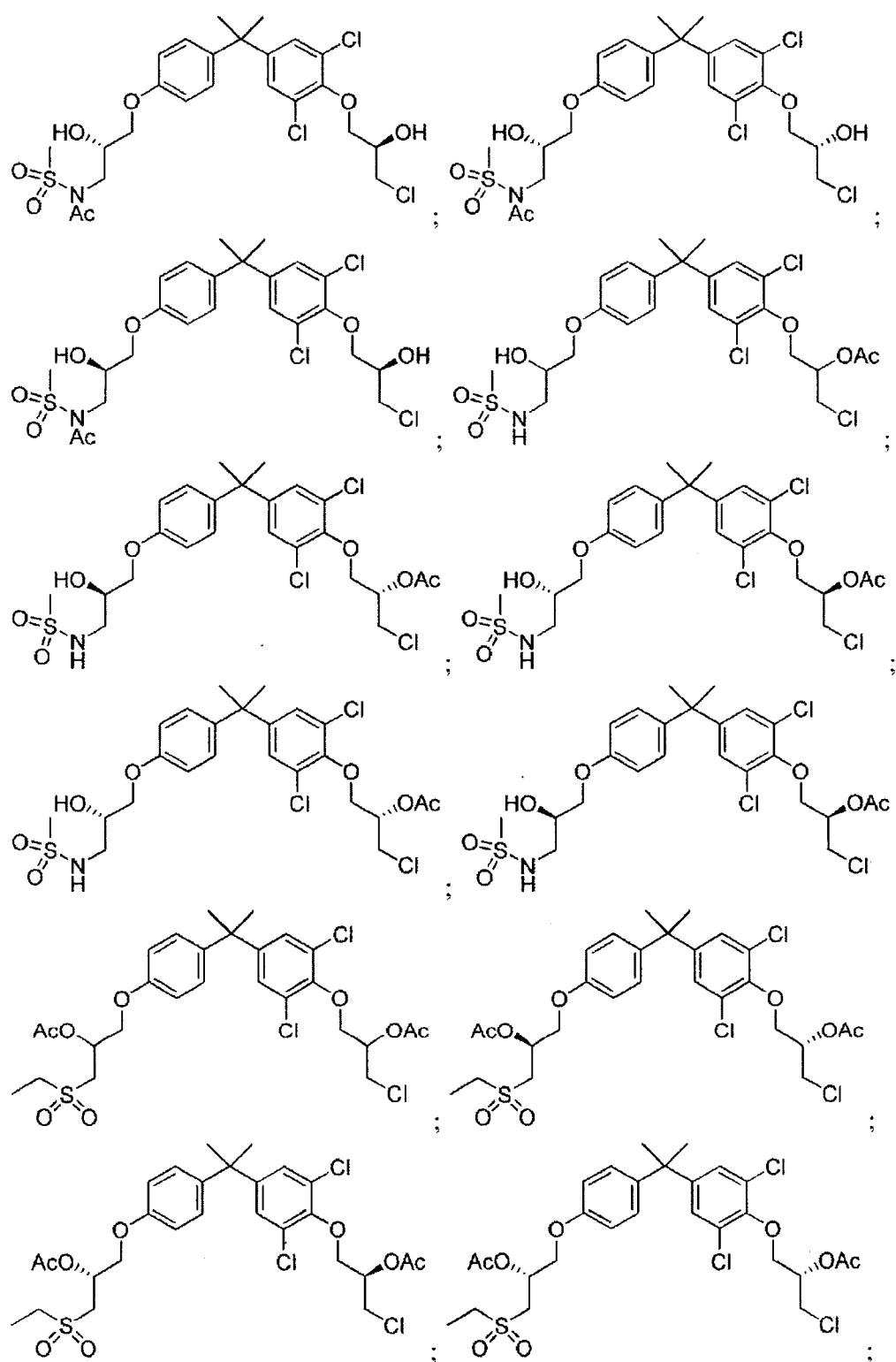


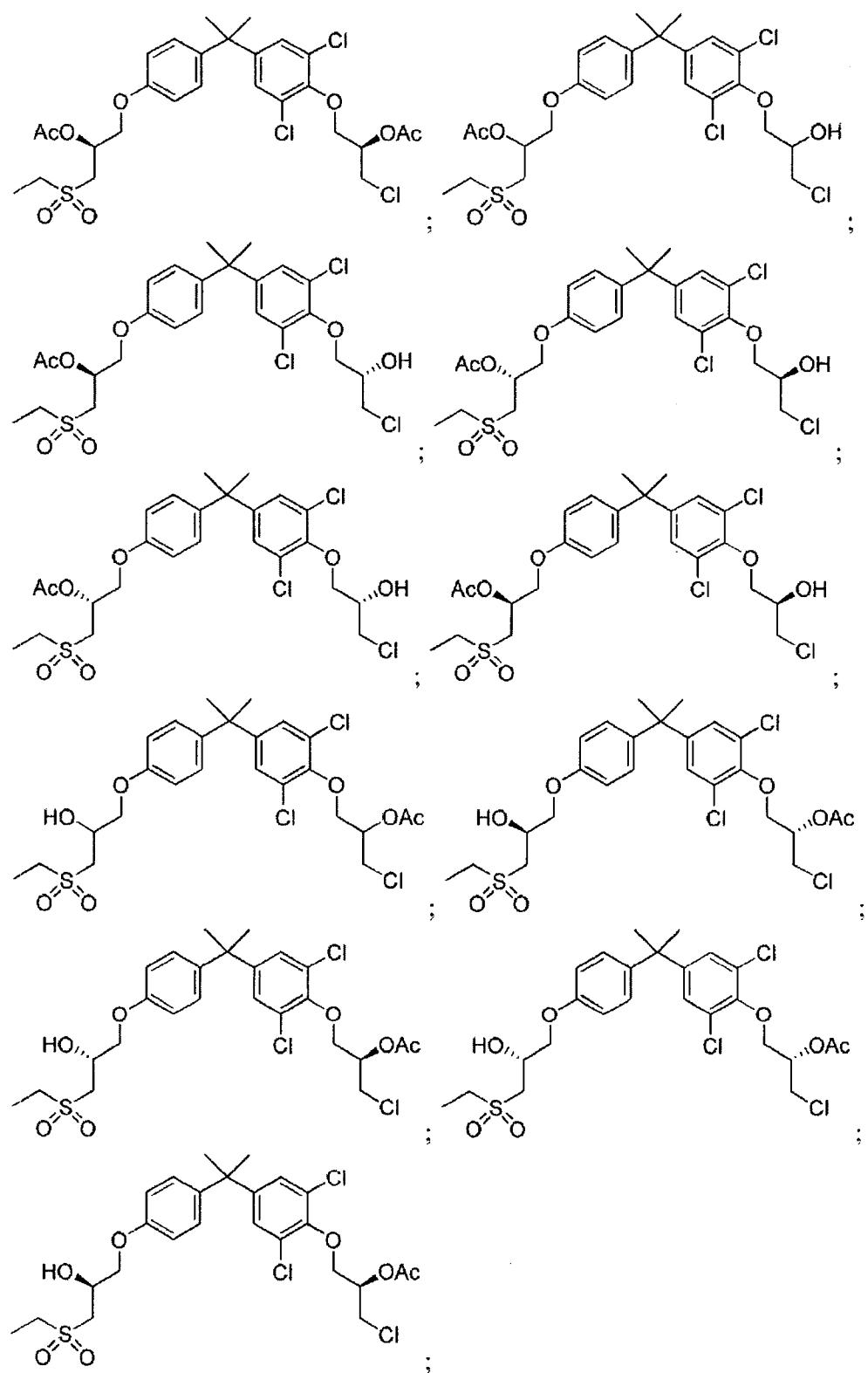


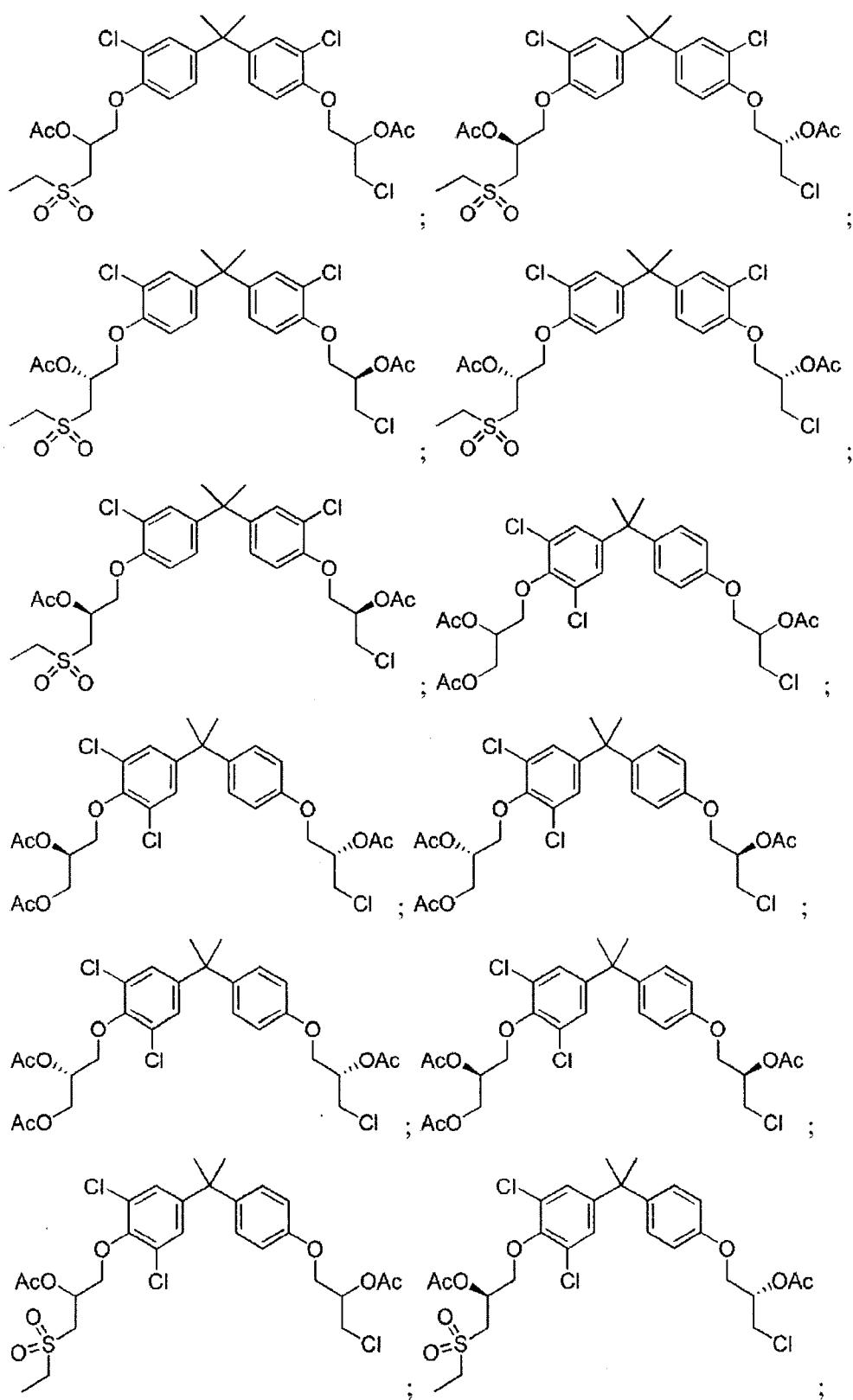


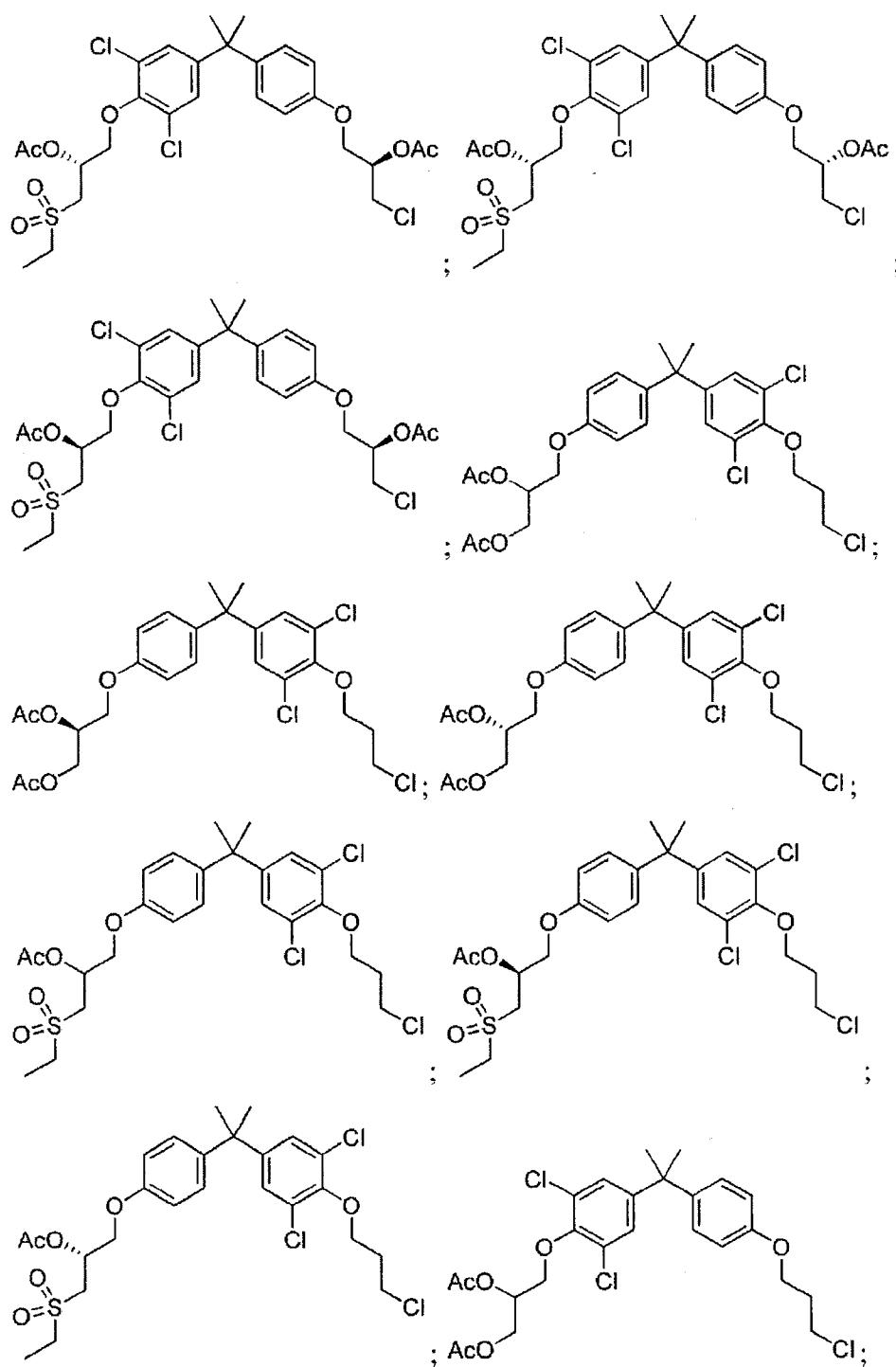


