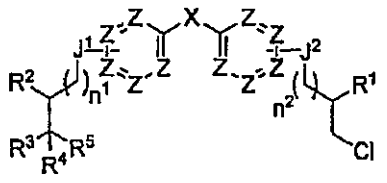
CLAIMS

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



(I)

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

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

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

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

R1 is hydroxyl, -OR12 or –OC(=O)R13;

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

R4 and R5 are each independently H or halo;

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

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

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

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

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

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

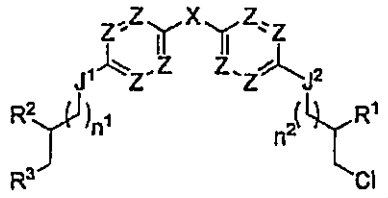
R14 is H, C1-C10 alkyl or aryl;

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

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

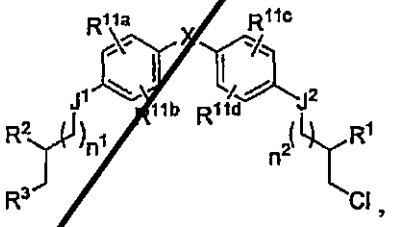
wherein at least one of R1, R2 or R3 is –OC(=O)R13.

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



(Ia)

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



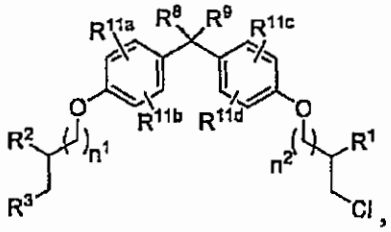
(Ib)

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

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

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

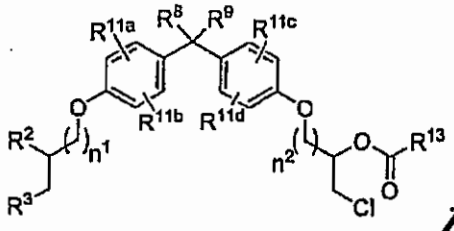
6. The compound of any one of claims 1-5, wherein the compound has the following structure (Ic):



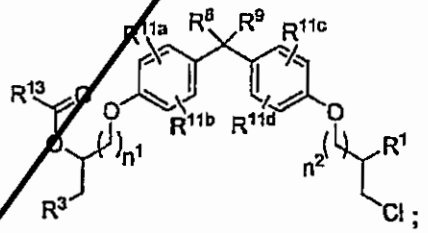
(Ic)

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

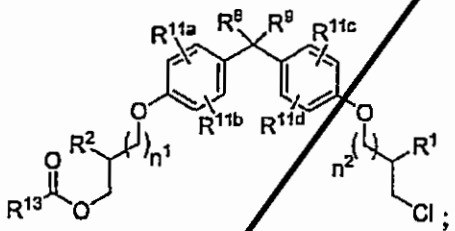
7. The compound of any one of claims 1-6, wherein the compound has one of the following structures (Id), (Ie), (If), (Ig), (Ih), (Ii) or (Ij):



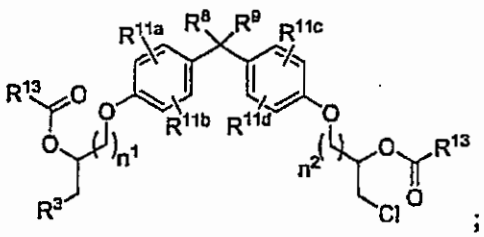
(Id)



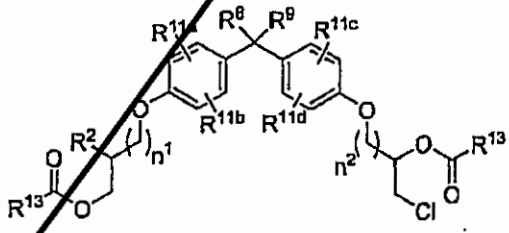
(Ie)



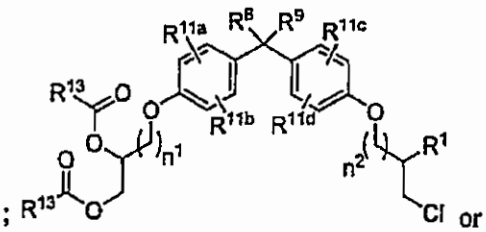
(If)



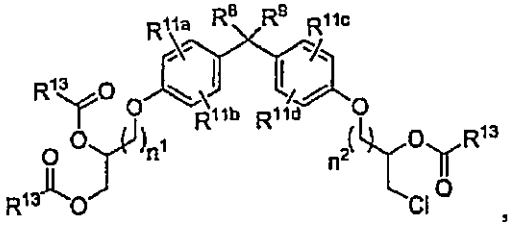
(Ig)



(Ih)



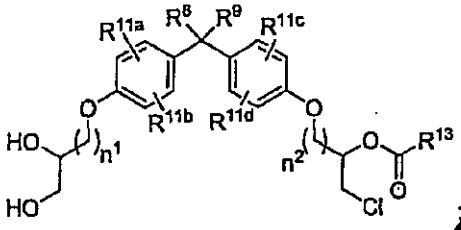
(Ii)



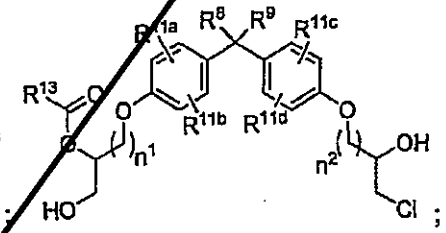
(Ij)

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

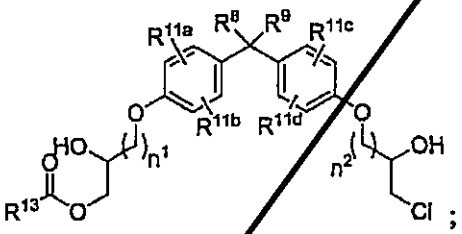
8. The compound of any one of claims 1-7, wherein the compound has one of the following structures (Ik), (Il), (Im), (In), (Io) or (Ip):



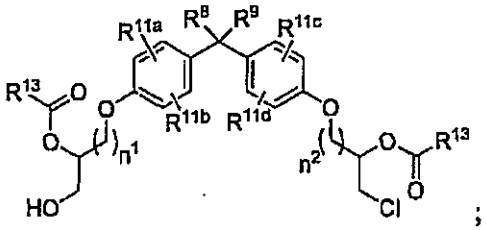
(Ik)