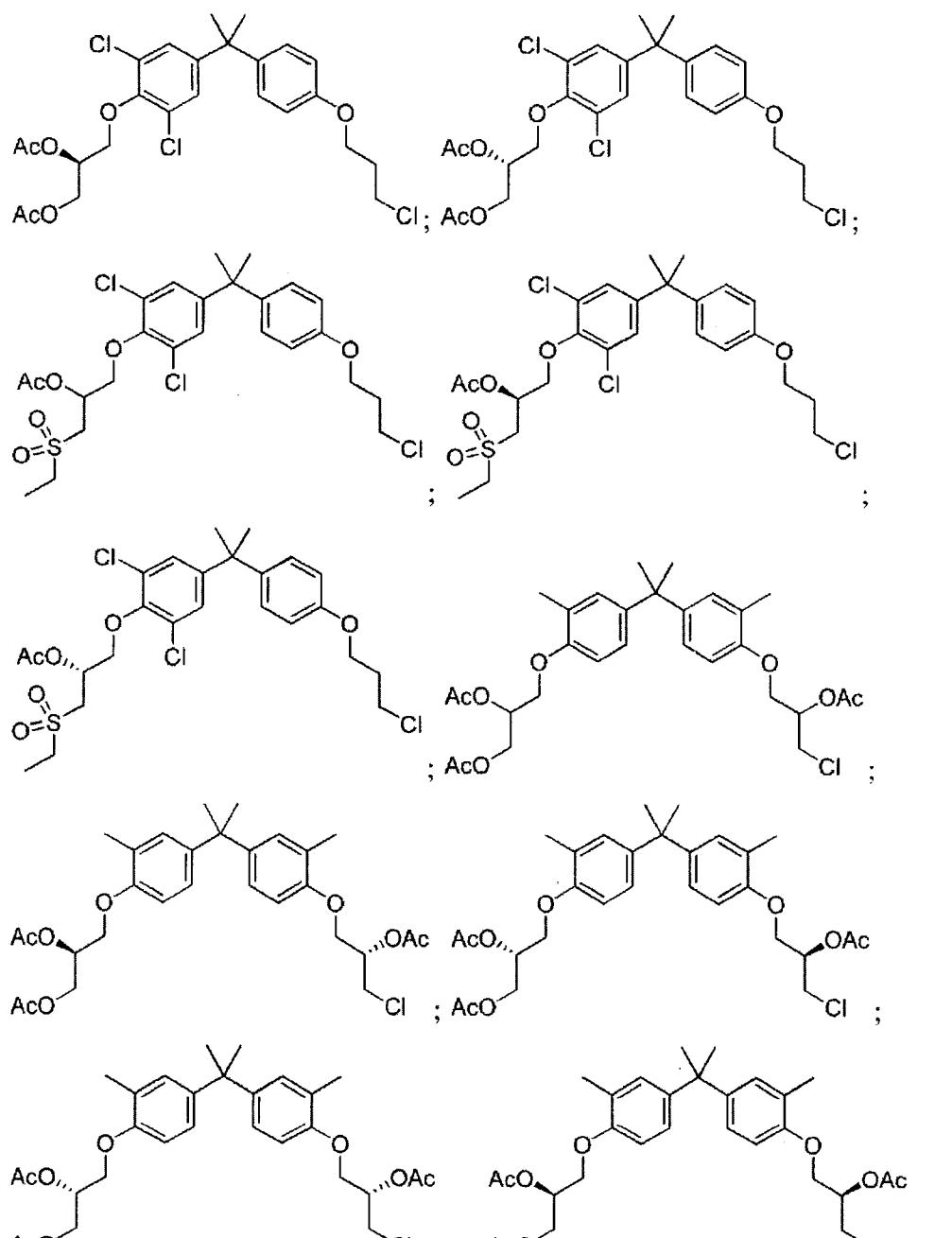






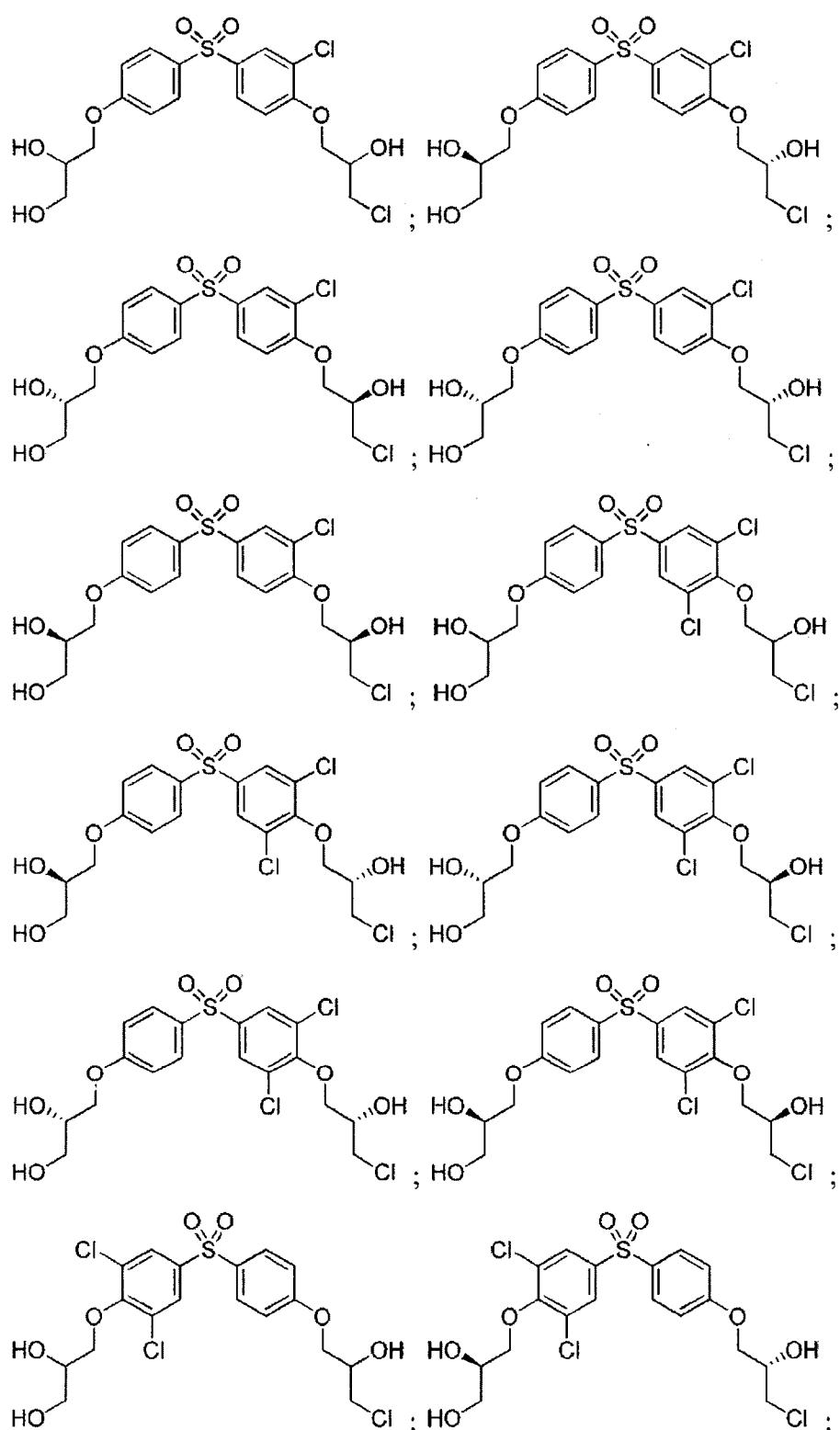


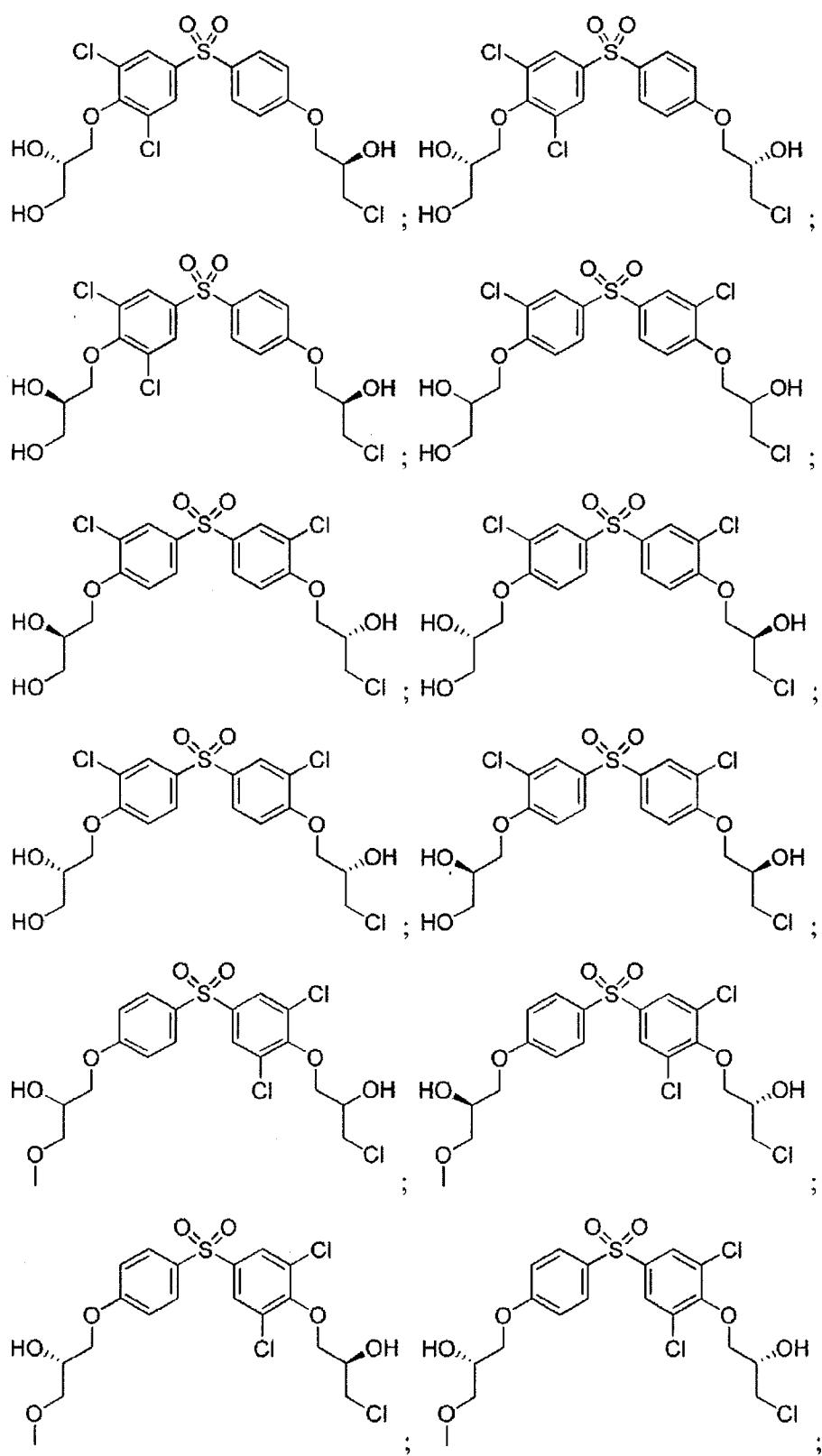


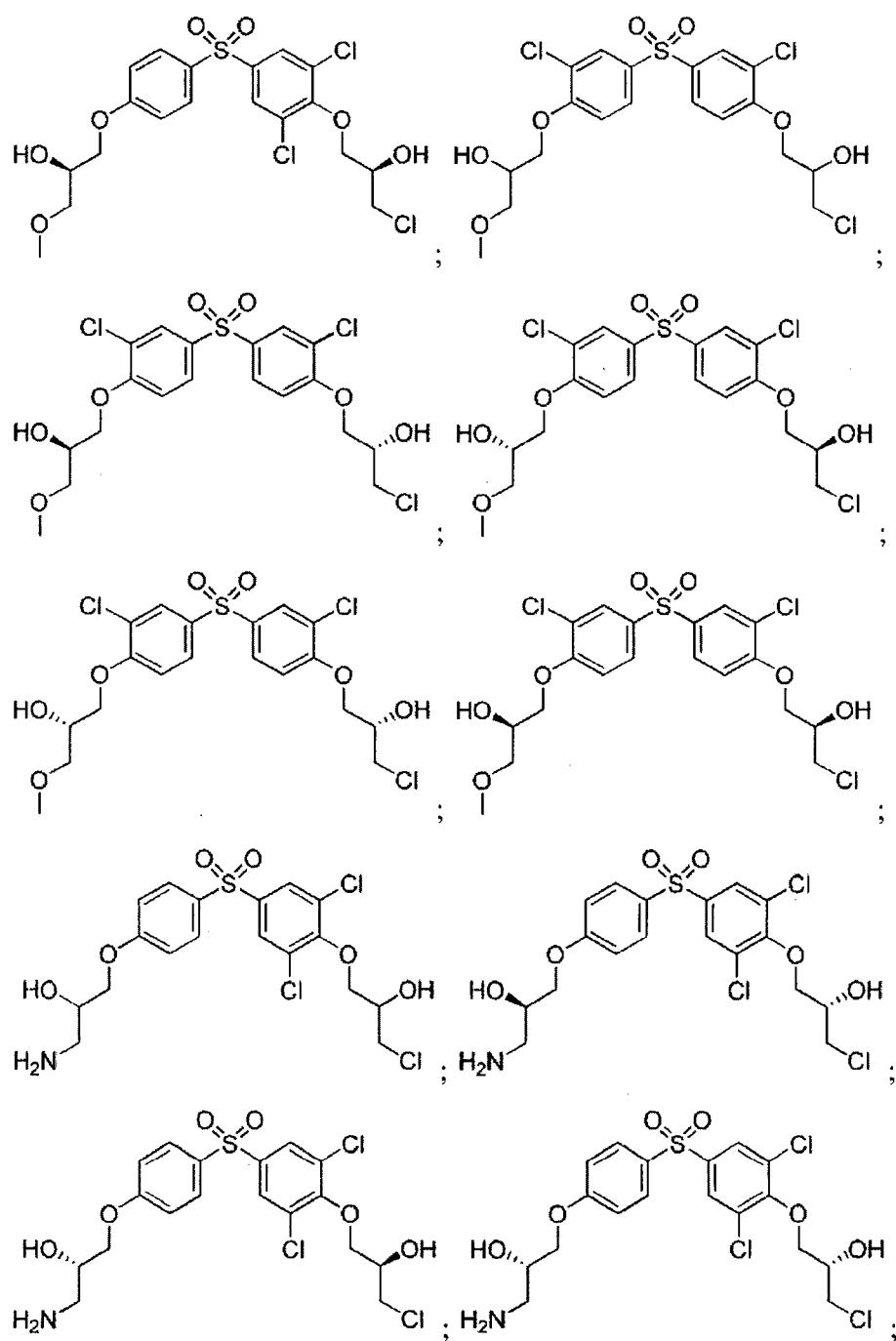


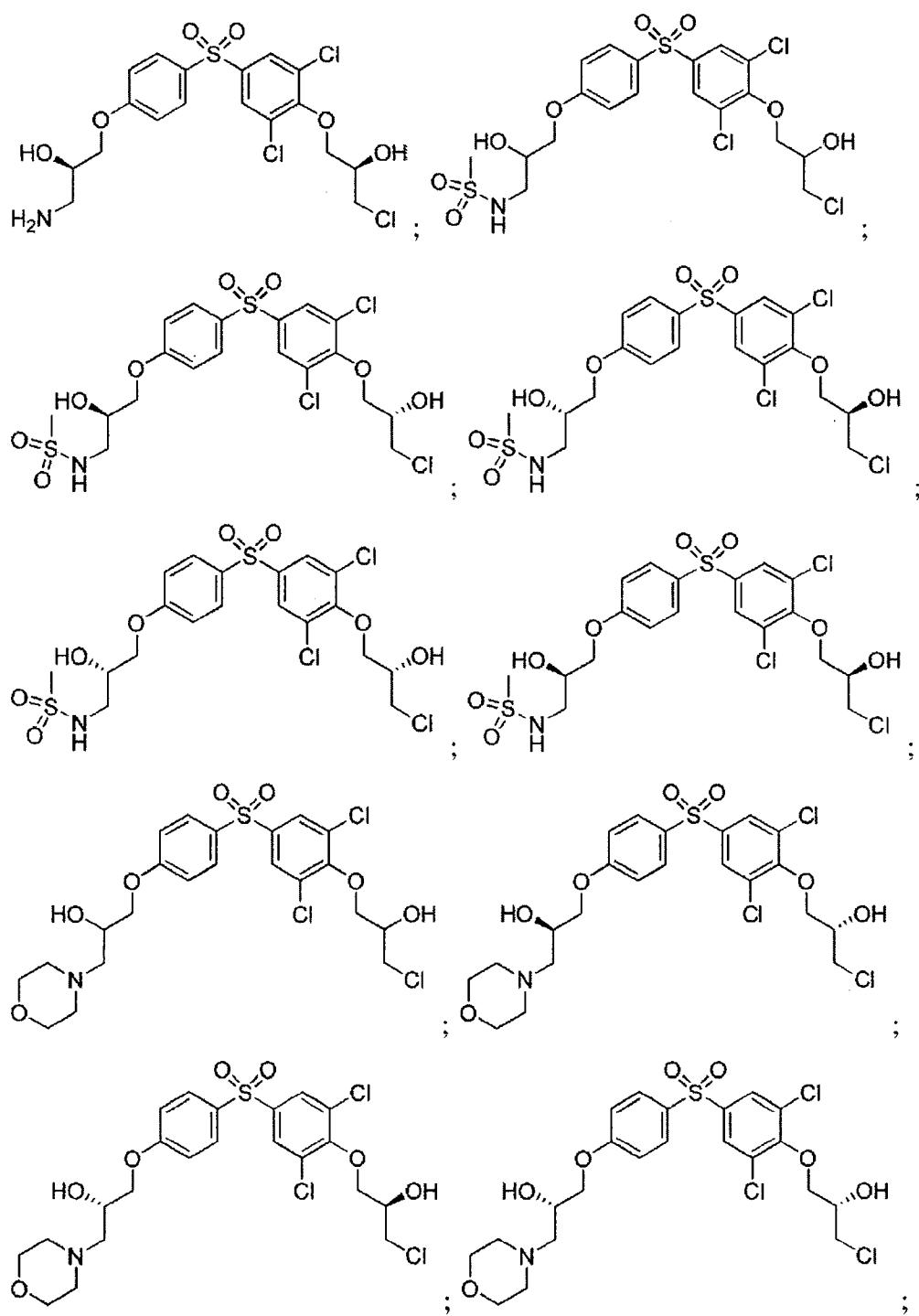
pharmaceutically acceptable salt thereof.

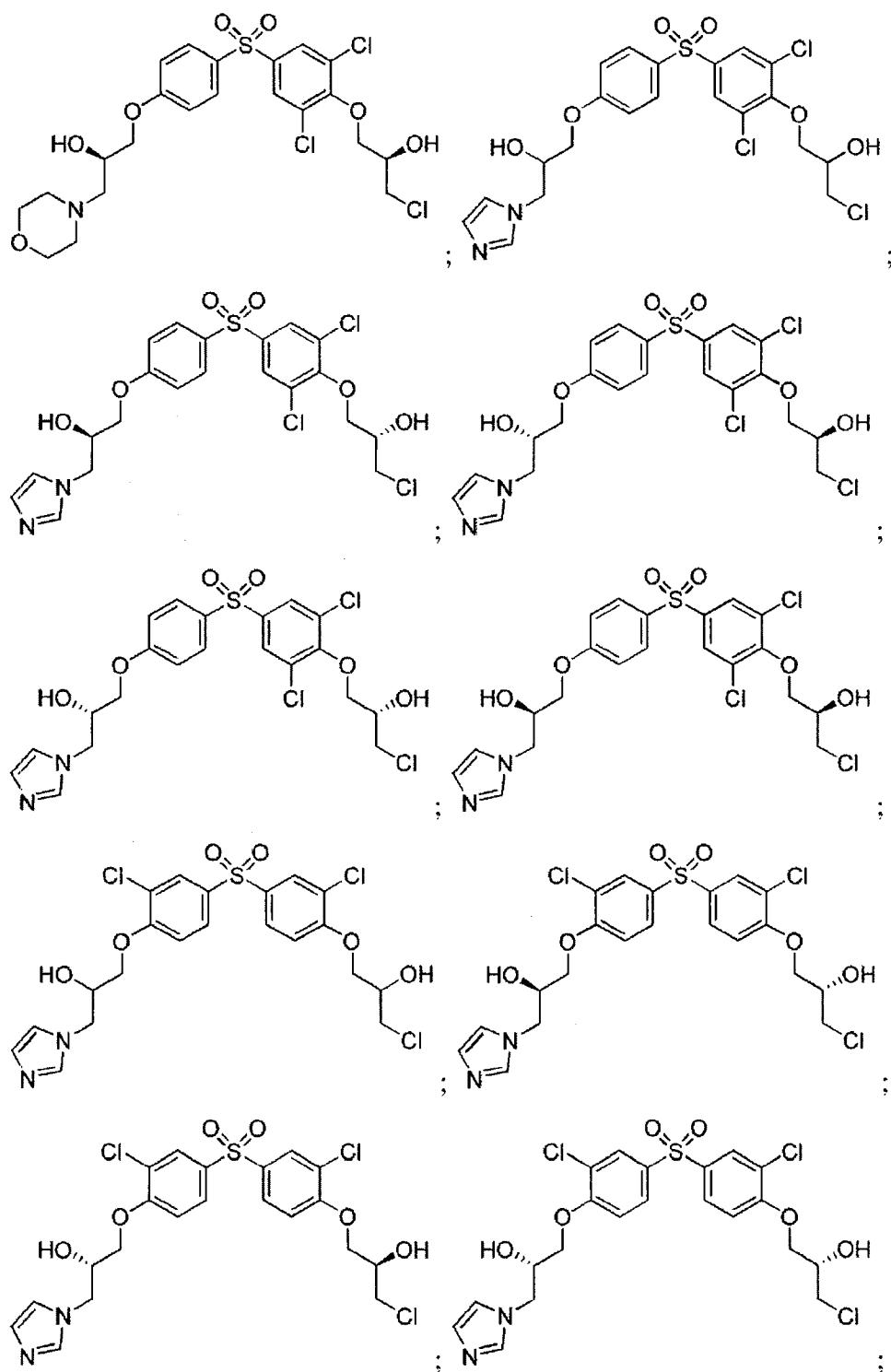
36. The compound of claim 1, wherein the compound has one of the following structures:

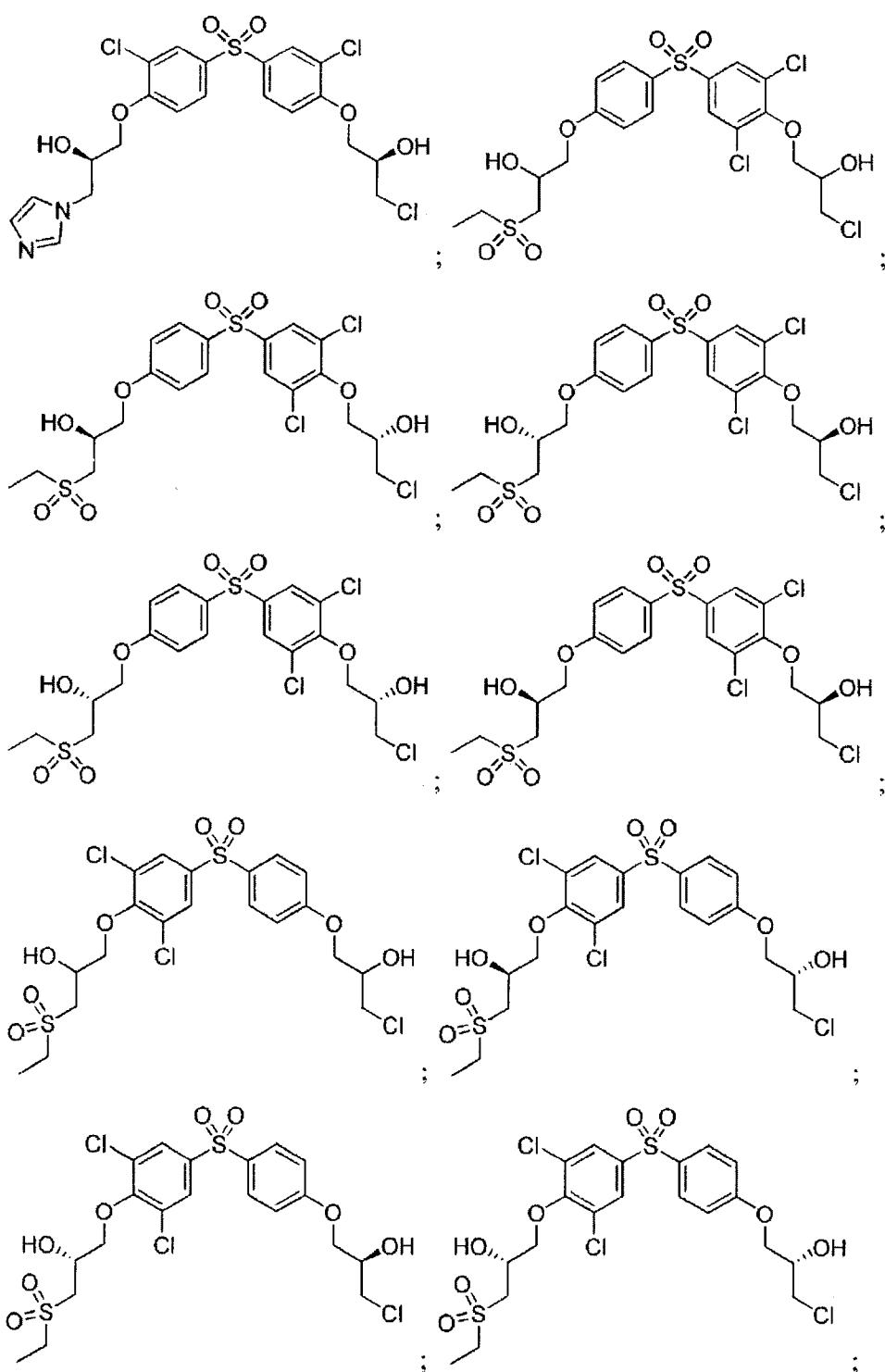


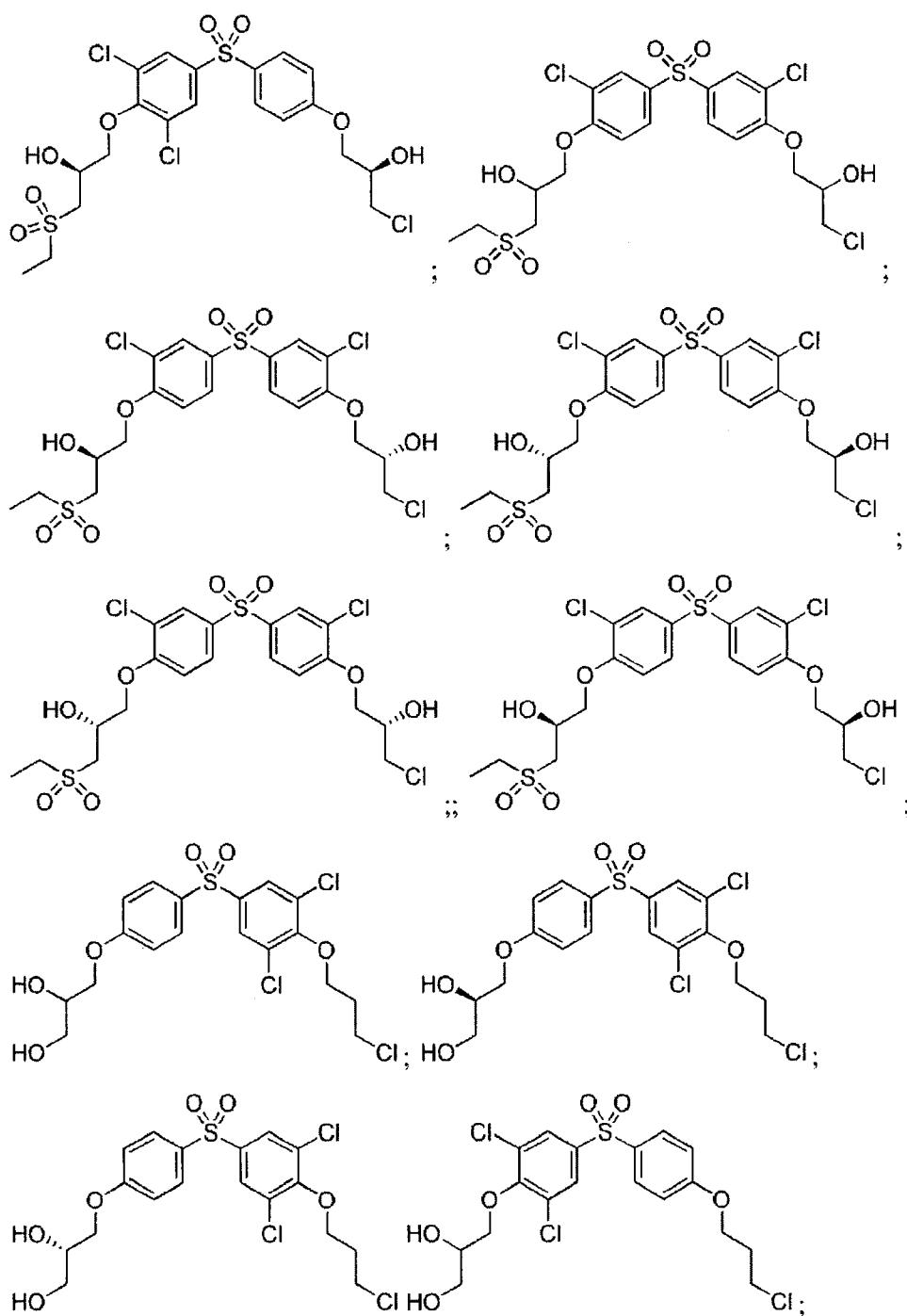


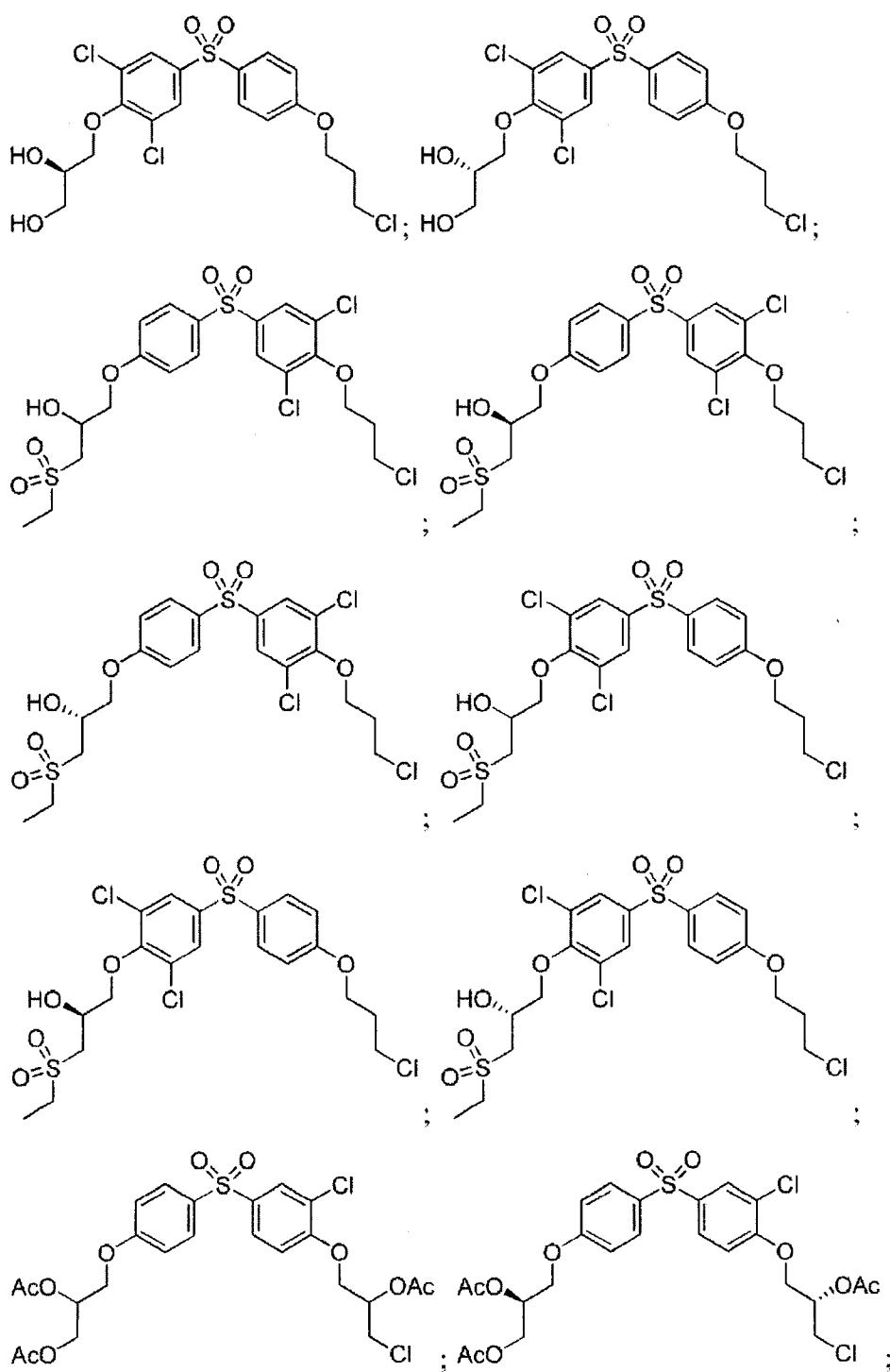


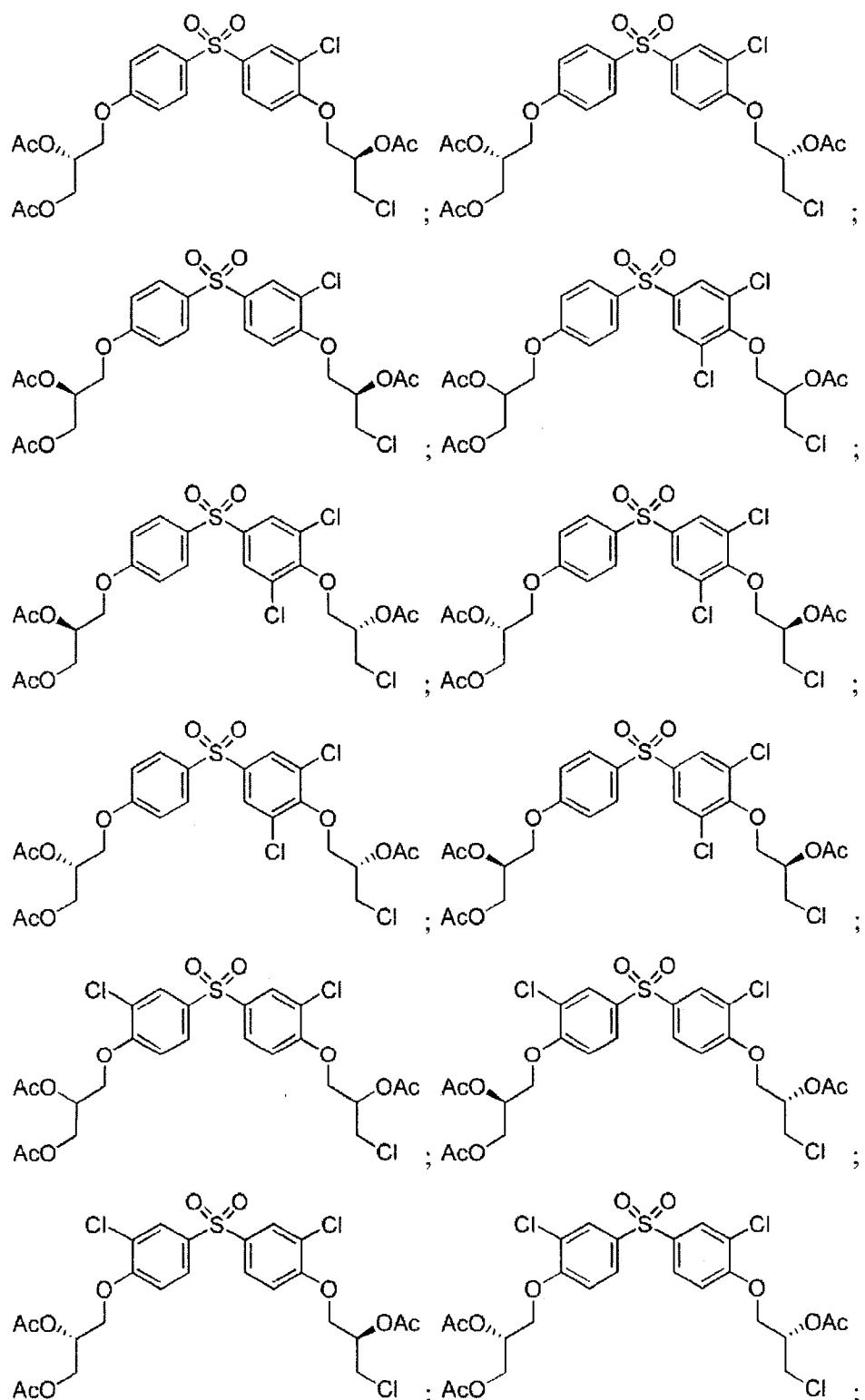


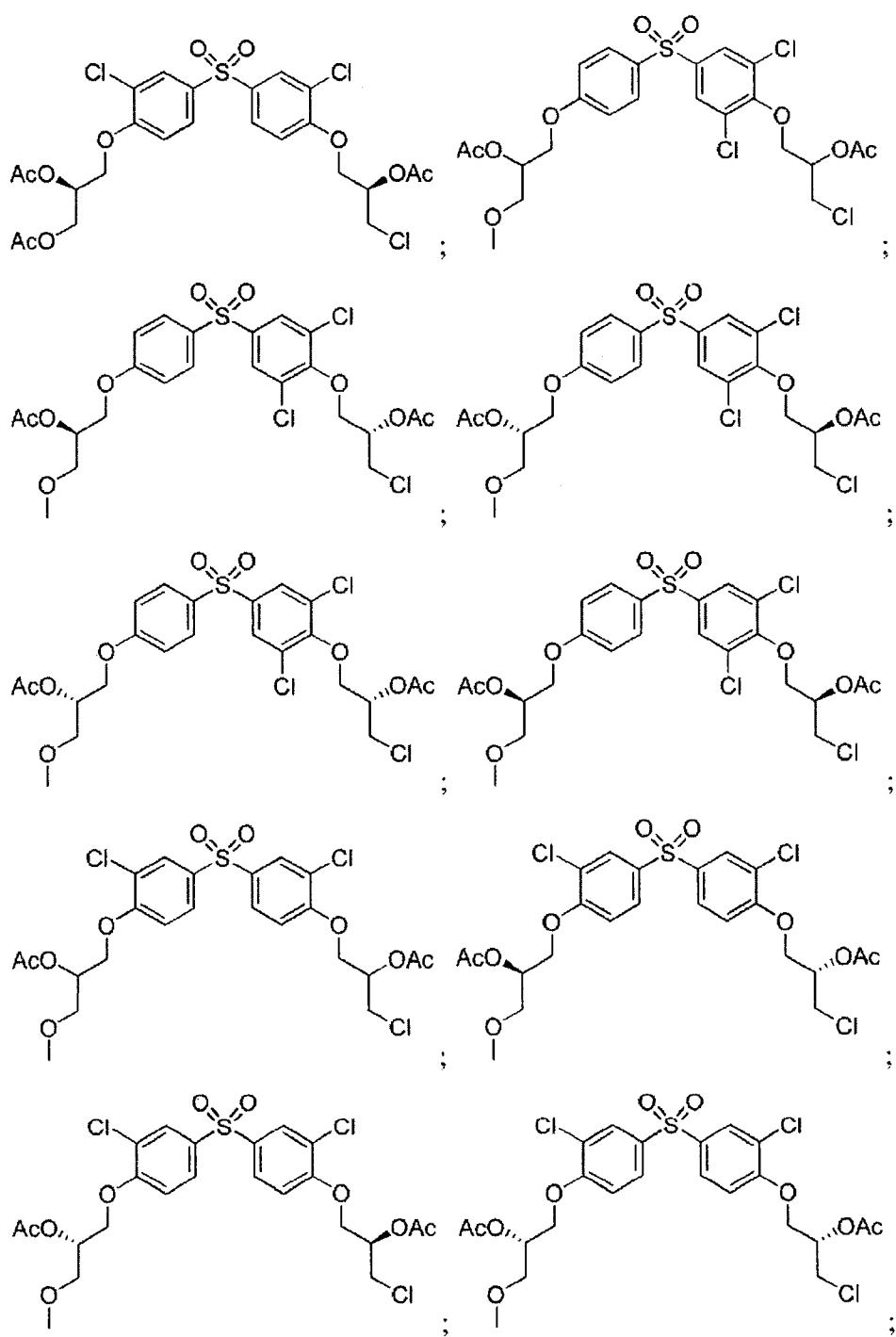


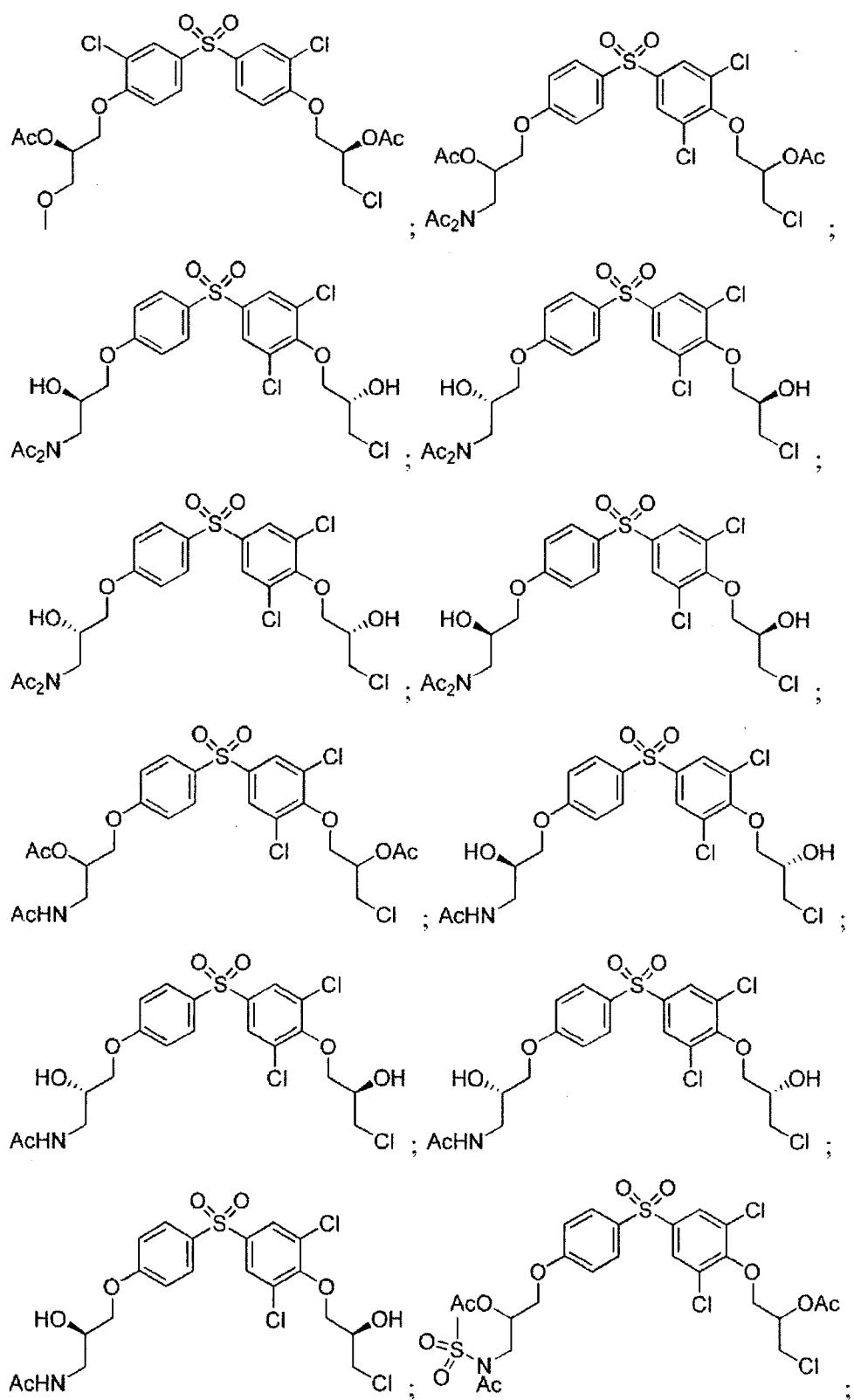


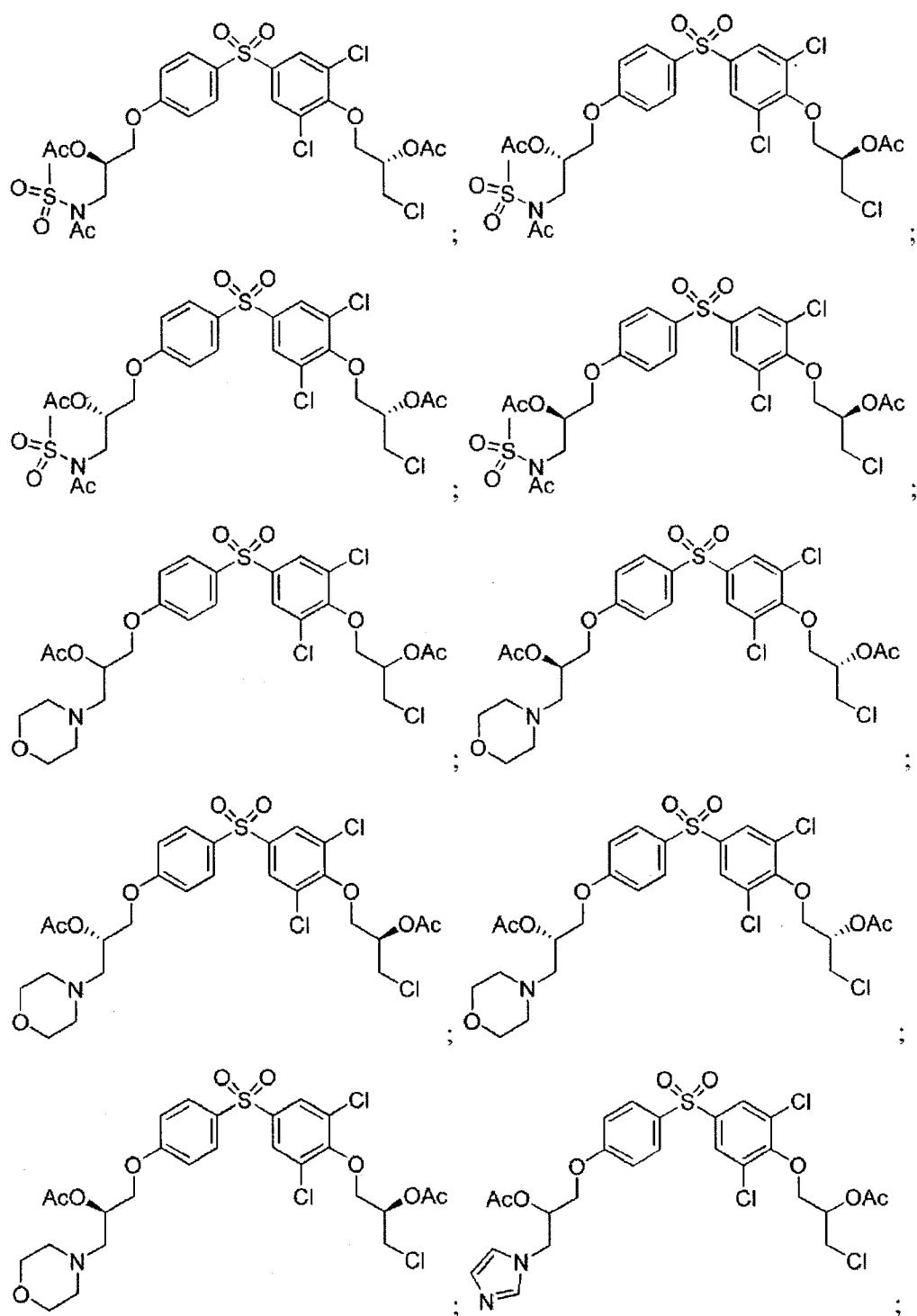


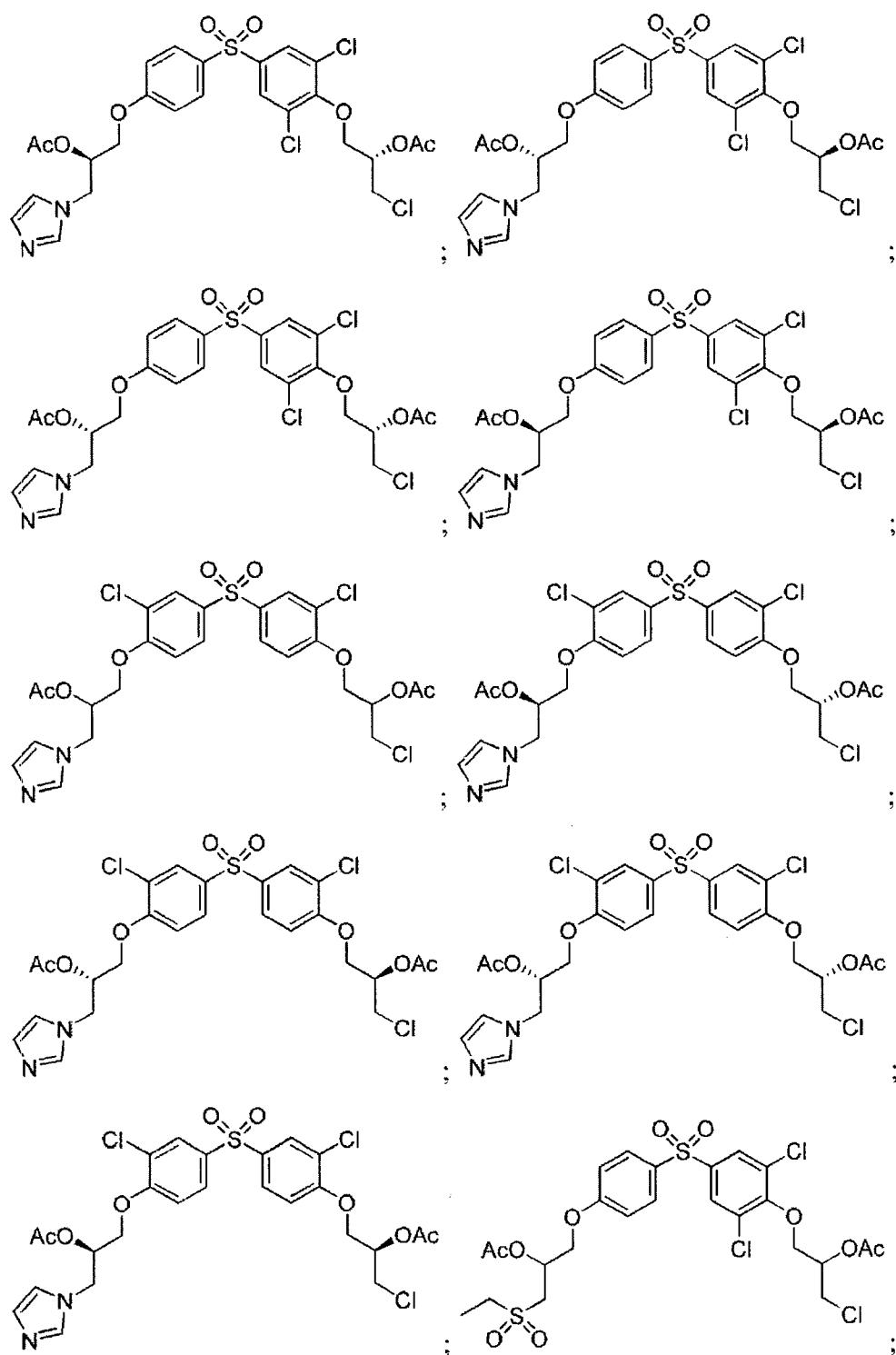


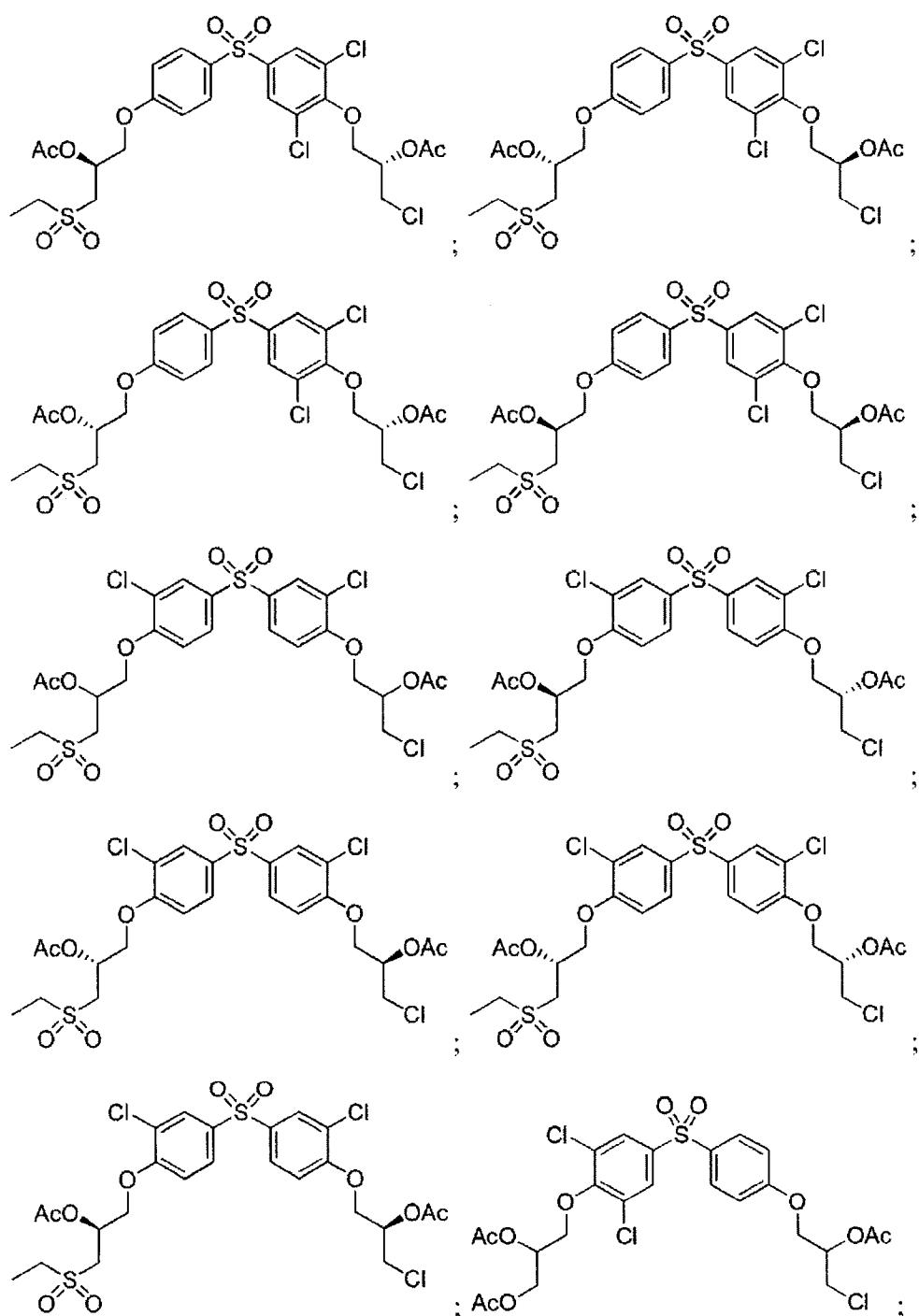


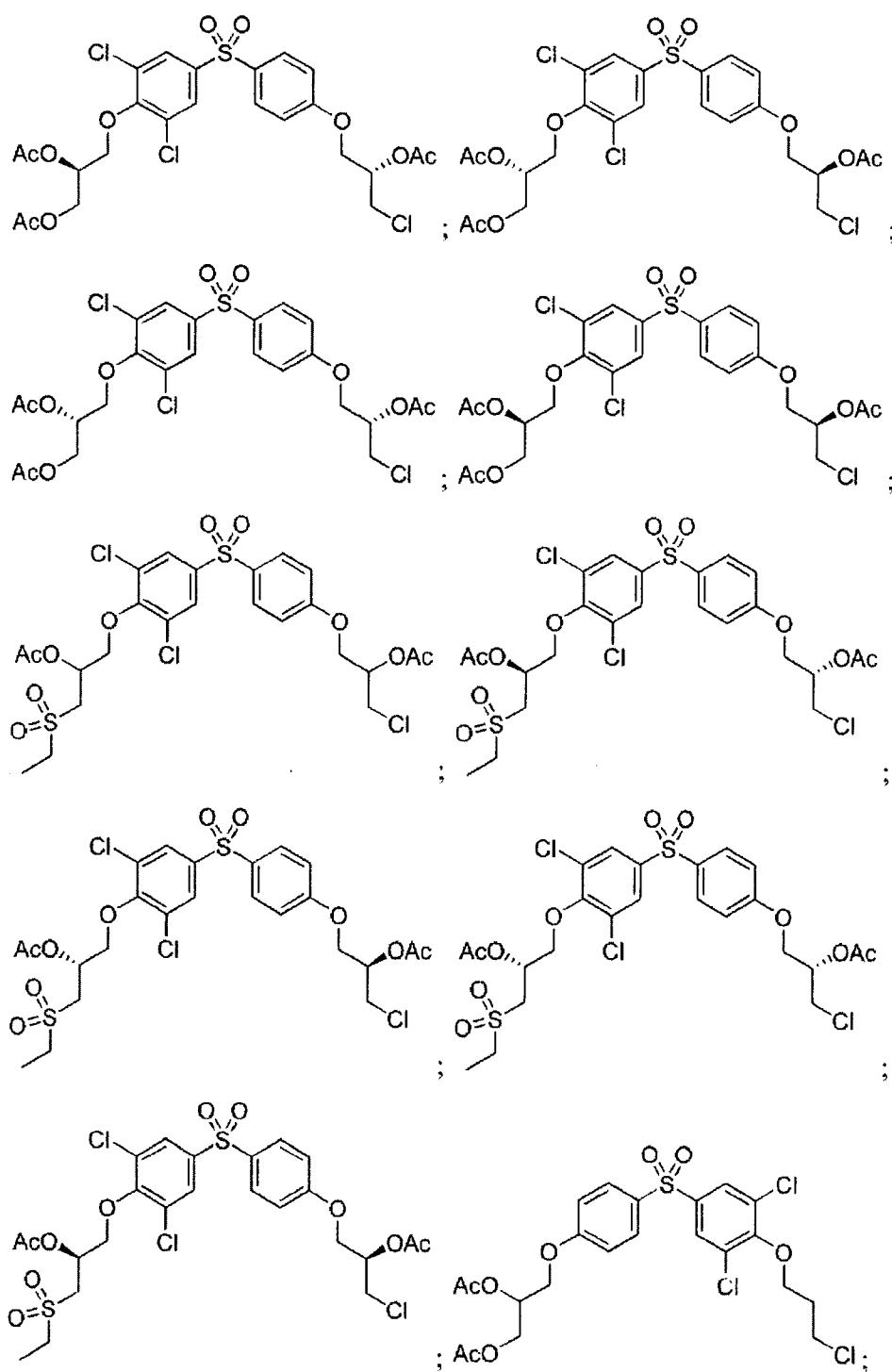


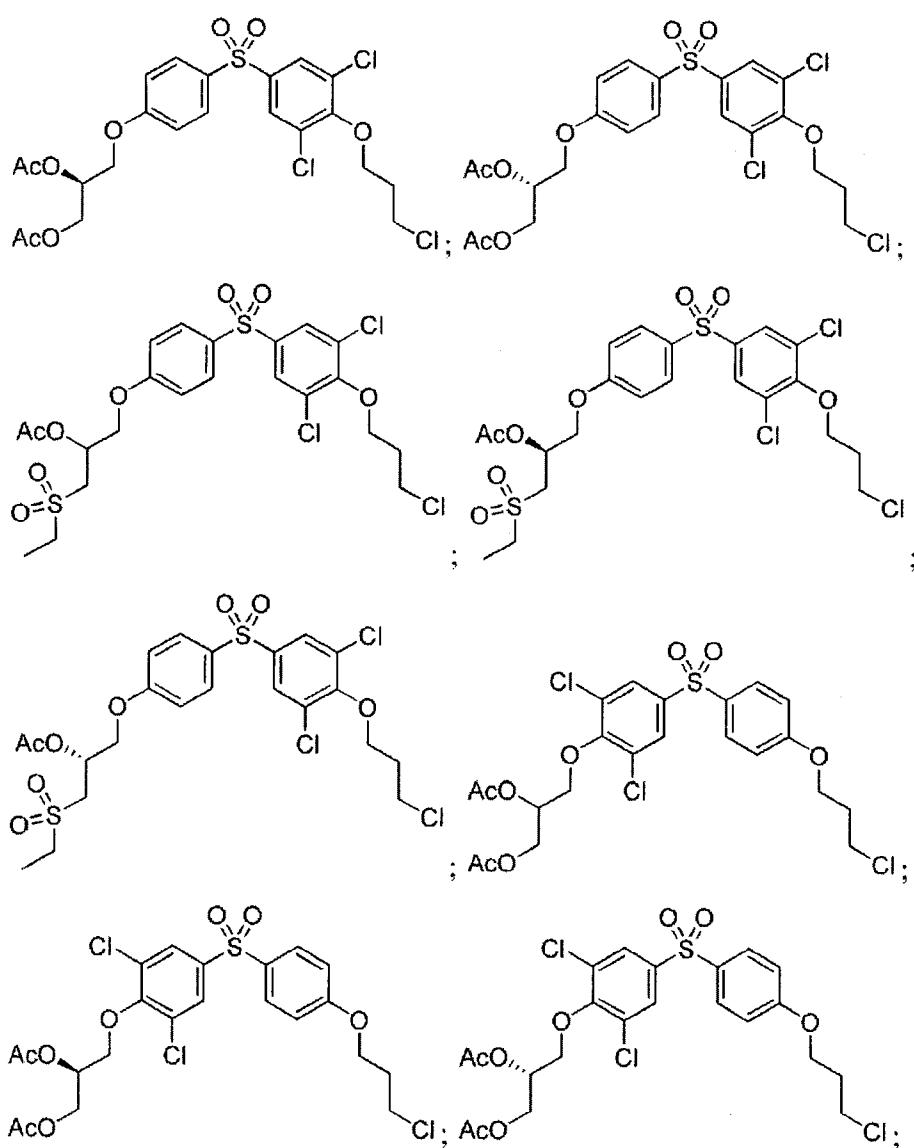


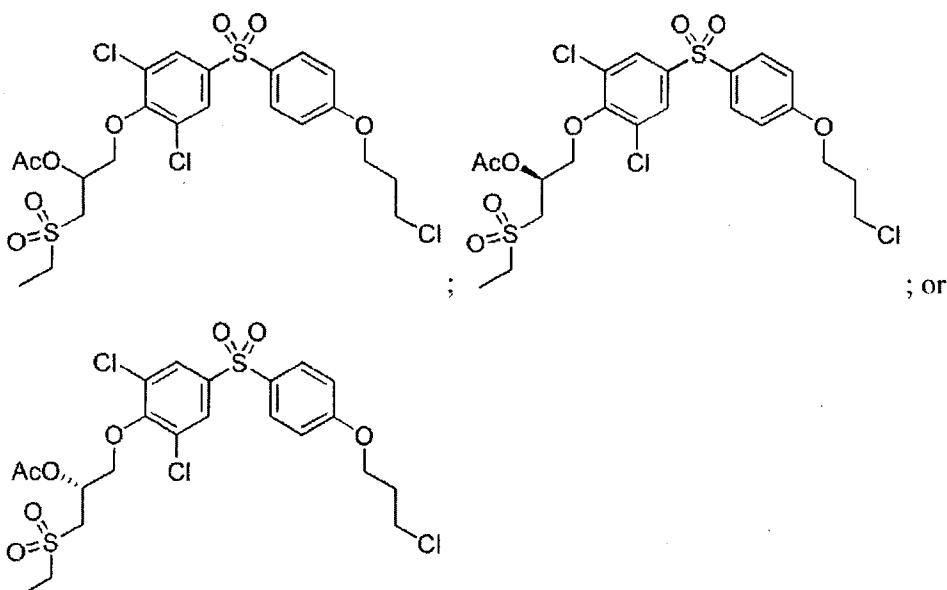






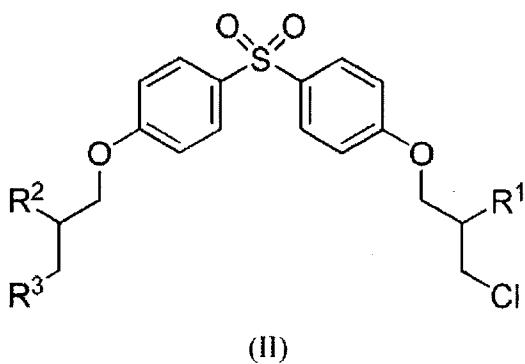






or a pharmaceutically acceptable salt thereof.

37. A compound having the following structure (II):



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

R^1 is H, -OH or $-OC(=O)R^{13}$;

R^2 is -OH or $-OC(=O)R^{13}$;