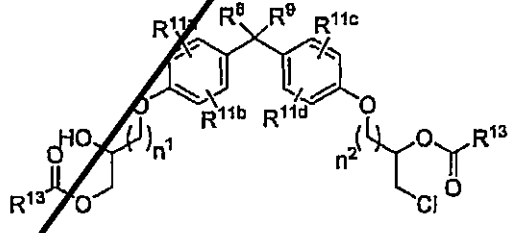
(Il)



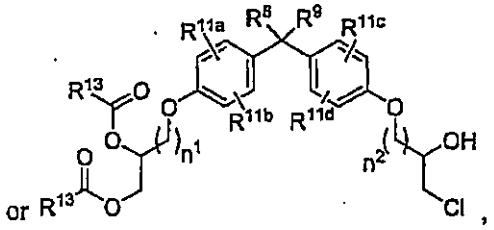
(Im)



(In)



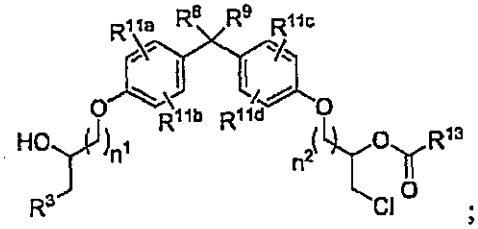
(Io)



(Ip)

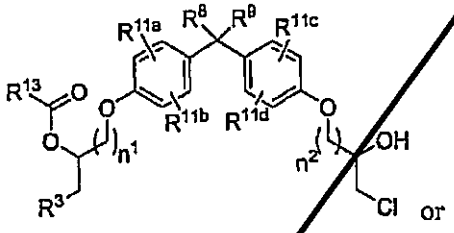
wherein R11a, R11b, R11c and R11d are each independently H, halo or C1-C10 alkyl.

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



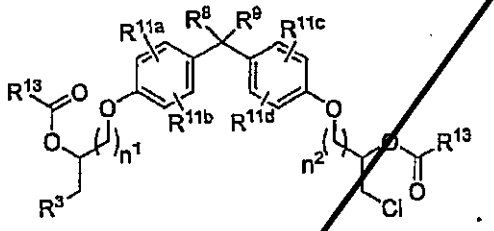
(Iq)

;



(Ir)

or



(Is)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

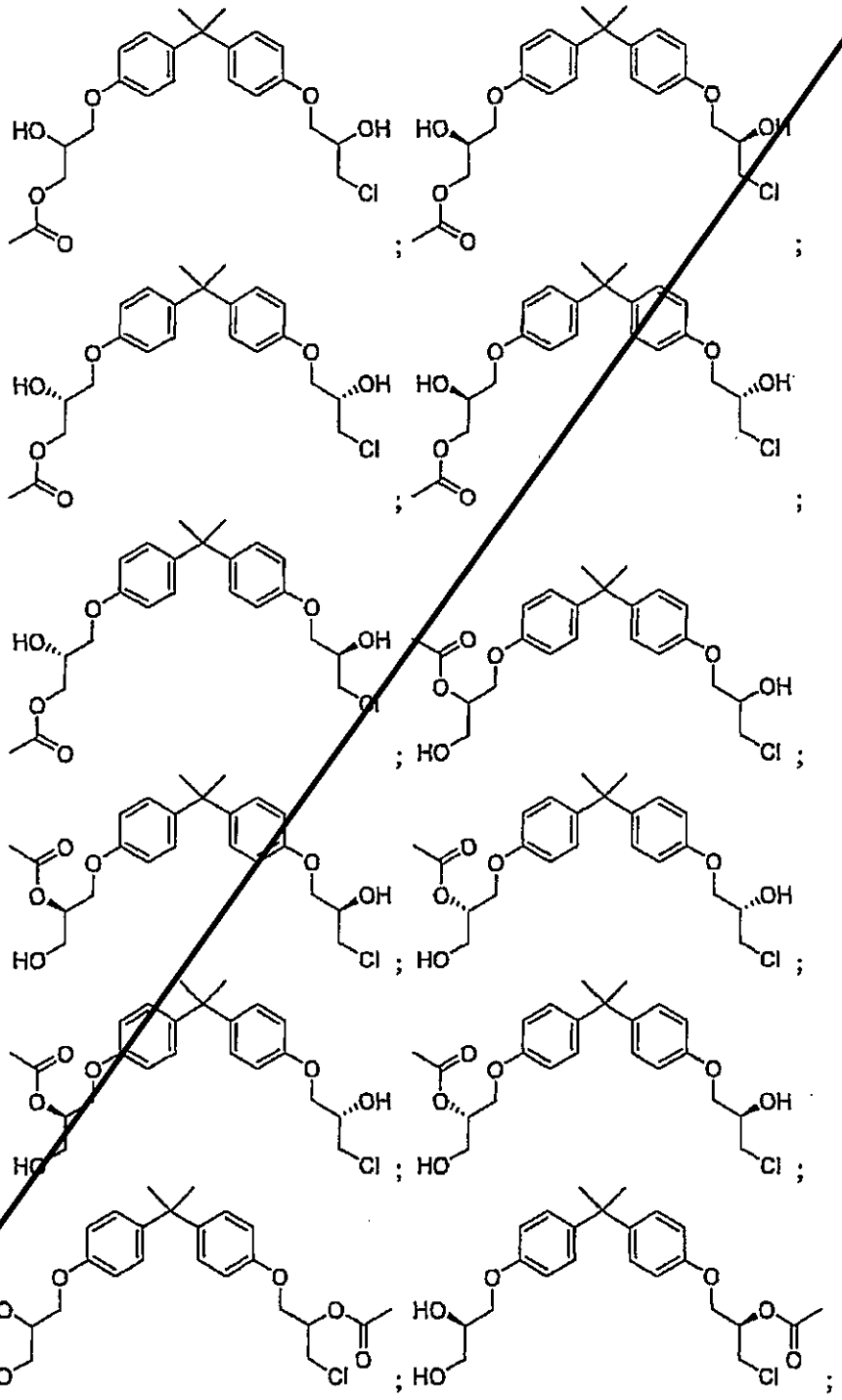
24. The compound of any one of claims 1-22, wherein R4 and R5 are each halo.