R^3 is halo, -OH, -OR⁴, $-OC(=O)R^{13}$, -NH₂, NHC(=O)R¹³, $-N(C(=O)R^{13})_2$, $-NHS(O)R^5$, $-N(C_1-C_6\text{ alkyl})S(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-S(O)_nR^5$, -N₃, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

R^4 is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

R^5 is each independently C_1 - C_6 alkyl or aryl which are optionally substituted with one or more R^6 ;

R^6 is each independently selected from the group consisting of H, F, Cl, Br, I, ^{123}I , hydroxyl, oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_6 - C_{12} aryl, wherein each R^6 is optionally substituted with one or more of halogen, ^{123}I , ^{18}F , hydroxyl, - $OS(O)_2$ -aryl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl; and

n is 0, 1, or 2.

38. The compound of claim 37, wherein R^1 is -OH or - $OC(=O)R^{13}$.
39. The compound of claim 37, wherein R^1 is H.
40. The compound of claim 37, wherein R^3 is -OH.
41. The compound of claim 37, wherein R^3 is - $OC(=O)R^{13}$, wherein R^{13} is methyl.
42. The compound of claim 37, wherein R^3 is - OR^4 , wherein R^4 is C_1 - C_6 alkyl.
43. The compound of claim 37, wherein R^4 is methyl.
44. The compound of claim 37, wherein R^3 is optionally substituted 5 or 6 membered heteroaryl or optionally substituted 3 to 7 membered heterocycl, wherein said heteroaryl or said heterocycl respectively comprise at least one N atom.
45. The compound of claim 37, wherein R^3 is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine.

46. The compound of claim 1, wherein R³ is -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), -N(C₁-C₆ alkyl)(S(O)_nR⁵) or -S(O)_nR⁵.

47. The compound of claim 46, wherein R³ is -NH₂, -NHC(=O)(C₁-C₄ alkyl), -N[(C(=O)(C₁-C₄ alkyl))₂, -NH[S(O)_n(C₁-C₃ alkyl)], -N[C(=O)(C₁-C₄ alkyl)][(S(O)_n(C₁-C₃ alkyl))], -N[C₁-C₆ alkyl][S(O)_n(C₁-C₃ alkyl)], or -S(O)_n(C₁-C₃ alkyl).

48. The compound of claim 37, wherein each R¹³ is C₁-C₄ alkyl.

49. The compound of claim 37, wherein R¹ and R² are each independently OH or -OC(=O)R¹³, wherein R¹³ is methyl.

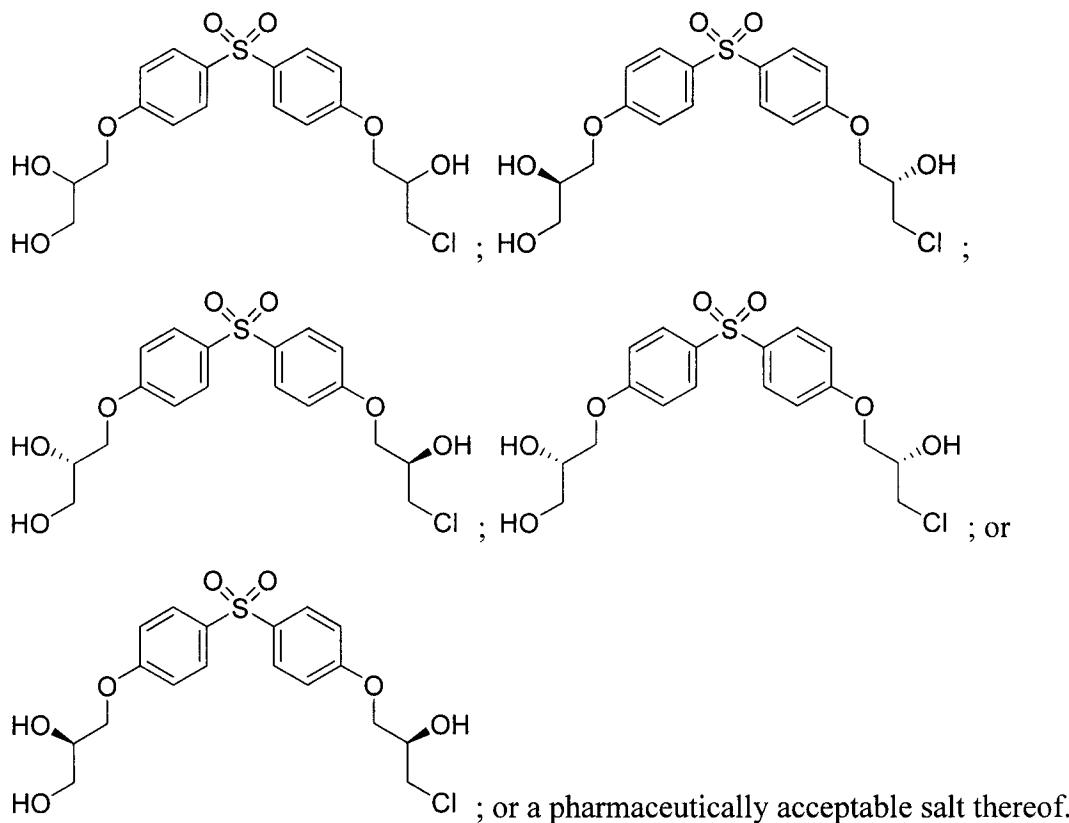
50. The compound of claim 37, wherein at least one of R¹, R² and R³ is -OC(=O)R¹³, wherein R¹³ is methyl.

51. The compound of claim 37, wherein any two of R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

52. The compound of claim 37, wherein R¹, R² and R³ are each -OC(=O)R¹³, wherein R¹³ is methyl.

53. The compound of claim 37, wherein R¹, R² and R³ are each -OH.

54. The compound of claim 37, wherein the compound is:



55. A pharmaceutical composition comprising a compound of any one of claims 1-54 and a pharmaceutically acceptable carrier.

56. The pharmaceutical composition of claim 55, further comprising an additional therapeutic agent.

57. The pharmaceutical composition of claim 56, wherein the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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.

58. The pharmaceutical composition of claim 56, wherein the additional therapeutic agent is enzalutamide, galeterone, 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, ODM-201, ODM-204, niclosamide, apalutamide, ARV-330, VPC-14449, TAS3681, 3E10-AR441bsAb, sintokamide, radium 233, or related compounds thereof.

59. A method for modulating androgen receptor activity, comprising: administering a pharmaceutical composition according to claim 55 to a subject in need thereof.

60. The method of claim 59, wherein the modulating androgen receptor (AR) is inhibiting androgen receptor.

61. The method of claim 60, wherein the modulating AR is inhibiting transactivation of androgen receptor N-terminal domain (NTD).

62. The method of claim 59, wherein the subject is human.

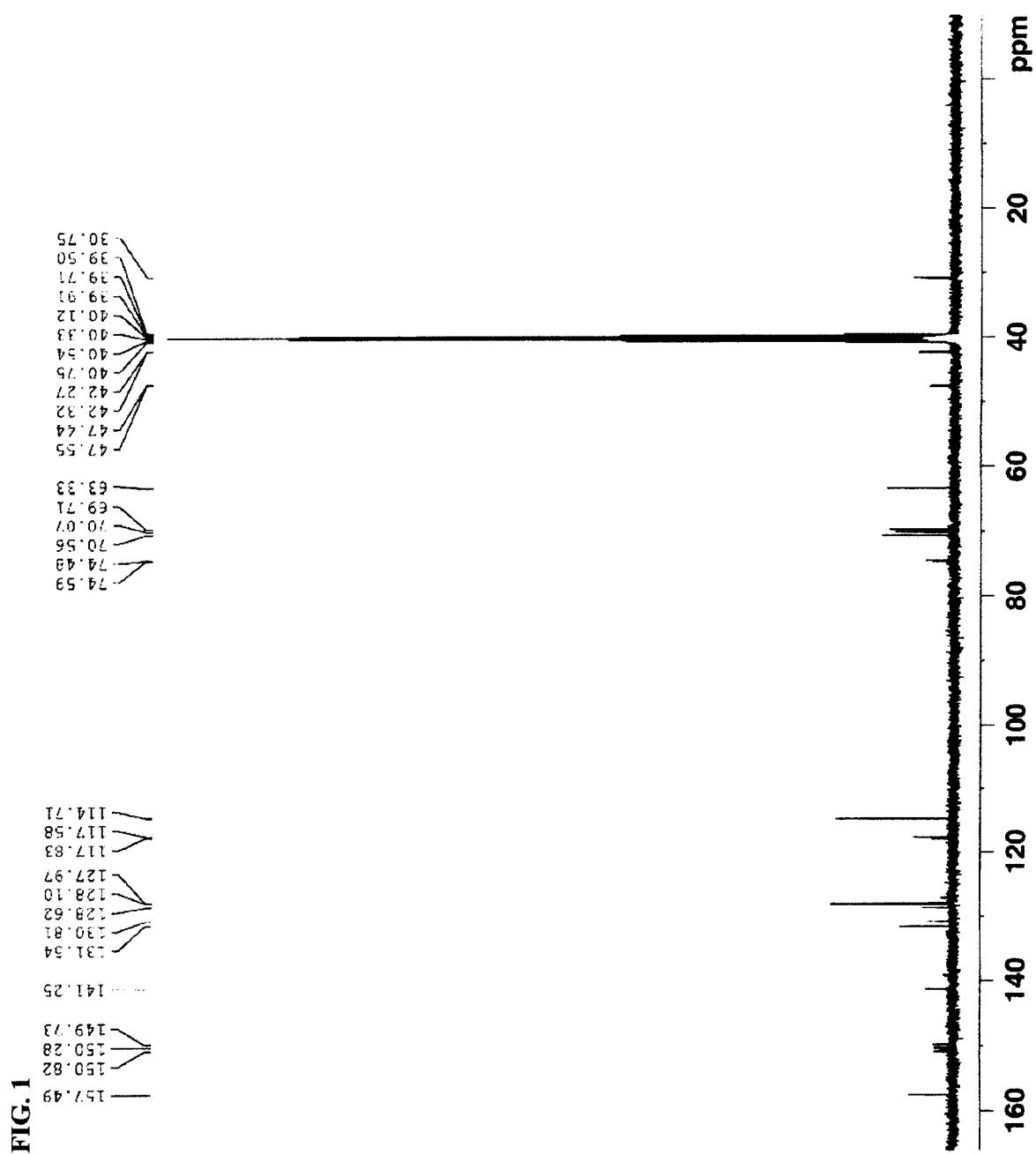
63. The method of any one of claims 59-62, wherein the modulating AR is for treating a condition or disease selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration.

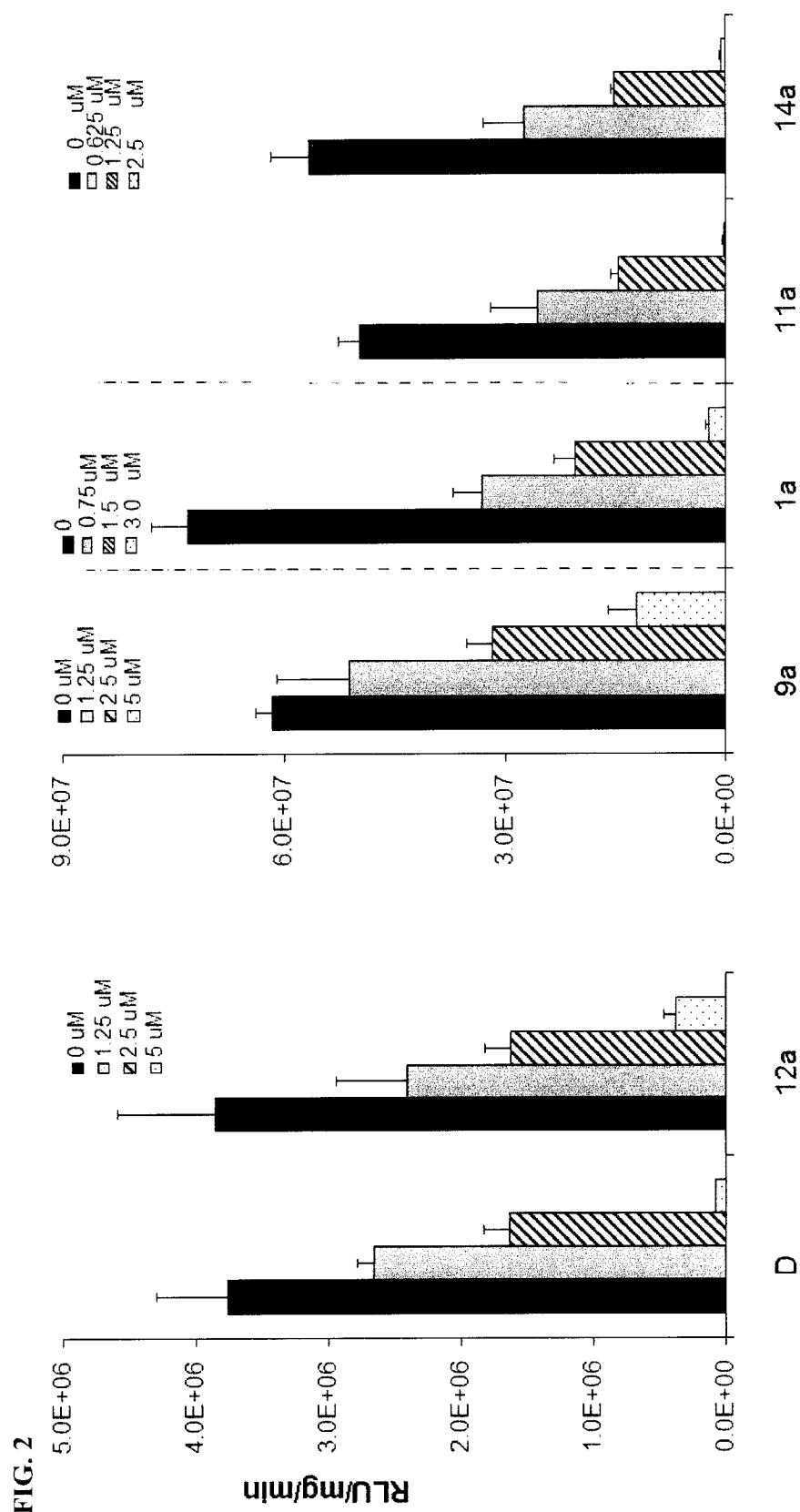
64. The method of claim 63, wherein the condition or disease is prostate cancer.

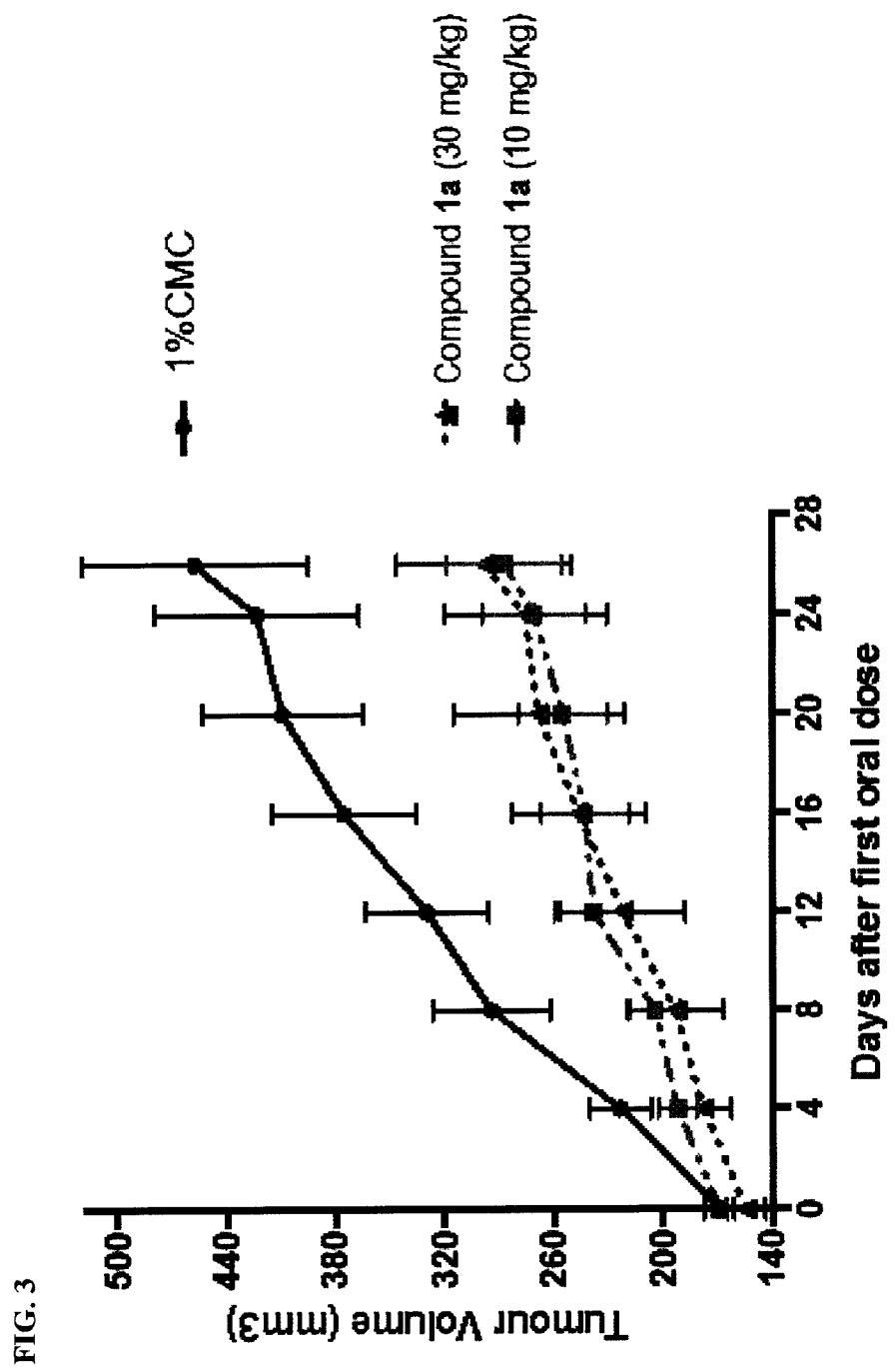
65. The method of claim 64, wherein the prostate cancer is primary or localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, advanced prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer (CRPC), and hormone-sensitive prostate cancer