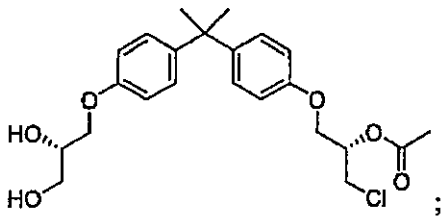
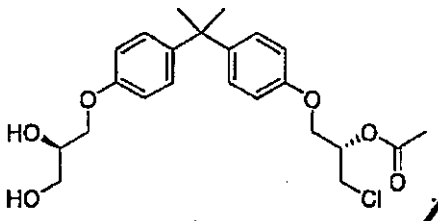
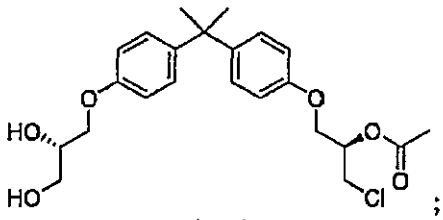
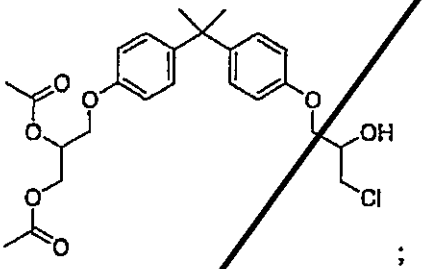
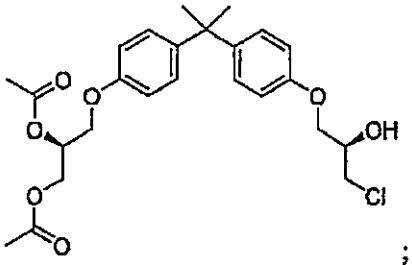
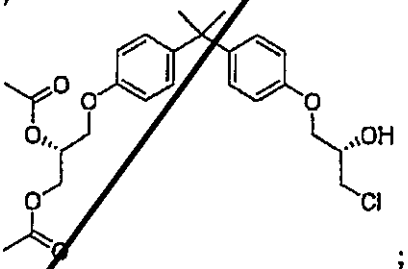
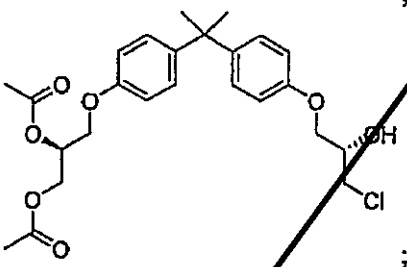
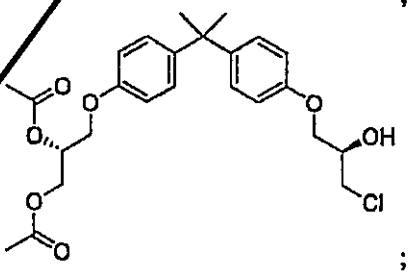
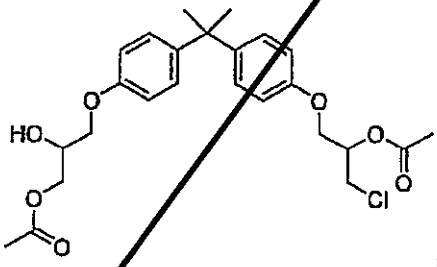
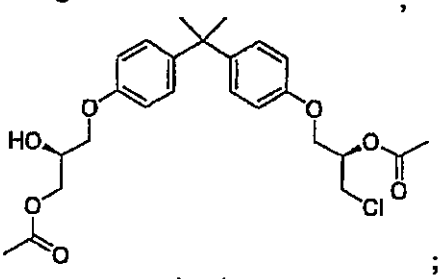
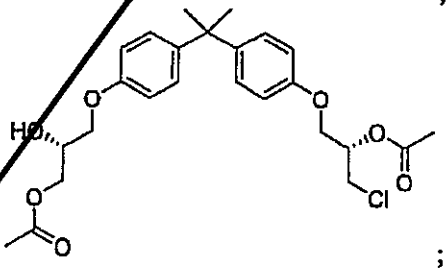
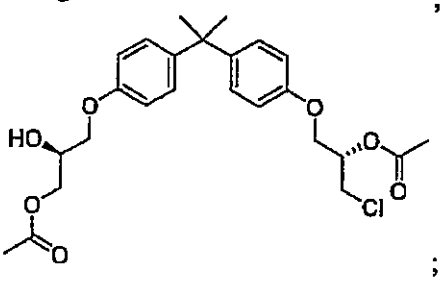
25. The compound of claim 24, wherein halo is fluoro.

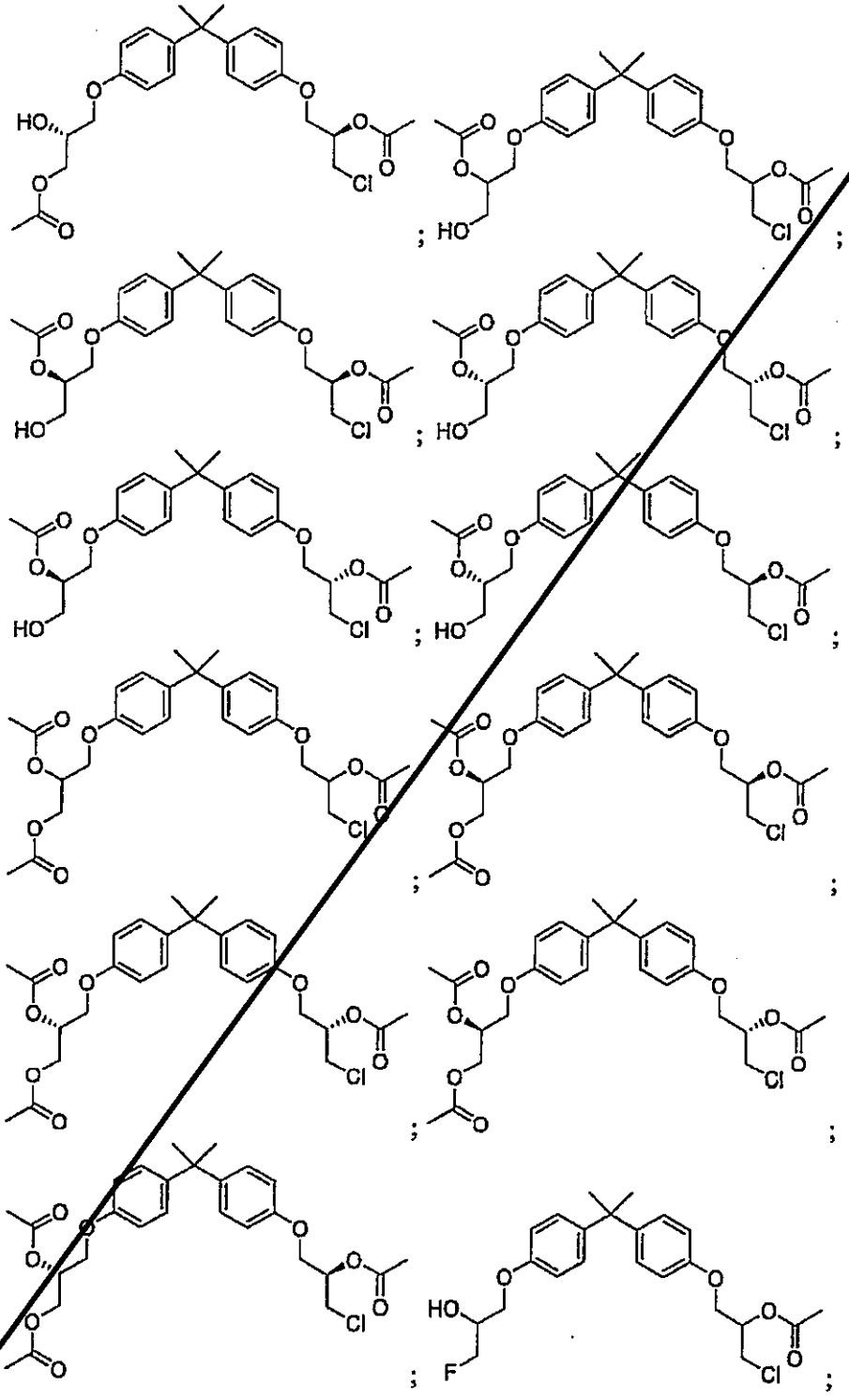
26. The compound of any one of claims 1-14, wherein R13 is C1-C20 alkyl, C2-C20 alkenyl or aralkyl, and at least one of the aliphatic carbons of the C1-C20 alkyl, C2-C20 alkenyl or aralkyl group is substituted with a substituent selected from hydroxyl, halo, oxo and alkoxy.

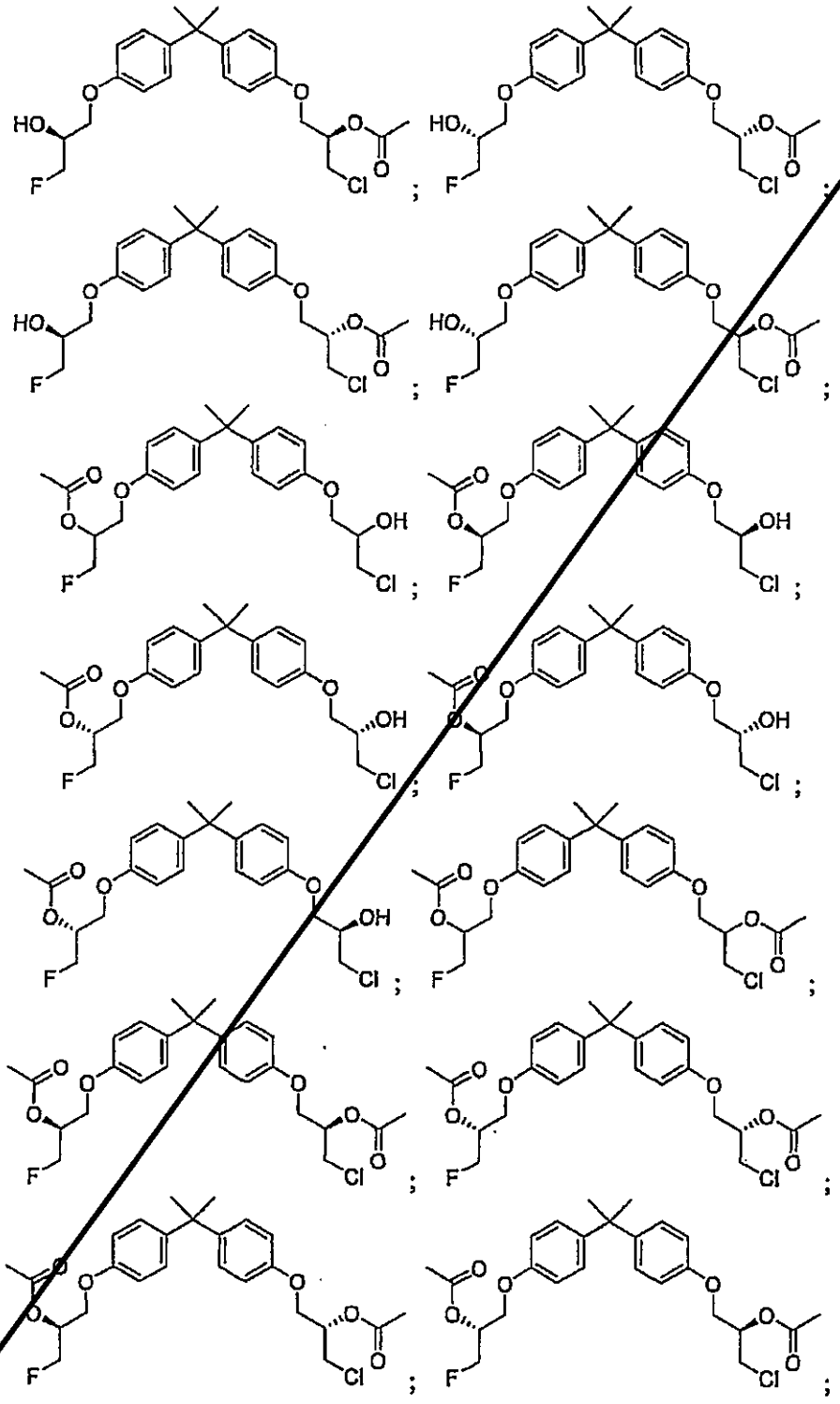
27. The compound of any one of claims 1-14, wherein R13 is aryl or aralkyl, and at least one of the aromatic carbons of the aryl or aralkyl group is substituted with a substituent selected from hydroxyl, halo and alkoxy.