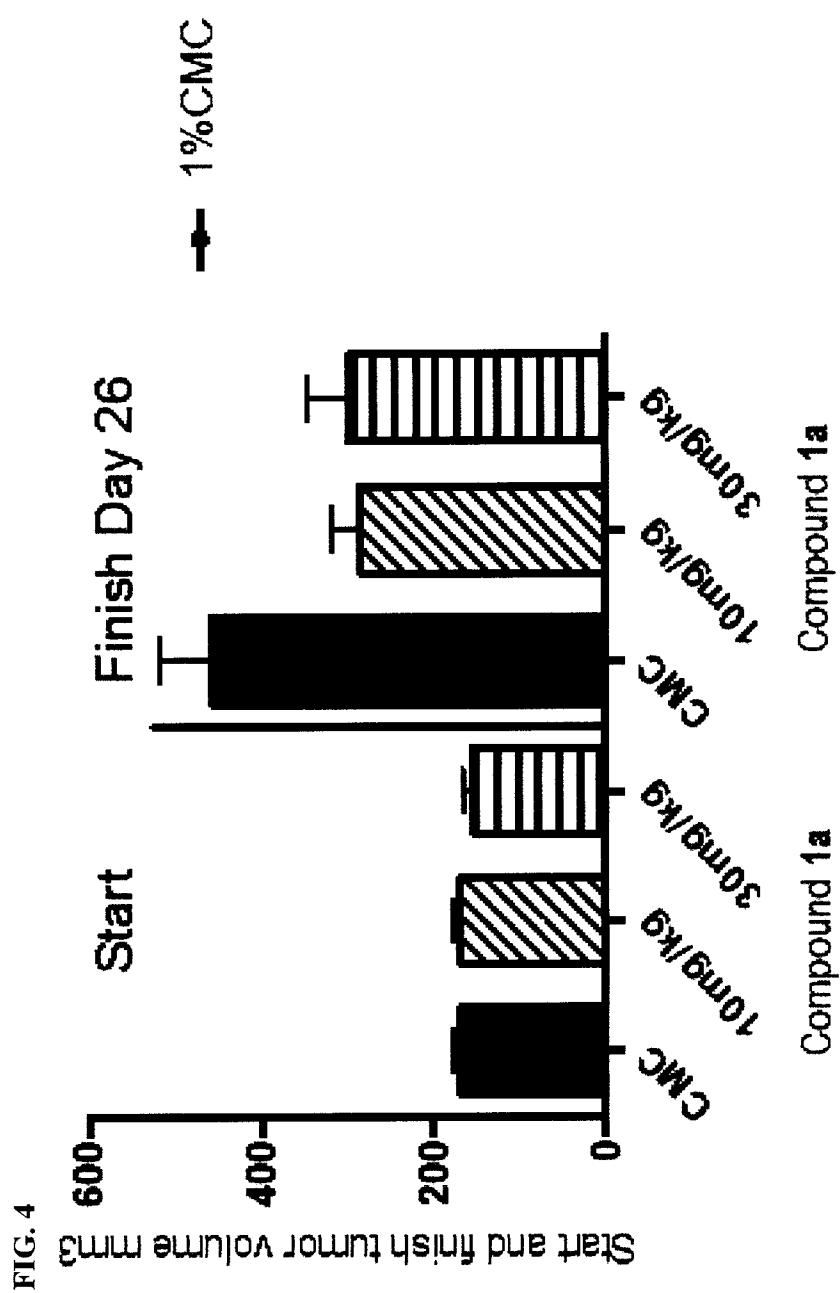
66. The method of claim 64, wherein the prostate cancer is CRPC.

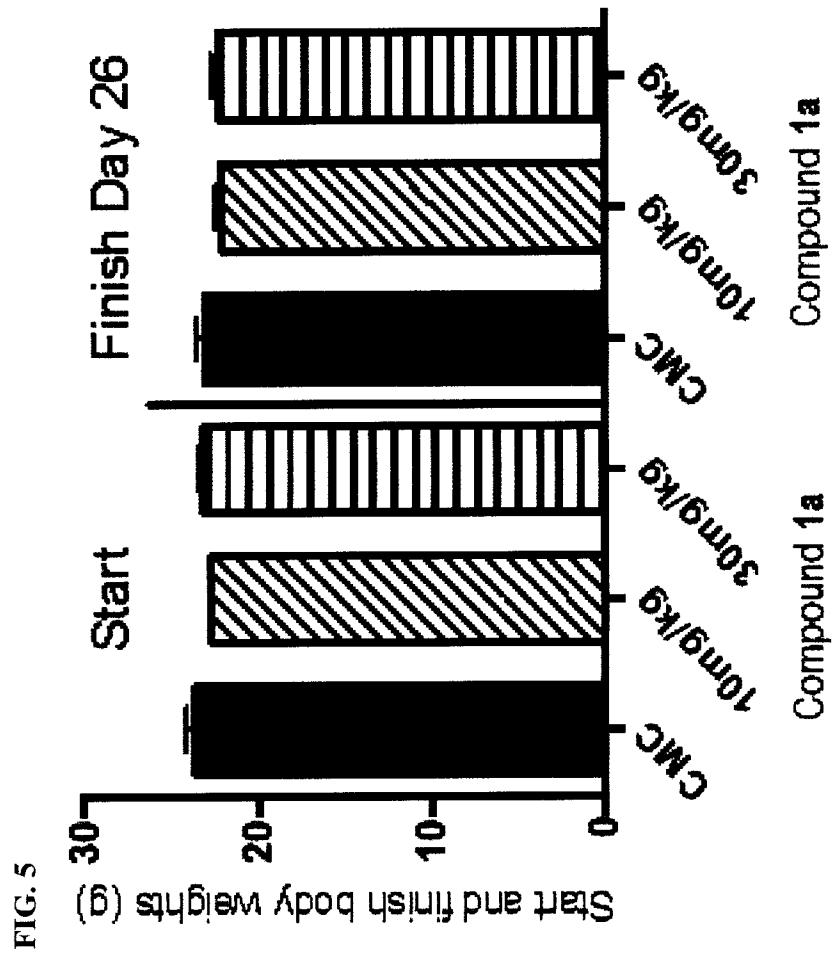
67. The method of claim 64, wherein the prostate cancer express full-length androgen receptor (AR) or truncated AR splice variant.

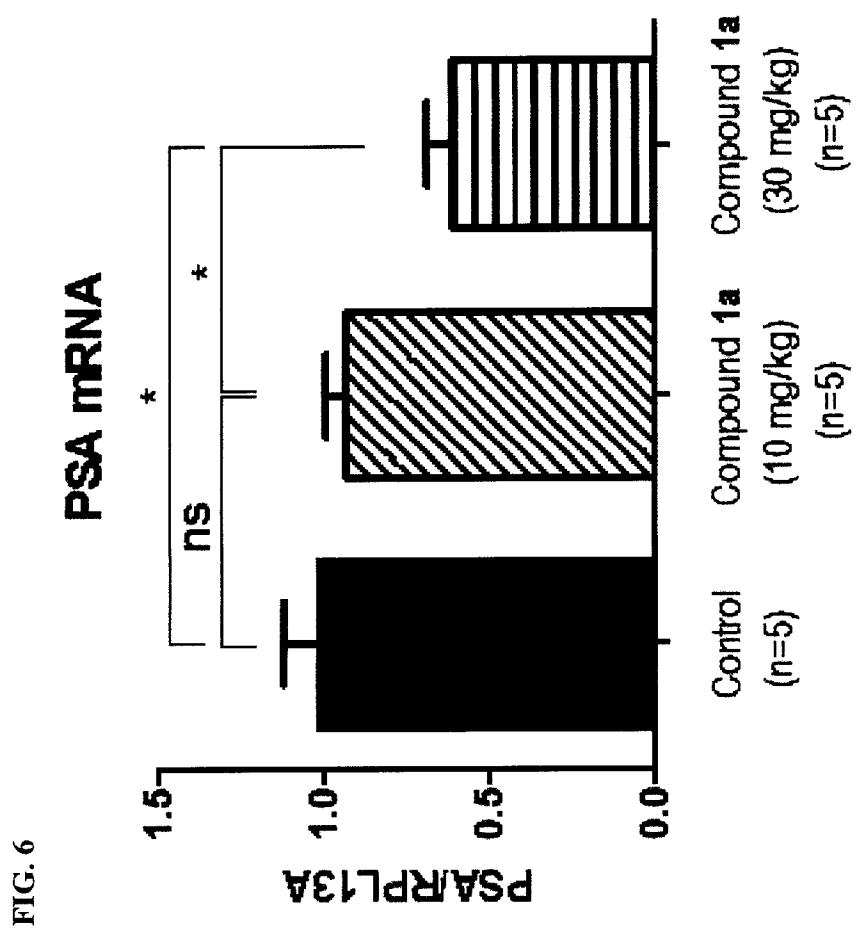












INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2017/000083

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C07C 31/16** (2006.01), **A61K 31/09** (2006.01), **A61K 31/10** (2006.01), **A61K 31/165** (2006.01), **A61K 31/222** (2006.01), **A61K 31/4164** (2006.01) (more IPCs on the last page)

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)

C07C 31/16 (2006.01), **A61K 31/09** (2006.01), **A61K 31/10** (2006.01), **A61K 31/165** (2006.01), **A61K 31/222** (2006.01), **A61K 31/4164** (2006.01), **A61P 35/00** (2006.01), **C07C 311/04** (2006.01), **C07C 317/22** (2006.01), **C07C 43/23** (2006.01), **C07D 233/60** (2006.01), **C07D 295/088** (2006.01)

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

n/a

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

Databases used: STN, Intellect, Espacenet, Questel-Orbit, American Chemical Society publication search, PubMed, Scopus, ScienceDirect and Google patents.

Keywords : bisphenol derivatives and androgen receptor, bisphenol-ether derivatives, androgen receptor modulator and prostate cancer, bisphenol and halogens. Also publication search using the applicant's and inventors' names respectively.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/031984 (ANDERSEN, Raymond J et al). 12 March 2015 (12-03-2015) Whole document	1-9, 11-22, 30-34 and 55-67
X	WO 2012/139039 (ANDERSEN, Raymond J et al.) 11 October 2012 (11-10-2012) Whole document	1-9, 11-14, 21, 22 and 55-67
Y	WO 2014/179867 (MAWJI, NR et al.) 13 November 2014 (13-11-2014) Whole document	1-67
P,X	WO 2016/112455 (SADAR, Marianne D et al.) 21 July 2016 (21-07-2016) Whole document	1-67
A	WO 2011/082487 (SADAR, Marianne D et al.) 14 July 2011 (14-07-2011) Whole document	1-67

Further documents are listed in the continuation of Box C.

See patent family annex.

* "A" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier application or patent but published on or after the international filing date 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) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	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 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 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
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Date of the actual completion of the international search
21 July 2017 (21-07-2017)

Date of mailing of the international search report
03 August 2017 (03-08-2017)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
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50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 819-953-2476

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2017/000083

A61P 35/00 (2006.01), ***C07C 311/04*** (2006.01), ***C07C 317/22*** (2006.01), ***C07C 43/23*** (2006.01),
C07D 233/60 (2006.01), ***C07D 295/088*** (2006.01)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2017/000083

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/0010469 (ANDERSEN, Raymond J et al.) 08 January 2015 (08-01-2015) Whole document	1-67
A	‘An androgen receptor N-terminal domain antagonist for treating prostate cancer.’ Jae-Kyung Myung et al. <i>The Journal of Clinical Investigation</i> July 2013, 12, 7, 2948-2960 Whole document	1-67
A	‘Regression of Castrate-recurrent Prostate Cancer by a Small-molecule Inhibitor of the Amino-Terminus Domain of the Androgen Receptor.’ Raymond J Andersen et al. <i>Cancer Cell</i> June 15, 2010, 17, 535-546 Whole document	1-67
A	‘EPI-001 is a selective peroxisome proliferator-activated receptor-gamma modulator with inhibitory effects on androgen receptor expression and activity in prostate cancer.’ Lucas J. Brand et al. <i>Oncotarget</i> February 2015, 6, 6, 3811-3824 Whole document	1-67

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2017/000083

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.: 59-67
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 59-67 are directed to methods of medical treatment comprising administering a compound of the present invention to modulate androgen receptor activity and to treat cancer. Nevertheless, the Authority has performed a search on the alleged therapeutic effects derived from the compounds on modulating androgen receptor activity and on treating cancer.
2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. 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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2017/000083

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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WO2016112455A1	21 July 2016 (21-07-2016)	None	
US2015010469A1	08 January 2015 (08-01-2015)	None	