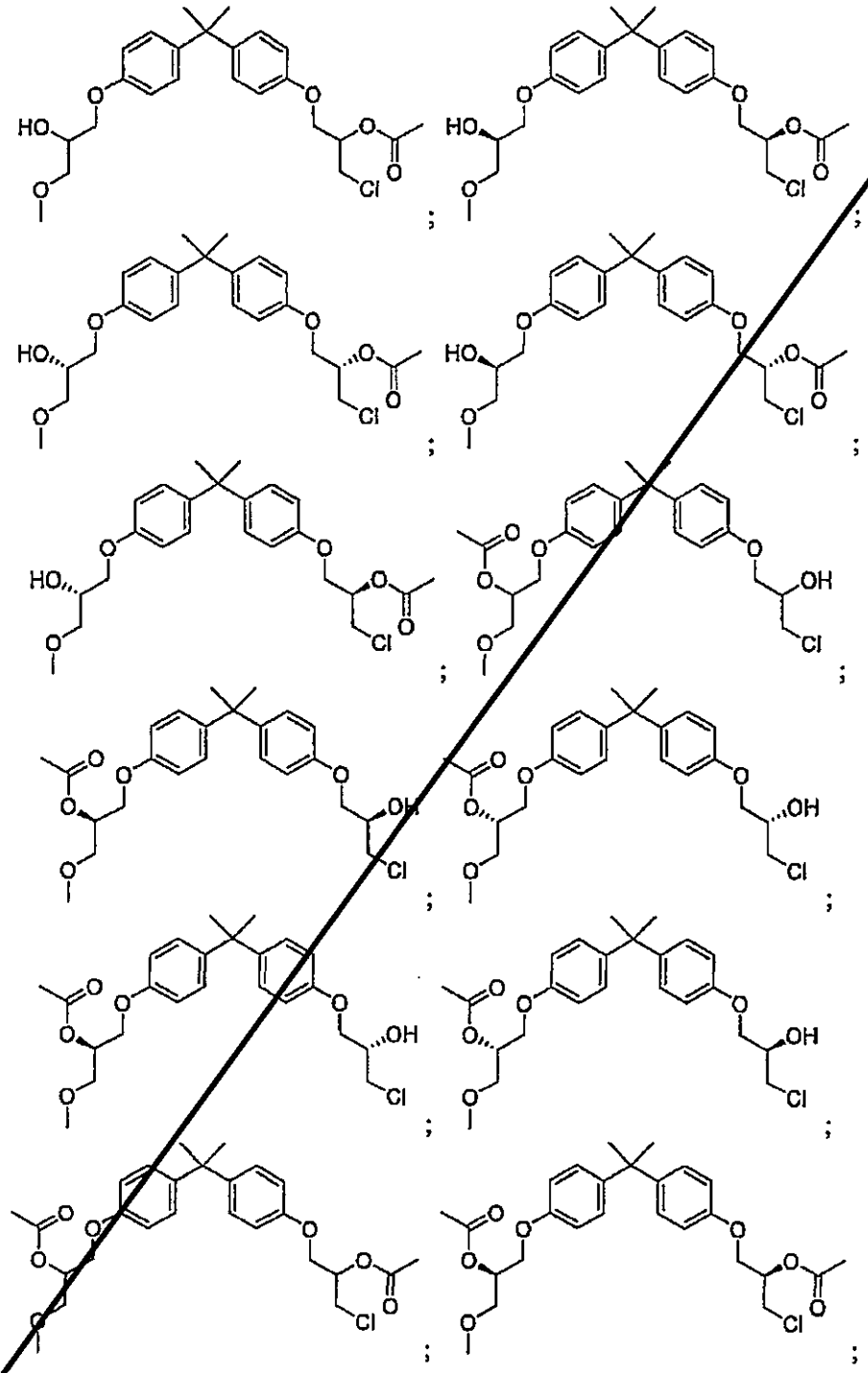
28. The compound of claim 1, wherein the compound has one of the following structures:

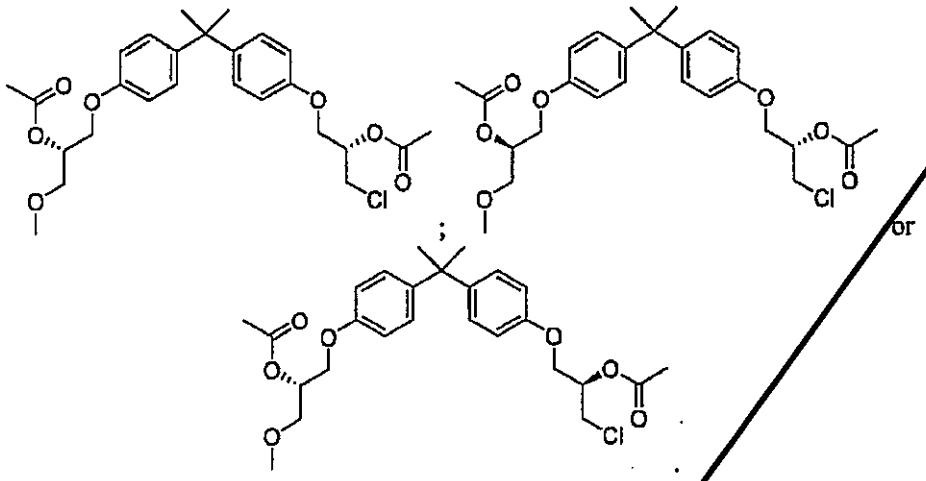



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29. A pharmaceutical composition comprising a compound of any one of claims 1 to 28 and a pharmaceutically acceptable carrier.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

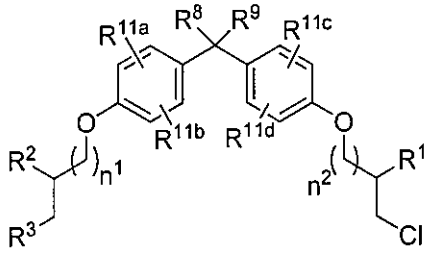
44. A method for increasing the bioavailability of a hydroxyl-containing androgen receptor modulator, the method comprising replacing at least one hydroxyl moiety with an alkyl, alkenyl, aryl or aralkyl ester.

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

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

Claims:

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



(Ic),

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

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

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

R^3 is hydroxyl, halo, or $-OC(=O)R^{13}$;

wherein, halo is selected from the group consisting of F, Br, and I;

R^8 is methyl;

R^9 is methyl;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H;

R^{13} is C_1-C_6 alkyl;

n^1 and n^2 are each independently 1; and

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

wherein R^3 is not $-OC(=O)CH_3$ when R^1 and R^2 are both hydroxyl;

wherein R^1 and R^2 are not both $-OC(=O)CH=CH_2$; and

wherein R^1 and R^2 are not both $-OC(=O)C(CH_3)=CH_2$.

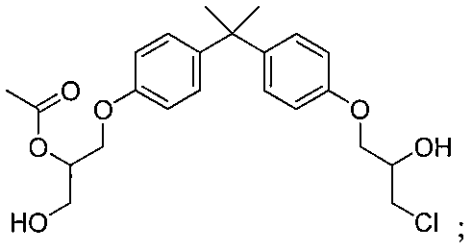
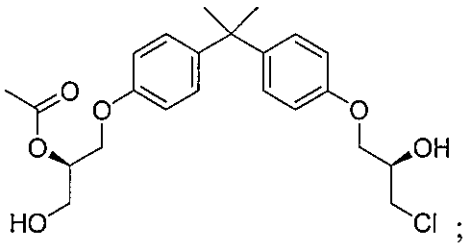
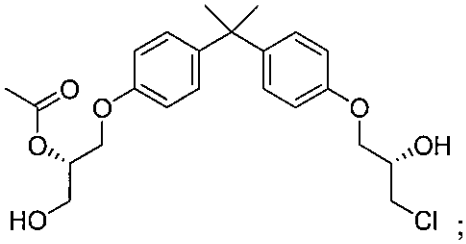
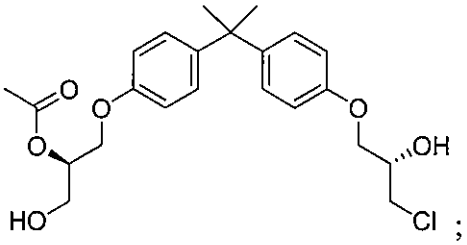
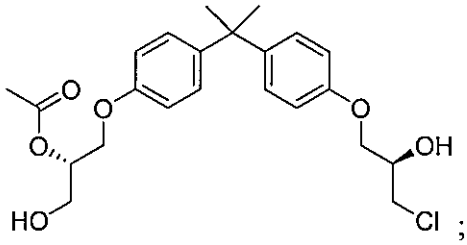
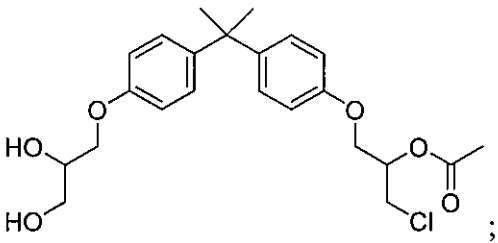
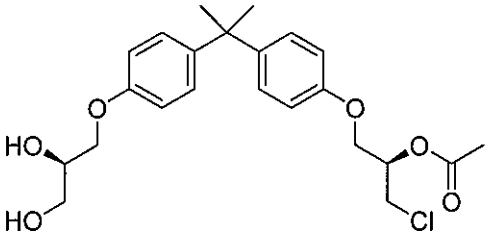
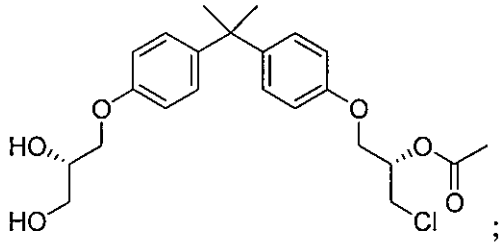
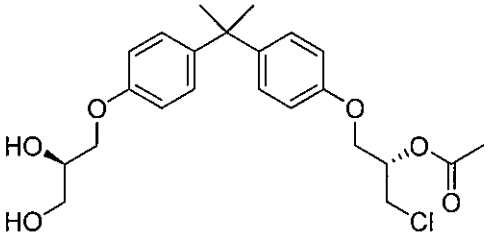
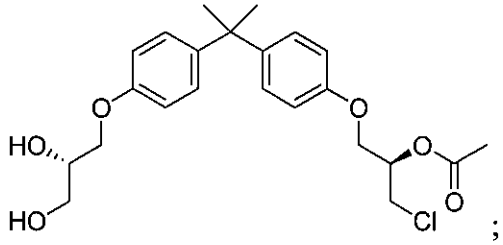
2. The compound of claim 1, wherein R^3 is halo.

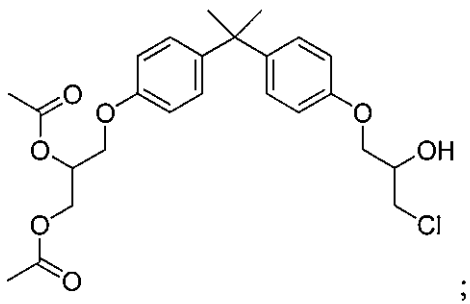
3. The compound of claim 1, wherein R^3 is fluoro.

4. The compound of claim 1, wherein each R^{13} is independently methyl, ethyl or propyl.

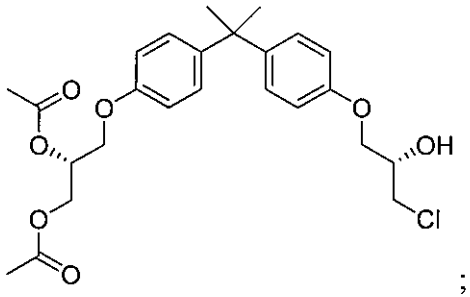
5. The compound of claim 1, wherein each R^{13} is methyl.

6. The compound of claim 1 selected from one or more of :

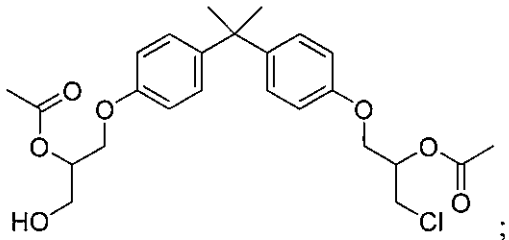
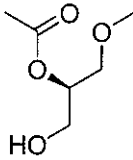

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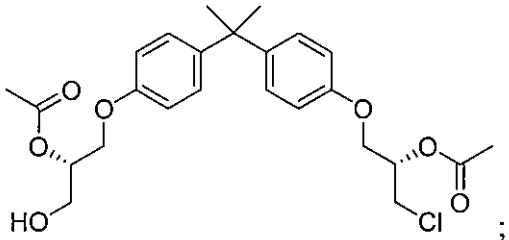
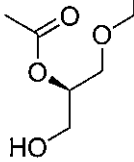

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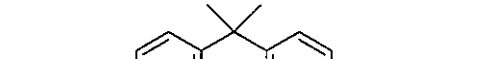
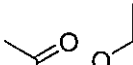
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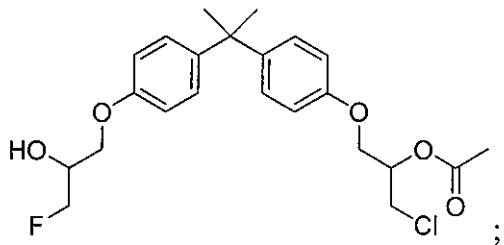
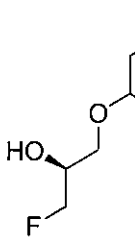

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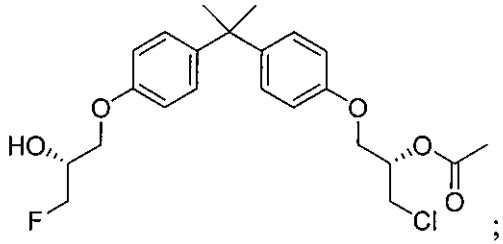
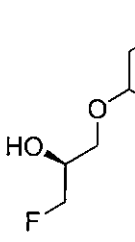
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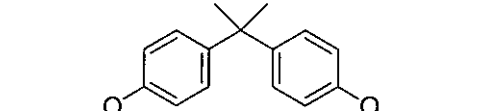
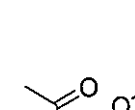

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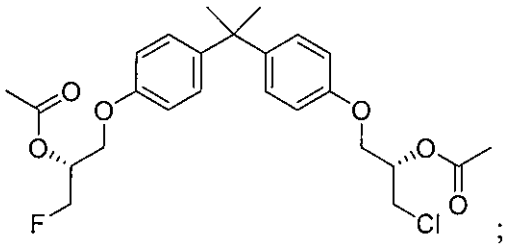
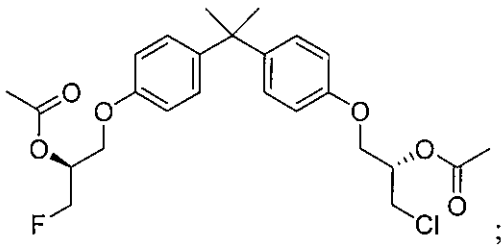
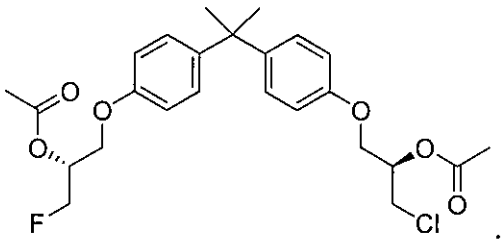

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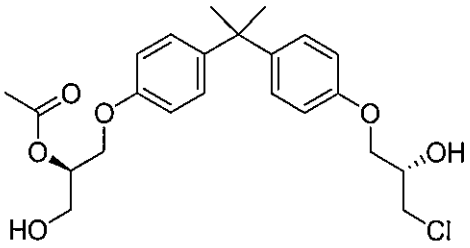
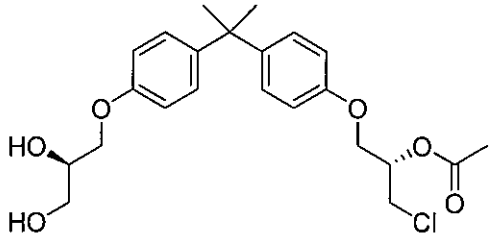
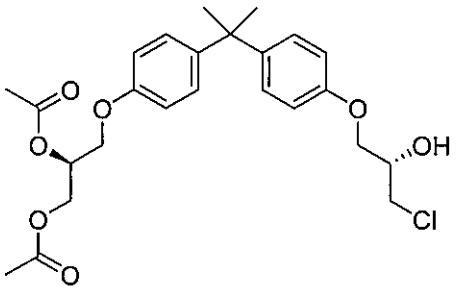
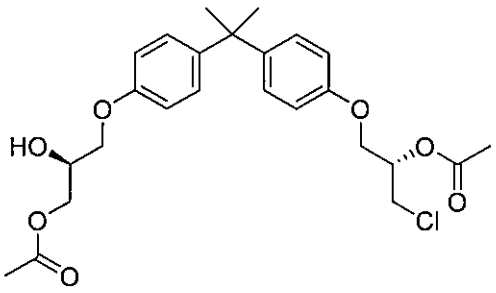
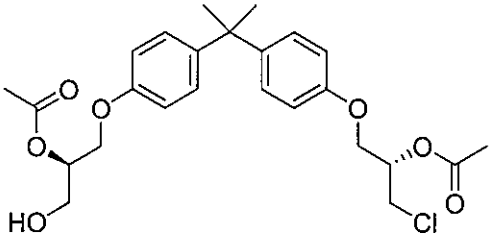

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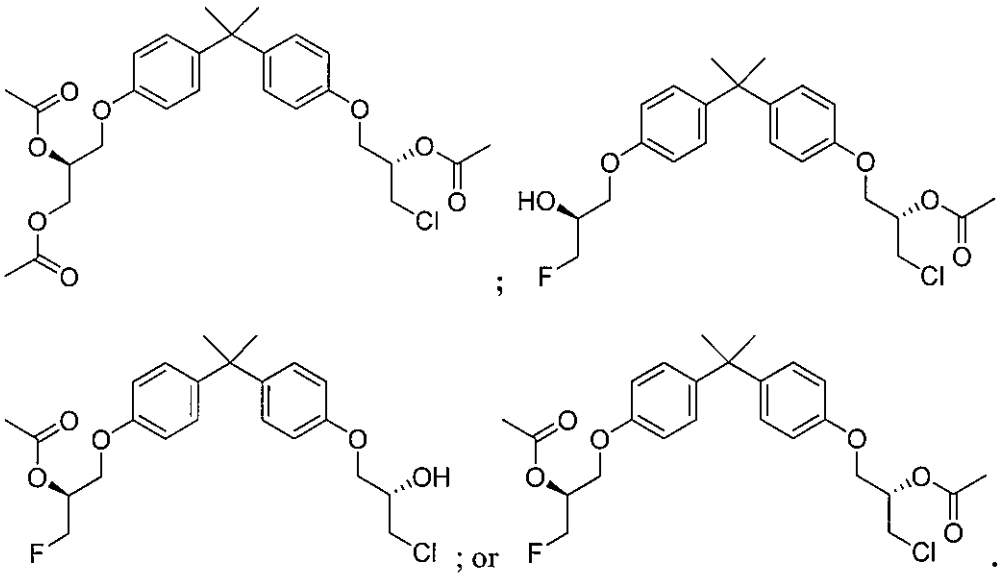

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7. The compound of claim 1 selected from one or more of:




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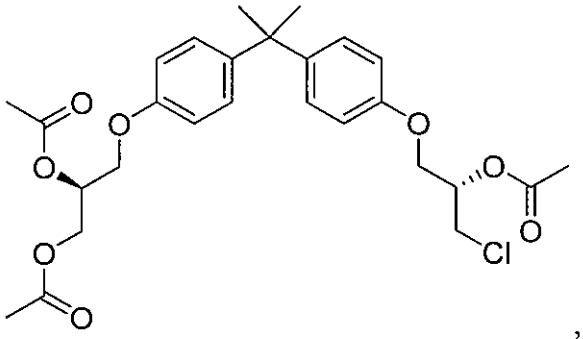


8. A pharmaceutical composition, comprising: a compound according to claim 1; and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition, comprising: a compound according to claim 1; a pharmaceutically acceptable carrier; and an additional therapeutic agent selected from the group consisting of enzalutamide, galeterone, ARN-509 (4-(7-(6-cyano-5-(tlifluoromethyl)pylidin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3,4]octan-5-yl)-2-tluoro-N-methylbenzamide), abiraterone, bicalutamide, nilutamide, flutamide, cyproterone acetate, docetaxel, bevacizumab, OSU-HDAC42 ((S)-(+)-N-Hydroxy-4-(3-methyl-2-phenyl-butyrylamino)benzamide, monoclonal antibody against the vascular integrin αvβ3, sunitumib, ZD-4054 (zibotentan), cabazitaxel (XRP-6258), MDX-010 (ipilimumab), OGX 427 (apatorsen), OGX 011 (custirsen), finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260 ((lS,3aS,3bS,5aR,9aR,9bS,11aS)-9a,11a-dimethyl-7-oxo-N-(1,1,1-trifluoro-2-phenylpropan-2-yl)-1,2,3,3a,3b,4,5,5a,6,9b,l0,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide), SKF105,111 (17β-(Di-isopropyl-aminocarbonyl)androsta-3,5-diene-3-carboxylic acid), radium 233, and related compounds thereof.

10. The pharmaceutical composition of claim 9, wherein the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration.

11. A pharmaceutical composition, comprising: a compound having the following structure:



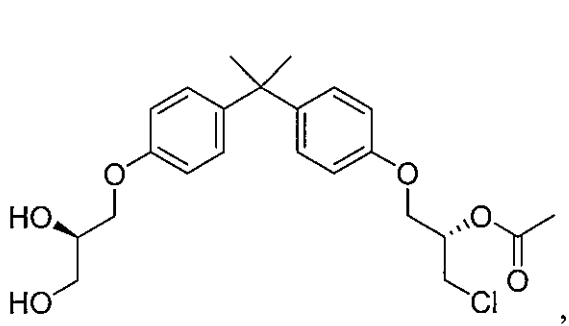
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or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

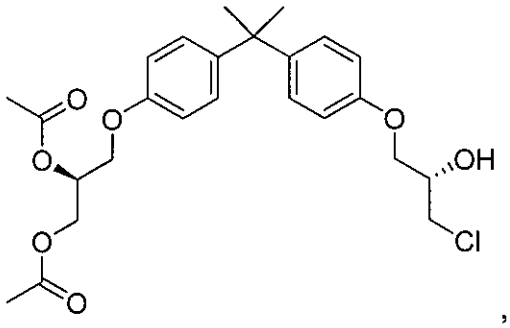
12. The pharmaceutical composition according to claim 11, further comprising: an additional therapeutic agent selected from the group consisting of enzalutamide, galeterone, ARN-509 (4-(7-(6-cyano-5-(tlifluoromethyl)pylidin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3,4]octan-5-yl)-2-tluoro-N-methylbenzamide), abiraterone, bicalutamide, nilutamide, flutamide, cyproterone acetate, docetaxel, bevacizumab, OSU-HDAC42 ((S)-(+)-N-Hydroxy-4-(3-methyl-2-phenyl-butyrylamino)benzamide, monoclonal antibody against the vascular integrin αvβ3, sunitumib, ZD-4054 (zibotentan), cabazitaxel (XRP-6258), MDX-010 (ipilimumab), OGX 427 (apatorsen), OGX 011 (custirsen), finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260 ((lS,3aS,3bS,5aR,9aR,9bS,11aS)-9a,11a-dimethyl-7-oxo-N-(1,1,1-trifluoro-2-phenylpropan-2-yl)-1,2,3,3a,3b,4,5,5a,6,9b,l0,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide), SKF105,111 (17β-(Di-isopropyl-aminocarbonyl)androsta-3,5-diene-3-carboxylic acid), radium 233, and related compounds thereof.

13. The pharmaceutical composition of claim 12, wherein the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration.

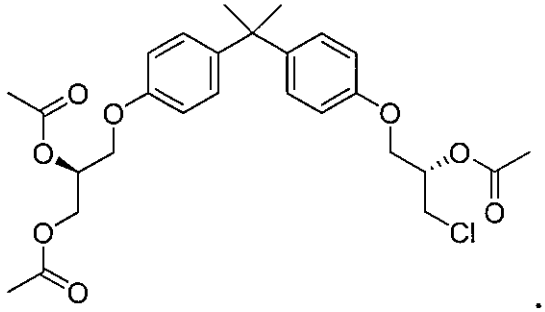
14. The compound of claim 1 selected from one or more of :



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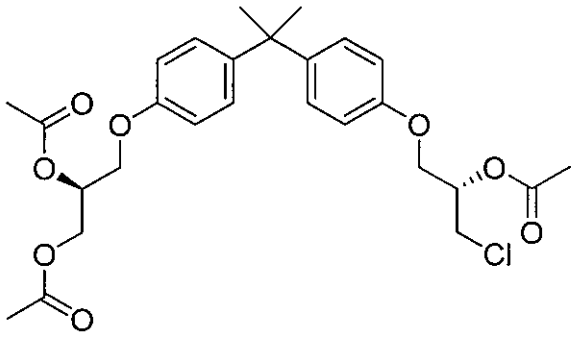


, or



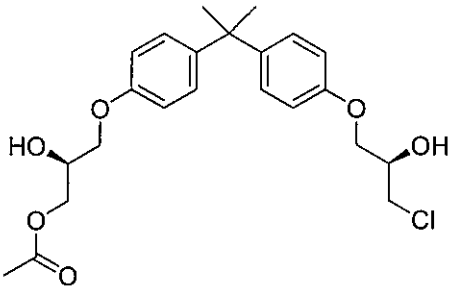
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15. The compound of claim 1, wherein the compound has the following structure:

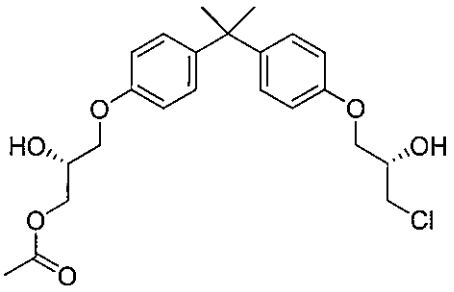


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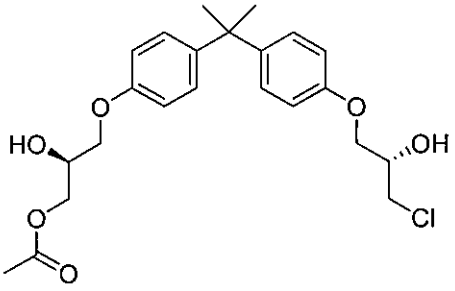
16. A compound selected from one of the following:



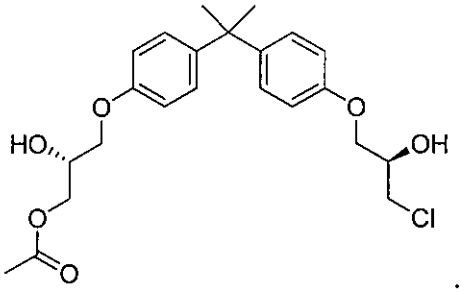
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